

Bioavailability study of dronabinol oral solution versus dronabinol capsules in healthy volunteers

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Background: Dronabinol, a pharmaceutical Δ -9-tetrahydrocannabinol, was originally developed as an oral capsule. This study evaluated the bioavailability of a new formulation, dronabinol oral solution, versus a dronabinol capsule formulation.

Methods: In an open-label, four-period, single-dose, crossover study, healthy volunteers were randomly assigned to one of two treatment sequences (T-R-T-R and R-T-R-T; T = dronabinol 4.25 mg oral solution and R = dronabinol 5 mg capsule) under fasted conditions, with a minimum 7-day washout period between doses. Analyses were performed on venous blood samples drawn 15 minutes to 48 hours postdose, and dronabinol concentrations were assayed by liquid chromatography–tandem mass spectrometry.

Results: Fifty-one of 52 individuals had pharmacokinetic data for analysis. The 90% confidence interval of the geometric mean ratio (oral solution/capsule) for dronabinol was within the 80%–125% bioequivalence range for area under the plasma concentration–time curve (AUC) from time zero to last measurable concentration (AUC_{0-t}) and AUC from time zero to infinity ($AUC_{0-\infty}$). Maximum plasma concentration was also bioequivalent for the two dronabinol formulations. Intraindividual variability in $AUC_{0-\infty}$ was >60% lower for dronabinol oral solution 4.25 mg versus dronabinol capsule 5 mg. Plasma dronabinol concentrations were detected within 15 minutes postdose in 100% of patients when receiving oral solution and in <25% of patients when receiving capsules.

Conclusion: Single-dose dronabinol oral solution 4.25 mg was bioequivalent to dronabinol capsule 5 mg under fasted conditions. Dronabinol oral solution formulation may provide an easy-to-swallow administration option with lower intraindividual variability as well as more rapid absorption versus dronabinol capsules.

Keywords: pharmacokinetics, Δ -9-tetrahydrocannabinol, safety, variability

Introduction

Dronabinol, a pharmaceutical formulation of Δ -9-tetrahydrocannabinol (Δ 9-THC), is orally active (ie, oral administration results in adequate bioavailability to produce physiologic effects) and, similar to other cannabinoids, has complex effects on the central nervous system.^{1,2} Dronabinol has demonstrated efficacy in the treatment of anorexia associated with weight loss in patients with AIDS^{3,4} and nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments^{5–8} and has been approved by the US Food and Drug Administration (FDA) for these indications.

Dronabinol was originally developed as a soft gelatin capsule. In this capsule formulation, oral dronabinol is almost completely absorbed (90%–95%) after

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single dosing.⁹ However, only 10%–20% of oral dronabinol reaches the systemic circulation due to first-pass hepatic metabolism and high lipid solubility. In multiple-dose pharmacokinetic studies using healthy adults, the mean (standard deviation [SD]) maximum plasma concentration (C_{\max}) of oral dronabinol capsule 5 mg twice daily was 3.0 (1.8) ng/mL, the median time to C_{\max} (T_{\max}) was 2.5 hours (range, 0.5–4.0 hours), and the mean (SD) area under the plasma concentration–time curve (AUC) from time zero to 12 hours (AUC_{0-12}) was 6.2 (1.8) h×ng/mL.⁹ However, high variability in the pharmacokinetic parameters of oral THC, including dronabinol capsules, has been demonstrated in studies of healthy adults.^{10–12} Dronabinol has been shown to undergo extensive first-pass hepatic metabolism yielding the major metabolite 11-OH- Δ^9 -THC that is pharmacologically active and has an AUC similar to that of the parent drug.⁹

The oral delivery of dronabinol via a capsule may be less than ideal, such as in those with nausea and vomiting associated with cancer chemotherapy or swallowing difficulties. Thus, an easy-to-swallow oral solution formulation of dronabinol has been developed to provide an alternative delivery method. This study was designed to evaluate the bioequivalence of dronabinol oral solution 4.25 mg versus dronabinol capsule 5 mg.

Methods

Participants

Males and females aged 18–55 years were eligible for the study if they were in good health as assessed by medical history, physical examination, and clinical laboratory investigations; had a body weight ≥ 50 kg and a body mass index of 19.0–29.9 kg/m²; and females were neither pregnant nor lactating. Individuals were excluded if they had used any prescription medicines (other than hormonal contraceptives) within 14 days, any over-the-counter medication within 7 days, or any vitamins or herbal supplements within 3 days before the first dose of study medication. Other exclusion criteria included marijuana use in the previous 90 days; smoking or other tobacco use in the previous 6 months; a history of mental illness, alcohol abuse, or physical dependence on any opioid, barbiturate, amphetamine, cocaine, or benzodiazepine in the past 10 years; or a positive screening test result for drugs of abuse. The study was conducted in accordance with the International Conference on Harmonisation principles of Good Clinical Practice and the Declaration of Helsinki. The study received institutional review board approval (IntegReview IRB, Austin, TX), and all patients provided written informed consent.

Study design and treatment

This randomized, open-label, two-treatment, four-period, two-sequence, single-dose, crossover study was conducted between September 2012 and October 2012 (ClinicalTrials.gov identifier: NCT01448772). Participants were randomly assigned to one of two treatment sequences: sequence 1 (T-R-T-R) and sequence 2 (R-T-R-T), where T was the test product (single oral dose of dronabinol oral solution 4.25 mg, lot number 100310 [Syndros™]; INSYS Therapeutics, Inc., Phoenix, AZ, USA) and R was the reference product (single oral dose of dronabinol capsule 5 mg, lot number 277967A [Marinol®]; expiration date December 2013; AbbVie, Inc., North Chicago, IL, USA). Each dose was administered under fasted conditions (overnight; ≥ 10 hours) with 240 mL of water. Additional water was permitted as needed during the study except 1 hour predose through 1 hour postdose. Standardized meals were allowed starting 4 hours postdose. Each dose of study medication (test or reference product) was separated by a minimum 7-day washout period.

Assessments

Blood samples were collected by venipuncture before (pre-dose) and at 0.25 hour, 0.5 hour, 0.75 hour, 1 hour, 1.5 hours, 2 hours, 2.5 hours, 3 hours, 3.5 hours, 4 hours, 6 hours, 8 hours, 12 hours, 16 hours, 24 hours, 36 hours, and 48 hours postdose. The plasma was harvested and frozen at -20°C until analysis. Plasma concentrations of dronabinol and the primary metabolite 11-OH- Δ^9 -THC were analyzed by Worldwide Clinical Trials Drug Development Solutions (Austin, TX, USA) using a validated liquid chromatography–tandem mass spectrometry method, with a range of 0.025–10.0 ng/mL for each analyte, based on the analysis of 0.500 mL of plasma. Adverse events (AEs) were monitored throughout the study.

Statistical analysis

The safety population included all patients who received ≥ 1 dose of study medication. The pharmacokinetic analysis population included all patients who completed the first two periods (T-R or R-T) within the sequence in which they were randomized. All statistical analyses were performed using SAS® (version 9.3; SAS Institute Inc., Cary, NC, USA).

Pharmacokinetic parameters for dronabinol and 11-OH- Δ^9 -THC were determined using standard noncompartmental methods. The C_{\max} and T_{\max} were determined using observed data. The terminal elimination rate constant, λ_z , was calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration–time curve. Elimination half-life ($t_{1/2}$) was calculated according to the

following equation: $t_{1/2} = 0.693/\lambda_z$. AUC from time zero to the final sample with a concentration greater than or equal to the lower limits of quantitation (AUC_{0-t}) was calculated using the linear trapezoidal method and extrapolated to infinity using the equation

$$AUC_{0-\infty} = AUC_{0-t} + C_{if}/\lambda_z$$

in which C_{if} was the final concentration that is greater than or equal to the lower limits of quantitation.

A linear mixed-effects model was used to compare dronabinol oral solution and dronabinol capsule formulations using natural log-transformed pharmacokinetic parameters (C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$), uncorrected for dose, with sequence, treatment, period, and group as fixed effects and subject as a random effect. Geometric mean (GM) ratios (solution/capsule) were calculated for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$, and corresponding 90% confidence intervals (CIs) were determined using the two one-sided *t*-tests procedure¹³ on log-transformed data. The point estimates and confidence limits were back-transformed to the original scale. The two treatments were considered bioequivalent if the 90% CIs for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ were within the range of 80%–125%. For products demonstrating high intraindividual variability, the bioequivalence acceptance limit is sometimes adjusted based on the intraindividual variability of the capsule (reference) formulation.^{14–16} In accordance with the FDA-recommended algorithm, if the intraindividual SDs (IISDs) for C_{max} and/or AUC of the reference product, as observed in the bioequivalence study, is or exceeds the cutoff value of 0.294, then the bioequivalence limits for the test product are scaled based on the degree of variability of the reference product.¹⁶ A sample size of 60 individuals was determined to provide at least 80% power, $\alpha = 0.05$, to determine that the 90% CI for the treatment comparison was between 80% and 125%, assuming a difference in intraindividual coefficient between formulations of $\leq 5\%$ for C_{max} .

A post hoc analysis evaluated intraindividual variability on pharmacokinetic parameters and time to detectable plasma dronabinol level for the oral solution and capsule formulations. The intraindividual coefficient of variation (CV) was calculated for each pharmacokinetic parameter according to $100 \times (IISD/LN[GM])$, where LN was the natural logarithmic function.

Results

A total of 52 patients were included in the safety population and 51 patients were included in the pharmacokinetic analysis population. Twenty-eight (53.9%) of the 52 individuals were

female, and 67.3% of individuals were white. The mean (SD) age was 33 ± 10 years (range, 18–53 years) with a mean body mass index of 25.4 ± 2.4 kg/m² (range, 21.0–29.9 kg/m²). One participant withdrew prior to completion of the first two study periods and was excluded from the pharmacokinetic analysis population. Fifty of the 51 individuals in the pharmacokinetic analysis population completed all four periods (ie, received two doses each of test and reference products, with each dose separated by a 7-day washout period), and one participant withdrew after period 2.

Pharmacokinetic profile

The mean plasma concentration–time curves of dronabinol and 11-OH- Δ^9 -THC are presented in Figure 1A and B, respectively. Pharmacokinetic parameters are summarized in Table 1. The median T_{max} of dronabinol was shorter and the mean $t_{1/2}$ was longer for dronabinol oral solution 4.25 mg versus dronabinol capsule 5 mg. For the primary active metabolite 11-OH- Δ^9 -THC, the median T_{max} and mean $t_{1/2}$ were similar for the two dronabinol formulations.

For dronabinol, the 90% CIs of the GM ratios for AUC_{0-t} and $AUC_{0-\infty}$ were within the bioequivalence range of 80%–125% (Table 2). The 90% CI for dronabinol C_{max} fell outside the bioequivalence range of 80%–125%. Because the IISD for the C_{max} of the reference product (0.364) was ≥ 0.294 (FDA criterion for a highly variable drug^{15,16}) and the point estimate of the GM ratio of dronabinol C_{max} (82.50%) was within the bioequivalence range, the bioequivalence of C_{max} was evaluated using reference-scaled criteria. Using the reference-scaled approach, the point estimate of the GM ratio for dronabinol C_{max} (81.96%) was within the range of 80%–125%, and the 95% upper confidence bound (-0.01) was ≤ 0 , thereby meeting the FDA criteria for bioequivalence.¹⁵ For 11-OH- Δ^9 -THC (Table 2), the GM values for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ were lower for dronabinol oral solution than for dronabinol capsule, and the lower limits of the 90% CIs of the GM ratios were $< 80\%$.

In a post hoc analysis of the intraindividual variability in dronabinol pharmacokinetic parameters (Table 3), the intraindividual CV for $AUC_{0-\infty}$ was lower for dronabinol oral solution 4.25 mg compared with dronabinol capsule 5 mg (13.5% versus 36.8%, respectively). Regarding C_{max} , intraindividual variability was greater for dronabinol oral solution versus dronabinol capsule (CV, 66.3% versus 53.8%, respectively). A faster onset of detectable plasma concentrations was observed for dronabinol oral solution, with 100% of individuals with a detectable plasma dronabinol concentration at 15 minutes postdose when compared with 16.8%

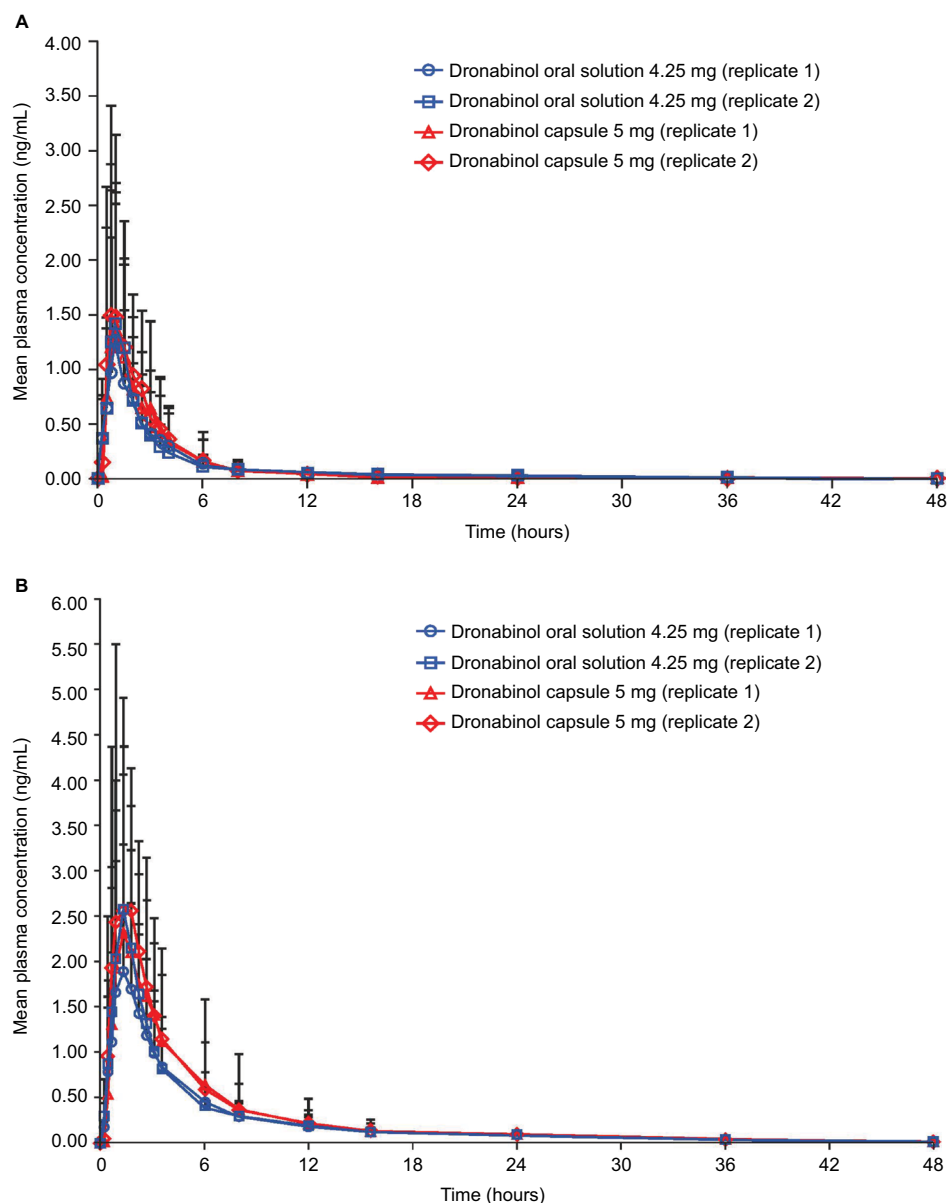


Figure 1 Linear mean plasma concentration–time curves for **(A)** dronabinol and **(B)** 11-OH- Δ^9 -THC, after single-dose administration of dronabinol oral solution 4.25 mg or dronabinol capsule 5 mg, under fasted conditions.

Notes: N=51 for replicate 1. N=50 for replicate 2.

Abbreviation: THC, tetrahydrocannabinol.

of individuals after administration of dronabinol capsule (Figure 2).

Adverse events

Single-dose administration of dronabinol oral solution 4.25 mg and dronabinol capsule 5 mg was generally well tolerated. A total of 90 AEs were reported by 25 individuals during the study, with 48.9% and 51.1% of AEs reported with dronabinol oral solution and dronabinol capsule, respectively. The most commonly reported AEs in the safety population were nausea (n=14; dronabinol oral solution, n=8, versus dronabinol capsule, n=6), dizziness (n=13; dronabinol oral

solution, n=6, versus dronabinol capsule, n=7), somnolence (n=12; dronabinol oral solution, n=7, versus dronabinol capsule, n=5), and headache (n=11; dronabinol oral solution, n=7, versus dronabinol capsule, n=4). All AEs were considered mild (50%) or moderate (50%) in intensity.

Discussion

This comparative bioavailability study demonstrated the bioequivalence of single-dose dronabinol oral solution 4.25 mg to dronabinol capsule 5 mg in healthy volunteers, under fasted conditions. The 90% CI of the GM ratio (oral solution/capsule) was within the standard bioequivalence range

Table 1 Pharmacokinetics of dronabinol and 11-OH- Δ^9 -THC after single-dose administration of dronabinol oral solution or dronabinol capsule

Parameter ^a	Dronabinol oral solution 4.25 mg		Dronabinol capsule 5 mg	
	Replicate 1, N=51	Replicate 2, N=50	Replicate 1, N=51	Replicate 2, N=50
Dronabinol				
C_{max} (ng/mL)	1.81 (1.26)	2.08 (1.30)	2.20 (1.51)	2.61 (1.69)
T_{max} (hours)	1.50 (0.50–4.00)	1.00 (0.50–3.02)	1.00 (0.50–6.00)	1.50 (0.50–6.00)
AUC_{0-t} (h \times ng/mL)	3.44 (1.98)	3.62 (1.75)	3.75 (2.36)	4.23 (2.65)
$AUC_{0-\infty}$ (h \times ng/mL)	3.75 (2.04) ^b	3.94 (1.50) ^c	3.85 (2.32) ^d	4.27 (2.70) ^e
λ_z (1/h)	0.16 (0.07) ^b	0.14 (0.06) ^c	0.36 (0.16) ^d	0.29 (0.15) ^e
$t_{1/2}$ (hours)	5.41 (3.06) ^b	5.78 (2.13) ^c	2.68 (2.39) ^d	3.52 (2.87) ^e
11-OH-Δ^9-THC				
C_{max} (ng/mL)	2.53 (1.38)	3.01 (1.56)	3.28 (1.78)	3.98 (2.51)
T_{max} (hours)	1.50 (0.75–4.00)	1.50 (0.50–3.02)	1.60 (0.75–6.00)	1.50 (0.50–6.00)
AUC_{0-t} (h \times ng/mL)	10.1 (5.21)	11.1 (5.05)	12.2 (6.20)	13.5 (7.12)
$AUC_{0-\infty}$ (h \times ng/mL)	10.7 (5.5) ^f	11.8 (5.19) ^g	13.3 (6.41) ^h	14.3 (7.34) ^b
λ_z (1/h)	0.07 (0.05) ^f	0.07 (0.04) ^g	0.08 (0.08) ^h	0.07 (0.03) ^b
$t_{1/2}$ (hours)	11.6 (4.39) ^f	11.7 (3.61) ^g	11.8 (4.17) ^h	11.9 (3.6) ^b

Notes: λ_z , terminal elimination rate constant; AUC_{0-t} , AUC from time zero to last measurable concentration; $AUC_{0-\infty}$, AUC from time zero to infinity; C_{max} , maximum plasma concentration; $t_{1/2}$, elimination half-life; T_{max} , the median time to C_{max} . ^aData are mean (SD) except T_{max} , which is median (range): ^bn=49. ^cn=42. ^dn=46. ^en=40. ^fn=50. ^gn=47. ^hn=48.

Abbreviations: AUC, area under the plasma concentration–time curve; SD, standard deviation; THC, tetrahydrocannabinol.

Table 2 Determination of bioequivalence of single-dose dronabinol oral solution versus dronabinol capsule

Parameter	Dronabinol oral solution 4.25 mg, geometric LSM	Dronabinol capsule 5 mg, geometric LSM	Geometric mean ratio (90% CI) ^a	Intraindividual SD	
				Dronabinol oral solution 4.25 mg	Dronabinol capsule 5 mg
Dronabinol					
C_{max}	1.62	1.97	82.50 ^b (74.62–91.22)	0.32	0.36
AUC_{0-t}	3.12	3.32	94.07 (84.59–104.61)	0.19	0.43
$AUC_{0-\infty}$	3.45	3.43	100.39 (89.47–112.65)	0.17	0.45
11-OH-Δ^9-THC					
C_{max}	2.36	3.05	77.33 (72.50–82.49)	0.29	0.26
AUC_{0-t}	9.05	10.90	82.97 (77.98–88.28)	0.21	0.22
$AUC_{0-\infty}$	9.67	11.53	83.92 (79.02–89.11)	0.19	0.22

Notes: $AUC_{0-\infty}$, AUC from time zero to infinity; AUC_{0-t} , AUC from time zero to last measurable concentration; C_{max} , maximum plasma concentration. Results were calculated for all participants who completed ≥ 2 study periods (N=51). ^aBased on analysis of natural log-transformed data. ^bUsing the reference-scaled approach, the point estimate of the geometric mean ratio was 81.96, and the 95% upper confidence bound was -0.01 , which met the criteria for bioequivalence.

Abbreviations: AUC, area under the plasma concentration–time curve; CI, confidence interval; LSM, least-squares mean; SD, standard deviation; THC, tetrahydrocannabinol.

Table 3 Intraindividual variability of dronabinol pharmacokinetic parameters after single-dose administration of dronabinol oral solution or dronabinol capsule

Parameter	GM		IISD		Intraindividual CV (%) ^a	
	Dronabinol oral solution 4.25 mg	Dronabinol capsule 5 mg	Dronabinol oral solution 4.25 mg	Dronabinol capsule 5 mg	Dronabinol oral solution 4.25 mg	Dronabinol capsule 5 mg
C_{max}	1.62	1.97	0.321	0.364	66.3	53.8
$AUC_{0-\infty}$	3.45	3.43	0.167	0.453	13.5	36.8

Notes: $AUC_{0-\infty}$, AUC from time zero to infinity; C_{max} , maximum plasma concentration. ^aCalculated from the GM and the IISD according to $100 \times (IISD/LN[GM])$, where LN is the natural logarithmic function.

Abbreviations: AUC, area under the plasma concentration–time curve; CV, coefficient of variation; GM, geometric mean; IISD, intraindividual standard deviation.

of 80%–125% for AUC_{0-t} and $AUC_{0-\infty}$. C_{max} was comparable for the oral solution and capsule formulations based on FDA-recommended reference-scaled criteria. Intraindividual variability in total exposure ($AUC_{0-\infty}$) was >60% lower for the oral solution compared with capsules. In addition, faster absorption was observed for the oral solution formulation.

The bioequivalence of dronabinol oral solution with dronabinol capsules was established using FDA-recommended study design and methodology.^{17,18} For reference drugs identified as highly variable (ie, IISD ≥ 0.29 in a bioequivalence study), a reference-scaled approach is recommended.^{15,16} The IISD for dronabinol capsule 5 mg in

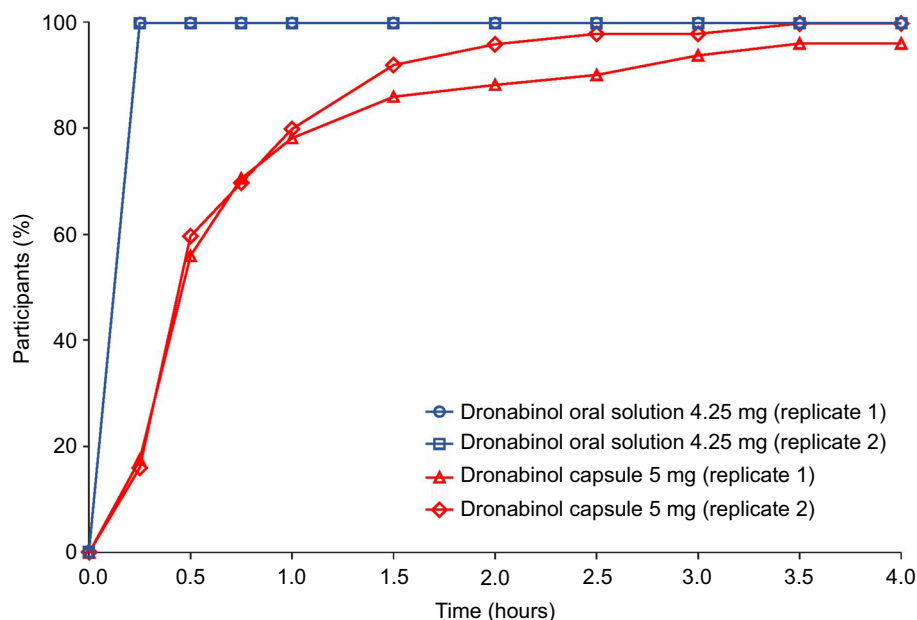


Figure 2 Percentage of participants with measurable plasma dronabinol concentration (≥ 0.025 ng/mL) after single-dose administration of dronabinol oral solution 4.25 mg or dronabinol capsule 5 mg, under fasted conditions.

Notes: N=51 for replicate 1. N=50 for replicate 2.

the current study was >0.29 for dronabinol C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$. Despite this variability, the 90% CIs for the GM ratios (oral solution/capsule) of dronabinol AUC_{0-t} and $AUC_{0-\infty}$ were within the bioequivalence range (80%–125%). The point estimate for the C_{max} GM ratio (82.5%) was within the bioequivalence range, but the lower limit of the 90% CI (74.6%) fell outside the range. Therefore, dronabinol C_{max} for the oral solution was evaluated using a reference-scaled approach and met the FDA-recommended criteria for bioequivalence.¹⁵ For the primary active metabolite of dronabinol (11-OH- Δ^9 -THC), the mean plasma concentrations were slightly lower after administration of oral solution when compared with capsule and were considered indicative of the similarity between the oral solution and capsule products.

This post hoc analysis demonstrated important attributes for dronabinol oral solution relative to dronabinol capsules, with lower intraindividual CV for $AUC_{0-\infty}$ (13.5% versus 36.8%, respectively) and faster onset of detectable plasma concentrations in 100% and 16.8% of individuals, respectively, at 15 minutes postdose. Variability for C_{max} was greater for dronabinol oral solution versus dronabinol capsule (66.3% versus 53.8%, respectively). The frequency of AEs was comparable between dronabinol oral solution and dronabinol capsule. Limitations of the study include that the study population was composed of only healthy adults; the pharmacokinetics of dronabinol may differ in patients with cancer or AIDS and in the presence of antineoplastic agents or other concomitant medications. In addition, this was a single-dose study and does not reflect the steady-state pharmacokinetics of dronabinol.

Furthermore, because this study was conducted in healthy adults, additional studies may be needed to assess the clinical relevance of faster onset of detectable plasma concentrations and lower intraindividual variability in a patient population.

The efficacy of dronabinol (Δ^9 -THC) as an antiemetic for patients with chemotherapy-induced nausea and vomiting and as an appetite stimulant for patients with AIDS is supported by multiple studies of capsule formulations.^{3-5,7,8,19-24} Potential limitations of prior dronabinol formulations have included variable bioavailability and delayed absorption, which are important considerations that limit the optimal treatment of patients.²⁵ Specifically, it has been noted with prior formulations, as stated by Lucas and Laszlo⁷ in 1980, that “ Δ^9 -tetrahydrocannabinol is erratically absorbed from the gastrointestinal tract, and dosage individualization may be necessary to control these patients.” Consequently, intraindividual and interindividual variabilities are likely to have important implications for safety and efficacy with dronabinol products, as well as patient adherence. In this regard, the $>60\%$ lower intraindividual variability in absorption with the oral solution compared with the capsule formulation is noteworthy. Another important finding of this study was that detectable concentrations of dronabinol oral solution were observed in a substantially greater percentage of patients within 15 minutes postdose with dronabinol oral solution versus dronabinol capsule. The faster onset of detectable concentrations observed with dronabinol oral solution may be an additional consideration for physicians in selecting the appropriate dronabinol formulation for their patients. Furthermore, the oral solution may offer flexibility in dosing calculations in

cancer settings (eg, as an antiemetic for patients undergoing chemotherapy, for which the recommended dronabinol dose is based on body surface area⁹).

Conclusion

This pharmacokinetic study demonstrated the bioequivalence of dronabinol oral solution 4.25 mg and dronabinol capsule 5 mg under fasted conditions in healthy volunteers. The attributes of the dronabinol oral solution formulation, including lower intraindividual variability and faster onset of detectable concentrations relative to dronabinol capsule, may be important considerations in the selection of the optimal formulation of dronabinol for the treatment of patients.

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Disclosure

NP, VK, CCS, and SV are full-time employees of INSYS Therapeutics, Inc. WGK is a paid consultant to INSYS Therapeutics, Inc. The authors report no other conflicts of interest in this work.

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