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Formulation of chewable nutraceuticals prepared from banana fruit pulp and hemp seed oil

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ABSTRACT: This study aimed to develop a chewable tablet nutraceutical by combining dried banana powder and cold-pressed hemp seed oil as two major raw materials. Powdered bananas (*Musa* AA group) and hemp seed oil (*Cannabis sativa* L.) were obtained by grinding their respective lyophilized fresh fruit pulps. The chewable nutraceutical formula is composed of 70% w/w banana powder and 5% w/w hemp seed oil. The RP-HPLC analysis revealed that the banana powder contained 1,076.9±147.1 µg of β-carotene per gram. Oil extracted from hemp seeds contained 56.23% w/w linoleic acid (18:2n6) and 15.19% w/w alpha-linolenic acid (18:3n3) (omega 6 to omega 3; 4:1). In addition, the developed HPLC method showed that the oil contained cannabidiol (CBD) at a level of $21.85\pm0.91\times10^{-4}$% w/w, with no traces of tetrahydrocannabinol (THC). The hardness of the nutraceutical was in the range of 45±5 N with the thickness in the range of 4±0.3 mm. It contained 1,080.0±55.2 µg of β-carotene per 1,200 mg tablet. The remaining content of β-carotene after one month of storage at temperatures of 5±3 °C and 32±3 °C with relative humidity of 75±5% was 98.4% w/w and 90.5% w/w, respectively. Tablets must be protected against high heat and moisture to prevent β-carotene oxidation. More study is required to establish the tablet effectiveness in the container under the label parameters such as dry air at room temperature for 1–2 years.

KEYWORDS: nutraceutical, beta-carotene, hemp seed oil, PUFAs

INTRODUCTION

Several fruits are sources of bioactive compounds with health benefits such as antioxidants, which are often referred to as "nutraceuticals". For example, our recent studies have shown that *Musa* AA (Kluai Khai, in Thai) fruit pulp is enriched with β-carotene [1, 2]. Dietary intake of this fruit pulp has demonstrated its ability to prevent skin damage in a repeated UVB-irradiated mouse model. This effect is achieved through the induction of γ-glutamylcysteine synthetase expression and the reduction of oxidation end product production in the irradiated mouse skin [2]. These findings highlight the potential of β-carotene-enriched fruits as nutraceuticals in reducing the risk of diseases associated with oxidative damage. However, due to the lipophilic nature of β-carotene, achieving an effective level of this compound in target organs through oral administration of β-carotene-enriched fruits is limited by low intestinal absorption. Another limitation associated with consuming fresh fruits is the oxidative decomposition of β-carotene during fruit harvesting, storage, and processing. Therefore, one possible approach to overcome these limitations is the formulation of β-carotene-enriched fruits into pharmaceutical dosage forms. This can help minimize decomposition and enhance the bioavailability of β-carotene, thus maximizing its potential health benefits.

To focus on the absorption process of β-carotene, it is necessary to consider the formation of chylomicrons in the intestinal cells. These chylomicrons act as carrier vehicles for β-carotene, facilitating its transport across the intestinal epithelial cells into the systemic circulation via the lymphatic system [3]. This process helps to avoid the first-pass metabolism of β-carotene in the liver, thereby increasing its bioavailability. There has been a study that reports the benefits of using oils such as olive oil and flaxseed oil as carriers for β-carotene [4]. These oils contain polyunsaturated fatty acids (PUFAs), including omega-3 (α-linolenic acid), omega-6 (linoleic acid), and omega-9 (oleic acid), which can stimulate the formation of chylomicrons in the intestine [5]. Therefore, incorporating other types of oils such as hemp seed (*Cannabis sativa* L.) oil that contain these PUFAs into the formulation, which primarily consists of β-carotene from a natural source, should also facilitate chylomicron formation and enhance the absorption of β-carotene. Additionally, hemp seed oil contains natural antioxidants such as tocopherols which can help protect β-carotene against oxidative decomposition [6, 7].

Nowadays, chewable tablet formulation has gained popularity as a preferred nutraceutical form for children and elderly consumers who may have difficulty swallowing conventional hard tablets. The process of chewing the tablet can reduce the dissolution time of the active ingredients in the gastrointestinal tract, leading to an increased absorption rate [8]. This makes chewable tablets an advantageous option for enhancing the bioavailability and effectiveness of the active compounds in the body. Additionally, by employing tablet production methods that minimize exposure to oxidative stressors such as high temperature, humidity, oxygen, and light, the degradation of natural actives like β- carotene can be prevented.

Therefore, this study focused on formulating chewable tablets using the β-carotene-enriched fruits of banana as a bioactive ingredient for nutraceutical application. The fresh fruit pulps of bananas were freeze-dried and ground into a powder prior to the tablet manufacturing process. Alongside the pharmaceutical excipients employed to facilitate tablet formation, hemp seed oil was incorporated into the formulation in varying amounts to enhance the bioavailability of β-carotene. The resultant tablets were assessed for their appearance and physical properties. Furthermore, the physical and chemical stability of the formulated tablets were evaluated under low and ambient temperature conditions.

MATERIALS AND METHODS

Materials

Fresh fruit pulps of bananas (*Musa* AA group (var.), Khai (Kamphaeng Phet) in Thai), were purchased from natural banana farming in Lower Northern Thailand from November to December 2021. *Cannabis sativa* L. (hemp) (RPF3 var.) seeds were obtained from Highland Research and Development Institute (a public organization) in Chiang Mai, Thailand. The β-carotene standard was bought from Sigma-Aldrich, Missouri, USA. The standard delta-9-tetrahydrocannabinol (Δ9-THC) and delta-8-tetrahydrocannabinol (Δ8-THC) were ordered from Lipomed, Arlesheim, Switzerland, and Cayman Chemical, Michigan, USA, respectively. The standard tetrahydrocannabinolic acid (THCA) and CBD were ordered from Cayman Chemical, Michigan, USA. Butylated hydroxy toluene (BHT), tetrahydrofuran (THF), and methanol (MeOH) were analytical grade, and ethyl acetate (EtOAc) and acetonitrile (ACN) were HPLC grade and purchased from RCI Labscan Limited, Bangkok, Thailand. Ammonium formate and formic acid were purchased from Sigma-Aldrich. All excipients used in the tablet formulations were pharmaceutical grade.

Preparation of the banana fruit pulp powder (K powder)

The preparation process of the banana fruit pulp powder was modified from our previous study [1]. Briefly, the banana fruit pulps at ripening stages 2 to 3 regarding their peel color and 25% Brix were peeled off and cut into small pieces before lyophilization by using a freeze dryer (Telstar, Terrasna, Spain). The freeze-dried pulps were ground into a fine powder, namely K powder, and kept in a well-closed and light-protected container at −20 °C. The schematic of K powder preparation is shown in Fig. 1.

Determination of β-carotene content of the K powder

For the determination of β-carotene content in the K powder, a solvent extraction process was first conducted to extract β-carotene from the powder, according to our previous study [1]. Briefly, a 50-mg portion of the K powder was mixed with 500 ml of 0.25% BHT in a THF:MeOH (1:1, v/v) by using a vortex mixer for 30 s. The obtained suspension was centrifuged at 14,000 rpm for 15 min, and the supernatant was collected for β-carotene analysis by using reverse phase-high performance liquid chromatography (RP-HPLC). The HPLC instrument consisted of a UV/VIS detector and an LC-20AP pump (Shimadzu Co., Ltd., Kyoto, Japan). The C18 column (Hyper Clone, Phenomenex, California, USA) with 5 μm and 250 × 4.6 mm was a stationary phase. The separation was performed at room temperature, utilizing a mobile phase composed of a 10% mixture of EtOAc and MeOH (1:1, v/v) in ACN. The flow rate of the mobile phase was set at 1 ml/min. The quantification of β-carotene was based on the peak area at 450 nm using a calibration curve of the standard β-carotene. The assay was performed in triplicate. According to our previous study [1], the HPLC technique was validated by determining the selection of analytical parameters, including linearity range, limit of detection, limit of quantification, intra-day precision, inter-day precision, and accuracy.

Preparation of the dehulled hemp seed oil

The hemp seeds were washed with 95% ethanol and dried at 40 to 45 °C for 6 h. Their shells were then removed by using a dehuller machine (GG-5 Hemp Seed Dehuller, Gelgoog, Henan, China) and shell sorting (Gladiator color sorting solution G-1, Belt and Bearings Co., Ltd., Bangkok, Thailand). The hemp seed oil was obtained from cold-pressing dehulled seeds (hemp seed kernel). The cold-pressed seed oil was kept in a well-closed and light-protected container at 4 to 8 °C. The schematic of hemp seed oil preparation is shown in Fig. 1.

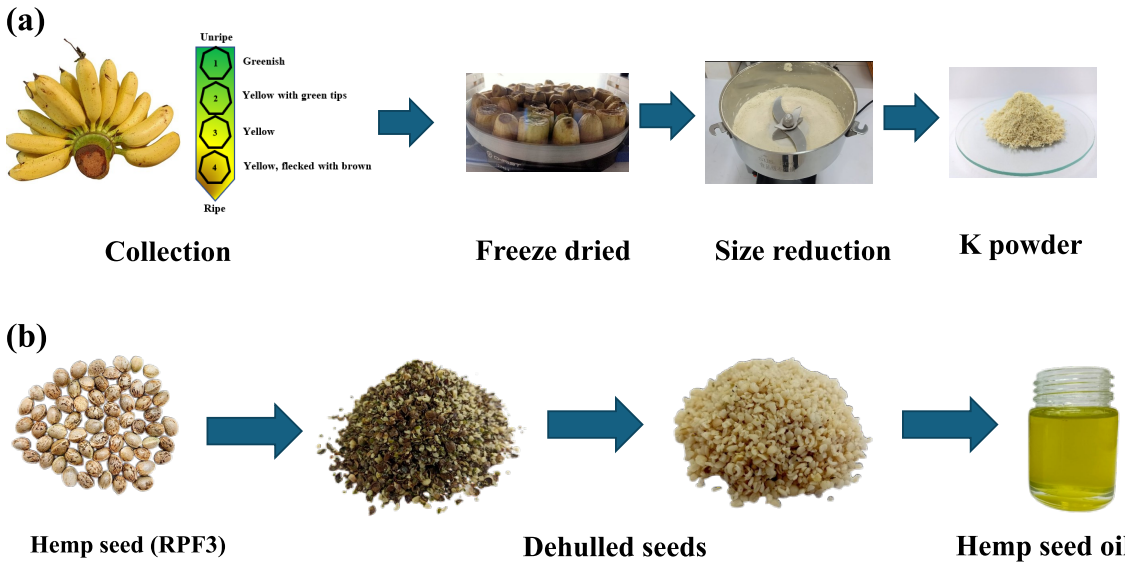

Fig. 1 (a) Preparation process of banana powder, namely K powder, from the banana fruit pulps at ripening stages 2 to 3. The selected fruit pulps were freeze dried and then ground into powder form. (b) Preparation process of hemp seed oil. The hemp seeds were dehulled, and the dehulled seeds were cold pressed to obtain the oil.

Determination of omega-3, -6, and -9 contents and characteristics of the dehulled hemp seed oil

The amount of omega-3 (alpha-linolenic acid, ALA), omega-6 (linoleic acid, LA and gamma-linolenic acid, GLA) and omega-9 (oleic acid) in the dehulled hemp seed oil was analyzed using the method of AOAC (2019) 996.06. The chemical characteristics, including acid value, iodine value, saponification value, moisture and volatile matter, and insoluble impurities of the oil, were evaluated using the methods modified from AOCS (2003) Cd 3a-63, AOCS (2017) Cd 1b-87, AOAC (2000) 920.160, AOCS (2017) Ca 2d-25, and AOCS (2017) Ca 3a-46, respectively.

Determination of CBD and THC contents of the dehulled hemp seed oil

To analyze the THC, THCA, and CBD content, the oil was first extracted by using MeOH. Briefly, 500 mg of oil was mixed with 25 ml of MeOH by using a vortex mixer for 10 s and then a sonicator for 15 min. The CBD, Δ9-THC, and Δ8-THC in the methanolic extract were determined by using HPLC. The HPLC system consisted of a photodiode array detector (G7115A 1260 DAD WR detector, Agilent Technologies, California, USA) and a quaternary pump (G711A 1260 Quat pump VL, Agilent Technologies). Agilent Infinity Lab Poroshell 120 EC-C18, 150 mm × 4.6 mm, 2.7 µm was the stationary phase. The mobile phase was a gradient run of mobile phase A: 20 mM ammonium formate (pH 3.6) and mobile phase B: 0.1% formic acid in ACN at a flow rate of 1 ml/min. The signal of CBD and THC was monitored at 220 nm using a photodiode array detector. The quantification of CBD, THC, and THCA was based on comparing the standard curves of CBD, Δ9-THC, and Δ8-THC. The HPLC technique was validated, according to the previous study [9]. The study was performed in triplicate.

Table 1 The chewable tablet formulations (1,200 mg/tablet) composed of K powder, dehulled hemp seed oil, and other excipients for a direct compression tableting process.

Ingredient	F1 (%w/w)	F2 (%w/w)	F3 (%w/w)
Starch Diluent	21.3	16.3	11.3
Lubricant	3.0	3.0	3.0
Preservative	0.3	0.3	0.3
Antioxidant	0.1	0.1	0.1
Absorbent	0.3	0.3	0.3
K powder	70.0	70.0	70.0
Dehulled hemp seed oil	5.0	10.0	15.0

Formulation of the chewable tablet containing the K powder and the dehulled hemp seed oil

According to our previous study, 1,200 mg of the chewable tablet formula consisted of 70% w/w of the K powder [10]. The amount of the dehulled hemp seed oil was varied in the range of 5–15% w/w (F1, F2, and F3) (Table 1). The other excipients such as absorbent, diluent, binder, and lubricant were used to facilitate compression tableting and improve the physical characteristics of the tablets. All components were blended under controlled conditions, avoiding exposure to elevated temperature and humidity. Subsequently, the resultant mixture was compressed to form the tablet.

Determination of physicochemical properties of the chewable tablets

The appearances, including color, integrity, and oily surface, of the formulated tablets were observed by visualization. The physical characteristics, including hardness, thickness, friability, weight variation, and diametrical breaking force of the chewable tablets, were measured by the following instruments: hardness by using a Stoke-Monsanto hardness tester (Stokes Tablet Hardness Tester Model 539, CCS, Pennsylvania, USA); thickness by using a Teclock micrometer caliper (SM112, Teclock, Nagano, Japan); and breaking force values by using a texture analyzer (Model TA-XT plus, Stable Micro Systems, Godalming, UK). Moreover, the weight variation of the chewable tablet was determined according to the United States Pharmacopeia (USP) guidelines. For chemical characteristics, β-carotene in the selected formulation was measured using RP-HPLC.

Stability test

The tablets produced from the selected formulation were kept in a light-protected container and stored at room temperature (32±3 °C and 75±5% RH) or in a refrigerator (5±3 °C) for 1 month to observe physical and chemical stability. The storage condition was modified from the Asian guideline on stability study and shelf-life of health supplements (version 1.0, 2013).

RESULTS AND DISCUSSION

Characteristics of the K powder and its β-carotene content

The K powder prepared from the lyophilized fresh fruit pulps followed by grinding was a fine-sized powder with a light-yellow color (Fig. 1). Thirty grams of the dried powder were from 100 g of fresh fruit pulps. Drying under a high vacuum and low temperature would prevent the heat-accelerated degradation of β-carotene contained in the fruit pulps.

Generally, banana fruit is not a main source of β-carotene. However, according to our previous studies, we found that some varieties of banana, including *Musa* AA (Khai), contain a significant level of β-carotene, and oral administration of *Musa* AA at a proper dose provided a photoprotective effect in a UVB-irradiated mouse model [1, 2]. For this reason, in the present study, β-carotene was selected as a major marker representing the quality of the K powder and the selected tablet formulation. From the chromatograms obtained from RP-HPLC (Fig. 2), the content of β-carotene in the K powder was 1,076.9±147.1 µg/g of powder. The ripening stage of fruits such as strawberry was reported to affect the amount of antioxidant bioactive compounds [11]. According to our previous study, the amount of β-carotene in Khai fruit pulps at ripening stages 2 to 3 was quite large but lower than that at the higher ripening stage. Moreover, the total soluble solids (TSS, degrees Brix) value was directly proportional to the ripening stage of the fruit pulps [1]. As TSS represents the amount of sugar and soluble minerals in fruits or vegetables, the K powder from the fruit pulp with a lower TSS value would provide a lesser hygroscopic property, thus minimizing the sticking phenomenon during the tableting process. For this reason, the Khai fruit pulps at ripening stages 2 to 3 were selected as a source for K powder production in this study.

Table 2 The fatty acid profile (omega-3, -6, and -9) of the dehulled hemp seed oil.

Fatty acids	g/100 g of oil
1. Omega-3	
1.1 Alpha-linolenic acid (ALA) (18:3n3)	15.19
2. Omega-6	
2.1 Linoleic acid (LA) (18:2n6)	55.29
2.2 Gamma-linolenic acid (GLA) (18:3n6)	0.83
Omega-6:Omega-3	3–4:1
3. Omega-9	
3.1 Oleic acid (18:1n9)	15.67

Characteristics of the dehulled hemp seed oil and its omega-6, omega-3, CBD, and THC contents

The oil obtained from cold pressing (mechanical extraction process) hemp seeds, in which their shells and chlorophyll skins were removed (namely dehulled hemp seeds), was a yellow-golden liquid (Fig. 1). The yield of extracted oil was between 20–25% w/w of the whole hemp seeds. The chemical characteristics of the oil were as follows: acid value (0.11 mg KOH/g), iodine value (153.11% iodine absorbed), saponification value (201.97 mg KOH/g), moisture and volatile matter (0.057%), and insoluble impurities (0.05%), which correspond to announcement of the Ministry of Public Health on the properties of the hemp seed oil.

According to the AOAC (2019) 996.06 method, the amount of omega-3 (ALA), omega-6 (LA and GLA), and omega-9 (oleic acid) in the dehulled hemp seed oil is shown in Table 2. We found that the oil contained a high concentration of PUFA, 70% w/w approximately. Monounsaturated fatty acids such as oleic acid (18:1n9) were found about 16% w/w. A previous study reported 9% of oleic acid and 82% of PUFA found in the cold-pressed oil from hemp seed that was cultivated in Finland [7, 12]. The difference in percentage composition of fatty acids would be due to the difference in hemp variety and cultivation area.

Hemp seed oil is a good source of nutraceutical because the present of omega-3 and the proper ratio of omega-6 to omega-3 (2–3:1) [7, 12]. Interestingly, we found that the composition ratio between omega-6

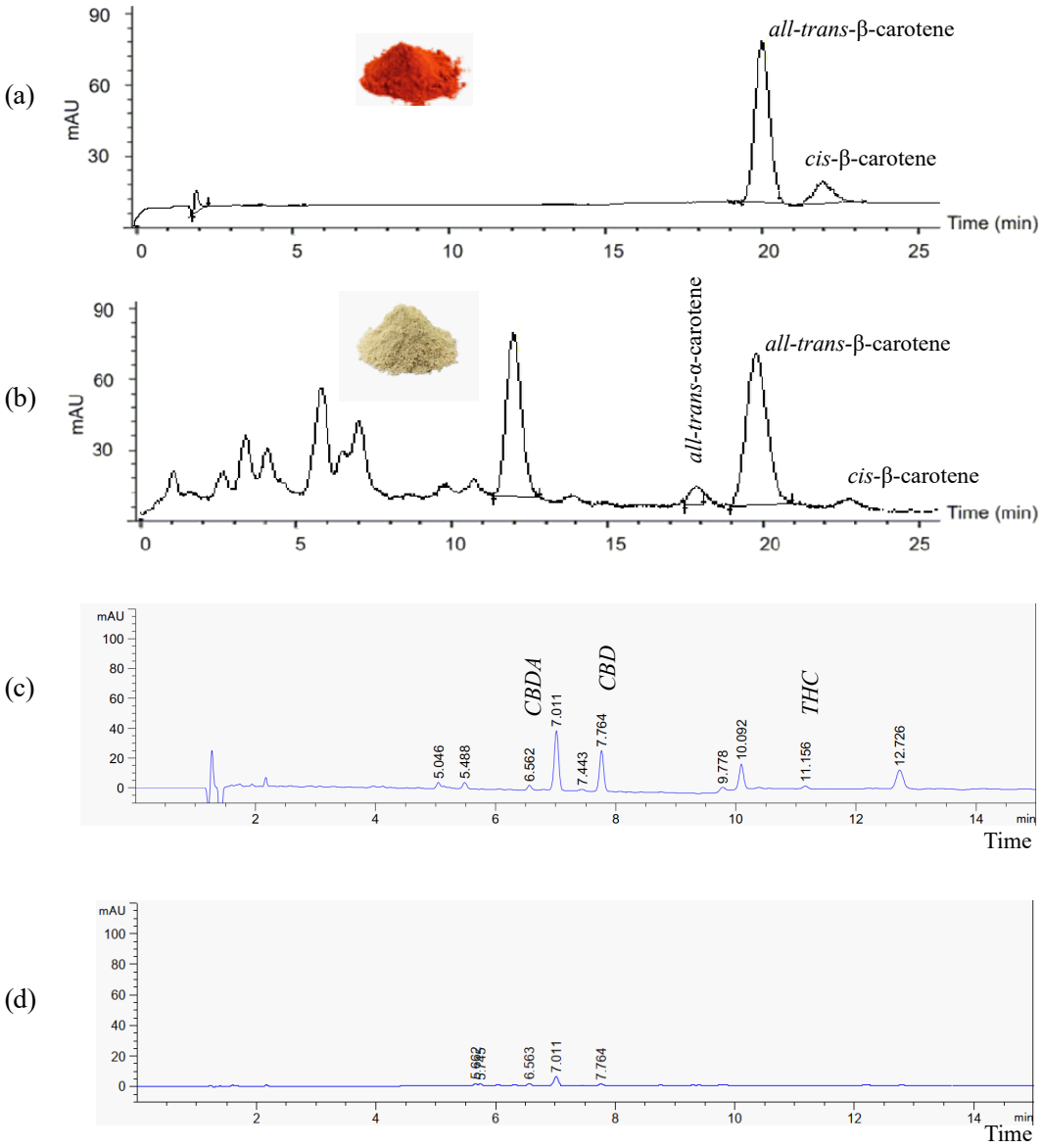

Fig. 2 HPLC chromatograms of β-carotene in (a) standard and (b) banana fruit pulp powder (K powder) and chromatograms of CBD and THC in (c) standard and (d) hemp seed oil.

and omega-3 in the oil from kernel of RPF3 hemp seeds was about 3–4:1. Generally, fatty acids, particularly LA is an essential component for structure and barrier function of skin. However, high consumption of LA or omega-6:omega-3 ratio ($\geqslant 10:1$) increase the risk for several diseases including cardiovascular diseases [13]. In contrast, a proper ratio of omega-6 to omega-3 in the oil would provide an appropriate inflammatory response and anti-inflammatory action [14]. For this reason, the oil from the dehulled hemp seed was a good source of ingredients in nutraceuticals. Moreover, as the oil contained a moderate amount of omega-3, it may help enhance the absorption of β-carotene by facilitating the formation of lipoprotein particles, which serve as carriers for β-carotene in the intestines [15].

According to HPLC analysis (Fig. 2), the Δ8-THC and THCA were not detected while the amount of Δ9-THC was lower than the limit of quantification (LOQ, 8.33×10^{-4}% w/w). The CBD in an amount of $21.85\pm0.91\times10^{-4}$% w/w was found in the oil. It seems that the resultant total THC and CBD contents were lower than those in the previous reports [16]. Generally, most cultivated hemp seed varieties have been found to have a low level of CBD and THC. The washing seeds with ethanol [17] together with removing outer shell and chlorophyll skin may lead to

Table 3 Appearances of the formulated chewable tablets.

Formulation (%w/w of oil)	Appearance	Color	Integrity	Oily surface
F1 (5)		Yellow	+++	–
F2 (10)		Yellow	++	+
F3 (15)		Yellowish brown	+	+++

The symbols (+) and (−) represent appearance and no appearance, respectively. The number of the symbol (+) indicates the degree of the appearance (+++ is maximum).

Table 4 Physicochemical properties of the formulated chewable tablets ($n = 10$). * $p < 0.05$ and ** $p < 0.01$ when compared with the F1 formula (Student's t-test).

Formula (%w/w of oil)	Hardness (N)	Thickness (mm)	Weight (mg)	Friability (%)	Breaking force (N)	Moisture content (%)	Water activity (aw)
F1 (5)	46.45±2.23	4.37±0.071	1,200.7±1.02	0.65±0.13	29.79±7.24	0.097±0.03	0.57±0.22
F2 (10)	43.92±1.32*	4.36±0.084	1,200.8±1.23	0.56±0.09	19.25±3.20*		
F3 (15)	42.75±1.45*	4.35±0.074	1,200.8±0.75	0.51±0.06	9.91±3.12**		

lower content of CBD and THC in the oil obtained from kernel seeds, as compared to that from whole seeds.

Physicochemical properties and stability of the chewable tablets

In the present study, the amount of K powder in the formulation was selected based on the quantity of K powder (70% w/w, 840 mg/1,200 mg tablet) that could provide an appropriate content of β-carotene (0.8–1.0 mg/1,200 mg tablet) for nutraceutical benefits. The content of hemp seed oil varied in the range of 5–15% w/w. The appearances of the formulated tablets (F1, F2, and F3), including color, integrity, and oily surface, were summarized in Table 3 regarding the variation of hemp seed oil content. Furthermore, the physical properties, including hardness, thickness, friability, weight variation, diametrical breaking force, moisture content, and water activity, are presented in Table 4 and Fig. 3. The tablets from 3 formulas (F1 to F3) exhibited a consistent thickness of around 4 mm. Their weight variation and friability values were below 10% and 1%, respectively, aligning with the specifications in the USP for a 1,200 mg tablet. However, we found that as the amount of hemp seed oil was increased (from 5 to 15% w/w) and the amount of starch diluent was decreased (from 21.3 to 11.3% w/w), the hardness and breaking force of the tablets significantly decreased (hardness: from 46.45±2.23 N to 42.75±1.45 N; breaking force: from 29.79±7.24 N to 9.91±3.12 N). The investigation revealed a water activity value of 0.57±0.22. This value suggests minimal likelihood of microbial development, considering that the majority of microorganisms thrive within a water activity range of 1.0 to 0.75 [18]. Furthermore, the moisture content is reported as 0.097±0.03. These products are compliant with the regulations established by the USP. This suggests that the tablets became softer and more brittle. Moreover, the presence of oil droplets deposited on the tablet surface was observed in F2 and F3, which contained an amount of hemp seed oil exceeding 5%. Due to the potential impact of oil deposition on the tablet surface and its effect on the remaining oil in the product, the 1,200 mg of F1 tablets containing 70% w/w K powder (0.8–1.0 mg β-carotene) and 5% w/w hemp seed oil (40–45 mg PUFA and 1.3–1.4×10^{-3} mg CBD) were chosen as the optimal formulation for further stability studies. Additionally, in accordance with the guidance provided by the US FDA, which recommends an upper limit of 12 kilo ponds (kp) or 118 Newtons (N) for the hardness of chewable tablets [19], the tablets from the F1 formula with a hardness value of approximately 50 N would be able to withstand the manufacturing processes and could be easily chewed.

The stability results of the F1 formula tablets stored at a temperature of 5±3 °C or 32±3 °C (room temperature) with a relative humidity of 75±5% for 1 month are shown in Table 5. As K banana was the major excipient in the formula, β-carotene was used as the chemical marker for monitoring the stability of the tablets. The physical appearances of the chewable tablets, including color, smell, and shape, did not change significantly after stability testing compared to those before the testing. However, when considering chemical stability, the β-carotene content in the tablets stored at a cold temperature (5±3 °C) for 1 month re-

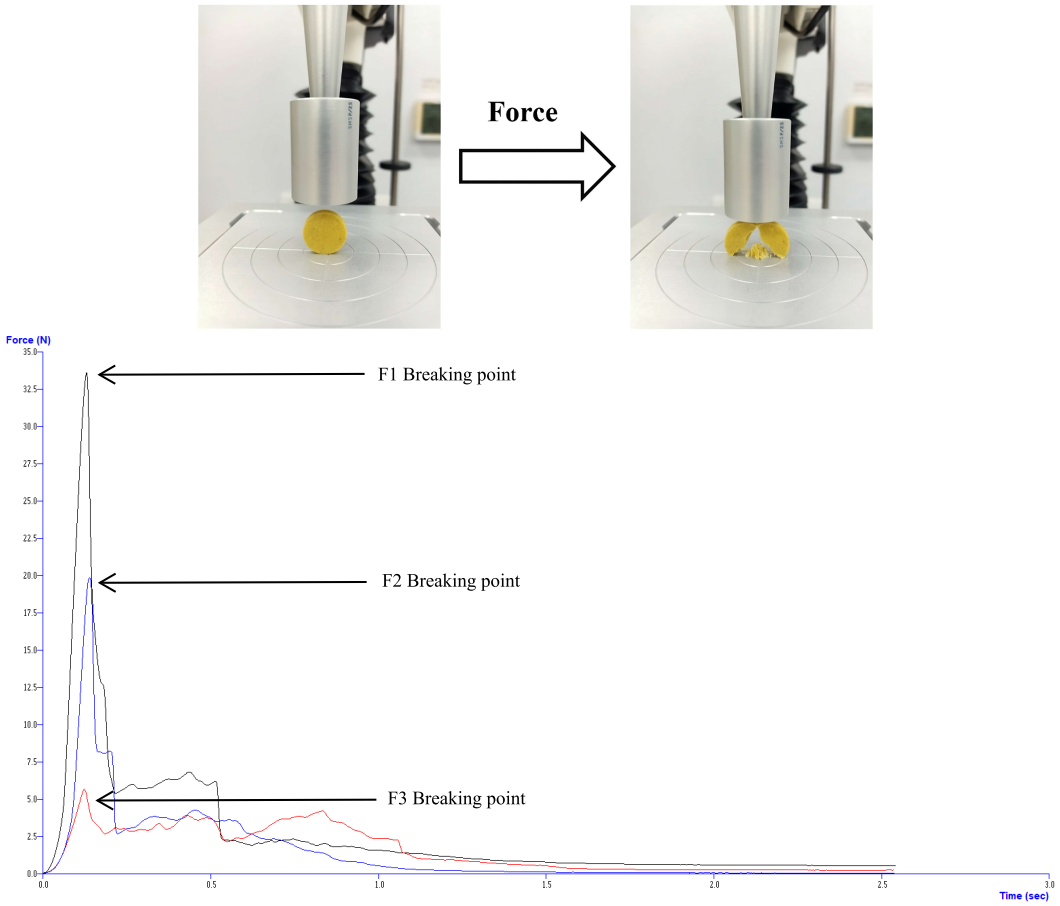

Fig. 3 Breaking force test and force-deformation curve of the formulated chewable tablets.

Table 5 Physical appearance and content of β-carotene before and after stability testing for 1 month. $^{*}p < 0.05$ when compared with the β-carotene content before the stability test (Student's *t*-test).

	Appearance	β-carotene content (µg/tablet)	% w/w	*p**
Before test		1,080.0±55.2	100	
After test for 1 month				
at 5±3 °C		1,063.0±36.6	98.4	0.6796
at 32±3 °C, 75±5% RH		977.3±19.3	90.5	0.0383

mained at around 98% w/w of the initial state. Under storage conditions with higher temperature (32±3 °C) and humidity (75±5% RH), the remaining β-carotene content was 90.5% w/w. The obtained results suggest that the formulated tablets should be adequately protected from high temperatures and moisture, as these conditions can accelerate the decomposition of β-carotene through oxidative activity. Additionally, to

prevent the oxidative activity of β-carotene and PUFA in the tablets during storage and prior to consumer consumption, it is necessary to employ a nitrogen flush during the packaging process to remove oxygen [20]. For further study, the determination of the shelf-life of the tablets stored in the designed packaging (light and moisture protection with nitrogen flush) under label conditions such as a dry place at ambient temperature for 1–2 years should be conducted. This study will help monitor the remaining β-carotene content over an extended period and provide valuable information on the long-term stability of the tablets.

CONCLUSION

Our chewable nutraceutical tablet formulation combines 70% w/w banana powder, fortified with β-carotene, and 5–15% w/w hemp seed oil enriched with omega-6 and omega-3 fatty acids. This synergistic blend offers a delightful and nutritious supplement in a convenient chewable form. The physical properties of the chewable nutraceuticals were oil content dependent. When the amount of starch diluent was decreased while the amount of hemp seed oil was increased, the tablet hardness and breaking force decreased significantly. β-carotene is susceptible to oxidative degradation at high temperatures and high humidity; therefore, it is essential to store the tablets in a dry and cool environment.

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