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Pharmacotechnical and Analytical Preformulation Studies for Cannabidiol Orodispersible Tablets

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Pharmacotechnical and Analytical Preformulation Studies for Cannabidiol Orodispersible Tablets

Abstract: Obtaining orodispersible tablets (ODT) containing substances from the 2nd Biopharmaceutical Class has raised concerns as the dissolution test is challenging. This study aimed to select suitable excipients for developing orodispersible tablets containing cannabidiol (CBD) by direct compression method. No similar studies were found in the literature. Excipients from different classes were characterized using the SeDeM-ODT tool: fillers - lactose (LCT) and microcrystalline cellulose (CelMC), sweeteners - sorbitol (SRB) and mannitol (MNT), disintegrants - sodium starch glycolate (SSG), sodium croscarmellose (CCS), soy polysaccharides (Emcosoy® - EMCS) and two co-processed excipients (Prosolv®-ODT G2 – PODTG2 and Prosolv® EasyTab sp - PETsp). Drug compatibility with excipients in binary mixtures (1:1) was verified by Differential Scanning Calorimetry (DSC) and Fourier Transform-Infrared (FTIR) spectroscopy. Using the SeDeM-ODT expert system, the fillers and the co-processed excipients showed good properties regarding compressibility and disintegration behavior. Also, the DSC and FTIR results showed that small or no interactions between the CBD and the excipients took place.

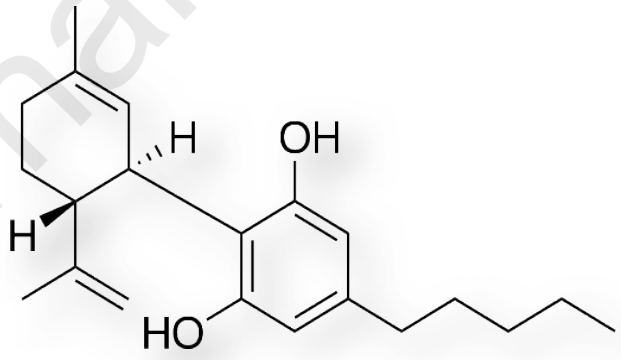
Keywords: cannabidiol; SeDeM-ODT; FTIR; DSC; orodispersible tablets; direct compression

CBD – cannabidiol, LCT – lactose, CelMC – microcrystalline cellulose, SRB – sorbitol, MNT – mannitol, sodium starch glycolate – SSG, sodium croscarmellose – CCS, soy polysaccharised – Emcosoy – EMCS, Prosolv®-ODT G2 - PODTG2 and Prosolv® EasyTab sp – PETsp, tetrahydrocannabinol – THC, Food and Drug Administration – FDA, European Medicine Agency – EMA, Biopharmaceutics Classification System – BCS, CBD-ODTs – cannabidiol orodispersible tablets, IGCB - index of good compressibility and bucodispersibility, Bulk density – Da, Tapped density – Dt, Porosity – ξ, Carr Index – IC, Cohesion Index – Icd, Hausner ratio – RH, Angle of repose – α, Powder flow – F, Loss on drying - %HR, Hygroscopicity - %H, Particles < 50µm - % Pf, Homogeneity Index – Iθ, Effervescence – E, Disintegration with disk – Td, Disintegration without disk – Tfd, Limits value – v, PI – parameter index, PPI – parameter profile index, active pharmaceutical ingredient – API, r- radius value, f – reliability factor

1. Introduction

Cannabidiol (CBD) is an active ingredient that can be found in the *Cannabis sativa varietas indica* plant (Millar et al., 2020) which is considered a pharmaceutical ingredient that does not induce addiction unlike tetrahydrocannabinol (THC) (Batalla et al., 2019). Numerous studies were conducted to establish a disease that can be cured with this substance. The number of approved pharmaceutical formulations with CBD is very small, as many formulations are registered as supplements. The latest pharmaceutical formulation approved in 2018 by Food and Drug Administration (FDA) and European Medicine Agency (EMA) is named Epidiolex®, a 10% CBD oil used in treating Lennox Gastaut and Dravet syndromes (Vlad et al., 2020; Senn et al., 2020). Sativex® is another pharmaceutical formulation that has in composition CBD, but this spray contains also THC. Both Sativex® and Epidiolex® are available with a prescription in the countries where they are marketed (Giacoppo et al., 2017;Calapai et al., 2020). Taking into consideration the fact that a first-pass effect might occur in the case of Epidiolex, and the therapeutic effect might decrease, a new pharmaceutical formulation containing CBD, as orodispersible tablets (ODTs), could be developed that has the capability of bypassing the first-pass effect. Recently, several studies indicated that CBD might be a solution for the following diseases: epilepsy, Parkinson disease, Alzheimer disease and, cancer (Vlad et al., 2020; Hayakawa et al., 2010). Other studies showed that CBD might be used in the cosmetic industry due to its antioxidant properties (Paul et al., 2019; Van Elsue et al., 2019), due to the presence of hydroxyl groups.

Figure 1 CBD – chemical structure**.**



CBD is a BCS class II drug, with a low water solubility and high permeability to the cell membrane (Vlad et al., 2020).

Developing CBD-ODT represents an opportunity taking into consideration the reduced number of pharmaceutical formulations with CBD that can be found on the market. Other drugs that are already present on the pharmaceutical market or were used to obtain orodispersible tablets are loperamide, sulpiride, desloratadine, loratadine, olanzapine, some of them having also solubility issues just as CBD (desloratadine and loratadine) (Alejandro et al., 2020; Tawfeek et al. 2020; Novick et al. 2017; Montgomery et al., 2012). Taking into consideration the palatability, the use of flavouring and sweetener

agents needs to be taken into consideration when developing a new formulation (Desai et al., 2020; Casian et al., 2018).

The development of CBD orodispersible tablets (CBD-ODT) encounters a challenge in matters of compressibility. To select the best excipients and their amounts SeDeM-ODT expert system was used to characterize the evaluated powders. Using the SeDeM-ODT tool the advantages and disadvantages of the powders were established. This tool can be applied to: establish the quantity of excipient needed to obtain a tablet if the active pharmaceutical ingredient (API) does not have a good compressibility profile; observe the differences between the quality of different batches of similar powder; differentiate the excipients that have the same chemical formulation but have different physical properties; differentiate the excipients from the same class (disintegrants, fillers, sweeteners) (Agular-Diaz et al., 2012; Flórez Borges et al. 2018; Sipos et al., 2017; Agular Diaz et al. 2014; Suñé-Negre et al. 2014;).

The SeDeM-ODT expert system provides the following advantages in comparison to classical experimental design: the number of excipients required in the final formulation is optimized; a formulation with only one excipient combined with the API – CBD can be obtained; the critical parameters represented by the short disintegration time, compressibility, and mechanical resistance are fulfilled; the decreased time needed to develop a new ODT compared to a classical experimental design where numerous studies were needed to obtain ODTs that accomplished all the critical parameters, especially, disintegration time and compressibility. (Agular-Diaz et al., 2012; Flórez Borges et al. 2018; Agular Diaz et al. 2014; Suñé-Negre et al. 2014)

Beside the characterization of powders, the SeDeM diagram has been used recently to characterize granules characteristics (mechanical strength, disintegration behaviour and, flow properties) (Khan, 2019).

The SeDeM ODT methodology can be used to develop orodispersible tablets by direct compression. This tool has the advantage of assessing the quantity of excipients needed to obtain good compressibility and a fast disintegration (Agular-Diaz et al., 2012; Agular Diaz et al. 2014; Suñé-Negre et al. 2014).

The purpose of this study was to establish the quantity and compatibility of excipients with cannabidiol taking into consideration both analytical and technological points of view.

2. Materials and Methods

The materials used were CBD (Hügel Pharma, Austria), LCT (DFE Pharma, New Zealand), CelMC (Alfa Aesar, Germany), MNT (VWR Pharmaceuticals, France), SRB (Roth, Germany), EMCS (JRS Pharma, Germany), SSG (JRS Pharma, Germany), CCS (JRS Pharma, Germany), PETsp (JRS Pharma, Germany), PODTG2 (JRS, Pharma), KBr (PharmaPeer, Germany), Magnesium stearate (Alfa Aesar, Germany), Hydrophilic fumed silica (Degussa, Germany).

2.1. SeDeM-ODT characterization

The SeDeM-ODT methodology uses 15 tests to establish if a powder is suitable to develop orodispersible tablets whilst SeDeM uses twelve tests. The 15 parameters evaluated using the SeDeM-ODT expert system can be found in Table 2. When SeDeM is used to describe a powder, the disintegration ability is not evaluated.

Table 1 Parameters and equations used for SeDeM-ODT Expert system.

Incidence	Parameter	Symbol of the parameter	Unit of measure	Equation	Determination	Abbreviations
Dimension	Bulk density	D_a	g/mL	$D_a = M/V_a$	Eph 9 – Section 2.9.34	M – sample mass (g) V_a – bulk volume (mL) V_t – tapped volume (mL)
	Tapped density	D_t	g/mL	$D_t = M/V_t$		
Compressibility	Porosity	ξ	-	$\xi = D_t - D_a / D_t * D_a$		
	Carr Index	IC	%	$IC = (D_t - D_a)/D_t * 100$		
	Cohesion Index	I_{cd}	N	Experimental [1]		
	Hausner ratio	RH	-	$RH = D_t/D_a$		
Flowability	Angle of repose	α	°	$tg\alpha = h/r$	Eph 9 -Section 2.9.36	h – powder cone height r – radius of the powder cone
	Powder flow	F	S	Experimental	Eph 9 – Section 2.9.16	
Lubricity/stability	Loss on drying	%HR	%	Experimental	Eph 9 – Section 2.2.32 [2, 3]	
	Hygroscopicity	%H	%	Experimental		
Lubricity/dosage	Particles < 50µm	$\% P_f$	%	Experimental	Eph 9 – Section 2.9.12	
	Homogeneity Index	Iθ	-	$I\theta = F_m/100+F_{mn}$	Eph 9 – Section 2.9.12	
Disintegration ability	Effervescence	E	Minute	Experimental	USP 32nd Edition – Monograph 701	
	Disintegration time (with disk)	T_d	Minute	Experimental		
	Disintegration time (without disk)	T_{fd}	Minute	Experimental	Eph 9 – Section 2.9.1	

[1] The Cohesion Index (I_{cd}) was achieved by using an eccentric press with which the powder was compressed. The mechanical resistance (expressed in N) of the resulted tablets was determined and the mean mechanical resistance was determined.

[2] For substances that had lower than 105°C melting points, a temperature of 10°C beneath the melting point was used.

[3] To determine the Hygroscopicity of the powders HR73 Halogen Moisture Analyzer Mettler Toledo was used.

The radius values were established as presented in Table 3. For each of the evaluated parameters, a factor was applied to obtain a radius value between 0-10. If the value exceeded the maximum value obtained the value of ten was attributed, while if values lower than the admitted limits values were obtained, the zero value was allocated.

Table 2 Establishing the radius values for the selected powders

Parameter	Limit value (v)	Radius range	Factors applied to v
$\mathbf{D_a}$	0-1 g/mL	0-10	10*v
$\mathbf{D_t}$	0-1 g/mL	0-10	10*v
ξ	0-1.2	0-10	10*v/1.2
CI	0-50%	0-10	v/5
$\mathbf{I_{cd}}$	0-200 N	0-10	v/20
RH	3-1	0-10	(30-10v)/2
α	50-0°	0-10	10-(v/5)
F	20-0	0-10	10-(v/2)
%HR	0-10%	0-10	10-v
% H	20-0%	0-10	10-(v/2)
$\mathbf{\% P_f}$	50-0%	0-10	10-(v/5)
Iθ	$0\text{-}2*10^{-2}$	0-10	500*v
E	5-0	0-10	10-(v*2)
$\mathbf{T_d}$	3-0	0-10	10-(v*3.33)
$\mathbf{T_{fd}}$	3-0	0-10	10-(v*3.33)

2.1. Determination of the quantity excipient needed to obtain compressibility of at least 5

To determine the IGCB (Eq. 3) two other indexes have to be determined previously the first one is the parameter index (Eq. 1) and the parameter profile index (Eq. 2) (Aguilar-Díaz et al., 2012; Aguilar-Díaz et al., 2014; Suñé-Negre et al., 2014).

$$\mathbf{IP} = \frac{\mathbf{N°P \geq 5}}{\mathbf{N°Pt}}, \quad (1)$$

N°P ≥ number of parameters with value ≥ 5.

N°Pt total number of studied parameters

$$\mathbf{IPP = mean\ r\ of\ all\ studied\ parameters}, \quad (2)$$

The acceptance minimum limit for IPP is 5.

The IGCB has the following equation (Aguilar-Díaz et al., 2012; Aguilar-Díaz et al., 2014; Suñé-Negre et al., 2014).

$$\mathbf{IGCB = IPPxf} \quad (3)$$

Where f represents a reliability factor calculated as the ratio of polygon area with the circle area.

2.2. FTIR characterization

Experimental conditions:

The FTIR spectra belonging to the API, excipients and, binary mixtures were obtained by an IR Thermo Nicolet 380 FTIR, spectrophotometer. Spectra were obtained using 128 scans between 4000-400 cm^{-1} at a spectral resolution of 8 using Omnic 8.0 to achieve the results and Spectragryph 1.2 to interpret the results. The substance used as a background was potassium bromide and the background was updated every 30 min. To obtain the tablets of simple and binary mixtures a hydraulic press was used.

2.3. DSC characterization

The DSC analysis was used to predict possible interactions. The thermal analysis was carried out with a DSC Shimadzu 60. The quantities of the samples between 4.9-5.2 mg were introduced in - 40 µL aluminum crucibles using as ambient atmosphere the air. The temperature range was between 25-300°C while the heating rate was 5°C/min. The samples verified were the same as in the case of FTIR analysis.

3. Results and discussions

The SeDeM/SeDeM-ODT tools were used and the following parameters were described: dimension, compressibility, flowability, stability, dosage and, disintegration ability. Before starting the SeDeM-ODT characterization, Differential Scanning Calorimetry (DSC) and Fourier Transform-Infrared (FTIR) spectroscopy studies were conducted to observe the eventual analytical incompatibilities (Moisei et al., 2014; Todoran et al., 2018; Rus et al., 2019). To obtain orodispersible tablets, excipients from various classes are needed (Alejandro et al., 2020; Tawfeek et al., 2020). In this study excipients from different classes were used, and the compatibility of each excipient with CBD by the means of a binary system (1:1) using DSC and FTIR analysis has been evaluated.

The IUPAC names, physical-chemical properties, and the advantages for the excipients used are listed below: CelMC (2-[4,5-dihydroxy-2-(hydroxymethyl)-6-methoxyoxan-3-yl] oxy-6-(hydroxymethyl)-5-methoxyoxane-3,4-diol) is an odorless, tasteless, porous white powder that presents various chemical technical and economic benefits such as robust tablets with low friability, high production yields, and compatibility with most of the APIs. LCT (2R,3R,4S,5R,6S)-2-(hydroxymethyl)-6-[(2R,3S,4R,5R,6S)-4,5,6-trihydroxy-2-(hydroxymethyl) oxan-3-yl] oxyoxane-3,4,5-triol is a white, odorless, tasteless powder with a mild sweet taste that is soluble in water with 98% of the particle size less than 250 µm. EMCS is a natural tablet disintegrant obtained from soy-plant on which no genetically processed were used. It is a white odorless, tasteless powder that is preferred in the nutritional industry as a result of the natural origins and consistent disintegration with a small impact regarding the tensile strength.SSG (sodium starch glycolate or carboxymethyl starch sodium salt) is a superdisintegrant obtained from potato starch by crosslinking and carboxymethylation that presents strong swelling properties in contact with water or saliva forming a translucent gel. CCS (sodium croscarmellose – sodium acetate 2,3,4,5,6-pentahydroxyhexanal) is a white, odorless, tasteless powder. CCS is described as a cellulose-based disintegrant with high efficiency even in small concentrations that provides good flowability, mixing properties, and a good behavior regarding both compression and granulation processes. SRB ((2R,3R,4R,5S)-hexane-1,2,3,4,5,6-hexol) is an odorless, sweet, white crystalline powder with hygroscopic properties. MNT ((2R,3R,4R,5R)-hexane-1,2,3,4,5,6-hexol) is an odorless, white, crystalline dry, powder with a sweet taste. PODTG2 is a free-flowing white, with an average particle size between 40-80 µm. This co-processed excipient is used to obtain ODTs. It provides good palatability properties offering a smooth and creamy mouthfeel. PETsp is a co-processed ready to use white excipient. This excipient presents advantages such as good API stability, good flowability, good mechanical properties, and low friability (Vlad et al., 2020, Andriotis et al., 2020).

The SeDeM-ODT methodology has been chosen because of its main advantage which is represented by the reduced number of steps necessary to obtain ODTs compared to the traditional development, in this

case, the amount of excipient is established to obtain good compressibility properties, also, if the excipient presents good orodispersible properties two of the critical parameters are accomplished (Aguilar-Díaz et al., 2012; Aguilar-Díaz et al., 2014; Hamman et al. 2018; Zieschang et al., 2019). This innovative tool, predicts if the chosen excipients can be used to obtain ODTs by direct compression by identifying the index of compressibility and bucodispersibility (IGCB) that indicates if a powder can be compressed by direct compression. The IGCB shows the suitability of the powders in developing ODTs. Taking into consideration the number of experiments that take place in the laboratory, the unnecessary preformulation experiments are eliminated. The steps needed to be followed to achieve ODTs can be found in **Figure 2**.

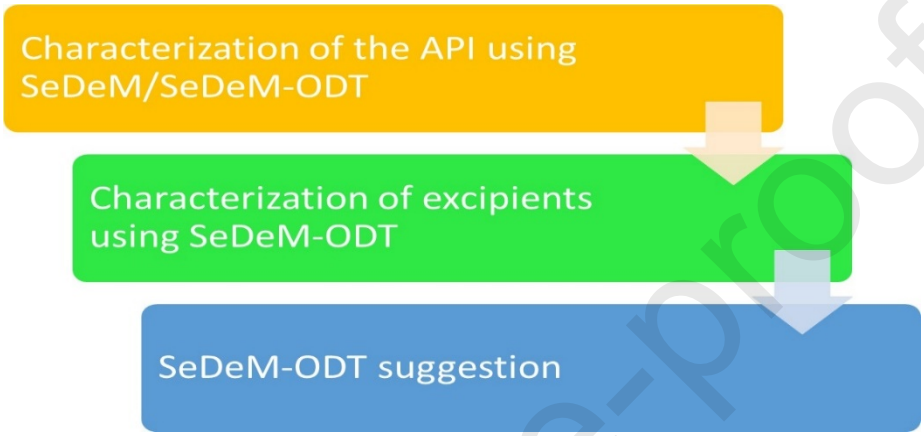


Figure 2 Stages needed to follow in order to obtain an ODT with a robust formula.

3.1. SeDeM/SeDeM-ODT results

Table 3 SeDeM-ODT characterization of the CBD, PODTG2 and PETsp.

Factor/Incidence	**Parameter's (unit)**	**symbol**	**Obtained value**	**Average radius value**	**Factor mean r**	**Obtained value**	**Average radius value**	**Factor mean r**	**Obtained value**	**Average radius value**	**Factor mean r**
				CBD			**PETsp**			**PODTG2**	
Dimension	D_a (g/mL)		0.43	4.35	4.67	0.39	3.98	4.43	0.59	5,98	6.59
	D_t (g/mL)		0.50	5.00		0.48	4.87		0.72	7.20	
		ξ	0.29	2.49		0.45	3.82		0.28	2.35	
Compressibility	IC (%)		13.04	2.60	3.55	18.30	3.66	5.56	16.90	3.38	5.24
		I_{cd} (N)	111.44	5.57		184.12	9.20		200.00	10.00	
	RH		1.15	9.25	4.41	1.22	8.87		1.20	8.98	
Flowability	α (°)		30.01	3.99		28.07	4.38	7.10	16.21	6,75	7.41
	F(s)		88.00	0.00		3.88	8.06		7.00	6.50	
Lubricity/stability	% HR		1.14	8.85	8.87	1.94	8.05	7.80	0.40	9.60	9.16
	% H		2.20	8.89		4.89	7.55		2.56	8.72	
Lubricity/dosage		% P_f	0.00	10.00	5.00	3.95	9.21	7.16	3.75	9.24	7.83
		Iθ	$6.1*10^{-6}$	0.00		$10.22*10^{-3}$	5.11		$1.28*10^{-2}$	6.42	
	E (min)		>5.00	0.00		0.16	9.66		1.16	7.66	
Disintegration ability	T_d (min)		>3.00	0.00	0.00	0.17	9.41	9.52	0.75	7.49	7.52
	T_{fd} (min)		>3.00	0.00		0.15	9.47		0.77	7.42	

Table 4 SeDeM (SSG)/SeDeM-ODT characterization of the disintegrants.

Factor/Incidence	Parameter's symbol	Obtained value	Average radius value	Factor mean r	Obtained value	Average radius value	Factor mean r	Obtained value	Average radius value	Factor mean r
		EMCS			**SSG**			**CCS**		
Dimension	D_a	0.25	2.58	3.05	0.78	7.82	8.26	0.57	5.71	6.44
	D_t	0.35	3.53		0.86	8.69		0.71	7.14	
	ξ	0.95	7.97		0.12	1.06		0.35	2.91	
Compressibility	IC	26.95	5.39	4.54	9.99	1.98	1.01	20.00	4.00	5.63
	I_{cd}	5.26	0.26		0.00	0.00		200.00	10.00	
	RH	1.36	8.20		1.11	9.44		1.25	8.75	
Flowability	α	41.63	1.67	3.29	15.94	6.81	8.12	41.60	1.68	3.47
	F	58.66	0.00		3.74	8.13		57.66	0.00	
Lubricity/stability	HR	1.12	8.87	9.43	1.14	8.85	4.42	1.01	8.98	4.49
	H	0.00	10.00		37.50	0.00		28.78	0.00	
Lubricity/dosage	P_f	0.39	9.92	5,97	1.57	9.68	5.38	7.14	8.57	6.36
	Iθ	$4.05*10^{-3}$	2.02		$2.16*10^{-3}$	1.07		$8.3*10^{-3}$	4.15	
	E	3.20	3.60			0.00		>5.00	0.00	
Disintegration ability	T_d	2.00	3.33	3.53	-	0.00	0.00	>3.00	0.00	0.00
	T_{fd}	1.89	3.68			0.00		>3.00	0.00	

Table 5 SeDeM-ODT characterization of the MNT and SRB.

Factor/Incidence	Parameter's symbol	Obtained value	Average radius value (r)	Factor mean r	Obtained value	Average radius value (r)	Factor mean r
			MNT			**SRB**	
Dimension	D_a	0.58	5.86	6.32	0.43	4.39	4.69
	D_t	0.67	6.78		0.50	5.00	
	ξ	0.23	1.92		0.27	2.28	
Compressibility	IC	13.57	2.71	2.58	12.05	2.41	4.89
	I_{cd}	62.13	3.10		200.00	10.00	
	RH	1.15	9.21		1.13	9.31	
Flowability	α	50.00	0.00	3.07	16.70	6.66	8.44
	F	147.33	0.00		1.30	9.35	
Lubricity/stability	HR	0.06	9.93	9.37	0.53	9.46	4.99
	H	2.36	8.81		18.93	0.53	
Lubricity/dosage	P_f	1.05	9.78	4.99	0.02	9.99	5.02
	Iθ	$0.42*10^{-3}$	0.20		$0.10*10^{-3}$	0.05	
Disintegration ability	E	0.19	9.61		>5.000	0.00	
	T_d	0.55	8.15	9.05	2.200	2.66	0.88
	T_{fd}	0.18	9.37		>3.000	0.00	

Table 6 SeDeM-ODT for LCT and CELMC.

Factor/Incidence	Parameter's symbol	Obtained value	Average radius value (r)	Factor mean r	Obtained value	Average radius value (r)	Factor mean r
			LCT			**CELMC**	
Dimension	D_a	0.66	6.66	7.05	0.51	5.14	5.79
	D_t	0.74	7.45		0.64	6.45	
	ξ	0.15	1,31		0.39	3.28	
Compressibility	IC	10.53	2.10	2.17	20.27	4.05	4.53
	I_{cd}	62.13	3,10		125.12	6.25	
	RH	1.11	9.41		1.25	8.72	
Flowability	α	10.78	7.84	8.49	34.92	3.01	5.51
	F	3.56	8.22		10.39	4.80	
Lubricity/stability	HR	0.04	9.95	9.23	0.51	9.48	4.74
	H	2.98	8.50		52.75	0.00	
Lubricity/dosage	P_f	0.89	9.82	9,91	0.29	9.94	8.90
	Iθ	0.02	10.00		0.01	7.86	
Disintegration ability	E	0.30	9.40		0.18	9.64	
	T_d	0.25	9.15	9.30	0.24	9.17	9.41
	T_{fd}	0.19	9.35		0.16	9.43	

Table 7 Critical indexes used to establish the optimal formulation.

Code	Parametric Index (PI)	Parameter profile Index (IPP)
CBD	0.40	4.42
PETsp	0.66	6.93
PODTG2	0.86	7.29
LCT	0.80	7.69
CELMC	0.66	6.48
MNT	0.60	5.90
SRB	0.46	4.82
EMCS	0.40	4.97
SSG	0.46	4.53
CCS	0.40	4.40

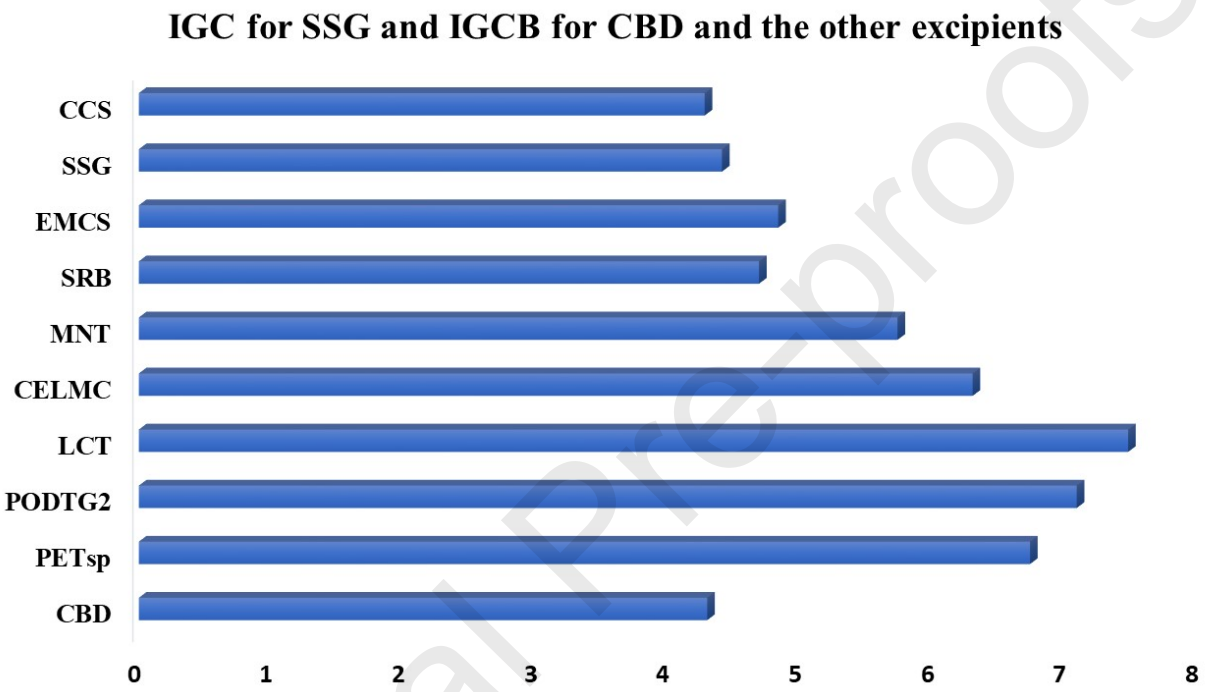


Figure 3 IGCB/IGC for the CBD and excipients verified using SeDeM (SSG)/SeDeM-ODT Expert System

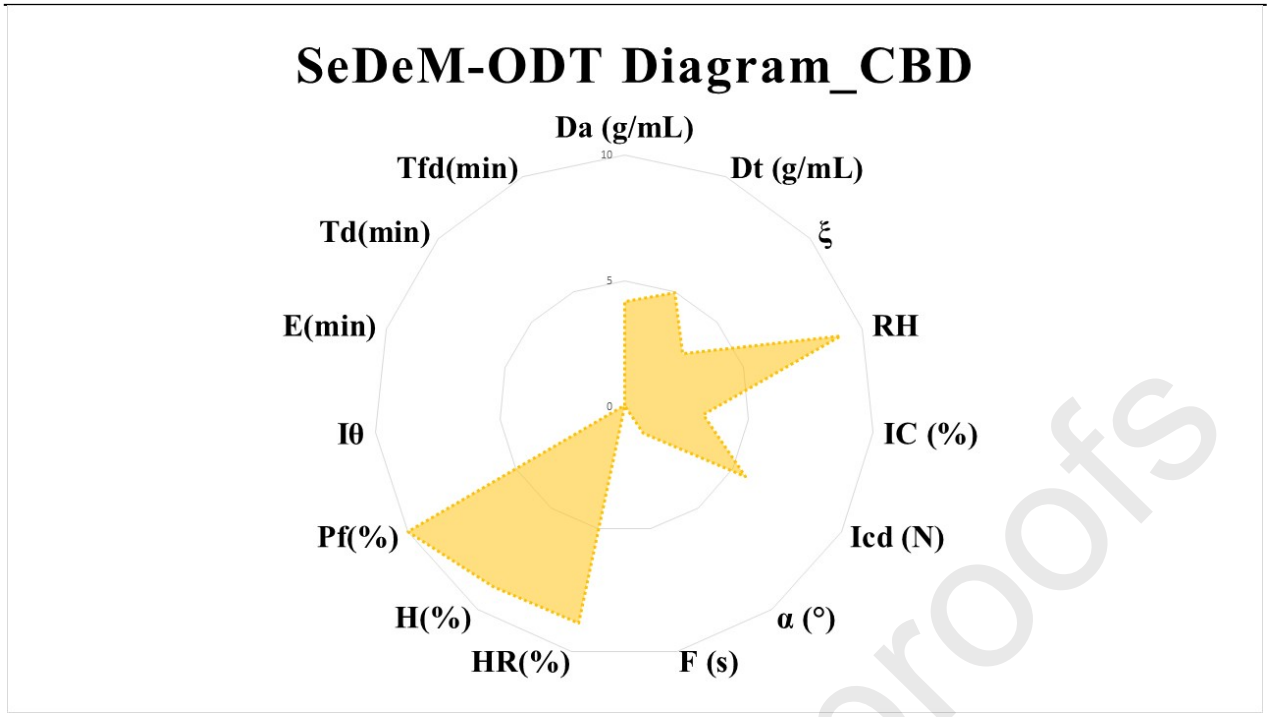


Figure 4 SeDeM-ODT Diagram for CBD

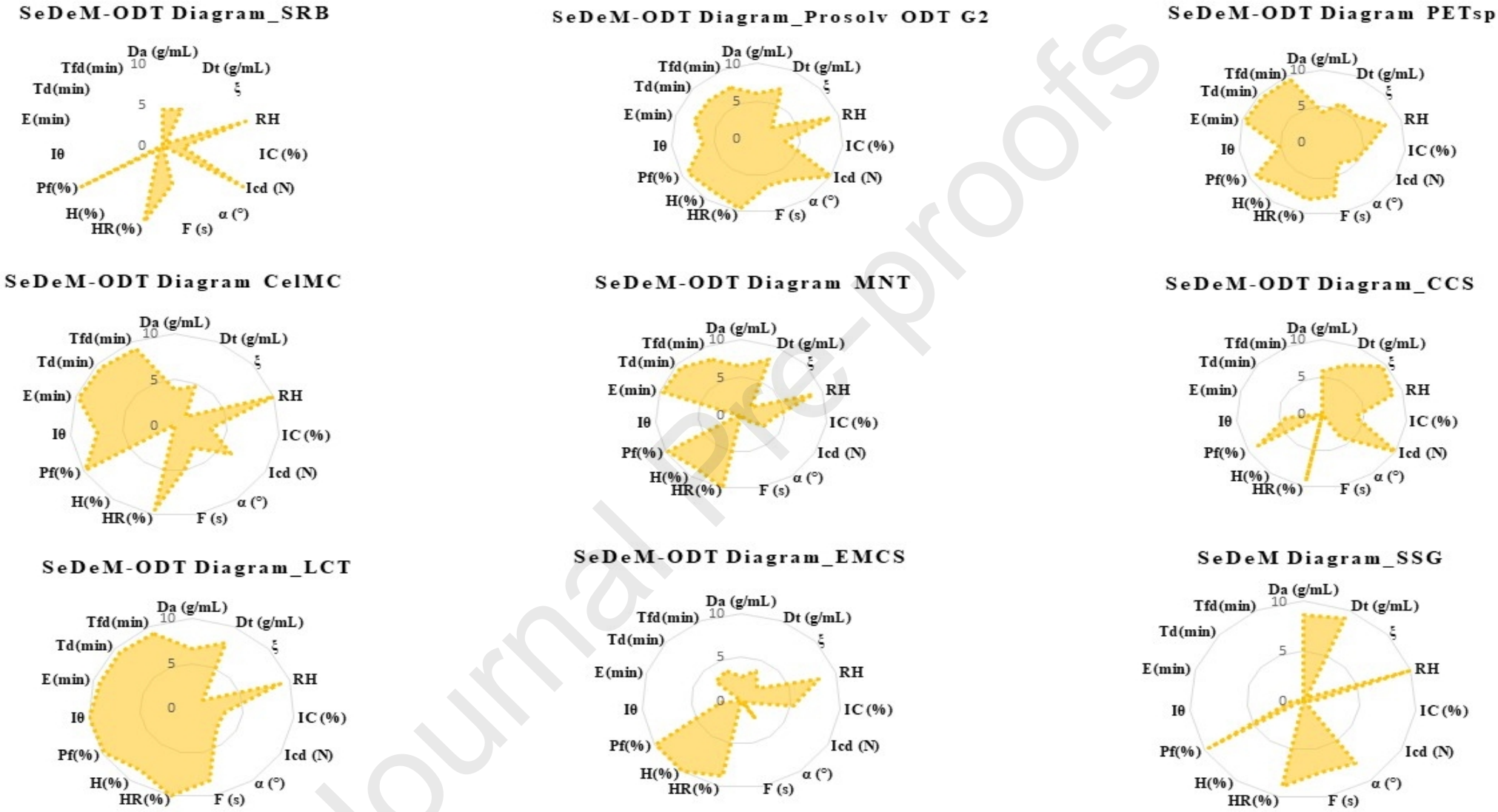


Figure 5 SeDeM-ODT Diagram for: SRB, PODTG2, PETsp, CELMC, MNT, CCS, LCT, EMCS, and SeDeM for SSG.

3.2. Properties that need improvement in the case of CBD and excipients used

The API presents the most properties that need correction (Table 8). The most important properties of an orodispersible tablet are compressibility and disintegration ability. To obtain orodispersible tablets the indicated excipients are the co-processed ones; PODTG2 satisfying all the needed standards while in the case of PETsp only the dimension factor needs improvement. As stated in Table 6 the other excipients studied CELMC and LCT showed a reduced number of properties that need improvement. Another aspect highlighted by this study is represented by the increased value of the disintegration time in the case of the tablets containing only superdisintegrants where the disintegration times were near the superior limit or no disintegration was observed after three or five minutes. This process can be explained by the fact that there is a superior limit of the superdisintegrant concentration which after is reached the disintegration time tends to increase to values that are not accepted by the pharmacopeias (Desai et al., 2014). To obtain good disintegration times different levels of disintegrants should be used respecting the superior limit admitted. For PETsp the only factor that did not accomplish the admitted value was the dimension factor, both of the densities presenting values smaller than five.

Table 8 Properties that need improvement for both API and excipients.

Substance code	Properties that need improvement
CBD	Dimension, Compressibility, Flowability, Disintegration ability
PETsp	Dimension
PODTG2	-
LCT	Compressibility and flowability
CELMC	Compressibility and stability
MNT	Compressibility, flowability, and lubricity (dosage)
SRB	Dimension, Compressibility, Stability, Disintegration ability
EMCS	Dimension, Compressibility, Flowability, Disintegration ability
SSG	Compressibility, Stability, Disintegration ability
CCS	Flowability, Stability and Disintegration ability

3.3. SeDeM-ODT expert system for the fillers

According to the results presented in Table 7, Figure 3 the most suitable filler will be LCT due to its highest IGCB value of 7.47 and also the highest IPP of 7.69. In order to calculate the IGCB, the PI and IPP for each of the evaluated substances were needed to be previously obtained, their values are presented in Table 7. Since LCT is an excipient manufactured to ease the tableting process, the values obtained were expected. The smaller values were recorded in the case of compressibility where the excipient presented values lower than the values admitted, but these values can be corrected by increasing the compaction force (the breaking hardness was 62 N so it can be increased to values up to 200 N so that the compressibility factor to be increased). The bucodispersibility is a factor suggesting that LCT can be used easily to obtain a good disintegration time. The other excipient evaluated using the SeDeM-ODT tool was CELMC. This excipient presented an IGCB of 6.29, and the PI, IPP were also higher than the limits admitted. As in the case of LCT neither in this case, the values regarding the compressibility weren't achieved but the bucodispersibility properties were worthy of consideration. Considering the PI, IPP and, IGCB, CELMC presents physical and pharmaco-technical properties that need small adjustments to realize the direct compression. The fillers presented only two properties that needed correction, for LCT

the compressibility and the flowability needing adjustments whilst for CELMC the compressibility and lubricity/stability did not exhibit a radius value higher than five. The compressibility is low since the porosity presented low radius values of 1.31 for LCT and 3.28 for CELMC. Also, the Carr Index was less than five for both fillers fact that conducted in the end to a lack of compressibility according to the SeDeM-ODT expert system. In the case of CELMC, an increasing compression force might conduct to a better value of compressibility because the I_{cd} was not maximum and with a possible value of ten for the I_{cd} the compressibility factor will exceed the five radius value.

3.4. SeDeM-ODT expert system for sweeteners

The results obtained for the two sweeteners are presented in Table 5. The two sweeteners evaluated with the help of the SeDeM-ODT tool were MNT and SRB. Besides the sweetener property, MNT could be used as a filler. Alongside LCT and CELMC the powder that had the good IGCB values, MNT, presented also a value higher than 5 of 5.73. The compressibility value is situated between the values of the two fillers presented previously but lower compared to the SRB. Neither in the case of MNT or SRB were achieved values of compressibility of at least five. MNT is differentiating from the SRB with the better ability of disintegration this parameter had values higher than nine in the case of MNT while in the case of SRB the values were lower than one. This parameter indicates the fact that MNT is more appropriate for and fast dispersion compared to SRB. The advantage of using SRB consists of the flow rate property, which even though it is smaller than the value admitted, is larger compared to the one belonging to MNT. This fact can be explained by the lubricity/dosage parameter where it can be observed the fact that a thirty-eight times bigger quantity crossed the sieve with a dimension of 50 μm in the case of MNT compared with the SRB. Since MNT can be included in the class of fillers it was expected to present good properties regarding the IGCB and IPP. As a result of its property of being sweet MNT, might be a good candidate for an excipient used for ODTs fulfilling the palatability properties. In this case, three parameters need improvement, compressibility and flowability, and lubricity (dosage). For the MNT an excipient that has good flowability properties should be taken into consideration when developing ODTs whilst for SRB the dimension factor, compressibility, and disintegration behaviour need improvement. For SRB both densities were less than five and the disintegration behaviour was poor with a radius value less than 1.

3.5. SeDeM-ODT expert system for CBD and the co-processed excipients

In compliance with the aim of this paper, the API must be retrieved in a formulation in which an excipient with good properties for both compressibility and good dispersibility can be found. One factor that needs to be calculated is IGCB. Because CBD presents a deficit regarding compressibility this parameter needs improvement, to achieve a value of the radius of at least five. From the verified excipients the ones with both compressibility and disintegration ability radius values higher than five were PODTG2 and PETsp. In the case of CBD, both of these parameters need adjustments. The results for the API and co-processed excipients can be found in Table 3. The composition of the co-processed excipients could be found in Table 9.

Table 9 The composition of the co-processed excipients.

Name	Manufacturer	Excipient	Role
PODTG2	JRS Pharma	CELMC	Filler
		SiO_2	Lubricant
		MNT	Sweetener/filler
		Fructose	Sweetener
		Crospovidone	Disintegrant
PETsp	JRS Pharma	CELMC	Filler
		SiO_2	Lubricant
		SSG	Disintegrant
		Sodium stearyl fumarate	Lubricant

Besides the good properties regarding the compressibility and disintegration, the presence of SSG in PETsp and Crospovidone in PODTG2 represents an advantage because it can improve the bioavailability of CBD due to the fact that disintegrants are increasing the specific surface that is in contact with the saliva, also; their hydrophilic character sustained by the presence of numerous hydroxyl groups could help in the bioavailability improvement of CBD. To accomplish the palatability in the case of using PETsp a sweetener should be used. From the results obtained the most suitable sweetener is MNT. A flavoring agent should be taken into consideration to obtain a complete formulation. The other co-processed excipient used, PODTG2, presents more advantages regarding palatability because in its composition it can be found the fructose and MNT, excipients with sweetening properties. CBD has four factors that do not exceed the limit value of five represented by dimension, compressibility, flowability, and disintegration ability, whilst the lubricity/stability and lubricity/dosage exceeded the limit values of five. For PETsp the only parameter that needs adjustment is the dimension whilst the PODTG2 represents the excipient that is the most suitable for the development of CBD-ODTs. The IGCB for both of the co-processed excipients was higher than five, whilst for CBD was less than five. PODTG2 has the second-highest value for IGCB while PETsp presents the third-highest value, the biggest value regarding the IGCB belonging to LCT. Also, the IP and IPP were higher than 0.5 and 5 for the co-processed excipients.

3.6. SeDeM (SSG) SeDeM-ODT expert system for disintegrants

The results describing the disintegrants can be found in Table 4. Two disintegrants were evaluated using the SeDeM-ODT methodology: CCS and EMCS while in the case of SSG, the SeDeM tool was used because of the lack of compressibility. To improve this parameter a mixture of talc (2.36%), Aerosil® 200 (0.14%), and magnesium stearate (1%) was used, but even with this mixture, no improvements regarding the compressibility were obtained. Another disintegrant with low properties regarding mechanical strength was EMCS. The most interesting fact in the case of the CCS and EMCS was recorded during the disintegration test where the disintegration times were higher than expected. In the case of CCS, the times regarding the disintegration times were exceeded while in the case of EMCS, were observed better disintegration properties compared with CCS. In both cases, a value of five radii was not achieved. In the case of CCS, an explanation for the lack of disintegration could be explained by the compression force used which might have been higher enough to delay the disintegration.

In some articles, it has been presented that there is a limit after which in each case of the disintegrant the disintegration does not occur. For the CCS it is mentioned by Desai et al. a concentration of 6 % whilst in

the case of SSG were used concentration of 8%. Soy polysaccharides were recently used to obtain sublingual tablets with sildenafil the maximum concentration used to develop sublingual tablets was 8% (Desai et al., 2014; Soularol et al., 2017; Hosny et al., 2015).

From the three disintegrants, the best IGCB belongs to EMCS, which could be explained by the high value of the lubricity/stability parameter. Even though none of the super-disintegrants presents an IGCB higher than five, taking into consideration that the value is very close to five in all of the disintegrants could be used. Also, a mixture of two disintegrants could conduct in an improvement of the disintegration ability of the obtained tablet. The IP was less than 0.5 in all of the three cases whilst the IPP was less than five for all three disintegrants. The lower values for IP, IPP, and IGCB can be attributed in the case of EMCS to the dimension, compressibility, flowability, and disintegration ability factors that exhibited values lower than five. EMCS presented one of the highest porosities but the I_{cd} was less than one. In future studies, a higher compression force might conduct to a better compressibility factor. For SSG besides the compressibility factors that had a value lower than five the lubricity/stability factor needs to be improved. CCS represents one of the excipients that presented the worst disintegration behaviour because no disintegration occurred after 3 or 5 minutes, also, the flowability and lubricity/stability factors need improvement. In the case of CCS, a value higher value of the compressibility factor might be obtained through the adjustments of the compression force just as in the case of EMCS. For SSG beside the compression force increasement a mixture of lubricants needs to be used as a result of the lack of compaction.

3.7. Determination of the quantity of PETsp and PODTG2 needed to obtain compressibility of at least 5

As it has been established the excipients that can be used to obtain orodispersible are PODTG2 and PETsp which comply with both good compressibility and bucodispersibility. The quantity of PETsp needed to obtain a tablet with good compressibility and bucodispersibility properties is 71.72%. The percent of API in the tablet will be 5 %. Up to 100 %, other excipients can be added such as sweeteners, flavour agents and, solubility increasing agents. In the case of PODTG2, the quantity needed to obtain a tablet that satisfies all the proposed requirements is 85.57%. Due to the presence of fructose and MNT in this case no sweetener is needed, only a flavour agent should be used to accomplish all the palatability properties.

4. Compatibility studies

4.1. FTIR results and discussions

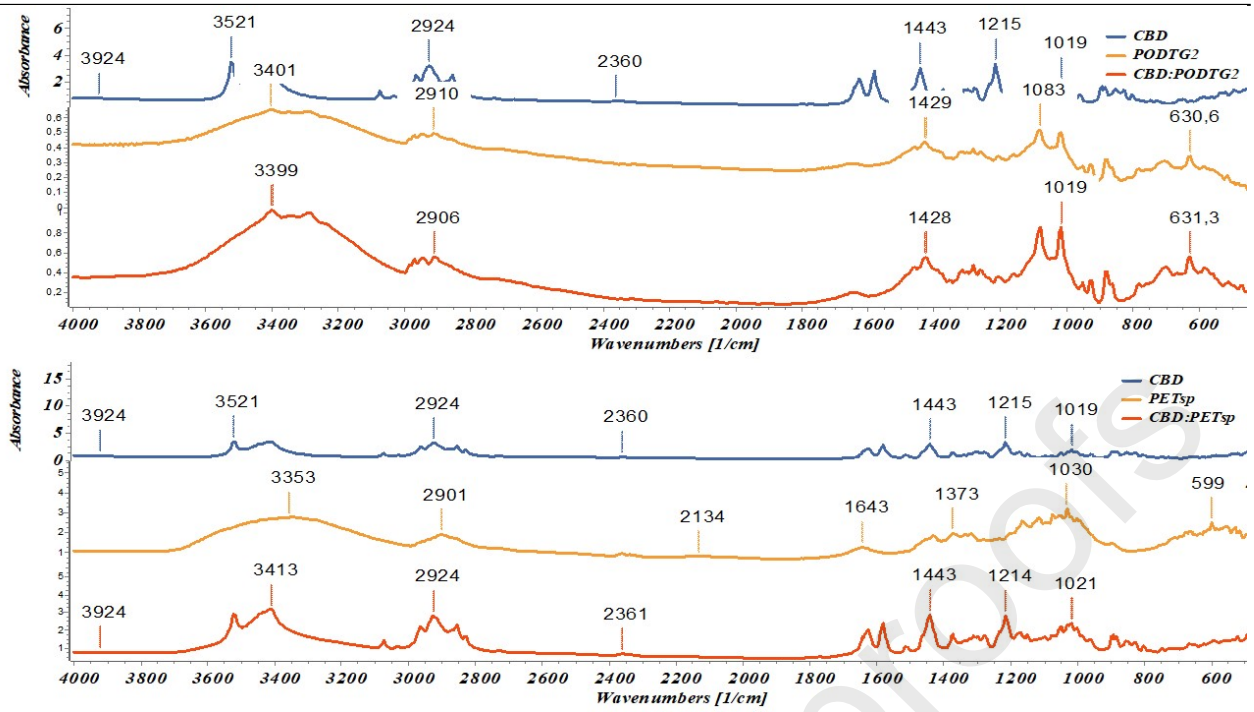


Figure 6 FTIR spectra for CBD, co-processed excipients, and binary mixture (1:1).

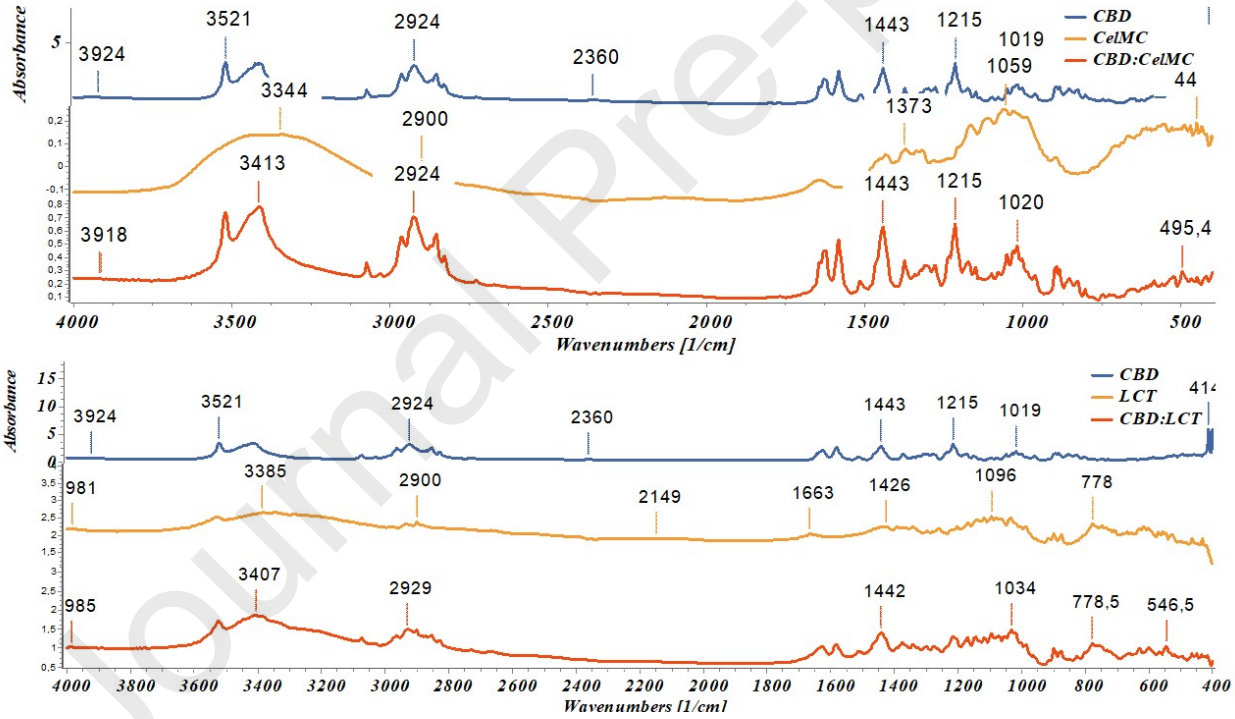


Figure 7 FTIR spectra for CBD, fillers, and binary mixture (1:1)

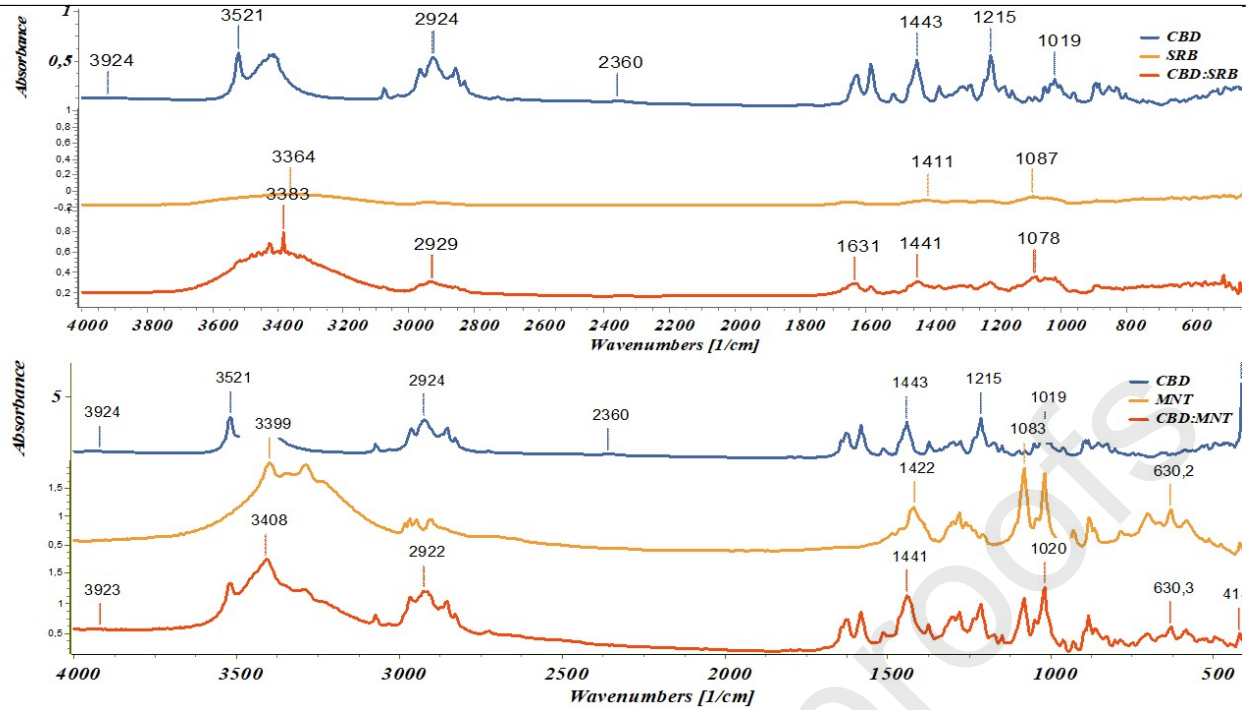


Figure 8 FTIR spectra for CBD, sweeteners and their binary mixtures (1:1)

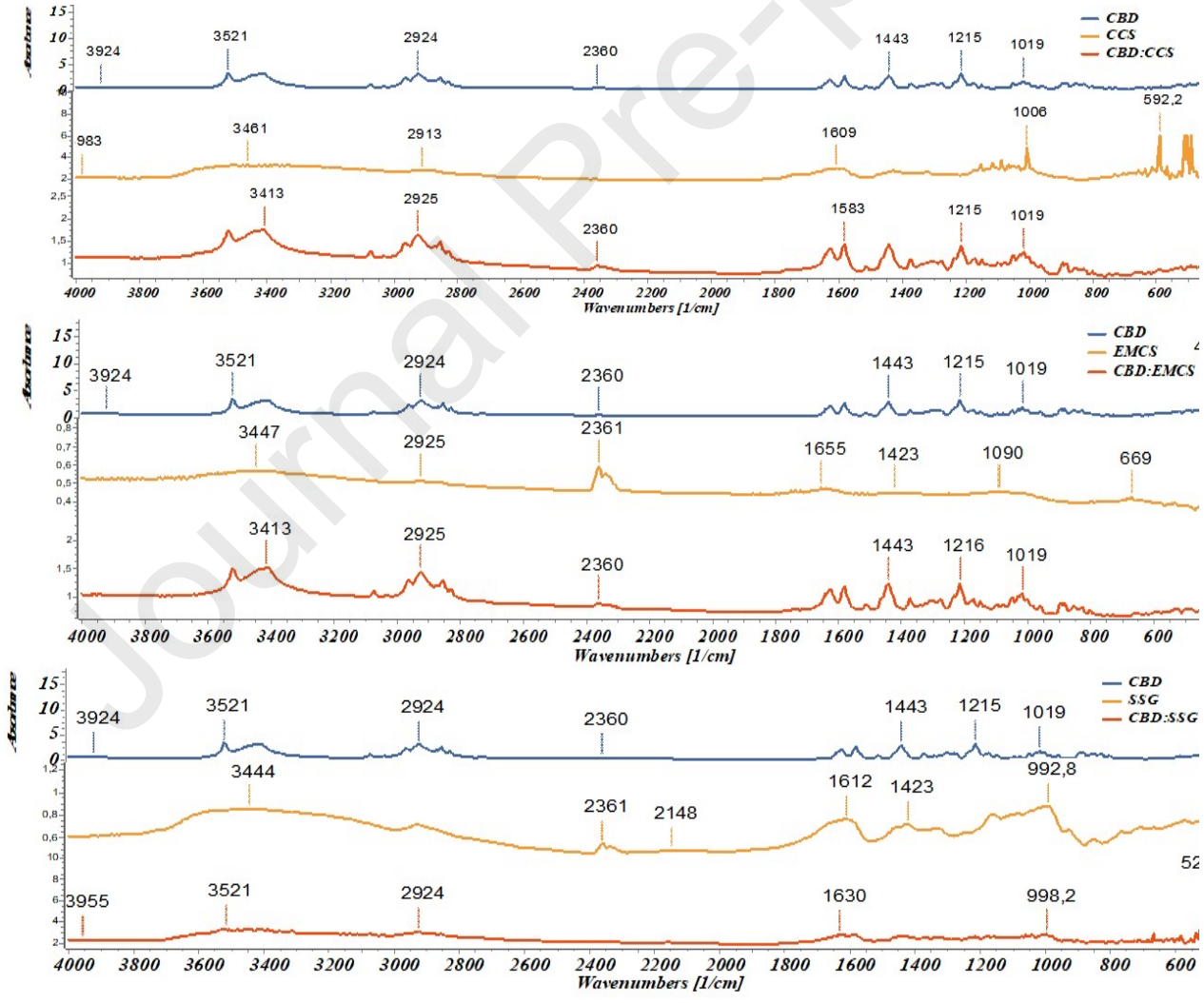


Figure 9 FTIR spectra for CBD, disintegrants and their binary mixtures (1:1)

Table 10 Characteristic wavenumbers of the API, raw materials and binary mixtures.

Raw materials binary mixture	Characteristic wavenumbers (cm^{-1})
CBD	3922; 3522, 3439, 3073; 2923; 2858; 2728; 2669; 2476; 2361; 2029; 1770; 1627; 1582; 1513; 1445; 1374; 1278; 1216; 1098; 1020; 885; 658
LCT	3981; 3814; 3526; 3384; 2900; 2668; 2197; 2148; 1663; 1425; 1342; 1261; 1096; 1035; 900; 777; 617
CBD:LCT	3985; 3857; 3522; 3407; 3074; 2929; 2668; 2154; 1770; 1627; 1582; 1441; 1374; 1276; 1215; 1145; 1096; 1033; 897; 778; 600
CelMC	3344; 2900; 2133; 1641; 1431; 1373; 1321; 1059
CBD:CelMC	3918; 3849; 3520; 3413; 3073; 2924; 2855; 2728; 1769; 1627; 1583; 1513; 1443; 1374; 1308; 1215; 1020; 897; 748
PETsp	3353; 2901; 2361; 2134; 1642; 1430; 1372; 1321; 1114; 1073; 1030; 663
CBD:PETsp	3923; 3520; 3412; 3073, 2923; 2855; 2728; 2360; 2157; 1770; 1627; 1582; 1442; 1374; 1214; 1021; 897; 665
PODTG2	3994; 3400; 3289; 2910; 1899; 1654; 1428; 1286; 1082; 1019; 927; 880; 783; 705; 630;
CBD:PODTG2	3993; 3399; 3289; 2906; 1642; 1427; 1283; 1082; 1019; 927; 880; 699; 631
MNT	3993; 3399; 3287; 2969; 2905; 2720; 1422; 1282; 1082; 1019; 929; 881; 784; 700; 630
CBD:MNT	3923; 3520; 3408; 3074; 2922; 2856; 2728; 1627; 1583; 1441; 1281; 1215; 1082; 1020; 882; 701; 630
SRB	2939, 1649; 1410; 1087; 890; 750
CBD:SRB	3425; 3382; 2929; 2358; 1631; 1440; 1375; 1308; 1217; 1077; 1018; 891; 751
EMCS	3993; 3904.8; 3841.1; 3736; 2925.4; 2361.3; 1872.1; 1735.2; 1654.6; 1423; 1250.9; 1089.7; 766.35; 669.04
CBD:EMCS	3849; 3727; 3520; 3413; 3073; 2924; 2855; 2728; 2360; 1627; 1582; 1513; 1443; 1374; 1215; 1019; 896; 749; 650
CCS	3982; 3460; 3374; 2913; 1608; 1429; 1323; 1265; 1087; 1005
CBD:CCS	3849; 3520; 3412; 3073; 2924; 2855; 2360; 1583; 1512; 1442; 1374; 1215; 1019; 897; 664
SSG	2928; 2360; 2147; 1611; 1423; 1334; 1161; 992; 853; 707
CBD:SSG	3520; 3418; 3073; 2923; 2360; 1630; 1586; 1442; 1325; 1175; 998; 849; 765; 669.

The characteristic bands for the binary mixtures and single powders can be found in Table 11. The obtained spectrums are presented in Figures 6-9. The CBD presence (Figure 6-9) can be highlighted in comparison with the excipients by the presence of the bands belonging to C=C and =C-H aliphatic groups (1582 and 1627 cm^{-1}). These two specific bands were observed also in the studies conducted by Andriotis et al. (Andriotis et al., 2020) In most of the cases the previously mentioned bands could be observed in the binary mixtures, the only exceptions being represented by CBD:PODTG2 (Figure 7) where a prominent band was observed at 1642 cm^{-1}. In the case of PODTG2, a characteristic band was observed at 1654 cm^{-1} and an explanation for the shifted characteristic band in the binary mixture might be the reciprocal interference between these two close bands. In the case of CBD:SRB (Figure 8) only one band was

observed at 1631 cm^{-1} and no band was registered by the software used in the case of =C-H. The last excipient that in a binary mixture with CBD gave only one representative band for CBD was CBD:CCS (Figure 10), where the characteristic band was situated at 1583 cm^{-1}. In the other binary mixtures studied small differences regarding the characteristic groups belonging to CBD were observed. The tensile vibration given by the OH group was present in most of the binary mixtures (2900-2926 cm^{-1}). The band at 1445 cm^{-1} could not be considered a representative band for CBD because it is characteristic of methylene or methoxy groups (C-H deformation). In most of the cases, a band near 1445 cm^{-1} was observed also, for excipients between 1410-1430 cm^{-1}. The absorption band at approximatively 1250 cm^{-1} can be assigned to the asymmetric stretching of the C-O-C function belonging to CBD, EMCS, and CCS. An interesting fact is represented by the co-processed excipients which due to the multiple excipients found in the composition was expected to be very hard to be interpreted but if the co-processed excipient is considered as one singular excipient further characterization could be realized. In the case of PETsp and PODTG2 interferences between the characteristic bands might occur. The LCT and CelMC are compatible with CBD, too (Figure 8). FTIR analysis proved that CBD could be identified in mixtures and the excipients did not have a major influence on the characteristic bands of the API and as a conclusion, all the studied excipients could be used in combination with CBD.

4.2. DSC results and discussions

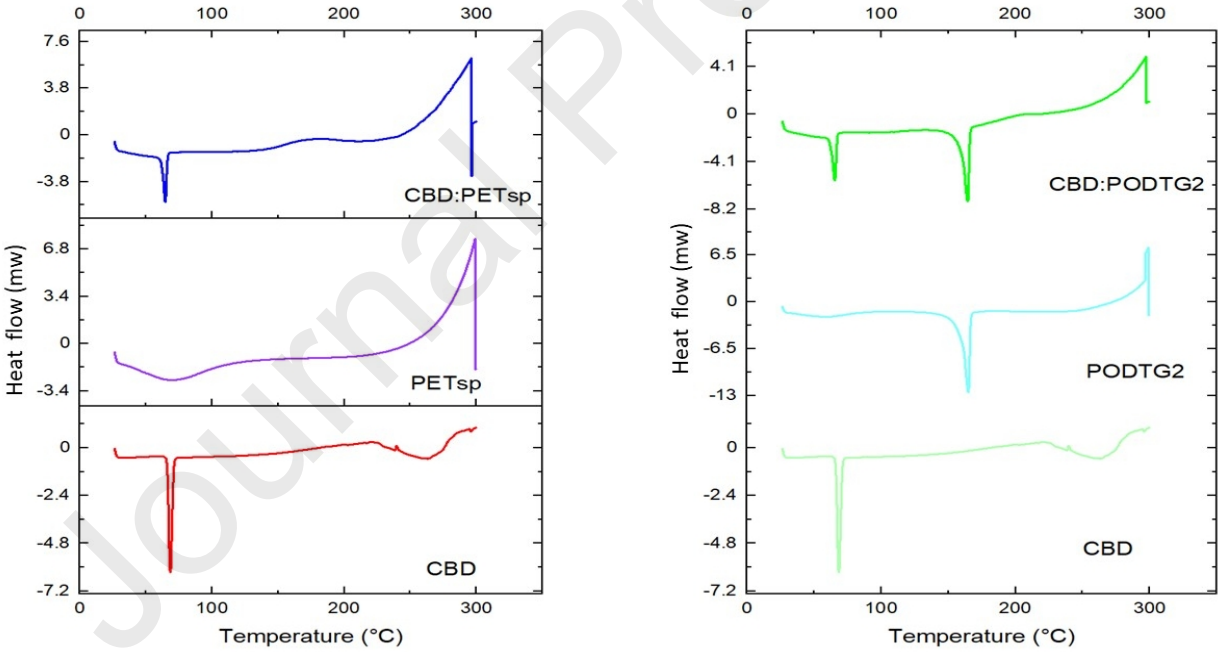


Figure 10. Thermograms for CBD, co-processed excipients, and the binary mixtures (1:1)

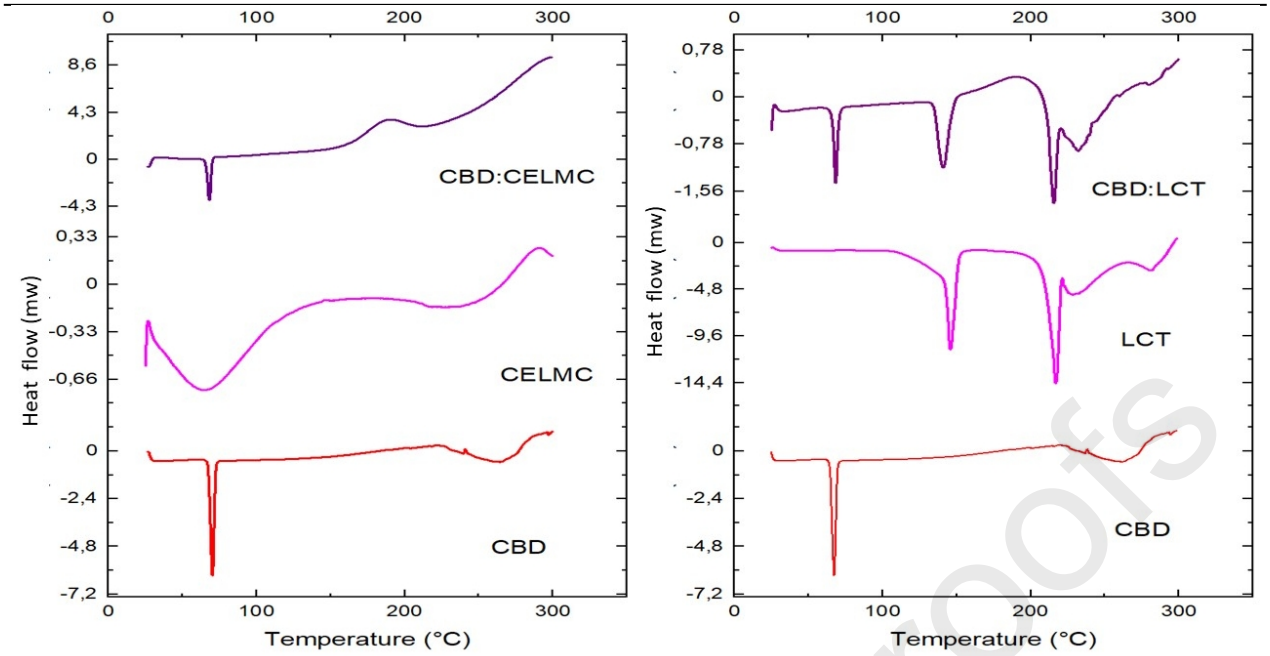


Figure 11. Thermograms for CBD, fillers and the binary mixtures (1:1)

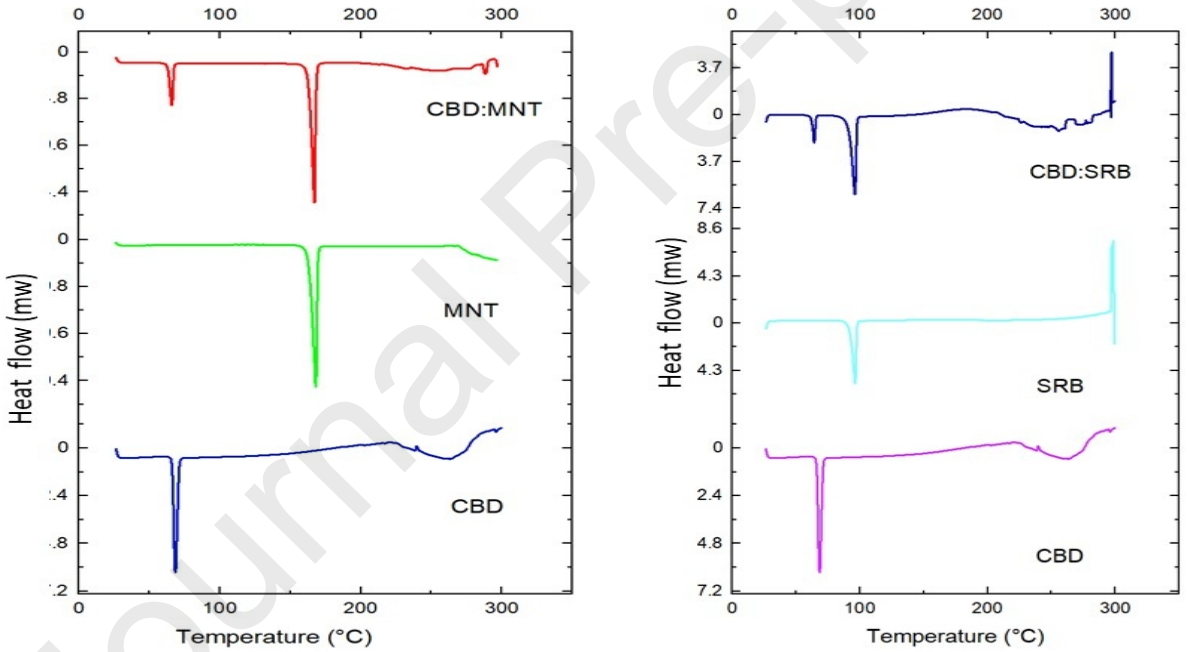


Figure 12. Thermograms for CBD, sweeteners, and the binary mixtures (1:1)

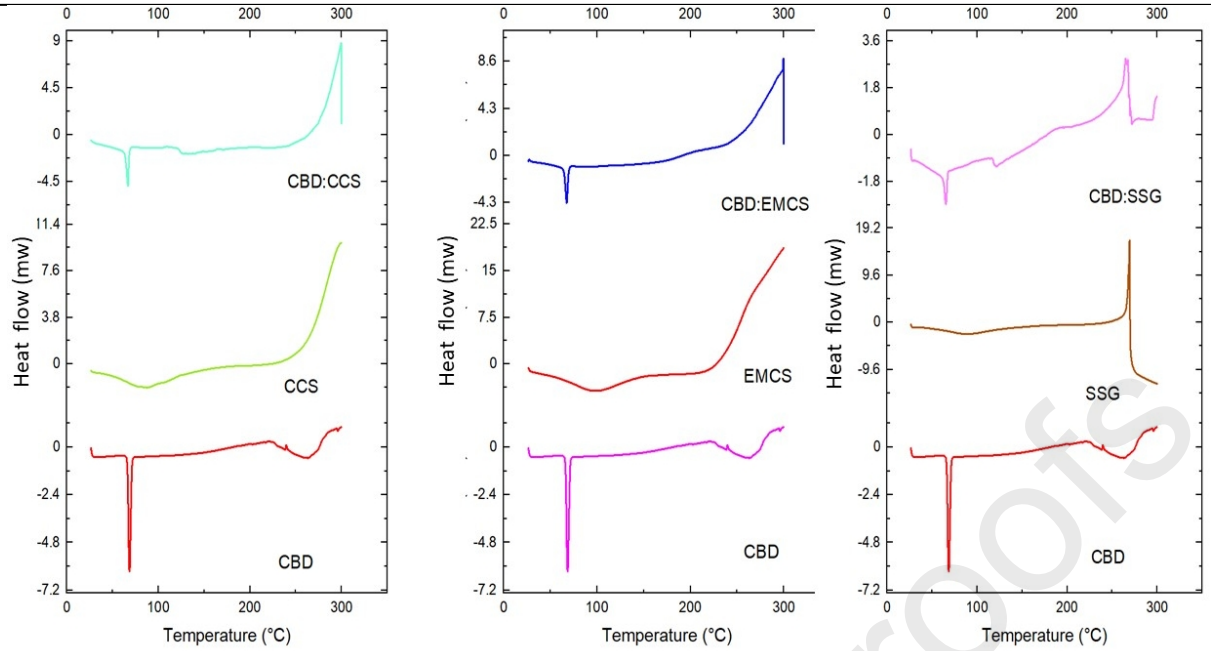


Figure 13. Thermograms for CBD, disintegrants, and the binary mixtures (1:1)

The DSC curve belonging to CBD (Figure 10-13) presented an endothermic peak that indicates the melting point of 68.97°C confirming the results of Andriotis and his co-authors (69°C) (Andriotis et al., 2020). The T_{onset} was 66.45°C, the T_{endset} was 71.43°C while the ΔH=20.12 J/g. This peak represents a water loss. The decomposition of CBD might take place at temperatures higher than 300°C.

In the case of PETsp (Figure 10), a wide peak could be observed that started at 26.54°C and ended at 99.5°C with a T_{peak} at 70.84°C, representing the water loss. Not the same results were obtained in the case of PODTG2 (Figure 10) where an endothermic peak could be observed with the T_{peak} at 166.83°C, T_{onset} of 162.06°C, and T_{endset} of 169.22°C. According to the thermal results, we can conclude that the peak belongs to MNT one of the compounds retrieved in the co-processed excipient. We could highlight this fact because MNT (Figure 12) was one of the sweeteners with which we have characterized with the help of the SeDeM-ODT Expert System. In the case of the previously mentioned sweetener, the T_{peak} was 169.01°C, T_{onset} was 165.83°C and T_{endset} was 172.38°C results obtained also by Agatonovic-Kustrin et al. where the compatibility between MNT and omeprazole isomers was studied (Agatonovic-Kustrin et al., 2008). As it can be seen a small shifting can be observed in the co-processed excipient which is normal due to the number of excipients found in PODGT2 (five components). The other sweetener studied for the thermal properties was SRB (Figure 12) which had a T_{peak} of 99.05°C, a T_{onset} of 95.49°C and, T_{endset} of 100.98°C.

The disintegrants studied presented also different behaviour in terms of thermal results (Figure 13). EMCS just as CELMC presented a wide peak which could be attributed to water loss and an exothermic peak at about 300°C. Also, an exothermic peak could be observed at SSG with a T_{peak} of 270.8°C, a T_{onset} of 265.66°C and, a T_{endset} of 270.13°C that could be observed also in the binary mixture. In the case of CCS, the endothermic peak could be associated with water loss and an exothermic event

occurred just as in the case of the other two disintegrants. The same results regarding the CCS were obtained by Thadkala et al. and Faroongsarng and Peck (Thadkala et al., 2012; Faroongsarng et al., 2003).

The fillers presented a different thermal behaviour, as in the case of CELMC (Figure 11) just an endothermic peak could be observed which could be linked to water loss. LCT (Figure 11) presented two distinctive endothermic peaks. The first endothermic peak represents the melting point (started at 106.07°C and ended at 150.02°C with a T_{peak} of 146.05°C). The second peak revealed the decomposition which started at 176.34°C and ended at 222.25°C with a peak at 218.04°C. The same results were noticed in the study of Lahrib et al. Where α and β-lactose were thermally characterized (Lahrib et al., 2003). By comparison, we can conclude that α-lactose was present in our mixture because it presents two endothermic peaks compared to β-lactose which has only one peak and its maximum is at temperatures higher than 230°C.

The binary mixtures presented small shifting regarding the T_{peak}, T_{onset} and, T_{endset} were recorded. CBD characteristic peak is distinguished at 69°C in most of the binary mixtures, a domain where water loss is registered for many of the excipients used. Also, in most of cases, the intensity of the CBD peak was reduced fact that can be explained by the halved quantity of CBD present in the binary mixture. This was the case of CELMC, EMCS, CCS, SSG and, PETsp. In the case of excipients, the characteristic exothermic or endothermic peaks appeared also in combination with the API. The shifting regarding the melting peak of the API in the binary mixtures was recorded. In most of the cases, small shifting less than 1°C was registered. The excipients where the melting point of CBD shifted less than 1°C were: MNT, SRB, EMCS, LCT, and, CELMC. In the case of the co-processed excipients, a shift less than 2°C was recorded. If we consider the number of excipients reunited in the co-processed excipients the results are unexpectedly good concerning compatibility. The two cases with a bigger shift recorded were in the case of CCS (2.41°C) and SSG (4.61°C). In the case of CCS, the shift might be explained by the number of hydroxyl groups that could interact with the hydroxyl groups of CBD as in the case of SSG where also a high number of hydroxyl groups are displayed.

5. Conclusions

Taking into consideration the results obtained using the SeDeM-ODT diagrams, the API and possible excipients that could be used for developing orodispersible tablets were evaluated. The most important critical factors considered were compressibility and disintegration ability. IGCB showed us that the best excipients that could be used to obtain orodispersible tablets were PODTG2 and PETsp, also LCT and CELMC presented good IGCB values. From the two co-processed excipients PODTG2 needs just one improvement represented by the taste, while if PETsp is used to obtain ODT, a sweetener and a flavour should be added to the composition. Fast disintegration represents another critical parameter. The possibility of using a mixture of super disintegrants could improve this property. The analytical preformulation studies (DSC and FTIR) presented the fact the in most cases no interactions occurred.

In the end, we can conclude that from an analytical point of view each excipient could be used to obtain ODTs but from a pharmacotechnical point of view, some of the excipients need improvement. Another important fact is the concentration of the excipient in the final mixture, if a small quantity of an excipient with an IGCB less than 5 is used its influence won't have the same impact as if a higher concentration of an excipient with poor pharmacotechnical properties would be used. Future studies will be conducted to obtain CBD-ODT taking into consideration the obtained results.

Author Contributions:

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All authors have read and agreed to the published version of the manuscript.

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