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Giovanna Brunelly Lima Galvão

A Compatibility Study between Cannabidiol and Pharmaceutical Excipients Commonly Used in Lipid Systems by Thermal Analysis and Fourier Transform Infrared Spectroscopy

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Trabalho de Conclusão de Curso apresentado ao Curso de Graduação em Farmácia da Universidade Federal do Rio Grande do Norte, como requisito parcial para obtenção do título de Bacharel em Farmácia.

Orientador: Prof. Dr. Eryvaldo Sócrates Tabosa do Egito
Coorientadora: Msc. Ízola Morais de Medeiros Ramalho

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SUMÁRIO

A Compatibility Study between Cannabidiol and Pharmaceutical Excipients Commonly Used in Lipid Systems by Thermal Analysis and Fourier Transform Infrared Spectroscopy

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RESUMO

O canabidiol (CBD) é o segundo maior componente principal da Cannabis sativa, dotado de atividade terapêutica e não alucinógeno. No entanto, o CBD apresenta desvantagens, como baixa biodisponibilidade oral e baixa solubilidade em água, o que dificulta sua administração por via oral. Assim, a fim de melhorar sua solubilidade e biodisponibilidade oral, formulações à base de lipídios, como sistemas emulsionados, foram desenvolvidas. No entanto, há uma falta de informações sobre a compatibilidade do CBD com os óleos e tensoativos usados em sistemas emulsionados. Além disso, o conteúdo lipídico dessas formulações não é relatado. Assim, o objetivo deste trabalho foi avaliar a compatibilidade entre CBD e excipientes comumente usados na produção de sistemas emulsionados, a fim de fornecer informações para o desenvolvimento de formulações lipídicas veiculando o CBD. Os tensoativos Tween® 20, Tween® 80, Span® 80 e Span® 85 e os óleos de gergelim, soja, oliva, cártamo e Miglyol® 812 N foram analisados separadamente e em misturas binárias (CBD:excipiente) na proporção de 1:1 (p/p) através de análise simultânea de DSC-TGA. As amostras foram escaneadas em um ATR-FTIR entre 700 e 4000 cm^{-1}. A correlação de Pearson foi adicionada através de um script gerado por docking usando a linguagem R. Todas as misturas binárias de CBD:óleo apresentaram comportamento térmico semelhante, exceto Miglyol® 812 N. A ausência do pico de oxidação nas misturas binárias de CBD com óleos e tensoativos permitiu inferir que eles protegiam o CBD da oxidação. Além disso, a perda de massa das misturas binárias apresentou mostrou-se mais lenta quando comparada ao CBD isoladamente, o que confirma a melhoria do perfil térmico do CBD através da mistura binária entre CBD:óleos e CBD:tensoativos. A análise do FTIR pela correlação de Pearson confirmou pequenas interações CBD:excipiente que não representam incompatibilidades farmacêuticas. Todos os óleos naturais e tensoativos testados eram compatíveis e, portanto, adequados para possíveis formulações de sistemas emulsionados contendo CBD.

Palavras chave: Canabidiol; Técnicas termoanalíticas; FTIR; Óleos naturais; Tensoativos; Estudo de compatibilidade.

ABSTRACT

Cannabidiol (CBD) is the second largest major component of *Cannabis sativa*, with therapeutic and non-hallucinogenic activity. However, CBD presents disadvantages such as low oral bioavailability and low water solubility, which makes its administration challenging. Thus, in order to improve its solubility and oral bioavailability, lipid-based formulations, such as emulsified systems, have been developed. Nevertheless, there is a lack of information about CBD compatibility with the oils and surfactants used in emulsified systems. Also, the lipid content of these formulations are not reported. Thus, the aim of this work was to evaluate the compatibility between CBD and excipients commonly used in the production of emulsified systems in order to provide information for the development of CBD lipid formulations. CBD, Tween® 20, Tween® 80, Span® 80, and Span® 85, Miglyol® 812 N, and sesame, soybean, olive, and safflower oils were analyzed separately and in binary mixtures (CBD:excipient) at a 1:1 (w/w) ratio by DSC-TGA simultaneous analysis. The samples were further scanned in an ATR-FTIR between 700 and 4000 cm^{-1}. Pearson's correlation was added through a docking script using R language. All CBD:oil binary mixtures showed similar thermal behavior, except for Miglyol® 812 N. The absence of the oxidation peak in the binary mixtures of CBD with oils and surfactants allowed us to infer that they protected CBD from oxidation. Moreover, the mass loss of the binary mixtures displayed slower rates when compared to CBD itself, which confirm the improvement of the thermal profile of CBD by addition of other emulsion components of the formulation. FTIR analysis by Pearson's correlation confirmed minor interactions between CBD:excipient that do not represent pharmaceutical incompatibilities. All tested natural oils and surfactants were compatible and, therefore, suitable for prospect emulsified system formulations containing CBD.

Keywords: Cannabidiol; Thermo-analytical techniques; FTIR; Natural oils; Surfactants; Compatibility study.

1. Introduction

Cannabidiol (CBD) is the second major phytocannabinoid present in *Cannabis sativa*. This compound shows non-hallucinogenic effect and displays several therapeutic effects that highlight its use in medical research [1, 2]. Studies have confirmed its pharmacological potential as anxiolytic, antidepressant, antipsychotic, anti-inflammatory and analgesic [3]. Furthermore, CBD has proven to be an important therapeutic alternative in the treatment of chronic diseases, such as Parkinson's disease [4], Alzheimer [5], schizophrenia [6], rheumatoid arthritis [7] and diabetes [4, 8].

Although promising, CBD has pharmaceutical limitations. This molecule is classified as a class 2 drug according to the Biopharmaceutical Classification System (BCS). Therefore, it has low solubility and high permeability. Such characteristics are responsible for the low oral bioavailability of this drug. In addition, when orally administered, it is susceptible to first-pass metabolism [9], which further compromises the development of possible formulations for this administration route [10-12].

In current therapy, CBD has been orally administered in oily dispersions to increase solubility and consequently improve bioavailability via this route. For this purpose, the most commonly used lipid vehicles are hemp, olive, sesame, coconut, and other oils, [13] which have unpleasant taste and odor that may lead to a lack of patient compliance.

In order to overcome the disadvantages of CBD oil solutions administration, the incorporation of this drug into an oil/water (O/W) type emulsified system become as a suitable alternative, since this system can provide the CBD degradation protection as well as the bioavailability improvement [2][14, 15].

In order to develop an optimized and robust emulsion system, preformulation studies are required. The characterization and understanding of physical and chemical interactions between inactive and active pharmaceutical ingredient (API) of a formulation provides important data regarding incompatibilities [16]. Moreover, drug-excipients compatibility studies allows to predict, monitor and characterize the incompatibilities involving APIs, avoiding the excessive use of raw materials and reducing the time spent in the preparation of a suitable formulation [16, 17].

Moreover, the broad chemical composition of the excipients used to produce the emulsified systems increases the complexity of the formulation, which may compromise the

stability of the formulation and impact on the drug therapeutic efficacy due to possible incompatibilities. Nonetheless, compatibility studies with lipid components are limited. Thus, it becomes necessary for the development of lipid-based formulations containing CBD that compatibility data between this drug and oils/surfactants are available for a rational production of an optimized emulsified formulation [18].

Therefore, the aim of this study was to analyze the compatibility between CBD, oils and surfactants used as pharmaceutical excipients through possible physical and/or chemical interactions by Differential Scanning Calorimetry (DSC), Thermogravimetry (TG) and Fourier Transform Infrared Spectroscopy (FTIR) as a tool in preformulation studies.

2. Materials and methods

2.1. Materials

CBD (> 99.5% purity, obtained by organic synthesis) was produced by BSPG/Trigal Pharm (Sengenthal, BY, Germany). Span® 80 (sorbitan monooleate 80), Span® 85 (sorbitan monooleate 85) and Tween® 20 (Polysorbate 20) were purchased from Sigma-Aldrich Inc. (St. Louis, MO, USA). Tween® 80 (Polysorbate 80) was obtained from Synth (Diadema, SP, Brazil). Miglyol® 812 N (Caprylic/Capric Triglyceride) was produced from CONDEA Chemie GMBH (Hamburg, Germany). Safflower, Soy, Olive and Sesame oils were purchased from CRODA (Campinas, SP, Brazil).

2.2. Preparation of binary mixtures

The binary mixtures were obtained by mixing the CBD with the surfactants Tween® 20, Tween® 80, Span® 80, and Span® 85; and Miglyol® 812 N, sesame, soybean, olive, and safflower oils in a ratio of $1{:}1_{(w/w)}$ using a mortar and pestle for 5 minutes by the geometric dilution method. The $1{:}1_{(w/w)}$ ratio was chosen in order to maximize the probability of observing any interaction [19].

2.3. Thermal characterization

DSC and TG curves of the samples were obtained using a Simultaneous Thermal Analyzer, model STA 449 F1 Jupiter – Netzsch (Deutschland/Germany). The binary mixtures

and the individual compounds were weighed in aluminum crucibles (approximately 5 mg of each sample) and analyzed under nitrogen atmosphere with flow of 10 mL min^{-1}, from 30 to 500 °C with heating rate of 10 °C min^{-1}.

2.4. Fourier Transform Infrared Spectroscopy (FTIR)

Aliquots of the binary mixtures and the individual samples were placed on a spectrophotometer ATR-FTIR IR Prestige-21 – Shimadzu (Barueri, SP, Brazil) and analyzed from 700 to 4000 cm^{-1}, with 20 scans per sample with resolution of 4 cm^{-1}. The resulting spectra of the binary mixtures were analyzed considering the appearance or disappearance of peaks between the samples based on the bands corresponding to CBD, surfactants and oils functional groups. The obtained data were analyzed using a docking script in RStudio (Boston, MA, USA) software version 1.1.463, through a spectra comparator capable of simulating computational data of a mixture without interactions (theorical spectra) with experimental spectra. The difference between them is given by Pearson's correlation, in order to verify if the changes found are statistically significant.

3. Results and discussion

Regarding the excipients chosen for this study according to the necessary constituents of emulsified systems, vegetable oil triglycerides that are: (i) commonly ingested in the daily diet, (ii) fast absorbed and (iii) non-toxic effect after administration, including synthetic and natural oils. Concerning the surfactants, the non-ionic group is currently the most widely used in the development of drug delivery systems since they are less irritating and which allow them to be suitable for both oral and parenteral use [20]. In this context, olive, sesame, soybean, safflower and Miglyol® 812 oils and Tween® 20, Tween® 80, Span® 80 and Span® 85 non-ionic surfactants were combined in binary mixtures with CBD and analyzed according to the described in sections 2.3 and 2.4, displaying the results bellow.

[Insert Fig. 1 here]

3.1. Thermal behavior of CBD and binary mixtures

Figure 1 shows the DSC/TG curves of CBD in the heating rate of 10 °C min^{-1}. The DSC curves exhibit two endothermic peaks and one exothermic peak. The first one is attributed to the melting point of the CBD (T_{peak} 74.4 °C). The second event was accompanied by an exothermic peak suggestive of oxidation (T_{peak} 284.0 °C) followed by the decomposition (T_{peak} 361.5 °C), represented by the third endothermic event. Mass loss started near 300 °C and about 80% was lost at 400 °C. Therefore, the DSC has been proposed for evaluating physicochemical interactions between the API and excipients.

[Insert Fig. 2 and Fig.3 here]

Regarding the binary mixtures, the endothermic peak attributed to CBD melting point did not appear (Figure 2A). However, as CBD and phytocannabinoids are highly lipophilic molecules (logP 6-7) [21], the disappearance of this peak can be attributed to the fact that CBD was highly solubilized in the mixture with oils and surfactants. Therefore, the absence of this event in the mixtures is not considered a pharmaceutical incompatibility once in prospect formulations it is expected that the CBD will be solubilized in these vehicles. All Oil-CBD mixtures, except Miglyol® 812 N-CBD mixture, showed a similar thermal behavior (Figure 2). The mass loss was observed in two stages for the safflower, soy, sesame and olive oils-CBD mixtures. The first loss happened around 300 °C and the second, corresponding to the decomposition of the oils, around 400 °C (Figure 2B). On the other hand, Miglyol® 812 N-CBD mixture showed an apparent one stage of mass loss around 250 °C, suggesting an early degradation of CBD compared to the natural oils. Concerning the oxidation exothermic peak of CBD observed at 284 °C (Figure 2B), it was absent in all oil-CBD binary mixtures, inferring that the fatty acids present in the oils acted protecting the drug through their antioxidant activity [22-24]. CBD has a lower stability under oxygen presence due to the possibility of oxidation reaction [25]. Although performed under nitrogen environment, the DSC analysis suggested an improvement of the oxidative stability of the CBD generated by the oils, probably against reminiscing oxygen in the system or impurities that may induce autoxidation. This result might directly imply in the improvement of the final quality of prospect pharmaceutical products containing CBD considering that the occurrence of

instability phenomena can impact not only the physicochemical quality of the product, but also reduce drug effectiveness [26].

Olive, sesame, soybean and safflower oils are natural oils composed of a wide variety of fatty acids, notably oleic acid, linoleic acid and linolenic acid, since they are considered their major components. These fatty acids are able to protect the human body against the action of reactive oxygen species, responsible for oxidative damage to macromolecules [27]. In addition to presenting important bioactive properties to the human body, natural antioxidants protect vegetable oils against the action of free radicals that initiate and propagate the process of degradation by lipid peroxidation [28]. This process is one of the main concerns of the pharmaceutical industry given that oxidation reduces the stability of pharmaceutical products and generates significant financial loss. Therefore, the use of such oils appears to be advantageous not only to generate stable blank formulations but, according to this study, to prevent the CBD oxidation.

On the other hand, Miglyol® 812 N differs from the studied natural oils because it has median carbon chains and saturated fat acids (capric and caprylic acids). Furthermore, it is known that the melting point of oils increases with the size of fatty acid chains and decreases with the enhancement of the unsaturation degree; and, that the lower the melting point, the greater oxidation resistance. Therefore, since Miglyol® 812 N has shorter carbon chains and no unsaturation, it becomes more susceptible to thermal action, as saturated compounds have lower temperature resistance compared to compounds that have unsaturated carbon chains [29, 30]. Considering that Miglyol® 812 N-CBD mixture shows mass loss starting from 250 °C, while CBD itself shows mass loss starting around 300 °C, it is possible to suggest that Miglyol® 812 was not only unable to prevent CBD degradation, but considerably increased the rate of the thermal degradation process. Overall, based on these results and as supported by the literature [29, 30], it is possible to infer that natural oils based on polyunsaturated fatty acids should be considered in preformulation as vehicle for CBD opposed to synthetic oils based on medium chain saturated fatty acids since those provided a better oxidative and thermal stability to CBD by protecting it thought their antioxidant potential.

As shown in Figure 3, the surfactant-CBD mixtures presented a thermal behavior similar to the oil-CBD mixtures. Similarly, the endothermic peak related to the oxidation of CBD disappear on the surfactant-CBD mixtures given that the surfactants are also able to provide oxidative stability to lipid systems [31-33]. Although surfactants have been reported

to have antioxidant activity, further studies to analyze this property are limited [34]. To this regard, a study demonstrated that Tween® 80 was able to eliminate free radicals when the DPPH (2,2-diphenyl-1-picrylhydrazyl) method was used [35]. Therefore, it is suggestive that the surfactants herein studied were able to protect CBD from oxidation and to improve its thermal profile by eliminating free radicals.

Similar to the observed for oil-CBD mixtures, TG curves show that mass losses occurred in two stages for the surfactant-CBD mixtures. For Tween® 20 and Tween® 80 the first mass loss occurred near 350 °C (65 % and 75 %, respectively) and the second near 450 °C (30 %) for Tween® 80 and near 420 °C (28 %) for the Tween® 20. The Span® 80 first mass loss occurred near 350 °C (65 %) and the second near 480 °C (23 %), while Span® 85 showed its first mass loss at 300 °C (80 %) and the second at 440 °C (20 %). DSC curves show that binary mixtures containing surfactant had a single endothermic peak between 350 and 400 °C characteristic of decomposition. Therefore, these results allow us to suggest that the CBD degradation process in the surfactant-CBD mixtures underwent a lower degradation at the same heating rate than the pure drug which presents its first mass loss event around 250 °C and approximately 80 % of mass was lost up to 400 °C.

Although some excipients changed the thermal behavior of CBD at high temperatures, when DSC data were considered, no incompatibilities were suggested to appear in the mixtures of CBD with the following excipients: Safflower Oil, Soy Oil, Olive Oil, Sesame Oil, Span® 80, Span® 85, Tween® 20 e Tween® 80 which evidence to be compatible towards CBD. Moreover, a binary mixture containing Miglyol® 812 N showed greater and faster mass loss at the same temperatures in comparison to CBD alone, allowing us to infer that there was incompatibility between this oil and CBD. Although predictive, thermal analysis by itself cannot fully elucidate chemical interactions. Thus, the relevance of possible minor interactions and the elucidation of the suggestive incompatibility were further studied by FTIR in the following section.

3.2 *Compatibility study of the binary mixtures by FTIR*

FTIR is a quick tool and uses a non-destructive method to obtain infrared spectra. In compatibility studies, FTIR demonstrates to be a complementary analysis of great importance

considering that the results of the thermal analysis may be inconclusive and interactions do not necessarily result in incompatibilities [26].

Binary mixtures between CBD and all excipients showed a low to moderate correlation (r = 0.3 – 0.6) with the theorical spectra generated by the docking script for RStudio [36] in the region between 4000 and 3000 cm^{-1}. This low correlation suggests the possibility of strong chemical interaction between the components of the binary mixtures. Furthermore, the FTIR analysis were conducted to further understand the thermal profile improvement of the mixtures by the disappearance of the endothermic oxidation peak observed in the DSC curves.

In the spectrum showed in Figure 4 the characteristic bands of CBD are present. In the 1521 cm^{-1} region it is possible to observe the O-H in stretching, this peak disappears when in solution. Thus, this region had a greater emphasis in our study since interactions might have happened to functional groups shown in this region. In addition, it is possible to observe that the fingerprint region of the CBD molecule (Figure 4), from 1750 to 700 cm^{-1}, remained unchanged when compared to the binary mixtures' spectra (Figure 5).

[Insert Fig. 4 here]

Figure 5 shows the comparison between the theoretical and experimental spectra of the binary mixtures using Pearson's correlation. The correlations in the fingerprint region of the different mixtures with CBD were considered acceptable for the purposes of drug-excipients compatibility studies by FTIR (r = 0.8 – 0.9), which demonstrated a reduced possibility of chemical interactions in this region. The integrity of the fingerprint region highlights the maintenance of the chemical structure of the molecule in the binary mixtures. However, there were significant changes (r = 0.3 – 0.6) in the region between 4000 and 3000 cm^{-1}.

[Insert Fig. 5 here]

The comparison between the theoretical and experimental spectra from the binary mixture demonstrated the disappearance of the CBD characteristic peak at 3521 cm^{-1} in all spectra (Figure 5). On the solid state, CBD is found on the crystalline form and has its hydroxyl groups with different vibrational energy represented by two signals at around 3500

cm^{-1}. However, when in solution CBD presents a different spectrum. Under such conditions both the benzene and the cyclohexene ring of the CDB have free rotation and the hydroxyl groups, represented by the two signals, merge into a single signal demonstrating that there was a physical interaction that generates a conformational change. In addition, the literature shows that the FTIR spectrum of CBD may also present only one peak in the region between 3400 and 3500 cm^{-1} [37]. Accordingly, it may be suggested that the disappearance of one of the peaks in the hydroxyl region is related to a conformational change. Nevertheless, this change cannot be confirmed to be an incompatibility. Therefore, further studies are needed to elucidate the impact of this conformational change on a pharmaceutical product and on CBD activity.

Overall, considering thermal and FTIR analysis, safflower, sesame, olive, soybean oils and the surfactants Tween® 20, Tween® 80, Span® 80 and Span® 85 are compatible with CBD. Finally, these excipients can be considered suitable for CBD delivery since they have improved oxidative stability, are easily accessible, have analytical grade, low toxicity and have wide use in the food, cosmetic and pharmaceutical industry.

4. Conclusion

The use of thermal analysis led to the conclusion that all excipients, except Miglyol® 812 N, were able to improve the CBD thermal profile. Thus, to corroborate these data, FTIR analysis by Pearson's correlation confirmed that despite showing chemical interactions sesame oil, soybean oil, olive oil, safflower oil, Tween® 20, Tween® 80, Span® 80 and Span® 85 did not have any incompatibility that could compromise the pharmaceutical properties of CBD. Among all tested oils only Miglyol® 812 N (a synthetic medium chain triglycerides mixture) was found to be incompatible with CBD. Therefore, the use of natural oils with unsaturated fatty acids is an interesting alternative as vehicle for CBD in drug delivery systems. In addition, further studies to elucidate minor interactions might be an alternative to avoid long term incompatibilities in marketed formulations. Finally, thermal analysis and FTIR combined with Pearson's correlation were useful to elucidate the pharmaceutical relevance of the physicochemical interactions found between CBD-excipients in this study.

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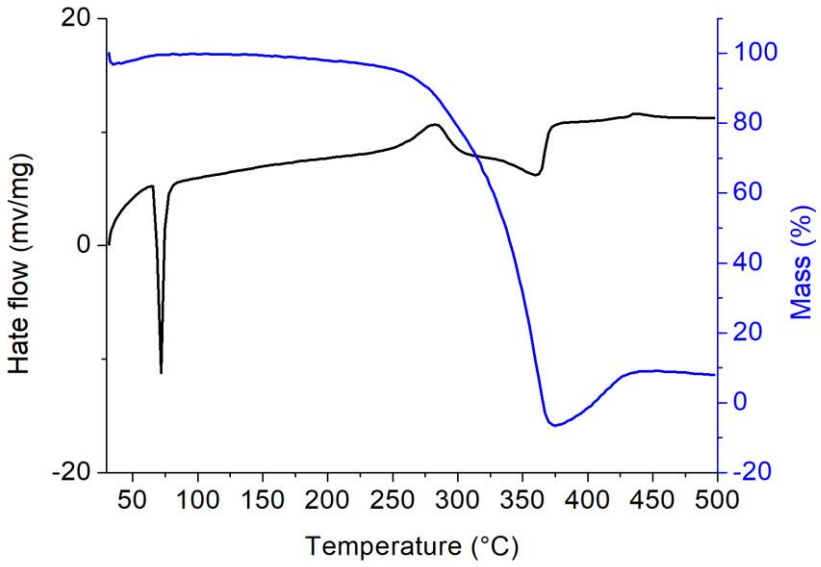

Figure 1 – Thermogravimetry (*blue*) and Differential Scanning Calorimetry (*black*) curves of Cannabidiol (heating rate of 10 °C min^{-1}).

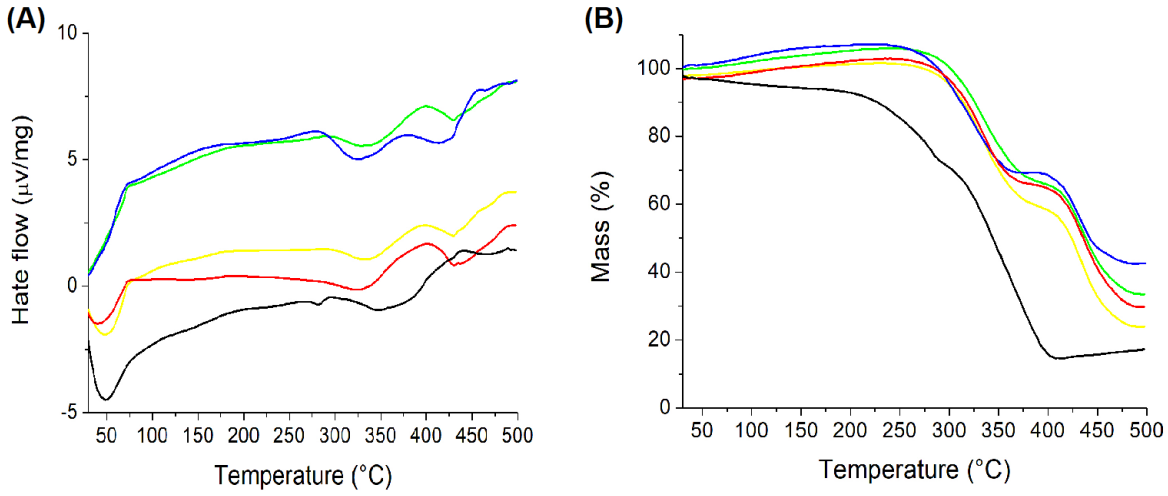

Figure 2 – Differential Scanning Calorimetry (A) and Thermogravimetry (B) curves of binary mixtures 1:1 (w/w) of Cannabidiol and oils under the heating rate of 10 °C min^{-1}: Sesame oil (*yellow*), Soybean Oil (*green*), Olive oil (*blue*), Safflower oil (*red*) and Miglyol® 812 (*black*).

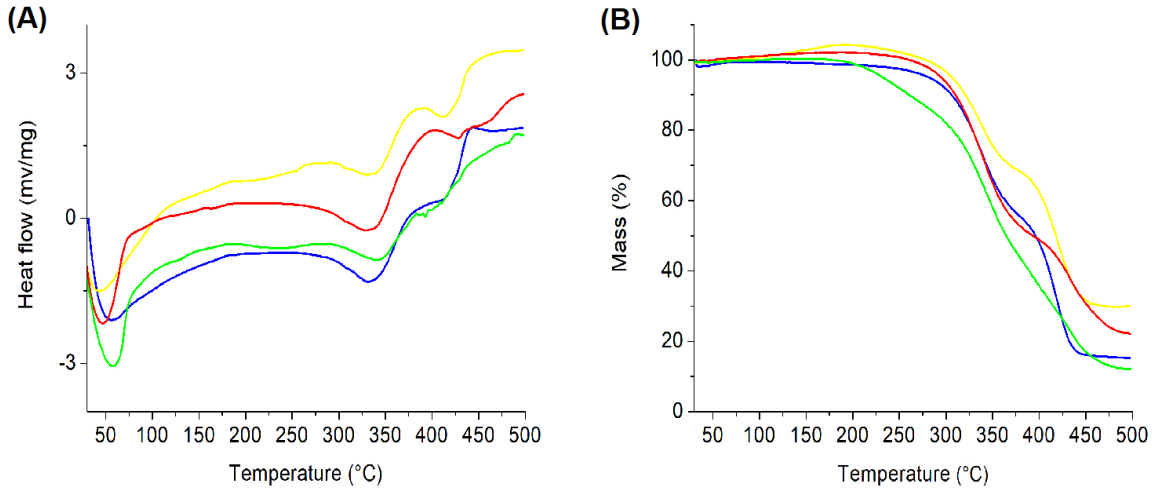

Figure 3 – Differential Scanning Calorimetry (A) and Thermogravimetry (B) curves of binary mixtures 1:1 (w/w) of Cannabidiol and surfactants under heating rate of 10 °C min^{-1}: Tween® 20 (*blue*), Tween® 80 (*yellow*), Span® 80 (*red*), and Span® 85 (*green*).

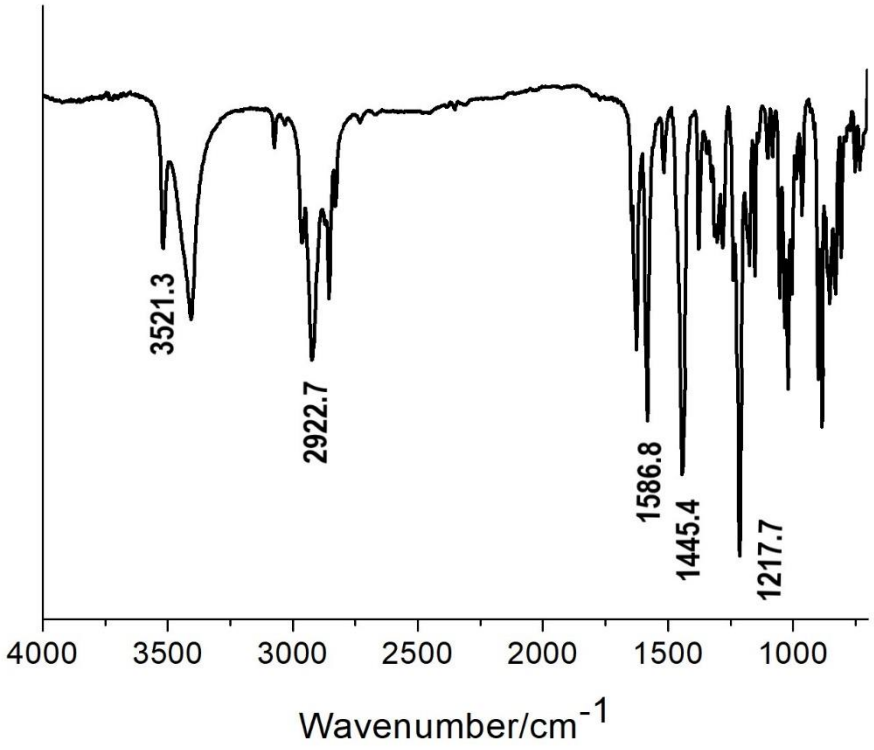

Figure 4 – Characteristic spectra of Cannabidiol by Attenuated Total Reflectance - Fourier Transform Infrared Spectroscopy (ATR-FTIR)

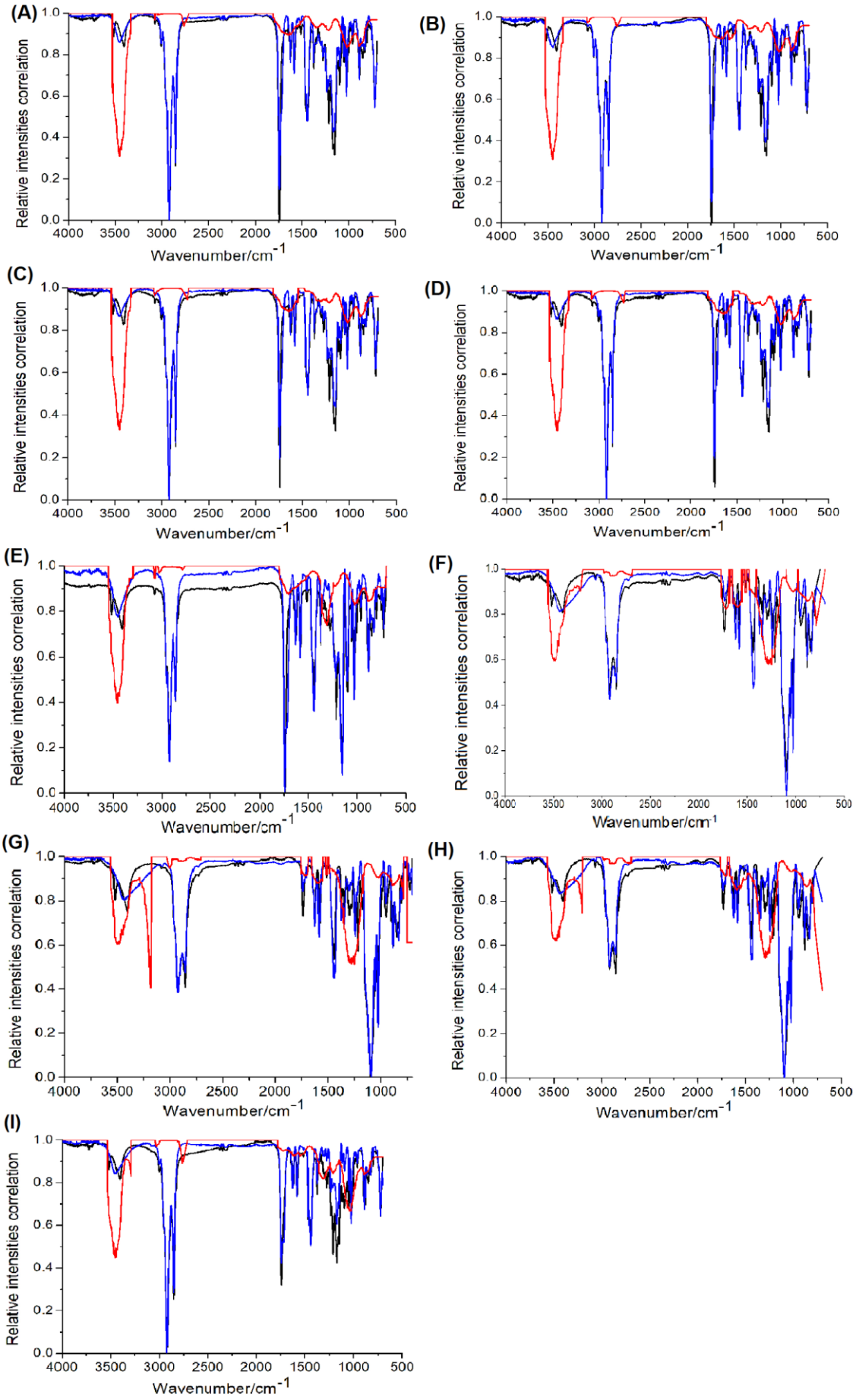
(A)
(B)
(C)
(D)
(E)
(F)
(G)
(H)
(I)
Relative intensities correlation
Wavenumber/cm^{-1}
4000 3500 3000 2500 2000 1500 1000 500
0.0 0.2 0.4 0.6 0.8 1.0

Figure 5 – Experimental spectra of Cannabidiol-Excipient binary mixtures obtained by Attenuated Total Reflectance (*blue*). Theoretical spectra of the mixtures are shown as compatible samples (*black*). Red line is the comparator generated by RStudio docking script using Pearson's correlation. (A) Sesame oil, (B) Soybean oil, (C) Olive oil, (D) Safflower oil, (E) Miglyol® 812, (F) Tween® 20, (G) Tween® 80, (H) Span® 80 and (I) Span® 85.

Highlights

· Natural oils with unsaturated fatty acids improved the oxidative stability of CBD.

· Sorbitan monooleates and polysorbates may be considered suitable for CBD-delivery.

· Tested CBD-natural oils and CBD-non-ionic surfactants mixtures were compatible.