Research Article

Fabrication and Optimization of Directly Compressible Self-Emulsifying Tablets Containing Cannabis Extract Obtained from Supercritical Carbon Dioxide Extraction

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Abstract
Δ^9-Tetrahydrocannabinol and cannabidiol, which are present in cannabis extract, exhibit low bioavailability when administered orally due to significant first-pass metabolism. The use of a self-emulsifying drug delivery system (SEDDS) can enhance their dissolution and bioavailability. However, liquid SEDDS formulations are prone to inadequate stability. To address this issue, the development of a solid SEDDS formulation was explored. This study aimed to optimize directly compressible self-emulsifying tablets containing cannabis extract obtained from supercritical carbon dioxide extraction. Initially, a liquid SEDDS of cannabis extract was solidified by adsorption onto solid carriers (colloidal silicon dioxide and microcrystalline cellulose). The resulting solid mixture was then combined with other pharmaceutical excipients and compressed into tablets. Three factors were optimized using the Box-Behnken design: compressional force (1,000–2,000 psi), quantity of hydroxypropyl methylcellulose (0–6%), and quantity of croscarmellose sodium (0–6%). The results revealed that a mass

ratio of colloidal silicon dioxide, microcrystalline cellulose, and liquid SEDDS of cannabis extract at 0.65:2:1 successfully solidified the mixture. The optimal tablet formulation was achieved with a compressional force of 2,000 psi, without the addition of hydroxypropyl methylcellulose or croscarmellose sodium. Verification data indicated that the predictions made by the computer software were accurate and reliable. The developed tablets exhibited improved dissolution of the cannabis extract, with Δ^9-tetrahydrocannabinol demonstrating higher dissolution compared to cannabidiol. Additionally, the compressed tablets were capable of emulsifying small nano-sized droplets (approximately 200 nm). However, the droplets exhibited a larger size and broader polydispersity index compared to the liquid SEDDS. In conclusion, the study successfully developed directly compressible self-emulsifying tablets that enhanced the dissolution of cannabis extract.

Keywords: Box-Behnken design, Compressional force, Croscarmellose sodium, Hydroxypropyl Methylcellulose, Response surface methodology, Solidification

1 Introduction

Supercritical fluid extraction (SFE) is an advanced, environmentally friendly, and sustainable technique used for extracting active components from plant materials. This process utilizes supercritical fluids as the extraction solvent [1]. A supercritical fluid is a gas that has been subjected to pressure and temperature above its critical points, resulting in a state that exhibits properties of both liquids and gases. These supercritical fluids possess a density similar to that of a liquid, a viscosity similar to that of a gas, and a diffusion coefficient that falls between those of liquids and gases. SFE offers significant advantages, especially in terms of its efficient diffusion through the plant matrix and its ability to penetrate deeper compared to other extraction methods [2]. Supercritical carbon dioxide ($scCO_2$) is a commonly used supercritical fluid for SFE. This selection is primarily due to the fact that CO_2 is approved as a food-grade solvent. Moreover, it possesses desirable qualities such as being inert, non-toxic, non-corrosive, non-flammable, affordable, easily accessible, and leaving no solvent residue, making it suitable for medicinal purposes [1], [3], [4]. However, the main drawback of SFE is its high cost, which makes it economically viable primarily for value-added products [5], [6]. SFE finds applications in various fields, including engineering [7], food sciences [8], pharmaceuticals [9], etc. An illustrative example is the extraction of active components from cannabis plants, such as marijuana and hemp, where SFE has undergone extensive research and application [9]–[14].

Cannabis belongs to the Cannabaceae family and contains several bioactive compounds. Among these compounds, cannabinoids are the most significant. The primary cannabinoids found in fresh cannabis plants are Δ^9-tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA). These acid forms can be decarboxylated to neutral forms: Δ^9-tetrahydrocannabinol (THC), which psychoactive compound, and cannabidiol (CBD), which is mostly a non-psychoactive compound; when the fresh plant is dried or exposed to temperatures above 90 °C [15]. However, other cannabinoids are also reported such as tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), cannabigerol (CBG), cannabigerovarin (CBGV), cannabinol (CBN), cannabinolic acid (CBNA), cannabichromene (CBC), cannabichromevarin (CBCV), etc. [16]. THC acts as a partial agonist at CB_1 and CB_2 receptors and has broad pharmacological implications. It is used as an analgesic, antiemetic, and anticonvulsant. CBD, on the other hand, is a partial agonist of the CB_2 receptor and exhibits low affinity for the CB_1 receptor. CBD acts as a CB_1 antagonist and may have benefits as an anxiolytic, for improving cognitive and movement disorders, as an anti-nociceptive, and as an anti-epileptic agent [16]. Recently, cannabis-derived products have been introduced in the market. For example, nabiximols, marketed as Sativex®, is an oral spray containing a mixture of THC and CBD used for treating spasticity and neuropathic pain in multiple sclerosis patients. Epidiolex®, a CBD oral solution, is used for the treatment of Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis [17].

A significant drawback of cannabis extracts, as well as cannabinoids, when administered orally, is their low bioavailability due to their poor water solubility characteristics [18], [19]. Previously, a successful development was achieved with the implementation of a self-emulsifying drug delivery system (SEDDS) to

enhance the solubility of cannabis extract and cannabinoids. SEDDS encompasses lipid-based formulations that consist of uniform mixtures of oils, surfactants, and occasionally cosolvents. When these formulations are gently stirred and diluted with the water phase in the gastrointestinal tract, they have the ability to form microemulsions or fine oil-in-water emulsions. This technique holds significant potential for improving the absorption of hydrophobic substances that exhibit limited dissolution rates [20]. A specific SEDDS formulation, consisting of surfactants (in a mass ratio of 2:1 Tween® 80:Span® 80), coconut oil, and cannabis extract, with a mass ratio of 45:40:20, successfully demonstrated significant improvements in the dissolution of the cannabis extract [9].

THC and CBD exhibit low bioavailability when administered orally due to significant first-pass metabolism [18], [21], [22]. SEDDS typically have a log P value exceeding 5. Once they reach the enterocyte, they can form chylomicron-drug associates, which have notable access to the intestinal lymphatic system. This enables them to bypass the first-pass metabolism by the liver, ultimately leading to enhanced drug bioavailability [23]. Moreover, it is widely recognized that P-glycoprotein plays a crucial role in reducing the oral bioavailability of numerous medications. This protein contributes to the excretion of drugs from hepatocytes and renal tubules, thereby diminishing absorption and oral bioavailability [24]. Tween® 80, a commonly employed surfactant in SEDDS formulations, has been reported as a P-glycoprotein inhibitor [25]–[27]. It functions by permeabilizing the lipid bilayer of the plasma membrane, where it inserts itself among the lipid tails. Additionally, Tween® 80 can disrupt hydrogen and ionic bonds with the polar head of the plasma membrane through interactions, potentially contributing to the inhibition of P-glycoprotein activity [28], [29].

Traditional SEDDSs are ordinarily in liquid forms called liquid SEDDS, and can improve pharmacokinetic and pharmacodynamic parameters [30], but are vulnerable to inadequate stability [23], [31]. Therefore, this work aimed to solidify the liquid SEDDS that developed in the previous work [9]. The solid SEDDS can improve pharmacokinetic and pharmacodynamic parameters, improve stability, and increase industrial feasibility [30]. This work solidified liquid SEDDS using a simple method of adsorption to solid carriers like colloidal silicon dioxide and microcrystalline cellulose. It was further prepared as directly compressible tablets based on the Design of Experiments approach using the Box-Behnken design. Furthermore, the dissolution enhancement of cannabis extract from the developed directly compressible tablets was also proved.

2 Materials and Methods

2.1 *Materials*

Tween® 80 and Span® 80 were purchased from P. C. Drug Center Co., Ltd., Bangkok, Thailand. Coconut oil was obtained from Thai Pure Coconut Co., Ltd., Samut Sakhon, Thailand. Colloidal silicon dioxide (CSD) (Aerosil® 200) was purchased from P.C. Drug Center, Bangkok, Thailand. Microcrystalline cellulose (MCC) (Comprecel® M102) was purchased from Maxway Co., Ltd., Bangkok, Thailand. Magnesium stearate was gifted from Sun Herb Thai Chinese Manufacturing, Pathum Thani, Thailand. Hydroxypropyl methylcellulose (HPMC) (Methocel® F4M) was purchased from Union Chemical 1986 Co., Ltd., Bangkok, Thailand. Croscarmellose sodium (CCS) was gifted from Onimax Co., Ltd., Bangkok, Thailand. Cannabis was obtained from the Narcotics Suppression Bureau with the permission of the Office of the Narcotics Control Board, Thailand.

2.2 *Extraction of cannabis using the $scCO_2$ extraction technique*

The extraction procedure followed the optimal condition reported in the previous work [9]. Dried cannabis inflorescences were ground into a coarse powder using a grinder. The resulting powder was then sieved using a 40-mesh sieve. Cannabis powder with a particle size larger than 40-mesh (600 g) was introduced into a 5 L extraction container and processed using the SFE instrument (LAB 5 L, Extratex-SFI, Neuves-Maisons, France). The compressed CO_2 gas (purity ≥ 99%, Air Liquide (Thailand) Ltd., Bangkok, Thailand) was employed as the solvent. The operational parameters were set as follows: the pressure was maintained at 18 MPa, and the temperatures of the extraction vessel, separators I, II, and III were set at 40 °C, 65 °C, 45 °C, and left uncontrolled, respectively. After a duration of

1 h, the cannabis extract was obtained. Subsequently, the extract was dissolved in ethanol, subjected to ultrasonic treatment for 1 h, winterized through freezing for 2 h, vacuum filtered, and finally evaporated using a rotary evaporator (Buchi Labortechnik AG, Flawil, Switzerland).

2.3 *Preparation and solidification of liquid SEDDS of cannabis extract*

The liquid SEDDS of cannabis extract was prepared based on the optimal formulation of the previous work [9]. The surfactant mixture (2:1 (w/w) Tween® 80:Span® 80), coconut oil, and winterized cannabis extract in a mass ratio of 45:40:20 were mixed at ambient temperature using a Vortex-Genie® 2 mixer (Scientific Industries, Inc., New York, USA) until homogenous liquid SEDDS was formed. Then, the liquid SEDDS was solidified by adsorption to solid carriers like CSD and MCC in various ratios, i.e., MCC:liquid SEDDS (1:1 and 2:1), CSD:liquid SEDDS (0.5:1 and 0.33:1), and CSD:MCC:liquid SEDDS (0.3:1:1, 0.1:2:1, 0.5:2:1, 0.33:2:1, and 0.65:2:1), until solid SEDDS was obtained.

2.4 *Preparation and optimization of directly compressible self-emulsifying tablets containing cannabis extract*

The tablet formulation was composed of solid SEDDS, HPMC as a binder, CCS as a disintegrant, CSD as a glidant, and magnesium stearate as a lubricant. According to 100 g of the powder mixture, 38.325 mg of solid SEDDS was mixed with half of MCC for 3 min. The other excipients, i.e., 0–6 g of HPMC, 0–6 g of CCS, 1 g of CSD, and 1 g of magnesium stearate, were premixed with half of MCC for 1 min, then, the two parts of powder mixture were mixed homogeneously for 3 min. The powder mixture was individually weighed for 600 mg and compressed to a tablet by a hydraulic press connected with a pressure gauge using specific compressional force. The internal diameter of a die was 12.8 mm.

The values of the factors, i.e., the compressional force, the quantity of HPMC, and the quantity of CCS, were varied based on the Box-Behnken design (Table 1). The twelve axial points (Formula 1–12) with 5 center points (Formula 13–17) of the design were obtained.

Table 1: Values of the factors, i.e., the compressional force, the quantity of HPMC, and the quantity of CCS, of the Box-Behnken design

Formula	Compressional Force (psi)	HPMC (%)	CCS (%)
1	1000	0	3
2	2000	0	3
3	1000	6	3
4	2000	6	3
5	1000	3	0
6	2000	3	0
7	1000	3	6
8	2000	3	6
9	1500	0	0
10	1500	6	0
11	1500	0	6
12	1500	6	6
13*	1500	3	3
14*	1500	3	3
15*	1500	3	3
16*	1500	3	3
17*	1500	3	3

An asterisk (*) denoted formulas 13–17 were the formulations replicated at the center point of the Box-Behnken design.

The tablets' physical properties, namely weight and weight variation, diameter, thickness, hardness, disintegration time (DT), and friability were assessed. However, during the optimization process, only four properties, specifically thickness, hardness, DT, and friability, were taken into consideration. The impact of each factor was considered significant when the p-value was less than 0.05.

Design-Expert® (v. 11) program was used to analyze the thickness, hardness, DT, and friability data obtained from 17 different formulations. The software generated three-dimensional response surfaces for each property. Design spaces were established to include formulations with hardness exceeding 5 kP, DT exceeding 0.5 min, and friability not exceeding 1%. Within this design space, the optimal formulation was selected to validate the accuracy of the predictions made by the Design-Expert® program.

2.5 *Evaluation of directly compressible self-emulsifying tablets containing cannabis extract*

Individual weights of twenty tablets were measured

using an analytical balance (Entris224i-1S, Sartorius AG, Göttingen, Germany). The weight variation was determined by calculating the percentage difference between each tablet's weight and the average weight, divided by the average weight. For tablets weighing 600 mg, the acceptable weight variation should be below 5%. The thickness and diameter of the twenty tablets were measured using a thickness gauge. The hardness of ten tablets was assessed using a hardness tester (TBH 220 TD, Erweka GmbH, Heusenstamm, Germany). DT of six tablets in water at 37 °C was evaluated using a disintegration tester (BJ-2, Tianjin Guoming Medicinal Equipment Co., Ltd., Tianjin, China). To determine friability, tablets with a total weight close to 6.5 g were dedusted, weighed, and subjected to a friability test using a friability tester (CS-2, Tianjin Guoming Medicinal Equipment Co., Ltd., Tianjin, China) at 25 rpm for 4 min. The dedusted tablets were weighed again, and the friability was calculated by comparing the percentage difference in weight before and after the test to the weight before the test.

2.6 *Evaluation of morphology of the optimal directly compressible self-emulsifying tablets containing cannabis extract*

The optimal tablets were gold-coated using a sputter coater (Q150R ES Plus, Quorum, East Sussex, United Kingdom) before being evaluated their surface and cross-sectional morphologies by field emission scanning electron microscope (FESEM) (Sigma 500VP, Carl Zeiss, Deutschland, Germany). The powders of CSD, MCC, and solid SEDDS were also evaluated and compared.

2.7 *Determination of THC and CBD content*

Ten optimal tablets were crushed, and weighed to obtain 600 mg each (n = 3) in a 50-mL volumetric flask. Methanol was added, and the mixture underwent ultrasonication for 30 min, followed by cooling and volume adjustment using methanol. The resulting solution was thoroughly mixed and passed through a nylon syringe filter (0.45 µm) before being subjected to analysis using the validated high-performance liquid chromatography (HPLC) method, as described in previous studies [9], [32], [33].

2.8 *Dissolution test*

The THC and CBD dissolution study was conducted using dissolution apparatus II (Hanson Research Corp., California, USA) on the optimized tablets (n = 3). The paddle speed was maintained at 100 ± 1 rpm, and the dissolution medium consisted of 0.1 N hydrochloric acid (900 mL) at a temperature of 37 ± 0.5°C. At specific time intervals (5, 10, 15, 30, 45, 60, and 120 min), samples of 2 mL were withdrawn and replaced with fresh medium. The withdrawn samples were neutralized with 0.1 N sodium hydroxide (2 mL), filtered, and subsequently analyzed using a validated HPLC technique. The residue remaining after the dissolution test was completed was collected via vacuum filtration. It was then dispersed in methanol, ultrasonicated for 30 min, and the resulting supernatant was collected. The supernatant was subsequently filtered and analyzed using HPLC.

2.9 *Measurement of droplet size, size distribution, and zeta potential*

The directly compressible self-emulsifying tablets were pulverized and dispersed in deionized water and 0.1 N hydrochloric acid aqueous solutions, gently vortexed, and filtered using a 0.45 µm syringe filter to remove insoluble excipients. The liquid SEDDS was diluted 200 times with deionized water and 0.1 N hydrochloric acid aqueous solutions, and gently vortexed to emulsify the formulation. Measurement of droplet size, size distribution, and zeta potential was performed using particle size and zeta potential analyzer (Zetasizer Nano Series, Malvern Instruments, Worcestershire, United Kingdom). Droplet size was measured based on dynamic light scattering (also known as photon correlation spectroscopy) and zeta potential was measured based on laser doppler velocimetry. All samples were measured at 25 °C (n = 3). The average value and SD were reported.

3 Results and Discussion

3.1 *Solidification of liquid SEDDS of cannabis extract*

The liquid SEDDS was solidified through adsorption onto two solid carriers, namely CSD and MCC. Various

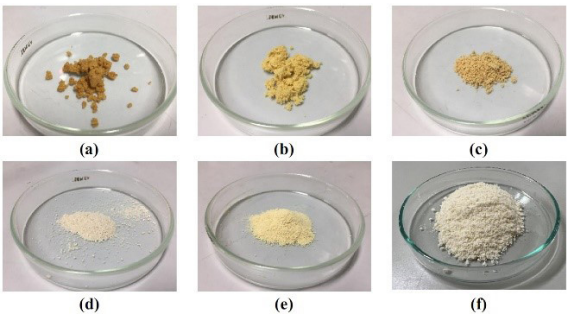

Figure 1: Physical appearance of solid SEDDS of cannabis extract prepared using different weight ratios of carriers and liquid SEDDS; MCC:liquid SEDDS of (a) 1:1 and (b) 2:1; CSD:liquid SEDDS of (c) 0.33:1 and (d) 0.5:1; and CSD:MCC:liquid SEDDS of (e) 0.33:2:1, and (f) 0.65:2:1.

ratios of a single carrier or combined carriers to the liquid SEDDS were prepared, including MCC:liquid SEDDS (1:1 and 2:1), CSD:liquid SEDDS (0.5:1 and 0.33:1), and CSD:MCC:liquid SEDDS (0.3:1:1, 0.1:2:1, 0.5:2:1, 0.33:2:1, and 0.65:2:1). The physical appearance of the solid SEDDS is shown in Figure 1. When a single carrier was used, complete dryness was not achieved. Figure 1(a)-(d) demonstrate that the use of CSD resulted in better dryness of the solid SEDDS compared to MCC, even when a lower quantity was utilized. The combination of CSD and MCC exhibited improved dryness compared to a single carrier. Among the ratios tested, a CSD:MCC:liquid SEDDS ratio of 0.33:2:1 [Figure 1(e)] appeared to be completely dry. However, when compressed into tablets, it did not provide sufficient hardness. Therefore, the ratio of CSD:MCC:liquid SEDDS of 0.65:2:1 [Figure 1(f)] was chosen as the suitable ratio since it yielded acceptable hardness when compressed into tablets.

Several pharmaceutical excipients can be used as solid carriers to solidify liquid SEDDS, for example, calcium carbonate, Aerosil® 200, lactose, and mannitol for SEDDS of azithromycin [34]; Sylysia® 350, Aerosil® 300, Aerosil® 200, and Aerosil® R 972 for celecoxib [35]; graft copolymer Soluplus® for curcumin [36]; trehalose, sucrose, sorbitol, and mannitol for papain [37]; Aerosil® 200, hydroxypropyl-β-cyclodextrin, polyvinyl alcohol, sodium carboxymethyl cellulose, MCC PH102, lactose, Syloid® 244FP, Syloid® XDP 315, and magnesium stearate for simvastatin [38].

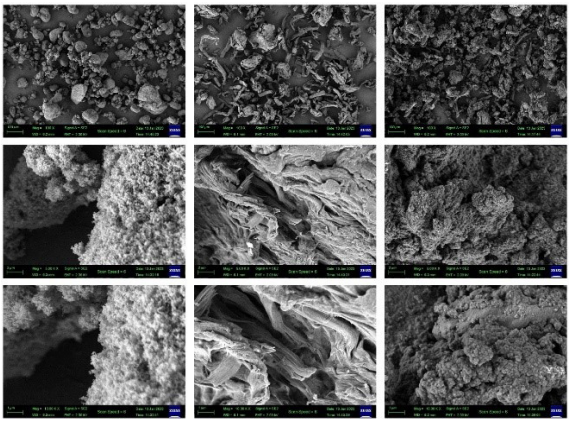

Figure 2: Morphologies of (a) CSD, (b) MCC, and (c) solidified SEDDS containing cannabis extract obtained from $scCO_2$ extraction by FESEM with magnification ×100 (upper), ×5,000 (medium), and ×10,000 (bottom).

Among them, Aerosil® 200 (CSD) was the candidate solid carrier in terms of the best solidification capacity. Furthermore, it provided the smallest droplet size as well as the minimized size distribution of emulsified SEDDS compared with other carriers [34]. In this study, a combination of CSD and MCC was employed as solid carriers. It was anticipated that CSD would have a high adsorption capacity for the liquid SEDDS, while MCC was chosen to enhance the flowability of the mixture. Additionally, MCC is known for its effective binding properties in tablet formulations [39].

The morphologies of the two solid carriers and the solid SEDDS composed of CSD:MCC:liquid SEDDS at a ratio of 0.65:2:1 were examined using FESEM at different magnifications, as shown in Figure 2. The morphology of CSD displayed loose agglomerates [Figure 2(a)], while the morphology of MCC exhibited a fibrous structure [Figure 2(b)]. At a magnification of ×100, the solid SEDDS composed of CSD:MCC: liquid SEDDS of 0.65:2:1 exhibited combined characteristics of both CSD and MCC (Figure 2(c), upper). The adsorption of the liquid SEDDS promoted the aggregation of CSD and MCC, as observed at magnifications of ×5,000 (Figure 2(c), middle) and ×10,000 (Figure 2(c), bottom). The SEM photomicrographs provide support for the adsorption of the liquid SEDDS by the mixture of the two solid carriers, CSD and MCC.

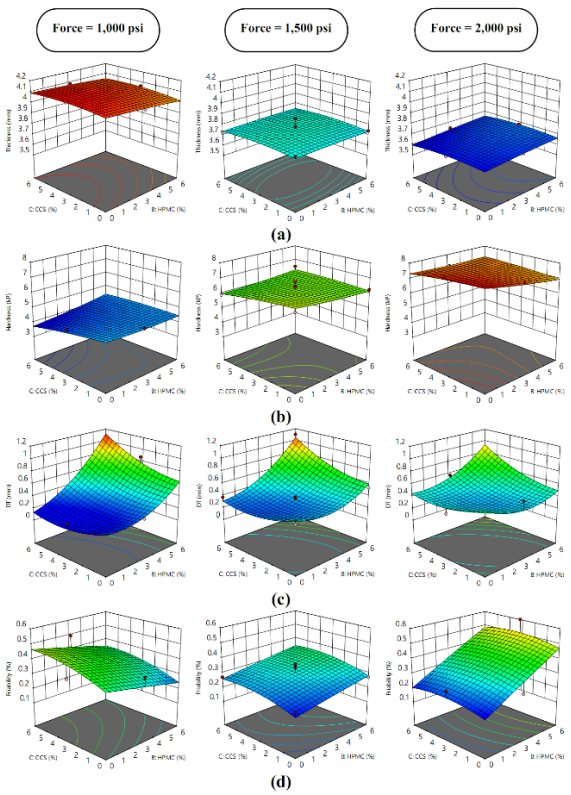

Figure 3: Three-dimensional response surfaces of (a) thickness, (b) hardness, (c) DT, and (d) friability of directly compressible self-emulsifying tablets containing cannabis extract obtained from $scCO_2$ extraction when different compressional forces were applied.

In this study, the aggregation of the solid carriers was observed after the addition of the liquid SEDDS. Similar to previous findings, SEM analysis revealed the aggregation of SEDDS adsorbed on CSD. This phenomenon is consistent with the observation made when PEG-35 castor oil (Cremophor® EL) was adsorbed onto Aerosil® 200 at a mass ratio of 1:1 [40]. Since CSD (Aerosil®) is a microporous silica, the liquid SEDDS cannot be adsorbed into its internal structure. Instead, it is adsorbed onto the surface of CSD [35], [40].

3.2 *Effect of the compressional force, the quantity of HPMC, and the quantity of CCS on physical properties of directly compressible self-emulsifying tablets containing cannabis extract*

Figure 3 displays the three-dimensional response surfaces illustrating the effects of compressional force, quantity of HPMC, and quantity of CCS on the tablet thickness, hardness, DT, and friability of the directly compressible self-emulsifying tablets containing cannabis extract. Figure 3(a) and (b) demonstrate that increasing the compressional force significantly reduces the tablet thickness while increasing the tablet hardness. However, the quantity of HPMC and CCS does not have a significant impact on the tablet thickness and hardness. In Figure 3(c), it can be observed that the compressional force and the quantity of CCS do not significantly affect the DT, whereas increasing the quantity of HPMC notably prolongs the DT. Figure 3(d) illustrates that the compressional force, quantity of HPMC, and quantity of CCS do not have a significant effect on the friability of the tablets.

Generally, increasing compressional force decreased tablet thickness and friability but increased tablet hardness and prolonged DT [41]–[45]. CCS is a well-known pharmaceutical excipient used as a tablet disintegrant. It is insoluble in water in their nature, but when in contact with water, it can swell to 4–8 times its original volume [39]. Due to its exhibiting good fluid absorption and swelling properties, therefore it was categorized as a superdisintegrant [46]. However, the quantity of CCS beyond 5% of the total weight of the tablet can prolong DT because a viscous gel layer is formed and acts as a barrier to tablet disintegration [46]. Occasionally, it has been claimed that using CCS exceeding 7.5% of the total weight of a tablet prolonged the DT of several active pharmaceutical ingredients such as ascorbic acid, aspirin, and ibuprofen from orally disintegrating tablets [43]. However, CCS did not an important excipient for this formulation, because directly compressible tablets developed in this work had a short DT. Therefore, incorporating CCS into the formulation cannot be more shorten the DT of the product that already short DT. However, superdisintegrant is relatively expensive. Production of tablets without the addition of superdisintegrant could reduce the cost of the product.

CSD is a low-density excipient (tapped density of 0.05 g/cm^3) [39], therefore, the presence of a high quantity of CSD (7.825%) of the directly compressible self-emulsifying tablets as solid carrier and glidant, gave tablet easily disintegrated due to loose binding between particle. This phenomenon was previously reported that increasing CSD increased tablet thickness

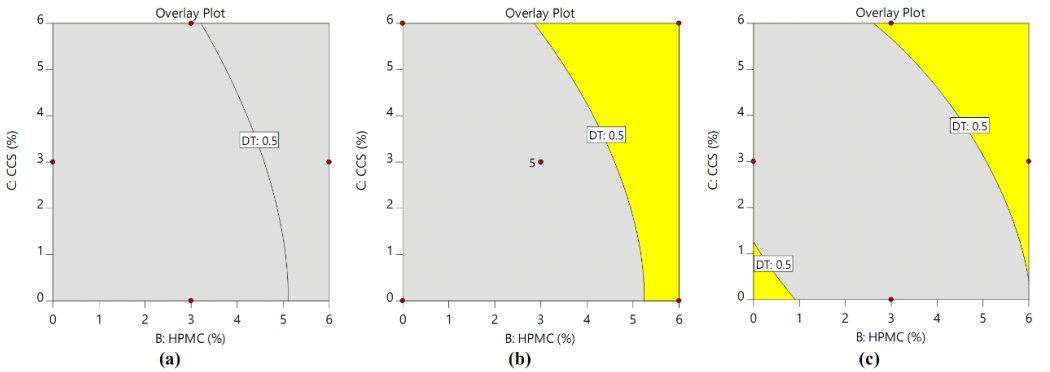

Figure 4: Design spaces (yellow area) that the directly compressible self-emulsifying tablets containing cannabis extract obtained from $scCO_2$ extraction had a hardness of more than 5 kP, DT of more than 0.5 min, and friability of not more than 1% when different compressional forces were applied: (a) 1,000 psi, (b) 1,500 psi, and (c) 2,000 psi.

and friability of *Boesenbergia rotunda* extract tablet [47]. However, the insignificant effect of CSD on tablet thickness was previously reported for Semha-Pinas extract effervescent tablets [48]. The developed tablets in this present work contained 4.5% of surfactant (Tween® 80 and Span® 80) which can shorten the disintegration time of the tablet by increasing the water-wicking rate [49]. MCC demonstrated the nature of rapid water wicking and small elastic deformation. These characteristics enable tablet disintegration [50]. The authors mentioned that a high quantity of CSD and MCC, and the presence of surfactant played an important role on DT and friability and might hinder the effect of compressional force and disintegrant property of CCS, resulting in compressional force did not affect DT and friability, and CCS did not affect DT of directly compressible self-emulsifying tablets.

HPMC is primarily used as a tablet binder, film-coating agent, and an extended-release matrix. The concentration range of 2–5% can be used in either wet or dry granulation [39], [51]. This work used HPMC as a dry binder for direct compression to improve tablet hardness, prolong DT, and reduce friability. HPMC can form a gel layer when in contact with water [52], resulting in prolonged DT of the tablet formulation. However, this work found that HPMC only prolonged DT but did not affect tablet hardness and friability. HPMC had higher resistance to compaction, lower plasticity, and promotes lower tablet hardness compared with MCC when they were used as a dry binder [53]. According to the present work, a high quantity of MCC was used either as the solid carrier for SEDDS (21%) and as the tablet diluent (47.675–59.675%). Overall MCC used for tablet preparation was 68.675–80.675%. It seemed that binding activity was principally affected by MCC rather than HPMC. Therefore, HPMC did not significantly affect tablet hardness and friability. It can be concluded that the presence of a high quantity of CSD and MCC, and the presence of surfactant could hinder the binding effect of HPMC.

3.3 *Optimal formulation of directly compressible self-emulsifying tablets containing cannabis extract*

The design spaces in which tablet hardness was more than 5 kP, DT was more than 0.5 min, and friability was not more than 1% are shown in Figure 4. Design space represented the desired properties of the tablet cannot be found when the compressional force of 1,000 psi was applied, but it was found when the compressional forces of 1,500 and 2,000 psi were applied. The optimal formulation within the design space: the compressional force of 2,000 psi with neither HPMC nor CCS used, was selected to confirm the accuracy of the prediction by the Design-Expert® program. The experimental values including, tablet thickness, hardness, DT, and friability of the optimal tablets obtained from the optimal condition; compared with the predicted values calculated as the percent error are shown in Table 2. Verification results showed that the percent errors were

less than 10%, indicating the accuracy and reliability of the Design-Expert® program.

Table 2: Verification data presented as predicted values, experimental values, and percent error

Responses	Predicted Values	Experimental Values	Error (%)*
Thickness (mm)	3.62	3.57 ± 0.02	–1.40
Hardness (kP)	7.82	8.25 ± 0.28	5.21
DT (min)	0.60	0.64 ± 0.06	6.25
Friability (%)	0.19	0.19	0.00

* Error = (Experimental value – Predicted value) × 100/Experimental value

Typically, the DT of the herbal tablets should be not more than 30 min. However, this work sets the criteria for design space of DT more than 0.5 min because the DT from this work was short and ranged from 0.17–1.1 min, which might be defined as an orally disintegrating tablet as the official in US Food and Drug Administration: DT less than 0.5 min [54]. Therefore, the criteria for the design space of DT were set at more than 0.5 min. Because the authors did not require it to disintegrate rapidly in the mouth as the orally disintegrating tablets.

According to the optimal formulation, they were also sampled to evaluate morphology, dissolution, droplet size, size distribution, and zeta potential of emulsified directly compressible self-emulsifying tablets. The physical appearance of the optimal tablets is shown in Figure 5(a). The tablets were yellow, flat face beveled edge in shape, compact, and smooth surface. The optimal tablets prepared using the optimal condition were sampled to evaluate surface and cross-sectional morphologies using the FESEM with different magnifications. Figure 5(b) at magnification ×100 exhibits a smooth surface and compact characteristics. The aggregation of the solid SEDDS was observed at magnifications ×5,000 and ×10,000 as same as found in powder of solid SEDDS [Figure 2(c)].

A tablet contained 12 mg extract, which was equivalent to approximately 1.90 mg THC and 1.40 mg CBD. The dissolution profile of THC and CBD from the optimal tablets in 0.1 N hydrochloric acid aqueous solutions is shown in Figure 6. THC could

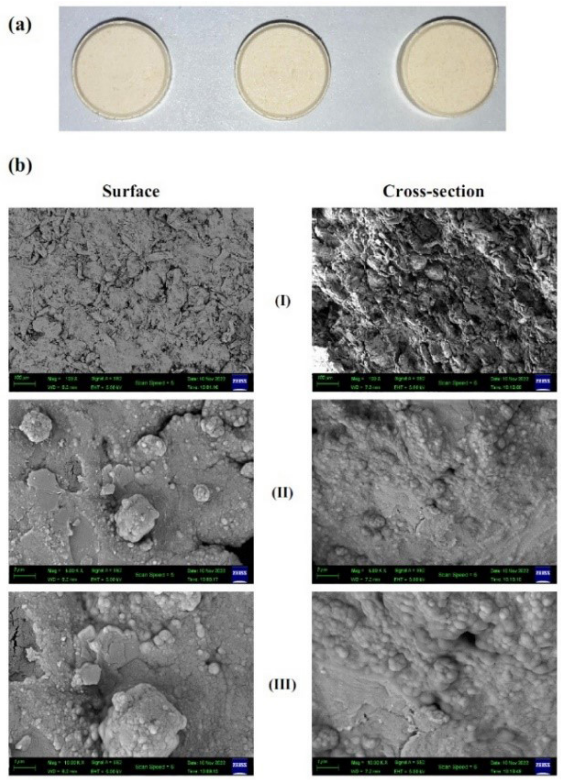

Figure 5: Morphology of the optimal directly compressible self-emulsifying tablets containing cannabis extract obtained from $scCO_2$ extraction by (a) mobile phone's camera and (b) FESEM in surface view and cross-sectional view with magnification (I) ×100, (II) ×5,000, and (III) ×10,000.

dissolve from the optimal tablet better than CBD; THC and CBD dissolved 97.90% (solid blue line) and 14.30% (solid red line) within 120 min, respectively. Analysis of the residue remaining after the dissolution test was accomplished, found that the CBD has remained in the insoluble residue. Furthermore, THC could dissolve from the optimal tablets better than the liquid SEDDS while CBD could dissolve lower than the liquid SEDDS (dashed line) obtained from the previous work [9].

According to the regimen of commercial products in Thailand, The initial dose for drug titration of 1:1 THC:CBD product was 1 mg THC and 1 mg CBD, and can be increased to THC maximum dose of 30 mg/day [55]. Therefore, the quantity of cannabis extract as well as THC and CBD in each tablet was

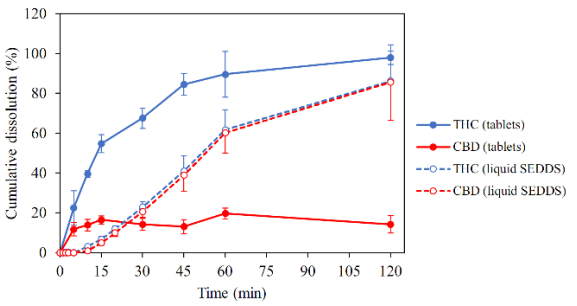

Figure 6: Dissolution profiles of THC and CBD from the optimal directly compressible self-emulsifying tablets containing cannabis extract obtained from $scCO_2$ extraction (n = 3) (solid lines) when 900 mL of 0.1 N hydrochloric acid aqueous solution was used as dissolution medium, compared with the dissolution profiles of THC and CBD from the optimal liquid SEDDS (dash lines) from the previous work [9] (reproduced with permission from Elsevier).

within the usual range of cannabis products available in Thailand. However, response to cannabis seemed highly vary among patients [56], [57]. So, titration of the dose for each patient is necessary.

THC and CBD could not be dissolved from a cannabis extract in 0.1 N hydrochloric acid aqueous solutions in their nature [9]. However, the directly compressible self-emulsifying tablets developed in this work could enhance the dissolution of cannabis extract in terms of THC and CBD dissolved (Figure 6). THC and CBD dissolved from liquid SEDDS had a similar profile but THC had a slightly shorter lag time [9]. According to the dissolution testing method of the previous work, to ensure a certain weight of the sample in each dissolution vessel, liquid SEDDS was filled into a hard gelatin capsule before being evaluated for its dissolution [9]. After the hard gelatin capsule was disintegrated and dissolved in a short time. Liquid SEDDS formed an agglomeration in the dissolution medium, resulting in it being initially emulsified from the surface of the agglomeration. In this case, THC and CBD contacted the medium simultaneously; therefore, they were dissolved with a similar dissolution rate. The present work found that the dissolution of THC from the developed tablets was superior to liquid SEDDS (Figure 6). The tablet was disintegrated into a small particle by its short DT characteristics, furthermore, the tablets contained diluent MCC that also exhibited disintegrant property [39], resulting in acceleration of the emulsification process of SEDDS. Therefore, THC could be dissolved from the developed tablets better than liquid SEDDS. In the case of CBD, it exhibited low dissolution from the tablets compared with liquid SEDDS even though the tablets easily disintegrated than liquid SEDDS. Theoretically, CBD was eluted from the RP-HPLC before THC, therefore, CBD was more polar than THC [32]. CSD used in this work was Aerosil® 200, which was a hydrophilic grade [35], therefore it had a higher affinity to the CBD than THC, resulting in the low dissolution of the CBD and it could be found in the insoluble residue that remained after the dissolution test was accomplished.

The droplet size, size distribution, and zeta potential of the liquid SEDDS and emulsified directly compressible self-emulsifying tablets containing cannabis extract in different solvents are presented in Table 3. The liquid SEDDS emulsified in deionized water and 0.1 N hydrochloric acid aqueous solution exhibited comparable nano-sized droplets, approximately 100 nm, with a narrow size distribution. The emulsified liquid SEDDS showed a negative zeta potential, and when emulsified in deionized water, the zeta potential had a more negative charge compared to liquid SEDDS emulsified in 0.1 N hydrochloric acid aqueous solution. On the other hand, the solid SEDDS emulsified in deionized water had droplet sizes close to 200 nm. The emulsified solid SEDDS displayed a broader size distribution compared to the emulsified liquid SEDDS. The zeta potential of the emulsified solid SEDDS also exhibited a negative charge, and when emulsified in deionized water, the zeta potential had a more negative charge compared to the solid SEDDS emulsified in 0.1 N hydrochloric acid aqueous solution. These results were similar to those observed for the liquid SEDDS.

The liquid SEDDS of cannabis extract prepared in the previous work had a droplet size of 201.8 ± 1.2 nm with a polydispersity index of 0.277 and zeta potential of –39.66 mV [9]. The liquid SEDDS of cannabis prepared in this work had a smaller droplet size; 99.73 ± 0.15 nm. The liquid SEDDS from the two lots had different droplet sizes. The polydispersity index was lower than in the previous work indicating that the size distribution was narrow. The zeta potential was a negative charge but lower than the previous work. The authors mentioned that they were measured

Table 3: Droplet size, polydispersity index, and zeta potential of liquid SEDDS and emulsified directly compressible self-emulsifying tablets containing cannabis extract in different solvents

Samples	Solvents	Droplet Size (nm)	Polydispersity Index	Zeta Potential (mV)
Liquid SEDDS	Deionized water	99.73 ± 0.15	0.17 ± 0.00	–18.99 ± 0.62
	0.1 N hydrochloric acid aqueous solution	95.42 ± 0.15	0.13 ± 0.02	–1.46 ± 1.61
Emulsified solid SEDDS*	Deionized water	190.27 ± 4.29	0.35 ± 0.01	–25.69 ± 15.29
	0.1 N hydrochloric acid aqueous solution	221.79 ± 41.99	0.42 ± 0.06	–1.18 ± 0.64

An asterisk (*) denoted the emulsified solid SEDDS was the pulverized directly compressible self-emulsifying tablet that dispersed in deionized water or 0.1 N hydrochloric acid aqueous solution, gently vortexed, and filtered using a 0.45 µm syringe filter to remove insoluble excipients before being measured the droplet size, size distribution, and zeta potential.

using different machines that sometimes cause different results. Furthermore, batch-to-batch variation could occur. However, the droplet size was still in a small nano-size range.

It was found that liquid SEDDS emulsified in 0.1 N hydrochloric acid aqueous solutions were simulated when it was swallowed and contacted with the fluid in the stomach. Typically, emulsions had a bigger size in acidic conditions. It exhibited lower ionization of the functional group in an acidic medium, resulting in decreased zeta potential as well as lower repulsion force [58], [59]. Therefore, emulsion droplets come close to each other [60]. However, it was found that the developed SEDDS had droplet size close to when it was dispersed in deionized water, indicating that the droplet size was stable even though it was in contact with a strong acid. But the zeta potential was lower when the SEDDS was dispersed in an acid medium compared with deionized water as a reason that the functional group could not ionize [58]–[60]. However, it did not affect the droplet size of the emulsified liquid SEDDS.

The zeta potential was lower when the SEDDS was dispersed in an acid medium, resulting in emulsion droplets coming close to each other [58]–[60]. Therefore, the emulsified solid SEDDS had a bigger droplet size with a broader polydispersity index compared with liquid SEDDS. However, the droplet size was still a small nano-size. Even though the droplet size was higher when 0.1 N hydrochloric acid aqueous solutions were used as a medium, it was insignificantly different compared with deionized water. The reason that the emulsified solid SEDDS had a bigger droplet size compared with liquid SEDDS could be described by the order of mixing the ingredients during preparation. If water was mixed in the first step of preparation, a bigger emulsion droplet can be obtained [61]. Liquid SEDDS can form an agglomeration when in contact with the medium, emulsification was gradually formed at the surface of the agglomeration. Therefore, a small emulsion droplet was formed. In the case of the tablet, it was disintegrated into a small particle where the medium contact rapidly, therefore, a bigger emulsion droplet could be obtained.

4 Conclusions

This study aimed to solidify the liquid SEDDS of cannabis extract obtained through the $scCO_2$ extraction technique for the formulation of directly compressible self-emulsifying tablets. By adsorbing the liquid SEDDS, which contained cannabis extract, onto two solid carriers (CSD and MCC) in a ratio of 1:0.65:2, respectively, the SEDDS was effectively solidified. The solidified SEDDS was then utilized to produce directly compressible self-emulsifying tablets, which were optimized using the Box-Behnken design. The optimization involved varying the compressional force, the quantity of HPMC, and the quantity of CCS. The optimal formulation was achieved by applying a compressional force of 2,000 psi without the use of HPMC and CCS. The predictions made by the Design-Expert® program were proven to be accurate and reliable. The resulting tablets exhibited smooth surfaces and a compact structure. They demonstrated enhanced dissolution of the cannabis extract, although CBD showed lower dissolution compared to THC. Moreover, the developed tablets were capable of emulsifying droplets into small nano-sized particles

(approximately 200 nm). In conclusion, the successful development of directly compressible self-emulsifying tablets containing cannabis extract obtained from $scCO_2$ extraction resulted in improved dissolution of the cannabis extract.

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Author contribution

C.M.: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition; N.C.: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft; S.D.: Methodology, Formal analysis, Investigation, Writing – original draft. J.S.: Methodology, Formal analysis, Investigation, Writing – original draft; O.N.: Methodology, Formal analysis, Investigation, Writing – original draft; L.C.: Methodology, Formal analysis, Visualization, Resource, Writing – original draft; T.S.: Conceptualization, Visualization, Resource.

Conflicts of Interest

The authors declare no conflict of interest.

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