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Article

Pharmacokinetics and pharmacodynamics of five distinct commercially available hemp-derived topical cannabidiol products

C. Austin Zamarripa[1], Hayleigh E. Tilton[1], Spencer Lin[1], Edward J. Cone[1], Ruth E. Winecker[2], Ronald R. Flegel[3], David Kuntz[4], Melissa Beals[4], Martin Jacques[4], Michael Clark[4], Eric R. Welsh[5], Lynn Wagner[5], Marcel O. Bonn-Miller[6], Ryan Vandrey[1], Tory R. Spindle[1,*]

[1]Behavioral Pharmacology Research Unit, Johns Hopkins University School of Medicine, 5510 Nathan Shock Dr., Baltimore, MD 21224, USA
[2]RTI International, Research Triangle Park, 3040 East Cornwallis Rd., Durham, NC 27709, USA
[3]Substance Abuse and Mental Health Services Administration (SAMHSA), Division of Workplace Programs (DWP), 5600 Fishers Lane, Rockville, MD 20857, USA
[4]Clinical Reference Laboratory, 8433 Quivira Rd, Lenexa, KS 66214, USA
[5]Department of Defense (DoD), Office of Drug Demand Reduction Program (ODDR), 4100 Defense Pentagon, Room 5D636, Washington, DC 20301, USA
[6]Charlotte's Web, 700 Tech Ct, Louisville, CO 80027, USA

*Corresponding author: Behavioral Pharmacology Research Unit, Department of Psychiatry & Behavioral Sciences, Johns Hopkins University School of Medicine, 5510 Nathan Shock Dr., Baltimore, MD 21224, USA. Email: tspindle@jhmi.edu

Abstract

Products containing cannabidiol (CBD) have proliferated after the 2018 Farm Bill legalized hemp (cannabis with ≤0.3% delta-9-tetrahydrocannabinol (Δ^9-THC)). CBD-containing topical products have surged in popularity, but controlled clinical studies on them are limited. This study characterized the effects of five commercially available hemp-derived high CBD/low Δ^9-THC topical products. Healthy adults (*N* = 46) received one of six study drugs: a CBD-containing cream (*N* = 8), lotion (*N* = 8), patch (*N* = 7), balm (*N* = 8), gel (*N* = 6) or placebo (*N* = 9; matched to an active formulation). The protocol included three phases conducted over 17 days: (i) an acute drug application laboratory session, (ii) a 9-day outpatient phase with twice daily product application (visits occurred on Days 2, 3, 7 and 10) (iii) a 1-week washout phase. In each phase, whole blood, oral fluid and urine specimens were collected and analyzed via liquid chromatography with tandem mass spectrometry (LC–MS-MS) for CBD, Δ^9-THC and primary metabolites of each and pharmacodynamic outcomes (subjective, cognitive/psychomotor and physiological effects) were assessed. Transdermal absorption of CBD was observed for three active products. On average, CBD/metabolite concentrations peaked after 7–10 days of product use and were highest for the lotion, which contained the most CBD and a permeation enhancer (vitamin E). Δ^9-THC/metabolites were below the limit of detection in blood for all products, and no urine samples tested "positive" for cannabis using current US federal workplace drug testing criteria (immunoassay cut-off of 50 ng/mL and confirmatory LC–MS-MS cut-off of 15 ng/mL). Unexpectedly, nine participants (seven lotions, one patch and one gel) exhibited Δ^9-THC oral fluid concentrations ≥2 ng/mL (current US federal workplace threshold for a "positive" test). Products did not produce discernable pharmacodynamic effects and were well-tolerated. This study provides important initial data on the acute/chronic effects of hemp-derived topical CBD products, but more research is needed given the diversity of products in this market.

Introduction

In 2018, the US Federal Agricultural Improvement Act (or the "Farm Bill") removed hemp (defined as cannabis with no greater than 0.3% delta-9-tetrahydrocannabinol, Δ^9-THC, the primary psychoactive constituent of cannabis) from the list of controlled substances. This legislation created a pathway for hemp-derived cannabinoid products to be legally sold across the USA. As a result, hemp-derived products containing cannabidiol (CBD) as the primary phytochemical constituent have become widely available in both retail stores and on the internet throughout the USA, largely due to the growing interest in the use of CBD for its purported medicinal benefits (1).

As the hemp market has expanded and cultural views on cannabinoids have become more favorable (2), novel product classes and routes of administration have emerged. The cannabinoid product classes that have seen arguably the largest growth since the passing of the Farm Bill are those meant for topical or transdermal administration (e.g., lotions, creams, patches, etc.). In fact, among hemp-derived CBD products, topicals are currently the second most popular product class in the USA (following tinctures), with a 2021 market value of over 826 million (3). Furthermore, a recent national survey estimated that 64 million Americans had tried CBD products, and 21% of those surveyed reported having used a topical CBD product (4). As with other hemp-derived products, consumers of topical CBD products report primarily using them for therapeutic purposes, most often with the intent to manage pain (e.g., joint stiffness, tendonitis or muscle soreness) or dermatological conditions (e.g., acne,

dermatitis or eczema), but these products are also sometimes used for cosmetic purposes (e.g., anti-aging) (2, 5, 6).

Relative to other routes of administration (e.g., oral ingestion and inhalation), topical application of cannabinoids has historically shown poor bioavailability. In one preclinical study with canines, for example, systemic bioavailability of topically applied CBD was approximately 90% lower compared to two oral CBD formulations of the same dose (7). That being said, the bioavailability of topically applied cannabinoids can be improved via certain skin permeation enhancers (8–11). *In vitro* studies utilizing models of human skin have shown that the permeability of several cannabinoids (e.g., CBD, cannabinol (CBN) and Δ^9-THC) is enhanced in the presence of chemicals such as ethanol, oleic acid and dimethyl sulfoxide (DMSO). In addition, preclinical studies have also found that transdermal delivery of cannabinoids can be increased by permeation enhancers. For example, in a study with guinea pigs, Transcutol HP increased CBD concentrations in plasma by 3.7-fold when added to a topical CBD gel (12). Similarly, one clinical study demonstrated that acute topical application of a product that contained a 1:1 ratio of Δ^9-THC and CBD in combination with various chemical agents to enhance skin permeation (i.e., penetrating agents, membrane disruptors and vasodilators) resulted in transdermal delivery of both Δ^9-THC and CBD, although blood concentrations were about 1.5 times higher for CBD than Δ^9-THC. In addition to chemical permeation enhancers, physical permeation enhancers (e.g., microneedles and ultrasound) have also been proposed as possible mechanisms to increase transdermal cannabinoid absorption, although research in this area is limited (8–11).

Notably, many hemp-derived topical CBD products contain low levels of Δ^9-THC, including those that do not mention Δ^9-THC on their label or which are purported to be "Δ^9-THC-free" (13); this raises important questions regarding whether these products can produce psychoactive effects and/or positive results on drug tests designed to detect illicit cannabis use. Drug testing is still prevalent across many sectors, including safety-sensitive occupations, military and law enforcement positions and treatment or criminal justice settings. Cannabis drug tests typically probe for Δ^9-THC or metabolites of Δ^9-THC (e.g., 11-OH-Δ^9-THC and Δ^9-THC-COOH) in various biological matrixes like blood, oral fluid or urine. While CBD is not intoxicating (14, 15) and has not been demonstrated to result in a positive drug test on its own (16), several studies have shown that oral and inhaled CBD products containing low concentrations of Δ^9-THC can cause positive drug test outcomes for some individuals (16–18). Only one study ($N = 3$) has assessed whether topical high CBD/low Δ^9-THC product use could impact drug testing outcomes for cannabis (19). In that study, participants applied two topical CBD salves "extensively" to different areas of the body, including the neck, arms/legs and torso, every 2–4 h for 3 days; these salves contained 1.7 and 102 ng/mg of Δ^9-THC (the authors estimated that approximately 0.1 mg of THC was topically applied per application). Δ^9-THC and Δ^9-THC metabolites were not detected in blood or urine for any of the three study participants. However, this study was limited by the very small sample size, examination of only Δ^9-THC (and not CBD or CBD metabolites), short product application window of 3 days without monitoring to ensure compliance with dosing procedures and lack of oral fluid testing (an increasingly popular drug testing matrix) (19). Moreover, it is unclear if the products used in the study by Hess et al. (19) contained skin permeation enhancers, which are common in commercially available topical CBD products. Thus, many unanswered questions remain regarding the influence of topical CBD products on cannabis drug testing, especially considering the vast array of product formulations available in today's market that vary widely with respect to Δ^9-THC concentrations and the presence of permeation enhancers.

The aim of the present study was to evaluate the pharmacokinetics of five different commercially available topical CBD products (cream, lotion, balm, gel and patch) and to compare the pharmacodynamic effects of these products to analogous placebo products containing no cannabinoids. The CBD products all contained $\leq$0.3% THC and were therefore federally legal in the US products that were chosen to capture a range of formulations (e.g., different permeation enhancers), methods of application (e.g., continuously worn patch vs repeatedly applied lotions/creams, etc.), Δ^9-THC concentrations and source of retail availability (e.g., available online only vs in national retail stores). Pharmacokinetic (i.e., blood, urine and oral fluid) and pharmacodynamic (i.e., subjective, cognitive and physiological effects) outcomes were assessed throughout 10 days of product use and after a 7-day washout period; LC–MS-MS was used to quantify concentrations of CBD and Δ^9-THC, along with the primary metabolites of each (7-OH-CBD, 7-COOH-CBD, 11-OH-Δ^9-THC and Δ^9-THC-COOH), in each biological matrix, and qualitative (screening) drug tests were also performed on all urine specimens.

Methods

All study procedures were completed in the Cannabis Science Laboratory at the Johns Hopkins University Behavioral Pharmacology Research Unit (BPRU) in Baltimore, MD. Experimental procedures were approved by the Institutional Review Board of the Johns Hopkins University School of Medicine and were conducted in accordance with the Declaration of Helsinki. The study was registered on ClinicalTrials.gov (NCT04741477).

Participants

Participants were recruited for the study via media advertising (e.g., flyers and internet) and word-of-mouth communication. Advertisements were targeted toward healthy adults with a history of cannabis and/or CBD product use. Interested participants received an initial screening over the telephone or online to collect basic health and drug use information, and those who appeared eligible completed a detailed screening assessment in person that included a physical examination, assessment of mental health/substance use status, qualitative urine drug testing and determination of concomitant medications. Prior to the in-person assessment, written informed consent to participate in the study was obtained.

Inclusion criteria included the following: (i) 18–55 years old; (ii) in good general health based on a physical examination, medical history, vital signs and routine blood testing; (iii) negative urine test for drugs of abuse (including cannabis)

and negative breath test for alcohol at screening; (iv) negative serum pregnancy test at screening and negative urine pregnancy test at each subsequent study visit, if female; (v) a body mass index (BMI) between 19 and 36 kg/m^2; (vi) prior experience in using cannabis or CBD products (but no use in the past 30 days); (vii) have not donated blood in the prior 30 days; (viii) have a smartphone, tablet, computer, etc. capable of recording videos and operating Research Electronic Data Capture (REDCap); (ix) willing to use an effective form of contraception during the study and for at least 30 days after the last product application; and (x) no known allergies to any ingredients in the selected study products.

Exclusion criteria included the following: (i) self-reported non-medical use of psychoactive drugs other than nicotine, alcohol or caffeine in the month prior to the screening visit; (ii) history of or current evidence of significant medical condition (e.g., cardiac arrhythmias or vasospastic disease, epilepsy or a history of seizures skin diseases that would be exacerbated by use of the study drugs) or psychiatric illness; (iii) use of an over-the-counter, systemic or topical drug(s), herbal supplement(s), vitamin(s) or prescription medications (with the exception of birth control prescriptions) within 14 days of study entry that, in the opinion of the investigator or medical monitor, would interfere with the study results or the safety of the participant; (iv) use of hemp seeds or hemp oil in any form in the past 3 months; (v) use of dronabinol (Marinol) within the past 6 months; (vi) history of xerostomia (dry mouth) or the presence of mucositis, gum infection or bleeding or other significant oral cavity disease or disorder that would potentially affect the collection of oral fluid samples, (vii) enrolled in another clinical trial or having received any drug as part of a research study within 30 days prior to dosing; and (viii) individuals with anemia.

Study design and procedures

The study utilized a between-subjects, double-blind design. The study was conducted in five stages, which corresponded to the five topical product categories of interest: lotion, cream, patch, balm and gel. Within each stage, participants were assigned to receive an active or placebo topical product (see later) at an approximately 4:1 ratio; a greater emphasis was placed on enrolling participants in active study conditions because pharmacokinetic data were considered primary outcomes, while pharmacodynamic measures were secondary outcomes. We aimed to complete approximately 10 total participants (active and placebo combined) in each of the five product stages. In total, 46 participants completed the study [(37 were randomized to active products (6–8 participants per stage), and nine were randomized to placebo products (1–2 per stage)].

All participants completed the protocol in three phases, lasting a total of 17 days. In Phase 1 (Day 1), participants completed an acute product application session in the laboratory that lasted approximately 8 h. During this session, participants applied their assigned study product by rubbing one-fourth tsp of lotion, cream, balm or gel into a 5-inch × 5-inch marked area on both upper arms (half tsp total); participants were instructed to rub in the product for exactly 1 min per arm. A half tsp measuring spoon was used to ensure dosing precision. Participants assigned to a patch condition simply applied the patch to one of their upper arms, where it remained for the entire day. Participants also provided biospecimens (i.e., blood, oral fluid and urine) and completed pharmacodynamic assessments (i.e., subjective questionnaires and cognitive/psychomotor performance tasks) at designated 30- to 60-min intervals. For sessions involving a lotion, cream, balm or gel, participants applied the study product again in the same manner at the end of the 8-h experimental session; this was done to give participants additional practice applying the study drug and training on uploading their dosing compliance videos (see later) while still under staff supervision.

Phase 2 (Days 2–10) was an outpatient dosing period, during which participants continued to use their assigned product in the same manner twice daily (morning and evening) in their home environment; patches were worn continuously for 96 h as per the instructions of the active patch manufacturer (after 96 h, participants would remove the patch and place a new one on the same arm). During Phase 2, participants filmed themselves applying their study drug on their personal smartphones and uploaded these videos to a secure database (REDCap), so that the study team could confirm adherence with dosing procedures. There was 99.8% compliance across all participants for study product application adherence, as confirmed by video upload (872 doses and uploaded videos in total). One participant unexpectedly had to leave town and completed the final day of Phase 2 on Day 9 instead of Day 10, but all other participants completed the protocol as designed. During this outpatient phase, participants also completed a questionnaire each day that inquired about adverse events as well as activities that may impact transdermal drug absorption (e.g., showers and use of saunas). The daily activity data were collected primarily to assist with reconciling aberrant pharmacokinetic findings. During Phase 2, participants returned to the laboratory for brief visits on study Days 2, 3, 7 and 10 to complete the same pharmacodynamic assessments and to provide additional biospecimens.

Phase 3 consisted of a final follow-up visit after a 1-week washout from study product use (i.e., Day 17). Participants also completed a final round of pharmacodynamic assessments and provided a final set of biospecimens at this visit. Participants were also given the option to provide a hair sample on Day 1 and Day 17. A total of 18 participants agreed to give hair specimens, although the results from these analyses are pending and are not included in this manuscript.

Study drug and materials

To inform product selection for this study, 105 hemp-derived topical CBD products were purchased from national retail locations ($N = 45$) and online ($N = 60$) and tested for cannabinoids [(as described elsewhere (13)]. For the present study, we selected five products that we believed would have the highest likelihood of impacting cannabis drug testing in the real world and that would capture a range of formulations currently available on the retail market. The first consideration was the presence of Δ^9-THC (i.e., each product selected was confirmed to contain Δ^9-THC). The second consideration was whether the product was purported to contain skin permeation enhancers. The third consideration was diversity with respect to the formulation of the product (e.g., lotion, cream, patch, etc.). The final consideration was the accessibility of the product (e.g., online only versus available in national retailers). Ultimately, five products were selected including a lotion,

a cream, a patch, a balm and a gel. A full list of ingredients in the five products can be found in Supplementary Table 1.

The lotion was chosen because it had the highest CBD and Δ^9-THC concentrations of all topical products tested (CBD concentration = 4.03%; THC concentration = 0.19%) and because it was purported to contain a permeation enhancer [(vitamin E (20);]. The cream (CBD concentration of 0.48% and Δ^9-THC concentration of 0.03%) was chosen because it included known skin permeation enhancers DMSO and various terpenes purported to facilitate absorption on the list of ingredients (21). The patch contained 73 mg of CBD and 0.4 mg of Δ^9-THC (CBD concentration of 9.52% and Δ^9-THC concentration of 0.05%) and was chosen due to the distinct nature of use from the other products (i.e., continuously worn as opposed to intermittently applied) and because it included known permeation enhancers (oleic acid and various terpenes, including limonene) in the list of ingredients (21). The gel (CBD concentration of 1.3% and Δ^9-THC concentration of 0.03%) was chosen because it listed skin permeation enhancers, menthol and ethanol, on the list of ingredients. Lastly, the balm (CBD concentration of 0.67% and Δ^9-THC concentration of 0.04%) was chosen for its popularity in the hemp market; specifically, this product was available at several national retail stores at the time of the study and was made by one of the leading brands in the industry. This product also contained the permeation enhancer vitamin E. The concentrations of CBD and Δ^9-THC were verified in all products; however, the other listed ingredients were not verified.

Given the measured CBD/Δ^9-THC concentrations in our independent testing of each product and an application of half tsp, or 2.35 g, per product application, participants were exposed to the following CBD and Δ^9-THC doses per application: lotion (CBD dose = 94.7 mg; Δ^9-THC dose = 4.2 mg), cream (CBD dose = 11.3 mg; Δ^9-THC dose = 0.7 mg), gel (CBD dose = 30.6 mg; Δ^9-THC dose = 0.7 mg), balm (CBD dose = 15.7 mg; Δ^9-THC dose = 0.9 mg) and patch (73 mg CBD and 0.4 mg Δ^9-THC; given the 96-h application period, participants used three patches over the course of the 10 days).

Five non-hemp comparator "placebo" products that were similar in formulation/consistency to each respective hemp product but did not contain any cannabinoids (i.e., a commercially available lotion, cream, balm and gel as well as an inert adhesive patch) were selected. All placebo products were available at major national retailers at the time of the study. To preserve the study blind, active and placebo lotions, creams, balms and gels were placed in nondescript containers and active/placebo patches were comparable in size, shape and appearance. The BPRU pharmacy prepared and dispensed all study products.

Outcome measures

During Phase 1 (laboratory session at the BPRU on study Day 1), pharmacodynamic assessments and blood/oral fluid collection occurred at baseline (prior to product application) and again at 0.5, 1, 1.5, 2, 3, 4, 5 and 6 h after product application; urine samples were collected at baseline and 1, 2 and 3 h after product application, and a pooled urine sample (multiple samples collected and combined) was collected across the 4- to 6-h post-application timeframe. During Phases 2 and 3 (outpatient product application period and washout period, respectively), pharmacodynamic assessments were completed and biospecimens were collected at brief laboratory visits on study Days 2, 3, 7, 10 and 17. All urine specimens were spot collections during Phases 2 and 3.

Pharmacokinetics

Blood

Whole blood samples were collected via intravenous catheters into "gray-top" Vacutainer® tubes at each timepoint, mixed by inversion, and then transferred to two 5-mL cryotubes, which were stored at −80°C until they were sent on dry ice for testing at Clinical Reference Laboratory (CRL, Lenexa, KS). Bloods were analyzed using liquid chromatography with tandem mass spectrometry (LC–MS-MS; see later).

Oral fluid

Collection of native oral fluid specimens were performed by expectoration for a period of up to 5 min per sample into labeled, 8-mL glass screw culture tubes (Thermo Fisher Scientific, Waltham, MA, 16 × 100 mm, #14-959-35AA), which contained a PTFE liner (Thermo Fisher Scientific, #4506615). Prior to collection, the inner surface of the collection tubes was silanized with Sylon-CTTM (Sigma-Aldrich, St. Louis, MO, USA, #33065U), rinsed with ethanol and dried. Participants were not allowed to consume food or drinks for at least 10 min prior to each collection. After the collections were completed, the tubes were immediately capped, sealed with parafilm and stored in a refrigerator until shipped overnight to the CRL in insulated, refrigerated shipping containers on cold packs in order to prevent freezing. Samples were stored refrigerated for a maximum of 3 weeks before being shipped for analysis and were analyzed within 1 month of collection. Oral fluid samples were analyzed using LC–MS-MS (see later).

Urine

Upon collection, urine samples were split into two labeled 30-mL polypropylene bottles, covered with parafilm and frozen at −20°C until they were sent overnight on dry ice to the CRL. Urine specimens were analyzed using the Diagnostic Reagents Inc Cannabinoid Assay via the manufacturer's procedure (Thermo Fisher Scientific, Fremont, CA) utilizing cut-off concentrations of 20, 50 and 100 ng/mL. Immunoassay methods and cross-reactivity data have been previously described elsewhere (22). Creatinine was determined with the Siemens-modified Jaffe reagent. Data below are presented and analyzed based on the non-creatinine normalized values. In addition to the qualitative immunoassay analyses, urine samples were also analyzed using LC–MS-MS (see later).

LC–MS-MS analyses

All biospecimens were analyzed using LC–MS-MS analysis. Analytes included in analyses of all matrixes are as follows: Δ^9-THC, 11-OH-Δ^9-THC, Δ^9-THC-COOH, CBD, 7-OH-CBD, 7-COOH-CBD, cannabidiolic acid (CBDA), Δ^8-THC-COOH, cannabigerol (CBG), CBN, cannabicyclol (CBL), cannabichromene (CBC) and Δ^8-THC. Additional analytes in both urine and oral fluid analyses included Δ^9-tetrahydrocannabivarin (Δ^9-THCV) and Δ^9-COOH-tetrahydrocannabivarin (Δ^9-COOH-THCV). Analytes specific to oral fluid analysis included cannabigerolic acid (CBGA), cannabinolic acid (CBNA), cannabicyclolic acid (CBLA), cannabichromenic acid (CBCA), 8-β-OH-Δ^9-THC

and Δ^8-tetrahydrocannabivarin (Δ^8-THCV). A liquid–liquid phase extraction technique was used for these analyses followed by mass spectral detection using electrospray ionization in both positive and negative multiple reaction monitoring (MRM) modes. A conversion control was extracted in each batch to monitor the potential conversion of CBD and its metabolites to Δ^9-THC and Δ^8-THC and corresponding metabolites; the conversion control contained CBD, 7-OH-CBD, 7-COOH-CBD and CBDA at 5.0 ng/mL. No conversion from CBD/CBD metabolites to Δ^9-THC or Δ^8-THC was identified in the assays.

The limit of quantitation (LOQ) varied for individual analytes and between matrixes. See LOQ information below, all values listed in ng/mL: blood: Δ^9-THC, CBG, CBL, CBC = 0.50; all other analytes = 0.20. Oral fluid: 8-β-OH-Δ^9-THC = 0.050; all other analytes = 0.025. Urine: Δ^9-THCV = 1.0; CBL, CBC = 2.0; all other analytes = 0.50. The following analytes were not detected or were detected inconsistently and at trace concentrations when present across all participants and are, therefore, not reported in this manuscript: CBDA, Δ^8-THC, Δ^8-THC-COOH, CBG, CBGA, CBN, CBNA, CBL, CBLA, CBC, CBCA and 8-β-OH-Δ^9-THC.

Hydrolysis and extraction procedures

For blood, samples were prepared by mixing a 0.400 mL aliquot of whole blood sample with internal standard solution and cold 0.1% formic acid in acetonitrile, adding 0.1% formic acid in deionized (DI) H_2O and loading the solution onto an Agilent Captiva EMR-Lipid 3 mL cartridge in a silanized glass culture tube. Following sample elution, the cartridge was rinsed with 80:20 acetonitrile:DI H_2O and eluted into the same tube. A liquid–liquid extraction was then performed using the combined eluent and 2:1 hexanes:ethyl acetate; the organic components were subsequently dried and reconstituted with 0.1% formic acid in 50:50 DI H_2O:methanol. Separation was performed using a Shimadzu Nexera LC40D X3 HPLC system utilizing a Waters™ CORTECS C18+ column and aqueous mobile phase (A), 0.1% acetic acid in water and organic mobile phase (B), 0.1% acetic acid in acetonitrile at a flow rate of 0.5 mL/min over a 15-min gradient. MS-MS analysis was conducted with a Sciex API7500 tandem mass spectrometer using electrospray ionization in both positive and negative MRM modes.

For oral fluid, a liquid–liquid extraction was performed using a 0.500-mL sample aliquot mixed with 0.1 molar (M) ammonium bicarbonate (pH 10.5), *tert*-butyl methyl ether and isopropanol, followed by drying and reconstitution with 50:50 0.1% acetic acid in DI H_2O: acetonitrile. A Shimadzu Nexera LC30AD HPLC system equipped with a Phenomenex Kinetex C18 column was used for separation; aqueous mobile phase (A), 0.1% acetic acid in water, and organic mobile phase (B), 50:50 acetonitrile: methanol, combined in a gradient over the 16.00-min run at a 0.750 mL/min flow rate. MS-MS analysis was performed by a Sciex API7500 tandem mass spectrometer using electrospray ionization in both positive and negative MRM modes.

For urine, sample preparation involved dual hydrolysis of a 0.500-mL aliquot of urine specimen using BG Turbo β-glucuronidase/0.1 M phosphate buffer (pH 6.8) solution, followed by the addition of 5N potassium hydroxide. Samples were neutralized with 5 N formic acid, and the mixture was eluted through an Agilent Captiva EMR-Lipid 3 mL cartridge in a silanized glass tube. The cartridge was then rinsed with 80:20 acetonitrile: DI H_2O and eluted into the same tube. A liquid–liquid extraction was performed using the eluent, pH 4.8 0.4 M ammonium acetate buffer and 2:1 hexanes:ethyl acetate. The organic components were decanted, dried and then reconstituted with 0.1% formic acid in 50:50 DI H_2O: methanol. Analysis was performed using a Shimadzu Nexera LC40D X3 UHPLC equipped with a Waters™ CORTECS C18+ column coupled to a Sciex API6500 tandem mass spectrometer. The aqueous mobile phase (A), 0.1% acetic acid in water, and organic mobile phase (B), 0.1% acetic acid in acetonitrile, flowed at a rate of 0.5 mL/min over the 15-min gradient. MS-MS analysis was conducted using electrospray ionization in both positive and negative MRM modes.

Pharmacodynamics

Subjective drug effects

A 21-item Drug Effect Questionnaire (DEQ) was used to evaluate subjective drug effects (23, 24). Individual items included drug effect, good effect, bad effect, and drug liking, among other behavioral/mood states often associated with cannabis intoxication (e.g., relaxed, paranoid and hungry/have munchies). Participants rated each item individually using a 100-mm visual analog scale (VAS) anchored with "not at all" on one end and "extremely" on the other.

Cognitive performance tasks

A battery of four computerized performance tasks were conducted on aspects of cognitive/psychomotor functioning known to be sensitive to the acute effects of cannabis/Δ^9-THC (23, 25, 26). These tasks included the Divided Attention Task (DAT), the Digit Symbol Substitution Task (DSST), the Paced Auditory Serial Addition Task (PASAT) and driving under the influence of drugs (DRUID) iOS application. All tasks were administered via a computer except for the DRUID application, which was administered using an iPad.

On the DAT (27), participants tracked a central stimulus across the screen using their mouse cursor, while also simultaneously monitoring a number at the center of the screen and peripheral numbers in the corners of the screen, all of which were constantly changing. Participants were instructed to click the mouse once when they saw a match between the central number and any of the four peripheral numbers. The primary outcome of this task was the distance between the mouse cursor and central stimulus (in computer pixels).

The DSST (28) is a measure of psychomotor ability, in which participants are instructed to replicate patterns presented to them on a computer screen for 90 s by using the computer keyboard. Primary outcome for this task includes the number of correct responses.

The PASAT (29) measures working memory by presenting participants with a string of single-digit numbers on the computer screen at 2.4- to 2.8-s intervals. Participants were instructed to add the prior two integers presented and click the correct number response. The primary outcome was the number correct out of 90 trials.

The DRUID application requires users to perform four 30- to 45-s tasks, each of which measures different aspects of performance (e.g., reaction time, decision-making, hand–eye coordination, time estimation, balance and divided attention

(25). Scores on all four tasks were integrated using a statistical algorithm to yield a global impairment score (the primary outcome measure for the DRUID).

Physiological measures

Vital signs [(heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP)] were measured in the seated position using an automated monitor.

Data presentation and analysis

Descriptive statistics were used to summarize participant demographics and LC–MS-MS biospecimen results. All pharmacokinetic data are presented as raw values. For pharmacokinetic analyses, the six analytes of interest were Δ^9-THC, 11-OH-Δ^9-THC, Δ^9-THC-COOH, CBD, 7-OH-CBD and 7-COOH-CBD (as noted earlier, other analytes were rarely detected, if at all, and are thus not included). Placebo products did not produce increases for any analyte measured in blood, oral fluid or urine. As such, concentrations of each of the six analytes of interest were only compared between the active topical product conditions. Maximum concentrations (C_{max}) of each analyte were determined by selecting the highest concentration following drug administration, and time to maximum concentrations (T_{max}) was determined when C_{max} occurred. Area under the curve (AUC) for each analyte was determined by using the trapezoidal rule (30). All outcomes were determined using excel. Nonparametric tests were employed for all analyte comparisons due to non-normal data distributions. Specifically, C_{max}, AUC values and T_{max} were compared using the Kruskal–Wallis test, followed by Dunn's multiple comparison test to compare each active condition (cream, lotion, patch, balm and gel).

For pharmacodynamic outcomes (subjective, cognitive/psychomotor and physiological effects), peak effects for each outcome during the acute (i.e., Day 1 laboratory session) and chronic phase (outpatient Days 2–10) were analyzed separately using one-way analysis of variance (ANOVA) with the lone between-subjects factor of drug condition; this factor had six levels: active lotion, active cream, active patch, active balm, active gel and all placebo conditions collapsed together. When a significant main effect of drug condition was detected, Bonferroni's multiple comparisons were used to compare the respective drug conditions. Within each drug condition, the peak change-from-baseline values for subjective drug effects (DEQ) and the peak raw scores for the cognitive (DAT, DSST, PASAT and DRUID) and physiological outcomes (HR) observed in Phase 1 were compared to the same values observed during Phase 2 using paired-samples *t*-tests. Statistical analyses for both pharmacokinetic and pharmacodynamic outcomes were conducted using Prism 9 for macOS (Version 9.3.0, GraphPad Software, LLC); the α level was set at 0.05 for all analyses.

Results

Participants

Participant demographics are shown in Table I. Participants were predominantly White ($N = 26$; 57% of total sample) or African American ($N = 11$; 24% of total sample) and mostly female ($N = 31$; 67% of total sample). Across the various study conditions, participants did not differ on their mean age, BMI, alcohol consumption, average number of cigarettes per day or time since the last use of a cannabis product (all P values > 0.05). Of note, seven participants (two each in the active cream, lotion and balm conditions and one in the active gel condition) had healed tattoos on at least one of their upper arms (site of drug application); we were insufficiently powered to formally examine whether the presence of tattoos influenced drug absorption, but overall, pharmacokinetic data were similar among tattooed and non-tattooed participants. There were no unanticipated or serious adverse events during the study. However, a few minor adverse events occurred in the active cream, lotion and patch conditions. For the active cream, two participants experienced somnolence during their acute dosing session on Day 1; one of these participants reported that this effect persisted through the 10-day application period but ceased once they stopped using the product. Another participant who used the active cream experienced skin irritation/itchiness throughout the 10 days of application, but these effects subsided after they stopped using the product. One participant reported dizziness following application of the active lotion during their acute dosing session on Day 1, but this effect was not present during outpatient dosing. Finally, one participant who used the active patch reported dizziness and soreness of the upper arm containing the patch during most of the outpatient dosing period (Days 2–9).

Pharmacokinetics

Whole blood

Figure 1 illustrates the mean concentrations of CBD, Δ^9-THC and their respective metabolites (7-OH-CBD; 7-COOH-CBD; 11-OH-Δ^9-THC; Δ^9-THC-COOH) in whole blood over time. None of these six analytes were detected in baseline whole blood specimens of any participant. During the acute dosing session (Phase 1), two participants had detectable levels of CBD in whole blood following active lotion application at a single timepoint (the 3-h timepoint for one participant and the 5-h timepoint for the other). Additionally, one of these participants had detectable levels of 7-COOH-CBD in whole blood from the 1-h timepoint until the end of the acute dosing phase. CBD, Δ^9-THC and their respective metabolites were not detected in blood following use of any other active product during Phase 1. No cannabinoids were detected in blood during Phase 1 for the cream, patch, balm or gel products.

During Phase 2 (10-day chronic dosing period), the lotion, cream and gel each produced an increase in CBD and 7-COOH-CBD concentrations that peaked after 7–10 days. Overall, whole blood concentrations of CBD and 7-COOH-CBD were highest for the lotion. Notably, whole blood concentrations of all detected analytes aside from 7-COOH-CBD dropped below the limit of detection by the end of the 7-day washout phase; for five out of eight participants in the active lotion condition, 7-COOH-CBD was still detected at the Day 17 washout visit, albeit at much lower levels than those observed on Day 10. In all other active conditions, 7-COOH-CBD was not detected after drug washout. There were no significant differences observed for pharmacokinetic outcomes (C_{max}, T_{max} and AUC values) between the active cream, lotion and gel conditions for CBD or 7-COOH-CBD (all P values > 0.05). During the chronic product application period, 7-OH-CBD, Δ^9-THC, 11-OH-Δ^9-THC and Δ^9-THC-COOH were not detected in blood for any of the active drug conditions (Table II). Additionally, the patch and balm

Table I. Participant Demographics

Characteristics		Topical condition					
		Placebo ($N = 9$)	Cream ($N = 8$)	Lotion ($N = 8$)	Patch ($N = 7$)	Balm ($N = 8$)	Gel ($N = 6$)
Age (in years)	Mean (SD)	30.0 (10.2)	30.9 (7.8)	27.5 (6.2)	30.4 (6.7)	26.5 (3.6)	32.0 (11.6)
Gender (*n*, %)	Male	1 (1.1)	0 (0)	4 (50.0)	3 (42.9)	4 (50.0)	3 (50.0)
Race (*n*, %)	Caucasian	7 (77.8)	5 (62.5)	2 (25.0)	3 (42.9)	4 (50.0)	5 (83.3)
	African American	2 (22.2)	3 (37.5)	3 (37.5)	1 (14.3)	1 (12.5)	1 (16.7)
	Asian	0 (0)	0 (0)	3 (37.5)	2 (28.6)	2 (25.0)	0 (0)
	More than one	0 (0)	0 (0)	0 (0)	1 (14.3)	1 (12.5)	0 (0)
	Hispanic	2 (22.2)	0 (0)	0 (0)	1 (14.3)	1 (12.5)	0 (0)
BMI	Mean (SD)	24.8 (4.7)	25.2 (2.3)	23.6 (3.1)	24.9 (4.0)	25.0 (2.7)	27.5 (2.2)
Average number of drinks per week	Mean (SD)	1.7 (1.8)	2.3 (3.2)	1.6 (1.7)	1.3 (1.5)	3.8 (4.4)	3.4 (2.1)
Average number of cigarettes per day	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Time in days since the last cannabis product use	Mean (SD)	393.7 (480.0)	341.9 (391.7)	125.4 (149.5)	237.9 (251.9)	100.3 (118.2)	339.3 (728.2)

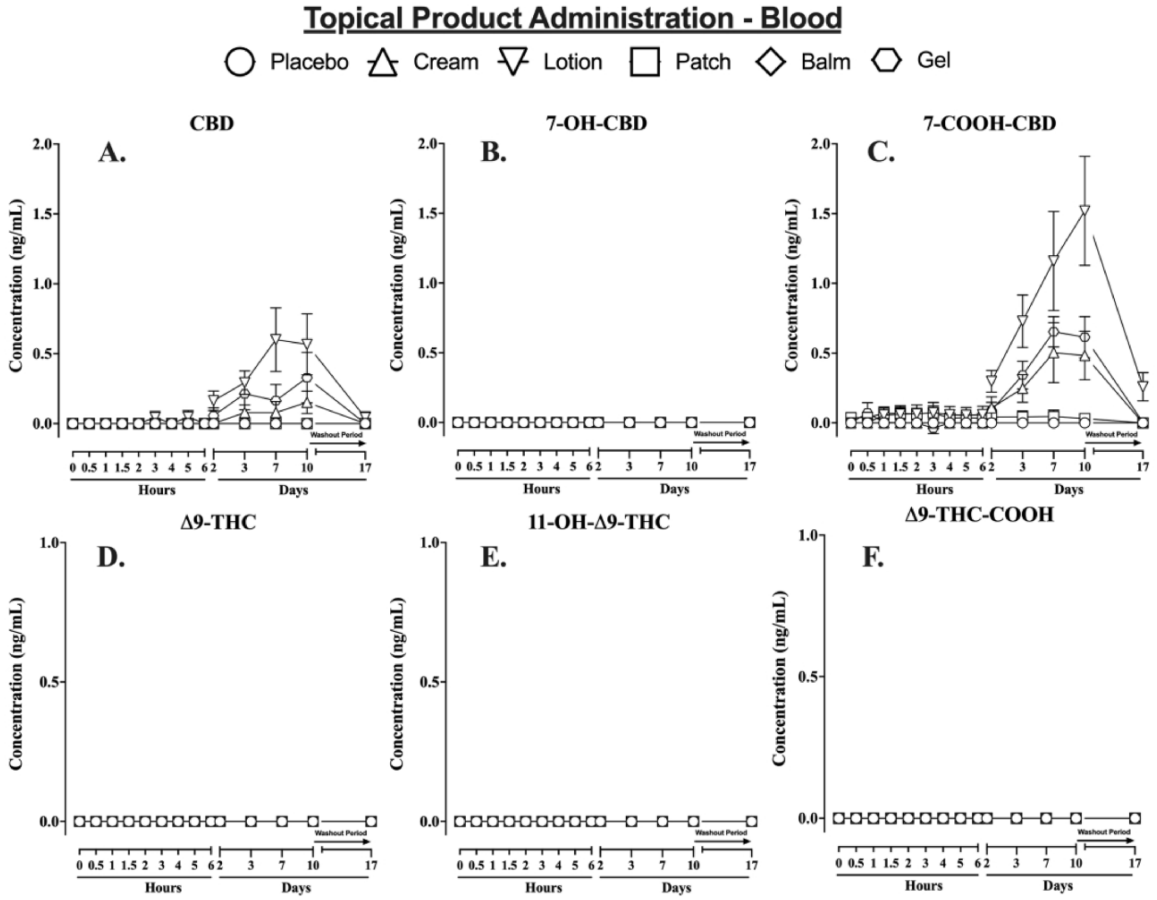

Figure 1. Mean whole blood concentrations (±SEM) for (a) CBD, (b) 7-OH-CBD, (c) 7-COOH-CBD, (d) Δ^9-THC, (e) 11-OH-Δ^9-THC and (f) Δ^9-THC-COOH before and after placebo (circle), cream (upward triangle), lotion (downward triangle), patch (square), balm (diamond) and gel (hexagon) product use. Drug administration occurred during the first 10 days followed by a 7-day washout period.

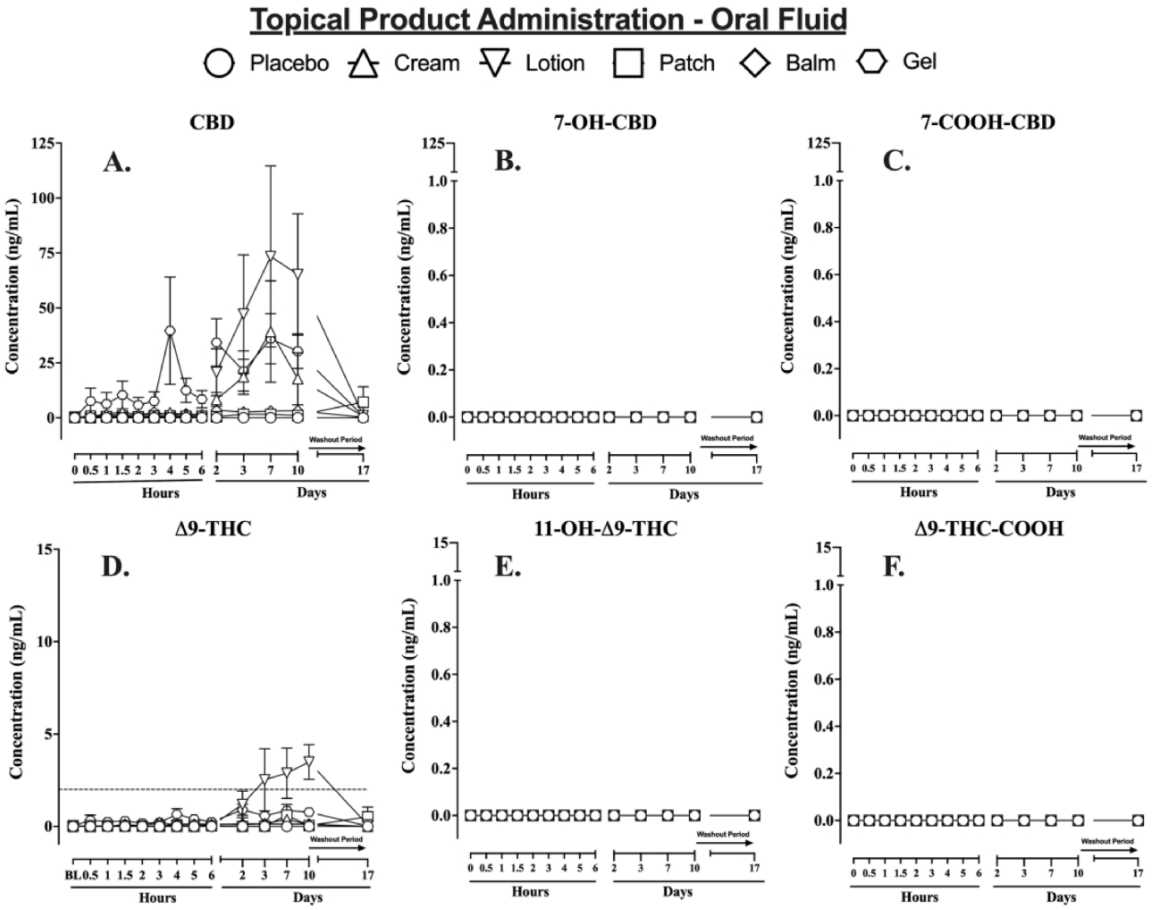

Figure 2. Mean oral fluid concentrations (±SEM) for (a) CBD, (b) 7-OH-CBD, (c) 7-COOH-CBD, (d) Δ^9-THC, (e) 11-OH-Δ^9-THC and (f) Δ^9-THC-COOH before and after placebo (circle), cream (upward triangle), lotion (downward triangle), patch (square), balm (diamond) and gel (hexagon) product use. Drug administration occurred during the first 10 days followed by a 7-day washout period. The dashed line represents the federal workplace drug testing criteria for oral fluid established by SAMSHA as a LC–MS-MS Δ^9-THC concentration ≥2 ng/mL (29).

products did not produce detectable whole blood concentrations for any of the six analytes of interest at any study timepoint.

Oral fluid

Figure 2 illustrates the mean concentrations of CBD, Δ^9-THC and their respective metabolites in oral fluid over time. Only CBD and Δ^9-THC were detected in oral fluid samples; 7-OH-CBD, 7-COOH-CBD, 11-OH-Δ^9-THC and Δ^9-THC-COOH were not detected in any participants. All active drug conditions produced detectable levels of CBD and Δ^9-THC. On average, peak oral fluid concentrations for Δ^9-THC and CBD were observed in phase 2 (between study Days 7–10) for all active products. Consistent with whole blood, oral fluid cannabinoid concentrations were generally highest for the lotion and lowest for the balm and patch. The lotion produced significantly greater C_{max} and AUC values for CBD and Δ^9-THC relative to the patch and balm (P values < 0.05); the lotion also produced higher C_{max} and AUC Δ^9-THC values compared to the cream (Table II). Additionally, the lotion produced significantly longer CBD and Δ^9-THC T_{max} values relative to the patch (P values < 0.05). For the gel, the CBD C_{max} and AUC values were significantly greater and the T_{max} value was significantly longer relative to the patch (P values < 0.05).

At baseline, prior to drug administration, five participants (two in the lotion group, one in the patch group, one in the balm group and one in the gel group) had detectable concentrations of Δ^9-THC in oral fluid, ranging from 0.04 to 0.25 ng/mL; thus, none of these baseline oral fluid samples exceeded the cut-off for a positive quantitative test for cannabis based on current federal workplace drug testing criteria established by the Substance Abuse and Mental Health Services Administration (SAMHSA) ([(LC–MS-MS concentration ≥2 ng/mL (31)]. Following initiation of product use, seven of the eight participants in the active lotion condition, one of seven participants in the active patch condition and one of six participants in the active gel condition tested positive for Δ^9-THC (LC–MS-MS concentration ≥2 ng/mL). There were no positive oral fluid Δ^9-THC samples for any of the other active conditions at any timepoint. One participant was excluded from presentation of oral fluid data (Figure 2a) and from analyte analyses because of suspected self-contamination of several samples. This individual displayed very high concentrations of CBD and Δ^9-THC at various timepoints throughout Day 1 (after baseline and well before peak values would be expected for transdermal drug delivery) and also at Day 10; these values were extreme outliers (i.e., >10 SD from the mean observed at these respective timepoints) and may be attributed to accidental oral cavity contamination (e.g., placing fingers in

Table II. Maximum Concentration (C_{max}), Time to Maximum Concentration (T_{max}), AUC and Ranges for Cannabis Analytes in Oral Fluid, Urine and Whole Blood following Topical Administration over the Entire 17-Day Period

Study Product	Blood			Oral fluid			Urine		
	C_{max} (ng/mL + range)	T_{max} (h + range)	AUC (range)	C_{max} (ng/mL + range)	T_{max} (h + range)	AUC (range)	C_{max} (ng/mL + range)	T_{max} (h + range)	AUC (range)
					CBD				
Cream	0.3 (0.0–0.6)	108.0 (0.0–240.0)	32.3 (0.0–85.2)	47.9 (2.1–191.5)	387.0 (240.0–408.0)	7,553.7 (545.1–34,835.2)	3.6 (0.0–7.2)	228.0 (0.0–408.0)	745.3 (0.0–1,536.0)
Lotion	0.7 (0.3–2.0)	237.0 (48.0–408.0)	149.9 (21.4–508.4)	294.3 (22.3–1,422.5)	408.0 (480.0–480.0)	32,711.8 (3,985.7–128,601.0)	9.8 (0.0–20.9)	315.0 (0.0–408.0)	2,472.0 (0.0–6,033.0)
Patches	ND	ND	ND	7.5 (0.1–49.4)[a]	240.9 (6.0–408.0)[a]	67.2 (1.0–4,562.2)[a]	0.3 (0.0–1.6)[a]	41.1 (0.0–240.0)[a]	48.4 (0.0–259.4)[a]
Balm	ND	ND	ND	6.0 (1.2–12.5)[a]	345.0 (240.0–408.0)	986.0 (47.9–2,275.1)[a]	1.6 (0.0–7.2)[a]	144.0 (0.0–240.0)[a]	383.0 (0.0–1,792.7)[a]
Gel	0.4 (0.0–1.1)	124.0 (0.0–240.0)	73.1 (0.0–192.0)	55.6 (0.0–154.2)[b]	408.0 (480.0–480.0)[b]	8,280.9 (0.0–19,293.1)[b]	4.8 (0.0–13.1)	200.0 (0.0–408.0)	780.5 (0.0–1,868.4)
					7-OH-CBD				
Cream	ND	ND	ND	ND	ND	ND	6.5 (1.5–15.4)	366.0 (240.0–408.0)	1,262.8 (536.7–2,333.1)
Lotion	ND	ND	ND	ND	ND	ND	25.7 (5.7–37.5)	408.0 (408.0–408.0)	6,834.6 (1,596.1–10,510.8)
Patches	ND	ND	ND	ND	ND	ND	1.5 (0.0–3.4)[a]	147.4 (0.0–408.0)[a]	333.7 (0.0–767.2)[a]
Balm	ND	ND	ND	ND	ND	ND	4.0 (0.0–12.6)[a]	171.0 (0.0–408.0)[a]	1,066.8 (0.0–3,169.8)[a]
Gel	ND	ND	ND	ND	ND	ND	12.1 (0.0–40.6)	216.0 (0.0–408.0)	3,558.7 (0.0–13,042.0)
					7-COOH-CBD				
Cream	0.6 (0.0–1.9)	180.0 (0.0–240.0)	129.2 (0.0–448.7)	ND	ND	ND	1.2 (0.0–4.1)	114.0 (0.0–240.0)	226.7 (0.0–1,098.8)
Lotion	1.5 (0.2–3.3)	324.0 (240.0–408.0)	384.5 (49.2–815.7)	ND	ND	ND	7.2 (0.8–15.8)	315.4 (3.0–408.0)	1,568.5 (42.5–3,663.9)
Patches	ND	ND	ND	ND	ND	ND	0.5 (0.0–1.7)[a]	79.7 (0.0–408.0)[a]	52.0 (0.0–238.3)[a]
Balm	ND	ND	ND	ND	ND	ND	0.8 (0.0–2.7)[a]	108.0 (0.0–240.0)[a]	169.6 (0.0–784.0)[a]
Gel	0.8 (0.3–1.0)	252.0 (144.0–408.0)	182.1 (45.3–272.7)	ND	ND	ND	2.1 (0.0–4.2)	200.0 (0.0–240.0)	507.2 (0.0–915.8)
					Δ^9-THC				
Cream	ND	ND	ND	0.5 (0.0–1.2)[a]	249.0 (144.0–408.0)	62.6 (3.7–197.7)[a]	ND	ND	ND

(continued)

Table II. (Continued)

Study Product	Blood			Oral fluid			Urine		
	C_{max} (ng/mL + range)	T_{max} (h + range)	AUC (range)	C_{max} (ng/mL + range)	T_{max} (h + range)	AUC (range)	C_{max} (ng/mL + range)	T_{max} (h + range)	AUC (range)
Lotion	ND	ND	ND	6.4 (1.3–12.5)	345.0 (240.0–408.0)	915.6 (206.4–1,566.8)	ND	ND	ND
Patches	ND	ND	ND	0.6 (0.0–4.2)[a]	58.3 (0.0–408.0)[a]	109.1 (0.0–764.5)[a]	ND	ND	ND
Balm	ND	ND	ND	0.3 (0.0–1.0)[a]	198.0 (0.0–240.0)	42.0 (0.0–100.4)[a]	ND	ND	ND
Gel	ND	ND	ND	1.1 (0.0–2.1)	268.0 (240.0–408.0)	209.7 (0.0–445.2)	ND	ND	ND
11-OH-Δ^9-THC									
Cream	ND	ND	ND	ND	ND	ND	ND	ND	ND
Lotion	ND	ND	ND	ND	ND	ND	0.4 (0.0–1.4)	60.0 (0.0–408.0)	25.8 (0.0–102.7)
Patches	ND	ND	ND	ND	ND	ND	ND	ND	ND
Balm	ND	ND	ND	ND	ND	ND	ND	ND	ND
Gel	ND	ND	ND	ND	ND	ND	ND	ND	ND
Δ^9-THCA									
Cream	ND	ND	ND	ND	ND	ND	ND	ND	ND
Lotion	ND	ND	ND	ND	ND	ND	1.7 (0.8–5.1)	237.0 (144.0–408.0)	288.8 (116.8–750.0)
Patches	ND	ND	ND	ND	ND	ND	0.2 (0.0–1.1)[a]	41.1 (0.0–144.0)[a]	43.6 (0.0–223.6)[a]
Balm	ND	ND	ND	ND	ND	ND	ND	ND	ND
Gel	ND	ND	ND	ND	ND	ND	0.1 (0.0–0.8)[a]	24.0 (0.0–144.0)[a]	18.1 (0.0–108.8)[a]

[a]A significant difference from the active lotion condition ($P < 0.05$);
[b]A significant difference from the active patch condition ($P < 0.05$)
Abbreviations: ND, not detected.

mouth following product application) prior to providing these samples. For the remaining participants, positive oral fluid Δ^9-THC tests ranged from 2 to 12 ng/mL and mainly occurred during the outpatient dosing phase (typically on Day 7 and/or Day 10 study visits). Specifically, excluding the participant with suspected contaminated samples, five participants in the lotion group exhibited a positive oral fluid test (>2 ng/mL THC) only after 7–10 days of product use, while the remaining participant tested positive on Days 2 and 3, but not on Days 7 or 10.

Two additional participants provided a positive oral fluid THC sample during the study: one individual in the active gel condition and one individual in the active patch condition. The gel participant provided a single positive sample (2.1 ng/mL) on Day 2. The patch participant provided positive samples on Day 7 and Day 17 (washout visit). Given that this patch participant had detectable levels of THC in oral fluid at baseline (0.3 ng/mL) and tested positive at the washout visit (3.7 ng/mL), it is possible that they were using a non-assigned cannabinoid product during the study. Aside from this one individual, all remaining participants tested negative for Δ^9-THC (LC–MS-MS concentration <2 ng/mL) at the Day 17 washout visit.

Urine

Figure 3 illustrates the mean urinary concentrations of CBD and its metabolites as well as Δ^9-THC-COOH (the primary target of urine drug tests for cannabis). All active products produced detectable levels of CBD, 7-OH-CBD and 7-COOH-CBD in urine following product initiation. During the Phase 1 laboratory session, all three analytes were detected in trace amounts (or not detected at all) following active drug administration. In general, CBD/metabolite concentrations peaked between Days 7 and 10 of the chronic dosing phase. The lotion produced significantly greater C_{max} and AUC values and significantly longer T_{max} values relative to the patch and balm for all three CBD analytes (P values < 0.05; Table II). Following the 7-day washout period, urine analyte concentrations were detectable for the following number of participants: CBD in eight participants (two in the cream group, five in the lotion group and one in the balm group), 7-OH-CBD in 21 participants (six in the cream group, eight in the lotion group, two in the patch group, three in the balm group and two in the gel group) and 7-COOH-CBD in six participants (five in the lotion group and one in the balm group).

At baseline, prior to drug administration, no participant had a positive urine test result based on current federal workplace drug testing criteria (Δ^9-THC-COOH urine concentration ≥50 ng/mL immunoassay screen and ≥15 ng/mL LC–MS-MS confirmation (31)). However, four participants (one in the placebo group, two in the lotion group and one in the gel group) had detectable concentrations of Δ^9-THC-COOH at baseline, ranging from 0.5 to 0.7 ng/mL. For the participant in the placebo group, this baseline Δ^9-THC-COOH value was the only analyte detected across all three biospecimens and timepoints. Δ^9-THC-COOH was only detected following the use of the lotion, patch and gel. The range of detectable concentrations of Δ^9-THC-COOH across all participants was 0.6–5.1 (0.6–2.3 among those with no Δ^9-THC-COOH detected in urine at baseline). Thus, all Δ^9-THC-COOH concentrations following product use were well below the current federal workplace confirmatory cut-off of 15 ng/mL (31).

Urine samples were also tested for Δ^9-THC-COOH using qualitative immunoassays at three different cut-offs (20, 50 and 100 ng/mL); the current federal workplace drug testing cut-off is 50 ng/mL. No participants tested positive for Δ^9-THC-COOH using these three immunoassay cut-offs. The lotion produced significantly greater C_{max} and AUC values for Δ^9-THC-COOH, and significantly longer T_{max}, relative to the patch and gel. Finally, Δ^9-THC was never detected in urine, and 11-OH-Δ^9-THC was only detected in two participants (each only at one timepoint) in the active lotion condition.

Pharmacodynamic effects

Subjective drug effects

Figure 4 illustrates the mean change-from-baseline VAS scores for drug effect, pleasant drug effect and unpleasant drug effect following topical administration. There were no significant differences in subjective drug effect ratings across any of the items based on the ANOVAs, except for "hungry/ have munchies." Specifically, a main effect of drug condition was observed for "hungry/have munchies" ($P = 0.0059$) and Bonferroni post hoc comparisons revealed that ratings for this item were significantly higher for the cream relative to the patch, balm and gel.

Comparisons conducted between the acute and chronic product application phases revealed that the placebo group, but no other group, reported significantly higher subjective ratings of "feel drug effect," "pleasant drug effect" and "drug liking" during the acute phase relative to the chronic phase (P values < 0.05; Table III). Additionally, for the cream, significantly lower subjective ratings of "hungry/ have munchies" were observed in the chronic dosing phase relative to the acute phase ($P = 0.0178$).

Cognitive/psychomotor performance

Figure 5 illustrates the mean total correct on the DSST and PASAT, mean average distance from the target stimulus on the DAT and mean global impairment score on the DRUID. There was no indication that any of the study products impaired cognitive/psychomotor performance throughout the study. There was a significant main effect of drug condition on the DAT during the acute phase ($P = 0.0249$). Specifically, the balm group demonstrated significantly lower mean average distance from the target stimulus (i.e., better performance) relative to the placebo group ($P = 0.041$). However, this effect was no longer present during the chronic phase (Table III).

Physiological effects

Figure 5e illustrates the mean beats per minute (BPMs) for HR. None of the topical products influenced HR during either the acute or chronic dosing phases, and there were no significant differences across study conditions. Additionally, there were no significant differences in BPM between the acute and chronic phases for any specific product. Likewise, there were no changes in SBP or DBP following acute or chronic topical administration (Table III).

Discussion

Due to the passing of the 2018 Farm Bill in the USA, hemp-derived CBD products of various formulations and routes of administration have increased in popularity considerably. One category of CBD products that has seen particularly

Table III. Acute (Left) and Chronic (Right) Mean Peak Values for Pharmacodynamic Measures

Acute dosing phase							Chronic dosing phase						
Characteristics	Placebo (*N* = 9)	Cream (*N* = 8)	Lotion (*N* = 8)	Patches (*N* = 7)	Balm (*N* = 8)	Gel (*N* = 6)	Characteristics	Placebo (*N* = 9)	Cream (*N* = 8)	Lotion (*N* = 8)	Patches (*N* = 7)	Balm (*N* = 8)	Gel (*N* = 6)
Subjective measures													
DEQ							DEQ						
Drug effect	8.7 (10.6)	8.0 (15.8)	8.1 (21.6)	4.9 (8.2)	0.6 (1.2)	9.7 (10.7)	Drug effect	1.0 (3.0)	2.8 (7.4)	7.3 (20.7)	5.3 (13.5)	3.6 (6.8)	0.2 (0.8)
Unpleasant	7.3 (16.2)	0.8 (1.4)	0.4 (0.7)	1.7 (4.1)	6.1 (17.7)	1.0 (2.0)	Unpleasant	0.4 (1.3)	2.8 (6.6)	2.4 (6.7)	0.1 (0.4)	2.5 (7.5)	0.3 (1.4)
Pleasant	9.6 (12.2)	8.0 (17.4)	11.5 (30.2)	7.4 (19.7)	6.8 (17.5)	12.0 (11.8)	Pleasant	0.4 (1.3)	2.9 (7.7)	7.0 (19.2)	12.0 (30.9)	7.6 (17.5)	0.8 (1.6)
Drug liking	19.6 (20.6)	16.3 (43.5)	23.3 (31.2)	8.1 (41.3)	–5.3 (18.3)	17.0 (22.2)	Drug liking	5.9 (15.8)	12.4 (18.2)	12.4 (20.8)	13.1 (31.8)	0.0 (4.9)	–0.2 (1.0)
Sick	1.7 (2.6)	4.0 (21.0)	0.4 (0.5)	–0.3 (5.2)	1.4 (3.1)	0.2 (1.7)	Sick	1.6 (3.2)	–2.8 (11.5)	0.0 (0.0)	–1.3 (3.9)	1.6 (4.6)	4.2 (10.4)
Heart racing	1.0 (2.3)	–7.1 (14.9)	0.9 (2.1)	1.9 (5.9)	1.3 (3.2)	2.5 (6.2)	Heart racing	0.2 (0.7)	–0.5 (18.3)	2.4 (6.7)	1.4 (5.2)	–0.6 (1.8)	2.7 (9.6)
Anxious/nervous	–0.2 (10.2)	–6.0 (21.3)	2.8 (8.7)	–7.0 (18.9)	9.1 (22.0)	0.8 (7.0)	Anxious/nervous	5.0 (14.1)	–8.0 (26.5)	5.6 (17.2)	9.3 (31.7)	2.3 (4.9)	7.8 (23.4)
Relaxed	–8.8 (37.8)	–14.5 (51.2)	–1.1 (43.6)	–12.0 (20.4)	–16.0 (48.6)	8.3 (51.3)	Relaxed	–32.4 (33.4)	–5.5 (37.6)	–18.9 (58.5)	–23.9 (42.1)	–4.1 (37.4)	7.7 (40.4)
Paranoid	0.1 (0.3)	0.8 (1.0)	0.4 (0.7)	–2.1 (5.7)	1.0 (2.1)	0.7 (1.2)	Paranoid	0.2 (0.4)	0.9 (2.5)	1.9 (5.3)	–1.7 (4.5)	–0.6 (1.8)	0.5 (0.8)
Sleepy/tired	20.6 (41.5)	12.4 (41.3)	23.4 (39.8)	3.7 (30.5)	7.6 (27.1)	3.7 (38.9)	Sleepy/tired	12.2 (32.0)	4.1 (60.6)	20.8 (49.4)	–9.6 (32.3)	2.8 (30.1)	3.8 (57.7)
Alert	–36.1 (26.3)	–27.1 (32.6)	–16.9 (35.3)	–11.3 (27.4)	–7.5 (38.2)	–8.5 (48.1)	Alert	–30.0 (19.0)	–25.1 (32.2)	–14.4 (33.5)	–7.7 (36.6)	–9.1 (40.3)	–15.2 (54.3)
Irritable	–2.2 (6.1)	6.9 (30.4)	6.3 (11.3)	–11.6 (21.5)	2.3 (5.2)	1.7 (3.6)	Irritable	–0.8 (7.6)	5.3 (30.5)	15.4 (30.9)	–12.6 (23.9)	2.9 (6.6)	1.3 (4.6)
Vigorous/motivated	–1.2 (16.6)	–21.8 (27.8)	5.9 (39.6)	–13.3 (43.5)	–10.6 (33.1)	5.3 (36.5)	Vigorous/motivated	–11.3 (20.6)	–13.3 (31.5)	–17.3 (35.6)	9.7 (27.9)	–8.8 (11.1)	5.7 (49.2)
Restless	1.2 (6.2)	–5.6 (25.6)	16.3 (30.4)	–15.6 (26.4)	8.5 (21.4)	10.7 (23.1)	Restless	0.1 (8.3)	–1.4 (30.2)	7.3 (13.4)	–17.4 (30.2)	5.5 (17.2)	6.8 (13.4)
Hungry/had munchies	16.4 (24.7)	36.8 (34.0)	4.4 (25.6)	8.9 (23.7)	24.0 (35.7)	29.5 (29.2)	Hungry/had munchies	1.9 (5.0)	–1.9 (12.4)	–6.8 (17.5)	1.1 (14.4)	4.8 (24.1)	14.5 (34.6)
Cannabis craving	0.3 (0.5)	0.6 (1.4)	0.3 (0.5)	0.0 (0.0)	0.0 (0.5)	–0.5 (0.8)	Cannabis craving	0.2 (0.7)	0.4 (0.7)	0.8 (1.4)	0.0 (0.0)	–0.1 (0.4)	0.2 (1.0)

(continued)

Table III. (Continued)

	Acute dosing phase							Chronic dosing phase					
Characteristics	Placebo (*N* = 9)	Cream (*N* = 8)	Lotion (*N* = 8)	Patches (*N* = 7)	Balm (*N* = 8)	Gel (*N* = 6)	Characteristics	Placebo (*N* = 9)	Cream (*N* = 8)	Lotion (*N* = 8)	Patches (*N* = 7)	Balm (*N* = 8)	Gel (*N* = 6)
Dry mouth	8.6 (17.8)	29.0 (35.5)	9.8 (18.7)	−0.3 (32.5)	6.0 (8.9)	18.2 (28.4)	Dry mouth	2.0 (4.2)	17.9 (35.4)	12.9 (29.9)	6.9 (46.8)	12.3 (27.2)	13.0 (22.1)
Dry/red eyes	4.8 (14.3)	1.6 (15.9)	1.5 (3.9)	−1.6 (4.8)	0.0 (0.9)	−1.8 (6.5)	Dry/red eyes	−3.6 (11.0)	−3.0 (13.1)	−0.1 (0.6)	13.0 (32.3)	−0.3 (0.7)	7.3 (25.1)
Memory impairment	0.7 (1.7)	−0.9 (7.2)	1.9 (4.9)	−6.9 (18.6)	1.8 (5.1)	0.5 (1.2)	Memory impairment	0.7 (1.4)	7.3 (24.5)	3.5 (10.7)	−7.0 (18.5)	−1.1 (2.1)	0.5 (2.3)
Throat irritation/coughing	6.3 (19.4)	−6.3 (18.9)	0.0 (0.0)	0.4 (1.1)	0.4 (0.7)	0.2 (0.8)	Throat irritation/coughing	2.9 (9.0)	1.1 (31.3)	0.1 (0.4)	−0.4 (1.1)	0.1 (0.4)	0.0 (0.6)
Difficulty in performing routine tasks	0.4 (3.0)	7.1 (13.0)	8.8 (23.5)	−2.9 (7.6)	2.8 (8.2)	0.5 (0.8)	Difficulty in performing routine tasks	−0.3 (1.9)	3.4 (6.0)	2.1 (5.6)	−2.9 (7.6)	0.6 (2.2)	0.8 (1.3)
Cognitive measures													
DSST	50.2 (6.7)	51.4 (6.8)	51.5 (10.8)	54.1 (6.4)	54.4 (5.0)	51.0 (9.6)	DSST	53.3 (6.1)	53.9 (6.3)	55.0 (9.6)	55.6 (7.7)	55.8 (5.8)	50.3 (9.0)
PASAT	78.1 (21.1)	81.8 (8.3)	82.5 (7.7)	82.6 (7.1)	77.0 (13.7)	85.0 (2.8)	PASAT	80.1 (22.0)	85.5 (5.3)	85.6 (6.5)	86.7 (4.8)	78.4 (13.8)	88.2 (2.1)
DAT	21.4 (6.3)	17.1 (3.8)	16.4 (3.9)	14.7 (4.1)	13.0 (2.8)	20.7 (9.6)	DAT	16.0 (3.6)	13.9 (2.2)	13.5 (4.0)	13.3 (3.2)	11.8 (1.9)	15.0 (4.1)
DRUID	50.3 (8.3)	47.5 (5.1)	48.6 (7.7)	46.1 (4.5)	44.0 (3.3)	47.2 (6.9)	DRUID	46.6 (7.7)	44.1 (5.1)	44.3 (6.1)	44.6 (4.9)	42.1 (3.0)	44.2 (6.0)
Physiological measures													
HR, beats/min	78.8 (7.4)	74.1 (10.4)	72.4 (11.6)	74.4 (5.4)	78.8 (12.3)	63.3 (8.2)	HR, beats/min	76.6 (8.1)	80.3 (9.8)	76.8 (13.1)	77.3 (10.5)	81.3 (9.9)	69.3 (14.4)
DBP, mmHg	84.3 (8.4)	81.8 (7.2)	83.9 (8.3)	80.3 (7.3)	83.3 (7.3)	75.0 (5.8)	DBP, mmHg	87.0 (7.8)	81.3 (9.0)	78.9 (5.9)	77.6 (7.2)	81.8 (7.1)	75.8 (5.7)
SBP, mmHg	131.7 (12.9)	125.4 (10.7)	133.6 (4.6)	130.3 (7.1)	132.9 (11.4)	129.3 (14.5)	SBP, mmHg	132.1 (10.7)	125.3 (6.6)	127.3 (8.7)	126.7 (4.8)	125.8 (11.3)	132.7 (12.8)

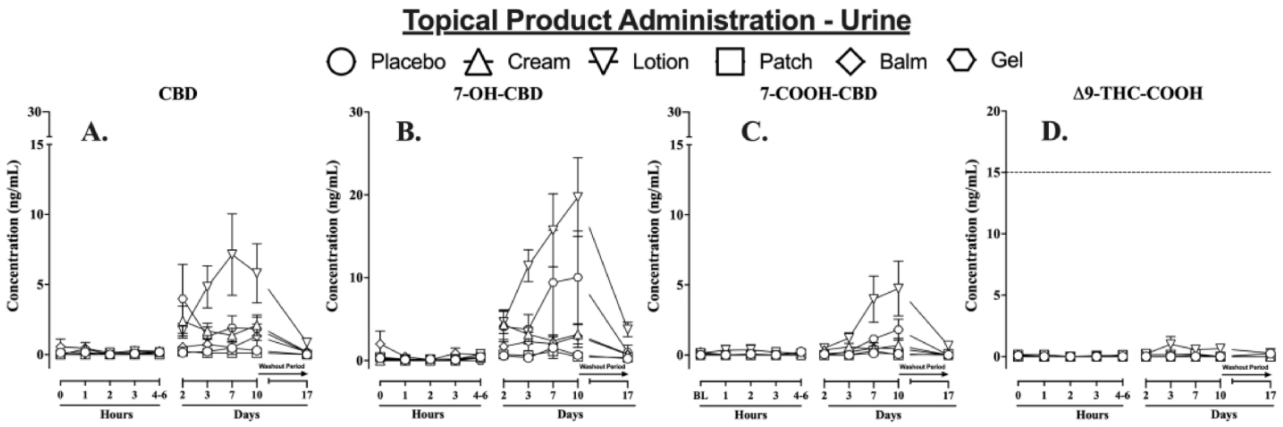

Figure 3. Mean urine concentrations (±SEM) for the analytes (a) CBD, (b) 7-OH-CBD, (c) 7-COOH-CBD and (d) Δ^9-THC-COOH before and after placebo (circle), cream (upward triangle), lotion (downward triangle), patch (square), balm (diamond) and gel (hexagon) product use. Drug administration occurred during the first 10 days followed by a 7-day washout period. The dashed line represents the federal workplace drug testing criteria for urine established by SAMSHA as a LC–MS-MS Δ^9-THC-COOH concentration ≥15 ng/mL (29).

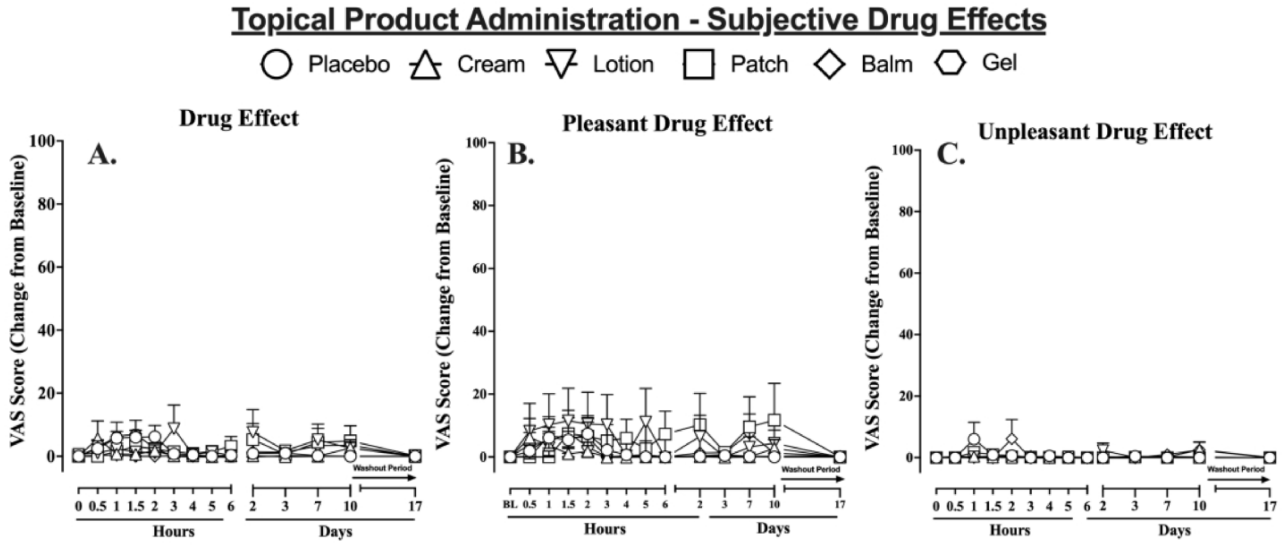

Figure 4. Mean ratings (±SEM) for the VAS items for (a) drug effect, (b) pleasant drug effect and (c) unpleasant drug effect from the DEQ before and after placebo (circle), cream (upward triangle), lotion (downward triangle), patch (square), balm (diamond) and gel (hexagon) product use. Drug administration occurred during the first 10 days followed by a 7-day washout period. Scores ranged from 0 (not at all) to 100 (extremely).

large market growth since 2018 are those intended for topical application (e.g., lotions, creams and patches). Given the considerable diversity of topical CBD products available for retail purchase, controlled research is needed to elucidate how product features such as formulation, dose and method of administration (e.g., repeated applications versus continuous wearing of a patch) influence cannabinoid absorption. Moreover, given that commercially available topical CBD products often contain low levels of the psychoactive cannabis constituent Δ^9-THC (13), research is needed to understand whether these products may influence drug testing outcomes for cannabis or produce any pharmacodynamic effects. This study sought to begin to fill these knowledge gaps by characterizing the effects of five commercially available high CBD/low Δ^9-THC topical products of different formulations among healthy adults who did not currently use cannabis/CBD products. Notably, each topical product examined contained Δ^9-THC at concentrations ≤0.3% and, thus, was federally legal. Because these products are often used repeatedly, study outcomes were assessed under both acute (controlled laboratory session) and chronic use conditions (outpatient use, twice daily for 9 days after the laboratory session).

Interestingly, use of three out of the five study products (the lotion, cream and gel) resulted in transdermal delivery of CBD as evidenced by increased whole blood concentrations of CBD and 7-COOH-CBD, a primary CBD metabolite. That being said, peak blood CBD concentrations were far lower than those observed previously following acute administration of oral or vaporized CBD (32). For example, in one prior human laboratory study, acute administration of 100 mg oral CBD and 100 mg vaporized CBD produced mean peak whole blood CBD concentrations of 13.7 and 104.6 ng/mL, respectively, while the highest blood CBD concentration observed across all participants in the present study was 2 ng/mL. Notably, each of the three products that exhibited transdermal CBD delivery contained a skin permeation enhancer and

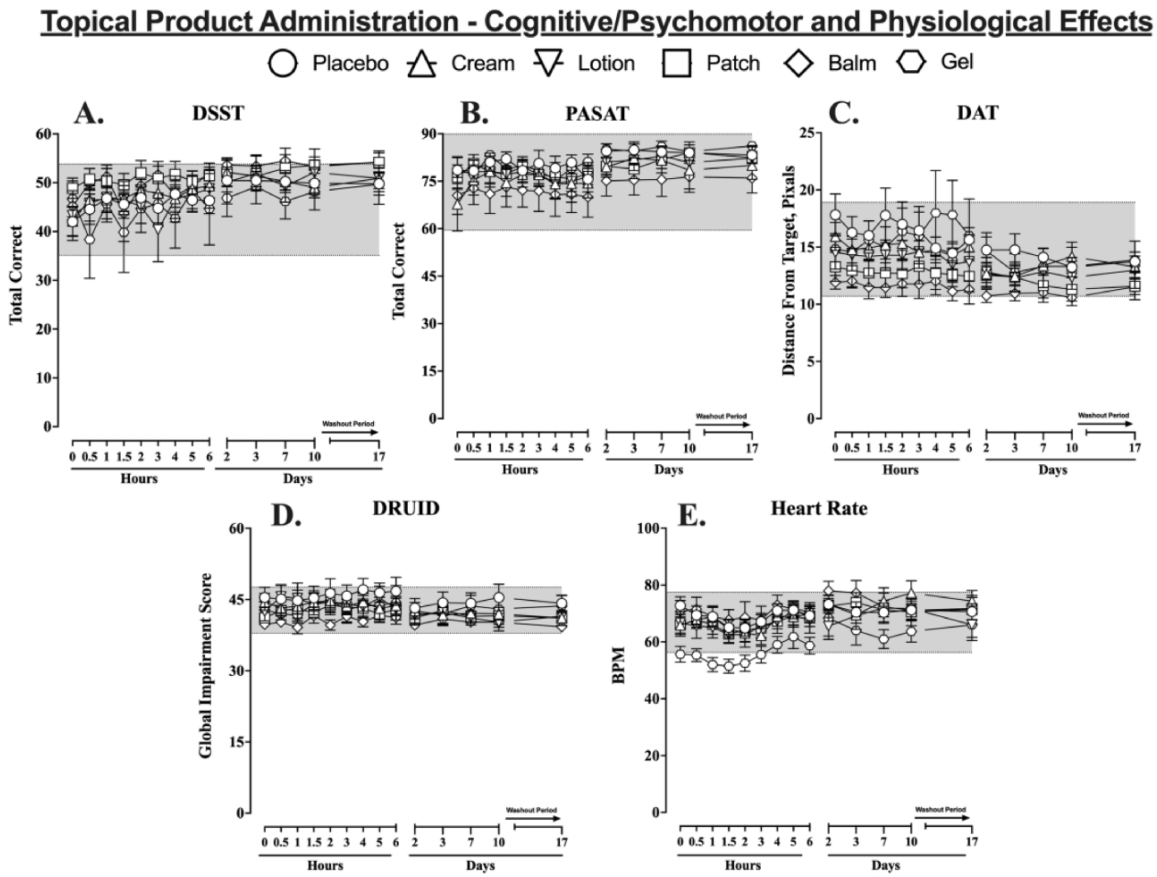

Figure 5. Mean (±SEM) cognitive and psychomotor performance on the (a) DSST, (b) PASAT, (c) DAT and (d) DRUID application. A decrease in total correct on the DSST and PASAT and an increase in the distance from the target and global impairment score on the DAT and DRUID, respectively, indicate poorer performance. Mean (±SEM) BPMs are shown for (e) HR. Data are shown before and after placebo (circle), cream (upward triangle), lotion (downward triangle), patch (square), balm (diamond) and gel (hexagon) product use. Shaded regions represent the mean + SD of all participants at baseline, providing a representation of the general range of performance expected from an individual under normal conditions. Drug administration occurred during the first 10 days followed by a 7-day washout period.

the product that delivered the most CBD (the lotion) also contained the highest concentration of CBD (~4% CBD or ~95 mg CBD per product application). Use of the balm and patch did not increase blood CBD concentrations, despite these formulations containing comparable amounts of CBD to some of the other study products. Taken together, these results highlight that twice daily use of topical CBD products can result in systemic absorption of small amounts of CBD, but that the extent of CBD delivery is influenced by dose, formulation (i.e., permeation enhancers) and method of administration (i.e., patch vs repeated topical application).

Another primary aim of the present study was to determine whether acute or chronic use of the study products could produce positive drug tests for cannabis. Urinary testing for Δ^9-THC-COOH (a metabolite of Δ^9-THC) remains the most common means of detection for cannabis use, although oral fluid testing for Δ^9-THC is becoming more prevalent. In the present study, all urine specimens screened negative for Δ^9-THC-COOH at three different immunoassay cut-offs (20, 50 and 100 ng/mL). Moreover, although Δ^9-THC-COOH was detected at low concentrations for some participants (particularly in the active lotion condition), no urine specimens had quantitative Δ^9-THC-COOH concentrations near the confirmatory cut-off for a positive test (15 ng/mL). These results contrast with prior studies which found that acute vaporization (17) or repeated oral ingestion (16) of high CBD/low Δ^9-THC products may result in positive urine drug tests for cannabis. However, our results are consistent with the lone prior clinical study (19, 32) involving topical application of high CBD/low Δ^9-THC commercial products; in that study, neither Δ^9-THC nor Δ^9-THC metabolites were detected in urine or blood following 3 days of repeated product application. While the use of high CBD/low Δ^9-THC topical products did not impact urine drug testing results in the present study, it is unclear whether more extreme or prolonged drug application conditions may lead to greater levels of Δ^9-THC exposure and higher chances of positive urine Δ^9-THC-COOH tests. Additional research should consider studying the pharmacokinetics of these products for longer periods of time, under more extensive application scenarios and with alternative skin permeation enhancement methods (e.g., microneedles and ultrasound) to determine unequivocally that they cannot impact urine drug tests for cannabis.

Notably, although Δ^9-THC was not detected in whole blood specimens of any participant and no positive urine tests were observed, seven out of eight individuals in the active lotion condition, one out of seven individuals in the

patch condition and one out of six individuals in the gel condition had oral fluid Δ^9-THC concentrations ≥2 ng/mL (the confirmatory cut-off for a positive oral fluid test for cannabis/Δ^9-THC). There are several possible explanations for these positive oral fluid tests. First, the positive samples could reflect systemic absorption of Δ^9-THC following topical product application. However, numerous prior controlled studies have demonstrated that Δ^9-THC transfer from systemic circulation in blood to oral fluid is negligible following cannabis inhalation or oral ingestion (33–35). That said, there are prior reports of discordance between systemic drug concentrations in blood versus oral fluid concentrations following transdermal drug exposure (36–38); the mechanism behind this discordance is not fully understood, but proposed explanations include the unique physiology of the salivary gland, which allows for more blood flow than most other tissues and the possibility that transdermally absorbed drugs may be uniquely transported to oral fluid via the lymphatic system (38). Second, another plausible explanation is that at least some positive Δ^9-THC tests were the result of inadvertent oral cavity contamination. Indeed, as described in the Results section, we strongly suspect this was the case for at least one participant in the active lotion condition. Curiously, however, outside of this one participant, most of the remaining positive oral fluid tests occurred during the outpatient dosing phase, often in the final days of product application (study Days 7 or 10); if contamination were the sole cause of the positive tests, we would have expected a similar rate of positive tests and similar concentrations of Δ^9-THC across all product application days. Third, the positive samples could be indicative of use of non-assigned cannabinoid products. However, this is unlikely given that, for all but one participant in the active patch condition, oral fluid samples were negative at baseline and at the 7-day washout visit and we did not observe unexpected values in blood or urine cannabinoid levels for these participants, suggesting that they were compliant with the protocol and did not use other cannabinoid products during the study. Finally, these unexpected Δ^9-THC concentrations could have been enhanced by artifacts of the analytical testing procedures, although this is unlikely as we mitigated this possibility by taking measures to ensure that CBD did not convert to Δ^9-THC during the extraction process (see the Methods section), as has been observed in prior studies using acidic buffers for sample extraction (39). Overall, given the discordance between blood/urine and oral fluid results, additional pharmacokinetic studies on topical cannabinoid products that evaluate each of these biological matrixes under highly controlled conditions are warranted.

Interpreting toxicology results for Δ^9-THC and Δ^9-THC metabolites is becoming ever-more complicated given the changing landscape of cannabinoid products (e.g., presence of Δ^9-THC in both federally legal hemp products and illegal cannabis products), and the findings from the present study may further add to this complexity. This study is the first to demonstrate that topical application of high CBD/low Δ^9-THC products that are federally legal (≤0.3% Δ^9-THC) may influence some drug testing outcomes for cannabis (i.e., oral fluid Δ^9-THC), but not others (i.e., urine Δ^9-THC-COOH). Importantly, however, positive oral fluid Δ^9-THC tests were primarily observed for one product (the lotion) which contained the highest amount of Δ^9-THC (~0.19% Δ^9-THC; ~4.2 mg Δ^9-THC per product application) of the 105 products that were tested to inform product selection for this study (13). Thus, the extent to which this product is representative of the extensive market of topical CBD products with respect to Δ^9-THC content and chances of impacting drug testing is unclear. Nevertheless, individuals who use CBD products and other relevant stakeholders (e.g., employers who drug test for cannabis) should be aware that the use of federally legal CBD products with low levels of Δ^9-THC (potentially including topicals) may result in positive drug tests for cannabis and that oral cavity contamination appears to be an important factor to mitigate for oral fluid testing. Such awareness is particularly important given that many hemp-derived CBD products with appreciable levels of Δ^9-THC claim to be "Δ^9-THC-free" or do not disclose that they contain Δ^9-THC (13, 40).

A final aim of the present study was to characterize the pharmacodynamic effects of the different high CBD/low Δ^9-THC topical products relative to placebo topical products. Overall, acute nor chronic use of any of the five active products produced any discernable subjective, cognitive or physiological effects relative to the placebo condition. Moreover, within active dosing conditions, none of these pharmacodynamic effects changed over the course of 10 days of product use. These results are perhaps not surprising given the relatively low doses of Δ^9-THC that participants were exposed to during each product application (0.4–4.2 mg Δ^9-THC). Indeed, transdermal exposure to far higher doses of Δ^9-THC has shown little to no psychoactive effects in prior studies. In one of the only prior studies to evaluate transdermal exposure of Δ^9-THC in humans (41), participants topically applied 100 mg of Δ^9-THC to their hand, wrist and forearm; Δ^9-THC was systemically absorbed following product application, but none of the participants reported feeling "high," and the product was generally well-tolerated. Overall, these data suggest that high CBD/low Δ^9-THC topical products appear to present little risk of inducing intoxication or impairment of cognitive/psychomotor functioning among those who use them and have negligible abuse liability.

There were several noteworthy limitations to the present study. First, while the use of commercially available products increased the external validity of the study, internal validity was reduced by the wide variability in product features. Future studies should systematically manipulate certain product features (e.g., permeation enhancers) while holding other relevant features constant (e.g., CBD/Δ^9-THC dose) to better characterize the individual factors that influence drug absorption. Second, the majority of study drug use occurred outside of the laboratory, meaning that we were unable to ensure that participants did not use other cannabinoid products during the study. However, cannabinoid concentrations in all three biological matrixes dropped substantially (generally below the limits of detection) at the 7-day washout visit, which strongly suggests that participants were not using other cannabinoid-containing products during the outpatient phase. Third, given the incredible diversity of topical cannabinoid products, it is unclear how representative the five products we chose to examine are of the larger market. Future research should continue to examine the effects of a diverse range of topical cannabinoid products (including Δ^9-THC-dominant topicals) under different use scenarios. In a similar vein, participants in this study used one product in isolation, but individuals in the real world may use multiple cannabinoid

products simultaneously, which may warrant future investigation; the extent to which the use of multiple hemp and/or cannabis products may impact drug testing outcomes has largely been unexplored. Finally, this study included a relatively small sample size of healthy adults and did not evaluate any therapeutic effects. Future work should consider studying the efficacy of commercial topical cannabinoid products for therapeutic conditions for which they are commonly used (e.g., pain/inflammation).

In conclusion, 10 days of repeated topical application of commercially available hemp-derived high CBD/low Δ^9-THC topical products resulted in transdermal absorption of CBD, although CBD pharmacokinetics varied considerably across products and appeared to be influenced by dose and the presence of permeation enhancers. The product that delivered the most CBD to participants (the active lotion) contained the highest amount of CBD and supposedly contained vitamin E, a well-known permeation enhancer. None of the topical products examined produced positive qualitative or quantitative urine drug tests for cannabis. However, the lotion (which also contained the most Δ^9-THC) produced positive oral fluid Δ^9-THC tests in seven out of the eight participants assigned to that condition, although the positive tests for at least one of these participants appeared to be attributed to contamination of the oral cavity. None of the study products had any discernable impact on pharmacodynamic outcomes (subjective, cognitive and physiological effects) relative to the use of comparable placebo products. This study provides important initial data on the acute and chronic effects of hemp-derived topical CBD products, a product class that has grown in popularity rapidly since the passing of the 2018 Farm Bill. Given the continual proliferation of cannabinoid products of various formulations and routes of administration, far more clinical research is needed to adequately inform regulatory actions and policy decisions related to these products, including those that pertain to drug testing for cannabis.

Supplementary data

Supplementary data is available at *Journal of Analytical Toxicology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Conflicts of Interest

Dr. Spindle has been a paid consultant for Canopy Health Innovations Inc. and has received research funding from Cultivate Biologics. Dr. Vandrey has been paid as a consultant or scientific advisory board member for Canopy Health Innovations Inc., Jazz Pharmaceuticals, MyMD Pharmaceuticals, Mira 1a Therapeutics, Syqe Medical Ltd., Charlotte's Web, and WebMD. Dr Cone has served as a consultant to Research Triangle Institute and the CDM Group. Dr. Bonn-Miller is a paid employee of Charlotte's Web. The remaining authors have no conflicts of interest to disclose.

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