FORMULAITE

Simulaite Report

CBD / CBN Multi-Formulation Bioavailability Comparison

Pharmacokinetic Simulation — Gummies, Tinctures, and Oral Strips

April 22, 2026

Executive Summary

This report compares the oral bioavailability of CBD and CBN across 7 delivery formulations — buccal strips, sublingual strips, sublingual tincture, oral tincture, and gummies — at 25 mg dose per compound, using the Simulaite PBPK engine on a virtual population of n=100 American individuals under both fasted and fed conditions. The simulation reveals dramatic differences between delivery routes — from <2% for swallowed formats (oral tincture, gummy) to >79% for ideal-patient buccal strips — driven by first-pass metabolism bypass, mucosal absorption kinetics, and food effects.

Key Takeaways

• Buccal strips achieve 22-78% CBD bioavailability (depending on patient swallowing) — significantly higher than oral formats (gummy, tincture) which deliver <2% when administered non-sublingually and while fasted

• For transmucosal routes (buccal/sublingual), CBN outperforms CBD by 8-16% — but for swallowed routes, CBD actually does better than CBN (e.g., 1.3% vs 0.3% for gummy)

• Patients should minimize swallowing during strip dissolution — natural swallowing drops bioavailability about 4× (from 78% to 22%) as drug is lost to GI tract before full mucosal absorption

• Sublingual underperforms buccal by ~32-47% (depending on patient swallowing) — smaller surface area (10 vs 14 cm²) and higher salivary flow

• Food intake dramatically boosts oral formats: 4.8× improvement for tincture (1.1% to 5.5% CBD) and 3.4× for gummy (1.3% to 4.3% CBD) — lipids stimulate lymphatic transport and slow GI transit

• Fed vs fasted makes little difference for transmucosal routes — absorption happens before swallowing, so first-pass bypass is already achieved

Table of Contents

Molecule Profiles

Name	SMILES	Formula
CBD (Cannabidiol)	CCCCCC1=CC(=C(C(=C1)O)[C@@H]2C=C(CC[C@H]2C(=C)C)C)O	$C_{21}H_{30}O_2$
CBN (Cannabinol)	CCCCCC1=CC(=C2C(=C1)OC(C3=C2C=C(C=C3)C)(C)C)O	$C_{21}H_{26}O_2$

CBD and CBN are highly lipophilic phytocannabinoids derived from cannabis. Both compounds are significantly metabolized by CYP and UGT enzymes warranting transmucosal delivery to bypass first-pass metabolism. Their lipophilicity enables lymphatic transport with specialized delivery systems and/or having a fat-heavy meal while taking them. We use our suite of graph neural networks to predict relevant molecular properties and interactions with liver enzymes, plasma proteins, and the gut wall to inform the simulations.

Formulation Parameters

1. Buccal Strip

Delivery Type	Oral Fast-Dissolving Strip
Route	Buccal (cheek)
Surface Area	3.5 × 4 cm (14 cm²)
Dissolve Time	~30 min
Dose per Compound	25 mg
Lipid Excipient	None (polymer matrix)
Patient Type	Standard (includes natural swallowing)

2. Sublingual Strip

Delivery Type	Oral Fast-Dissolving Strip
Route	Sublingual (under tongue)
Surface Area	2.5 × 4 cm (10 cm²)
Dissolve Time	~20 min
Dose per Compound	25 mg
Lipid Excipient	None (polymer matrix)
Patient Type	Standard (includes natural swallowing)

3. Buccal Strip — Ideal Patient

Delivery Type	Oral Fast-Dissolving Strip
Route	Buccal (cheek)
Surface Area	3.5 × 4 cm (14 cm²)
Dissolve Time	~30 min
Dose per Compound	25 mg
Lipid Excipient	None (polymer matrix)
Patient Type	Ideal (refrains from swallowing)

4. Sublingual Strip — Ideal Patient

Delivery Type	Oral Fast-Dissolving Strip
Route	Sublingual (under tongue)
Surface Area	2.5 × 4 cm (10 cm²)
Dissolve Time	~20 min
Dose per Compound	25 mg
Lipid Excipient	None (polymer matrix)
Patient Type	Ideal (refrains from swallowing)

5. Oral MCT Tincture

Delivery Type	Liquid Tincture
Route	Oral (swallowed)
Volume	1 mL
Dose per Compound	25 mg
Lipid Excipient	MCT Oil
Administration	Swallowed immediately

6. Sublingual MCT Tincture

Delivery Type	Liquid Tincture
Route	Sublingual hold then swallow
Volume	1 mL
Dose per Compound	25 mg
Lipid Excipient	MCT Oil
Hold Time	1.5 min (90 sec)

7. MCT + Lecithin Gummy

Delivery Type	Solid Gummy
Route	Oral (swallowed)
Weight	~3 g
Dose per Compound	25 mg
Lipid Excipient	MCT Oil + Lecithin
Release Profile	Gradual release over ~45 min

Population Settings

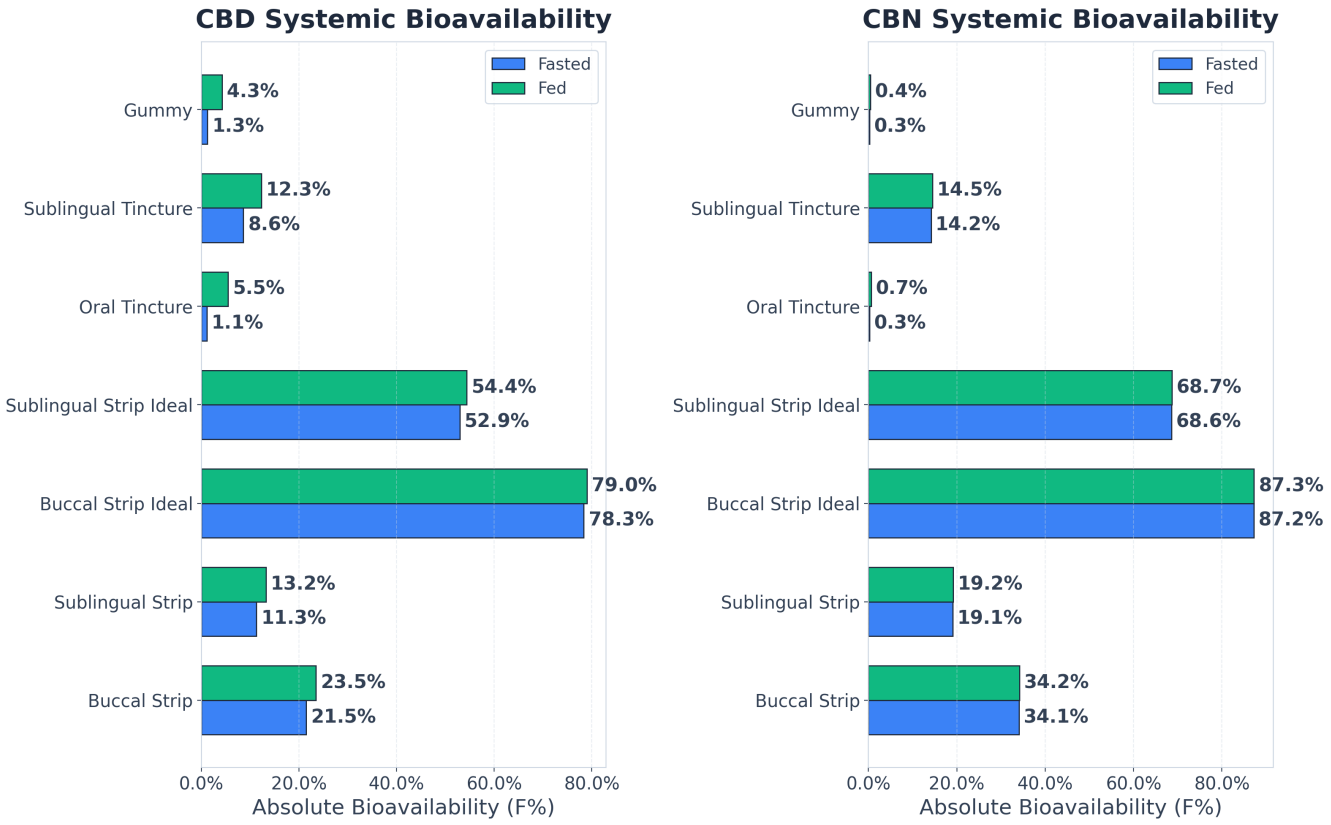
A virtual population of 100 American individuals was generated using population physiology from pharmaceutical databases. Each individual has unique organ volumes, blood flows, and enzyme expression levels derived from clinical datasets, capturing inter-individual variability in absorption, distribution, and clearance. Both fasted and fed states were simulated to assess the impact of food on bioavailability.

Parameter	Value
Sample Size (n)	100
Sex	49% female, 51% male
Age Range	18.0–64.2 years (mean 40.5)
Body Weight	47.3–133.4 kg (mean 78.7)
BMI Range	17.4–45.7 (mean 27.7)
Ethnicity	White 62% · Latino 19% · African American 13% · Asian 6%
Prandial States	Fasted & Fed (both simulated)

Bioavailability Results

Bioavailability (F%) Comparison

Absolute bioavailability (F%) for each formulation under fasted and fed conditions, computed as: F% = AUC(oral or transmucosal) / AUC(IV bolus) × 100. The IV bolus serves as the 100% reference — it bypasses all absorption barriers and delivers drug directly to systemic circulation.



AUC (ng/mL·h) — Fasted State

AUC captures the clinically relevant inter-individual variability — driven by differences in clearance, volume of distribution, and (for oral routes) GI absorption. CV% reflects real patient-to-patient exposure differences.

Formulation	CBD AUC (mean±SD)	CBD CV%	CBN AUC (mean±SD)	CBN CV%
Buccal Strip	3980 ± 842	21%	8780 ± 1874	21%
Sublingual Strip	2093 ± 436	21%	4917 ± 1046	21%
Buccal Strip — Ideal	14517 ± 3122	22%	22466 ± 4806	21%
Sublingual Strip — Ideal	9809 ± 2102	21%	17666 ± 3777	21%
Oral Tincture	204 ± 114	56%	64 ± 36	56%
Sublingual Tincture	1589 ± 529	33%	3668 ± 1266	35%
Gummy	227 ± 126	56%	73 ± 40	55%

Absorption Pathway Breakdown — Transmucosal Formulations (Fasted)

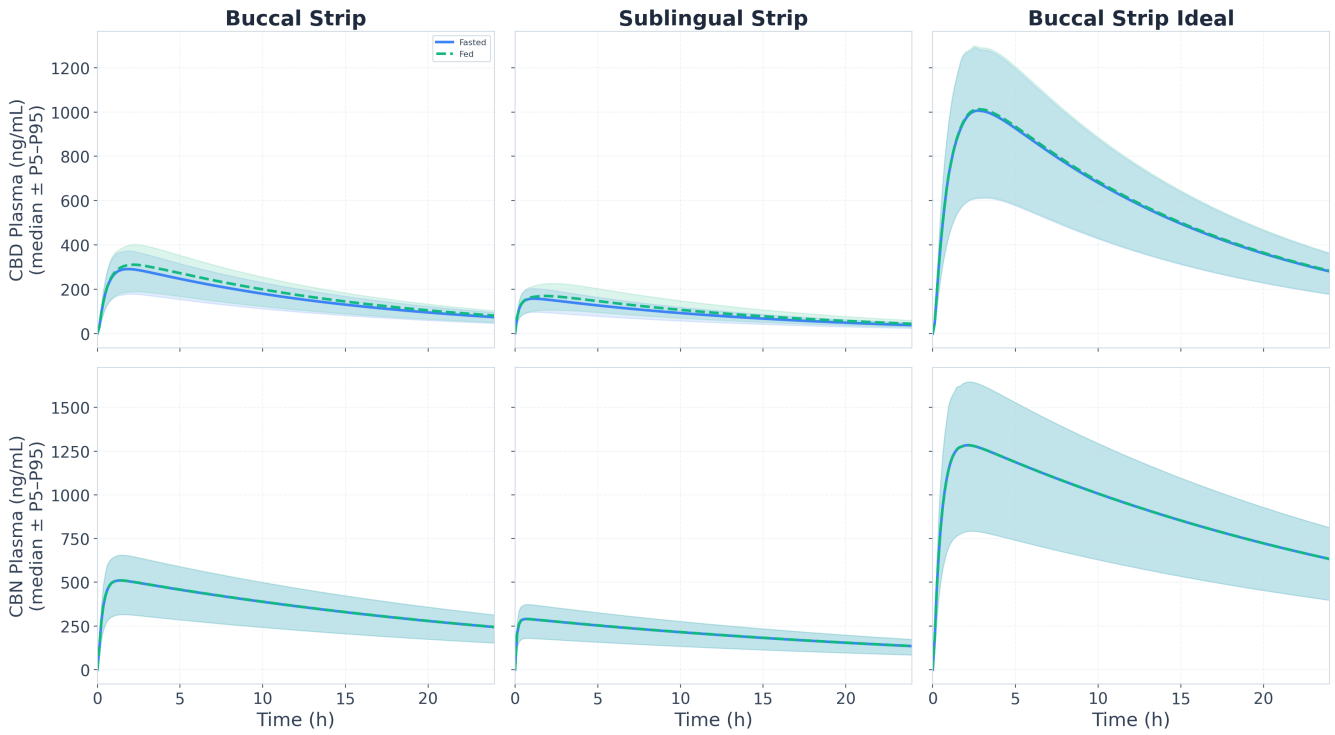
In standard patients, natural swallowing during strip dissolution significantly increases the swallowed fraction (drug lost to GI tract before full mucosal absorption). In ideal patients, only passive salivary flow contributes to swallowing, resulting in minimal loss.

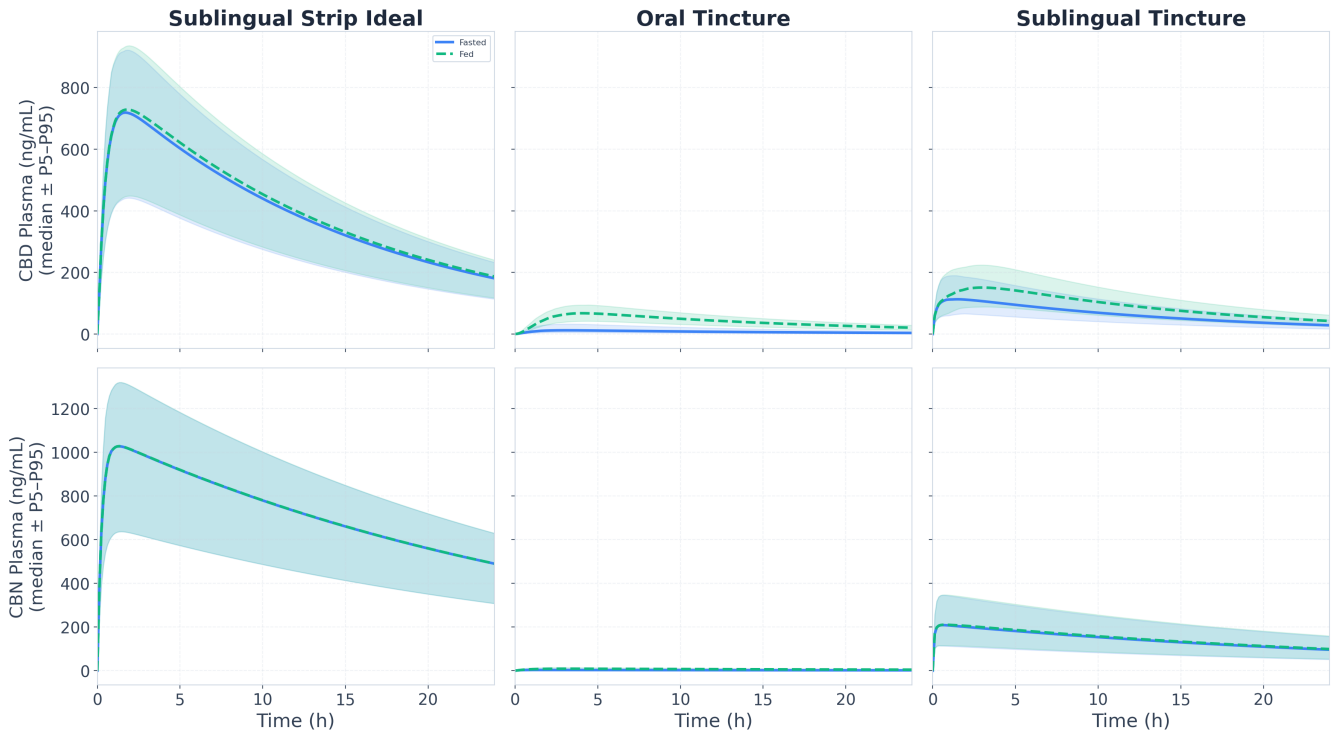
Formulation	CBD Absorbed %	CBD Swallowed %	CBN Absorbed %	CBN Swallowed %
Buccal Strip	**60.0%**	40.0%	**68.7%**	31.3%
Sublingual Strip	**45.0%**	55.0%	**51.4%**	48.6%
Buccal Strip — Ideal	**94.3%**	5.7%	**96.2%**	3.8%
Sublingual Strip — Ideal	**84.4%**	15.6%	**88.0%**	12.0%

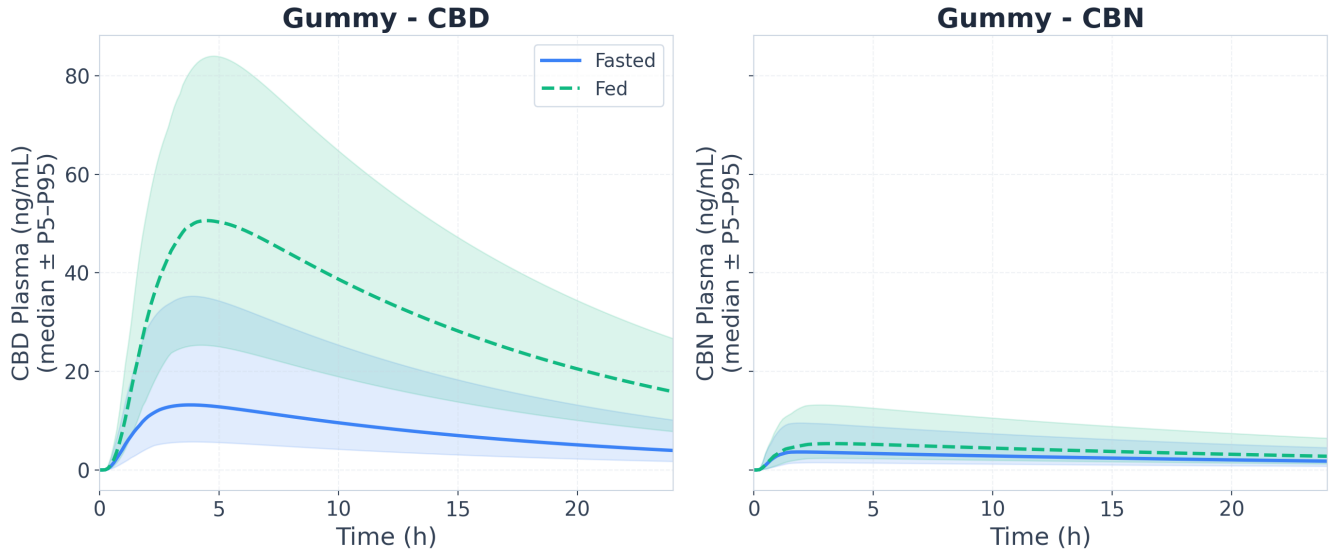
Absorbed = drug reaching systemic circulation via oral mucosa (bypasses first-pass). Swallowed = drug lost to GI tract before mucosal absorption.

Plasma Concentration–Time Profiles

Median plasma concentration–time profiles (P5–P95 shaded), fasted (solid) and fed (dashed), n=100.







Metabolic Fingerprint

CYP and UGT enzyme contributions to total intrinsic clearance, plus P-glycoprotein efflux substrate status. Values are compound properties derived from GNN predictions and integrated into the PBPK simulation. Substrate and inhibition magnitude is applied during simulation (not shown).

Substrate Profile — Enzymes & Transporters

Intrinsic clearance (CLint) fractions per compound. Bold teal = dominant clearance enzyme.

Compound	CYP1A2	CYP3A4	CYP2D6	CYP2C9	CYP2C19	UGT1A1	SULT1A1	P-gp Efflux
CBD	0.0%	28.3%	18.8%	11.5%	0.0%	**41.4%**	0.0%	Yes
CBN	0.0%	26.8%	17.2%	12.4%	0.0%	**43.6%**	0.0%	Yes

Metabolic Insights

• UGT1A1 glucuronidation is the dominant clearance pathway for both CBD (41.4%) and CBN (43.6%) — consistent with extensive Phase II conjugation of cannabinoids.

• CYP3A4 is the dominant CYP pathway for both (CBD: 28.3%, CBN: 26.8%). CYP2D6 is a consistent secondary pathway (CBD: 18.8%, CBN: 17.2%).

• SULT1A1 contribution is 0% for both compounds — sulfation is not a significant pathway for cannabinoids at these doses.

GNN predictions for enzyme inhibition. Inhibition magnitude is also predicted by our GNN suite and applied during simulation (not shown). CBD inhibits CYP3A4 and CYP2C9; CBN inhibits a broader panel including CYP1A2, CYP3A4, CYP2D6, CYP2C9, and CYP2C19. MCT Oil (excipient in tincture/gummy formulations) provides additional CYP3A4 inhibition at gut-wall concentrations.

Inhibition Profile — Enzymes & Transporters

Component	CYP1A2	CYP3A4	CYP2D6	CYP2C9	CYP2C19	UGT1A1	SULT1A1	P-gp
CBD	—	Yes	—	Yes	—	—	—	—
CBN	Yes	Yes	Yes	Yes	Yes	—	—	—
MCT Oil (C8 FFA) (excipient)	—	Yes	—	—	—	—	—	—

Both CBD and CBN inhibit CYP3A4 and CYP2C9 — clinically relevant for co-administration with statins, warfarin, immunosuppressants, and other CYP3A4/2C9 substrates. CBN additionally inhibits CYP1A2, CYP2D6, and CYP2C19 with high probability, giving it a broader DDI risk profile.

Clinical Literature Comparison

Our simulation results are contextualized against published clinical studies examining CBD bioavailability across different delivery routes and prandial states.

1. CURE Pharmaceutical OTF Study (2022)

Source: CURE Pharmaceutical OTF Study — worldpharmatoday.com/news/cure-pharmaceutical-cbd-oral-thin-film-

pharmacokinetic-study-shows-improved-bioavailability-compared-to-cbd-soft-gel/. CBD Oral Thin Film (OTF) pharmacokinetic study. CUREform™ delivery platform (solubilization + encapsulation). 25 mg CBD OTF vs 25 mg CBD soft gel in 14 healthy adults.

Relevance

Our buccal/sublingual strip delivery is mechanistically similar to OTF (oral transmucosal). Both show improved bioavailability vs swallowed formulations. The CURE study confirms that transmucosal delivery of CBD achieves significantly higher Cmax and faster Tmax than soft gel — consistent with our simulation showing 21.5% F for buccal strip vs 1.1% for oral tincture.

2. Della Rocca et al. (2022) — Oral vs OTM in Dogs

Source: Della Rocca et al. (2022) — https://doi.org/10.3389/fvets.2022.1104152. CBD 1 mg/kg oral vs oral transmucosal (OTM) in 12 dogs. Result: Cmax ~207 ng/mL (oral) vs ~200 ng/mL (OTM), Tmax ~2.2h vs ~1.9h — no significant difference.

Relevance to Our Simulation

• The dog study found no OTM benefit — consistent with our simulation showing that when swallowing is not controlled, sublingual bioavailability approaches oral levels.

3. Saals et al. (2025) — High-Fat Meal Effect

Source: Saals et al. (2025) — https://doi.org/10.1038/s41598-025-87621-4. Single oral dose CBD-rich extract (70 mg CBD equivalent). High-fat meal vs fasting in 11 healthy participants. Fed/Fasted Cmax ratio: 17.4× (90% CI 12.4–24.2). Fed/Fasted AUC ratio: 9.7× (90% CI 7.7–12.3).

Comparison to Our Simulation

• Our PBPK simulation shows a 4.8× fed/fasted ratio for CBD oral tincture and 3.4× for gummy — similar magnitude to the 9.7× AUC increase observed clinically (capsule format).

• The clinical study used a high-fat meal (55-65g fat) while our simulation uses 30g fat. Despite this difference, both show substantial fed-state enhancement, demonstrating the powerful effect of fat on cannabinoid bioavailability.

• The fed-state enhancement is driven by lymphatic transport and increased bile salt solubilization — mechanisms captured in our PBPK model.