AAPS PharmSciTech (2025) 26:83
https://doi.org/10.1208/s12249-025-03078-8

RESEARCH ARTICLE

Towards Enhanced Solubility of Cannabidiol: Preparation and Evaluation of Cannabidiol Solid Dispersions Using Vacuum Compression Molding

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Received: 20 November 2024 / Accepted: 20 February 2025
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Abstract

The present study aims to develop and characterize cannabidiol (CBD) solid dispersions using Vacuum Compression Molding (VCM) to enhance the drug solubility and release profile. Solid dispersions of CBD and polymers were processed using VCM at 130 °C for 4 min after a prior physical mixing. Five percent w/w of CBD was used with 5% w/w of poloxamer 188 and 90% w/w of polymeric carrier (Polyethylene Oxide, PEO-N80 or Hydroxypropyl cellulose, HPCEF). Discs were collected and milled to obtain formulations (F1V, F2V). The degradation temperature of CBD was determined using Thermogravimetric Analysis (TGA). The formulations were further characterized using differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and Fourier-Transform Infrared Spectroscopy (FTIR). *In vitro* dissolution testing of pure CBD and formulations was evaluated using USP apparatus II. TGA showed that CBD degradation occurs after 200 °C. FTIR spectra of formulations indicate potential interactions between the drug and polymers. DSC thermograms of F1V showed a thermal peak at 65 °C that could correspond to PEO-N80. F2V did not show any of the thermal event peaks, which suggests the conversion of the drug to the amorphous state. Images from the SEM showed irregular surfaces for both formulations. The release profile showed an increase in the CBD dissolution rate by 4.75 folds for F1V and 3.63 folds for F2V in four hours. In this study, solid dispersions of CBD formulations were successfully achieved. The VCM technology has proven to be successful in formulating solid dispersions of CBD for early-stage drug development.

Keywords cannabidiol · solid dispersion · solubility enhancement · vacuum compression molding

Introduction

Cannabidiol (CBD) is a non-psychoactive and non-addictive compound found in *Cannabis sativa*. It is known for its versatile potential use as an antipsychotic, anti-seizure, anxiolytic, antioxidant, and anti-inflammatory agent [1, 2]. CBD has been regarded as the most promising phytocannabinoid during the last decade, with multiple significant therapeutic applications. CBD, unlike Δ9-tetrahydrocannabinol (THC), is a non-intoxicating substance with an excellent safety profile. This is owing to the absence of drug misuse, associated with reinforcement, seeking, or obsessive intake. These elements contribute to its elaborate research and provide a considerable regulatory advantage [3]. CBD was approved by the FDA as Epidiolex®, an oral solution used to treat orphan epilepsy [4, 5]. It is also commercially available in combination with THC as an oromucosal spray called Sativex® used to treat multiple sclerosis-related spasticity [6, 7]. One of the major concerns with CBD is its low bioavailability, which is estimated at 6% and explained by the drug's low water solubility [8, 9]. As a hydrophobic molecule, CBD's absorption is influenced by different factors such as individual variations, food intake, and formulation [10]. The oral route is the most widely used method of medication administration. It is also the simplest way because it is non-invasive. Furthermore, oral drug administration is simple, has high patient compliance, requires no sterilizing, is cost-effective, and allows for greater versatility in the creation and tailoring of dosage forms. However, drug absorption via the oral route is more difficult than other modes of delivery. The medicine

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Published online: 11 March 2025

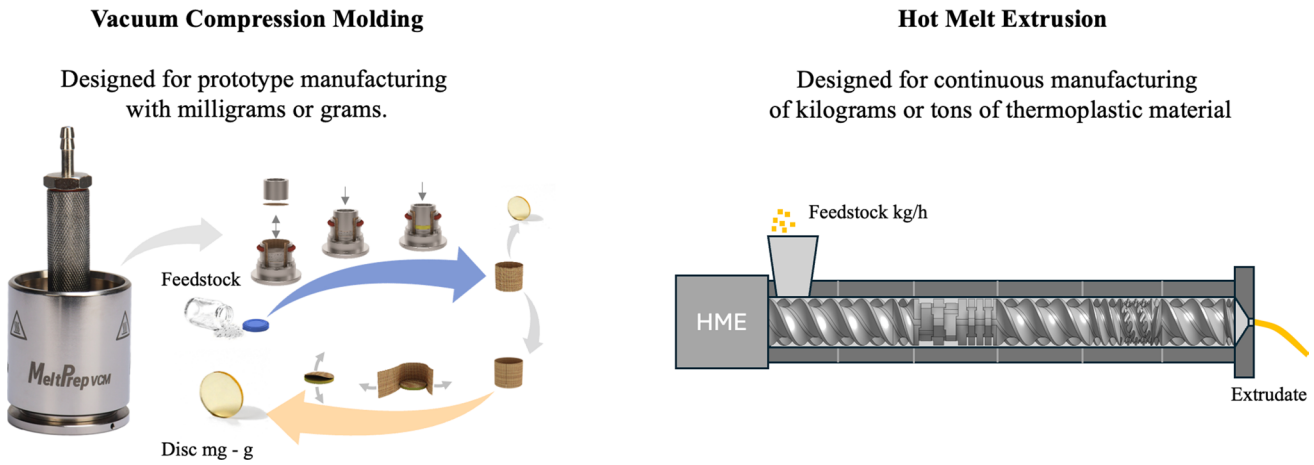

Fig. 1 Schematic diagram of VCM and comparison to HME

must dissolve in aqueous fluid before it can be absorbed in the stomach, intestine, or colon [11]. Several methods are described in the literature to develop sophisticated formulations to improve the solubility and dissolution of poorly soluble drugs such as solid dispersions (SD) [12, 13]. SDs can be classified into three generations: The first generation takes place when crystalline carrier molecules replace drug molecules and result in crystalline solid dispersions. On the other hand, second and third-generation SDs provide amorphous solid dispersions. Second-generation SDs use polymeric carriers. However, the third-generation SDs consist of a combination of amorphous polymers and surfactants [14]. Most of SD preparation methods disrupt the crystalline lattice to produce a higher energy amorphous form, which is responsible for solubility improvement. Bioavailability would then be enhanced by maintaining supersaturation in the gastrointestinal tract [13]. SDs can be developed using several methods, but the concept of their formation is the same. They can be formed using solvent-based or solvent-free methods. Solvent evaporation processes involve dissolving the drug and polymer in an organic solvent and then evaporating the solvent [15, 16]. Aqueous solvents can also be used in association with organic systems to enhance polymer solubility. Specifically, solvent evaporation is convenient for thermolabile formulation systems [17]. There are several solvent-based techniques used to achieve solid dispersion, including spray-drying, electro-spraying, fluidized bed-drying, supercritical fluid methods, spray freeze-drying, and other laboratory-scale methods [18]. Solvent-free methods are usually melt-based, where heat is applied to formulations to form solid dispersions, followed by cooling. A major concern with these methods is the high temperatures that might induce drug degradation [19, 20]. In melt-based methods, polymers are used to stabilize the dispersed form. Amorphous polymers and polymers with low melting points are usually preferred to avoid exposing the drug to high temperatures [21, 22]. Sufficient plasticization is also preferred to reduce the mixture's viscosity and minimize the processing temperature [23]. For commercial-scale production, Hot-Melt-Extrusion (HME) is one of the methods used to form SDs [24]. The drug and the polymer are mixed, melted, and extruded according to specific parameters used for processing [25–27]. KinetiSol® is another melt-based method to achieve solid dispersion. High shear force is combined with heat to melt the mixture and form SDs [28, 29]. Other solvent-free methods include 3D printing, microwave heating, and laboratory-scale methods such as Vacuum Compression Molding (VCM) and cryogenic milling. VCM is a novel technique presented as a screening tool to screen a mixture of drugs and polymers before using HME [30] (Fig. 1). The process was first reported in 2014 for sample preparation for rheological measurements of pharmaceutical polymers [30]. VCM is a melt-based method that produces solid dosage forms starting from powder. It is a rapid method capable of achieving a solid dispersion and producing formulations in a short period of time [31]. Additionally, VCM requires lower amounts of both drug and polymer and involves less cleaning compared to HME and other solid dispersion methods [32].

The VCM tool is the centerpiece of the VCM process. It is equipped with interchangeable chambers that can be as small as 0.3 mm or as large as 25 mm in diameter [32, 33]. The smaller dimensions can be used to formulate intraocular implants, and the larger dimensions can be used to form larger implants or discs for oral drug delivery. The chamber is fully lined by PTFE foils. Three pieces of foil cover the inner cylindrical surface, as well as the top and bottom of the chamber. PTFE foils prevent materials from accumulating in the chamber when heat is applied. The premixed powder mixture is filled inside the chamber at the desired weight

before the vacuum is applied. The vacuum compresses the piston against the powder at 150N. The VCM Tool is then placed on the hot plate at a set temperature. Specific temperatures require specific time on the hot plate. The VCM tool warms up quickly, and the heat fuses particles in the chamber to form a homogenous sample. The Tool is then moved to the cooling unit which operates under directed compressed air cooling. Samples are then obtained and peeled off from the foils [34]. A preconditioning mixing mechanism is necessary before using VCM because only minimum mixing happens during the melting process. Various methods could be used for preconditioning, including mortar and pestle physical mixing, cryogenic milling, ball milling, and even solvent casting [35]. Obtaining solid dosage forms with zero air inclusion and no material loss is the main advantage of VCM, which makes it an excellent tool for small-scale solid dispersions and early development studies such as drug delivery and animal studies. VCM also presents an excellent method to customize the dose to meet the individual needs of patients depending on their age, genetics, or metabolic functions [36]. Given the simplicity of the processing, VCM has great potential to produce personalized medicine while achieving solid dispersion. CBD, a drug approved for pediatric epilepsy [4, 5], would benefit from a technology that is able to customize the dose. However, this technology was never tested to formulate CBD discs for improved CBD oral delivery. Therefore, the present study aims to assess VCM's ability to prepare CBD formulations, achieve solid dispersion, and improve CBD solubility.

Materials and Methods

Materials

Cannabidiol (CBD) was kindly gifted by ElSohly Laboratories, Inc. (Oxford, MS, USA). Hydroxypropyl cellulose (Klucel™ EF) was gifted from Ashland (Wilmington, DE, USA). Polyethylene Oxide (Polyox™ N80) was gifted from Colorcon (Lower Salford Township, PA, USA). Poloxamer 188 and HPLC grade solvents were purchased from Fisher Scientific (Fair Lawn, NJ, USA).

Methods

Preparation of CBD Solid Dispersion by VCM

Solid dispersions of CBD and polymers (PEO-N80 and HPC-EF) were performed using VCM (MeltPrep, East Setauket, NY, USA). For the two formulations, 5% w/w of CBD was mixed with 5% w/w of Poloxamer 188 and 90% w/w polymer using a mortar and pestle. 300 mg of physical mixture was added to the VCM chamber. The physical mixture was heated in a hot plate at 130 °C for 4 min and then cooled in a cooling plate using compressed air. Discs of 20 mm diameter were collected and milled using a blade coffee grinder with dry ice to obtain pellets suitable to fill capsules (F1V, F2V) (Table I).

Table I VCM Solid Dispersion Formulations Composition

Formulation	CBD % w/w	Poloxamer 188% w/w	Polyethylene Oxide (PEO N80) % w/w	Hydroxypropyl cellulose (Klucel™ EF) % w/w
F1V	5	5	90	-
F2V	5	5	-	90

Characterization of the CBD Formulations Prepared by VCM

Thermogravimetric Analysis (TGA)

TGA 55 (TA Instruments, New Castle, DE, USA) was used to determine the thermal degradation temperature of CBD. A platinum pan was filled with approximately 10–15 mg of pure CBD. To monitor sample weight as a function of temperature, the sample was heated from 25ºC to 300 °C at a rate of 10 °C per minute under nitrogen.

Fourier-Transform Infrared Spectroscopy (FTIR)

FTIR analysis was performed for pure CBD, excipients, and formulations F1V and F2V to investigate interactions between CBD and polymers. The FTIR spectra were obtained using a Cary 630 FTIR spectrometer with a Cary FTIR ATR (Agilent Technologies, Santa Clara, CA, USA) fitted with a single-bounce diamond-coated ZnSe internal reflection element. A small sample was placed on the crystal surface and pressed using the built-in pressure tower to obtain uniform solid-crystal contact. The spectra were recorded in absorbance mode ranging from 600 to 4000 cm – 1 with 16 scans and 4 cm – 1 resolutions.

Differential Scanning Calorimetry (DSC)

Discovery DSC 25 instrument (TA Instruments, Newcastle, DE, USA) equipped with a refrigerator cooling system (RCS90) was used for the analysis. DSC analysis was performed for pure CBD, PEO, physical mixtures, and formulations. Five to ten milligrams of each sample were accurately weighed and loaded in hermetically sealed aluminum pans. Samples were then heated from 25 °C to 200 °C at a rate of 10 °C /min under an ultra-purified nitrogen environment at a 50 mL/min purge flow. The heat flow difference *vs.*

temperature plots were obtained using Trios software (TA Instrument, DE, USA).

Scanning Electron Microscopy (SEM)

Scanning electron microscopy was performed to examine the surface morphology of pure CBD and formulations (F1V, F2V) using a JEOL JSM-5600 scanning electron microscope (JEOL, Peabody, MA, USA) operating at an accelerated voltage of 5 kV. Samples were placed on an aluminum base using adhesive carbon pads and then coated with gold using a Hummer 6.2 Sputtering System (Anatech LTD, Springfield, VA) in a high vacuum evaporator. Gold-coated samples were then placed under the microscope to capture SEM images.

High-Performance Liquid Chromatography Analysis (HPLC)

CBD was quantified using an HPLC method reported in previous studies [37]. Waters HPLC system (Waters Corp., Milford, MA, USA) equipped with a Photo Diode Array (PDA) detector was used to perform the analysis. Chromatographic separation was achieved on a Phenomenex Luna® C18 column (150 mm × 4.6 mm, 5.0 µm). The mobile phase consisted of acetonitrile, water, and formic acid (77:23:0.1). Formic acid was used to sharpen the peaks. The flow rate was 1 mL/min, and the detection wavelength was set at 220 nm for the CBD analysis. The stock solution was prepared by dissolving CBD in acetonitrile. Samples were analyzed using Waters Empower 3.0 software chromatography data system. The calibration curve was linear over the CBD concentration range of 1.0–100 µg/mL with a 10 µL injection volume.

Drug Content

The drug content test of milled formulations was performed to check formulation content uniformity. An equivalent of 20 mg was sampled from three sections of milled formulations and placed in 20 mL scintillation vials. The samples were diluted with 20 mL acetonitrile and sonicated for 10 min. Samples were then centrifuged at 13000 rpm for 10 min and analyzed using high performance liquid chromatography analysis (HPLC).

In-vitro Dissolution Testing

The *in vitro* dissolution testing of pure CBD and VCM formulations were evaluated in triplicates using the USP II paddle method. Equivalent to 15 mg of CBD was used to perform dissolution tests. Each formulation was placed in 900 mL of phosphate buffer pH 7.4 with 0.1% v/v Tween.

80, heated at 37 °C, and the paddles were rotated at 100 rpm. Samples of 2 mL were withdrawn at 10, 30, 60, 120, 180, and 240 min for all formulations. Samples were then centrifuged at 13000 rpm for 10 min. The supernatants were analyzed using HPLC.

Results and Discussion

Solid Dispersions Preparation

Polymers (PE0-N80 and HPC-EF) were chosen for their hydrophilic properties and immediate-release applications [38, 39]. Poloxamer 188 was added as a surfactant to further enhance the drug's solubility [40]. SD formulations were prepared using VCM. VCM processing temperature was optimized based on CBD and PEO melting temperatures and CBD degradation temperature. The VCM processing time in the hot chamber was set at 4 min for both formulations. After processing physical mixtures, formulations (F1V, F2V) were obtained in the shape of 20 mm discs, as shown in Fig. 2. VCM's total processing time was 9 min for each formulation, which makes this fusion-based technology time-efficient and suitable for formulation development studies. The discs showed elastic behavior, explained by the nature of PEO and HPC [41, 42]. Disc shape and diameter were challenging to use as a final dosage form for oral drug delivery. According to the Food and Drug Administration's guidance (FDA), tablets larger than 8 mm present a risk of sticking in the esophagus and flat-shaped tablets have greater

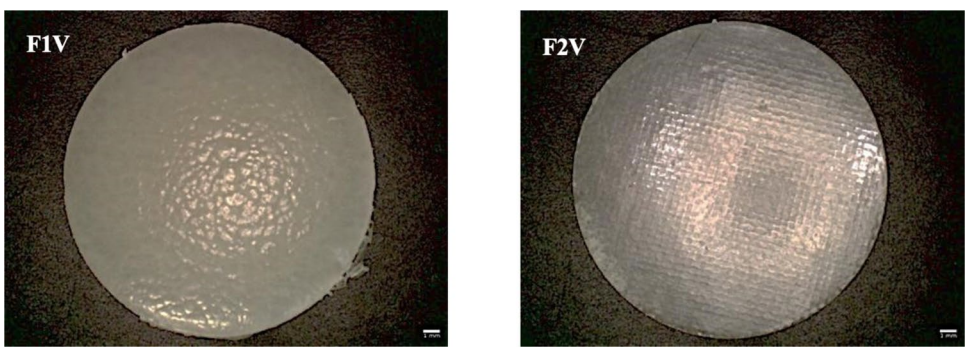

Fig. 2 Images of F1V and F2V discs after VCM processing

adherence to the esophagus than capsule-shaped tablets [43]. Therefore, discs were milled into pellets suitable for filling capsules. The plastic behavior made physical milling using mortar and pestle challenging. Thus, a blade coffee grinder with dry ice was used to obtain desired particles for formulations F1V and F2V. Formulations were then characterized and evaluated for solid-state changes and solubility enhancement.

Solid Dispersions Characterizations

Thermogravimetric Analysis

The thermal analysis of pure CBD is presented in Fig. 3. TGA was applied to determine the thermal degradation temperature of the pure drug and used to adjust the processing temperature for VCM. Weight loss started occurring after 200 °C. Thus, temperatures under 200 °C are considered safe for VCM processing. During the VCM heating process, the temperature was maintained at 130 °C throughout the experiment and did not exceed the thermal degradation temperature of CBD. Therefore, it can be concluded that F1V and F2V were not affected by the VCM heating processing that was maintained above the melting temperature of CBD and below the degradation temperature.

Fourier Transformed Infrared Spectroscopy

The FTIR spectra of pure CBD, excipients, and formulations were examined to explore compatibility and interactions between the drug, polymeric carriers (PEO-N80, HPC-EF), and Poloxamer 188, as shown in Fig. 4. The spectrum of pure CBD showed characteristic bands at 3518 and 3406 for (O–H) stretching. It also exhibited bands between 3075–2800 for (C-H) stretching, two bands at 1625 and 1580 for (C = C) stretching, bands at 1375 for (C-H) bending, and bands at 1215 for (C-O) stretching. These results

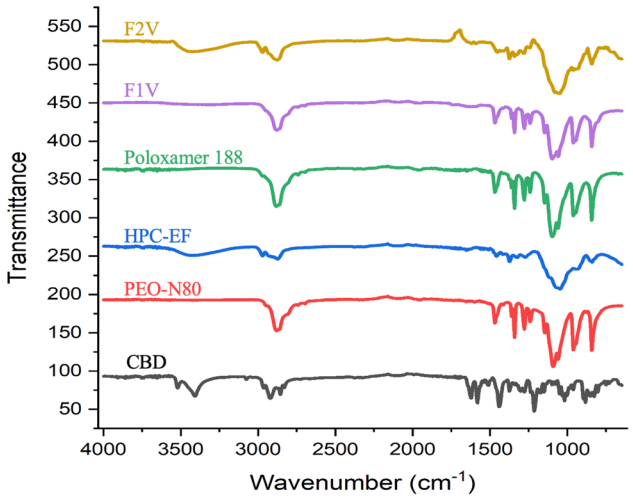

Fig. 4 FTIR spectra of pure CBD, excipients, and formulations

were consistent with the data found in the literature [44]. For F1V and F2V formulations, the bands corresponding to (O–H) and (C = C) stretching disappeared, which could be due to hydrogen interactions and hydrophobic interactions between the drug and polymers [45, 46]. These changes in spectra could also be explained by the phase transformation of the drug from crystalline to amorphous. Another plausible explanation is that the drug entity present could be too low to appear in the spectra. There were no new bands interfering with the spectra, which indicates no chemical incompatibilities between the drug and polymers in all formulations.

Differential Scanning Calorimetry (DSC)

DSC thermograms of pure CBD, physical mixtures (PM1, PM2), and formulations (F1V, F2V) are shown in Fig. 5. The pure CBD showed a melting endothermic peak at 69.9 °C that concurred with the crystalline nature of the drug. In

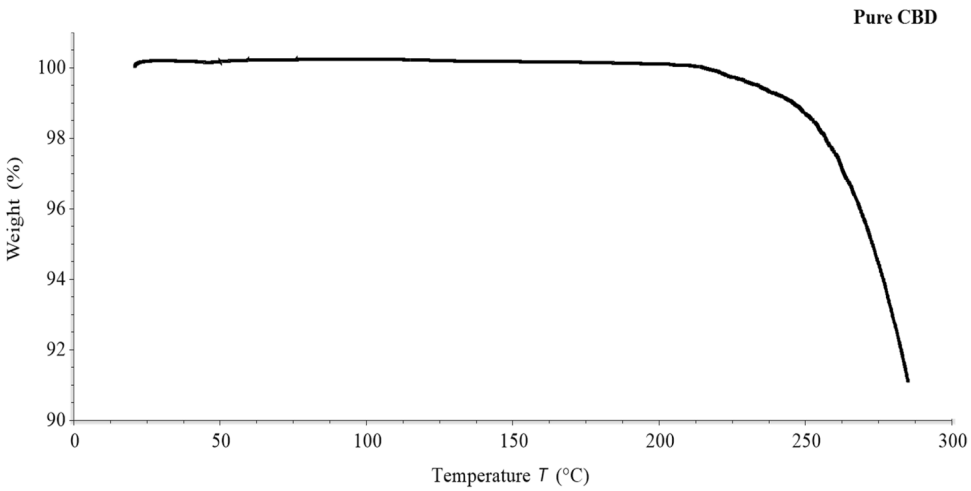

Fig. 3 TGA thermogram of CBD from 100 to 90% of the initial mass

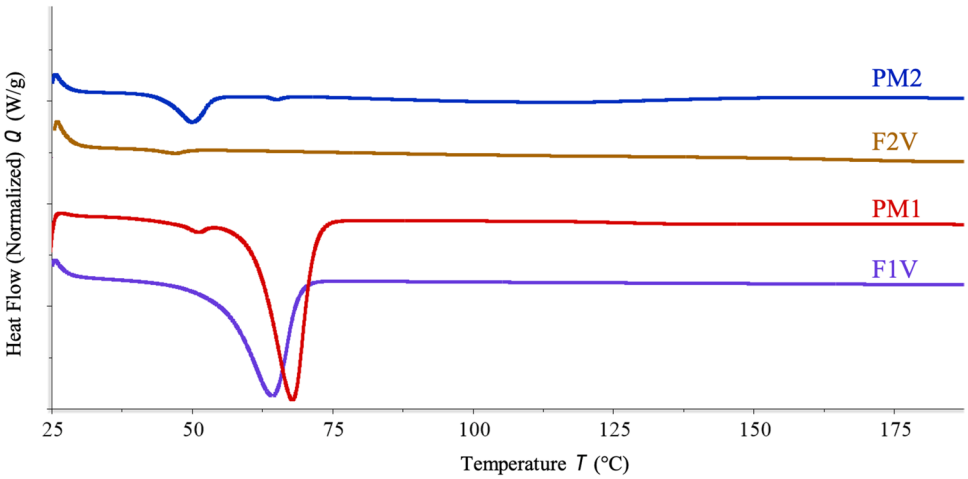

Fig. 5 DSC thermograms of physical mixtures, and formulations

Fig. 6, PM1 showed an endothermic peak at 55 °C that corresponds to Poloxamer 188 [47] and a broad peak at 65 °C that could correspond to either CBD or PEO N80 since they present very close melting points [48]. PM2 showed a peak that corresponds to poloxamer 188 and a very low intensity peak at 69.9 °C that indicates the presence of crystalline CBD in the formulation. F1V showed an endothermic thermal peak at 65 °C, which could indicate the presence of CBD or PEO N80 in crystalline form. Therefore, Scanning Electron Microscopy will be used to further investigate the formulation's morphology. On the other hand, F2V did not show any of the thermal event peaks, which can be explained by the conversion of the drug to the amorphous state, or the CBD fraction present could be too low to be shown as a peak in the thermogram. DSC thermograms indicate a possible transformation of the VCM processed formulations from the crystalline to the amorphous state.

SEM

Scanning electron microscopy of the pure drug and formulations was performed to evaluate the surface morphology of pure CBD and formulations, as shown in Fig. 7. Pure CBD showed hexagonal-shaped crystals, which indicate that the pure drug is in crystalline form. These findings are consistent with data found in the literature [49]. F1V and F2V SEM images showed irregular surfaces with microscopic cracks and cervices and no presence of crystals. The original morphology of pure CBD disappeared in VCM-processed formulations, which suggests that the drug is transformed to the amorphous form. This amorphization could result in enhanced drug solubility and improved *in-vitro* drug release of CBD. The VCM melt-based technology proved to be capable of changing the morphology of CBD crystals.

Drug Content Uniformity

After VCM processing, HPLC was used to analyze milled formulations F1V and F2V for drug content and content uniformity. Formulations showed uniform drug content with a standard deviation of less than 1%. F1V and F2V showed, respectively, a drug content of 99.68% and 93.11%. These results suggest that physical mixing coupled with heat fusion helped in preparing relatively uniform formulations. Since

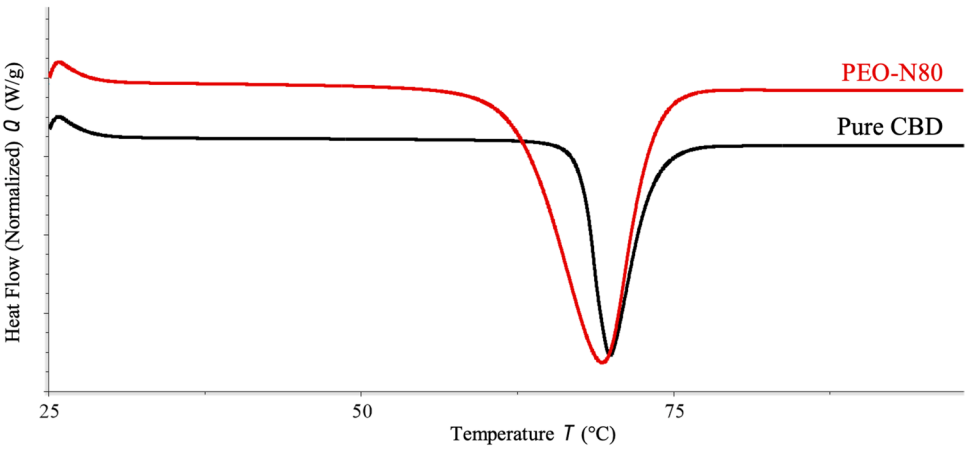

Fig. 6 DSC thermograms of pure CBD and PEO N80

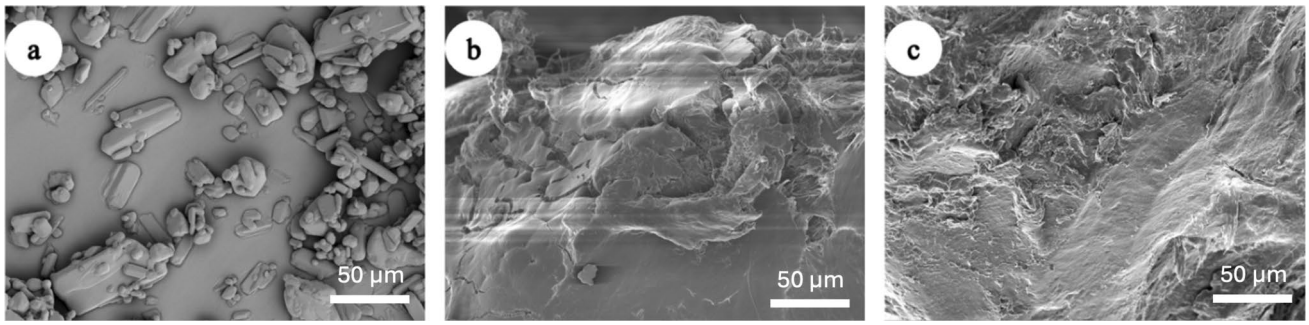

Fig. 7 Scanning Electron Microscopic images of **a** Pure CBD, **b** F1V, and **c** F2V

only minimum mixing happens during the melting process of VCM, a preconditioning mixing mechanism helped obtain the desired content uniformity.

In Vitro Drug Release

In vitro drug release was performed and continued for 4 h for pure CBD and SD formulations (Fig. 8). SD formulations showed a significant increase in the dissolution rate of CBD compared to pure CBD powder. After 4 h, formulations showed a drug release higher than 56% compared to 15.62% for CBD powder. This is explained by an increase in the solubility of CBD after achieving solid dispersion. F1V formulation showed rapid drug release compared to F2V, which suggests that PEO-N80 in the solid dispersion provides a faster release compared to HPC-EF. This is explained by PEO-N80's higher hydrophilicity and high molecular weight [50, 51]. The polymer's long polymeric chain could facilitate the molecule's ability to form hydrogen bonds with water, which promotes faster wetting and solubility. A formulation study using HME and 3D printing found a similar outcome using PEO-N80 and HPC-EF to formulate loratadine 3D printed tablets [52]. PEO-N80 also showed the advantage of maintaining a relatively uniform drug release, which is consistent with earlier published investigations [53].

The *in vitro* drug release study proved the efficiency of VCM in increasing cannabidiol's dissolution rate by respectively 4.75 for the formulation containing PEO-N80 and 3.63 for the formulation containing HPC-EF in four hours. This study showed that VCM can achieve solid dispersion and improve CBD's solubility and dissolution rate. Formulation composition and the technology used were both determining factors in improving CBD's release profile. VCM proved its ability to formulate CBD and improve the *in vitro* drug release. VCM is designed as a tool for formulation developers with a focus on flexibility to produce formulations fast and with zero waste by manual human operation. It presents an opportunity to prepare personalized medicine on demand. For traditional commercial supply, scale-up is typically done by transferring to established hot-melt extrusion equipment with continuous throughputs in kilograms per hour for products required in the kilogram or ton scale [34]. Scale up to manufacture dosage forms for demands up to a few kilograms, such as highly potent drugs or implant formulations, can be scaled by moving to larger VCM disc dimensions to obtain manufacturing volumes of hundreds

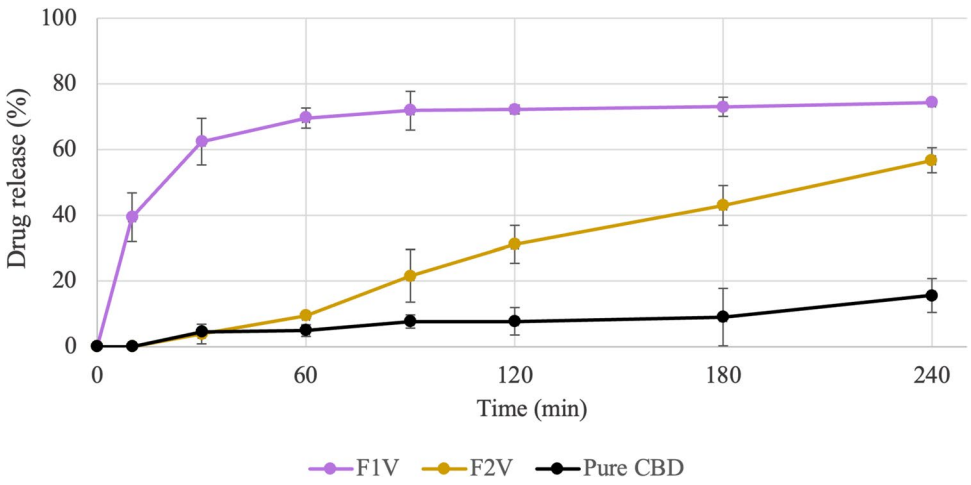

Fig. 8 Dissolution profile of pure CBD, F1V, and F2V

of grams, sufficient to supply demand in clinical trials or hospital pharmacies.

Conclusion

In this study, solid dispersions of CBD formulations with HPC-EF and PEO-N80 were successfully achieved using the VCM technology. Formulations were prepared and solid-state characterizations were performed. FTIR spectra analysis indicated a potential interaction between the drug and polymers. DSC and SEM suggested transformation of the drug from crystalline to the amorphous state, and the *in vitro* drug release study showed increased solubility of CBD for F1V and F2V compared to the pure drug. VCM has previously been applied to diverse objectives, such as screening polymers for hot melt extrusion. Our study demonstrated VCM efficiency in producing small-scale dosage forms and in achieving solid dispersion for CBD. The VCM method is believed to be promising for preparing solid dispersions. Although it is not suited for large-scale manufacturing, it is optimal for producing small-scale personalized medicine and early development studies.

Author Contributions Conceptualization: Eman A. Ashour; study design: Achref Cherif, and Eman A. Ashour; methodology: Achref Cherif, Janhavi Deshmukh, Kavish Sanil, Iman Taha; experimentation data analysis interpretation: Achref Cherif, writing–original draft: Achref Cherif; writing–review and editing: Achref Cherif, Daniel Treffer, and Eman A. Ashour; review data results and supervision: Eman A. Ashour. All authors have read and agreed to the published version of the manuscript.

Funding The authors declare that no funding was received for this study.

Declarations

Conflict of Interest The authors declare that there are no conflicts of interest regarding the publication of this paper. No financial support or other relationships that may pose a conflict were involved in the study or its preparation.

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