Stability of South African commercial and extemporaneously prepared cannabidiol (CBD) topical oil-in-water emulsions

Alyson Bennett

alyson.bennett@ru.ac.za

Rhodes University

Roderick B. Walker

Rhodes University

Research Article

Keywords: CBD, stability, emulsions, topicals, cannabis, South Africa

Posted Date: August 3rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10267854/v1

Additional Declarations: No competing interests reported.

Abstract

Background

Topical formulations containing cannabis in South Africa must comply with the legal standards of Schedule 0 products with a low CBD content and negligible amounts of THC. A selection of commercially available South African CBD and extemporaneously prepared topicals were evaluated and compared for formulation differences that may affect CBD stability.

Methods

The stability of CBD in the different topical formulations was assessed under in-use conditions of light exposure and elevated temperature. The physical properties of a selection of commercial and extemporaneously prepared CBD topical forms were characterized. The extemporaneous formulations were oil-in-water (o/w) emulsions with product attributes similar to those of commercially available aqueous cream. CBD content was determined using a validated HPLC method.

Results

Structural components of the emulsions resulted in high viscosity, particularly for the Pickering emulsion. The spreadability of the topical products was affected by both temperature and formulation type. CBD degraded on exposure to light and increased temperature. The commercially available CBD gel had significantly better stability than other products. Tissue oil exhibited a significant decrease in CBD content, which may lead to poor consumer acceptability. The Pickering emulsion may exhibit better stability of CBD; however, the spreadability at 37°C was lower than that of the other extemporaneously prepared o/w emulsion formulations.

Conclusions

Storage temperatures and light exposure significantly increase CBD degradation in formulations with fewer antioxidants and lower viscosity among the South African commercial products tested. Excipients such as Aerosil® R974 may be used to produce a Pickering emulsion for a high viscosity o/w emulsion for a CBD topical formulation that has improved CBD stability at 37°C.

1 Background

In South Africa, topical formulations with cannabidiol (CBD) require a license from the South African Health Products Regulatory Authority (SAHPRA) to manufacture. These commercial topical CBD products may not make a health claim related to cannabis, since the products are Schedule 0 under the Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended (Medicines Act)

(Medicines and Related Substances Act (101/1965) 2020). As per the regulations of the Schedule 4 exception in the Medicines Act, the CBD content must be < 0.001% THC, < 20 mg CBD daily dose, and < 600 mg CBD total in the sales package to be a Schedule 0 product (Medicines and Related Substances Act (101/1965) 2019). An alternative exception of Schedule 4 is when the product has < 0.001% THC, < 0.00075% CBD, and other non-specified naturally occurring cannabinoids (Medicines and Related Substances Act (101/1965) 2019).

Topical products containing CBD are often unreliable since CBD degradation or mislabeled content may lead to inactivity, consumer mistrust, and a waste of resources. CBD topical products marketed and labelled with the word “pain” may mislead the consumer since pain is the most frequent reason for consumers to use CBD products, insufficient medical evidence is available for topical pain treatment, and clinical trials without THC have reported mixed results (Johal et al. 2020; Lutge et al. 2013; Mücke et al. 2018; Vela et al. 2021; Moore et al. 2024). In addition, clinical trial designs for testing topical CBD products have been found to be biased because of small sample sizes, poor blinding, participant attrition, and indirectness due to exclusion of people with a history of major medical disease, current and or historical substance abuse, or both (Whiting et al. 2015; Kosiba et al. 2019). Furthermore, quality testing of commercial CBD products has shown inconsistent results, with CBD content reported as higher or lower than the product label indicates (Therapeutic Goods Administration 2020; Bonn-Miller et al. 2017; Smith 2020; Pavlovic et al. 2018). This prompted the development of a quality assessment for a small selection of commercial topical CBD products in South Africa. CBD stability was studied in the commercial products and in extemporaneously prepared oil-in-water emulsions. SAHPRA recommends that High Performance Liquid Chromatography (HPLC) be used for analysis, as the technique is reliable, cost-effective, and a commonly used analytical tool in the pharmaceutical and cannabis industries. There is no standardized extraction method reported for the analysis of cannabis products therefore, a new method was developed and validated following ICH guidelines for these studies (ICH Q2(R2) 2022). An in-use stability testing methodology was selected to test topical CBD products and compare single-sample commercial products from different manufacturers with extemporaneously prepared samples. The focus of the research was to monitor the degradation of CBD under light and temperatures typical of conditions in South Africa.

2 Materials

Commercial CBD products were donated by Dischem® Pharmacy (DisChem®, RSA) and included a body lotion, hand cream, muscle joint (MJ) cream, tissue oil, and gel. White soft paraffin (H&R South Africa Ltd., RSA), cetostearyl alcohol (Central Drug House, India), sodium lauryl sulfate and glycerine (Sigma®, Merck Life Science®, RSA), mineral oil, Tween 80 (polyoxyethylene sorbitan monooleate) (Sigma-Aldrich®, Merck, RSA), and phenoxyethanol (ThermoFisher Scientific®, USA) were purchased for use. Partially hydrophobic silica Aerosil® R974 and ViscOptima® SE, a polymeric emulsifying agent, were donated by Evonik Industries, Germany and Croda® Inc. A CBD isolate was donated by African CannaMed® Co. HPLC-grade methanol (MeOH) and acetonitrile (ACN) were purchased from Romil

(Microsep®, RSA). Phosphoric acid (85% v/v) was purchased from Supelco® (Supelco®, Inc., USA). All samples and HPLC solutions were degassed by sonication using a Branson® B12 ultrasonic bath (Branson® Inc., USA) prior to use. Phytocannabinoid 5®, containing CBD, CBDA, THC, THCA, and CBN, was purchased from Cayman Chemicals® (Cayman Chemicals®, USA), and ibuprofen was donated by Aspen Pharmacare®, RSA, for use as reference standards for chromatography. Sample filtration was achieved using a 0.45 µm hydrophilic PVDF syringe filter purchased from Millipore® Co., USA.

Commercial topical CBD products were characterized for comparison to extemporaneously prepared o/w emulsion formulations. Similarity in the rheological properties, viscosity, shear stress, yield stress, Zeta potential (ZP), and spreadability were used to identify the formulation compositions listed in Table 1.

Table 1
Extemporaneous o/w emulsion formulations shown in % w/w

Component % w/w	Aq. Cream	Pickering emulsion	Gel emulsion	Emulgel
Mineral oil	6.0	25.0	25.0	25.0
Soft paraffin	15.0	-	-	-
Cetostearyl alcohol	8.0	-	-	-
Sodium lauryl sulfate	0.9	-	-	-
Glycerine	-	4.0	4.5	3.7
Water	69.3	65.7	69.3	69.3
Aerosil® R974	-	4.5	0	0.8
ViscOptima® SE	-	0	0.4	0.4
Phenoxyethanol	0.8	0.8	0.8	0.8

3 Methods

3.1 Preparation of Extemporaneous Formulations

Formulations were optimized to minimize materials use, meet cold-processing conditions at a room temperature (RT) of 22°C, and achieve dispersed-phase droplet sizes < 200 nm. The desired formulation standard was an opaque, viscous, white, stable at RT, high-water-content, easily spreadable aqueous cream. The aqueous cream was prepared by mixing a wax emulsion at 70°C, while the components of the extemporaneous formulations were prepared using high shear homogenization at 20,000 rpm for 5 minutes using a Velp Scientifica® (Italy) OV5 rotor stator at 22°C. Samples were spiked with CBD at a 2 mg/ml concentration with a 202 mg CBD isolate and one (1) gram of Tween 80 was added and

dispersed using a Eurostar 40 IKA® (Germany) overhead stirrer with a 4 bladed propeller attachment at 1000 rpm for 5 minutes at 22°C. All formulations tested for stability are shown in Figure S1 of the Supplementary Information.

3.2 Rheology

The viscosity of the formulations was determined using a Model-RVDV Plus Brookfield® Viscometer fitted with a Helipath stand (Brookfield® Labs Inc., USA). The rotation and spindle speed were adjusted for each formulation and topical CBD product tested to ensure that sufficient torque (10–90%) was generated to accurately determine viscosity (Brookfield 2017). The torque, temperature, spindle, speed, and volume of the container used were recorded for each viscosity determination. The temperature of the sample at time of measurement, spindle type and speed are shown in Table 2.

Table 2
Viscosity of South African commercial topical products and extemporaneously prepared topical products with CBD temperature, spindle and speed for viscosity measurement.

Formulation	Temp °C	Spindle/ speed rpm
Body Lotion	20.1	T-F/10
Hand Cream	19.5	T-E/30
MJ Cream	20.4	T-F/10
Tissue Oil	18.9	RV-2/100
Gel	20.3	T-F/2
Aqueous cream	18.9	T-F/10
0% Aerosil® R974, 0.4% ViscOptima® SE	19.0	T-F/10
0.8% Aerosil® R974, 0.4% ViscOptima® SE	18.7	T-F/10
4.5% Aerosil® R974, 0% ViscOptima® SE	19.0	T-F/2

All samples were tested in triplicate. Further rheological properties were tested by Anton Paar® Midrand, RSA (Anton Paar Southern Africa (Pty) Ltd). Samples of each product (15 g) at 25°C were subjected to flow curve analysis to determine the shear stress and viscosity of the products at a shear rate of 1–100 1/s using an Anton Paar® MCR 92 Rheometer (Anton Paar®, Austria) and PP25/S measuring system. The rheological data generated by Anton Paar® provided the zero-shear-rate viscosity, which was used to calculate the dynamic yield stress for the dosage forms as recommended by the USP-NF for quality assessment of semi-solid dosage forms (USP and NF 2023). The dynamic yield stress was calculated from the extrapolated zero shear rate intercept in the shear stress versus shear rate plots by fitting the data to a polynomial model (ICH Q2(R2) 2022; Brookfield 2017).

3.3 Spreadability

A common method used to determine spreadability is the evaluation of laminar flow of creams or ointments between two glass plates set parallel to each other with the product between the plates, which is known as the parallel-plate method and is a simple, rapid, and inexpensive test procedure to conduct (Douguet et al. 2017). Approximately one (1) gram of each formulation was weighed and placed between two sheets of 20 cm x 20 cm clear glass plates, weighing 141.57 grams and 141.08 grams. The absolute diameter in the X and Y direction of the approximate circle formed was measured following placement of the 141.57-gram glass plate on top of the sample for one (1) minute. The outline of the sample was traced with a marker after pressure had been applied for one (1) minute, and the area of the approximate circle reported in mm^2 was determined using 1 mm x 1 mm graph paper. The spreadability measurements were performed in triplicate (n = 3) at room temperature (22°C), and the average spreadability and standard deviation were calculated. The formulations and plates were heated to 25°C, 30°C, and 35°C using a VWR® hot plate stirrer, and the formulations were mixed by hand with a glass stirring rod prior to determining spreadability.

3.4 Zeta potential (ZP)

A Model Nano-ZS Zetasizer (Malvern Instruments Ltd, England) was used to determine the average ZP of the dispersed phase in the emulsions. The samples were prepared using a method adapted from a procedure developed to determine the ZP of commercially available cannabis-infused topical products, in which turbid samples were tested without error (NCL and National Cancer Institute 2020; Quiñones et al. 2022). Test formulations were diluted with a 10 mM NaCl solution that had been sonicated for 30 min, then filtered through a 0.20 µm Sartorius Stedim cellulose filter using a Laboport® N820 vacuum pump (KNF Laboport®, Germany). A 25 mg aliquot of the CBD topical product or o/w emulsion to be tested was weighed and quantitatively added to a 10 mL 10 mM NaCl solution, then sonicated for 30 min. A fixed-volume 500 µL aliquot of the solution was added to 10 ml of a 10 mM NaCl solution in an A-grade volumetric flask, and sonicated for 30 min. Approximately 750 µL of the sample was placed into Malvern® Z-folded capillary cells (Malvern Instruments Ltd, England) for the ZP determination. All measurements were performed at 22°C in replicate (n = 6) with an applied field strength of 20 V/cm, and the ZP was determined using the Henry equation (Eq. 1) (NCL and National Cancer Institute 2020).

$$\mathrm{Ue} = \frac{2\,\epsilon\ z\,f\,(\kappa\,\alpha\,)}{3\eta}$$

Equation 1

Where,

U_e = electrophoretic mobility

ϵ = Dielectric constant

z = Zeta potential

η = Absolute zero-shear viscosity of the medium,

$f(\kappa\alpha)$ = the Henry function and is the ratio of the particle radius to the Debye length.

3.5 Extraction method

An extraction method was developed and validated for quantitative analysis of CBD content in topical formulations. A 50 mg sample of the formulation was shaken in and acetonitrile (ACN) and methanol (MeOH) extraction solution in a 5% v/v and 95% v/v ratio for 5 minutes, sonicated for 90 seconds and the solvent evaporated to dryness for 15 minutes with a rotational vacuum evaporator (RotaVap) (Stuart®, Cole-Parmer®, France), a Stuart® water bath set at 30°C and a Vacuubrand® 1C vacuum pump (Lasec®, RSA), after which the residue was reconstituted with 2 ml mobile phase (MP) which was 75% w/w ACN, 25% w/w H_2O and 0.005% phosphoric acid. The MP was prepared by measuring the ACN and water volumetrically in separate 300 ml A-grade graduated measuring cylinders, transferring them to a 1000 ml Schott® Duran bottle (Schott® Duran GmbH, Germany), and mixing with 0.7308 M phosphoric acid. A 50 µL aliquot of 85% v/v phosphoric acid was added using a P 20 pipette (Pipetman®, Gilson®, USA), and the solution was mixed using a VWR® magnetic stirrer (VWR®, England) at 650 rpm for 5 min. The pH of the MP was monitored at 22°C using an Accsen pH 8 pH meter (Lasec®, RSA), adjusted to 3.3 ± 0.2 with sodium hydroxide pellets, and subsequently degassed by ultrasonication for 10 minutes prior to use. The reconstituted solution was swirled in a round-bottom flask for 3 minutes, frozen for 5 minutes using a Defy® ECO Multimode Chest freezer (Defy®, RSA) set at -20°C, filtered with a 0.45 µm PVDF filter after which a 1400 µL aliquot was added to an HPLC vial and vortexed for 30 seconds Vortex Genie®-2 (Scientific Industries®, Germany) prior to analysis using a validated HPLC method (Bennett 2025).

3.6 HPLC method

HPLC with UV detection was used to determine the amount of CBD in the different o/w emulsions, lotions, creams, gels, and oils. A Waters® Model 2690 Alliance Separations®module, Waters® 2487 dual wavelength absorbance detector, and a 600-series solvent delivery module with a fixed 100 µL volume loop (Waters®, USA) were used with Empower® Version 3.7.0 software (Waters®, USA) to collect and analyze the chromatographic data. A Kinetex® core-shell C18 2.6 µm 150 x 4.6 i.d. mm column, preceded by a Restek® Trident HPLC guard column with a removable Restek® cap frit (Restek®, USA) was used at 22°C under isocratic conditions at a flow rate of 0.5 ml/min with UV detection at 228 nm for this separation.

A 0.5 mg/ml standard stock solution of CBD was prepared by accurately weighing approximately 2.5 mg of the CBD isolate and then adding it to 5 ml of the MP. The CBD isolate was dissolved in MP and sonicated for 90 seconds. The stock solution was diluted with MP to produce standard solutions of CBD at concentrations of 1.5, 3, 6, 10, 20, 50, 100, and 120 µg/ml. A standard stock solution of 0.4 mg/ml of the internal standard was prepared by accurately weighing approximately 2 mg of ibuprofen into a 5 ml

A-grade volumetric flask and adding 5 ml MP, then mixing for 5 minutes at 450 rpm using a VWR® magnetic stirrer (VWR®, England). A 200 µL aliquot of IS stock solution was added to the test samples prior to extraction.

Serial dilutions of the cannabinoid certified reference mixture were prepared by diluting 5, 10, 20, 25, 50, 100, and 200 µL with 1395, 1390, 1380, 1375, 1350, 1300, and 1200 µL of MP, respectively. Samples were analyzed in replicate (n = 6). Samples and standards were filtered and transferred into HPLC vials, then vortexed for 30 seconds using a Vortex Genie®-2 prior to HPLC analysis. Linearity was assessed by analyzing 1.5, 3, 6, 10, 20, 50, 100, and 120 µg/ml CBD standards in replicates (n = 6). The linear relationship between peak height ratio of CBD to IS and the concentration of CBD (µg/ml) is represented by the equation $y = 0.021x + 0.1003$, with a $R^2 = 0.9926$. The limit of quantitation was 0.844 µg/ml with an associated % RSD of 2.85%, and the limit of detection was 0.334 µg/ml.

3.7 Statistical evaluation

Statistical analysis of the CBD assay was performed using R® (R® Studio Team, USA). A one-way analysis of variance was conducted. Statistically significant differences ($p < 0.05$) between samples are indicated by different lowercase letters.

3.8 In-use CBD stability

The CBD content of the formulations was determined using the validated HPLC method. The analysis was conducted using three test conditions over a 12-week period. The conditions and duration of the stability study were in-use temperature at a slightly elevated temperature in a climatic chamber set to 37°C, and room temperature at 22°C in the laboratory. Products were exposed to light by storing in sealed clear glass vials on a benchtop in the laboratory, and were artificially irradiated with 4000K, 100 Watt ceiling lights similar to what a topical CBD product would typically be exposed to when used by purchasers. For the second condition, products were stored in the dark at room temperature, and each vial was wrapped in foil and placed in a closed cabinet at 22°C in a controlled-environment laboratory. A walk-in temperature- and relative humidity-controlled climatic chamber was set to 37°C ± 2°C/65% ± 5% RH for the foil-wrapped vials, which were stored away from light at 37°C. The samples were placed on a table and only briefly exposed to light when drawn for analysis. A storage temperature of 37°C was used for semi-solid dosage forms, as significant changes may occur at temperatures > 37°C due to the melting of formulation components. The samples at each time point were analyzed in triplicate.

3.9 Analytical determination of CBD preparations

CBD degradation occurs by a first-order reaction (Meija et al. 2022; Jaidee et al. 2021; Perrotin-Brunel et al. 2010). In a first-order reaction, the concentration of CBD is directly proportional to the degradation rate. A rate constant may be calculated as a logarithmic expression of the relationship between CBD concentration and time. The natural log of the change in CBD concentration was plotted versus time, and the slope, which is the first-order rate constant of the first-order reaction, was determined.

4 Results

The commercial product initial CBD content met the legal requirements for all commercial products tested, which sets the assay limits for CBD recovery to between 80 and 120% of the labelled content (Sarma et al. 2020).

4.1 Formulation characterization

4.1.1 Viscosity

The viscosity of each commercial CBD topical and extemporaneous o/w emulsion formulations are summarized in Table 3.

Table 3
Viscosity of commercially available CBD topical products and extemporaneously prepared o/w emulsions (n = 3)

Formulation	Torque %	Avg Viscosity cP	SD	% RSD
Body Lotion	85	250250	29.75	0.80
Hand Cream	81	336000	31.54	1.65
MJ Cream	80	244500	44.99	1.54
Tissue Oil	18.3	73.2	0.10	0.05
Gel	92	4595000	4.35	0.47
Aqueous cream	80	366666	21.86	1.95
0% Aerosil® R974, 0.4% ViscOptima® SE	81	200693	20.50	0.12
0.8% Aerosil® R974, 0.4% ViscOptima® SE	83	282136	24.65	0.17
4.5% Aerosil® R974, 0% ViscOptima® SE	80	5100000	30.10	0.10

The Pickering emulsion stabilised with 4.5% Aerosil® R974, 0% ViscOptima® SE had the highest viscosity, whereas the gel was the most viscous of the commercial topical products. The tissue oil is a low-viscosity Newtonian fluid that does not change over time, unlike the other formulations, which were shear-thinning.

The commercial product viscosity, determined using a Model-RVDV Plus Brookfield® Viscometer, was limited by the required spindle length and the minimum required volume for measurement at a slow speed. The availability of only a small sample volume resulted in a low torque measurement for the oil and the need to use a T-E T-bar spindle for the hand cream.

4.1.2 Yield stress

A rheometer is better suited to evaluating high-viscosity topical formulations, since the use of T-bar spindles may introduce variability, whereas a rheometer can increase shear rate from 1–100 s^{-1} to determine the product viscosity, shear-thinning properties, and yield stress using much smaller sample sizes. A rheometer was not used to evaluate the tissue oil, as it is a Newtonian fluid. Commercial CBD topical products had a yield stress in descending order for the gel, hand cream, body lotion, and MJ cream, as listed in Table 4.

Table 4
Dynamic yield stress and initial viscosity of commercially available and extemporaneously prepared CBD products following rheological analysis (n = 1)

Formulation	Dynamic Yield Stress Pa
Body Lotion	43.172
Hand Cream	58.846
MJ Cream	33.568
Gel	115.639
Aqueous cream	61.429
0% Aerosil® R974, 0.4% ViscOptima® SE	34.134
0.8% Aerosil® R974, 0.4% ViscOptima® SE	42.671
4.5% Aerosil® R974, 0% ViscOptima® SE	215.03

The Pickering emulsion had a much higher dynamic yield stress, 215.03 Pa, than all other samples. Aerosil® R974 has hydrogen-bonding capabilities due to silanol functional groups on the silica backbone, and its internal structure forms a gel-like network, resulting in increased viscosity and dynamic yield stress.

4.2 Spreadability

The spreadability of the gel and Pickering emulsion was lowest at 22°C (Table 5), and increasing the temperature to 35°C increased spreading for the body lotion, hand cream, MJ cream, gel, and aqueous cream.

Table 5. Average spreadability (mm^2 ± SD) for commercially available topical CBD products and extemporaneously prepared o/w emulsion formulations at 22°C, 25°C, 30°C and 35°C (n = 3)

Formulation	Temperature (°C)			
	22	25	30	35
	Average Area mm^2 ±SD			
Body Lotion	2188.00 ± 187.32	2751.69 ± 457.03	2960.80 ± 127.47	3449.33 ± 63.21
Hand Cream	2049.23 ± 141.97	2512.94 ± 132.50	2946.68 ± 72.26	6931.02 ± 385.71
MJ Cream	3204.80 ± 302.07	3352.12 ± 140.97	3647.89 ± 202.27	4378.20 ± 369.88
Gel	1125.17 ± 132.08	1141.81 ± 189.82	1163.63 ± 30.22	1287.40 ± 54.39
Aqueous cream	2423.72 ± 466.98	2454.38 ± 272.29	2523.76 ± 181.68	3100.23 ± 173.16
0% Aerosil®R974, 0.4% ViscOptima® SE	3176.63 ± 192.91	3234.46 ± 128.88	2991.69 ± 60.91	2904.50 ± 138.69
0.8% Aerosil® R974, 0.4% ViscOptima® SE	3418.94 ± 52.60	3011.05 ± 117.75	2969.13 ± 84.07	2716.88 ± 70.66
4.5% Aerosil® R974, 0% ViscOptima® SE	1439.19 ± 140.07	1307.81 ± 38.07	1081.91 ± 143.27	1270.90 ± 58.92

In contrast, an increase in temperature resulted in a decrease in the spreadability of the extemporaneously prepared gel, emulgel, and Pickering emulsions.

4.3 Zeta potential

The use of a standardized method for topical products, particularly those manufactured with non-ionic excipients, may be better for comparing ZP values. The ZP of the different topical formulations differs due to the excipients used, having different surface electrical charges, or may contain higher proportions of oil and or non-ionic surfactants to stabilize the emulsions, resulting in different ZP values (Table 6).

Table 6
Average Zeta potential (n = 6), for the commercially available CBD products and extemporaneously prepared aqueous cream and o/w emulsions

Formulation	Average Zeta Potential (mV)
Body Lotion	-20.10
Hand Cream	-13.33
MJ Cream	-28.85
Gel	-22.70
Aqueous cream	-30.73
0% Aerosil® R974, 0.4% ViscOptima® SE	-15.75
0.8% Aerosil® R974, 0.4% ViscOptima® SE	-15.18
4.5% Aerosil® R974, 0% ViscOptima® SE	-25.50

The ZP is primarily affected by the type and concentration of lipids and surfactants used in the formulation (Sęk et al. 2021). The Hand Cream had a ZP of -13.33 mV, which may be explained by its higher viscosity, non-ionic surfactants, and high shea butter content, which affect the contact angle and droplet formation, thereby influencing droplet size. Non-ionic surfactants stabilize emulsions through a combination of electrostatic and steric effects, resulting in an expected ZP of approximately ± 20 mV (NCL and National Cancer Institute 2020). The adsorption of non-ionic surfactant steric stabilizers decreases the ZP in systems, and the steric forces between dispersed particles minimize or prevent aggregation. The previously reported ZP of topical CBD lotions and creams ranged from − 6 mV to -19 mV; however, these values were determined using a 29 mM NaCl solution (Quiñones et al. 2022). The ZP is calculated from the electric potential at the interface between a particle and an electrolyte; therefore, high-concentration salt solutions produce a greater charge and result in lower absolute ZP values. A 29 mM NaCl solution used to determine the ZP will produce a lower absolute ZP than the 10 mM NaCl solution used in this research. The use of a low concentration of NaCl in solution may result in a higher absolute ZP, since fewer ions are produced by the NaCl in the layer between the particle and the dispersing medium (NCL and National Cancer Institute 2020). Therefore, the ZP determination for the commercially available CBD products, which ranged between − 13.33 and − 28.85 mV using the 10 mM NaCl solution, would be expected to be a higher absolute ZP than the previous findings of -6 mV to -19 mV when a 29 mM NaCl solution was used (Quiñones et al. 2022). The ZP of the Pickering emulsion was affected by hydrophobicity, which limits the impact of the negative charge of the silanol groups of the Aerosil® R974, and since the formulation does not contain any non-ionic surfactants, the ZP was − 25.5 mV. Non-ionic surfactants such as ViscOptima® SE resulted in a less negative ZP.

4.4 CBD stability

The rate of change in CBD concentration following storage was plotted, and the rate constants are reported in Table 7.

Table 7
First order degradation rate constants under storage conditions away from light at room temperature (22°C) (dark RT), light exposure at room temperature (22°C) (light RT) and away from light at 37°C (dark 37°C) for 12 weeks for the commercial CBD topical products and extemporaneous o/w formulations

Formulation	Storage Condition	k day^{-1}	R^2
Body Lotion	Dark 22°C	0.0030	0.9679
Hand Cream	Dark 22°C	0.0018	0.8927
MJ Cream	Dark 22°C	0.0027	0.8914
Tissue Oil	Dark 22°C	0.0021	0.9886
Gel	Dark 22°C	0.0018	0.8825
Aqueous cream	Dark 22°C	0.0040	0.9055
Gel emulsion	Dark 22°C	0.0055	0.9751
Emulgel	Dark 22°C	0.0054	0.9238
Pickering emulsion	Dark 22°C	0.0050	0.9651
Body Lotion	Light 22°C	0.0082	0.9848
Hand Cream	Light 22°C	0.0075	0.9829
MJ Cream	Light 22°C	0.0079	0.9985
Tissue Oil	Light 22°C	0.0090	0.9907
Gel	Light 22°C	0.0044	0.9886
Aqueous cream	Light 22°C	0.0107	0.9947
Gel emulsion	Light 22°C	0.0125	0.9932
Emulgel	Light 22°C	0.0127	0.9935
Pickering emulsion	Light 22°C	0.0118	0.9872
Body Lotion	Dark 37°C	0.0166	0.9755
Hand Cream	Dark 37°C	0.0112	0.9515
MJ Cream	Dark 37°C	0.0145	0.9671
Tissue Oil	Dark 37°C	0.0293	0.9642
Gel	Dark 37°C	0.0067	0.9921
Aqueous cream	Dark 37°C	0.0157	0.9824
Gel emulsion	Dark 37°C	0.0174	0.9830

Formulation	Storage Condition	k day^{-1}	R^2
Emulgel	Dark 37°C	0.0170	0.9751
Pickering emulsion	Dark 37°C	0.0156	0.9764

It is clear that CBD degradation occurred over the 12-week period, and a comparison of stability differences across storage conditions for the same sample over this period is possible. All samples exposed to light at 22°C or stored away from light at 37°C exhibited greater degradation than those stored away from light at 22°C, which is consistent with previous reports (Jaidee et al. 2021; Zamengo et al. 2019; Mazzetti et al. 2020). Increased temperature of 37°C resulted in a higher degradation rate than light exposure for all formulations.

The hand cream and body lotion exhibited the lowest degradation of CBD of 14.8 and 15.0% of the initial CBD concentration, respectively, over the 12-week period when stored away from light at 22°C, as shown in Fig. 1.

The degradation of CBD was significantly lower at 37°C in the hand cream than in the body lotion, with 61.6% lost after 12 weeks, compared to 74.3% in the body lotion. Both formulations included Vitamin E, which may impart antioxidant properties to the product; however, the Vitamin E content was not monitored before or during storage. Vitamin E may undergo thermal degradation at 37°C, as degradation rates have been reported to increase at pH 4 and at 40°C in emulsion formulations (Kim et al. 2018; Hategekimana et al. 2015).

The CBD content in MJ cream was sensitive to elevated temperatures since storage at 37°C had a major impact on stability, with 69.4% CBD lost over the 12-week test period, which was significantly ($p < 0.01$) greater than the 61.6% degradation observed for the hand cream and significantly ($p < 0.01$) less, than the 74.3% degradation observed for the body lotion. The degradation of CBD at 37°C in MJ cream was 0.0145 $day^{-1,}$ significantly slower than that of 0.0166 day^{-1} for the body lotion, which may be due to the presence of medium-length triglycerides, caprylic/capric triglycerides in the lotion formulation that have been reported to increase degradation rates when compared to the use of long-chain triglycerides (Wang1 et al. 2022).

The tissue oil exhibited 50.1% degradation when exposed to light and 90.4% when stored at 37°C after 12 weeks, significantly greater than that of the other commercially available topical CBD products tested, as shown in Fig. 2.

The immediate container was clear plastic, which, if removed from the secondary packaging, will provide no protection for the product from light during use. The opaque cream and lotion formulations are less sensitive to light exposure than the tested oil formulation. Light-catalyzed oxidation is likely to occur when topical CBD formulations are exposed to light; therefore, antioxidants and opaque packaging are necessary to ensure product quality and stability during manufacturing and storage.

The gel exhibited considerably lower CBD degradation under light than the other commercial products tested, as shown in Fig. 3. The high viscosity of the gel may limit the rate at which pro-oxidants penetrate the gel to the surface of the CBD entrapped in the dispersed oil droplets, thereby slowing CBD degradation (Wang1 et al. 2022).

The rate and extent of CBD degradation were greater for the extemporaneously prepared formulation, 0.0040 day^{-1} away from light at 22°C and 0.0107 day^{-1} at 22°C exposed to light, when compared to the commercially available topical CBD products with rates between 0.0018 and 0.0030 day^{-1} away from light at 22°C and between 0.0044 and 0.0090 day^{-1} at 22°C exposed to light. The 0.4% w/w ViscOptima® SE o/w emulsion exhibited a loss of 34.8% CBD when stored at 22°C away from light, which is slight greater than the 33.9% degradation of CBD observed for the aqueous cream stored under the same conditions. The degradation rate of CBD of 0.0125 day^{-1} for the 0% w/w Aerosil® R974, 0.4% w/w ViscOptima® SE o/w emulsion was more rapid than the 0.0107 day^{-1} for the aqueous cream, and the rates between 0.0044–0.0090 day^{-1} for the commercial CBD topical products following exposure to light at 22°C. The use of 0.8% w/w Aerosil® R974 did not have an impact on the stability of CBD when compared to the formulation in which 0.4% w/w ViscOptima® SE was used alone to produce the o/w emulsion. The rate of CBD degradation in the Pickering emulsion of 0.0050 day^{-1} was slightly slower than the 0.0054 day^{-1} observed for the 0.8% w/w Aerosil® R974, 0.4% w/w ViscOptima® SE o/w emulsion and the 0.0055 day^{-1} observed for the 0.0% w/w Aerosil® R974, 0.4% w/w ViscOptima® SE o/w emulsion stored away from light at 22°C. The rate of CBD degradation of 0.0118 day^{-1} for the Pickering emulsion was significantly lower than the 0.0127 day^{-1} for the 0.8% w/w Aerosil® R974, 0.4% w/w ViscOptima® SE o/w emulsion at and the 0.0125 day^{-1} for the 0.0% w/w Aerosil® R974, 0.4% w/w ViscOptima® SE o/w emulsion but was more rapid than the 0.0107 day^{-1} for the aqueous cream or the rates between 0.0044 day^{-1} and 0.0090 day^{-1} for the commercially available CBD products when stored under light exposure at 22°C (Supplementary Information Figure S2-4). The Pickering emulsion exhibited a significantly slower rate of degradation of 0.0156 day^{-1} for CBD when products were stored away from light at 37°C, when compared to that observed for the 0.8% w/w Aerosil® R974, 0.4% w/w ViscOptima® SE, and 0.0% w/w Aerosil® R974, 0.4% w/w ViscOptima® SE o/w emulsions of 0.0170 $day^{-1}$and 0.0174 day^{-1}, respectively, when stored at 37°C away from light.

5 Discussion

CBD stability was greater for commercial products than the extemporaneously prepared formulations particularly the gel formulation. Although the formulations of the commercial products are unknown, the listed materials and excipients for the gel formulation contained compounds with known antioxidant activity, in addition to CBD, which may have slowed CBD degradation. In addition, the high viscosity and low spreadability of the gel formulation may have improved the stability of oil droplets containing CBD by the internal structural properties. Increase in temperature without a large decrease in the spreadability of the gel and extemporaneous o/w emulsion formulations, particularly the Pickering emulsion may be due

to higher viscosity, higher droplet surface tension, and greater gel network strength. The solid-particle structure of Pickering emulsion, Aerosil® R974 is not affected by the temperature increase therefore the increased temperature to 35°C did not increase spreadability. Aerosil® R974 has been used previously to form a cold-processed Pickering emulsion (Evonik Industries 2021). The stable o/w Pickering emulsion using Aerosil® R974 developed in this study had a high viscosity and corresponding yield stress, was shear-thinning, exhibited thermally stable spreadability, and exhibited lower CBD degradation rates than the other, extemporaneously prepared cold-processed o/w emulsion formulations. The findings are in agreement with previous reports that o/w Pickering emulsions made using Aerosil® R974 are structurally stable, under thermal stress (Wu et al. 2020). The high viscosity of the Pickering emulsion may increase emulsion stability by decreasing the creaming index. Small oil droplets with Aerosil® R974 surrounding them may increase viscosity due to interfacial layering rather than a physical barrier, particularly for droplet sizes < 100 nm (Ahmadi et al. 2020). The Pickering emulsion ZP was more negative than the other extemporaneous formulations which also may be due to the hydrogen surface of the particles strong electrostatic repulsion.

Alternatively, the excipient, shea butter may have affected the spreadability, viscosity and therefore CBD stability of the commercial CBD lotion and hand cream. Inactive ingredients listed on the commercial CBD products includied medium-chain triglycerides, shea butter, emulsifiers, antioxidants, other natural oils, hydrocolloids, and preservatives. The emollient, shea butter, has a low melting point and a high viscosity at RT, and lower spreadability is expected at temperatures < 25°C and significantly greater spreadability at > 25°C. This is consistent with previous reports in which the viscosity of the emollient significantly affects the spreadability of a topical product (Douguet et al. 2017). The target application area of the topical product may influence viscosity; for example, a low-viscosity oil will cover a larger area of the skin following application, which may lead to runoff or loss of product during and after application. The viscosity of the joint cream and body lotion may be lower than the hand cream because the application is for a larger area of skin. The hand cream was packed in a 50 ml container compared to 100 and 200 ml for the joint cream and body lotion, which may also indicate the need for lower viscosity but higher sales volume per package. The data revealed that the lotion exhibits more rapid degradation, possibly due to the lower initial viscosity than the hand cream, which may indicate an interfacial structure more susceptible to light and heat-catalyzed degradation reactions. The rate of CBD degradation may be influenced by the low viscosity of the MJ Cream. Since the exact composition of the MJ cream formulation is unknown it is not clear what the impact of the composition could have had on the stability of CBD in this product however, the surfactants used included ceteareth-25, cetostearyl alcohol and cetyl alcohol which may affect the droplet size of the dispersed phase of the emulsion and the exposure of surfaces to thermal degradation or light catalysed oxidation (Wang1 et al. 2022). The hand cream greater viscosity than body lotion and MJ cream may have resulted in less CBD degradation however, thermal exposure may result in a lowering of viscosity as the droplets may begin to agglomerate causing the emulsion instability along with the CBD given the greater ZP.

Stable o/w emulsions were developed with widely available, generally recognized as safe (GRAS) excipients such as water, mineral oil, glycerine, and phenoxyethanol. The formulations were developed to use the lowest possible amounts of each excipient, and the products were made using a cold process at RT. The use of ViscOptima® SE facilitated the preparation of a self-emulsifying gel at RT that contained non-ionic long-chain fatty acid ester surfactants, which are known to increase the solubility of CBD and its permeation into the skin (Park et al. 2021; Vanti et al. 2021). The ViscOptima® SE stabilised the o/w emulsion by steric forces that provided a greater ZP, lower viscosity and high spreadability with similar CBD degradation rates of CBD under all storage conditions to the traditionally prepared aqueous cream.

6 Conclusions

The stability of CBD was decreased by temperature and or light exposure. The rheological properties, droplet size and type of excipients used in the formulation may have affected the stability. Furthermore, the degradation of CBD may be affected by the surfactant used, which can alter the particle size and packing density of the dispersed phase, resulting in greater oxidation when products are exposed to thermal stress (Ahmadi et al. 2020; Wang1 et al. 2022; Yang et al. 2017).

The development and optimization of novel extemporaneously prepared o/w emulsions produced a product that mimicked the physical characteristics of the commercially available topical CBD cream, using fewer excipients, whilst manufacturing at room temperature (22°C) was successful. The results revealed differences in the stability of each CBD product due to the composition and type of topical formulation used to deliver CBD. The stability of the Pickering emulsion using Aerosil® R974 was better than that of the others, with a slower rate of CBD degradation observed. Interfacial layering of the droplet may be affected by the presence of Aerosil® R974, and smaller droplet sizes may affect emulsion stabilization. The steric stabilization of the o/w emulsions through inclusion of ViscOptima→ SE, which is a proprietary mixture of sodium polyacrylate, ethylhexyl cocoate, PPG-3 benzyl ether myristate, and polysorbate 20, resulted in a ZP > -20 mV, resulting in the production of a stable emulsion. The least spreadable, high-viscosity gel with antioxidant inclusion in the CBD topical product exhibited the lowest extent of CBD degradation in the in-use study. The inclusion of rosmarinic acid, an antioxidant, did not result in greater stability of CBD when included in a whey protein maltodextrin Pickering emulsion; therefore, the use of antioxidants in the extemporaneously prepared o/w emulsion formulations may not enhance the stability of CBD (Wang et al. 2022). The CBD may be exposed to pro-oxidants at a higher rate with a lower-viscosity formulation than with an increase in surface area. Further studies should examine the relationship between high viscosity and low spreadability in gel or Pickering emulsion CBD formulations, and the oxidation rates of CBD, droplet size, and excipients.

7 Abbreviations

ACN	Acetonitrile
BP	British Pharmacopeia

CBD	Cannabidiol
GC	Gas Chromatography
HPLC	High Performance Liquid Chromatography
IS	Internal standard
ICH	International Council for Harmonisation
MS	Mass Spectrometry
MeOH	Methanol
MJ	Muscle Joint
RT	Room temperature
SAHPRA	South African Health Products Regulatory Authority
ZP	Zeta potential

Declarations

8 Availability of data

Data is provided within the manuscript or supplementary information files.

9 Competing interests

The authors declare no conflicts of interest.

10 Funding

The authors thank the Faculty of Pharmacy at Rhodes University for the funding to support this research.

11 Authors' contribution

AB and RW were responsible for the conceptualization of the project and the design of the methodology. AB was responsible for data collection, data processing, and drafting of the original manuscript. RW was responsible for supervision and the review and editing of the original manuscript.

12 Acknowledgments

The research was supported by Anton Paar Midrand, RSA (Anton Paar Southern Africa (Pty) Ltd) and SA/UK MRC Antimicrobial Drug Discovery Hub (ADD Hub) laboratory.

13 Authors' Information

Alyson Bennett https://orcid.org/0000-0003-3187-3325

Roderick B. Walker https://orcid.org/0000-0003-2781-4154

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Figures

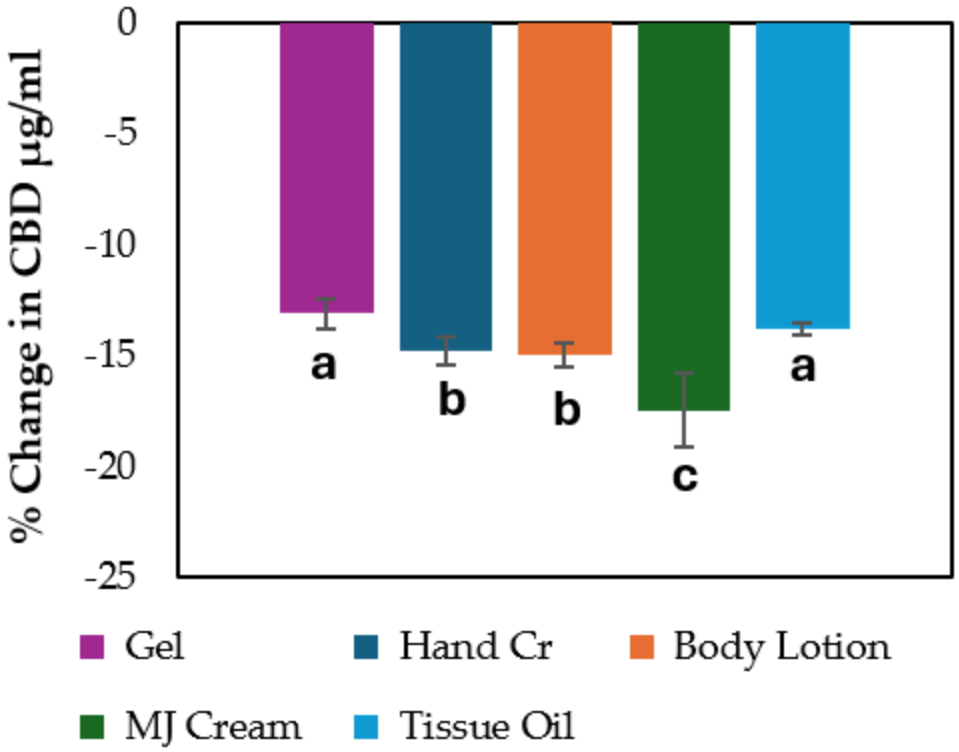

Figure 1

Percent (%) change in CBD concentration (µg/ml ± SD) for commercially available CBD topical products under the storage conditions away from light at room temperature (22°C) for 12 weeks (n =3) different lowercase letters a,b, and c indicate a significant differences ($p < 0.05$) between the different samples.

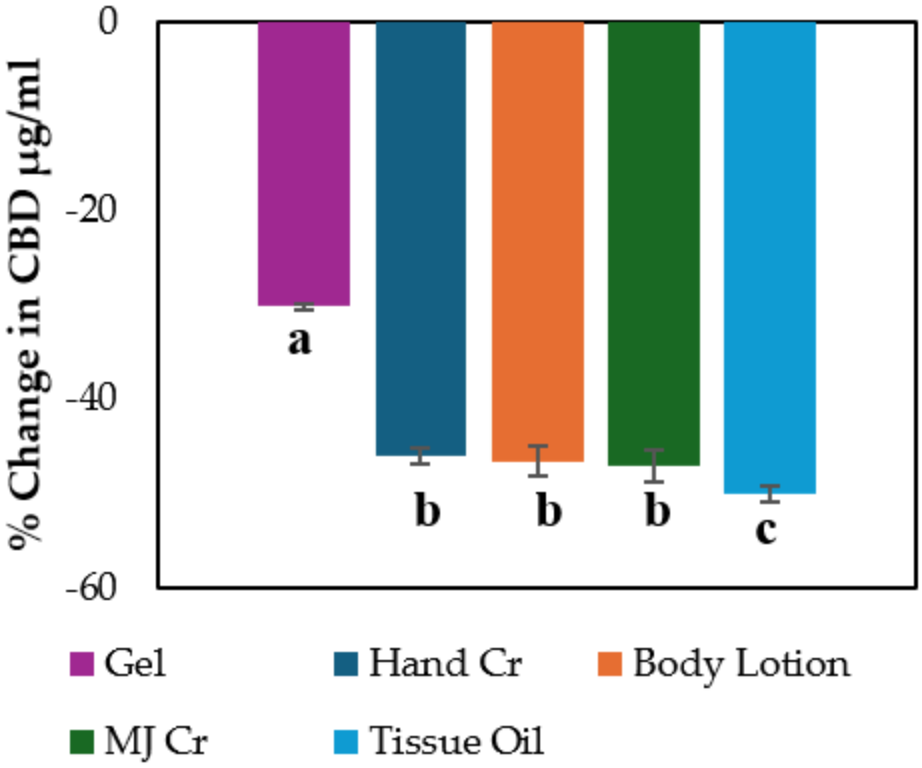

Figure 2

Percent (%) change in CBD concentration (µg/ml ± SD) for commercially available CBD topical products under the storage conditions, light exposure at room temperature (22°C) for 12 weeks (n =3) different lowercase letters a,b, and c indicate a significant differences ($p < 0.05$) between the different samples.

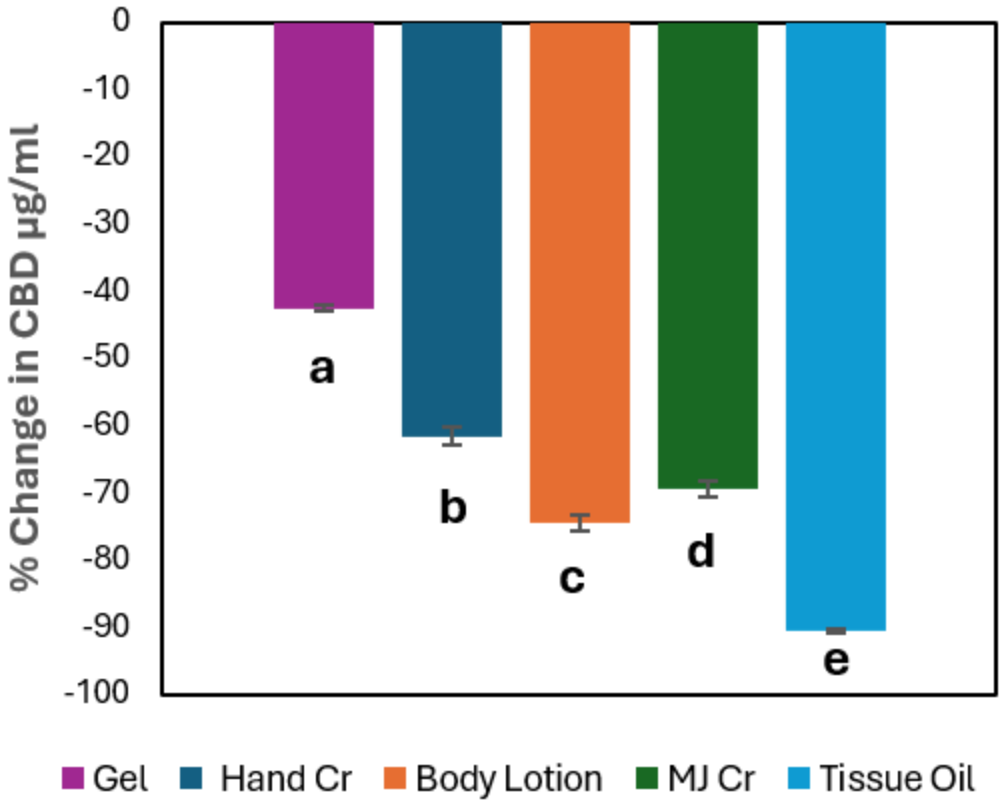

Figure 3

Percent (%) change in CBD concentration (µg/ml ± SD) for commercially available CBD Topical products under the storage conditions away from light at 37°C (dark 37°C) for 12 weeks (n =3) different lowercase letters a,b, c, d and e indicate a significant differences ($p < 0.05$) between the different samples

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