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Evaluation of interaction between natural antioxidants and chemical sunscreens aiming the photoprotective efficacy

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Abstract

To promote broad-spectrum protection, the most sunscreen products combine two or more filters for UVA and UVB. The photoprotective efficacy may be affected by the instability of the chemical combination and it is possible to use natural photo-stabilizing substances with antioxidant activity, adding value to the formulation. This study aims to evaluate the thermal behavior of the filters avobenzone (*BMBM/ Butyl Methoxydibenzoylmethane*) and octyl methoxycinnamate (*EHMC/Ethylhexyl Methoxycinnamate*) associated with the antioxidants *ferulic acid (FA)* and resveratrol (*RES*). To this, Thermogravimetry (TG) and Differential Scanning Calorimetry (DSC), tools very important for the thermal analysis were used. The results showed that the mixture *BMBM* with *FA* had physical interaction confirmed by TG profile. In the mixture of the ingredients *BMBM* with *RES*, probably it had *BMBM* hydrophobic bonds between hydroxyl groups of the phenolic rings of resveratrol, indicated chemical interaction. The mixture *EHMC* with *FA,* indicated chemical interaction. In the mixture *RES* with *EHMC*, EHMC solubilized *RES*, indicating physical interaction. In this mixture*, RES* probably would be bioavailable that is facilitate its penetration and action on the skin. The results showed that by DSC and TG techniques, it is possible to predict the stability profile of ingredients and formulations which will reflect in its efficacy and safety as UV photoprotection.

Keywords Ferulic acid · Resveratrol · Avobenzone · Octyl methoxycinnamate · Thermal analysis

Introduction

The use of sunscreen is the preventive way that protects the skin of people from the negative action of UV radiation, delaying the effects of extrinsic aging, improving its appearance, minimizing the marks of wrinkles, spots and aging. More important than the aesthetic focus is the health aspect, because the use of this type of product is one of the ways to protect the skin and delay the possibility of the appearance of skin cancer.

To promote broad-spectrum protection, most sunscreens available on the market have at least two organic filters in combination, at least one to protect the UVB rays and the other for the UVA. Two representatives of such classes of chemical UV filters are cinnamates (UVB filter), such as *Ethylhexyl Methoxycinnamate* and dibenzoylmethanes (UVA filter), such as *Butyl Methoxydibenzoylmethane*. They are associated with several commercially available formulations, but to promote the photostability of this combination, it is necessary to add a photo-stabilizer. In the study of [1], mangiferin increased the photostability and reduced the phototoxic potential of the combination of naringenin and avobenzone.

Photo-stabilizers are used in the market as cinnamates, camphor derivatives, or triazines in the development of sunscreens formulations containing *Butyl Methoxydibenzoylmethane*. However, due to the scientific literature, many of the substances used were not able to minimize the formation of species reactive oxygen (ROS), putting the user at risk. The photostability of *Butyl Methoxydibenzoylmethane* is believed to be biologically relevant and has been evidenced by studies about DNA damage, cytotoxicity of human keratinocytes, and lipid peroxidation [2, 3].

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The photochemical instability of photoprotective products containing various sunscreen ingredients represents a challenge to be overcome due to the relevance of the problem they cause. Systematic investigations of photo-induced changes in the absorption profile of commercial photoprotector products have revealed that neither the complex combination of organic filters nor the addition of inorganic filters can prevent the undesirable photoinactivation of sunscreens. The authors [4] obtained results that confirmed the high photostability of sunscreens in the UVB region, but there was a considerable reduction in photostability of UVA. The photochemical activation of UVA filters can result in the formation of ROS and toxic intermediates, which can cause damage to the skin. Investigation of the photostability of sunscreen in photoprotective formulations should be required before commercialization.

According to Pinto et al. [5], natural products of plant origin are important and promising sources of bioactive substances. Due to the structural similarity of the flavonoids with the chemical sunscreens, in addition to the antioxidant properties, this class has potential in the photostabilization of chemical sunscreens [6, 7]. A research mentioned in the scientific literature, the flavonoid rutin showed positive results in the photostabilization of sunscreen in photoprotective formulations with the chemical filters *BMBM* and *EHMC* [8].

The phenolic compounds belong to the class of hydroxycinnamic acids (ferulic acids) and they are antioxidants found in the most diverse natural sources (corn, coffee, beet and others). In the literature, there are reports of its photoprotective efficacy against UV radiation. The absorption of UV rays by ferulic acid catalyzes the stable formation of the radical phenoxy, enhancing its ability to interrupt the chain reactions of free radicals. It can neutralize EROS as peroxides and hydroxyls [9]. Due to its antioxidant properties, several studies involve this active ingredient in the prevention of oxidative stress in skin cells exposed to UV radiation.

Resveratrol (3,4,5-trihydroxystylbene) is a phenolic compound of the stilbenes class and has a potent antioxidant activity [10]. Its molecule may contain the trans and cis isomeric forms, but the cis cannot be found in the grape extraction, but its transform is easily found in nature. As a phenolic compound, resveratrol contributes to the antioxidant potential of red wine [11], and it has potential as a chemopreventive agent for skin cancer. Studies have shown that E-resveratrol is able to prevent skin damage from UV rays in vivo and chemical-induced skin cancer [12]. [13] evaluated the synergism and photoprotection of resveratrol with UVA and UVB filters.

Thermogravimetry (TG) and Differential Scanning Calorimetry (DSC) are included in the set of techniques called "Thermal Analysis" and a physical property is measured from a controlled variation of temperature and ambient condition. DSC and TG are powerful allies in choosing the formulation components since they can assess the physical and/or chemical compatibility between ingredients. The presence of interaction can influence in the stability of the formulation which, consequently, will interfere with the effectiveness of cosmetic ingredients. Recent studies have proven the importance of thermal analysis in compatibility studies between organic sunscreens and flavonoids, in addition to the fact that it is the low-cost technique when compared with others, as high-performance liquid chromatography [8].

The variation in mass (TG) and calorimetry (DSC) of a given sample is quantified as a function of the variation in temperature or time. Both techniques are applied in the evaluation of dehydration and investigation of polymorphism, in addition, TG and DSC can assess the stability and degree of purity of samples, respectively. Thus, such studies contribute to the characterization process, determination of the validity period, and calculation of kinetic parameters, allowing to evaluate the behavior of active ingredients in cosmetic formulations [8, 14, 15].

This study aims to characterize the mixture of filters and antioxidants, employing the techniques of DSC and TG. The objective was to establish relevant information to predict the stability profile and possible interactions that are associated with the antioxidant and photo-stabilizing efficacy of these ingredients of natural origin used in many products, especially in multifunctional formulations.

Materials and Methods

Materials

Ethylhexyl Methoxycinnamate (Fagron, content 98,6%), and *Butyl Methoxydibenzoylmethan* (Fagron, purity 98.2%), and *Ferulic Acid (*GAMMA, purity 98.6%)*, and* Resveratrol (Active *Pharmaceutica,* purity 99.8%) and Indian metallic standard (HITACHI, purity 99.94%).

Equipment

The analysis was conducted by analytical balance Shimadzu® Model AUX220; and Hitachi Exstar DSC 7020® e TG/DTA 7200®.

Methods

Thermoanalytical measurements were performed with antioxidants *FA* and *RES* and chemical filters (*EHMC*) and (*BMBM*). Additionally, binary mixtures containing the antioxidant with each of the *EHMC* or *BMBM* filters;

and the ternary mixtures (samples of *EHMC*, *BMBM* and antioxidants).

Differential scanning calorimetry (DSC)

DSC curves were obtained using a hermetically sealed aluminum cell containing mass between 2.0 and 3.0 mg, dynamic nitrogen atmosphere (50 mL min^{-1}), heating ratio 10.0 °C min^{-1}, temperature between 25 and 300 °C. The DSC cell was calibrated with an Indian metallic standard, content 99.94% ($T_{\text{fusion}} = 156.6$ °C; $\Delta H_{\text{Fusion}} = 28.7$ J g^{-1}) [16].

Thermogravimetry (TG)

The TG curves of the thermal behavior study of *BMBM* and *EHMC* filters and antioxidants, as well as filter mixtures and antioxidant combinations, were obtained with a thermobalance between 30.0 and 600.0 °C, dynamic N_2 atmosphere, 100 mL min^{-1}, and the heating ratio of 10 °C min^{-1}, Pt crucible and sample mass around 5 mg [16]. The derivative thermogravimetry curves (DTG) were plotted for better visualization of the results obtained from the TG curves.

Results and discussion

The variation in mass (TG) and in enthalpy (DSC) of a given sample is quantified as a function of the variation in temperature or time. Both techniques are applied in the evaluation of dehydration and investigation of polymorphism, in addition, TG and DSC can assess the thermal stability and degree of purity of a given sample, respectively. Thus, such techniques contribute the process of characterization, determination of the validity period and calculation of kinetic parameters, allowing to evaluate the behavior of the active ingredient in cosmetic formulations [8, 14, 15].

Figure 1 illustrates the overlapping TG/DTG and DSC curves of the chemistry filters, *Butyl Methoxydibenzoylmethane* (*BMBM*) and *Ethylhexyl Methoxycinnam*ate (EHMC).

The DSC curve (Fig. 1 and Table 1) of the sample *BMBM* revealed melting temperature (endothermic event) at 79.9 °C; with T_{onset} 77.3 °C and a ΔH 86.5 J g^{-1}. According to Daneluti et al. [17], the first *BMBM* endothermic event was between 78 and 110 °C with a peak of 85 °C. This difference from 79.9 to 85 °C is due to different experiment conditions.

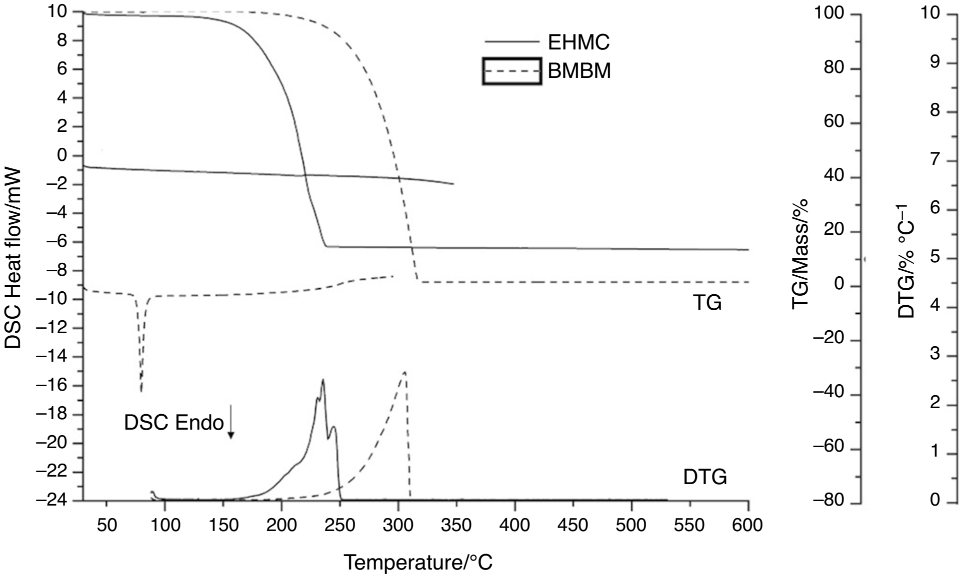

Fig. 1 TG/DTG and DSC curves obtained 10 °C min^{-1} and under a dynamic atmosphere of N_2 (50 mL min^{-1}) of the sample *Butyl Methoxydibenzoylmethane (BMBM)* and *Ethylhexyl Methoxycinnamate (EHMC)*. The direction of the events endothermics on the curves DSC calorimetric were indicated by Endo arrow (Endo↓)

Table 1 Thermal analysis data of the filter samples

Sample	TG/DTG			DSC		
	ΔT °C	T_{peak} °C	Δm %	T_{peak} °C	T_{onset} °C	ΔH/Jg^{-1}
BMBM	183.8–322.0	312.5	99.1	79.9	77.3	86.5
EHMC	120.0–240.0	220.8	85.0	232.8	195.6	149.0

TG/DTG results: mass (%) the range temperature (ΔT) and peak temperature (°C). DSC results: ΔH (J g^{-1}), the *onset* and *peak* temperatures (°C)

BMBM Butyl Methoxydibenzoylmethane; *EHMC* Ethylhexyl Methoxycinnamate; *ΔH* enthalpy variation; T_{onset} extrapolation of the beginning of the peak; T_{peak} temperature of the peak

The *EHMC* at room temperature is liquid, so it did not show a melting temperature. There was an endothermic event in DSC that when compared with TG/DTG was evidenced as decomposition volatility. According to Daneluti et al. [17] the endothermic event was T_{onset} 190 oC with T_{peak} 233 °C, similarly with the values of this work (T_{onset} = 195.6 °C and T_{peak} = 232.8 °C-Table 1).

The TG/DTG curves showed that *BMBM* filter is more thermally stable about 60.0 °C than the *EHMC* (Table 1), however, both filters presented only one event (temperature range) of mass loss each: *BMBM* between 183.8 and 322.0 °C, with T_{peak} 312.5 °C and mass variation of the 99.1% and *EHMC* between 120.0 and 240.0 °C, with T_{peak} 220.8 °C and Δm = 85.0% until 600.0 °C (Fig. 1, Table 1).

According to DANELUTI et al., 2018 [17] TG/DTG curves of *BMBM* presented two events of mass loss, the first one between 218 and 405 ºC with Δm = 97% and T_{peak} 351 ºC. The second one is 420–512 ºC (T_{peak} 465 ºC) with Δm = 1.4%. For the *EHMC* [17] was recorded two mass loss events on the TG/DTG, the first between 149—200ºC (T_{peak} DTG = 146), with a mass loss of 3,7%. The second was 203–338 ºC (T_{peak} DTG = 293), with a mass loss of 95.5%, an event related to the volatility of the material. These differences of Daneluti et al. [17] with this work may be due to different experimental conditions or filters suppliers. The authors [17] related that when T_{peak} shift to higher temperatures, it means thermal increase of the filter. Thus, *BMBM* is more thermally stable than EHMC because it started to degrade at a higher temperature than the *EHMC* filter.

In both sunscreens samples (BMBM/UVA and EHMC/UVB), the thermal decomposition began above 120 °C (high thermal stability), a very interesting data in the development of formulations containing sunscreens.

Thus, these filters become interesting to maintain the stability of the formulation when it is exposed in adverse conditions of high temperature and it will have more chance to maintain the photoprotective efficacy against ultraviolet radiation during the expiration date.

Table 2 and Fig. 2a–d illustrate the overlapping of the curves TG/DTG and DSC of the antioxidants *Resveratrol* (*RES*) and *Ferulic acid* (*FA*) and their associations with the sunscreens samples, *Butyl Methoxydibenzoylmethane* (*BMBM*) and *Ethylhexyl Methoxycinnamate* (*EHMC*).

For the sample of *EHMC* incorporated the both antioxidants *FA* and *RES*, separately, TG/DTG curves showed two mass losses events. In the mixture *FA* with *EHMC* (Fig. 2a), the first occurred from range 157.9—217.4 °C, corresponding to a decrease of 64.2% and other losses occurred in 217.4—239.2 °C, with mass loss of 10.2%. The sample of *FA* anticipated at 1 °C the T_{peak} decomposition (first events of TG in Table 2) in the mixture (of 211.3–210.4 ºC) and melting point (T_{peak} 170.5–162.4 ºC). According to Damasceno [18], *FA* melts at 177ºC, under different experimental conditions.

There was a chemical interaction in the mixture of *EHMC* with *FA*, evidenced by variation in the enthalpy (55.8 J g^{-1}) in approximately 1/3 of the *FA* when compared to the isolate (156.0 J g^{-1}). According to Cerasole [19], the ingredients that interacted chemically with *BMBM* had the T_{peak} DSC shifted to a lower temperature with a significant reduction in enthalpy. According to [19] other substances with *BMBM,* there was chemical interaction when the enthalpy value could be the average of the two substances. In this present study, we suggest two hypotheses to explain this phenomenon of the melting point with decreasing of their enthalpy (DSC data): (1) formation of a new compound which required less energy for the endothermic event occurs and

Table 2 Thermal analysis data of antioxidants isolated and the mixture of sunscreen and antioxidants

Sample	Ev	T_{peak} /°C	ΔT/°C	Δm/%	Ev	T_{peak} /°C	T_{onset} /°C	ΔH/J g^{-1}
FA	1	211.3	159.9–224.1	69.4	1	170.5	168.3	156.0
	2	317.3	263.5–342.0	8.8				
RES	1	262,9	238.3–268.1	1.5	1	267.2	265.4	232.0
	2	324.5	268.1–409.9	46.3				
EHMC + FA (1:1)	1	210.4	157.9–217.4	64.2	1	162.4	153.4	55.8
	2	225.4	217.4–239.2	10.2				
EHMC + RES (1:1)	1	226.4	116.4–234.3	17.9	1	215.7	187	79.1
	2	292.2	234.3–373.4	14.1	2	264.3	257.8	74.0
BMBM + RES(1:1)	1	288.5	169.9–365.2	65.5	1	80.4	77.4	88.6
BMBM + FA (1:1)	1	232.3	163.9–244.9	43.2	1	80.5	77.8	50.1
	2	311.6	244.9–324.4	52.1	2	152.9	133.9	39.1

TG/DTG results: the Δm /%, the range temperature /ΔT and peak temperature/°C. DSC results: ΔH/J g^{-1}, the *onset* and *peak* temperatures/°C

FA Ferulic acid; *RES* Resveratrol; *BMBM* Butyl Methoxydibenzoylmethane; *EHMC* Ethylhexyl Methoxycinnamate; *Ev.* event; *ΔH* enthalpy variation; T_{peak} temperature of the peak; $^{*}\Delta T$ temperature range of the decomposition; Δm = mass loss

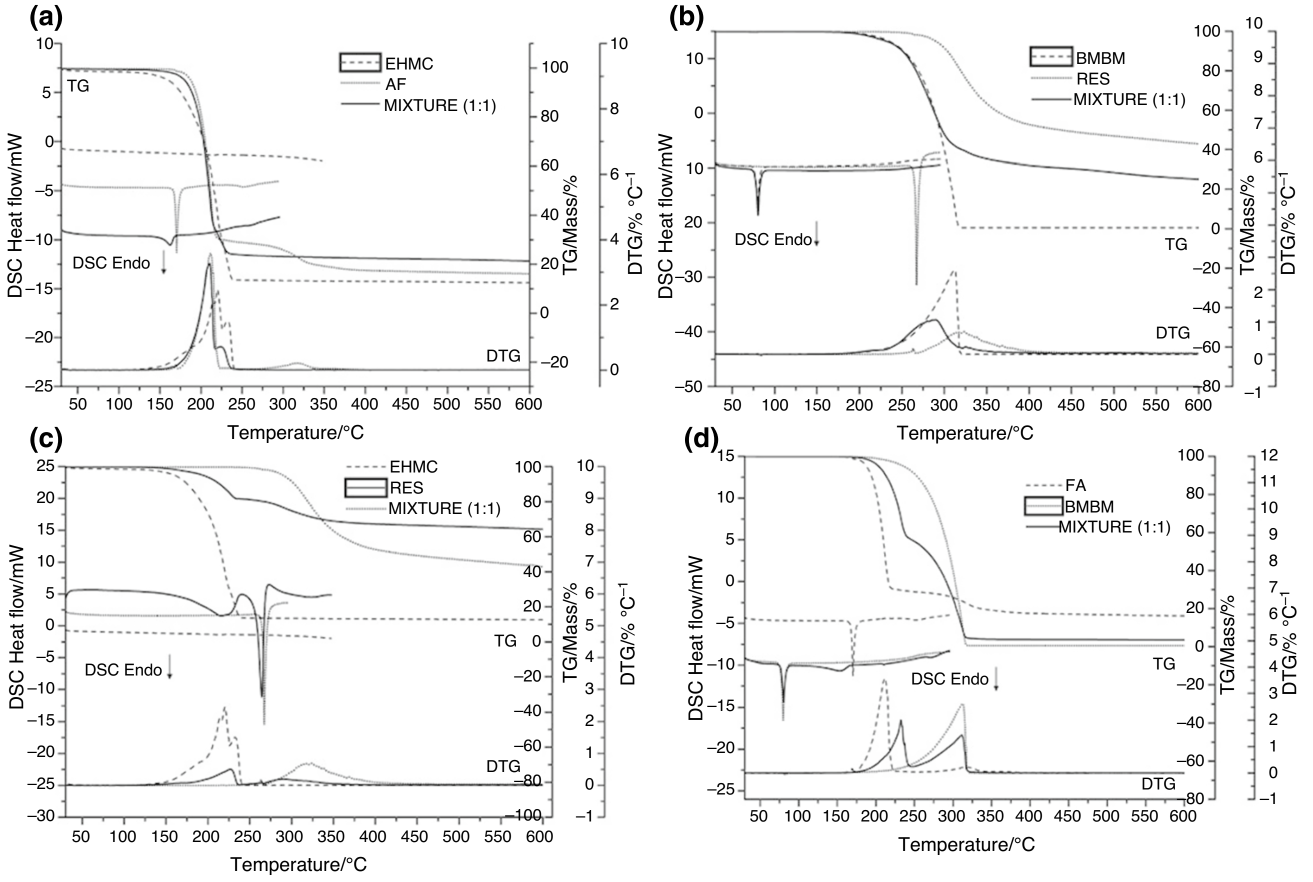

Fig. 2 TG/DTG and DSC curves obtained 10 °C min^{-1} and under a dynamic atmosphere of N_2 (50 mL min^{-1}) of the sample: (**a**) *Ethylhexyl Methoxycinnamate* (*EHMC*), *Ferulic acid* (*FA*) and *Ethylhexyl Methoxycinnamate* (*EHMC*) + *Ferulic acid* (*FA*); (**b**) *Ethylhexyl Methoxycinnamate* (*EHMC*), *Resveratrol* (*RES*) and *Ethylhexyl Methoxycinnamate* (*EHMC*) + *Resveratrol* (*RES*); (**c**) *Butyl Methoxydibenzoylmethane* (*BMBM*), *Resveratrol* (*RES*) and *Butyl Methoxydibenzoylmethane* (*BMBM*) + *Resveratrol* (*RES*); (**d**) *Butyl Methoxydibenzoylmethane* (*BMBM*), *Ferulic acid* (*FA*) and *Butyl Methoxydibenzoylmethane* (*BMBM*) + *Ferulic acid* (*FA*). The direction of the events endothermics on the curves DSC calorimetric were indicated by Endo arrow (Endo↓)

(2) the *cis* isomers of *EHMC or FA* reduced the enthalpy. In the second case, the efficacy and safety of antioxidant or photoprotective activity may be compromised.

In the association of *EHMC* with *RES* (Fig. 2b), the decomposition temperature range of the *EHMC* did not show significant changes, probably caused by their volatilization. This association showed two thermal events with mass loss, which occurred in the temperature range between 116.4–234.3 °C ($\Delta m = 17.9\%$) and 234.3–373.4 °C ($\Delta m = 14.1\%$), respectively, totalizing 32% of mass loss. The DSC curve showed two endothermic events with T_{peak} at 215.7 and 264.3 °C, with enthalpy of 79.1 and 74.0 J g^{-1}, respectively. The sum of enthalpies values in the mixture (153.1 J g^{-1}) corresponded to 40% the sum of the enthalpy of *EHMC* and *RES* (381 J g^{-1}). Comparing the DSC data of the sample *RES* isolated (T_{peak}^{DSC} 267.2 ºC) and in mixture (T_{peak}^{DSC} 264.3 ºC), it is observing a little shift of the melting point at 3 oC. Thus, it is possible to verify that there was a physical interaction without compromising *RES*, confirmed by TG/DTG curves, which evidenced that *RES* may be more available in the formulation for the cosmetic action. According to Oliveira [20], the decrease in the melting point and in the enthalpy value is indicative of interaction.

The TG/DTG curves of the association of *BMBM* with *RES* (Fig. 2c) showed one loss mass event occurred from the temperature range between 169.9 and 365.2 °C, with decrease of mass of 65.5%. DSC curve evidenced one endothermic event with $T_{peak} = 80.4$ °C and the disappearance of the melting peak of *RES* in the mixture with RES + *BMBM*. In DSC analysis of binary or multi-component mixture, the drug may be solubilized during heating by an excipient of the mixture. This occurs when the excipient has a lower temperature melting range and can solubilize the drug present in a mixture [20]. The enthalpy value of the mixture (88.6 J g^{-1}) was approximately 1/3 of the *RES* when compared with the isolate substance (232.0 J g^{-1}). In this case, there was chemical interaction confirmed by TG/DTG profile and only one peak of degradation for the mixture, probably by the reaction between the BMBM hydrophobic bonds and hydroxyl groups of resveratrol [21].

The TG curves showed the sample of *RES* isolated started to degrade at 238.3 ºC, and in the mixture at 169.9 ºC, which evidences *RES* is more thermally stable isolated than associated with the BMBM filter. Liu et al. [22], analyzed the azadiratchtin drug associated with cyclodextrins and they concluded the late decomposition may indicate that the compounds are thermally stable. The TG curves of the mixture of *BMBM* + *FA* (Fig. 2d) evidenced two thermal events occurred from 163.9 to 244.9 °C, with a decrease of 43.2% of the mass and 244.9–324.4 °C, with mass loss of 52.1%. In DSC curve of the respective mixture, evidenced two endothermic events with T_{peak} at 80.5 and 152.9 °C, respectively. The anticipation of the melting peak temperature of the FA isolated to *FA* in this mixture (170.5–152.9 ºC, respectively) with the *BMBM* can be explained by the solubilization of the *FA* (solid) in *BMBM* (liquid after melting).

This physical interaction was confirmed by profile of the TG curves of this association, which showed the occurrence of two peaks related to degradation of each ingredient present in the mixture. These results evidence the importance of the association of techniques DSC and TG, according to [20].

According to Oliveira [20], It is possible to evaluate an interaction (or not) between drug and excipient by DSC measurements associated with dynamic TG. If the mass loss obtained by TG curve of the binary mixture (association of the drug to excipient) is not the sum of the mass loss individual of these compounds (drug and excipient isolated) obtained by their respective TG curves, there is an incompatibility in the proposed mixture. These results achieve reinforce the conclusion about the physical interaction between *BMBM* + *FA* in the present research.

The TG curves of the mixture of *BMBM* + *FA* showed a shift to higher temperature the degradation of *FA* (211.3–232.3 ºC) and decreasing the **Δ**m of 62,4 to 43,2%, evidencing thus, there was an increase in the thermal stability of FA when incorporated to this mixture. This behavior is interesting for the greater stability of this ingredient in the formulation. The presence of fine and sharp peaks indicated that these ingredients *FA* and *BMBM* are pure [23] which is in accordance with the content in the certificate of analysis of the suppliers 98.6 and 99.8%, respectively.

The TG curves of the antioxidant isolated samples (Table 2) revealed that the *RES* (with $\Delta T = 238.3–409.9$ °C) is more thermally stable at least 78 °C than the *FA* (with $\Delta T = 159.9–342.0$ °C). Silva [24] reported the beginning of thermal decomposition of the *RES* started the decomposition at about 268.1 °C, similarly achieved in this present work. Bezerra [25] obtained different values of degradation temperature (147–407 ºC) evaluating FA samples, however, under different experimental conditions (synthetic air atmosphere—oxidative and heating rate 20 ºC) from those used here. According to Mendes [26], *RES* had two mass loss events observed by the DTG curve, the first observed in the region between 351.85 and 484.85 °C. It was reported in the literature that resveratrol was thermally stable up to 240 ºC. Endothermic peak accentuated at approximately 267 ºC and 50% of mass loss associated with its fusion [26], similarly to the values obtained in this work.

The DSC data corroborate the TG results, which show the sample of the *RES* antioxidant exhibited melting temperature at about 267.0 °C (T_{peak} DSC) [27]. The *FA* melts about 170.5 °C and the data are according to the scientific literature [18]. In this case, both, *FA* and *RES* started degrade em high temperatures. This information can be strategic before developing photoprotect formulations because they are often exposed to the sun, as in the beach or in transporting the product.

In view of the above, the DSC and TG techniques were used simultaneously to verify the occurrence (or not) of interaction between samples of the filters and antioxidants and what is the nature of that interaction (physical or chemical). Mixtures that have physical interactions can be indicated in studies of pre-formulations due to maintaining the effectiveness and safety of their ingredients (antioxidants and sunscreens).

Conclusions

The association of the techniques (TG and DSC) allowed to achieve evidence of the chemical interaction in the mixture *Ferulic Acid* (antioxidant) plus *Ethylhexyl Methoxycinnamate (EHMC/ UVB sunscreen)*, and Resveratrol (antioxidant) plus *Butyl Methoxydibenzoylmethane (BMBM/ UVA sunscreen).* These results confirm the thermal; photoprotective and antioxidant efficacy and safety of the formulations could be compromised.

In the other mixtures *EHMC* + *RES and BMBM* + *FA,* there was physical interaction with solubilization of *RES* in the mixture, which is adequate to formulate products multifunctional with photoprotective and antioxidant action. This work indicated that each sunscreen requires a specific antioxidant to potentiate the formulation efficacy. In the mixture *BMBM* with *RES,* the *Resveratrol* was solubilized and probably would be bioavailable.

The degradation of the *FA* was delayed in its mixture with *Butyl Methoxydibenzoylmethane (BMBM)* and could act as a thermal protector of *Ferulic Acid* in the mixture evenly with the anticipation of the fusion.

By the heat acceleration with DSC and TG techniques, it is possible to predict the stability profile and possible long-term interactions of cosmetic ingredients and formulations which will reflect the effectiveness of the active components.

In the formulation, other interactions with the components could be expected.

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Author contributions TBF: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing-Original Draft, Writing-Review & Editing, Visualization and Project administration. CRRCL: Conceptualization, Methodology, Software, Validation, Formal analysis, Data Curation, Writing-Original Draft, and Project administration. CASOP: Conceptualization, Methodology, Resources, Supervision, and Project administration. LFB: Methodology, Software, Validation, Formal analysis, and Data Curation. ARB: Validation, Resources, Visualization, and Project administration. MVRV: Conceptualization, Methodology, Investigation, Resources, Supervision, Project administration, Funding acquisition.

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