

# Fabrication of Orally Fast-Disintegrating Wafer Tablets Containing Cannabis Extract Using Freeze-Drying Method

Chaowalit Monton<sup>a, b, c</sup> Poj Kulvanich<sup>d</sup> Natawat Chankana<sup>b, e</sup>  
Jirapornchai Suksaeree<sup>f</sup> Thanapat Songsak<sup>b, c</sup>

<sup>a</sup>Drug and Herbal Product Research and Development Center, College of Pharmacy, Rangsit University, Pathum Thani, Thailand; <sup>b</sup>Medicinal Cannabis Research Institute, College of Pharmacy, Rangsit University, Pathum Thani, Thailand; <sup>c</sup>Department of Pharmacognosy, College of Pharmacy, Rangsit University, Pathum Thani, Thailand; <sup>d</sup>Industrial Pharmacy Program, College of Pharmacy, Rangsit University, Pathum Thani, Thailand; <sup>e</sup>Sun Herb Thai Chinese Manufacturing, College of Pharmacy, Rangsit University, Pathum Thani, Thailand; <sup>f</sup>Department of Pharmaceutical Chemistry, College of Pharmacy, Rangsit University, Pathum Thani, Thailand

## Keywords

Cannabinoids · Cannabis · Gelatin · Mannitol · Marijuana

## Abstract

**Introduction:** The development of a novel dosage form for cannabis extract is necessary to improve drug delivery and also enhance patient convenience. **Methods:** Orally fast-disintegrating wafer tablets containing cannabis extract, which were prepared using the freeze drying technique, were developed in this work. The formulation consisted of several key components: cannabis extract as the active compound, Tween® 80 as a surfactant and solubilizer, gelatin and mannitol as structural components, sucralose as a sweetening agent, and sodium methylparaben and sodium propylparaben as preservatives. **Results:** The optimized formulation consists of the following ingredients: 5% cannabis extract, 1.25% Tween® 80, 5% gelatin, 88.34% mannitol, 0.2% sucralose, 0.19% sodium methylparaben, and 0.02% sodium propylparaben. The resulting wafer tablets exhibited the following characteristics: a porous structure, an average weight of approximately 200 mg, minimal

weight variation (less than 1.4%), slightly acidic pH (pH 5.12), disintegration within 10 s, low moisture content (less than 3%), a  $\Delta^9$ -tetrahydrocannabinol content of approximately 2.8 mg, and a cannabidiol content of approximately 0.9 mg. Additionally, the wafer tablets rapidly dissolved in simulated saliva fluid containing sodium lauryl sulfate. **Conclusion:** This work succeeded in the fabrication of orally fast-disintegrating wafer tablets containing cannabis extract with desired properties.

© 2024 The Author(s).

Published by S. Karger AG, Basel

## Introduction

Cannabis (marijuana) (*Cannabis sativa* L. subsp. *indica*) is a plant belonging to the Cannabaceae family. The presence of approximately 540 compounds has been reported in cannabis plants. Cannabidiol (CBD) and  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) are the two most commonly used phytocannabinoids within the medicinal industry. Furthermore, more than 100 cannabinoids have been identified in cannabis plants [1]. The cannabinoids mimic endogenous cannabinoids by stimulating

cannabinoid-1 and cannabinoid-2 receptors which are mostly found in the central nervous system and immune system, respectively. Cannabinoid receptors constitute a part of the endocannabinoid system that plays an important role in emotional regulation, memory, appetite, and pain [2].  $\Delta^9$ -THC is a psychoactive compound. This compound can induce euphoria, analgesia, reduce nausea, vomiting, inflammation, and behave as an antioxidant. CBD is a nonpsychoactive compound and has the ability to modulate the effects of  $\Delta^9$ -THC. It possesses anxiolytic, antipsychotic, and anticonvulsive properties [2].

The oromucosal route can be used for the delivery of drugs locally and systemically. This route has many advantages, i.e., simple use, convenience, increased patient compliance, first-pass metabolism avoidance, low drug metabolism, avoidance of drug degradation via gastric digestion, and easy drug removal when side effect occurs. Various pharmaceutical dosage forms have been used via the oromucosal route such as oral sprays, oral strips, buccal films, and tablets. The most commonly found dosage form is orally disintegrating tablets (ODTs) or fast-disintegrating tablets. This dosage form has several advantages, rapid disintegration, without chewing or drinking water, improves patient compliance due to easy and convenience [3, 4].

There are various methods used for the preparation of ODTs, i.e., compression, freeze drying (lyophilization), molding, mass extrusion, spray drying, and candy cotton process [5]. However, only two major methods are mostly used for the preparation of ODTs on an industrial scale – compression and freeze-drying methods. According to the compression method, superdisintegrants incorporated with moderate compression applied are usually used. In the case of the freeze-drying method, water is removed from the solution or suspension of the drug and structure forming an excipient mixture by sublimation. It is usually prepared as wafer tablets. This method gave the highly porous structure, resulting in it being rapidly disintegrated or dissolved compared with tablets prepared by the compression method [3]. However, this preparation method has some drawbacks such as being fragile, having a high cost of production, and being hygroscopic [6].

Previously, the authors had developed cannabis products in the form of self-emulsifying drug delivery systems, available in both liquid [7] and solid [8] dosage forms, which were both administered orally. This current study expands upon their prior research efforts by introducing a novel cannabis dosage form referred to as orally fast-disintegrating wafer tablets. These tablets are prepared using the freeze-drying method and are intended for delivery through the oromucosal route.

## Materials and Methods

### Materials

Isolated  $\Delta^9$ -THC (purity 98.9%) and CBD (purity 97.4%) were obtained from the Medicinal Cannabis Research Institute, College of Pharmacy, Rangsit University. Tween<sup>®</sup> 80 was purchased from P.C. Drug Center Co. Ltd., Bangkok, Thailand. Gelatin (246 Bloom) and mannitol were purchased from Union Chemical 1986 Co. Ltd., Bangkok, Thailand. Sucralose was purchased from Chemipan Corporation Co. Ltd., Bangkok, Thailand. Sodium methylparaben and sodium propylparaben were purchased from Namsiang Co. Ltd., Bangkok, Thailand. The other chemicals and solvents used in this study were of AR or high-performance liquid chromatography (HPLC) grades.

### Preparation of Cannabis Extract

Seized cannabis bars which were obtained from the Narcotic Suppression Bureau of Thailand were pulverized using a grinder equipped with a 60-mesh sieve. Following this, 15 g of the resulting cannabis powder was placed into a 600-mL beaker, and 200 mL of ethanol was introduced. The mixture underwent a 30-min ultrasonication extraction process, followed by evaporation using a rotary evaporator (Büchi Labortechnik AG, Flawil, Switzerland). This step was repeated until a sufficient quantity of extract was achieved.

Cannabis extract emulsions were prepared by solvent injection and solvent evaporation methods. A 500 mg of cannabis extract was dissolved in 10 mL of ethyl acetate. Subsequently, this solution was injected into a 0.25% Tween<sup>®</sup> 80 aqueous solution (50 mL) using a 23 G needle. The injection process was carried out under high-speed homogenization (IKA Works (Thailand) Co. Ltd., Bangkok, Thailand) at 10,000 rpm for a minute. Following this, the ethyl acetate was removed under vacuum using a rotary evaporator, resulting in the formation of cannabis extract emulsions.

### Preparation of Orally Fast-Disintegrating Wafer Tablets Containing Cannabis Extract

Orally fast-disintegrating wafer tablets containing cannabis extract were prepared by preparing 50 mL of cannabis extract emulsions. Subsequently, mannitol and gelatin were added and then heated at 55°C until the gelatin dissolved. The obtained solution was standing until the mixture reached room temperature. Sucralose, sodium methylparaben, and sodium propylparaben were added and mixed. The obtained solution (1.2 g) was filled to each hole of an aluminum blister pack, frozen by liquid nitrogen, and freeze-dried for 18 h (model: LFD-12D, Labao, Henan, China). The quantity and functions of the ingredients of orally fast-disintegrating wafer tablets containing cannabis extract are shown in Table 1.

### Evaluations of Orally Fast-Disintegrating Wafer Tablets Containing Cannabis Extract

Orally fast-disintegrating wafer tablets containing cannabis extract were assessed for weight and weight variation, pH, disintegration time (DT), moisture content, scanning electron microscope (SEM) photomicrography, as well as the content and dissolution of  $\Delta^9$ -THC and CBD.

**Table 1.** Quantity and function of ingredients of orally fast-disintegrating wafer tablets containing cannabis extract

Ingredients	Quantity, g				Function
	B1	F1	F2	F3	
Cannabis extract	–	0.5	1	0.5	Active ingredient
Tween® 80	0.125	0.125	0.125	0.125	Surfactant/solubilizing agent
Gelatin	0.4	0.4	0.4	0.5	Structure-forming agent
Mannitol	9.434	8.934	8.434	8.834	Structure-forming agent
Sucralose	0.02	0.02	0.02	0.02	Sweetening agent
Sodium methylparaben	0.019	0.019	0.019	0.019	Preservative
Sodium propylparaben	0.002	0.002	0.002	0.002	Preservative
Water	50	50	50	50	Vehicle

#### Weight and Weight Variation

Ten wafer tablets were individually weighed using an analytical balance. The average value and standard deviation (SD) were then recorded. Subsequently, weight variation was calculated using Equation 1. Based on the total tablet's weight of the wafer tablet, weight variation should not exceed 7.5%.

$$\text{Weight variation (\%)} = \left( \frac{\text{individual weight} - \text{average weight}}{\text{average weight}} \right) \times 100 \quad 1$$

#### pH

A wafer tablet was placed on a glass Petri dish. Next, 2 mL of water was added and gently agitated. The pH of the resulting solution was measured using the pH meter (SevenCompact S220, Mettler Toledo, Greifensee, Switzerland). This procedure was carried out in triplicate, and the average value and SD were reported.

#### Disintegration Time

A wafer tablet was placed on a glass Petri dish containing 2 mL of water, gently agitating it every 5 s. The DT was recorded when the complete disintegration was observed. This procedure was carried out in triplicate, and the average value and SD were reported.

#### Moisture Content

The moisture content of wafer tablets was determined using a moisture balance (MAC 50/NH, Radwag, Radom, Poland). This procedure was carried out in triplicate, and the average value and SD were reported.

#### SEM Photomicrography

The wafer tablet was gold-coated before its surface and cross-section characteristics were assessed by SEM (Hitachi S-3400 N, Hitachi High-Technologies Corporation, Tokyo, Japan) at various magnifications.

#### $\Delta^9$ -THC and CBD Contents

The analysis of  $\Delta^9$ -THC and CBD contents in the wafer tablets was conducted using HPLC. Each wafer tablet ( $n = 3$ ) was individually placed into a 25-mL volumetric flask, and 2 mL of water was added to dissolve the tablet. The volume was then

adjusted using methanol. Following this, ultrasonication was performed for 10 min, after which the solution was filtered through a 0.45- $\mu$ m pore-size nylon syringe filter and subjected to HPLC analysis.

The analysis was carried out using an Agilent 1260 Infinity HPLC system (Agilent Technologies, CA, USA) which was equipped with a photodiode array detector. Separation was achieved using an ACE C18-PFP column (250  $\times$  4.6 mm, i.d., 5  $\mu$ m), which was coupled with a guard column (SecurityGuard Cartridge C18, 4.0  $\times$  3.0 mm, i.d.). The column temperature was maintained at 25°C. The mobile phase, consisting of methanol and water in a volume ratio of 90:10, was used with a flow rate of 1 mL/min. The injection volume was set at 10  $\mu$ L, and the detection wavelength was 222 nm. The total analysis time for each sample was 25 min [9].

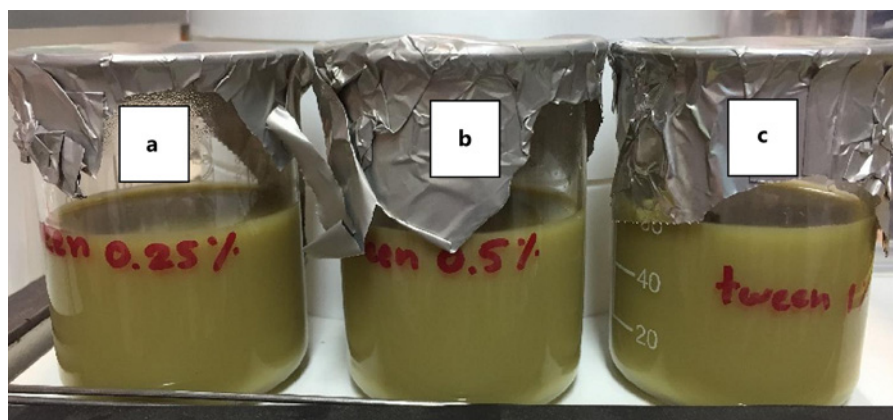
#### Dissolution

Dissolution testing of the wafer tablets ( $n = 3$ ) was conducted using the beaker method. A dissolution medium consisting of 200 mL of simulated saliva fluid (containing 8 g/L of sodium chloride, 0.19 g/L of potassium dihydrogen phosphate, and 2.38 g/L of disodium hydrogen phosphate) [10], as well as 0.5% sodium lauryl sulfate, was used. The temperature of the dissolution medium was maintained at 37°C, and the stirring speed was set at 100 rpm. Samples were collected at time intervals of 1, 3, 5, 10, 15, and 30 min. To keep the volume of the medium constant, fresh medium was added every time that a sample was taken. The collected solution was then filtered through a 0.45- $\mu$ m pore-size nylon syringe filter, and then it was subjected to an HPLC analysis. Dissolution profiles for  $\Delta^9$ -THC and CBD from the wafer tablets were then subsequently constructed.

## Results and Discussion

### *Investigation of Solubilization Procedure of Cannabis Extract in Aqueous Solution*

Initially, the authors investigated a procedure for solubilizing water-insoluble cannabis extract in an aqueous solution. The first method involved dissolving the cannabis extract in ethanol, which contained a solubilizing agent, including Tween® 80, propylene glycol,



**Fig. 1.** The appearance of cannabis extract emulsions prepared using solvent injection and solvent evaporation techniques with various concentrations of Tween<sup>®</sup> 80: 0.25% (a), 0.5% (b), and 1% (c).

or sodium lauryl sulfate. An equal weight ratio of cannabis extract and solubilizing agent was then utilized. Water was then added to the resulting emulsion under high-speed homogenization, resulting in a homogeneous cannabis extract emulsion. However, upon the removal of ethanol which involved using rotary evaporation, the cannabis extract separated from the water, despite the presence of the solubilizing agent. This phenomenon was observed with all solubilizing agents.

The second method was investigated using solvent injection and solvent evaporation techniques. Cannabis extract, which was dissolved in ethyl acetate, was injected into various concentrations of Tween<sup>®</sup> 80 aqueous solutions (0.25%, 0.5%, and 1%) under high-speed homogenization. The critical micelle concentration of Tween<sup>®</sup> 80 reported in the literature varies from 0.014 g/L to 0.025 g/L, with specific values as follows: 0.0140 g/L [11], 0.0197 g/L [12], 0.0211–0.0248 g/L [13]. The authors noted that all of the concentrations of Tween<sup>®</sup> 80 which were used in the present study exceeded the critical micelle concentration, which ensured the formation of emulsions. All mixtures remained stable even after the removal of ethyl acetate (Fig. 1).

When stored at room temperature for 1 day, the cannabis extract emulsions, which were prepared using 1% Tween<sup>®</sup> 80, showed signs of instability with sedimentation, while those, which were prepared using 0.25% and 0.5% Tween<sup>®</sup> 80, remained more stable. However, sedimentation occurred in all of the concentrations when stored for 2 days. The authors observed that using 0.25% Tween<sup>®</sup> 80 resulted in a more stable system compared to 0.5% Tween<sup>®</sup> 80, which suggests that an increased concentration of Tween<sup>®</sup> 80 led to an unstable emulsion. The instability of the emulsion system which was observed, when a higher concentration of Tween<sup>®</sup> 80 is introduced may be attributed to the presence of olefin

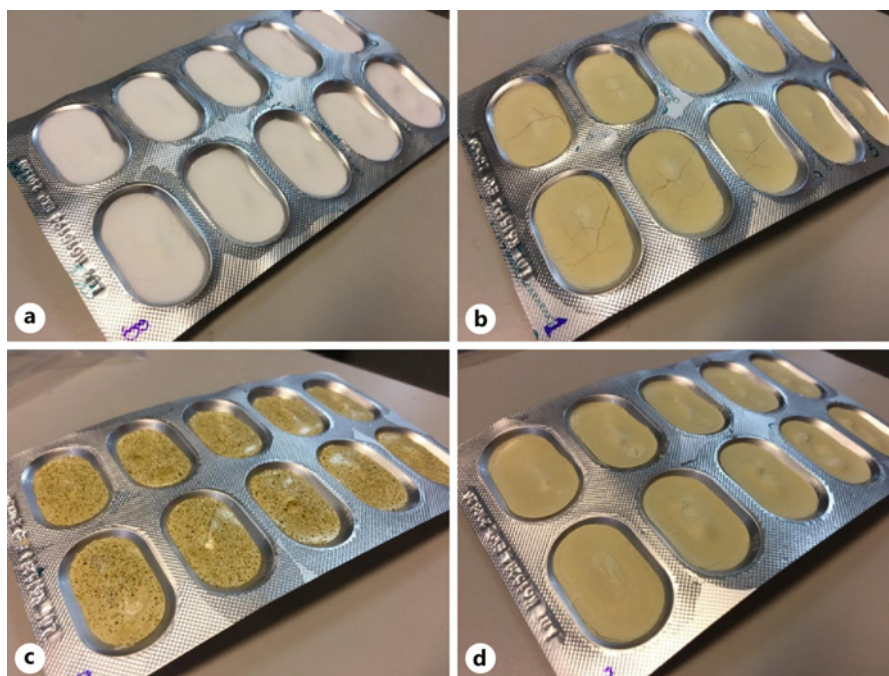
bonds in the surfactant's alkyl chain of Tween<sup>®</sup> 80, which destabilizes the emulsion system [14]. Therefore, a lower Tween<sup>®</sup> 80 concentration of 0.25% was chosen for any further experiments. Although sedimentation was observed, it did not cause any drawbacks in the preparation of wafer tablets as long as the cannabis extract emulsions were not stored for 2 days.

#### *Appearance of Orally Fast-Disintegrating Wafer Tablets Containing Cannabis Extract*

The physical appearance of wafer tablets is depicted in Figure 2. Placebo wafer tablets (B1), which contained 4% gelatin (dry weight basis), displayed some cleavages on the tablet surface (Fig. 2a). When B1 was developed into F1 through the addition of cannabis extract, an increase in surface cleavages was observed (Fig. 2b). Upon increasing the quantity of cannabis extract from 5% in F1 to 10% in F2 (dry weight basis), an issue arose during the cannabis extract emulsion preparation, which led to the separation of cannabis extract from the solution. This separation could be attributed to an imbalance between the quantity of cannabis extract and the quantity of Tween<sup>®</sup> 80. Consequently, distinct green spots of cannabis extract were visible in Figure 2c. These findings indicate that using 5% cannabis extract was the most suitable for the preparation of wafer tablets. F3 was derived from F1 by increasing the gelatin content from 4% to 5% (dry weight basis), which resulted in wafer tablets with enhanced strength [15] and a reduction in visible cleavages. As a result, the obtained wafer tablets, F3, did not exhibit any visible cleavages (Fig. 2d).

SEM photomicrographs of placebo and cannabis extract-incorporated wafer tablets are presented in Figure 3. The surfaces of the wafer tablets exhibited some cleavages, with the highest occurrence observed in F1. At higher magnification, a porous structure was observed,





**Fig. 2.** Physical appearance of B1 (a), F1 (b), F2 (c), and F3 (d) formulations.

which is typically associated with lyophilized wafers [15–20]. In the case of F2, where the separation of cannabis extract occurred during the preparation, insoluble cannabis extract was observed on the surface of the wafer tablet. Moreover, a lower porosity was observed in comparison to F1. In contrast, in F3, where the gelatin content was increased compared to the lower gelatin content in F1, a lower porosity was found compared to F1 but a higher porosity compared to F2.

The cross-sectional view revealed a porous structure and also revealed layers of structure-forming polymers. Increasing the quantity of cannabis extract from 0% to 10% in B1 to F2 (dry weight basis) demonstrated a reduction in the distance between each layer as well as a decrease in their porosity. Conversely, the increase in gelatin content from 4% to 5% between F1 and F3 (dry weight basis) resulted in an increased distance between the layers.

#### *Physicochemical Properties of Orally Fast-Disintegrating Wafer Tablets Containing Cannabis Extract*

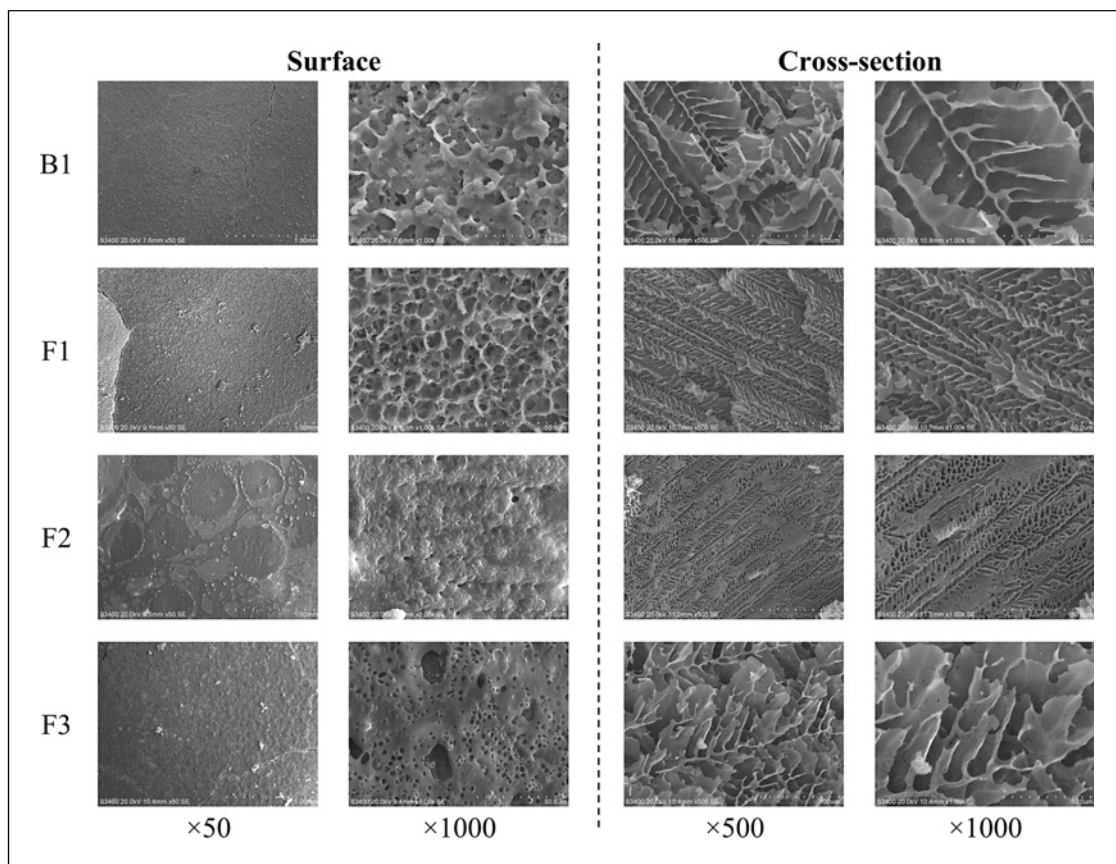
The physicochemical properties of orally fast-disintegrating wafer tablets which contained cannabis extract are presented in Table 2. The approximate weight of the wafer tablets was 200 mg. According to the average weight of the formulation, F1 exhibited the highest value, while F3 exhibited the lowest value. Additionally, F2

exhibited the highest weight variation due to the lack of homogeneity of the cannabis extract during the preparation step.

The pH value of the placebo (B1) tablets approached a neutral pH level. When the cannabis extract was increased to 5% in F1, the pH value decreased to 5.28. Moreover, as the cannabis extract was increased to 10% in F2, the pH value gradually decreased to 4.66. These results indicate that the pH of the cannabis extract was slightly acidic. When comparing F1 and F3, which differed in gelatin content, F3 exhibited a lower pH value of 5.12.

Formulations B1, F1, and F2 disintegrated rapidly within 5 s. Due to the inherent rapid disintegration of lyophilized wafer tablets, increasing the cannabis extract did not affect the DT of the formulation. In the case of F3, the gelatin content prolonged the DT. However, a short DT of 10 s remained, observed even when the gelatin content was increased from 4% to 5%. Gelatin acts as a binder; therefore, the tablet structure exhibited good binding properties when the gelatin content was increased. The prolongation of DT when increasing the gelatin content had been previously reported in lyophilized orodispersible tablets [19].

Wafer tablets had low moisture content (less than 3%) because freeze drying removes bulk water and bound water [21]. Therefore, the low moisture content was achieved. Regarding the  $\Delta^9$ -THC and CBD contents in the extract: 27.43%  $\Delta^9$ -THC and 8.34% CBD, as a



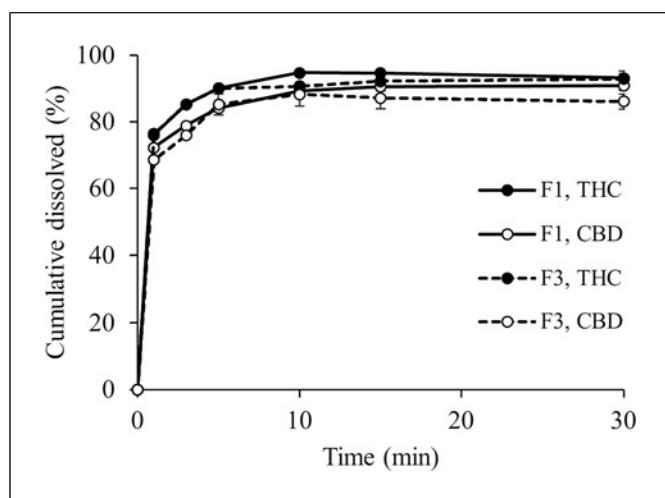
**Fig. 3.** SEM photomicrographs in surface and cross-sectional views of orally fast-disintegrating wafer tablets containing cannabis extract (F1, F2, and F3) and the placebo wafer tablets (B1).

**Table 2.** Physicochemical properties of orally fast-disintegrating wafer tablets containing cannabis extract and its placebo

Formulation	Weight, mg	Weight variation, %	pH	DT, s	Moisture content, %	Content, mg/tablet	
						$\Delta^9$ -THC	CBD
B1	203.82±1.46	0.60±0.34	7.27±0.07	5.0±0.0	2.31±0.19	–	–
F1	220.66±3.36	1.14±0.94	5.78±0.17	5.0±0.0	2.59±0.21	2.55±0.02	0.87±0.01
F2	210.40±6.14	2.39±1.48	4.66±0.03	5.0±0.0	2.58±0.12	4.27±0.59	1.40±0.19
F3	209.65±3.67	1.38±0.97	5.12±0.09	10.0±0.0	2.99±0.20	2.78±0.02	0.91±0.01

preliminary study, the authors observed that the percent recovery of both compounds for F2 was low. This was attributed to the cannabis extract separating from the formulation and adhering to glassware and laboratory equipment during the preparation step, resulting in the loss of some  $\Delta^9$ -THC and CBD contents during the recovery study. In contrast, F1 and F3 exhibited percent recoveries close to 100%, indicating the homogeneity of the mixture and that the active ingredients were not lost

during the preparation step. The  $\Delta^9$ -THC and CBD contents of F1 and F3 are shown in Table 2. However, a high content of  $\Delta^9$ -THC and CBD per tablet was observed in F2. This can be attributed to the separation of cannabis extract from the formulation, which was found on the surface of the solution. When the formulation was poured into the aluminum blister pack mold, the cannabis extract entered the mold, resulting in a high content of  $\Delta^9$ -THC and CBD in F2 compared with F1 and F3.



**Fig. 4.** Dissolution profiles of  $\Delta^9$ -THC and CBD from orally fast-disintegrating wafer tablets containing cannabis extract (F1 vs. F3) in simulated saliva fluid containing 0.5% sodium lauryl sulfate.

Based on the typical dosing guidelines for commercial products in Thailand, the starting dose for adjusting the 1:1  $\Delta^9$ -THC:CBD product was 1 mg of  $\Delta^9$ -THC and 1 mg of CBD. This dosage could then be gradually increased, with the maximum allowable  $\Delta^9$ -THC dose being 30 mg per day [22]. Consequently, the amount of cannabis extract, as well as the  $\Delta^9$ -THC and CBD content in each tablet, fell within the common range found in cannabis products available in Thailand. Nevertheless, individual responses to cannabis exhibited significant variability among patients [23, 24]. As a result, it is essential to tailor the dosage for each patient through a titration step. However, another approach involved preparing small-sized and low-dose ODTs, also known as mini-ODTs. This method offers the benefit of easily adjusting the cannabis product dosage. By administering the appropriate number of standardized mini-ODTs, healthcare professionals can tailor treatment to individual patient needs.

Dissolution profiles of orally fast-disintegrating wafer tablets containing cannabis extract (F1 vs. F3) in simulated saliva fluid containing 0.5% sodium lauryl sulfate are depicted in Figure 4. Due to the rapid disintegration nature of the orally fast-disintegrating wafer tablets containing cannabis extract and the presence of sodium lauryl sulfate in the dissolution medium, the tablets disintegrated immediately upon contact with the medium during the experiment.  $\Delta^9$ -THC and CBD had rapidly dissolved from both F1 and F3, reaching the plateau phase within 10 min. Specifically,  $\Delta^9$ -THC and

CBD had dissolved from F1 within 30 min and were 93.08% and 90.90%, respectively, while for F3, they were 92.84% and 86.12%, respectively. These results indicated that increasing the gelatin content did not affect the dissolution of both active compounds. This may be related to the rapid disintegration of both formulations. Based on the results mentioned above, F3 has been chosen as the optimized formulation. F3 comprises the following ingredients: 5% cannabis extract, 1.25% Tween<sup>®</sup> 80, 5% gelatin, 88.34% mannitol, 0.2% sucralose, 0.19% sodium methylparaben, and 0.02% sodium propylparaben. This selection is attributed to its short DT, the enhanced tablet strength due to the high gelatin content, and the ability to rapidly dissolve  $\Delta^9$ -THC and CBD.

The authors noted the bitterness of the formulation, attributed to the inherent nature of cannabis extract. Masking the taste could be one technique to improve palatability. However, further studies are needed to confirm if masking agents negatively impact disintegration, dissolution, and absorption at the absorption site.

## Conclusions

This study successfully achieved its objective of fabricating and evaluating orally fast-disintegrating wafer tablets which contained cannabis extract using the freeze-drying technique. The wafer tablets were characterized by a porous structure, minimal weight variation, a slightly acidic pH level, rapid disintegration, low moisture content, and they also contained approximately 2.8 mg of  $\Delta^9$ -THC and 0.9 mg of CBD. The most promising aspect of this study was the rapid dissolution of these wafer tablets in simulated saliva fluid containing sodium lauryl sulfate, which is essential for effective drug delivery. Altogether, this research has successfully realized the development of orally fast-disintegrating wafer tablets containing cannabis extract, achieving the desired properties and offering potential avenues for enhanced drug delivery and patient convenience. Furthermore, an in vivo study and a clinical trial are required to demonstrate the therapeutic benefits.

## Statement of Ethics

An ethics statement was not required for this study type, no human or animal subjects or materials were used. The authorization to conduct this research was obtained from the Office of the Narcotics Control Board, Food and Drug Administration, Ministry of Public Health in Thailand.

## Conflict of Interest Statement

The authors declare no conflicts of interest.

## Funding Sources

We extend our sincere thanks to the Research Institute of Rangsit University for research funding (No. 99/2560).

## Author Contributions

C.M.: conceptualization, research design, methodology, investigation, data analysis, funding acquisition, project administration, writing an original draft, and writing – reviewing and

editing; P.K.: conceptualization, research design, methodology, data analysis, funding acquisition, writing an original draft, and writing – reviewing and editing; N.C. and J.S.: investigation, methodology, and writing an original draft; and T.S.: conceptualization, funding acquisition, and writing an original draft. All authors have read and agreed to the published version of the manuscript.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

## References

- 1 National Center for Complementary and Integrative Health [Internet]. Cannabis (marijuana) and cannabinoids: What you need to know [cited 2023 Sep 3]. Available from: <https://www.nccih.nih.gov/health/cannabis-marijuana-and-cannabinoids-what-you-need-to-know>.
- 2 Birdsall SM, Birdsall TC, Tims LA. The use of medical marijuana in cancer. *Curr Oncol Rep*. 2016;18(7):40.
- 3 Fulzele S, Moe D, Hamed E. Lyoc (lyophilized wafer): an orally disintegrating tablet technology. [cited 2023 Nov 10]. Available from: <http://drug-dev.com/Main/Back-Issues/Lyoc-Lyophilized-Wafer-An-Orally-Disintegrating-Ta-50.aspx>.
- 4 Chinwala M. Recent formulation advances and therapeutic usefulness of orally disintegrating tablets (ODTs). *Pharmacy*. 2020; 8(4):186.
- 5 Ghourichay MP, Kiaie SH, Nokhodchi A, Javadzadeh Y. Formulation and quality control of orally disintegrating tablets (ODTs): recent advances and perspectives. *BioMed Res Int*. 2021;2021:6618934.
- 6 Lundegaard AR, Lund L, Larsen JN. GRAZAX: an oromucosal vaccine for treating grass pollen allergy with immunotherapy. In: Jorgensen L, Nielson HM, editors. *Delivery technologies for biopharmaceuticals: peptides, proteins, nucleic acids and vaccines*. Wiltshire John Wiley & Sons; 2009. p. 395–404.
- 7 Monton C, Chankana N, Leelawat S, Suksaeree J, Songsak T. Optimization of supercritical carbon dioxide fluid extraction of seized cannabis and self-emulsifying drug delivery system for enhancing the dissolution of cannabis extract. *J Supercrit Fluids*. 2022;179:105423.
- 8 Monton C, Chankana N, Duangjit S, Suksaeree J, Naksuriya O, Charoenchai L, et al. Fabrication and optimization of directly compressible self-emulsifying tablets containing cannabis extract obtained from supercritical carbon dioxide extraction. *Appl Sci Eng Prog*. 2024;17(1):6973.
- 9 Monton C, Madaka F, Settharaksa S, Wunakup T, Suksaeree J, Songsak T. Optimal condition of cannabis maceration to obtain the high cannabidiol and  $\Delta^9$ -tetrahydrocannabinol content. *An Acad Bras Cienc*. 2019; 91(3):e20190676.
- 10 Marques MRC, Loebenberg R, Almukainzi M. Simulated biological fluids with possible application in dissolution testing. *Dissolution Technol*. 2011;18(3):15–28.
- 11 Bide Y, Fashapoyeh MA, Shokrollahzadeh S. Structural investigation and application of Tween 80-choline chloride self-assemblies as osmotic agent for water desalination. *Sci Rep*. 2021;11(1):17068.
- 12 Mahmood ME, Al-Koofee DAF. Effect of temperature changes on critical micelle concentration for tween series surfactant. *Glob J Sci Front Res Chem*. 2013;13(4):1–7.
- 13 Tiwari S, Mall C, Solanki PP. CMC studies of CTAB, SLS & tween 80 by spectral and conductivity methodology to explore its potential in photogalvanic cell. *Surf Inter*. 2020; 18:100427.
- 14 Obradović S, Poša M. The influence of the structure of selected Brij and Tween homologues on the thermodynamic stability of their binary mixed micelles. *J Chem Thermodyn*. 2017;110:41–50.
- 15 Boateng J, Burgos-Amador R, Okeke O, Pawar H. Composite alginate and gelatin based bio-polymeric wafers containing silver sulfadiazine for wound healing. *Int J Biol Macromol*. 2015;79:63–71.
- 16 Costa JSR, de Oliveira Cruvinel K, Oliveira-Nascimento L. A mini-review on drug delivery through wafer technology: formulation and manufacturing of buccal and oral lyophilizates. *J Adv Res*. 2019;20:33–41.
- 17 Jafari H, Ramezani V, Nabi-Meibodi M, Ranjbar AM. Development of novel adhesive bilayer lyophilized wafer of moxifloxacin as a modern wound dressing. *Iran J Pharm Res*. 2021;20(3):271–84.
- 18 Nagra U, Barkat K, Ashraf MU, Shabbir M. Feasibility of enhancing skin permeability of acyclovir through sterile topical lyophilized wafer on self-dissolving microneedle-treated skin. *Dose Response*. 2022;20(2): 15593258221097594.
- 19 Bjelošević Žiberna M, Planinšek O, Ahlin Grabnar P. Oral lyophilizates obtained using aggressive drying conditions: effect of excipients. *J Drug Deliv Sci Technol*. 2023;82: 104379.
- 20 Hajhashemi H, Taymouri S, Shafiee F. Development and evaluation of wafer loaded with sertaconazole solid dispersion for the treatment of oral candidiasis. *Braz J Pharm Sci*. 2023;59:e22452.
- 21 Wang J-L, Kuang M, Xu H, Williams RO, Cui Z. Accelerated water removal from frozen thin films containing bacteria. *Int J Pharm*. 2023;630:122408.
- 22 Department of Medical Services (Ministry of Public Health) [Internet]. Guidance on cannabis for medical use [cited 2023 Sep 10]. Available from: <https://mnfda.fda.moph.go.th/narcotic/wp-content/uploads/2021/04/Guidance-Updated-v-update-V.4260464.pdf>.
- 23 Hryhorowicz S, Walczak M, Zakerska-Banaszak O, Słomski R, Skrzypczak-Zielińska M. Pharmacogenetics of cannabinoids. *Eur J Drug Metab Pharmacokin*. 2018; 43(1):1–12.
- 24 Davis BH, Beasley TM, Amaral M, Szaflarski JP, Gaston T, Perry Grayson L, et al. Pharmacogenetic predictors of cannabidiol response and tolerability in treatment-resistant epilepsy. *Clin Pharmacol Ther*. 2021;110(5): 1368–80.