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ORIGINAL ARTICLE

Development of a sustained-release matrix tablet formulation of DHEA as ternary complex with α-cyclodextrin and glycine

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Abstract Sustained-release matrix-tablets of dehydroepiandrosterone (DHEA) as ternary complex with α-cyclodextrin and glycine (c-DHEA) were prepared by direct compression with suitable excipients. The influence of the swelling properties of hydroxypropylmethylcellulose (HPMC) and the disintegrating power of Explotab® used in combination, as well as the effect of the presence, type and amount of suitable channelling agents (Emcocel® and spray-dried lactose, alone or in combination) on drug release behaviour from matrix-tablets has been evaluated.The best performances in terms of drug release was obtained from formulations containing a 75:25 w/w spray-dried lactose:Emcocel® combination in the presence of HPMC as matrix-forming polymer, leading to a more than 65% DHEA released at the end of the test, a value which was, respectively, 1.9 and 2.7 times higher than those achieved with the corresponding formulations containing spray-dried lactose or Emcocel® alone. The drug release profile from the most effective matrix-tablet formulation of c-DHEA allowed achievement of a more than 6-fold increase in the drug amount released within 24 h in comparison with the same formulation containing the simple physical mixtures of DHEA, α-cyclodextrin and glycine. Therefore the advantage of using DHEA as ternary complex, prepared by mechano-chemical treatment, was clearly demonstrated, thus allowing the development of an effective sustained-release formulation of the drug.

Keywords Cyclodextrin · Dehydroepiandrosterone · Matrix tablet · Sustained release · Ternary complex

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Introduction

Dehydroepiandrosterone (DHEA) is an adrenal steroid hormone that naturally decreases with age advancement. The progressive decline in DHEA production seems to be involved in the etiology of several age-related illnesses, even though epidemiological studies about its putative role as 'anti-ageing' hormone have generated discordant results [1–4]. On the other hand, there is clear evidence that DHEA treatment improves mood, well-being, sexuality and cognition in women with adrenal insufficiency [5, 6]. An extended-release formulation of the drug would be highly desirable to maintain therapeutic concentrations in the systemic circulation over a prolonged period, according to the hormone circadian rhythm, thus improving patient compliance by a reduction of the drug administration frequency as well as the total dose of drug administered and consequently the incidences of possible side effects.

However, the very low aqueous solubility of DHEA does not allow its use in sustained-formulation, giving rise to problems of excessively low and incomplete release, and thus scarce and variable bioavailability. Previous studies have pointed out the improved solubility and bioavailability of the drug by ternary

complexation with α-cyclodextrin and glycine prepared by mechano-chemical activation (c-DHEA) in women with adrenal insufficiency [7]. The use of DHEA as ternary cyclodextrin complex should make it possible to overcome the problems of the very poor drug solubility.

Among the different approaches studied to obtain sustained-release oral delivery systems, the direct compression matrix tablets appear to be one of the most attractive from both an economic as well as process development and scale-up point of view [8].

In the context of a broad research project aimed at developing an extended-release matrix-tablet formulation of c-DHEA, preliminary compatibility studies allowed to selection of two hydrophilic swellable polymers, i.e. sodium starch glycolate (Explotab®) and hydroxypropylmethylcellulose (HPMC), both endowed with good flow and compacting properties, as the most suitable candidates for obtaining direct compression matrix-tablets [9]. On the other hand, considering the limited solubility of the drug, even in its complexed form, the addition to the formulation of suitable highly soluble excipients, working as ''channelling agents'', has been considered opportune.

Then, in the present work, the influence on drug release behaviour of different combination ratios of the previously selected matrix-forming polymers, as well as the effect of the presence, type and amount of channelling agent (spray-dried lactose, or microcrystalline cellulose (Emcocel®)), added separately or in mixture, has been investigated. Release studies from the different tablet formulations were performed using the USP paddle apparatus. The drug release profiles were characterized in terms of Dissolution Efficiency and percent dissolved at different times and compared with those obtained from analogous formulations containing the simple physical mixture of DHEA, α-cyclodextrin and glycine, in order to evaluate the actual advantages of using the ternary complex prepared by mechano-chemical treatment.

Materials and methods

Materials

Dehydroepiandrosterone (DHEA) and glycine were supplied by Euphar Group s.r.l (Italy), α-Cyclodextrin was kindly donated by Wacker (Germany). Hydroxypropylmethylcellulose (HPMC, apparent viscosity of 2% aqueous solution 3.500–5.600 cP) was from Sigma (Italy). Explotab® (sodium starch glycolate) and Emcocel® (spray-dried microcrystalline cellulose) were a gift from Penwest Pharmaceuticals, Co. (U.K.). Spray-dried lactose was from Meggle (Belgium) and Magnesium stearate from Carlo Erba, (Italy). All other reagents were of analytical grade.

Preparation of DHEA ternary complex (c-DHEA)

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, Germany) at a vibration frequency of 24 Hz for 30 min, as previously described [7].

Preparation of matrix tablets

Matrix tablets (550 mg weight) containing 220 mg of c-DHEA (equivalent to 25 mg of native DHEA) were prepared by direct compression using a Perkin Elmer hydraulic press equipped with a 13 mm flat faced punch at a compression force of 2.5 ton for 2 min. The complexed drug and the other components were accurately blended together by mixing for 15 min. The resulting mixtures were sieved and tabletted. In all cases the amount of c-DHEA represented the 40% (w/w) of the total tablet weight. The remaining 60% was composed of polymers (HPMC and/or Explotab®), channelling agents (Emcocel® and/or spray-dried lactose) and lubricant (Magnesium stearate). The composition of the tablet formulations and their codes are listed in Table 1.

Compatibility studies

Compatibility studies of c-DHEA with each selected excipient were carried out by DSC analyses (TA4000 Star^e (Mettler Toledo, Switzerland) equipped with a DSC 25 cell) of their 1:1 (w/w) physical mixtures before and after compression. Samples (5–10 mg) were weighed (Mettler M3 microbalance) in pierced Al pans and scanned in the 30°–250° C temperature range at a heating rate of 10°C/min under static air. Compatibility of c-DHEA in all the examined complete formulations was also assessed.

Drug release studies

Drug release studies from matrix-tablets were performed in 700 ml of pH 1.1 HCl solution for the first 2 h and pH 6.5 phosphate buffer for 6 h for up to 24 h, by using the USP paddle apparatus. The dissolution

Table 1 Formulations of matrix-tablets prepared by direct compression containing the complexed drug and selected components

Components	Formulation					
	I	II	III	IV	V	VI
c-DHEA (mg)	220.00	220.00	220.00	220.00	220.00	220.00
HPMC (mg)	162.25	162.25	162.25	162.25	162.25	162.25
Explotab® (mg)	162.25	81.13	81.13	–	–	–
Emcocel® (mg)	–	81.12	–	162.25	–	–
Spray-dried (S.D.) lactose (mg)	–	–	81.12	–	162.25	–
S.D. lactose:Emcocel®75:25 w/w (mg)	–	–	–	–	–	162.25
Magnesium stearate (mg)	5.50	5.50	5.50	5.50	5.50	5.50

medium was thermostated at 37° ± 0.5 and stirred at a rotation speed of 100 rpm. At predetermined time intervals, aliquots of samples were withdrawn and assayed by HPLC. The same amount of fresh dissolution fluid was added to replace the amount withdrawn. Each test was performed in triplicate (C.V. < 1.5%).

HPLC assay

The HPLC apparatus was constituted by a LaChrome Elite® chromatograph (Merk Hitachi, Germany) equipped with a UV detector and a Purosphere® STAR RP18 (250 × 4.6 mm) column. The mobile phase (methanol/water 75:25 v/v) was pumped at room temperature at a flow rate of 1 ml/min. The injected volume was 20 μl and the detection wavelength 210 nm. Under these experimental conditions, the DHEA retention time was 7 min.

Results and discussion

Compatibility studies

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.

DSC analysis revealed the compatibility between c-DHEA and all the examined formulation components. Figure 1A shows, for example, the DSC profiles of c-DHEA, Emcocel® and their 1:1 (w/w) mixture before and after compression.

The thermal behaviour of c-DHEA was characterized by the presence of a broad endothermal effect, between 70 and 120° C, due to the cyclodextrin dehydration process, followed by a flat curve. Disappearance in the c-DHEA system of the sharp melting endotherm of DHEA at 150.9° C indicated the total amorphization and/or complexation of the drug induced by the mechano-chemical activation treatment. Emcocel® showed a flat DSC profile in the 30–250° C temperature range. The amorphous pattern of c-DHEA was well retained in the physical mixture with this excipient, and no modifications of the DSC curve were observed after compression, thus suggesting compatibility between the two components.

The compatibility of c-DHEA was also assessed in all the final complete formulations, as is shown for example in Fig. 1B where the DSC curves of pure HPMC, Emcocel®, spray-dried lactose, Mg stearate and c-DHEA, and the multi-component mixture after compression are reported.

The DSC profile of the tabletted blend was simply the sum of the curves of pure components, showing a broad endothermic effect between 70 and 120° C due to the dehydration processes of both cyclodextrin and polymer, followed by the endothermic peak due to lactose melting. The absence of additional thermal effects with respect to the pure substances confirmed the compatibility among the formulation components.

Drug release studies

The release profiles of the complexed drug from the different matrix-tablet formulations are illustrated in Fig. 2A, B, while the results in terms of Dissolution Efficiency (D.E.) and percent dissolved at different times (P.D.) are reported in Table 2. Formulation I, containing a 50:50 (w/w) combination of the two polymers HPMC and Explotab®, showed an initial undesirable burst effect in the acidic medium, attributable to the high level of Explotab® which did not allow the quick hydration of HPMC and the consequent gel formation [10]. Moreover, a subsequent very slow release was observed in the intestinal fluid, achieving only 25% of drug released at the end of the test. Therefore, in the attempt to improve the drug release behaviour, Explotab® was partially replaced by Emcocel® (Formulation II) or spray-dried lactose (Formulation III) as channelling agents. In both cases, the initial burst effect was avoided, but only a very slight increase in the drug release rate was obtained

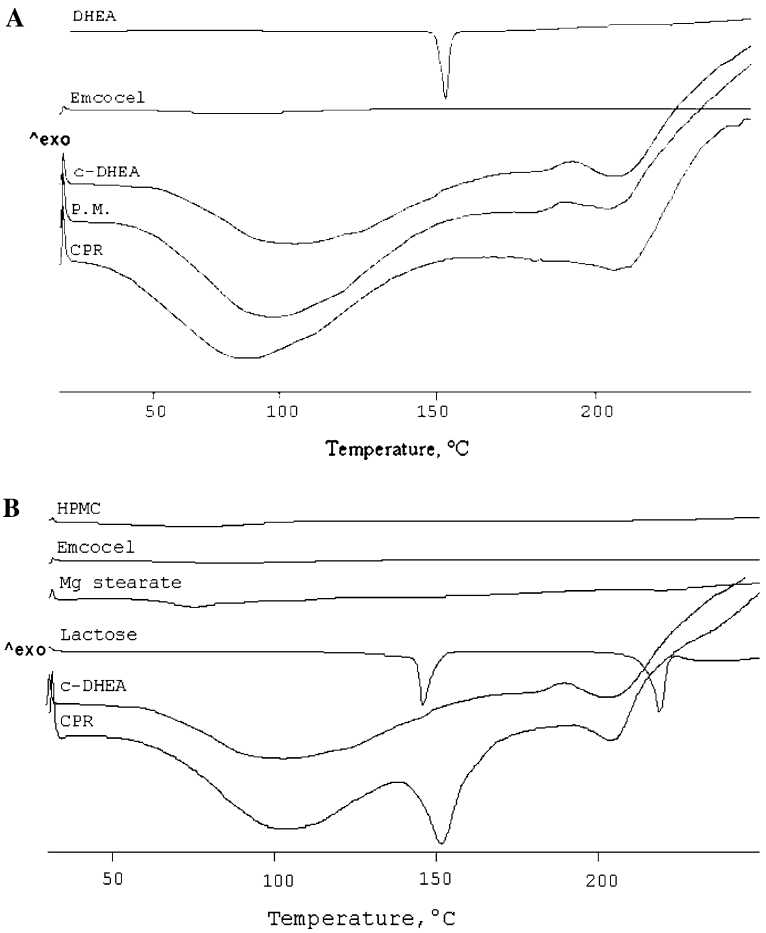

Fig. 1 (**A**) DSC curves of pure drug and Emcocel®, and their 1:1 w/w blends as simple physical mixtures (P.M.) or after compression (CPR); (**B**) DSC curves of the single components of the complete matrix tablet formulation and of their mixture after compression

with the formulation containing the spray-dried lactose:Explotab® combination, which reached 30% of the total drug released after 24 h. In order to further enhance the release rate of the complexed drug, further formulations were then tested, where Explotab® was totally replaced with the two selected channelling agents (Formulations VI and V, respectively). However, the release profiles obtained from these new matrix-tablets were very similar to the previous ones from tablets containing the corresponding combinations of each examined channelling agent with Explotab® (Formulations II and III, respectively). Much better results were found for tablets containing a 75:25 (w/w) combination of spray-dried lactose and Emcocel® (Formulation VI). In fact, a clear improvement of the drug release rate was achieved, leading to a more than 65% DHEA released at the end of the test. In particular, the simultaneous presence of the channelling agents in the HPMC tablets made it possible to reach percent dissolved values of 1.9 and 2.7 times higher than those achieved with formulations containing spray-dried lactose or Emcocel® alone, respectively, at the end of experiment. These findings indicated a synergistic effect of the two channelling agents, when used in an appropriate combination, in improving the drug release rate.

In order to evaluate the actual advantages of using the drug ternary complex prepared by mechanochemical treatment, the release profile from the most effective matrix-tablet formulation (i.e. Formulation VI) was compared with that obtained from tablets having the same composition, but containing the simple 1:2:3 mol/mol physical mixture of DHEA, α-cyclodextrin and glycine, instead of the complex. Figure 3 shows the release profiles of the tested formulations, whereas the results in terms of P.D. and D.E. at different times are summarized in Table 3. A marked increase in the extent and rate of drug release was achieved in the case of the formulation containing the drug in the complexed form with respect to that containing the simple mixture of the three components. In fact, the amount of drug released at the end of the experiment was about 10% in the case of the tablets containing the simple physical mixture of the components, whereas more than 65% drug delivery was achieved with tablets containing c-DHEA, thus leading

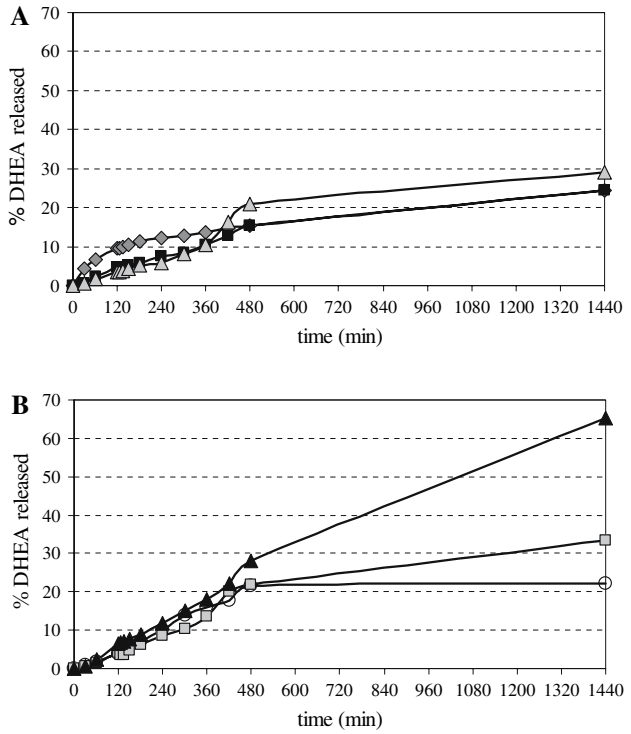

Fig. 2 Percent of DHEA released from the different matrix tablet formulations. Key: (**A**) (◆) HPMC-Explotab® (Form. I); (■) HPMC-Explotab®-Emcocel® (Form. II); (△) HPMC-Explotab®-spray-dried lactose (Form. III); (**B**) (○) HPMC- Emcocel® (Form. IV); (□) HPMC-spray-dried lactose (Form. V); (▲) HPMC-Emcocel®-spray-dried lactose (Form. VI)

Table 2 Dissolution Efficiency (DE) and % drug dissolved (P.D.) at 240 and 360 min from the different matrix-tablet formulations

	DE[a] 240′	P.D. 240′	DE[a] 360′	P.D. 360′
F I	11.06	12.25	11.99	13.63
F II	6.00	7.54	7.37	10.40
F III	4.98	5.95	6.57	10.42
F IV	7.08	10.09	10.24	15.89
F V	6.01	8.62	8.38	13.54
F VI	8.97	11.70	11.95	17.88

[a] Percentage of the area of the rectangle described by 100% dissolution in the same time

to a more than 6-fold increase in the drug amount released. Moreover, the use of the drug as multi-component complex made it possible to reach DE values after 6 h of test 7-fold higher than those obtained with the corresponding physical mixture.

These findings clearly demonstrate the considerable gain in using the DHEA:α-Cd:glycine ternary complex obtained from the drug mechano-chemical activation by co-grinding instead of the simple blend of these components. The improved wettability, drug amorphization and molecular dispersion in the carrier systems

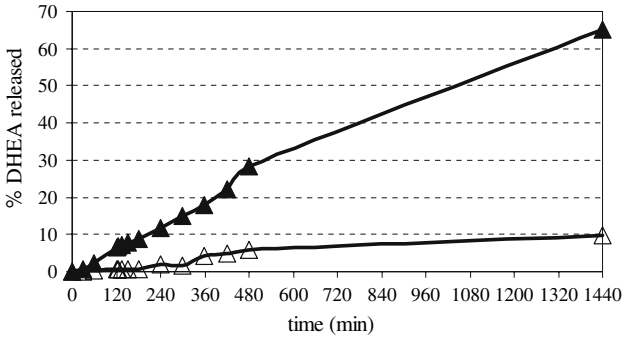

Fig. 3 Percent of DHEA released from the HPMC-Emcocel®-spray-dried lactose matrix tablets (Form. VI) containing c-DHEA (▲) or the corresponding DHEA-α-cyclodextrin-glycine 1:2:3 mol/mol physical mixture (△)

Table 3 Dissolution Efficiency (DE) and % drug dissolved (P.D.) at 240 and 360 min from the Formulation VI and the corresponding formulation containing the simple 1:2:3 mol/mol physical mixture of DHEA, a-cyclodextrin and glycine (P.M.)

	P.D. 120′	DE 240′	P.D. 240′	DE 360′	P.D. 360′
F VI	6.41	8.97	11.70	11.95	17.88
F VI P.M.	0.56	1.00	1.79	1.70	4.26

[a] Percentage of the area of the rectangle described by 100% dissolution in the same time

together with the reduced particle size obtained by the mechanical treatment could play an important role in enhancing the dissolution properties of the drug.

Conclusions

Preformulation studies allowed the selection of suitable excipients to obtain direct-compression, sustained-release matrix-tablets of c-DHEA, easy to prepare and to possibly scale-up. It has been shown that an accurate evaluation of the components and the search for a proper equilibrium among the characteristics of all excipients is an important step, at the preformulation stage, for the development of an effective formulation.

The combination of the swellable hydrophilic HPMC with an appropriate mixture of spray-dried lactose and Emcocel® seemed to be the most suitable for obtaining formulations with good release performances, enabling acceleration of the penetration rate of the dissolution medium in the tablets and facilitate the drug release by a concomitant swelling and erosion process.

The advantages of using the DHEA:α-Cd:glycine ternary complex prepared by mechano-chemical treatment instead of the simple blend of the components

was also clearly highlighted. The use of DHEA as ternary complex made it possible to overcome the problems of low and incomplete release due to the very poor drug solubility. In fact, formulation tablets of the same composition but containing the drug ternary complex allowed achievement of a more than 6-fold increase in the drug amount released compared to those containing the simple physical mixtures of the three components.

However, additional formulation studies will still be necessary, in order to further improve the drug release profile in terms of both percent dissolved and dissolution efficiency values, according to the hormone circadian rhythm.

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