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Thermal analysis of lipoic acid and evaluation of the compatibility with excipientes

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Abstract Differential scanning calorimetry (DSC) was used as a screening technique for assessing the compatibility of lipoic acid with some currently employed 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, methyl *p*-hydroxybenzoate, propyl *p*-hydroxybenzoate, butylated hydroxytoluene, non ionic self emulsifying wax, propylene glycol and acetylated lanolin were found to exhibit interaction with lipoic acid. Stressed binary mixtures (stored at 50 °C for 1 week) of lipoic acid and excipients were evaluated by HPLC. Binary mixtures were evaluated by IR spectroscopy.

Keywords Compatibility study · Differential scanning calorimetry · Lipoic acid · HPLC · IR

Introduction

Incompatibility between drugs and excipients can alter stability of drugs, thereby, affecting its safety and/or efficacy. Drug-excipient compatibility testing at an early stage helps in the selection of excipients that increase the probability of developing a stable dosage-form. In particular, the low availability of 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 whilst the substance is subjected to a controlled temperature program. Differential scanning calorimeter (DSC) technique 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 a sample and to a reference is monitored against time or temperature while the temperature is programmed in a specified atmosphere. As a result, energy associated with various thermal events (e.g., melting, glass transition temperature, crystallization, etc.) can be evaluated. This method has been extensively reported in the literature for testing compatibility of excipients with number of drugs [1–26] Therefore; the results with the DSC method are comparable and in good agreement with the results obtained with other methods. Use of DSC has been proposed as a rapid method for evaluating the physico-chemical interaction between two components. However, caution need to be exercised in the interpretation of DSC results. This is because of high temperature conditions required and the lack of moisture in conducting experiments. Though 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.

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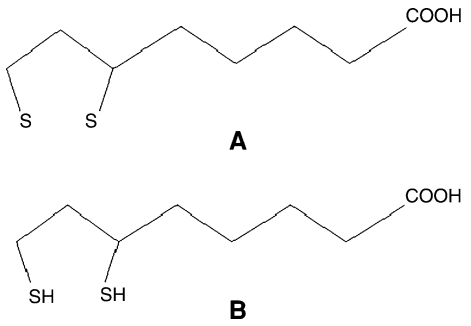

Fig. 1 **a** α-lipoic acid. **b** α-dihydrolipoic acid (reduced form)

Another method that is commonly employed for evaluating the drug-excipient compatibility is isothermal stress testing (IST). The method involves storing the drug-excipient blends with or without moisture at high temperature and determining the drug content [14]. DSC can be used in combination with IST to evaluate compatibility of drugs with selected excipients. In suspected cases of incompatibility, IR spectrum of pure drug was compared with that of drug-excipient mixture and pure excipient.

As a part of an ongoing project on the development of formulations containing lipoic acid, techniques of thermal analysis, IST and IR were utilized for drug-excipient compatibility testing. Lipoic acid, also called thioctic acid, is a powerful antioxidant within the cells and, at the same time, a coenzyme which participates in complex reactions of cellular metabolism. This vitamin has two forms of molecular structure: the oxidized form, a cyclic disulfide, and the reduced open-chain form, dihydrolipoic acid, which has two sulfhydryl groups. Both forms interconvert easily by oxidation-reduction reactions (Fig. 1) [27].

Materials and methods

Materials and reagents

Lipoic acid was received as a gift sample from Craveri S.A.I.C and was provided by (Changshu Fushilai Medice & Chemical Co. Ltd, China). Following chemical and excipients were purchased from commercial sources and used as such ascorbyl palmitate (La Roche Switzerland), sodium ascorbate (BASF, Germany), magnesium ascorbyl phosphate (Merck, Germany), butylated hydroxytoluene (Eastman Chemical Company, USA) Vitamin C (Kromberg, Argentina), Vitamin E (as Acetate) (Merck, Germany), silicone fluid (Dow Corning, Brazil); mineral oil, vaseline (R.A.A.M., Argentina), acetylated lanolin (Acelan L, Fabriquímica, Argentina), non ionic self emulsifying wax (Ceral PW, Fabriquímica, Argentina), anionic self emulsifying wax (Flamacer SX, Flamaquímica, Argentina), methyl p-hydroxybenzoate, propyl p-hydroxybenzoate (Clariant, United Kingdom); imidazolidinyl urea (ISP, United Kingdom), propylene glycol (Dow Chemical, USA), sorbitol 70% (water solution), (Unión Química Argentina, Argentina).

All chemicals used were of analytical grade. Methanol and water were of HPLC grade. Solvents were filtered through a 0.45 μm membrane and degassed.

Differential scanning calorimetry

A differential scanning calorimeter (DSC 822, Mettler Toledo, Switzerland) was used for thermal analysis of drug and excipients. Excipients that were expected to be used in the development of formulation (preservatives, surfactants, oil phase, aqueous phase, antioxidants) and the maximum expected ratio were selected for the present study. Physical mixtures of lipoic acid and each excipient (3 or 4 mg each) were prepared in a 1:1 w/w ratio by gently mixing with a glass capillary (both the ends of which were heated sealed) in a 5 ml glass vials ($n = 2$). Individual samples (active and excipients) as well as physical mixtures of active 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. Heating rate of 10 °C/min was used and thermograms obtained were observed for any interaction. The DSC cell was calibrated with indium (m.p. 156.6 °C; $\Delta H_{fus} = 28.5\ Jg^{-1}$) and Zinc (m.p. 419.6) as standards.

IR spectroscopy

IR spectra of active and active-excipient blends were recorded on an IR spectrophotometer FT-IR Bruker IFS-25, in the range of 4,000–500 cm^{-1}. Solid samples were analyzed using potassium bromide discs (lipoic acid, methyl *p*-hydroxybenzoate, propyl *p*-hydroxybenzoate, butylated hydroxytoluene, non ionic self emulsifying wax, Vitamin C, ascorbyl palmitate, magnesium ascorbyl phosphate, and their blends with lipoic acid). Liquid organic samples were examined directly as a thin film between two NaCl plates (acetylated lanolin, Vitamin E, silicone 350, mineral oil, propylene glycol, and their mixtures with lipoic acid).

Isothermal stress testing

For IST studies, active and different excipients were weighed directly in 5 ml glass vials ($n = 2$) and mixed on a vortex mixer for 2 min. In each of the vials, the active-excipient blend was further mixed with a glass capillary (both the ends of which were heated sealed). 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,

Argentina). These samples were periodically examined for any unusual color change. After 1 week of storage at the above conditions, samples were quantitatively analyzed using HPLC.

For sample preparation, an amount of power equivalent to 25 mg of lipoic acid were taken in a 25 ml volumetric flask, dissolved in 20 ml of methanol, stirred for about 5 min and then diluted to volume with methanol.

For standard preparation: 25 mg of lipoic acid were taken in a 25 ml volumetric flask, dissolved in 20 ml of methanol, stirred for about 5 min and then diluted to volume with methanol.

For the analysis of active-excipient mixtures an HPLC system equipped with a dual piston reciprocating Spectra Physics pump (Irvine, CA, United States, Model ISO Chrom. LC pump), a UV-Vis Hewlett Packard detector (Model 1050), a Hewlett Packard integrator (Loveland, CO, United States, Series 3395) and a Rheodyne injector (Model 7125) was used. Chromatographic quantification of lipoic acid was performed on a Microsorb-MV® 100 Å C18 (5 μm) Varian Analytical Instruments (Walnut Creek, United States). Mobile phase used was methanol:water (80:20, v/v) pH 3.0 adjusted with 85% of phosphoric acid. Separation was isocratically carried out at room temperature, the flow rate was 0.6 ml/min, with UV detection at 332 nm. The volume of each injection was 20 μl. Solutions of lipoic acid were prepared on a weight basis with volumetric flasks to minimize solvent evaporation.

Prior to 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 (RSD) was below 2.0%. The standard solution and lipoic acid in the physical mixtures yield a concentration of 1 mg/ml.

Formulation development and stability studies

The details of the formulation development can be found elsewhere [28, 29].

Results and discussion

Drug-excipient compatibility testing

DSC data of lipoic acid and excipient thermal events in single or binary systems are presented in Tables 1 and 2.

Table 1 Peak temperature and enthalpy values of excipients

Samples	T_{onset}/°C	T_{peak}/°C	ΔH/Jg^{-1}
Lipoic acid	58.9	61.9	−131.0
Ascorbic acid	190.8	191.3	−119.0
Sodium ascorbate	232.8	236.9	50.7
Anionic self	31.2	35.8	−17.5
emulsifying wax	51.0	57.7	−107.7
Ascorbyl palmitate	112.0	114.2	−112.6
Sorbitol 70%	80.0	105.6	−267.4
Propylene glycol	181.0	188.0	−1190.4
Propyl *p*-hydroxybenzoate	94.2	95.4	−145.6
Methyl *p*-hydroxybenzoate	125.6	128.6	−101.3
Butylated hydroxytoluene	67.6	69.0	−196.8
Non ionic self	35.0	38.7	−53.1
emulsifying wax	47.5	51.1	−85.0

Table 2 Temperature and enthalpy values of binary mixtures Lipoic acid/excipients

Samples	T_{onset}/°C	T_{peak}/°C	ΔH/Jg^{-1}
Vitamin E	50.4	56.8	−76.8
Ascorbic acid	55.0	58.0	−54.5
	187.5	191.3	−101.4
Sodium ascorbate	59.1	61.7	−65.5
	227.4	230.4	71.6
Anionic self	31.4	35.2	−15.8
emulsifying wax	47.1	55.6	−124.1
Magnesium ascorbyl phosphate	56.3	60.1	−81.1
Imidazolidinyl urea	57.9	61.5	−68.3
Ascorbyl	56.9	60.7	−64.0
palmitate	100.3	104.3	−59.0
Silicone fluid	57.9	62.0	−69.9
Sorbitol 70%	52.0	55.7	−104.4
Mineral oil	58.1	61.3	−88.1
Propylene glycol	31.9	32.1	−67.3
Propyl	52.8	57.0	−97.9
p-hydroxybenzoate	62.3	80.6	−22.6
Methyl *p*-hydroxybenzoate	53.1	58.0	−56.1
	91.7	104.8	−59.2
Butylated hydroxytoluene	49.3	52.8	−98.5
Non ionic self emulsifying wax	43.1	45.7	−59.9
Acetylated lanolin	51.9	58.6	−57.7

The DSC trace of lipoic acid showed a sharp endotherm peak at 62 °C, due to the drug melting with an associated enthalpy of −131.0 Jg^{-1}. In majority of the cases, melting endotherm of drug was well preserved with slight changes in terms of broadening or shifting towards the lower temperature. It has been reported that the quantity of material used, especially in active-excipient mixtures, affects the

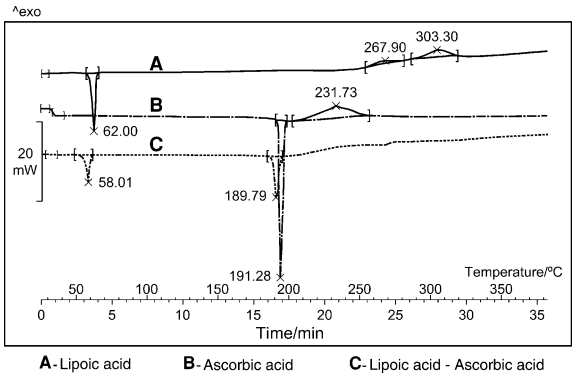

Fig. 2 DSC scan of lipoic acid with ascorbic acid

peak shape and enthalpy [25]. Thus, these minor changes in the melting endotherm of 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 [23]. 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) [14].

In the DSC of Vitamin E (acetate), no peak was observed in the temperature range of 25–400 °C. The melting point of Vitamin E (acetate) is 23 °C. In the DSC scan of lipoic acid and Vitamin E (acetate), the peak of lipoic acid shifted and broaded to lower temperature (56.8 °C).

The DSC scan of ascorbic acid showed an endothermic peak at 191.3 °C (corresponding to melting point). In the DSC scan of lipoic acid and ascorbic acid, both peaks were well retained. It was concluded that lipoic acid is compatible with ascorbic acid (Fig. 2).

The DSC scan of sodium ascorbate showed an exothermic peak at 236.9 °C due to melting point with thermal decomposition. The melting endotherm of lipoic acid (61.7 °C) was well retained in the DSC scan of lipoic acid–sodium ascorbate mixture, the band corresponding to lipoic acid was observed without any new bands. It was concluded that lipoic acid is compatible with sodium ascorbate.

The DSC of anionic self emulsifying wax showed two endothermic peaks at 35.8 °C and 57.7 °C, the second due to melting point. In the DSC scan of lipoic acid and anionic self emulsifying wax, the peak of lipoic acid and excipient shifted and broaded to lower temperature (55.6 °C).

In the DSC of magnesium ascorbyl phosphate, no peak was observed in the temperature range of 25–400 °C. In the DSC scan of lipoic acid and magnesium ascorbyl phosphate, the peak of lipoic acid is well retained (60.1 °C).

In the DSC scan of imidazolidinyl urea, no peak was observed in the temperature range of 25–400 °C. The melting endotherm of lipoic acid was well retained in the DSC scan of lipoic acid–imidazolidinyl urea mixture, the band corresponding to lipoic acid was observed without any new bands (61.5 °C).

The DSC scan of ascorbyl palmitate showed an endothermic peak at 114.2 °C due to melting point. In the DSC scan of lipoic acid and ascorbyl palmitate mixture, the peak of ascorbyl palmitate shifted to lower temperature (104.3 °C). The melting endotherm of lipoic acid was well retained in the DSC scan of lipoic acid–ascorbyl palmitate mixture (60.7 °C).

In the DSC of silicone fluid, no peak was observed in the temperature range of 25–400 °C. In the DSC scan of lipoic acid and silicone fluid, the peak of lipoic acid was well retained. The band corresponding to lipoic acid was observed without any new bands (62.0 °C).

The DSC scan of sorbitol 70% showed a broad endothermic peak at 105.6 °C (corresponding to loss of water). The DSC scan of lipoic acid–sorbitol 70% mixture showed broadening and shifting of drug peak to lower temperature 55.7 °C.

In the DSC of mineral oil, no peak was observed in the temperature range of 25–400 °C. In the DSC scan of lipoic acid and mineral oil, the peak of lipoic acid was well retained (61.3 °C). The band corresponding to lipoic acid was observed without any new bands.

FT-IR studies were performed in order to obtain more information and support DSC results.

The IR spectrum of lipoic acid is shown in Figs. 3, 4 and the following characteristic bands were observed: 3030 (OH); 2932(–CH_2–); 1693 (C=O); 1250 (OH); 945 (OH); 677 (S–C), 524 (S–S) cm^{-1}

Furthermore IR spectra of lipoic acid and its blends with the above mentioned excipients vitamin E (acetate), vitamin C (ascorbic acid), sodium ascorbate, anionic self emulsifying wax, magnesium ascorbyl phosphate, imidazolidinyl urea, ascorbyl palmitate, silicone fluid, sorbitol 70% and mineral oil), showed the presence of characteristic bands corresponding to lipoic acid. There was also no appearance of new

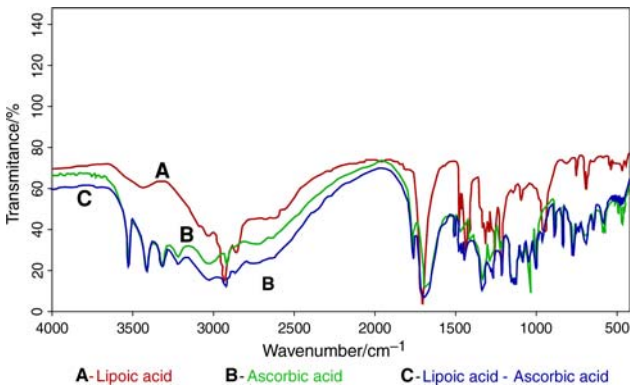

Fig. 3 IR of lipoic acid, ascorbic acid and the mixture

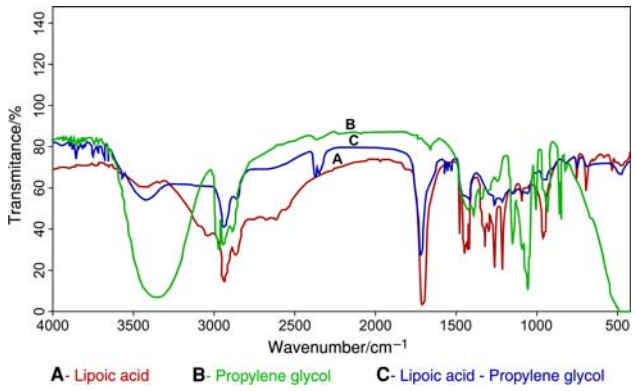

Fig. 4 IR of lipoic acid, propylene glycol and the mixture

bands in the FT-IR spectra of blends. Hence, there was strong evidence of unchanged active structure and lack of chemical interaction between lipoic acid and each one of those excipients. Thus, it was concluded there is no chemical incompatibility between lipoic acid and its blends with the previously mentioned excipients. These results confirmed DSC findings.

The DSC scan of propylene glycol showed an endothermic peak at 188.01 °C (corresponding to boiling point). The DSC scan of lipoic acid–propylene glycol mixture, the active and excipient peaks were missing. DSC results points toward some incompatibility between lipoic acid–propylene glycol mixture. There was also a significant reduction in the enthalpy value (Table 2) (Fig. 5).

The DSC scan of propyl p-hydroxybenzoate showed an endothermic peak at 95.4 °C (corresponding to melting point). The DSC scan of lipoic acid–propyl *p*-hydroxybenzoate mixture showed broadening and shifting of the excipient peak to lower temperature (80.6 °C) with an anomalous enthalpy value.

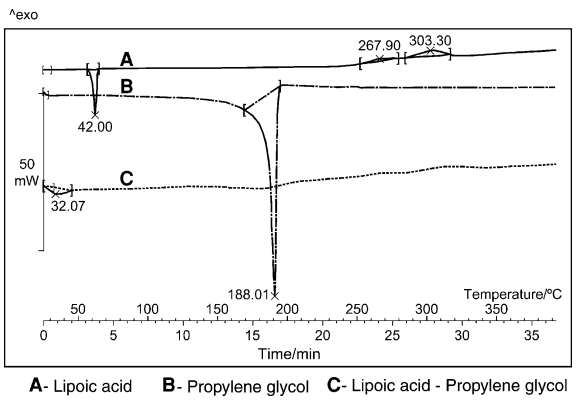

Fig. 5 DSC scan of lipoic acid with propylene glycol

The DSC scan of methyl p-hydroxybenzoate showed an endothermic peak at 128.6 °C (corresponding to melting point). The DSC scan of lipoic acid–methyl *p*-hydroxybenzoate mixture showed broadening and shifting of the excipient peak to lower temperature 104.8 °C with a reduction in the enthalpy value.

The DSC scan of butylated hydroxytoluene (BHT) showed an endothermic peak at 69.0 °C (corresponding to melting point). The DSC scan of lipoic acid–butylated hydroxytoluene mixture showed broadening and shifting of active and excipient peak to lower temperature (52.8 °C) with a significant reduction in the enthalpy value.

The DSC scan of non ionic self emulsifying wax showed two endothermic peaks at 38.7 °C and 51.12 °C (corresponding to melting point). The DSC scan of lipoic acid–non ionic self emulsifying wax mixture showed broadening and shifting of active and excipient peak to lower temperature (45.7 °C) with a significant reduction in the enthalpy value.

In the DSC of acetylated lanolin, no peak was observed in the temperature range of 25–400 °C. In the DSC scan of lipoic acid and acetylated lanolin, the peak of lipoic acid shifted and broaded to lower temperature (58.6 °C).

According to the results of DSC studies, some changes in the FT-IR spectra of binary blends of lipoic acid and some of the excipients, suggested a possible interaction between the mixtures components, in agreement with the thermal analysis findings. For instance, FT-IR spectrum of lipoic acid-propylene glycol blend did not show characteristic bands of lipoic acid at 3,030 and 945 cm^{-1}, and also presented a reduction of intensity of the band at 1,250 cm^{-1}. On the FT-IR spectrum of lipoic acid–propyl p-hydroxybenzoate mixture, the band at 1,250 cm^{-1} was not shown. Lipoic acid–methyl *p*-hydroxybenzoate blend's FT-IR spectrum did not show characteristic bands of lipoic acid at 1,250 and 945 cm^{-1}. In the same way, characteristic band of lipoic acid at 3,030 cm^{-1} was not observed in the FT-IR spectrum of its blend with BHT.

FT-IR spectrum of lipoic acid-non ionic self emulsifying wax blend did not present the characteristic band of lipoic acid at 3,030 cm^{-1}. In the same way, FT-IR spectrum of acetylated lanolin did not present characteristic bands of lipoic acid at 3030, 1250 and 945 cm^{-1}.

All the excipients were tested using the technique of IST and the quantitative results are shown in Table 3 (Figs. 6 and 7). As seen from the table, there are important changes in the drug content after storage of active-excipent blends under stresses conditions. Based on DSC, FT-IR and HPLC results, lipoic acid was found to be incompatible with methyl *p*-hydroxybenzoate, propyl *p*-hydroxybenzoate, butylated hydroxytoluene, non ionic self emulsifying wax, propylene glycol and acetylated lanolin.

Table 3 Results of analysis of IST samples after 1 week of storage at stressed conditions

Samples Ratio drug-excient (1:1)	% Remaining	RSD
Lipoic acid (in solution)	94.5	0.3
Lipoic acid + Vitamin E (acetate)	73.5	0.2
Lipoic acid + ascorbic acid	93.0	0.2
Lipoic acid + sodium ascorbate	95.1	0.6
Lipoic acid + anionic self emulsifying wax	73.6	0.4
Lipoic acid + magnesium ascorbyl phosphate	99.8	0.7
Lipoic acid + imidazolidinyl urea	87.1	0.3
Lipoic acid + ascorbyl palmitate	96.8	0.5
Lipoic acid + silicone fluid	99.8	0.6
Lipoic acid + sorbitol 70%	85.7	1.0
Lipoic acid + mineral oil	95.4	0.6
Lipoic acid + propylene glycol	47.8	0.1
Lipoic acid + propyl p-hydroxybenzoate	20.6	0.2
Lipoic acid + methyl p-hydroxybenzoate	14.2	0.3
Lipoic acid + butylated hydroxytoluene	25.4	1.8
Lipoic acid + non ionic self emulsifying wax	21.3	0.2
Lipoic acid + acetylated lanolin	24.6	0.1

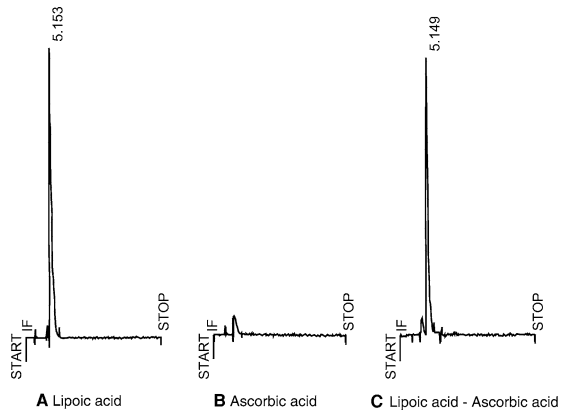

Fig. 6 HPLC of lipoic acid, ascorbic acid and the mixture

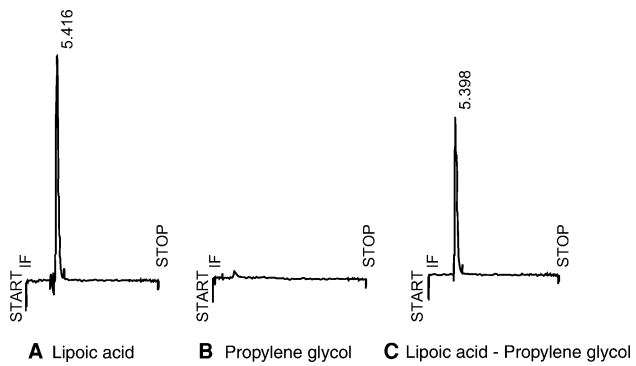

Fig. 7 HPLC of lipoic acid, propylene glycol and the mixture

Conclusions

The results confirmed the utility and reliability of DSC analysis at the earliest stage of preformulations studies as a valuable tool for a rapid screening of a wide range of candidate excipients, allowing a rapid evaluation of possible active-excipient interactions. However caution need to be exercised while interpreting the DSC results alone. Results of DSC along with IR and HPLC were successfully employed to assess the compatibility of lipoic acid with excipients used in the development of cosmetic formulations.

No evidence of interaction was observed between lipoic acid and majority of excipients used in the development of cosmetic formulations. However based on the DSC results alone, an interaction was suspected between lipoic acid and few of the excipients methyl *p*-hydroxybenzoate, propyl *p*-hydroxybenzoate, butylated hydroxytoluene, non ionic self emulsifying wax, propylene glycol and acetylated lanolin. These results were confirmed by HPLC and FT-IR studies.

Further stability studies will be performed using the excipients found to be compatibles with lipoic acid in cosmetic formulations.

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