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PURPOSE

Cannabidiol (CBD) is a non-psychoactive cannabinoid isolated from *Cannabis sativa*. It has been reported that CBD has anticonvulsant, anxiolytic, antipsychotic, and anti-inflammatory effects and was approved by the FDA as a treatment of epilepsy in pediatric. Despite the many pharmacological potentials of CBD, its drawbacks have limited its applications in therapeutics. Poor water solubility is the major drawback in addition to the first-pass metabolism and thus low bioavailability (approximately 6%). The primary purpose of the current project was to enhance the CBD bioavailability by improving its solubility and avoid the effect of first-pass metabolism using Hot-Melt Extrusion technology.

OBJECTIVE

The main objective of this project was to develop CBD muco-adhesive buccal film using HME in order to improve the water solubility, avoid the first pass metabolism and therefore enhance the CBD bioavailability.

METHODS

Different formulations were developed by mixing 10% w/w CBD with polymeric carrier/s and other excipients (Table 1). The resulted physical mixtures were fed into a Thermo Scientific HAAKE Mini lab II (Thermo Fisher Scientific) and a film die (1 mm thickness) was used to produce the CBD films. Differential scanning calorimetry DSC (TA DSC 25) was performed for CBD, the polymeric carriers and the extruded films to determine their thermal characterization. Samples were weighed in T-zero pans (3–5 mg). The temperature was elevated from 25 to 200 °C at a rate of 10 °C/min under a flow of ultrahigh purity nitrogen gas. CBD drug content and content uniformity were evaluated by HPLC. Bio-adhesion test was performed using a texture analyzer (TA-XT2) to evaluate the adhesiveness properties of each film. Solubility studies were performed for the developed films and the pure CBD using the shake-flask method at room temperature for 48 hours to evaluate the improvement of CBD solubility in the HME films. A drug release study was performed using a multi-position Stirring Hot Plate. The dissolution media used was 100 mL of simulated saliva (pH 6.8), 0.1 % w/v SLS at 37 ± 0.5 ºC. Samples withdrawal were at 15, 30, 60, 90, 120, 180 and 240 minutes for analysis using HPLC.

RESULTS

- The drug content in all the formulations was in the range of 93.6 - 103%.
- The DSC results show melting peaks at 69 ºC and 65 ºC for CBD and PEO N80 respectively. The CBD endothermic peak disappeared in all prepared HME films indicating the transformation of CBD from crystalline to amorphous state (Figure 1).
- The bio-adhesion results (Table 2) demonstrated higher adhesivenes.s for the formulation containing PEO N80 and carbopol compared to other formulations.
- The solubility studies showed an enhancement in CBD solubility for all HME buccal films (Figure 2). The CBD water solubility showed 125.60, 307.56, 318.22, and 362.72 µg/mL for formulations **F4**, **F6**, **F7**, and **F8** respectively. While the pure CBD water solubility was below the LOD of the analytical method.
- The drug release studies, as shown in Figure 3 showed significant enhancement in the CBD release in formulations **F4**, **F6**, **F7** and **F8** (2 to 5 fold) compared to the pure CBD.

Table 1. HME buccal film formulation composition

	PEO-N80 % w/w	Klucel™ EF % w/w	SOLUPLUS % w/w	TPGS % w/w	SLS % w/w	CBD % w/w	Carbopol 980 % w/w	Carbopol 934 % w/w
F1	68	0	10	0	2	10	0	10
F2	75	0	10	5	0	10	0	0
F3	0	75	10	5	0	10	0	0
F4	0	68	10	10	2	10	0	0
F5	30	38	10	10	2	10	0	0
F6	75	0	0	5	0	10	10	0
F7	75	0	0	5	0	10	0	10
F8	85	0	0	5	0	10	0	0

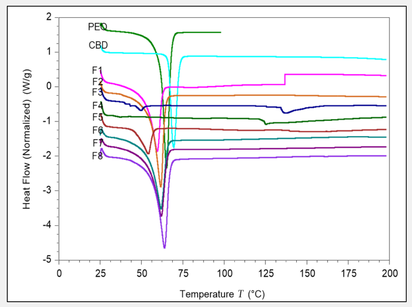

Figure 1. DSC Thermogram of CBD, polymers, and HME films (F1, F2, F3, F4, F5, F6, F7, and F8)

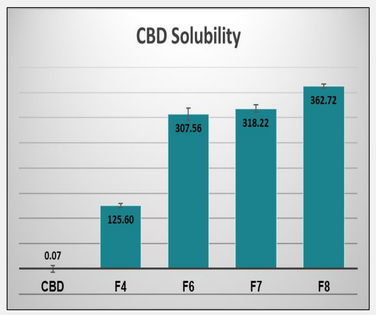

Figure 2. CBD water solubility in µg/mL for F4, F6, F7,F8, and pure CBD.

Table. 2 Ex-vivo adhesion results for CBD mucoadhesive buccal films

	peak force N	Adhesiveness N.mm	work of adhesion	Stringiness mm
F1	0.774	1.095	0.183	0.412
F2	0.670	0.726	0.061	0.221
F3	0.839	0.977	0.131	0.276
F4	0.565	0.781	0.078	0.208
F5	0.221	1.060	0.034	0.182
F6	0.846	1.663	0.258	0.512
F7	1.276	1.607	0.423	0.591
F8	0.944	1.126	0.320	0.637

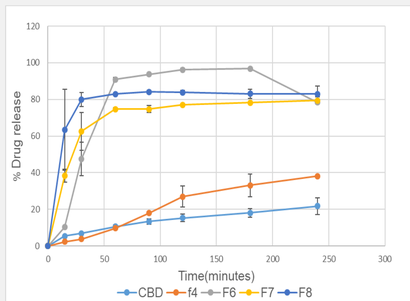

Figure 3. release study profiles for f4, f6, f7 and f8 and pure CBD

CONCLUSION

Successfully mucoadhesive buccal films have been developed using HME technology. The results of this study showed an enhancement of the solubility and drug release of CBD. This finding supports that the developed formulations promise to enhance the CBD bioavailability.

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