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Research paper

Preparation, characterization and featuring of an inclusion complex of nerol with β-cyclodextrin

Mayara Ladeira Coêlho [1], Herlane Oliveira Meireles da Silva [2], Muhammad Torequl Islam [1]*, Vicente Galber Freitas Viana [3], Ana Amélia de Carvalho Melo-Cavalcante [1]

[1] Post-graduate Program in Pharmaceutical Science, Federal University of Piauí, Teresina, Piauí, Brazil
[2] Integral Diferential College, Teresina, Piauí, Brazil
[3] Laboratory of Treatment of Materials, Federal Institute of Piauí, Teresina, Piauí, Brazil
**Corresponding author E-mail: rbiotufpi.br@gmail.com*

Abstract

Nerol is an acyclic type monoterpene with important biological activities. However, the low solubility in aqueous media is a limiting factor for its user. Cyclodextrins have been widely used in order to improve the solubility, stability and bioavailability of nonpolar molecules through the formation of inclusion complexes. Thus, the present study consists in the development of nerol inclusion complex in combination with the β-cyclodextrin (β-CD) followed by characterizing by thermal analysis and spectrophotometric absorption in the infrared (FTIR). The results suggest a complexation of nerol with β-CD having detours and changed the intensity of various bands. The thermo gravimetric curve of CI found to indicate an output of solvating water molecules from the complex cavity formed for replacement of drug molecules probably included. Thus, it is concluded a possibility to obtain inclusion complexes of nerol monoterpene with β-CD, which will increase its solubility and facilitate delivery process.

Keywords: *Nerol; Monoterpene; B-Cyclodextrin; Inclusion Complex; Solubility*.

1. Introduction

Medicinal plants are wide spread and nowadays they are being widely used as alternative medicine sources (Rodrigues 2013). Among the other chemical moieties, monoterpenes, a member of essential oils (EOs) under the class of terpenes have gained an attention with promising biological activities (Carvalho 2013). Generally, they are repellent or attractive properties, volatile in nature with low molecular weight (Knaak and Fiuza 2010; Angelis 2012). They are with 10 carbon atom molecules and constitute the most representative part (90%) in the class. The major interest of these compounds goes to accounts of perfumery and flavoring applications in food beyond a number of pharmacological effects. These substances are generally volatile and may be detected by antennae or tarsi insects (Marciel et al. 2011).

The nerol (cis-2,6-dimethyl-2,6-octadien-8-ol), an acyclic primary alcohol, is a monoterpene having used in a fragrance compound in perfumery found in various plant species. It is used as an anti-inflammatory, antiseptic, antispasmodic and antidepressant agent. It has also used in gastric ulcer (Angelis 2012). However, being an EO, it has poor solubility in aqueous medium, thus limiting its applications in vivo systems. Complexation with a suitable substance may increase the solubility of poorly soluble materials, which is helpful to attain a desired bioavailability in a number test system (Melo et al. 2007).

The CDs are cyclic oligosaccharides with D-glucose molecules, which enable them to form inclusion complexes with other substances. To be noted that CDs (alpha, beta and gamma) are the natural compounds containing six to eight glucose units. In the pharmaceutical area, the β-CD has mainly been explored in increasing the solubility, bioavailability, and to reduce the side effects of a variety of drugs (Silva 2014). Vectoring of a drug is an operation to modulate and, if possible, direct totally the distribution of a substance associating to an appropriate system called vector (Feuzer 2012). Several studies have been used to characterize inclusion complexes between the drugs and CDs, and the more experimental techniques used are: thermal analysis, nuclear magnetic resonance spectroscopy, ultraviolet-visible, and infrared (Arrais 2012). Given the above, the aim of this study is shot out to obtain a complexation between nerol and β-cyclodextrin and nerol, following by characterization thereby.

2. Material and methods

2.1. Materials

Nerol, β-CD and other chemicals and reagents required for this purpose were purchased from the Sigma-Aldrich (USA).

2.2. Methods

2.2.1. Preparation of inclusion complex

The inclusion complex of nerol was prepared with natural cyclodextrin, β-CD by applying the kneading method in a molar. Briefly, 1:1 of nerol and β-CD were grounded in a porcelain grail with the aid of a pistil adding a small amount of ethanol sufficient to obtain a paste. Then the grail containing the mixture was kept in a water bath protected from light with a temperature under 37 °C until it was completely dried. The resulting material was comminuted, desiccated, and placed in a sealed glass vial being stored in a desiccator.

2.2.2. Thermogravimetry (TG)

The thermo analytical characterization by TG was performed by a thermo balance (Shimadzu® TGA 51) in a nitrogen atmosphere inflow of 50 mL/min being the mass of the sample around 6.0 mg of nerol was put in a platinum crucible at a temperature range 25-600 °C with a heating rate of 10 ºC/min.

2.2.3. Differential scanning calorimetry (DSC)

Thermal analysis using DSC-60 (Shimadzu®) was performed in a dynamic atmosphere of nitrogen (50 mL/min) having a mass of about 5.0 mg and packaged in an aluminum sealed container. The temperature and heating rate were maintained as mentioned above.

2.2.4. Spectroscopy Fourier transform infrared (FTIR)

The absorption spectra in infrared by Fourier transforms were obtained by the attenuated total reflectance method (ATR). The nerol samples, β-CD, MF and the inclusion complex were obtained by Spectrometer ThermoNicolet is5 equipped with accessory ID5 of attenuated total reflectance and the control software and acquisition Omnic 9.0. The mid-infrared region comprises of 650-4000 cm^{-1}, was used for this analysis (Zeni 2005).

2.3. Statistics

The data were analyzed by using the software OriginPro, Ta-60ws, Microsoft Excel® and Graphpad Prism®.

3. Results and discussion

We conducted a complexation process of the monoterpene, nerol with β-CD in order to get a better solubility pattern in the viewpoint of applicability in a wider range of in vivo test systems. Characterization was performed by IR spectroscopy, and thermal analysis DSC and TG.

3.1. Identification by IR spectroscopy

Analysis of the spectra can be made by comparing the bands of the guest molecule (nerol) of the CD, and the physical mixture with the complex is shown in Figure 1 and 2.

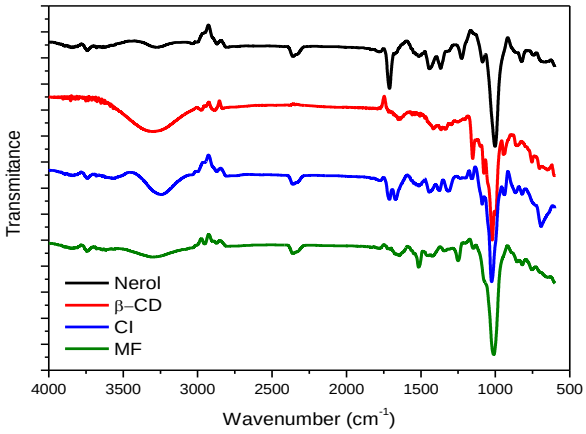

Fig. 1: FTIR Spectrum of Nerol and B-CD and Inclusion Complex, IC (Nerol: B-CD) and Their Physical Mixture, MF (Nerol: B-CD).

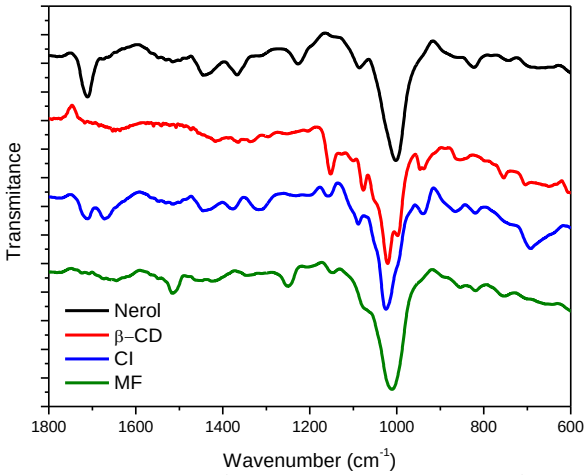

Fig. 2: Extended Spectrum from the Region "Finger Print" of the Nerol FTIR and B-CD FTIR and IC and MF.

Generally, the spectrum of the physical mixture and CI corresponds to the overlapping spectrum of the guest molecule and the spectrum of the CD, but with the bands of the guest molecule less evident due to its lower concentration. When there is a complexation, bands can change position, diminish or even may disappear (Nascimento 2013).

The infrared spectrum of β-CD showed absorption bands at 3381 cm -1 (stretching O - H,) 2922 cm-1 (C stretch - H), 1153 cm-1 (C stretch - O) and 1024 cm-1 (stretching C - O - C). The IR spectrum showed leading bands of the strong absorption of nerol at 1675 cm -1 (stretching C = O) of ketone and 1127 cm -1 (stretching C = C) of alkene. Although the interactions in the inclusion complex between the β-CD and nerol, are not very strong due to having noncovalent electrostatic bonds, it was observed detours and changes in the intensity of many bands when we compared with the complex and nerol. The disappearance of the absorption band of the carbonyl (C = O stretch) and bonds (C = C stretch) of nerol confirms the formation of a complex. In the physical mixture, there was a beginning of interaction between β-CD and nerol due to the disappearance of the carbonyl group, however, is continued with the connections (C = C stretch) reacting after inclusion complex between them.

3.2. Thermo gravimetric analysis

On this occasion, the most used techniques are the DSC and TG (Novak et al. 2006). In the TG analysis, the mass of a sample is under inert or oxidant atmosphere of gas being continuously monitored in function of temperature at a heating ramp. The obtained curves are two where one is related to the percentage weight (% wt) (Figure 3) and other derivative, in relation to the temperature, the weight percentage (Derived from %M/°C) as shown in Figure 4. The latter case allows the exact determination of the temperature at which is determined mass loss of the sample. [9].

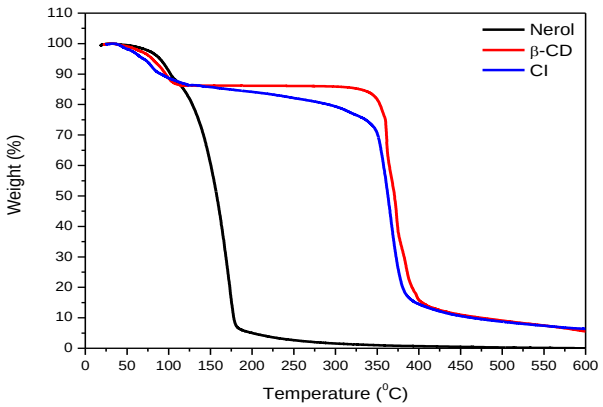

Fig. 3: TG Curve of the Free Species of Nerol, B-CD and Cl (Complex Nerol: Bcd).

The analysis of TG/DTG curves of β-CD shown in Figure 3, CD allows to identify that the 67-120 °C temperature range (~ 95 °C T_{peak}) occurred a mass loss event of 29.25% referring to the release of water molecules from the β-CD cavity. Then it's been a thermal stability level of between 124-320 °C, while in the temperature range was 334-415 °C (T_{peak} ~ 368 °C). There was a weight loss of 5.96%, related to rapid melting / decomposition of β-CD.

From the TG/DTG curves of nerol, two thermal events were observed. Firstly, at a temperature of 100 °C caused a slight loss of water with a weight loss of 7.64%. Secondly, at a temperature range of 109-192 °C caused a mass loss of 27% related to the boiling point of decomposition of the substance.

However, the TG/DTG curve of the complex showed a quite similar to the β-CD curve. In Table 1, one can observe an increase in mass loss between 334-415 °C from 5.9% to 62.49% indicating loss of water molecules from the complex cavity formed, possibly by the replacement of drug molecules included in. In comparison with the nerol absorption band, it was observed that within the range of 109-192 °C (T_{peak} ~ 124 °C), was evaporated completely, thus, indicating a complex formation.

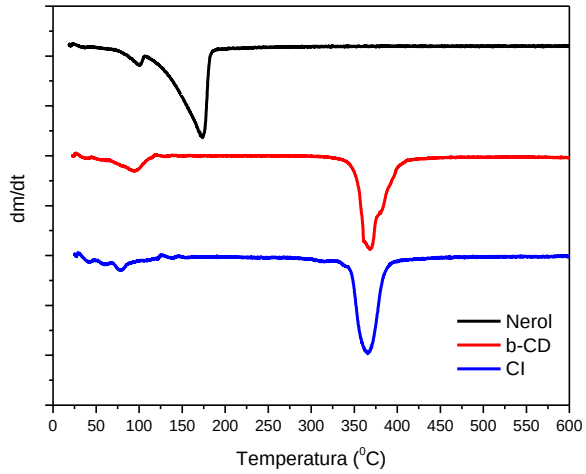

Fig. 4: Curves of the Derived of TG of Free Species of Nerol, B-CD, and Cl (Nerol Complex: B-CD).

Table 1: Percentage Mass Loss Obtained by TG Samples of Nerol, B-CD and CI (Nerol: B-CD).

Samples	% wt loss Step I (%)*	Step II (%)**
Nerol	7.64	27.00
β-CD	29.25	5.96
CI	43.58	62.49

* Percentage of released water to 120 °C; ** weight loss related to the onset of decomposition of the molecule

3.3. Differential scanning calorimetry analysis

DSC is one of the most widely used techniques to confirm the formation of the inclusion complex in solid state having sensitivity to detect possible changes in the characteristic thermal events of the guest molecule when it is inside the CD cavity, system stability and its crystallinity (Aguiar 2014). In our study, the thermal behavior of all materials was investigated by using DSC in an inert atmosphere. The curve of nerol shown in Figure 5 offering two endothermic events featuring as 1) water loss at 42 °C and b) boiling point and degradation of the substances at 150 °C.

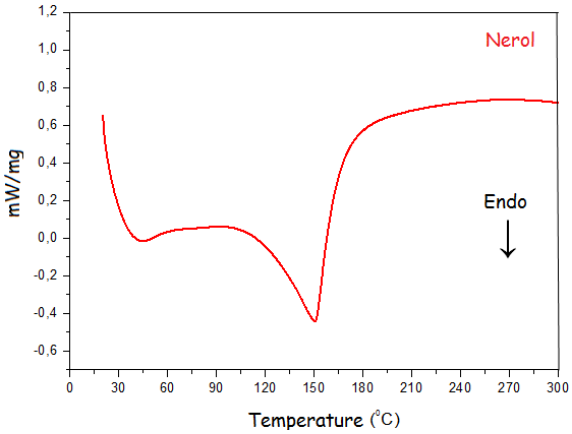

Fig. 5: DSC Thermogram of Pure Nerol Monoterpene.

The DSC curve of β-CD (Figure 6) telling three endothermic events followed by an exothermic event and subsequent decomposition stage. The endothermic events occurred in the temperature ranges 140, 165 and 307 °C, respectively. Initiation was occurring with the loss of water molecules within the hydrophobic cavity followed by an event caused by a physical process attributed to the change of crystalline phase. Then there was a fusion followed by degradation of β-CD.

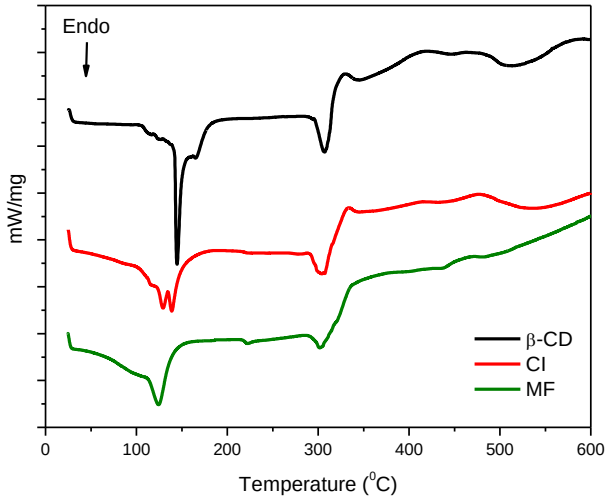

Fig. 6: DSC Thermogram of the B-CD, CI (Nerol: B-CD) and MF (Nerol: B-CD).

The DSC curve of MF also presented three endothermic events followed by a decomposition. The events occurred in the following temperature ranges: 108-161 °C, 217-230 °C and 285-348 °C. An initiation was occurred by the summation of pure nerol and β-CD, leading to a corroborate of crystals of β-CD, and finally the fusion of β-CD followed by decomposition.

The DSC curve of the complex showed an overlapping of the thermal events of β-CD. This demonstrates that the presence of the guest molecule (nerol) did not affect the thermal stability of β-CD. This result can be confirmed in the analysis of the TG/DTG curve of the complex and β-CD watching the mass losses in observed temperatures.

In curves of these last two methods (MF, E and IC) shown in Figure 6, significant differences were observed mainly related to the reduction of the intensity of the peak corresponding to the loss of water and disappearance of the endothermic event related to crystalline phase transition of the pure β-CD in CI.

It is also observed in the DSC curves of the MF and in the complex some changes in the profiles of β-CD curves at 307 °C temperature range showing a slight displacement in relation to curve Cl. This can be explained by the interaction of the drug with β-CD suggesting the inclusion of the nerol molecule in replacement and release of water into the β-CD cavity.

4. Conclusion

From this study, it is possible to obtain inclusion complexes of nerol with β-cyclodextrin, which may permit its high solubility in aqueous mediums. The results of the spectroscopy FTIR, DSC, TG of the nerol, βCD, physical mixture, and the obtained inclusion complexes allowed visualizing interactions between the drug and β-CD suggesting a successful complexation. Finally, the complex can be prepared from the blend of nerol and β-CD in highlighting the use of delivery systems in which there may be a real improvement in solubility.

5. Conflict of interest

None declared.

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