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Differential scanning calorimetry as a screening technique in compatibility studies of DHEA extended release formulations

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Abstract

Differential scanning calorimetry (DSC) was used as a screening technique for assessing the compatibility of DHEA as ternary complex with α-cyclodextrin and glycine (c-DHEA) with some excipients suitable for preparation of sustained-release matrix tablets by direct compression. The effect of sample mechanical treatment due to the compression process was also evaluated. In order to investigate the possible interactions between the components, the DSC curves of c-DHEA and each selected excipient were compared with those of their 1:1 w/w physical mixtures, before and after compression, in order to evaluate any possible solid state modification. FT-IR spectroscopy and X-ray powder diffractometry were used as complementary techniques to adequately implement and assist in interpretation of the DSC results. On the basis of DSC results, c-DHEA was found to be compatible with xanthan gum, hydroxypropylmethylcellulose, sodium starch glycolate (Explotab®), polyvinylacetate–polyvinylpirrolidone (Kollidon®SR) and sodium chloride. Some drug–excipient interaction was observed with dextrate hydrate (Emdex®), mannitol and Magnesium stearate. Finally, the behaviour of the complete formulation, in the presence of all the excipients selected by means of the compatibility study, was investigated, in order to verify the absence of reciprocal interactions among the components.

Keywords: DHEA; Sustained-release matrix tablets; Compatibility; Differential scanning calorimetry

1. Introduction

Studies of drug–excipient compatibility represent an important phase in the preformulation stage for the development of all dosage forms. In fact potential physical and chemical interactions between drugs and excipients can affect the chemical nature, the stability and bioavailability of drugs and, consequently, their therapeutic efficacy and safety. Differential scanning calorimetry (DSC) is a rapid analytical technique commonly used for evaluating drug–excipient interactions through the appearance, shift, or disappearance of endo- or exothermal effects and/or variations in the relevant enthalpy values [1–7].

However, the interpretation of the thermal data is not always easy and, to avoid misinterpretation and misleading of DSC results, it must be emphasized that the interactions observed at high temperatures may not always be relevant at ambient conditions [8–10]. Moreover, the presence of a solid–solid interaction does not necessarily indicate pharmaceutical incompatibility [9], but it might instead be advantageous, e.g. as a more desirable form of drug delivery system [10–12]. Therefore, the use of other analytical techniques, such as infrared spectroscopy, X-ray powder diffractometry, hot-stage microscopy and scanning electron microscopy as complementary tools to assist in the interpretation of DSC findings is greatly advisable [13,14].

Dehydroepiandrosterone (DHEA) is a poorly soluble adrenal secretory steroid hormone whose plasmatic levels naturally decrease with aging, until to almost ceasing at senescence [15]. The age-related decline in DHEA production has recently attracted increasing interest, due to its possible relevance in the treatment of a number of age-related illnesses. In fact, even though the results of epidemiological studies are sometimes contradictory, various reports indicated that DHEA replacement therapy in elderly people had beneficial effects on several diseases of aging, i.e. lipid metabolism, atherosclerosis, osteoporosis [16–20]. Moreover, it has been demonstrated that DHEA treatment can improve mood, well-being, sexual functions and cognition in young adults with primary and secondary adrenal insufficiency [21,22]. Pharmacodynamic studies suggest that

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daily doses of 30–50 mg of oral DHEA may produce physiologic hormone levels [22]. However, the very limited aqueous solubility and wettability of DHEA can give rise to both problems of formulation and low and variable bioavailability [23].

Previous studies aimed at improving the DHEA solubility and dissolution properties revealed that a significant enhancement in both solubility and bioavailability of the hormone can be attained by ternary complexation with α-cyclodextrin and glycine (c-DHEA) [23]. As a subsequent extension of these studies, we considered it worthy of interest to develop a once-a-day extended-release tablet dosage form of c-DHEA, with the purpose of both further increasing its therapeutic effectiveness, by obtaining a suitable drug release profile according to the hormone circadian rhythm, and improving patient compliance, by reducing the administration frequency.

Among the different approaches studied to obtain sustained-release oral delivery systems, direct-compression matrix-tablets offer several advantages such as rapid and simple formulation processes, in combination with easy scale-up and reduced manufacturing times and costs [24].

Therefore, as a part of an on-going project aimed at the development of an extended release matrix-tablet formulation of c-DHEA, in the present work we carried out compatibility studies between the complexed drug and a series of excipients in order to evaluate possible solid state interactions and choose the most proper components. Excipients were chosen on the basis of their potential suitability for the development of the intended prolonged-release matrix-tablet formulation. Natural (xanthan gum), semi-synthetic (hydroxypropylmethylcellulose (Methocel K4M), sodium starch glycolate (Explotab®)) or synthetic (polyvinylacetate-polyvinylpirrolidone (Kollidon®SR)) polymers were selected as matrix-forming materials suitable for direct-compression due to their good flow properties and dry binding capacities. Moreover, they have hydrophilic and swelling characteristics that are particularly desirable for the formulation to be developed, considering the limited solubility of the drug, even in its complexed form. For this same reason, we thought the presence in the tablet formulation of a suitable highly soluble excipient, which acted as "channelling agent", by rapidly dissolving itself in aqueous medium, was necessary, thus increasing the matrix porosity and favouring the drug release. Therefore, mannitol, dextrate hydrate (Emdex®) and sodium chloride were tested as highly soluble diluents. Finally, the addition of a classic lubricant such as Magnesium stearate was also evaluated.

To investigate the possible interactions between the components, the DSC curves of c-DHEA and each selected excipient were compared with those of their 1:1 w/w physical mixtures, before and after compression, in order to evaluate any possible solid state modification. The 1:1 w/w ratio was chosen in order to maximise the likelihood of observing any interaction [25,26]. Finally, the behaviour of a preliminary complete formulation, in the presence of all the excipients selected by means of the compatibility study, was investigated, in order to verify the absence of reciprocal interactions among the components. FT-IR spectroscopy and X-ray powder diffractometry were used as complementary techniques to adequately implement and assist in interpretation of the DSC results.

2. Materials and methods

2.1. Materials

DHEA and glycine were supplied by Euphar Group s.r.l (Piacenza, Italy), α-Cyclodextrin was kindly donated by Wacker

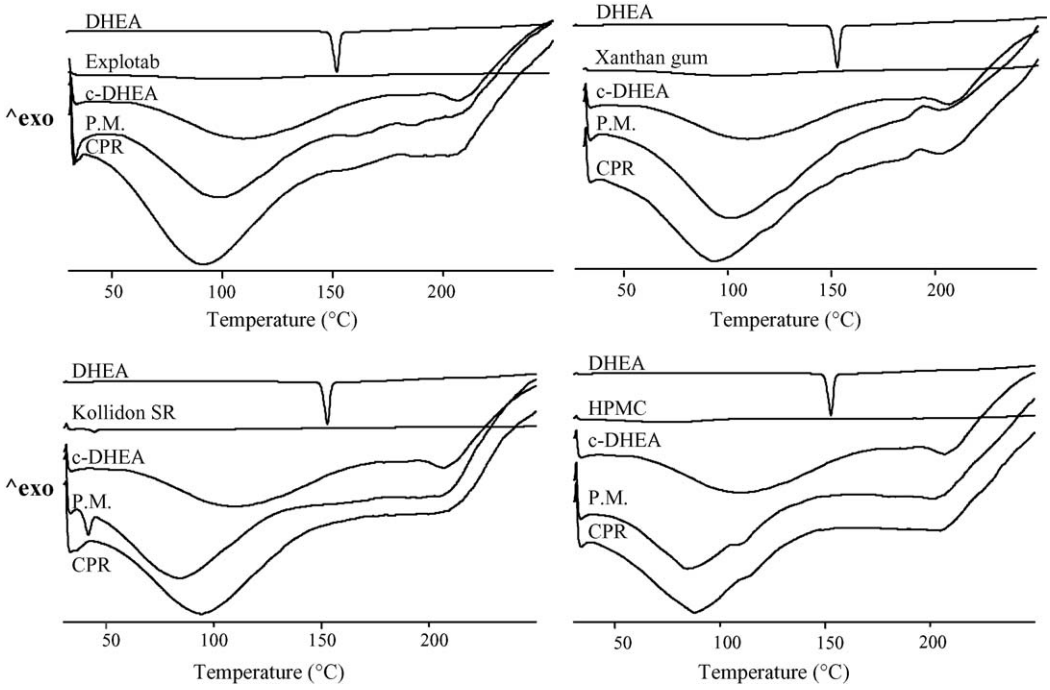

Fig. 1. DSC curves of pure drug and matrix-forming polymers, and their 1:1 w/w blends as simple physical mixtures (PM) or after compression (CPR).

(Germany). Xanthan gum (an anionic polyelectrolyte with a β-(1-4)-D-glucopyranose glucan backbone with side chains of -(3-1)-α-linked D-mannopyranose-(2-1)-β-D-glucuronic acid-(4-1)-β-D-mannopyranose, produced by fermentation from *Xanthomonas Campestris*) and hydroxypropylmethylcellulose (Methocel K4M, apparent viscosity of 2% aqueous solution 3500–5600 cP (HPMC)) were from Sigma, Italy; Kollidon®SR (a spray-dried mixture of polyvinylacetate 80%, polyvinylpirrolidone (PVP K-30) 19%, sodium lauryl sulphate 0.8% and silica 0.2%) was a gift of BASF, Germany; Explotab® (sodium starch glycolate) and Emdex® (dextrates hydrates) were a gift from Penwest Pharmaceuticals, Co., UK; D-mannitol, Magnesium stearate and sodium chloride were from Carlo Erba, Italy.

2.2. Preparation of samples

c-DHEA was prepared by co-grinding the DHEA:α-Cyclodextrin:glycine physical mixture (1:2:3 molar ratio) in a high energy vibrational micromill (Mixer Mill Type MM 200, Retsch, GmbH, Düsseldorf, Germany) at a vibration frequency of 24 Hz for 30 min. Physical mixtures of c-DHEA with each selected excipient were prepared in the 1:1 w/w ratio by simple blending of the components in a mortar for 10 min at room temperature. Uniformity of the physical mixtures was verified by comparing thermograms obtained from three samples all taken from the same mixture.

2.3. Differential scanning calorimetry (DSC)

DSC experiments were carried out with a Mettler TA4000 Star^e software apparatus (Mettler Toledo, Switzerland) equipped with a DSC 25 cell. Samples of about 5–10 mg were weighed (Mettler M3 microbalance) in pierced Al pans and scanned under static air over a temperature range of 30° to 250 °C at a heating rate of 10 °C/min. Calibration of temperature and heat flow were performed with standard Indium samples.

Table 1
Thermal parameters of the dehydration band of c-DHEA and its 1/1 (w/w) binary systems with the different polymers examined as physical mixtures (PM) or after compression (CPR)

Sample	T_{peak} (°C)	$\Delta H_{dehydr.}$ (J/g)
c-DHEA	108.8	1030
c-DHEA-Explotab PM	97.8	1294
c-DHEA-Explotab CPR	90.4	1311
c-DHEA-xanthan gum, PM	98.8	1099
c-DHEA-xanthan gum, CPR	92.6	1149
c-DHEA-Kollidon SR, PM	84.2	1230
c-DHEA-Kollidon SR, CPR	93.7	1302
c-DHEA-HPMC, PM	83.9	933
c-DHEA-HPMC, CPR	87.5	1019

2.4. X-ray powder diffraction

X-ray powder diffraction spectra were obtained with a Bruker D8 (θ/θ geometry) using a Cu Kα radiation over the 10–38 2θ range at a scan rate of 0.05° s^{-1}.

2.5. Fourier transform infrared spectroscopy

Fourier transform infrared (FT-IR) spectra were recorded on a Perkin-Elmer Model 1600 apparatus using KBr discs in the range of 4000–450 cm^{-1}.

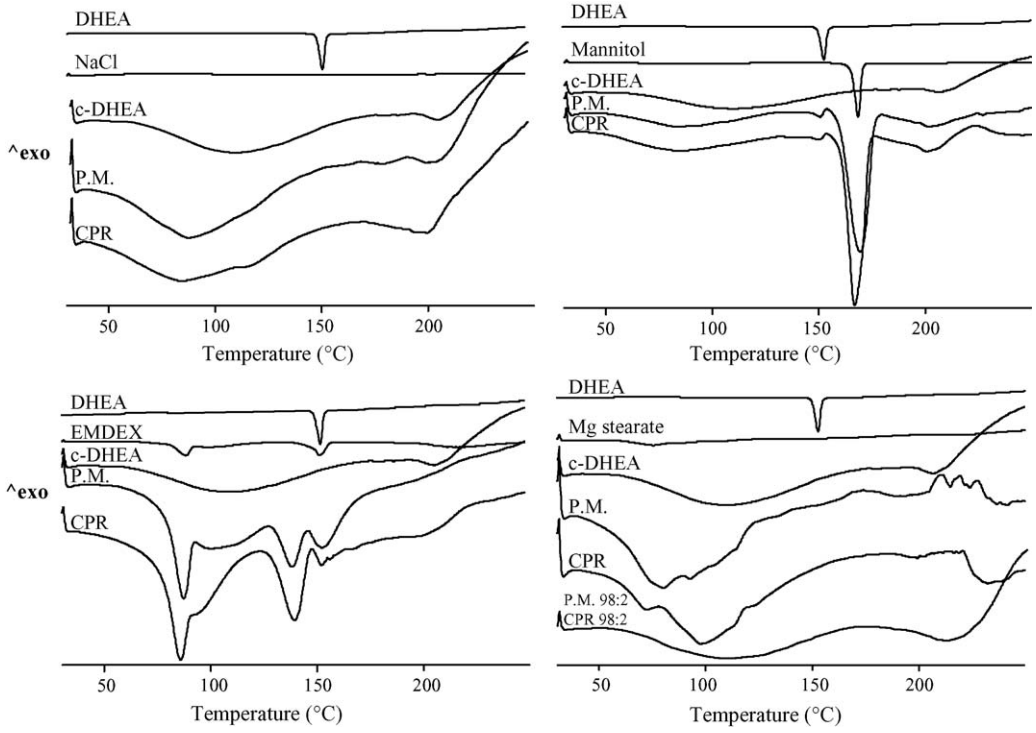

Fig. 2. DSC curves of pure drug and excipients, and their 1:1 w/w blends as simple physical mixtures (PM) or after compression (CPR).

3. Results and discussion

Four different polymers were selected as candidate matrix-forming excipients for the production of the c-DHEA sustained release matrix tablets, i.e. Explotab®, xanthan gum, Kollidon®SR and HPMC. DSC curves of c-DHEA, each selected polymer and their respective 1:1 w/w combinations are shown in Fig. 1 together with the thermal profile of pure DHEA, reported for reference purposes. The sharp melting peak of pure DHEA at 150.9 °C (ΔH_{fus} = 84.2 J/g) disappeared in the c-DHEA system, indicating the total amorphization and/or complexation of the drug induced by the mechanochemical activation treatment [21]; the broad endothermal effect between 70 and 120 °C is attributable to the cyclodextrin dehydration. The matrix-forming polymers Explotab®, xanthan gum, Kollidon®SR and HPMC all exhibited a shallow broad endothermal effect in the 80–120 °C range due to a dehydration process. The DSC curves of 1:1 w/w mixtures with all the examined polymeric materials were the simple superimposition of those of the pure components, with simply an intensification of the dehydration band, shifted to lower temperature. Only in the case of the binary systems with HPMC, a small shoulder following the broad endothermic effect was revealed, probably due to a partial recrystallization of α-cyclodextrin, without involving any solid-state modification of the drug, as demonstrated by the absence of further additional effects. The thermal profiles of all the mixtures remained almost unchanged after compression, indicating compatibility of the drug with all the examined polymers. The thermal parameters of the concomitant polymer and cyclodextrin dehydration phenomena of c-DHEA-excipient blends, before and after compression, are shown in Table 1. The slight influence of the compression process on the energetics of the evolution of the water molecules associated with both polymer and α-cyclodextrin could be attributed to diffuse and smooth surface phenomena probably induced by the mechanical treatment.

As for the selected channelling agents (Fig. 2), NaCl showed a flat DSC profile in the studied temperature range of 30–250 °C. The amorphous pattern of c-DHEA was well retained in the physical mixture with this excipient, before and after compression, thus suggesting compatibility between the two components. In the case of mannitol, a sharp melting endotherm was registered at 165.9 °C with an enthalpy fusion value of 273.9 J/g, indicative of the crystalline anhydrous state of this excipient. A drastic increase in the enthalpy value of mannitol with a concomitant appearance of a new small endothermal

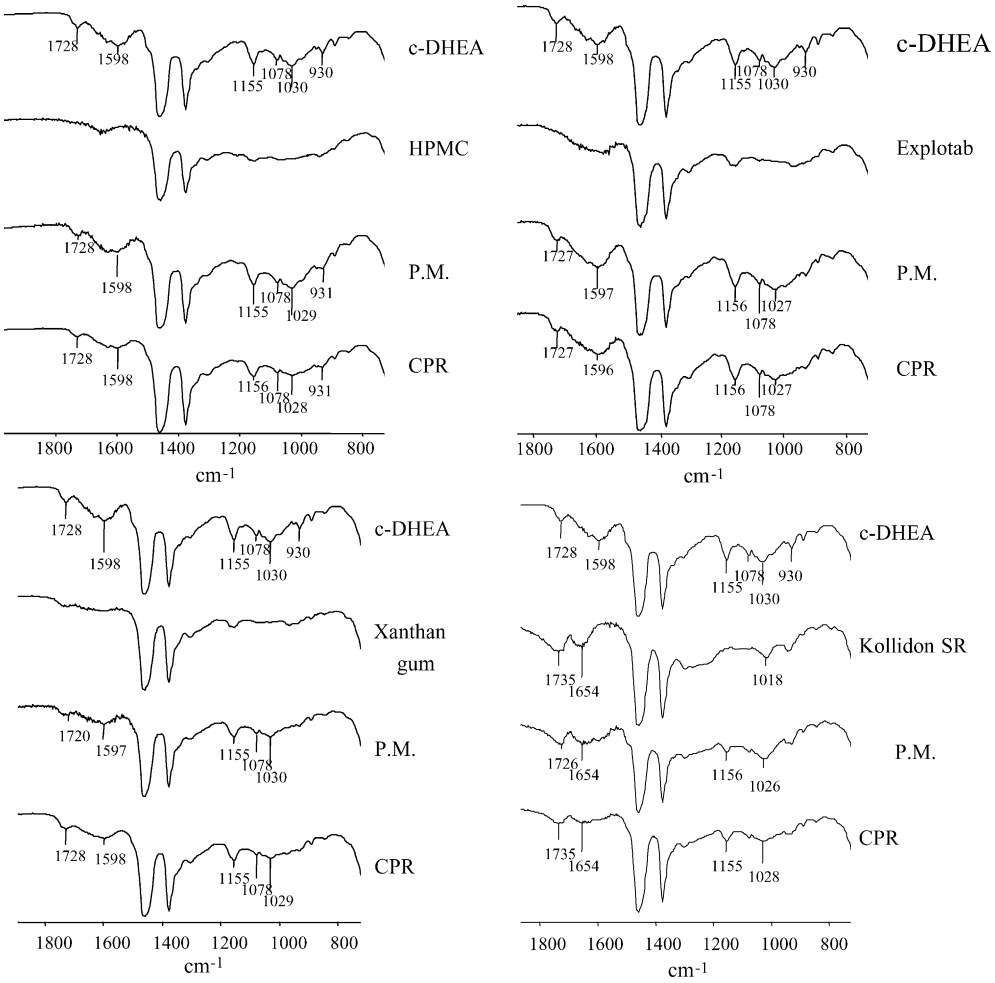

Fig. 3. FT-IR spectra of pure drug and matrix-forming excipient, and their 1:1 w/w blends as simple physical mixtures (PM) or after compression (CPR).

effect peaked at 150.3 °C in the physical mixture indicated a strong solid-solid interaction between the two components, both before and after compression, but not necessarily an incompatibility. Finally, the DSC curve of Emdex® showed a first endothermal effect at 87.8 °C with an enthalpy value of 60.0 J/g, probably due to loss of bound water, followed by the melting peak at 151.0 °C (ΔH_{fus} = 98.6 J/g). A broadening effect with a concomitant clear increase in the enthalpy value of these two peaks was observed in the physical mixture of the components, where an additional endothermal effect peaked at 138.6 °C was also registered. Moreover, a further modification of the thermal profile of the physical mixture was observed after compression. These effects pointed out a solid-state interaction between the two components.

The melting endotherm of the lubricant Magnesium stearate was followed by a small shoulder at higher temperature, probably due to the presence of the corresponding palmitate salt impurity [27]. The appearance in the DSC curve of the physical mixture of some extra-thermal effects, around to 90 and 120 °C, partially masked by the dehydration band of c-DHEA, and a further alteration of the thermal profile after the blend compression, pointed to a possible drug–excipient interaction. However, it must be taken into account that lubricants are generally present in pharmaceutical formulations at very low concentration (0.5–2% w/w), which is very different from the examined situation (50% w/w), and therefore compatibility of drug with this lubricant can be reasonably expected, owing to the severe conditions of the test. In fact the thermal curve of the mixture c-DHEA-Magnesium stearate 98/2 w/w, before and aftercompression, resembled that of pure c-DHEA, without showing any remarkable change (Fig. 2).

FT-IR and X-ray diffraction studies were then performed, in order to obtain more information and support DSC results. Some representative FT-IR spectra are reported in Figs. 3 and 4. The characteristic bands of c-DHEA [28] were well retained in the mixture with HPMC, Explotab® and xanthan gum before and after compression (Fig. 3), thus indicating the absence of interactions and confirming DSC findings. Similar results were obtained for Kollidon®SR, where the only noticeable phenomenon was the reduction of intensity and/or broadening of some bands observed in the pattern of the tabletted mixture, suggesting the presence of a less ordered structure, reasonably attributable to the mechanical treatment of the sample. Some changes in the FT-IR spectra of binary systems with

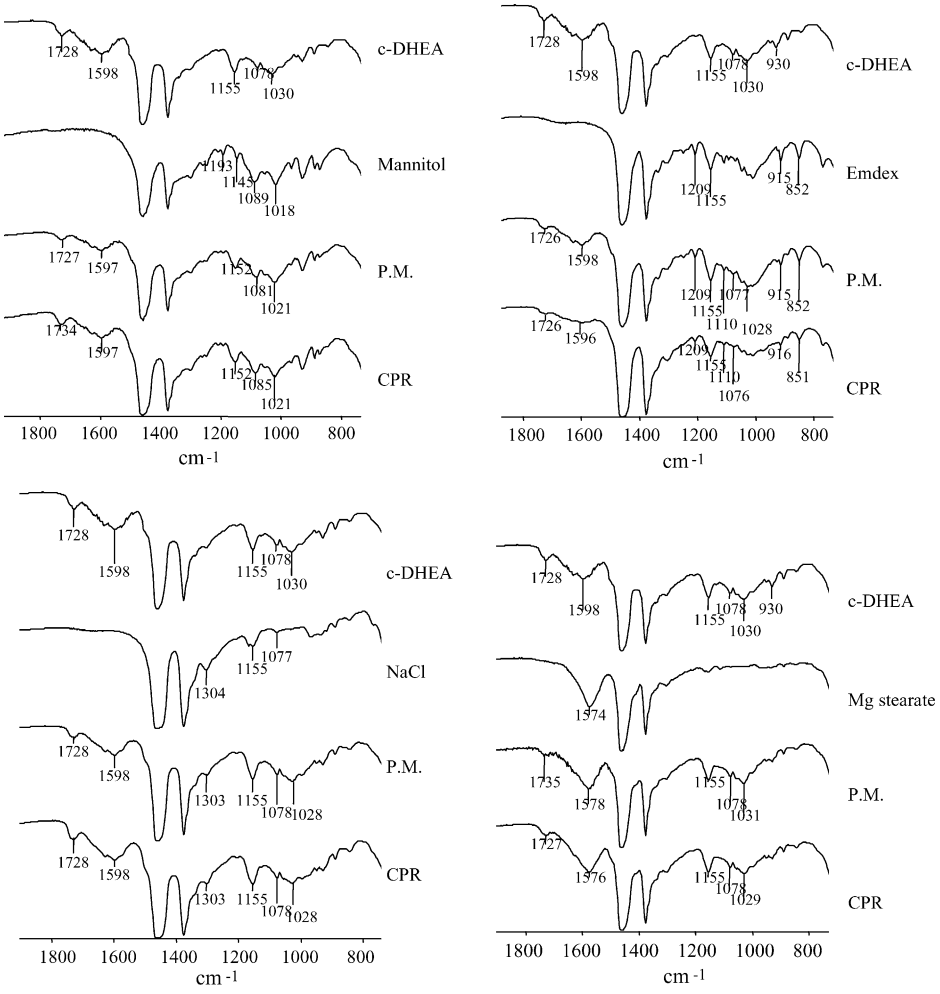

Fig. 4. FT-IR spectra of pure drug and excipients, and their 1:1 w/w blends as simple physical mixtures (PM) or after compression (CPR).

mannitol, such as the shift of the carbonyl stretching vibration band at 1728 cm^{-1} up to 1734 cm^{-1} suggested a possible interaction between the components (Fig. 4), in agreement with thermal analysis findings. On the contrary, even though DSC results pointed out a possible interaction between c-DHEA and Emdex®, the FT-IR profile of their blend was the simple superimposition of those of the two components and the minimal changes observed in the tabletted mixture spectrum were probably due to the mechanical treatment of the sample. Finally, no changes in the typical c-DHEA bands were observed in its mixtures with NaCl, thus confirming the compatibility of this excipient (Fig. 4). On the other hand, in the case of binary systems with Magnesium stearate, the partial overlapping of the typical band of c-DHEA at 1598 cm^{-1} with that at 1578 cm^{-1} of the excipient, made interpretation difficult.

An example of the typical behaviour observed in X-ray powder diffraction analysis for the mixtures of c-DHEA with the examined matrix-forming amorphous polymers is shown in (Fig. 5A) for the combinations of the complexed drug with Kollidon®SR. Both c-DHEA and the polymers showed an amorphous pattern, which was maintained in their mixtures, even after compression, thus allowing the exclusion of any recrystallization process, and confirming the absence of significant solid state modifications. The same behaviour was observed in the binary mixtures with all the other examined polymers (data not shown). On the contrary, in mixtures with crystalline mannitol (Fig. 5B), a strong reduction in peak intensities with a concomitant splitting of peaks, more evident after compression, suggested a possible solid-state interaction, in line with DSC and FT-IR results. The X-ray diffraction patterns of mixtures with NaCl (data not shown) were instead the simple superimposition of those of the pure components, thus corroborating the absence of any solid-state interaction.

The subsequent phase of the study was then devoted to evaluation of the compatibility of some model matrix-tablet formulations containing all the components together, in their actual weight proportions.

On the basis of the results of the above preliminary screening, NaCl was selected as the channelling agent and Magnesium stearate as the lubricant one. As for the direct-compression matrix-forming materials, xanthan gum and Kollidon SR were chosen to carry out the study, since they were considered more innovative and therefore more worthy of interest for a more in-depth evaluation than the extensively investigated and widely used HPMC. Moreover, a comparative study on xanthan gum and hydroxypropylmethylcellulose as matrices for controlled drug delivery showed some preferable properties of the former, such as the absence of initial burst release, more reproducibility in drug release and the possibility of zero order release kinetics [29]. On the other hand, Kollidon SR showed excellent flowability and dry binding properties and the drug release pattern from these matrices was less affected by tabletting conditions than from HPMC matrix tablets [30]. On the contrary, Explotab was discarded since preliminary release studies from complete matrix tablet formulations showed that, within the polymer concentration range usable in these formulations consistent with the DHEA dose (40 mg of DHEA correspond to 360 mg of c-DHEA), i.e. 30–45% of the total weight of the tablet, its superdisintegrant effect prevailed, giving rise to complete tablet disaggregation within 15 min in simulated gastric fluid.

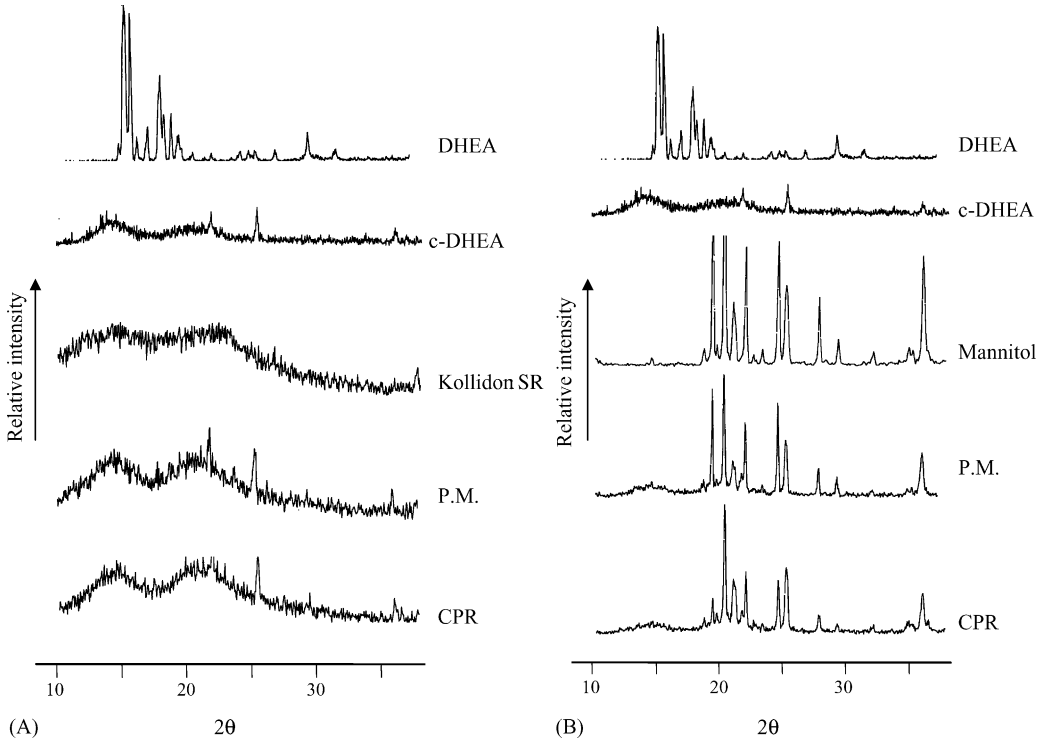

Fig. 5. X-ray diffraction spectra of pure drug and Kollidon®SR (A) or Mannitol (B), and their 1:1 w/w blends as simple physical mixtures (PM) or after compression (CPR).

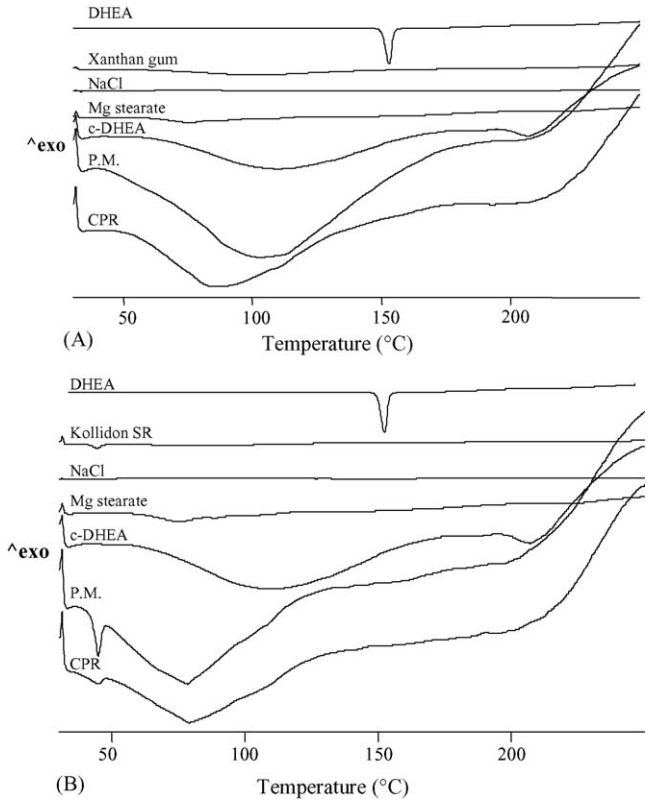

Fig. 6. DSC curves of the selected single components and their physical mixture, before (A) and after compression (B), in the complete matrix tablet formulation.

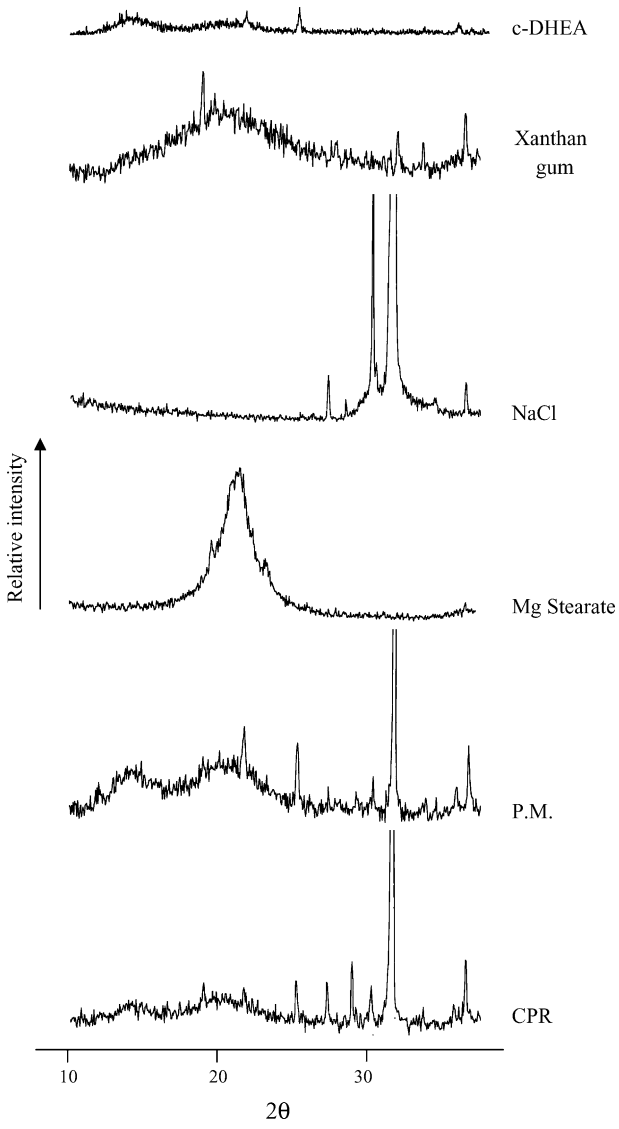

Fig. 7. X-ray diffraction spectra of the selected single components and their physical mixture, before (P.M.) and after compression (CPR), in the complete matrix tablet formulation.

Therefore, the final model formulations examined for compatibility were constituted by 33% w/w of c-DHEA, 33% of xanthan gum or Kollidon SR, 33% of NaCl and 1% of Magnesium stearate. The components were carefully mixed and then tabletted; after tablet pulverization and powder sieving, the mixture was tested by DSC. As shown in Fig. 6A, the thermal profile of the complete mixture formulation, before and after compression, containing xanthan gum as matrix-forming polymer exhibited a broad endothermic effect in the range 60–120 °C, due to the sample dehydration; no other relevant effects were observed, allowing the exclusion of any incompatibility between all the examined components. On the contrary, some changes in the thermal curves of the complete formulation containing Kollidon SR (Fig. 6B) were observed in comparison with the simple binary systems (Fig. 1), such as a change of the dehydration band shape, accompanied by a strong reduction in its enthalpy value after compression ($\Delta H = 1152.7$ J/g for the physical mixture versus 675.4 J/g for the compressed one), while a slight increase was observed for all the c-DHEA-polymer binary mixtures (see Table 1). This finding suggested a possible solid-state modification after compression, making it difficult to definitely exclude any interaction between the components.

Therefore, xanthan gum was finally chosen as matrix excipient. The results of X-ray diffraction analysis performed on the mixture of the final formulation components are shown in Fig. 7. The complete final mixture formulation exhibited an almost amorphous pattern, where only a few small peaks attributable to the presence of glycine and some characteristic peaks of crystalline NaCl were detected. A slight increase in intensity of NaCl peaks was the main modification observed after compression. In conclusion, the resulting pattern was almost the weighted superimposition of those of the single components, thus corroborating the expected compatibility between the tested components indicated by DSC analysis.

4. Conclusions

As a part of an on-going project aimed at the development of an extended release matrix-based formulation of c-DHEA, different excipients were tested for their compatibility with the ternary complex.

The results confirmed the utility and reliability of DSC analysis at the earliest stage of preformulation studies as a valuable tool for a rapid screening of a wide range of candidate excipients, allowing a rapid evaluation of possible drug–excipient interac-

tions. However, a careful evaluation of any modification of DSC trace is necessary, together with the support of other suitable techniques, in order to avoid misleading and misinterpretations of DSC results

Based on the obtained DSC results, supported by FT-IR and X-ray diffraction analyses, all the polymers tested as matrix-forming materials were found to be compatible with c-DHEA. In the case of crystalline excipients as mannitol or Emdex, some drug–excipient interaction was detected, and therefore these components were discarded; on the contrary, the absence of interactions was noted for NaCl, which was then selected as channelling agent in the model matrix-tablet formulation. On the other hand, despite some changes observed in the DSC behaviour of 1:1 w/w drug binary systems with Magnesium stearate with respect to the pure components, it was utilized as lubricant, since it was used in the formulation at the concentration of 1% w/w.

Finally, DSC studies on complete matrix-tablet formulations, allowed selection of the final preparation based on the combination of xanthan gum, NaCl and Magnesium stearate as the most suitable for the development of an extended-release dosage form of c-DHEA.

Further studies will be performed in order to find the matrix-tablet formulation with the proper polymer/diluent ratio, or polymer/polymer/diluent or polymer/diluent/diluent ratio (if the use of two polymers or two diluents in combination proves to be more effective) in order to obtain the desired drug release rate and kinetics.

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