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Drug–excipient compatibility studies in binary mixtures of avobenzone

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Synopsis

During preformulation studies of cosmetic/pharmaceutical products, thermal analysis techniques are very useful to detect physical or chemical incompatibilities between the active and the excipients of interest that might interfere with safety and/or efficacy of the final product. Differential scanning calorimetry (DSC) was used as a screening technique for assessing the compatibility of avobenzone with some currently used cosmetic excipients. In the first phase of the study, DSC was used as a tool to detect any interaction. Based on the DSC results alone, cetearyl alcohol, isopropyl myristate, propylparaben, diethylhexyl syringylidene malonate, caprylic capric triglyceride, butylated hydroxytoluene (BHT), glycerin, cetearyl alcohol/ceteareth 20, cetearyl alcohol/sodium lauryl sulfate/sodium cetearyl sulfate, and paraffinum liquidum exhibit interaction with avobenzone. Stressed binary mixtures (stored at 50°C for 15 days) of avobenzone and excipients were evaluated by high-performance liquid chromatography. Binary mixtures were further investigated by infrared (IR) spectroscopy. Based on DSC, isothermal stress testing, and fourier transform infrared results; avobenzone is incompatible with caprylic capric triglyceride, propylparaben, and BHT.

INTRODUCTION

This work is part of an ongoing systematic study to find and optimize a general method for the detection of drug–excipient interactions, with the aim of predicting rapidly and inexpensively the long-term stability of a cosmetic/pharmaceutical product and speed up its marketing. The study of drug–excipient compatibility represents an important phase in the preformulation stage for the development of a cosmetic/pharmaceutical form. In fact, potential physical and chemical interactions between actives and excipients can affect the chemical nature and the stability of a cosmetic product and, consequently, their efficacy and safety.

Among the different methods reported on drug–excipient's compatibility studies, differential scanning calorimetry (DSC) has been shown to be an important tool at the outset

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of any cosmetic/pharmaceutical product preformulation study to quickly obtain information about possible interactions among the formulation components according to appearance, shift, or disappearance of endothermic or exothermic peaks and/or variations in the corresponding enthalpy values in thermal curves of drug–excipient mixtures.

Drug–excipient compatibility testing at an early stage helps in the selection of excipients that increase the probability of developing a stable dosage form (1–34). In particular, the low availability of the drug and the time constraints associated with the early stages of formulation development have made such predictability particularly desirable. Despite the importance of drug–excipient compatibility testing, there is no universally accepted protocol for this purpose. The term thermal analysis refers to a group of techniques in which a physical property of a substance and/or a reaction product is measured as a function of temperature while the substance is subjected to a controlled temperature program. Differential scanning calorimeter (DSC) involves the application of a heating or a cooling signal to a sample and a reference. When the substance undergoes a thermal event, the difference in the heat flow to the sample and reference is monitored against time or temperature while the temperature is programmed in a specified atmosphere. As a result, the energy associated with various thermal events (e.g., melting, glass transition, and crystallization) can be evaluated. This method has been extensively reported in the literature for testing compatibility of excipients with a number of drugs (1–34). Although DSC cannot replace chemical methods for quantitative determination of drug concentration in long-term stability test, it gives fast and adequate data to classify acceptable and unacceptable excipients through the appearance, shift, or disappearance of endothermic or exothermic peaks, as well as variations in the relevant enthalpy values in DSC profiles of drug–excipient combinations.

Therefore, the results with the DSC method are comparable and in good agreement with the results obtained with other methods. DSC has, therefore, been proposed as a rapid method for evaluating physicochemical interactions between two components. However, caution needs to be exercised in the interpretation of DSC results. Interpretation of thermal data is not always straightforward and, to avoid misinterpretations and misleading of thermal analysis results, it must be emphasized that interactions observed at high temperatures may not always be relevant under ambient conditions. Moreover, the presence of a solid–solid interaction does not necessarily indicate incompatibility, but it might instead be advantageous, e.g., as a more desirable form of cosmetic/pharmaceutical formulation. DSC cannot replace chemical methods for quantitative determination of drug concentration in long-term stability tests.

In this work, DSC was used as a screening technique for assessing the compatibility of avobenzone with some currently used cosmetic excipients.

Isothermal stress testing (IST) is another method that involves storing the drug–excipient blends with or without moisture at high temperature to accelerate drug ageing and interaction with excipients. The samples are then visually observed and the drug content is determined quantitatively. Stressed binary mixtures (stored at 50°C for 15 days) of avobenzone and excipients were evaluated by high-performance liquid chromatography (HPLC).

Fourier transform infrared (FT-IR) spectroscopy is another approach used in compatibility tests, based on the hypothesis that some functional groups change during drug–excipient interaction. In cases of suspected incompatibility, FT-IR spectrum of the pure

drug is compared with that of the drug–excipient mixture and of the pure excipient. Disappearance of an absorption peak or reduction of the peak intensity combined with the appearance of new peaks gives a clear evidence for interaction between the excipient and the drug investigated.

Butyl methoxydibenzoylmethane (Avobenzone) (Figure 1) has strong absorption in the UVA1 range (λ maximum at 380 nm). Although it is a broad-spectrum UVA filter, the compound is photolabile and can be rapidly oxidized, and its oxidation will inactivate the antioxidant systems. Unfortunately, it has been shown that its photoprotective capacity decreases by 50% to 60% after 1 h of exposure to sunlight (35). Because of its instability, it is necessary to formulate the avobenzone with compatible excipients.

MATERIALS AND METHODS

MATERIALS AND REAGENTS

Avobenzone was received as a gift sample from Merck Química Argentina (Merck, Darmastadt, Germany). Following chemicals and excipients were purchased from commercial sources and used as such: ascorbyl palmitate (Hoffmann La Roche, Basel, Switzerland); butylated hydroxytoluene (BHT) (Eastman Chemical Company, Kingsport, TN); silicone fluid (Dow Corning, Campinas, Brazil); paraffinum liquidum (R.A.A.M., Buenos Aires, Argentina); acetylated lanolin (Acelan L, Fabriquímica, Buenos Aires, Argentina); cetearyl alcohol/sodium lauryl sulfate/sodium cetearyl sulfate (Flamacer SX, Flamaquímica, Buenos Aires, Argentina); methyl p-hydroxybenzoate, propyl p-hydroxybenzoate (Clariant, Aberdeen, United Kingdom); propylene glycol (Dow Chemical, Midland, MI); imidazolidinyl urea (Bioflama 115, Flamaquímica); sorbitol 70% (water solution), (Unión Química Argentina, Buenos Aires Argentina); cetearyl alcohol (Flamaquímica); glycerin (Flamaquímica); disodium EDTA (Merck, Darmstadt, Germany); caprylic capric triglyceride (Flamacer CC, Flamaquímica); titanium dioxide/silica (Eusolex T-AVO, Merck), and diethylhexyl syringylidene malonate (Oxynex ST, Merck).

DIFFERENTIAL SCANNING CALORIMETRY

A differential scanning calorimeter (DSC 822, Mettler Toledo, Greifensee, Switzerland) was used for thermal analysis of drug and excipients. Excipients that were expected to be used in the development of a formulation (preservatives, surfactants, oil phase, aqueous phase, and antioxidants) and the maximum expected ratio were selected for this

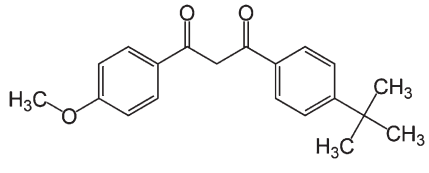

Figure 1. Avobenzone.

study. Individual samples (drug and excipients) as well as physical mixtures of the drug and selected excipients were weighed directly in the pierced DSC aluminum pan and scanned in the temperature range of 25–400°C under atmosphere of dry nitrogen. A heating rate of 10°C/min was used and the obtained thermograms were observed for any interaction. The DSC cell was calibrated with indium (m.p. 156.6°C; ΔH_{fus} = 28.5 J/g) and zinc (m.p. 419.6°C) as standards.

ISOTHERMAL STRESS TESTING

For IST studies, the active and different excipients were weighed directly in 5-ml glass vials (n = 2) and mixed on a vortex mixer for 2 minutes. In each of the vials, the active–excipient blend was further mixed with a sealed glass capillary. To prevent any loss of material, capillary was broken and left inside the vial. Each vial was sealed using a Teflon-lined screw cap and stored at 50°C (Hot air oven, Ionomex, Buenos Aires, Argentina). These samples were periodically examined for any unusual color change. After 15 days of storage at the above conditions, samples were quantitatively analyzed using HPLC.

For sample preparation, an amount of powder equivalent to 50 mg of avobenzone was taken in a 100-ml volumetric flask, dissolved in 60 ml of methanol, stirred for about 5 min, and then diluted to volume with methanol. A 1-ml aliquot of the solution was transferred to a 50-ml volumetric flask. The sample was diluted to volume with methanol.

For standard preparation, 25 mg of avobenzone was taken in a 50-ml volumetric flask, dissolved in 20 ml of methanol, stirred for about 5 min, and then diluted to volume with methanol. A 1-ml aliquot of the solution was transferred to a 50-ml volumetric flask. The sample was diluted to volume with methanol.

For the analysis of active–excipient mixtures, an HPLC system equipped with a dual piston reciprocating Spectra Physics pump (Model ISO Chrom. LC pump, Irvine, CA), a UV-Vis Hewlett Packard detector (Model 1050), a Hewlett Packard integrator (Series 3395, Loveland, CO), and a Rheodyne injector (Model 7125) were used. Chromatographic quantification of lipoic acid was performed on a Microsorb-MV® 100 Å C18 (5 µm) Varian Analytical Instruments (Walnut Creek, CA). The mobile phase used was methanol:water (95:5, v/v) (pH 3.2) adjusted with 85% of phosphoric acid. Separation was isocratically carried out at room temperature; the flow rate was 1.0 ml/min, with UV detection at 315 nm. The volume of each injection was 20 µl. Before injecting solutions, the column was stabilized for at least 30 min with the mobile phase flowing through the system. Quantification was accomplished using an external standard method. In the external standard method, the solute chosen as the reference is chromatographed separately from the sample. However, results from two chromatograms will be compared, so chromatographic conditions must be maintained extremely constant. Each solution was prepared in duplicate and was injected in triplicate, and the relative standard deviation was below 2.0%.

IR SPECTROSCOPY

IR spectra of active and active–excipient blends were recorded on an IR spectrophotometer Perking Elmer FT-IR Spectrum One **(Shelton, CT)**, in the range of 4000–450 cm^{-1}. Solid and liquid samples were analyzed using nujol suspensions.

RESULTS AND DISCUSSION

The thermal behavior of the pure drug, respective excipient, and the combination of drug and excipient is compared in the DSC thermograms. The thermogram of avobenzone showed an endothermic peak at 86.4°C (corresponding to its melting point) with an associated enthalpy of −75.01 J/g.

DRUG–EXCIPIENT COMPATIBILITY TESTING

In a majority of the cases, melting endotherm of the drug was well preserved with slight changes in terms of broadening or shifting toward a lower temperature. It has been reported that the quantity of material used, especially in active–excipient mixtures, affects the peak shape and enthalpy (33). Thus, these minor changes in the melting endotherm of a drug could be attributed to the mixing of active and excipient, which lowers the purity of each component in the mixture and may not necessarily indicate potential incompatibility (31). Variations in the enthalpy values for the binary mixtures can be attributed to some heterogeneity in the small samples used for the experiments (3–4 mg) (22). The enthalpy values are reduced to half, less the binary mixtures mentioned.

DSC data of avobenzone and excipient thermal events in single or binary systems are presented in Tables I and II. The melting endotherm of avobenzone was well retained in the blends of avobenzone with silicone, imidazolidinyl urea, sorbitol 70%, ascorbyl palmitate (Figure 2), propylene glycol, titanium dioxide/silica, and disodium EDTA. In the DSC scan of avobenzone with acetylated lanolin or methyl p-hydroxybenzoate (Methylparaben), the peak of avobenzone shifted to a lower temperature and broadened. There was also a significant reduction in the enthalpy value.

In the DSC scan of avobenzone with cetearyl alcohol, isopropyl myristate, propyl p-hydroxybenzoate (Propylparaben), diethylhexyl syringylidene malonate, caprylic capric triglyceride, BHT (Figure 3), cetearyl alcohol/ceteareth 20, cetearyl alcohol/sodium lauryl sulfate/sodium cetearyl sulfate (Figure 4), and paraffinum liquidum; the peak of avobenzone shifted to a lower temperature, broadened, and there was also a significant reduction in the enthalpy value or the enthalpy value could be the average of both substances.

In the DSC scan of avobenzone–glycerine mixture, the peak of avobenzone showed broadening and shifting to a higher temperature (93.12°C) with an anomalous enthalpy value. Appreciable decreasing or the absence of the melting temperature and its respective values of fusion enthalpy suggests a process that takes place with low intensity or even disappears (the case of the binary mixture of avobenzone–acetylated lanolin). A higher value of fusion enthalpy shows an overlapping of two processes (the case of the binary mixture of avobenzone–BHT). The small variations in the enthalpy values for the binary mixtures can be attributed to some heterogeneity in the small samples used for the DSC experiments (3–4 mg). The difference of enthalpy for the binary mixtures of avobenzone with acetylated lanolin, imidazolidinyl urea, and sorbitol 70% can suggest a physical interaction that does not determine an incompatibility.

On the basis of the DSC results, cetearyl alcohol, isopropyl myristate, propylparaben, diethylhexyl syringylidene malonate, caprylic capric triglyceride, BHT, glycerin, cetearyl alcohol/ceteareth 20, cetearyl alcohol/sodium lauryl sulfate/sodium cetearyl sulfate, and paraffinum liquidum seem to exhibit interaction with avobenzone. These excipients were

Table I
Peak Temperature and Enthalpy Values of Excipients

Samples	T_{onset} (°C)	T_{peak} (°C)	ΔH (Jg^{-1})
Avobenzone	82.99	86.40	−75.01
Ascorbyl palmitate	113.31	115.60	−133.12
BHT	69.00	70.98	−89.58
Silicone	—	—	—
Paraffinum liquidum	—	—	—
Acetylated lanolin	—	—	—
Cetearylalcohol/ceteareth 20	49.87	52.13	−63.67
Cetearylalcohol/sodium lauryl sulfate/sodium cetearyl sulfate	37.78 53.15	43.37 60.06	−74.11 −133.04
Methylparaben	125.52	126.51	−182.64
Propylparaben	96.03	97.41	−157.09
Imidazolidinyl urea	158.41 164.25	158.54 164.61	−12.60 −18.38
Propylene glycol	187.43	188.24	−409.44
Sorbitol 70%	115.60	118.82	−153.29
Cetearyl alcohol	36.63 52.46	41.08 54.93	−58.98 −108.39
Glycerin	262.45	286.54	−521.48
Isopropyl myristate	300.69	318.09	−286.32
Disodium EDTA	244.88	251.85	−97.52
Caprylic capric triglyceride	—	—	—
Titanium dioxide/silica	—	—	—
Diethylhexyl syringylidene malonate	—	—	—

tested using the IST technique, and the quantitative results are shown in Table III. It can be seen from the experimental results that there is an irregular decrease or increase in the drug content after storage of drug–excipient blends under stressed conditions for isopropyl myristate, glycerin, BHT, caprylic capric triglyceride, paraffinum liquidum, and propylparaben.

FT-IR studies were then performed to obtain more information and support for the DSC and IST results. FT-IR spectroscopy was used as a supplementary technique to investigate the possible chemical interaction between drug and excipient and to confirm or reject the results obtained by thermal analysis. Among the nondestructive spectroscopic methods, IR spectroscopy is the most suitable technique and has become an attractive method in the analysis of pharmaceutical solids since the materials are not subject to thermal and mechanical energy during sample preparation, thereby preventing solid-state transformations. The appearance of new absorption bands, broadening of bands, and alteration in their intensity are the main characteristics to evidence of interactions between drug and excipients (12, 24).

Table II
Temperature and Enthalpy Values of Binary Mixtures Avobenzone/Excipients

Samples	T_{onset} (°C)	T_{peak} (°C)	ΔH (Jg^{-1})
Ascorbyl palmitate	81.75	85.45	–39.99
	103.48	107.65	–427.75
BHT	54.23	57.91	–70.02
Silicone	81.62	84.95	37.10
Paraffinum liquidum	71.62	78.84	–37.14
Acetylated lanolin	73.46	81.66	–15.30
Cetearylalcohol/ceteareth 20	49.56	52.36	–35.59
	60.81	71.24	–20.45
Cetearylalcohol/sodium	37.75	40.96	–7.24
lauryl sulfate/sodium	52.26	56.95	–10.24
cetearyl sulfate	72.41	80.16	–72.89
Methylparaben	74.87	80.40	–47.76
	96.86	116.95	–44.48
Propylparaben	67.51	73.82	–115.38
Imidazolidinyl urea	81.04	84.70	–27.68
	158.82	160.54	–2.05
Propylene glycol	79.60	83.92	–40.40
	155.20	172.38	–34.00
Sorbitol 70%	81.07	85.36	–24.62
	109.47	123.15	–82.99
Cetearyl alcohol	37.65	42.69	–33.17
	53.42	56.48	–71.99
	63.56	70.82	–12.47
Glycerin	89.85	93.12	–26.97
	286.68	287.26	–78.44
Isopropyl myristate	49.79	63.54	–17.78
	146.09	180.74	–46.57
Disodium EDTA	82.17	85.49	–30.83
	246.59	251.05	–45.50
Caprylic capric triglyceride	59.76	75.59	–15.44
Titanium dioxide/silica	84.94	88.58	–33.44
Diethylhexyl syringylidene malonate	59.06	75.58	–12.25

In the IR spectrum of avobenzone in nujol, the following bands were observed: 1605 (asym ring); 1305 (O-C-C); 1259 (C-O); 1229; 1171, 1111, and 1035 (C-C); 844; and 788 (p-di subst.) cm^{-1}.

IR spectra of avobenzone and its blends with the above-mentioned excipients cetearyl alcohol, isopropyl myristate, diethylhexyl syringylidene malonate, glycerin, cetearyl alcohol/ ceteareth 20, cetearyl alcohol/sodium lauryl sulfate/sodium cetearyl sulfate, and paraffinum liquidum showed the presence of characteristic bands corresponding to avobenzone. This suggests that avobenzone is kept unaltered in these blends.

FT-IR spectrum of avobenzone–caprylic capric triglyceride blend did not present the characteristic bands of avobenzone at 1171, 1035, and 788 cm^{-1}. FT-IR spectrum of

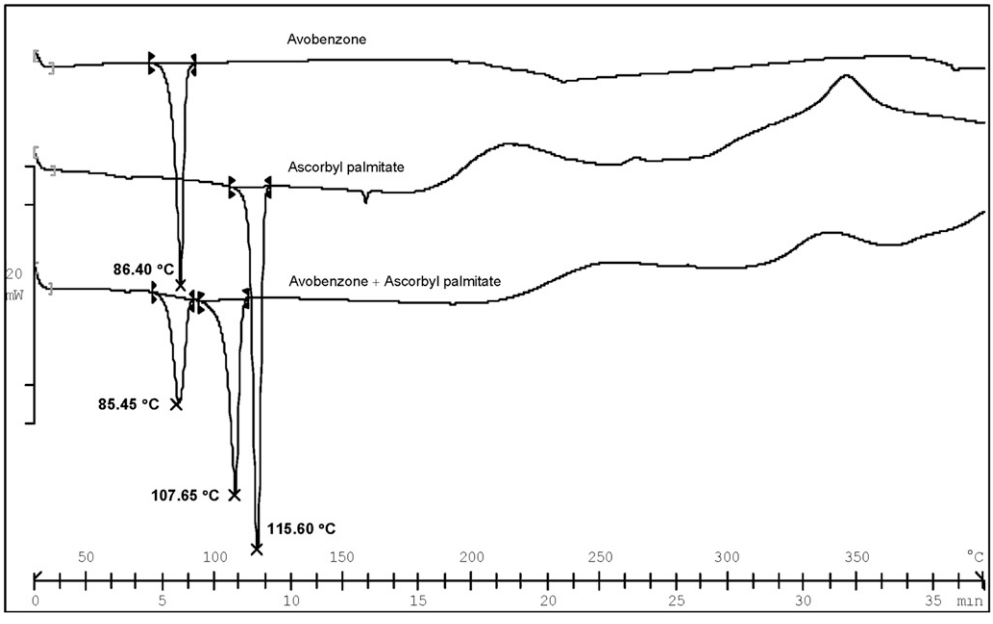

Figure 2. DSC scan of avobenzone with ascorbyl palmitate.

avobenzone–propylparaben blend and avobenzone–BHT blend did not present the characteristic band of avobenzone at 1305 cm^{-1}. On the basis of mentioned differences, it may be considered that avobenzone interacts with caprylic capric triglyceride, propylparaben, and BHT.

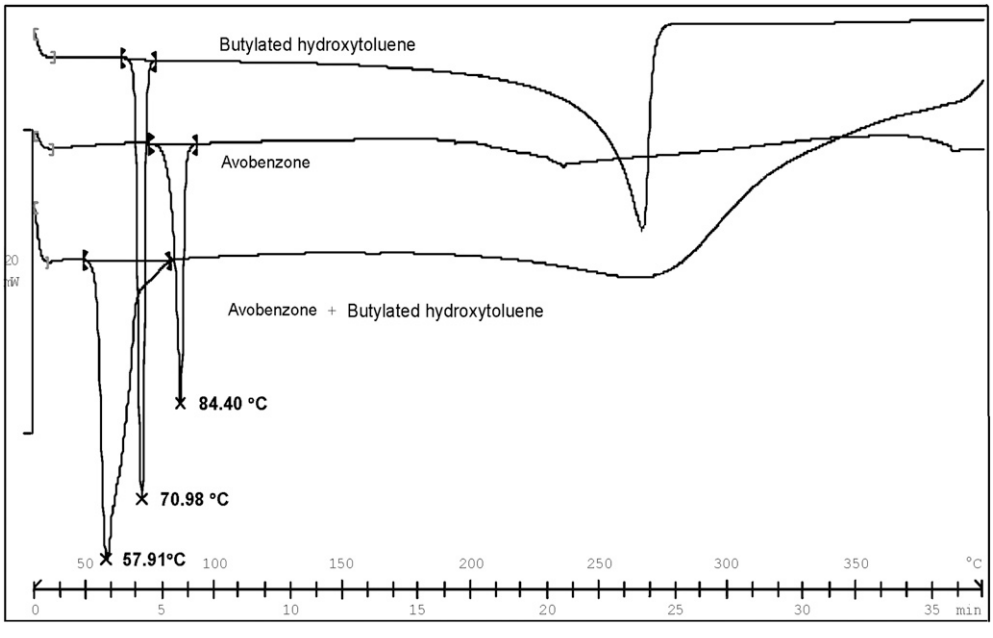

Figure 3. DSC scan of avobenzone with BHT.

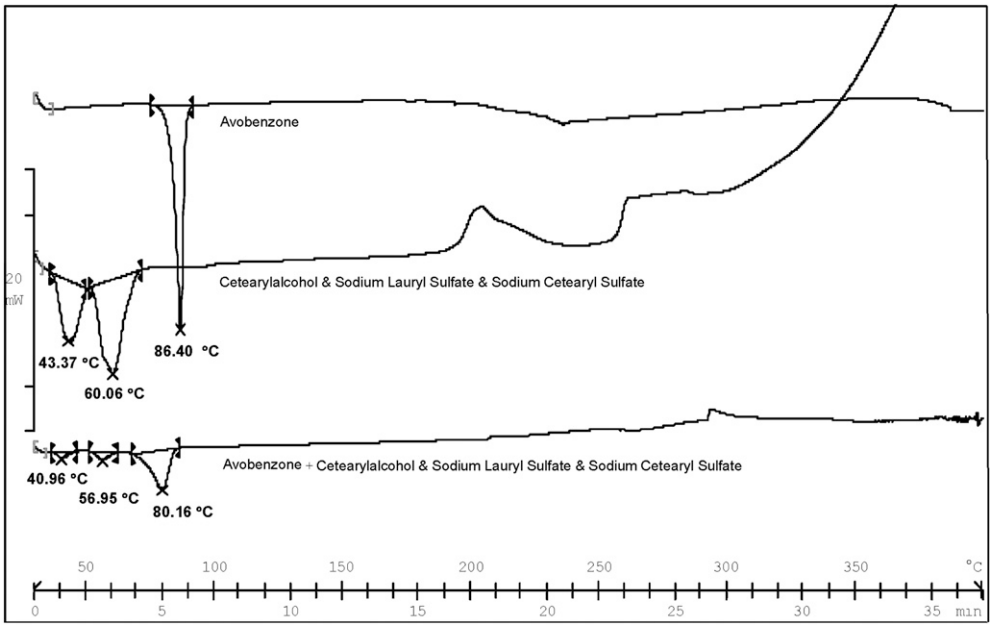

Figure 4. DSC scan of avobenzone with cetearyl alcohol/sodium lauryl sulfate/sodium cetearyl sulfate.

CONCLUSIONS

The compatibility and stability of avobenzone with different excipients was studied by DSC, IST, and FT-IR spectroscopy. The results confirmed that DSC supported by IST/HPLC and FT-IR could be used collectively to study compatibility of drug–excipient mixtures. The DSC technique offers significant advantages, therefore it is considered as a fast screening tool for drug–excipient interaction in a preformulation process. No evidence of interaction was observed between avobenzone and the majority of excipients

Table III
Results of Analysis of IST Samples After 15 Days of Storage at Stressed Conditions

Samples Ratio drug–excipient (1:1)	% Remaining
Avobenzone	101.5
Avobenzone + cetearyl alcohol/sodium lauryl sulfate/sodium cetearyl sulfate	98.8
Avobenzone + cetearyl alcohol/ceteareth 20	98.7
Avobenzone + isopropyl myristate	95.6
Avobenzone + glycerin	91.3
Avobenzone + BHT	103.3
Avobenzone + diethylhexyl syringylidene malonate	98.0
Avobenzone + cetearyl alcohol	97.7
Avobenzone + caprylic capric triglyceride	92.1
Avobenzone + paraffinum liquidum	93.4
Avobenzone + propylparaben	94.7

used in the development of cosmetic formulations. However, based on the DSC results alone, an interaction was suspected between avobenzone and few of the excipients cetearyl alcohol, isopropyl myristate, propylparaben, diethylhexyl syringylidene malonate, caprylic capric triglyceride, BHT, glycerin, cetearyl alcohol/ceteareth 20, cetearyl alcohol/sodium lauryl sulfate/sodium cetearyl sulfate, and paraffinum liquidum, bearing in mind that the presence of solid–solid interaction does not necessarily indicate incompatibility; other analytical techniques were also used, such as IST/HPLC and FT-IR, which can generally help in the interpretation of thermal results. The interaction of caprylic capric triglyceride, propylparaben, and BHT with avobenzone was confirmed by IST/HPLC and FT-IR results. These results are in accordance with our accelerated stability studies in which avobenzone seemed to be less stable in the presence of caprylic capric triglyceride (36). The FT-IR technique did not indicate any incompatibility of avobenzone with cetearyl alcohol, isopropyl myristate, diethylhexyl syringylidene malonate, glycerin, cetearyl alcohol/ceteareth 20, cetearyl alcohol/sodium lauryl sulfate/sodium cetearyl sulfate, and paraffinum liquidum, considering that the absorption bands of avobenzone remained unchanged in the physical mixtures.

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