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Thermal analysis and compatibility studies of prednicarbate with excipients used in semi solid pharmaceutical form

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Abstract Differential Scanning Calorimetry (DSC), thermogravimetry/derivative thermogravimetry (TG/DTG) and infrared spectroscopy (IR) techniques were used to investigate the compatibility between prednicarbate and several excipients commonly used in semi solid pharmaceutical form. The thermoanalytical studies of 1:1 (m/m) drug/excipient physical mixtures showed that the beginning of the first thermal decomposition stage of the prednicarbate (T_{onset} value) was decreased in the presence of stearyl alcohol and glyceryl stearate compared to the drug alone. For the binary mixture of drug/sodium pirrolidone carboxilate the first thermal decomposition stage was not changed, however the DTG peak temperature ($T_{peak\ DTG}$) decreased. The comparison of the IR spectra of the drug, the physical mixtures and of the thermally treated samples confirmed the thermal decomposition of prednicarbate. By the comparison of the thermal profiles of 1:1 prednicarbate:excipients mixtures (methylparaben, propylparaben, carbomer 940, acrylate crosspolymer, lactic acid, light liquid paraffin, isopropyl palmitate, myristyl lactate and cetyl alcohol) no interaction was observed.

Keywords Prednicarbate · Thermal analysis · IR spectroscopy · Compatibility study

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Introduction

Thermoanalytical techniques, especially differential scanning calorimetry (DSC) and thermogravimetry/derivative thermogravimetry (TG/DTG) have been used a long time ago by pharmacists for characterization of the materials before their use and/or at any other stages of the preformulation [1–3].

These techniques allow a fast acquisition of results and require relative simple experimental conditions [3, 4]. In several cases the thermoanalytical findings have to be completed by the results of other analytical techniques (IR, XRD, NMR, etc.) [3–5]. Preformulation means the starting point in the formulation in which several physical and chemical information on the drug—excipients mixture are obtained [6]. The physical and chemical interactions between the active ingredient and excipients of formulation can affect the chemical characteristics, the stability and bioavailability of the given drug and therefore the therapeutic effect and effectiveness of the medicine.

Thermal analysis allows studying potential physical and chemical interactions between the active ingredient and excipients in their formulas and predicting possible incompatibilities in the final product as it have been published in several cases, e.g. [7–10].

The objective of this work was to reveal compatibility studies using DSC and TG/DTG techniques between prednicarbate and excipients commonly used in semi solid formulation.

Prednicarbate is a nonhalogenated corticosteroid, double-ester derivative of prednisolone with high anti-inflammatory activity being used for atopic dermatitis treatment to patients whose risk/benefit rate is high such as children, old people and people need of continuous treatment. This drug has a low effect in the suppression of interleucin (IL)-1α and IL-6 in fibroblasts having low risk to cause skin atrophy [11–14]. Because of its wide activity in immune and inflammatory systems the semi-solid pharmaceutical form this corticosteroid is frequently used in the treatment of atopic dermatitis. The features of this disease are turning the skin dry, inflamed and with intense itching and its prevalence and gravity in general decrease with the age [11, 12, 15].

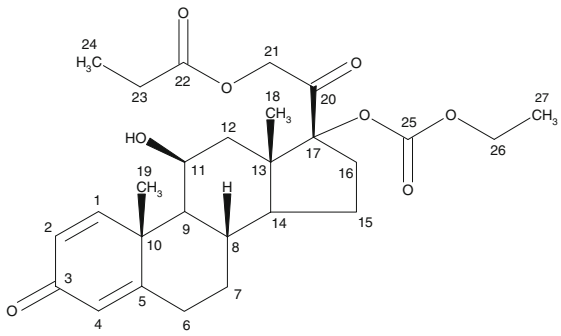

Fig. 1 Chemical structure of prednicarbate

Materials and methods

Materials

The chemical structure of prednicarbate ($C_{27}H_{36}O_8$, MW: 488.57) is given in Fig. 1. Its elemental composition is 66.38%, 7.43% and 26.20% C, H, O, respectively.

Besides the active compound, the names of the used excipients are listed in Table 1.

Methods

Thermal analysis

The DSC curves were recorded using Shimadzu model DSC-50 under dynamic N_2 atmosphere (100 mL min^{-1}) and at a heating rate (β) of 10 °C min^{-1} in the 25–550 °C temperature range, using aluminum crucibles and weighed approximately 2 mg of samples. DSC cell was calibrated with In^0 (ΔH_{fus} = 28.57 J g^{-1}; m.p. = 156.6 °C) and Zn^0 (m.p. = 419.6 °C) standards. The TG/DTG curves were obtained with a thermobalance Shimadzu model TGA-50 under dynamic N_2 atmosphere (100 mL min^{-1}) and at β = 10 °C min^{-1} between 25 and 900 °C, using platinum crucibles with approximately 4 mg of sample loads.

The compatibility study was accomplished using 1:1 (m/m) physical mixtures of prednicarbate and of the excipients. For TG measurements Shimadzu model TGA-51 thermobalance with platinum crucibles, with approximately 12 mg of samples under dynamic N_2 atmosphere (50 mL min^{-1}), β = 10 °C min^{-1}, between 50–220 °C and at 264 °C for isothermal runs (time of heat treatment was 30 min).

Table 1 Raw materials used in the compatibility study

Sample	Classification	Manufacturer	Lot
Drug			
Prednicarbate	Active ingredient	Hawon Biochemical Science	HW05PDC002
Excipients			
Methylparaben	Preservative	San Fu Chemical CO., Ltd	03050429
Propylparaben	Preservative	San Fu Chemical CO., Ltd	04050403
Carbomer 940	Gelling agent	Noveon	CC473BC994
C10-30 alkyl acrylate crosspolymer	Film-forming agent	Permulen–Noveon	CC378CT810
Stearyl alcohol	Emulsifier	Noveon	CR5022500
Lactic acid	To adjust pH	PURAC biochem	0206001297
Light liquid paraffin	Emollient	Ipiranga	IEX-333/05
Sodium pirrolidone carboxylate	Moisturizing agent	Ajinomoto CO, INC	505162
Isopropyl palmitate	Emollient	Dubois-Natural Esters	P509291
Myristyl lactate	Emollient	ISP Technologies, Inc	015001135987
Glyceryl stearate	Emulsifier	Oxiteno	050917M12676
Cetyl alcohol	Emulsifier	Cognis	HN6A112669

IR spectroscopy

FTIR absorption spectra of prednicarbate and of 1:1 physical mixtures (drug/excipient) were recorded at room temperature in the 4,000–400 cm^{-1} range in KBr pellets.

Results and discussion

Thermal behaviour of prednicarbate

TG/DTG curves (Fig. 2) showed that prednicarbate was thermally stable up to 200 °C and then four mass loss stages could be observed. The DSC curve showed an endothermic event between 175 and 200 °C indicating the melting (T_{onset} = 183 °C; ΔH_{fus} = 75.6 J g^{-1}). In this temperature range the TG/DTG curves did not show mass loss. The second event observed in DSC curve was also an endothermic one which started immediately after the complete melting and corresponds to the first stage of thermal decomposition (see TG/DTG curves, $T_{onset\ TG}$ = 243 °C; $T_{DTG(dm/dt=0)}$ = 195 °C).

Table 2 summarizes the mass losses (Δm, %) of the thermal decomposition stages and the corresponding DTG and DSC peak temperatures.

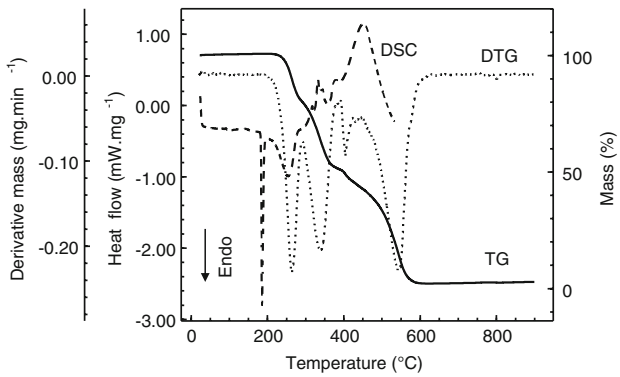

Fig. 2 DSC and TG/DTG curves of prednicarbate

Table 2 Thermal data of the decomposition of prednicarbate

Prednicarbate	Melting	Thermal decomposition events[a]			
		1st	2nd	3rd	4th
T_{onset} (°C) DSC	183	–	–	–	–
T_{peak} (°C) DSC	187	254.3	332.5	451.5	–
T_{peak} (°C) DTG	–	264	339	404	543
Δm (%) TG	–	20.7	28.4	7.6	42.6

[a] DSC curves were obtained in the 25–550 °C temperature range

Compatibility study of prednicarbate and excipient mixtures

Thermal analysis results

Figures 3, 4 and 5 show the TG, DTG and DSC curves of the substances used in the compatibility study.

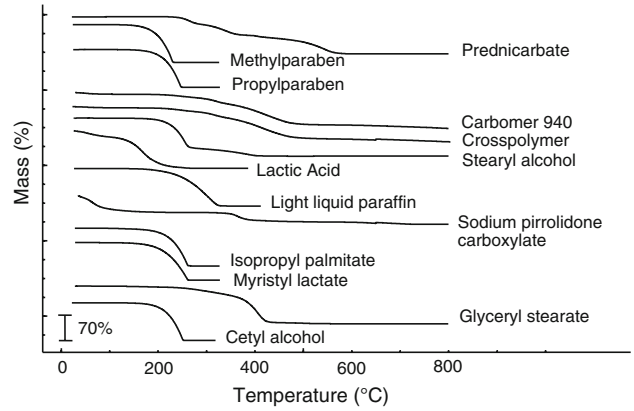

Fig. 3 TG curves of all substances used in the compatibility study

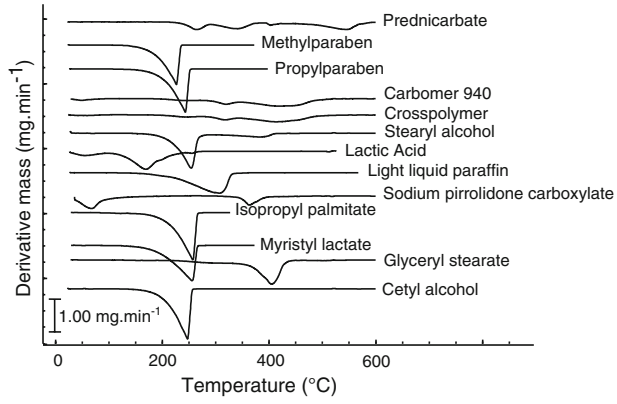

Fig. 4 DTG curves of all substances used in the compatibility study

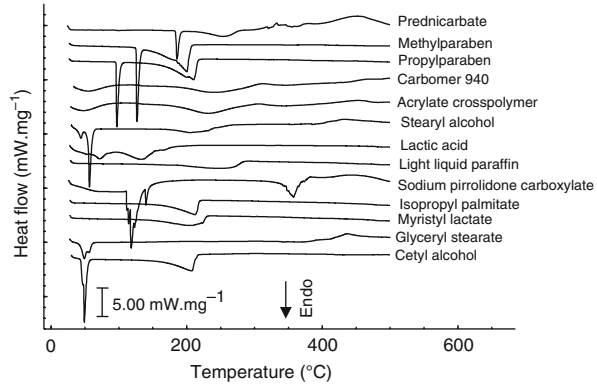

Fig. 5 DSC curves of all substances used in the compatibility study

In the 1:1 physical mixtures when there is no any interaction between drug and excipient the T_{onset} value of melting event (DSC curve) and the first stage of the decomposition (T_{onset} of TG/DTG curves) should remain practically unchanged, similarly when the drug is alone. In the DSC curve the T_{onset} values of melting of the drug should remain almost the same when the drug is alone or in its mixtures when there is no interaction between drug and excipient. In the DSC curve of the 1:1 physical mixture of prednicarbate and carbomer 940 does not show any alteration in the melting of the active compound compared when the drug is alone (Fig. 6).

The same phenomenon was observed in the DSC curves of the 1:1 physical mixtures of prednicarbate/acrylate crosspolymer and prednicarbate/light liquid paraffin (Fig. 7) denying any interaction upon heating.

When sodium pirrolidone carboxylate was used as excipient the melting enthalpy of prednicarbate was lower ($\Delta H = 20.4$ J g^{-1}) than it was expected from the 1:1 mechanical mixture without any interaction among the chemical species (Fig. 8). The T_{onset} value (179.4 °C) of the prednicarbate melting was also decreased.

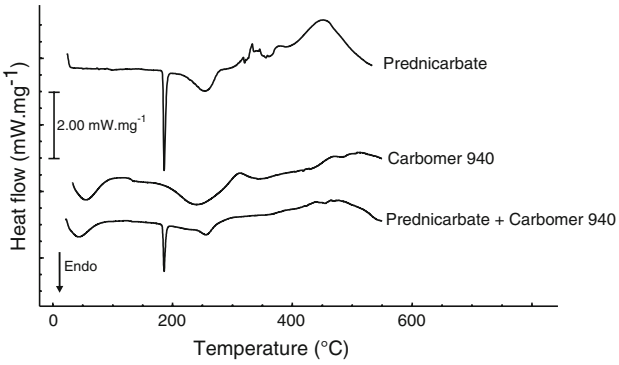

Fig. 6 DSC curves of prednicarbate, carbomer 940 and 1:1 physical mixtures of prednicarbate

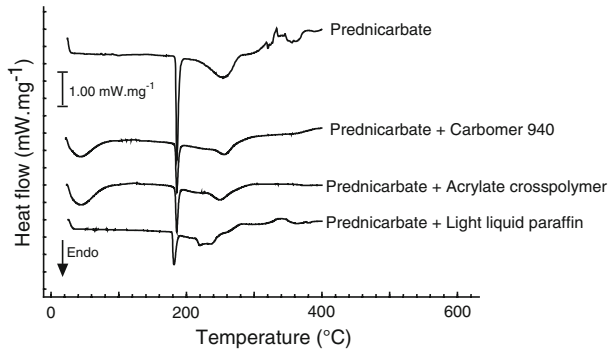

Fig. 7 DSC curves of prednicarbate and its 1:1 physical mixtures with carbomer 940, acrylate crosspolymer and light liquid paraffin

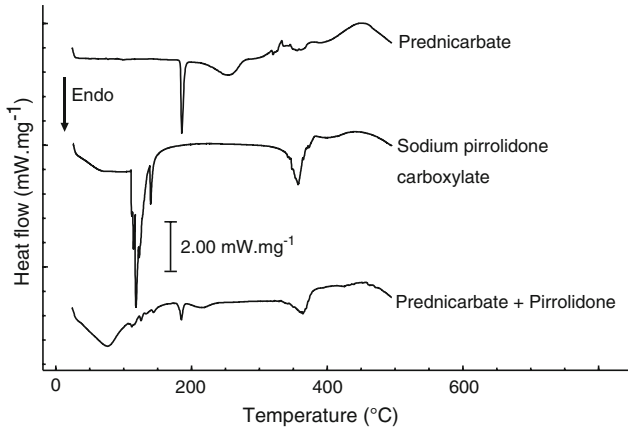

Fig. 8 DSC curves of prednicarbate, sodium pirrolidone carboxylate and their 1:1 physical mixture

The changes observed in the thermoanalytical profile of prednicarbate did not show necessarily an incompatibility with pirrolidone but demonstrated a sort of interaction due to heating. Some kind of modification in the thermoanalytical profile of drug melting in the binary mixtures of prednicarbate/lactic acid and prednicarbate/isopropyl palmitate were also observed (Fig. 9).

In the DSC curve of prednicarbate/lactic acid mixture the melting of drug exhibited a small enthalpy variation (2.2 J g^{-1}), which can be attributed to the almost complete dissolution of the drug in the lactic acid (Fig. 9). The T_{onset} (191.4 °C) temperature also changed compared to the T_{onset} of the pure drug.

According to the DSC curve of the prednicabate/isopropyl palmitate system, some interaction was also found. The melting enthalpy and T_{onset} temperature of prednicarbate was changed to 14.12 J g^{-1} and 164.9 °C, respectively, and the melting peak was widened compared to the melting peak of the pure drug (Fig. 9).

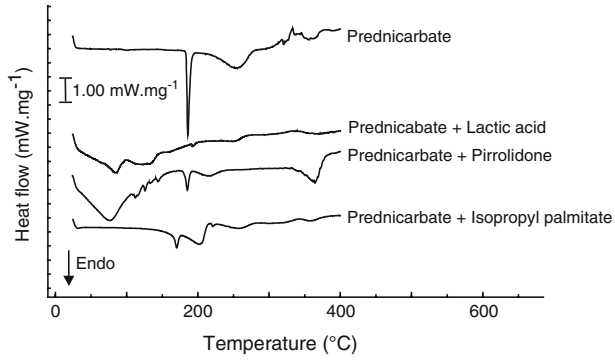

Fig. 9 DSC curves of prednicarbate and its 1:1 physical mixtures of with lactic acid, sodium pirrolidone carboxylate and isopropyl palmitate

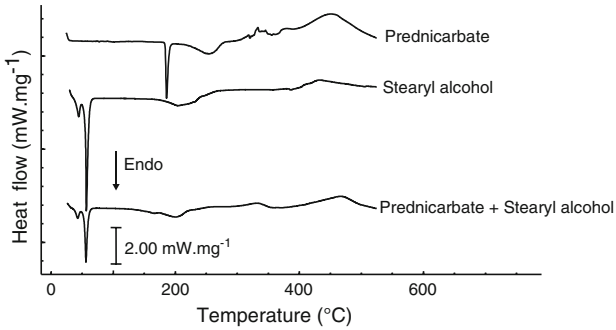

Fig. 10 DSC curves of prednicarbate, stearyl alcohol and their 1:1 physical mixture

Due to the complete dissolution of the drug in the melt of the excipient, no melting of prednicarbate was observed in the DSC curve of the prednicarbate/stearyl alcohol mixture (see Fig. 10).

The lack of melting of prednicarbate was also observed in the DSC curves of the mixtures of prednicarbate with methylparaben, propylparaben, myristyl lactate, glyceryl stearate and cetyl alcohol (Fig. 11) indicating a strong interaction between the drug and the above excipients.

Table 3 lists the T_{onset} and T_{peak} values and the enthalpy change (J g^{-1}) taken from the DSC curves, involved in the melting process of the prednicarbate evaluated alone and this compound in the 1:1 physical mixture with the excipients.

In the TG/TDG curves prednicarbate and methylparaben one can see, methylparaben did not affect the first stage of thermal decomposition of the prednicarbate (Fig. 12).

The first thermal event corresponds to the evaporation and/or decomposition of methylparaben. TG/DTG curves of prednicarbate/methylparaben mixture show that the volatilization methylparaben started at higher temperature.

The starting temperatures of the first thermal decomposition stage of prednicarbate did not present any modification compared to its 1:1 physical mixture with propylparaben, C10-30 alkyl acrylate crosspolymer, carbomer 940, lactic acid, light liquid paraffin, isopropyl palmitate, myristyl lactate and cetyl alcohol (Figs. 13, 14).

In case of the prednicarbate–glyceryl stearate system the beginning of the first and second thermal decomposition steps shifted towards the lower temperatures (Fig. 15).

The beginning of the first thermal decomposition stage of prednicarbate has also decreased in the 1:1 physical mixture with stearyl alcohol (Fig. 16). In the binary mixture of prednicarbate and sodium pirrolidone carboxylate

Table 3 T_{onset}, T_{peak} and melting enthalpy values of prednicarbate from the DSC curves of the 1:1 physical mixtures

Sample	T_{onset} DSC (°C)	T_{peak} DSC (°C)	Enthalpy of fusion (J g^{-1})
Drug			
Prednicarbate	182.7	186.2	75.6
Drug/excipient (1:1)			
Methylparaben[a]	–	–	–
Propylparaben[a]	–	–	–
Carbomer 940	183.0	185.9	34.8[b]
C10-30 alkyl acrylate crosspolymer	183.2	185.7	31.7[b]
Stearyl alcohol[a]	–	–	–
Lactic acid	191.4	192.7	2.2
Light liquid paraffin	179.1	181.6	28.9[b]
Sodium pirrolidone carboxylate	179.4	185.2	20.4
Isopropyl palmitate	164.9	170.1	14.2
Myristyl lactate[a]	–	–	–
Glyceryl stearate[a]	–	–	–
Cetyl alcohol[a]	–	–	–

[a] 1:1 physical mixtures in which the melting of prednicarbate was not observed

[b] 1:1 physical mixtures in which was not observed any interaction between them

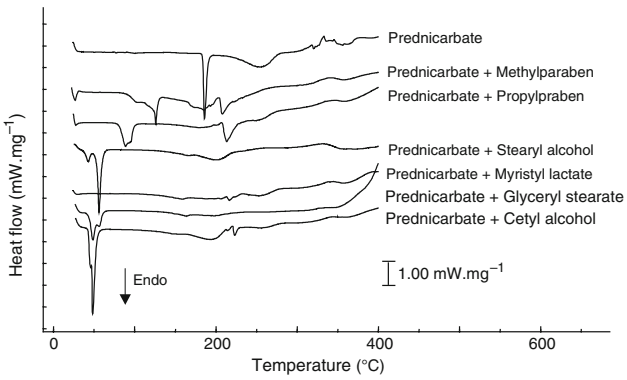

Fig. 11 DSC curves of prednicarbate and its 1:1 physical mixtures with methylparaben, propylparaben, stearyl alcohol, myristyl lactate, glyceryl stearate and cetyl alcohol

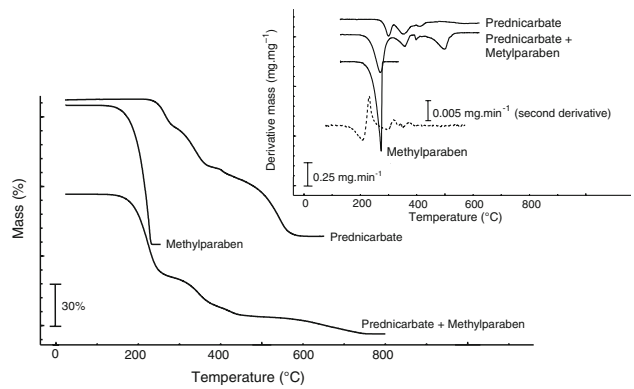

Fig. 12 TG/DTG curves of prednicarbate, methylparaben and their 1:1 physical mixture

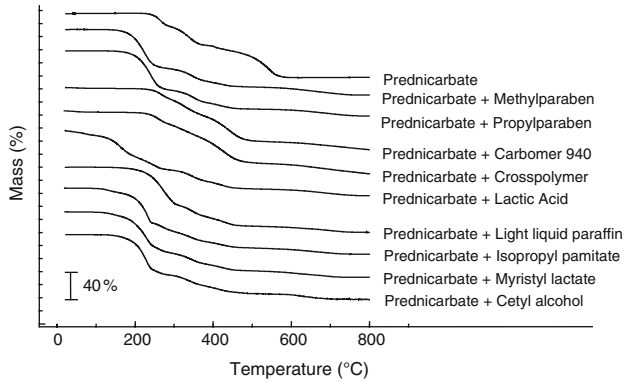

Fig. 13 TG curves of prednicarbate and its 1:1 physical mixture with methylparaben, propylparaben, carbomer 940, C10-30 alkyl acrylate crosspolymer, lactic acid, light liquid paraffin, isopropyl palmitate, myristyl lactate and cetyl alcohol

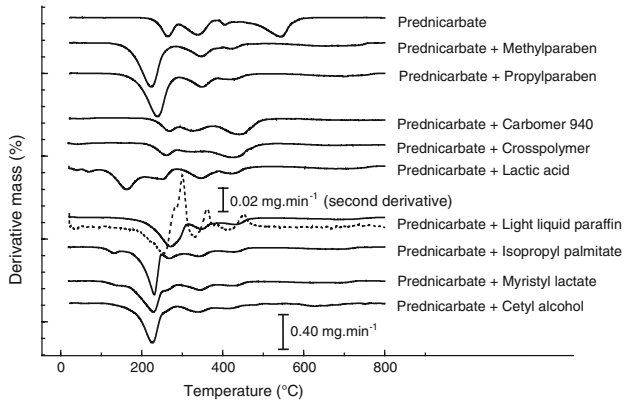

Fig. 14 DTG curves of prednicarbate and its 1:1 physical mixture with methylparaben, propylparaben, carbomer 940, C10-30 alkyl acrylate crosspolymer, lactic acid, light liquid paraffin, isopropyl palmitate, myristyl lactate and cetyl alcohol

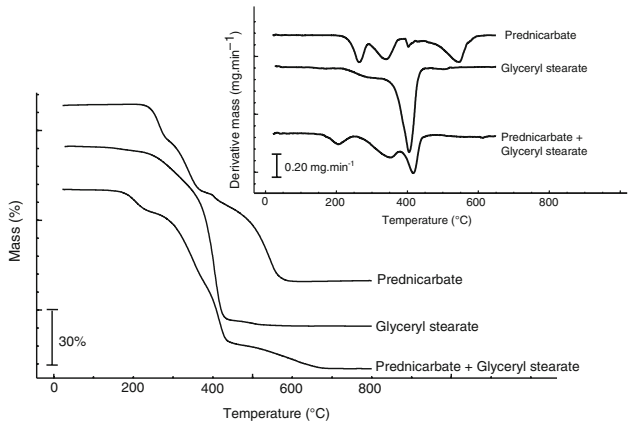

Fig. 15 TG/DTG curves of prednicarbate, glyceryl stearate and their 1:1 physical mixture

the beginning of the first thermal decomposition stage of drug (T_{onset} 221 °C) was different to that presented by drug alone (T_{onset} 243 °C) (Fig. 17).

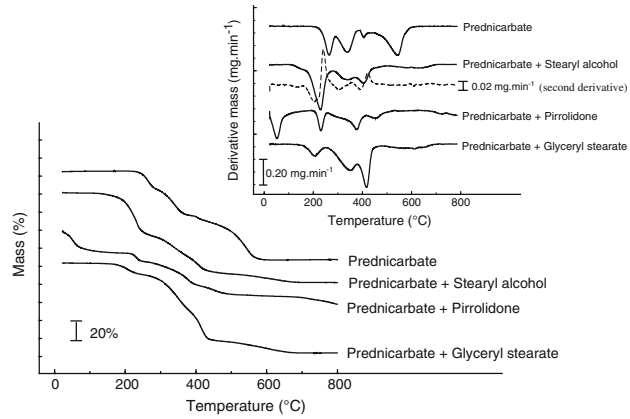

Fig. 16 TG/DTG curves of prednicarbate and 1:1 physical mixtures between prednicarbate and the excipients stearyl alcohol, sodium pirrolidone carboxylate and glyceryl stearate

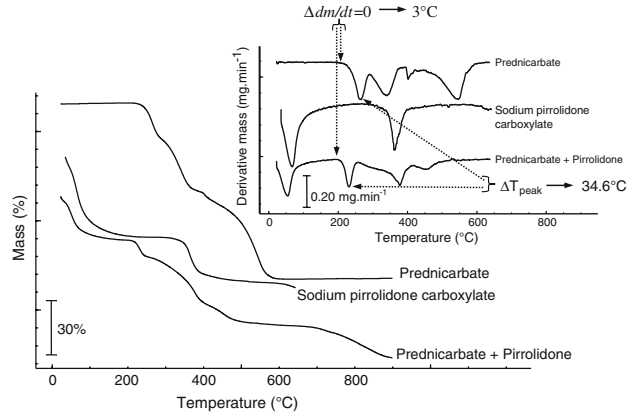

Fig. 17 TG/DTG curves of prednicarbate, sodium pirrolidone carboxylate and 1:1 physical mixtures of prednicarbate/sodium pirrolidone carboxylate

By the comparison of the DTG curves of prednicarbate, sodium pirrolidone carboxylate and the binary mixtures of these compounds it was concluded that that the thermal stability of prednicarbate in these mixtures changed a little. Thus it was concluded that the sodium pirrolidone carboxylate accelerated the thermal decomposition of prednicarbate ($\Delta T_{peak} = 35$ °C) but practically did not influence the beginning of the reaction (Fig. 17).

Table 4 lists the T_{onset} (TG curve) and T_{peak} (DTG curve) corresponding to the first thermal decomposition stage of prednicarbate alone and this drug in 1:1 physical mixture with stearyl alcohol, sodium pirrolidone carboxylate and glyceryl stearate.

IR spectroscopy results

The IR spectrum of prednicarbate at room temperature (Fig. 18) showed absorption band assigned to C=O group (ν C=O) at 1,752 cm^{-1} that is characteristic of the ester (C_{22}) and carbonate (C_{25}) groups. Furthermore, absorption

Table 4 Thermoanalytical data of prednicarbate alone and with stearyl alcohol, sodium pyrrolidine carboxylate and glyceryl stearate excipients

Sample	$T_{onset\ TG}$ (°C)	$dm/dt = 0_{DTG}$	$T_{peak\ DTG}$ (°C)
Drug			
Prednicarbate	243	195	264
Drug/excipient (1:1)			
Stearyl alcohol[a]	223	–	232
Sodium pirrolidone carboxylate	221	192	229
Glyceryl stearate	173	158	205

[a] T_{onset} value from of the second derivative of TG curve. T_{peak} value from of the first derivative of TG curve

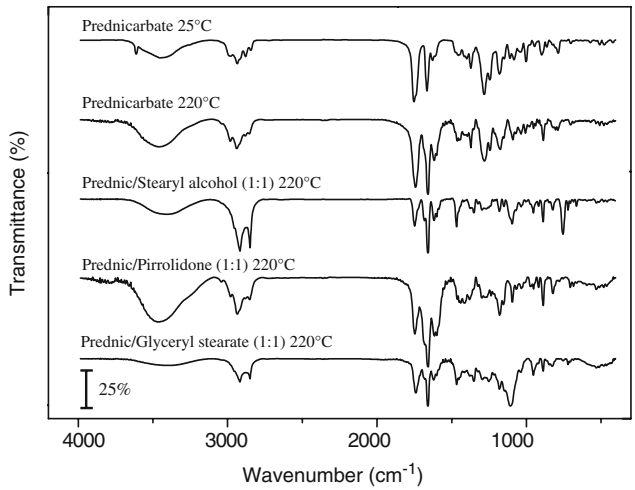

Fig. 18 IR spectra of prednicarbate room temperature and heat treated at 220 °C and its 1:1 (m/m) physical mixtures with stearyl alcohol, sodium pirrolidone carboxylate and glyceryl stearate heat treated at 220 °C

bands at 1,282 and 1,083 cm^{-1} assigned to asymmetric stretching of C–O (ν_{as} C–O) in carbonate group and symmetric stretching of C–O (ν_{s} C–O) in ester group can be also observed. The presence these representative bands in the IR spectrum of prednicarbate heat treated at 220 °C (Fig. 18) confirms its thermal stability up to the above temperature.

The IR spectrum of 1:1 (m/m) physical mixture between drug and stearyl alcohol (Fig. 19) treated at 220 °C showed the disappearance of stretching band at 1,280 cm^{-1} which indicates an instability (a supposed interaction) in the drug–excipient mixture. The disappearance of stretching band at 1,280 cm^{-1} together with the presence of stretching band with less intensity at 1,750 cm^{-1} indicate that the first thermal decomposition stage of prednicarbate takes place with the elimination of the carbonate group.

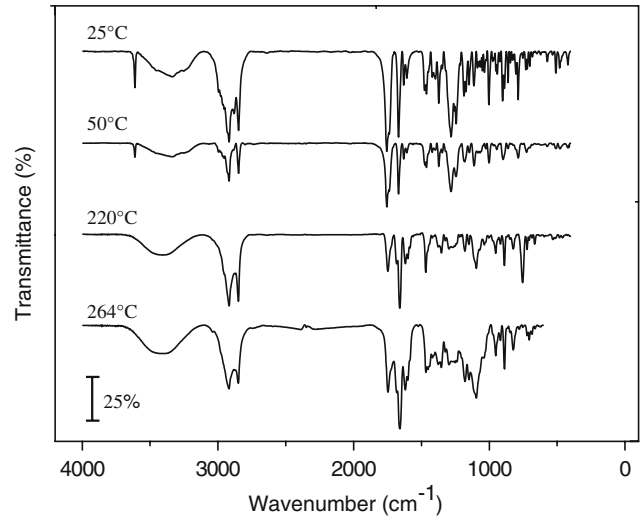

Fig. 19 IR spectra of 1:1 (m/m) physical mixtures of drug and stearyl alcohol at room temperature and heat treated at 50, 220 and 264 °C

The same thermal behavior was observed in the IR spectra of 1:1 (m/m) physical mixture between drug/sodium pirrolidone carboxylate and drug/glyceryl stearate (Fig. 18).

Conclusions

According to the obtained results it can be concluded that thermal analysis is an effective and reliable technique in the compatibility studies of drug–excipient mixtures.

The changes in the thermoanalytical profiles in the DSC and TG/DTG curves in case of some binary mixtures indicated the formation of some interaction as a function of heating.

The TG/DTG curves of the binaries of drug and stearyl alcohol and glyceryl stearate showed a change in the first thermal decomposition stage of prednicarbate. For the 1:1 physical mixture between prednicarbate and sodium pirrolidone carboxylate the TG/DTG curves showed an accelerated reaction corresponding to the first thermal decomposition stage of drug.

The results of the IR studies of the drug and their mixtures were consistent with thermal analysis experiments. The disappearance of specific absorption bands in the IR spectra of the drug in the physical mixtures treated at 220 °C confirmed the thermal decomposition path of prednicarbate.

Consequently, prednicarbate did not present any interaction versus heating with methylparaben, propylparaben, carbomer 940, C10-30 alkyl acrylate crosspolymer, lactic acid, light liquid paraffin, isopropyl palmitate, myristyl lactate and cetyl alcohol. However, the mixture of the drug with stearyl alcohol, glyceryl stearate and sodium pirrolidone carboxylate to develop a semi solid pharmaceutical form is not recommended.

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