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|---------------------------------------------------|--------------------------------------------|
| SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO          |                                            |
| RAD: 14-134491- -5                                | FECHA: 2016-05-24 15:52:22                 |
| DEP: 2020 DIRECCION DE NUEVAS CREACIONES          | EVE: 378 FASE NACIONAL INCLUIDO CAPITULO I |
| TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II | FOLIOS: 14                                 |
| ACT: 519 TRASLADOINFORME                          |                                            |

DIRECCIÓN DE NUEVAS CREACIONES

2020  
Bogotá, D.C.,

Abogado(a)/Señor(a)  
SILVANA MARÍA LÓPEZ DÍAZ

Asunto:      Radicación:      14-134491- -5  
                 Trámite:            11  
                 Evento:            378  
                 Actuación:            519  
                 Oficio:                    6280  
                 Folios:                    14

|                                     |                   |            |   |                               |  |
|-------------------------------------|-------------------|------------|---|-------------------------------|--|
| Patente de Invención                | X                 |            |   | Patente de Modelo de Utilidad |  |
| Vía Nacional                        |                   |            |   |                               |  |
| Vía PCT (Fase Nacional)             | X                 | Capítulo I | X | Capítulo II                   |  |
| No. Solicitud Internacional         | PCT/IB2011/056023 |            |   |                               |  |
| Fecha de Presentación Internacional | 29/12/2011        |            |   |                               |  |

1. Documentos estudiados

|                  |                                 |                  |
|------------------|---------------------------------|------------------|
| Descripción:     | Radicado N°14-134491-00000-0000 | Junio 20 de 2014 |
| Reivindicaciones | Radicado N°14-134491-00000-0000 | Junio 20 de 2014 |

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del Capítulo Primero del Título 10 de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada.

Por lo tanto, las reivindicaciones 1 a 13 del Radicado N° N°14-134491-00000-0000 son aceptadas para ser estudiadas en su totalidad, porque se registra el pago de las reivindicaciones adicionales 11 a 13, de acuerdo con el recibo presente en la página 3 del radicado N°14-134491-00000-0000.

Título de la solicitud: “Anillo vaginal que comprende DHEA o DHEA sulfato y opcionalmente un agente modulador de la liberación del principio activo, útil para aumentar la reserva ovárica en mujeres y para aliviar síntomas asociados a la menopausia”.

El problema planteado en esta solicitud consiste en la necesidad de obtener una composición farmacéutica de liberación sostenida que entregue dehidroepiandrosterona (DHEA) o dehidroepiandrosterona sulfato, para ser administrada una vez al mes o más tiempo para facilitar la terapia a largo plazo.

Para resolver este problema técnico, la solicitud en estudio divulga composiciones farmacéuticas en forma de anillo vaginal que contiene dehidroepiandrosterona (DHEA) o dehidroepiandrosterona sulfato y excipientes farmacéuticamente aceptables que modifiquen la liberación del principio activo, para aumentar la reserva ovárica y para aliviar los síntomas asociados a la menopausia.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61F 6/06; A61K 31/5415; A61K 9/00; A61M 31/00.

#### **4. Reivindicaciones relativas al uso o a un segundo uso (Arts. 14 y 21 D 486)**

El uso de las reivindicaciones 9 a 13 no es patentable, de acuerdo con el artículo 14.

#### **5. De la Solicitud de la Patente**

##### **Título**

Se solicita eliminar del título las referencias establecidas para el uso de las composiciones reclamadas en la solicitud. Además, la expresión “y opcionalmente un agente modulador de la liberación”, se consideran como una expresión general y ambigua, porque incluye muchas sustancias posibles, pero no comprendidas dentro del objeto de la solicitud, por lo que se requiere definir los excipientes específicos.

##### **Reivindicaciones (Art 30 D 486, Art 22 PCT)**

Las reivindicaciones 4 a 6 no son claras, porque los tiempos de liberación sostenida del principio activo “por al menos 90 días, por al menos 60 días o por al menos 30”, se consideran como resultados a alcanzar, porque no solo se

menciona una solución presente, sino que incluye alternativas presentes y futuras que conduzcan a obtener estos mismos tiempos de liberación. Se sugiere eliminar estas reivindicaciones.

Se sugiere incluir dentro de la reivindicación 1 las características esenciales descritas en las reivindicaciones 7 y 8 relacionadas con los porcentajes de dehidroepiandrosterona y de polivinilpirrolidona K-30, puesto que la reivindicación 1 como reivindicación independiente, debe incluir todas las características técnicas esenciales de la solicitud.

## 6. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de Publicación Internacional: 29 de diciembre de 2011 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

| Item | Documento                                                               | Título                                                                                           | Fecha de Publicación |
|------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------|
| D1   | US2009/0054383                                                          | “Pharmaceutical compositions”                                                                    | 26/Febrero/2009      |
| D2   | <i>American Journal of<br/>Drugs Delivery.</i><br>2006. 4; 2: 105 – 112 | “The Role of Excipients in the Control of Dehydro<br>epiandrosterone Inclusion Complex Delivery” | Mayo 12 de 2005      |

El documento D1<sup>1</sup> divulga composiciones alternativas para administrar dehidroepiandrosterona, para aprovechar los efectos androgénicos positivos y evitar los efectos secundarios sistémicos (Pág. 1, párr. [0001]).

El documento D2<sup>2</sup> divulga composiciones farmacéuticas que comprenden dehidroepiandrosterona y plivinilpirrolidona K-30 (Kollidon®) (Pág. 106, tabla 2).

## 8. Examen de Patentabilidad.

### Nivel inventivo (Art 18 D 486)

La reivindicación 1 divulga *“Un anillo vaginal de liberación sostenida caracterizado porque comprende como agente activo dehidroepiandrosterona, dehidroepiandrosterona sulfato o una sal farmacéuticamente aceptable de estos y además comprende polivinilpirrolidona K30 como un agente modulador de la liberación del agente activo”* (Pág. 45 del Radicado N° 14–134491–00000–0000).

1 [http://worldwide.espacenet.com/publicationDetails/originalDocument?](http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=US&NR=2009054383A1&KC=A1&FT=D&ND=3&date=20090226&DB=EPODOC&locale=en_E)

CC=US&NR=2009054383A1&KC=A1&FT=D&ND=3&date=20090226&DB=EPODOC&locale=en\_E  
P

2 <http://link.springer.com/article/10.2165/00137696-200604020-00006#page-1>

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

| Solicitud                                                                                              | D1                                                                                                          | D2                                                                                                                       |
|--------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| Anillo vaginal de liberación sostenido                                                                 | Composición farmacéutica en forma de anillo vaginal (Pág. 26, reiv. 1, 3, 19, 20; pág. 27, reiv. 32)        | Composición farmacéutica de liberación sostenida (Pág. 106, col. der., ln. 7 – 12, tabla 2; pág. 108, col. izq., fig. 2) |
| Comprende dehidroepiandrosterona, dehidroepiandrosterona sulfato o una sal farmacéuticamente aceptable | Comprende dehidroepiandrosterona o dehidroepiandrosterona sulfato (Pág. 26, reiv. 1 y 3; pág. 27, reiv. 32) | Comprende dehidroepiandrosterona                                                                                         |
| Comprende polivinil pirrolidona K30 como agente modulador de la liberación                             | Comprende monoglicéridos, ácidos grasos hidrogenados, esteres glicéridos (Pág. 27, reiv. 32)                | Comprende HPMC (Methocel® 4KM), polivinilpirrolidona (Kollidon® PK30 ) para modular la liberación                        |

El documento D1 es considerado el estado de la técnica más cercano a la composición divulgada en la reivindicación 1, porque divulga un anillo vaginal que contiene dehidroepiandrosterona o dehidroepiandrosterona sulfato como principio activo, como una forma alternativa para administrar dehidroepiandrosterona, para aprovechar los efectos androgénicos positivos y evitar los efectos secundarios sistémicos (Pág. 26, reiv. 1, 3, 19, 20; pág. 27, reiv. 32).

La diferencia entre las composiciones divulgadas en la solicitud con respecto a la definida en el documento D1, consiste en que el anillo vaginal de la solicitud contiene polivinilpirrolidona K30, mientras que el anillo divulgado en el documento D1 contiene monoglicéridos, ácidos grasos hidrogenados, esteres glicéridos, entre otros excipientes hidrofóbicos.

El efecto técnico asociado a esta diferencia es que anillo intravaginal de la solicitud permite liberar de manera prolongada el principio activo por un periodo que oscila entre 30 y 90 días.

El problema técnico objetivo que se pretende resolver es el siguiente: Como modificar el anillo vaginal divulgado en el documento D1 para obtener una composición farmacéutica de liberación sostenida que entregue dehidroepiandrosterona (DHEA) o dehidroepiandrosterona sulfato, para ser administrada una vez al mes o más tiempo para facilitar la terapia a largo plazo.

El documento D2 divulga composiciones farmacéuticas para liberación prolongada de principios activos que comprende dehidroepiandrosterona y polivinilpirrolidona K30 (Pág. 106, col. der., ln. 7 – 12, tabla 2; pág. 108, col. izq., fig. 2).

Por lo tanto, una persona normalmente versada en la materia y conocedora de los conceptos divulgados en los documentos D1 y D2, sin ningún esfuerzo modificaría el anillo vaginal del documento D1, incluyendo polivinilpirrolidona K30 para

incrementar el tiempo de liberación del principio activo, tal como lo sugiere el documento D2, para obtener de esta forma la composición propuesta en la presente solicitud, de manera obvia o evidente.

En consecuencia, la reivindicación 1 de acuerdo a lo divulgado en los documentos D1 y D2, carece de Nivel Inventivo.

Las reivindicaciones 2 a 8, dependientes de la reivindicación 1, no divulga características inventivas adicionales para la composición de la reivindicación 1. Por lo tanto, estas reivindicaciones también carecen de Nivel Inventivo.

## 9. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

| Item | Documento                                                           | Reivindicaciones afectadas | Requisito que afecta |
|------|---------------------------------------------------------------------|----------------------------|----------------------|
| D1   | US2009/0054383                                                      | 1 a 8                      | Nivel Inventivo      |
| D2   | <i>American Journal of Drugs Delivery.</i><br>2006. 4; 2: 105 – 112 | 1 a 8                      | Nivel Inventivo      |

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Si como respuesta a este requerimiento el solicitante llegara a modificar: i) el capítulo reivindicatorio, ii) la descripción de la invención a proteger, iii) o presente un nuevo capítulo reivindicatorio, y desee que se realice un nuevo examen de patentabilidad a esta modificación, no deberá pagar la tasa de modificación voluntaria pero sí la correspondiente a la tasa de examen de patentabilidad. En todo caso, el número de requerimientos por no patentabilidad estará supeditado a que el término del estudio de patentabilidad no sea superior a 18 meses, contados desde la publicación de la solicitud de patente de invención. Adicionalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones deberá pagar la tasa por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



**JOSÉ LUIS SALAZAR LÓPEZ**  
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2016-05-31

Elaboró: Dayron Alexander Ramirez Reyes

Revisó: Olga Rosa Gonzalez Fonseca

# The Role of Excipients in the Control of Dehydroepiandrosterone Inclusion Complex Delivery

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## Abstract

**Aim:** The aim of this study was to develop systems containing dehydroepiandrosterone (DHEA), in the form of an inclusion complex with  $\alpha$ -cyclodextrin (c-DHEA), which are able to change the release profile of the hormone according to time and excipient composition.

**Method:** Twenty-five formulations were prepared containing DHEA (prasterone) in the chemical form of an inclusion complex with  $\alpha$ -cyclodextrin (57.3% w/w). The drug was mixed with three different excipient systems: the first 'fast' one was a mixture of two disintegrants (microcrystalline cellulose and sodium carboxymethyl starch at prefixed 4.15 weight ratio); the second 'gelling' excipient contained two gel-forming agents (high viscosity hydroxypropyl methylcellulose and cross-linked polyvinyl pyrrolidone) at three weight ratios: 0.31, 1.00, and 2.45; and the third type of 'binary' mixture was prepared by combining 'fast' and 'gelling' systems at three weight ratios: 1 : 2, 1 : 1, and 2 : 1. Tablets were prepared by direct compression or after wet granulation of these formulations.

**Results:** 'Fast' tablets induced a rapid release of the drug while 'gelling' tablets were found to modify the release, according to composition. A profile, characterized by an initial phase of rapid drug release, followed by a period of slower release is achieved with series 1 : 1 tablets. Series 1 : 2 tablets provide linear release of the drug; while an undifferentiated profile was found for series 2 : 1 tablets.

**Conclusion:** Different release mechanisms and the control of drug release were obtained by using DHEA in its inclusion complex and varying the weight ratios of the excipients.

Dehydroepiandrosterone (DHEA; prasterone) and its sulfate conjugate have received attention after the discovery that their endogenous levels decline with human aging.<sup>[1]</sup> Clinical studies have associated restoration of serum DHEA levels in elderly men, by exogenous administration, with physical and psychological well-being.<sup>[2]</sup> Unfortunately DHEA is a non-ionizable compound with poor water solubility, low dissolution rate, and inconstant oral availability due to its variable intestinal absorption and high metabolism.

Cyclodextrins are currently proposed as carriers to increase the solubility of drugs that are poorly soluble in water.<sup>[3-6]</sup> Recently, a ternary system containing DHEA complexed with  $\alpha$ -cyclodextrin (c-DHEA), in the presence of glycine as a co-solubilization

agent,<sup>[7]</sup> was found to improve the oral availability of the drug, displaying increased solubility and dissolution properties.<sup>[8,9]</sup> Moreover, based on *in vivo* studies in volunteers, this system presented surprising new pharmacological characteristics:

- its oral administration led to increased levels of DHEA in the blood without any increase of its bioconversion into testosterone;<sup>[7]</sup> and
- an increased transformation of DHEA into 17- $\beta$ -estradiol was reported.<sup>[7]</sup>

These characteristics suggest that the use of c-DHEA may be of interest as hormonal replacement therapy in the elderly. In order to offer a solution to the practical problems of DHEA administration, formulations using combinations of excipients which take advan-

**Table I.** Weight composition of a 'fast' powder of dehydroepiandrosterone complexed with  $\alpha$ -cyclodextrin (c-DHEA)

| Component          | Content (%) |
|--------------------|-------------|
| c-DHEA             | 57.30       |
| Avicel® PH101      | 33.20       |
| Explotab®          | 8.00        |
| Aerosil® 200       | 0.50        |
| Magnesium stearate | 1.00        |

tage of the solubility of its inclusion complex with  $\alpha$ -cyclodextrin are required. The present study aims to develop c-DHEA-containing systems that are able to change the release profile of the hormone according to time and excipient composition.

Tablets containing c-DHEA were prepared using a balanced combination of compressed mixtures of excipients with different technological properties. Microcrystalline cellulose and sodium carboxymethyl starch were expected to provide rapid release (disintegrants accelerate water absorption in the tablet and promote its disintegration, by swelling or fast water absorption). High viscosity hydroxypropyl methylcellulose (HPMC) and cross-linked polyvinyl pyrrolidone (PVP), for its binding and swelling properties, were used to introduce a gelling behavior into the formulation, with or without previous wet granulation (gel polymers create a barrier to water and drug diffusion). The effects of these formulation parameters are examined and the release profiles discussed in order to suggest formulations suited to the particular purposes of DHEA administration.

## Materials and Methods

### Materials

DHEA was supplied by Sigma-Aldrich, Italy; c-DHEA by Actimex, Italy; high-viscosity grade HPMC (Methocel® K4M [22.6% methoxyl content and 9.6% hydroxypropyl content, with 4126 cPs apparent viscosity as a 2% aqueous solution])<sup>1</sup> by Polichimica, Italy; microcrystalline cellulose (Avicel® PH101) by Prodotti Gianni, Italy; colloidal silica dioxide (Aerosil® 200) by Eigenmann Veronelli, Italy; sodium carboxymethyl starch (Explotab®) by Deimos, Italy; PVP (Kollidon® PK30) by Kollidon® CLM-BASF, Germany; and magnesium stearate by Tradeco, Italy. All other reagents were obtained from Merck (Darmstadt, Germany) and were of the highest quality available.

### Excipient Design

Three lots of different excipients, as physical mixtures, were designed:

- The first lot (only one physical mixture) contained a mixture of Avicel® PH101 and Explotab® and at a prefixed 4.15 weight ratio; this sample is referred to as 'fast' powder (table I).
- The second lot (three physical mixtures) contained a combination of Methocel® K4M and Kollidon® PK30 at three different weight ratios: 0.29, 1.00, and 2.45 (formulations Aw and Ad, Bw and Bd, and Cw and Cd, respectively; 'd' for direct compression and 'w' for wet granulation mode of preparation); these samples are identified as 'gelling' powders (table II).
- The third lot (nine physical mixtures) contained 'fast' and 'gelling' powders (or granules) in different weight ratios (table III). Samples of this lot are referred to as 'binary' powders and identified with a capital letter A, B, and C (indicating the weight ratio composition used of the 'gelling' powder) and a number index (indicating the weight ratio of the two 'fast' and 'gelling' components; 1 : 2, 1 : 1, and 2 : 1).

### Wet Granulation

'Gelling' granules were prepared by wet granulation of 'gelling' powders of the second lot. The mixture, moistened by a small volume of ethanol, was kneaded and the mass forced across a grid and then left to dry in an oven at 40°C for 2 hours. The dry material was sieved and powder with a dimensional size <800µm was collected and used for further tests and preparations.

### Preparation of Tablets

The drug was added to the selected excipient mixture up to a final content of 57.3% w/w of c-DHEA, corresponding to 3.12mg

**Table II.** Weight composition of 'gelling' powder formulations of dehydroepiandrosterone complexed with  $\alpha$ -cyclodextrin (c-DHEA)<sup>a</sup>

| Component          | Content (%) |           |           |
|--------------------|-------------|-----------|-----------|
|                    | Aw and Ad   | Bw and Bd | Cw and Cd |
| c-DHEA             | 57.30       | 57.30     | 57.30     |
| Kollidon® PK30     | 31.85       | 20.60     | 11.95     |
| Methocel® K4M      | 9.35        | 20.60     | 29.25     |
| Aerosil® 200       | 0.50        | 0.50      | 0.50      |
| Magnesium stearate | 1.00        | 1.00      | 1.00      |

a Methocel® K4M : Kollidon® PK30 weight ratio: 0.29, 1.00, and 2.45 for formulations Aw and Ad, Bw and Bd, and Cw and Cd, respectively.

d = direct compression; w = wet granulation.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

**Table III.** Percentage weight composition of the excipients for 'binary' tablets of dehydroepiandrosterone complexed with  $\alpha$ -cyclodextrin (c-DHEA), containing a mixture of 'fast' (Avicel® PH101 and Explotab®) and 'gelling' (Kollidon® PK30 and Methocel® K4M) powder (or granules) at three different weight ratios

| Mixture <sup>a</sup> | Content (%) |               |           |                |               |
|----------------------|-------------|---------------|-----------|----------------|---------------|
|                      | c-DHEA      | Avicel® PH101 | Explotab® | Kollidon® PK30 | Methocel® K4M |
| A21                  | 57.30       | 22.95         | 5.53      | 10.86          | 3.36          |
| B21                  | 57.30       | 22.95         | 5.53      | 7.14           | 7.12          |
| C21                  | 57.30       | 22.95         | 5.53      | 4.12           | 10.10         |
| A11                  | 57.30       | 17.20         | 4.15      | 16.29          | 5.05          |
| B11                  | 57.30       | 17.20         | 4.15      | 10.68          | 10.68         |
| C11                  | 57.30       | 17.20         | 4.15      | 6.18           | 15.16         |
| A12                  | 57.30       | 11.47         | 2.76      | 21.73          | 6.73          |
| B12                  | 57.30       | 11.47         | 2.76      | 14.23          | 14.23         |
| C12                  | 57.30       | 11.47         | 2.76      | 8.25           | 20.22         |

a Each mixture is identified with a capital letter A, B, or C (indicating the weight ratio composition used of the 'gelling' powder [see table II]) and a number index (indicating the weight ratio of the two 'fast' and 'gelling' components; 1 : 2, 1 : 1, and 2 : 1).

of pure DHEA. In the case of the wet granulation, the complex was added to the 'gelling' mixture prior to granulation. Final mixtures were compacted using an EKO single punch tableting machine (Berlin, Germany). The hardness of the tablets, in the range of 3.5–4.0kg, is a result of a manual tableting process, and this machine was only able to prepare one type of tablet. All the tablets were tested for drug content.

Twelve tablets were prepared by direct compression containing c-DHEA associated with the three 'gelling' powders (A, B, and C) or with the nine mixtures of 'fast' and 'gelling' powders at three weight ratios (1 : 2, 1 : 1, and 2 : 1) [d series]; an additional twelve different tablets of similar composition were prepared, using 'gelling' granules (w series) obtained by wet granulation. For example, Aw21 means that the final tablet contains a 2 : 1 weight ratio of the 'fast' powder and 'gelling' granules A; Ad21 indicates the same formulation obtained by direct compression of the powder, without any granulation step.

As a reference, a sample containing only 'fast' powder was also tested.

#### *In Vitro* Drug Releasing Test

Drug release was analyzed using an USP XXVI (Erweka DT600, Milan, Italy) dissolution paddle, using the method A for the delayed-release systems. Dissolution medium was 1000mL of phosphate buffer (pH 6.8) at  $37 \pm 0.5^\circ\text{C}$ . Aliquots of 2mL were withdrawn, filtered with 0.22 $\mu\text{m}$  millipore nylon filters at preset intervals and immediately replaced with thermostated distilled water. The content of drug in the aliquots was measured by high performance-liquid chromatography (HPLC). All experiments were carried out in triplicate.

#### Fitting of Experimental Data

Experimental data, shown in figures 1, 2, and 3, were evaluated by fitting the following semi-empirical equation 1:<sup>[10]</sup>

$$\frac{M_t}{M_\infty} = kt^n \quad (\text{Eq. 1})$$

for  $0 < M_t/M_\infty < 0.6$ , where  $M_t/M_\infty$  is the fractional amount of the drug released at time  $t$ ,  $k$  is a kinetic constant incorporating the characteristics of the release system indicative of mechanism of release, and  $n$  is the release exponent. Values for  $n$  and  $k$  for each system were graphically obtained by plotting the logarithm of the fractional release against the logarithm of time:  $n$  represents the

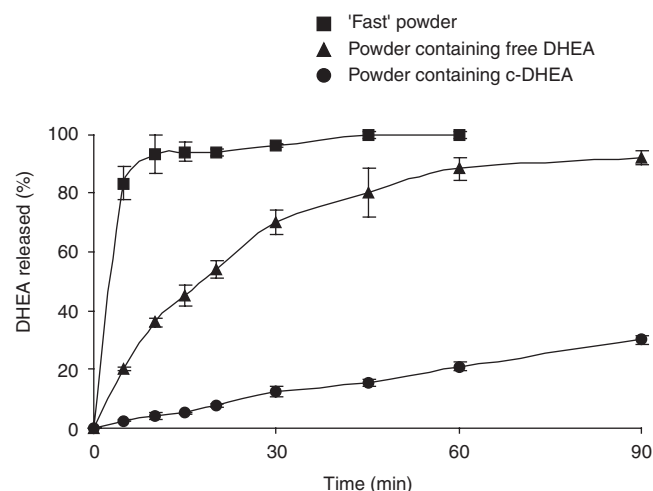


**Fig. 1.** Release profiles of complexed dehydroepiandrosterone (c-DHEA) from 'fast' powder (containing  $\alpha$ -cyclodextrin-c-DHEA coupled with disintegrants) and from powder containing only free DHEA and c-DHEA.

slope while  $\log k$  is the intercept, and the two values were calculated by regression analysis. Results are shown in table IV.

Alternatively, when evident from the dissolution profiles, data were fitted by a zero-order kinetic equation, and these parameters are also reported.

Linearity tests were performed by ANOVA (lack of fit tests) using Matlab built-in functions (Matlab statistical toolbox, The Mathworks, Natick, MA, USA).

#### Dehydroepiandrosterone Analysis

DHEA in samples was determined by an adapted HPLC reversed-phase method, described elsewhere.<sup>[9,11]</sup> Briefly, a Dionex P580 (HPLC Pump P480 Dionex, Milan, Italy) system equipped with a variable-wavelength ultraviolet detector UVD 170S (helios thermo Optek, Milan, Italy) was used for this purpose. The mobile phase, a mixture of acetonitrile (55%) and water (45%), was pumped at a flow rate of 1 mL/min through a Nova-Pak C18 (150 × 3.9mm, 4mm, Waters, Milan, Italy) at room temperature. The injected volume was 20 µL, and the detection wavelength was 210nm. Under these conditions, the retention time of DHEA was 7.2 minutes and no differences were identified between free DHEA and c-DHEA.

## Results

Figure 1 shows the release profile of the drug (c-DHEA) from 'fast' powder (containing disintegrants) in comparison with the release from powders containing free DHEA or c-DHEA. The drug is rapidly released from 'fast' powder, reaching 80% in 5 minutes; this result is even better than that previously found, using an unformulated drug,<sup>[8]</sup> which released only 40% after 10 minutes.<sup>[8]</sup>

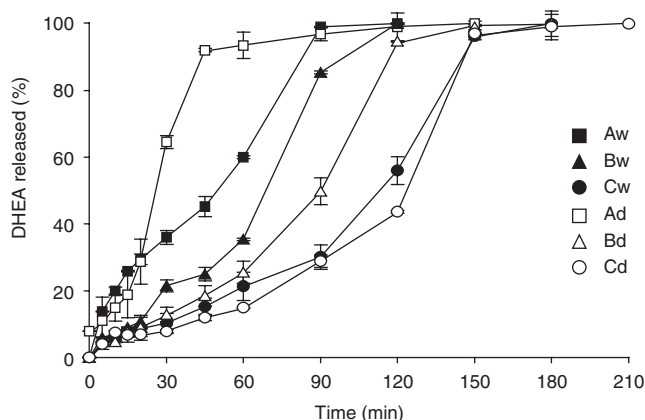


**Fig. 2.** Release profiles of  $\alpha$ -cyclodextrin complexed dehydroepiandrosterone (c-DHEA) from tablets prepared by direct compression of 'gelling' powders (Ad, Bd, and Cd) or by 'gelling' granules after wet granulation (Aw, Bw, and Cw).

The drug-releasing profiles from the 'gelling' tablets, prepared using direct compression (Ad, Bd, and Cd) or by previous wet granulation (Aw, Bw, and Cw), are shown in figure 2. The release of the drug at different rates depends on the excipient composition, i.e. on the Methocel® K4M : Kollidon® PK30 ratio (table II). In 'gelling' tablets, c-DHEA is strongly bound to hydrophilic and gelling polymers, which allow swelling after contact with water. These polymers cause a slower release with respect to 'fast' powder that takes  $\geq 3$  hours to be complete; this is documented by the overall slope of the profiles.

The profiles in figure 2 appear to be divided into two linear portions: an initial step, which lasts for about 1 hour in all cases, except Ad, followed by a second step with a steeper slope, indicating a clear acceleration of the release rate. This is particularly evident for B, while it is fairly visible for A and suggests the different role of the two polymers forming the 'gelling' excipients. Due to the formation of gel domains inside the tablet when it comes in contact with water, the properties of Methocel® K4M appear to be of greater importance than those of Kollidon® PK30. Initial wetting and subsequent hydration of the formulations are, therefore, influenced and delayed; thus, the slopes of the release profiles decrease as the amount of Methocel® K4M increases inside the tablets, at least in the first portions of the profiles.

The tablet preparation method has little effect on the release of the drug in the case of formulations B and C; however, Ad tablets released the drug faster than Aw tablets. In both cases a linear release can be observed, suggesting the use of these formulations for a zero-order release of the drug. Differences in formulations of B and C appear less evident; therefore, in terms of practical applications the two methods of preparing the tablets produce almost equivalent results.

Figure 3 shows release profiles of c-DHEA from 'binary' tablets, prepared compacting a mixture of 'fast' and 'gelling' powders (d series) or granules (w series) using different weight ratios of these components: 2 : 1, 1 : 1, and 1 : 2 (table III).

Series 21 tablets behave similarly to each other (figure 3). In this series the gelling portion is 33% w/w of the whole excipient mass and at this concentration no more able to overcome or control the action of disintegrants: as a consequence the release occurs in an undifferentiated mode.

In the 11 and 12 series tablets, the amount of disintegrant over the whole composition of the tablets is lower and a slower release could be observed (figure 3). Different excipients affect the release according to their different properties and amounts; the profiles appear almost linear and differentiated. The formulations of the series 12 tablets offer a linear and constant release, according to zero-order kinetics; kinetic constants are in the rank order: A > B > C. In the case of the A formulation, the release is complete in <1

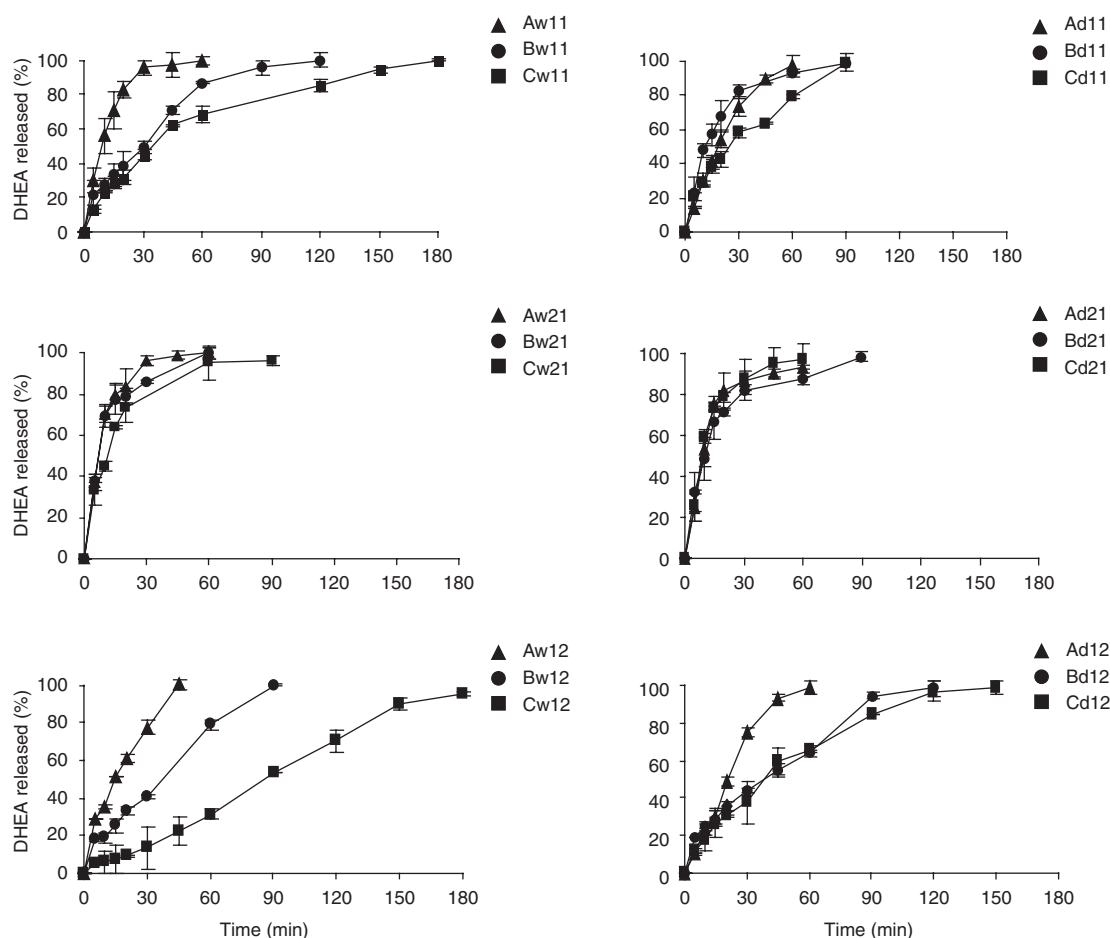


**Fig. 3.** Release profiles of  $\alpha$ -cyclodextrin complexed dehydroepiandrosterone (c-DHEA) from 'binary' tablets formed from mixtures of 'fast' powder and 'gelling' powders prepared by direct compression (d) or 'fast' powder and 'gelling' granules after wet granulation (w), at different weight ratios of these components. For example, Aw21 means that the final tablet contains a 2 : 1 weight ratio of the 'fast' powder and 'gelling' granules A; Ad21 indicates the same formulation obtained by direct compression of the powder, without any granulation step.

hour; in the case of C formulation it takes >3 hours. The same behavior can be observed for the B11 and C11 formulations, where Methocel® K4M is still present at a concentration suitable to control the release through the formation of a gel; higher percentages of disintegrants allow a higher release rate with respect to series 12 tablets.

Also, very small differences in the 'binary' tablets were caused by the mode of the preparation (dry or wet granulation), even though the wet granulation appeared to offer a better differentiation of composition.

## Discussion

In the present study, the active agent DHEA was in a pre-formed inclusion complex with  $\alpha$ -cyclodextrin, a formulation recently made available on the pharmaceutical market. This complex has improved solubility and dissolution rate, which in turn guarantees better oral availability of the active agent. This paper

proposes a solution for the oral delivery of this hormone. The complex was associated with each excipient, simple or in mixture, in the form of powder or granules in such an amount that all the final formulations contained the same amount of c-DHEA. Excipients were designed as multicomponent systems, coupling commercial compounds with different behavior, i.e. disintegrant and gel-forming agents mixed at different weight ratios. They were prepared as physical mixtures, which were in some cases wet granulated prior to compacting into tablets.

'Fast' tablets were prepared using microcrystalline cellulose, with binding/disintegrating properties which do not promote swelling,<sup>[12]</sup> and sodium carboxymethyl starch, a well known super-disintegrant excipient, able to reduce disintegration time when present in tablets. As a consequence the 'fast' formulation contained only disintegrants as excipients. The contiguity of c-DHEA to hydrophilic polymers improves its wettability, when in contact with the dissolution medium and, thus, its dissolution

**Table IV.** Release exponent ( $n$ ) and kinetic constant ( $k$ ) from the release profiles of dehydroepiandrosterone from 'binary' tablets containing mixtures of 'fast' powder and 'gelling' powders prepared by direct compression (d) or from 'fast' powder and 'gelling' granules after wet granulation (w)

| Series <sup>a</sup> | $n$  | $k$ (t <sup>n</sup> )              | R <sup>2</sup> (correlation coefficient) |
|---------------------|------|------------------------------------|------------------------------------------|
| Aw21                | 0.51 | 0.46                               | 0.93                                     |
| Bw21                | 0.46 | 0.45                               | 0.99                                     |
| Cw21                | 0.43 | 0.19                               | 0.83                                     |
| Ad21                | 0.46 | 0.17                               | 0.96                                     |
| Bd21                | 0.45 | 0.18                               | 0.94                                     |
| Cd21                | 0.49 | 0.16                               | 0.89                                     |
| Aw11                | 1    | 0.83                               | 0.97                                     |
| Bw11                |      | 0.58 (0.60 min), 0.17 (60–120 min) | 0.98; 0.99                               |
| Cw11                |      | 1.33 (0.90 min), 0.32 (90–150 min) | 0.98; 0.99                               |
| Ad11                | 0.44 | 0.16                               | 0.91                                     |
| Bd11                | 0.48 | 0.14                               | 0.92                                     |
| Cd11                | 0.52 | 0.09                               | 0.99                                     |
| Aw12                |      | 2.08                               | 0.95                                     |
| Bw12                |      | 1.12                               | 0.96                                     |
| Cw12                |      | 0.54                               | 0.99                                     |
| Ad12                |      | 0.89                               | 0.87                                     |
| Bd12                |      | 0.80                               | 0.95                                     |
| Cd12                |      | 0.72                               | 0.92                                     |

a Each mixture is identified with a capital letter A, B, or C (indicating the weight ratio composition used of the 'gelling' powder [see table II]) and a number index (indicating the weight ratio of the two 'fast' and 'gelling' components; 1 : 2, 1 : 1, and 2 : 1).

propensity, resulting in a very rapid availability of the drug compared to simple powders containing free DHEA or c-DHEA (figure 1).

The excipient of 'gelling' tablets is a mixture of gelling polymers (PVP and HPMC), which allows swelling when it comes in contact with water. HPMC, commonly used in hydrophilic matrix drug delivery systems, contains methoxyl and hydroxypropyl groups; its hydration rate increases with the increase of the hydroxypropyl moieties, but it only dissolves slowly in cold water, forming a viscous solution. When HPMC is present in pharmaceutical formulations and comes into contact with water, it quickly forms a gel that controls the diffusion of water and sustains the release.<sup>[13,14]</sup> Therefore, the choice of a high molecular weight HPMC (i.e. Methocel® K4M) is an important consideration for controlling drug release from hydrophilic gels. It has been reported that the combination of small amounts of this high-viscosity polymer and a low-viscosity grade polymer can decrease or extend release characteristics,<sup>[15,16]</sup> making it possible to obtain a bimodal release.<sup>[13]</sup>

While HPMC behaves as a gelling excipient, cross-linked PVP (Kollidon® K30) not only has gelling properties but also displays binding ability and modifies the release of the active substance in such a way that it leads to sustained drug release.

It can be hypothesized that there is a change of mechanism in formulations A to C, i.e. with an increase of Methocel® K4M in the excipient composition (table II). An initial rapid gel formation slows drug release and slows the swelling; after about 1 hour, the extent of drug release is no more than 45% (figure 2). After the initial release, an enhanced release can be observed, probably due to the complete swelling and/or possible erosion/de-aggregation of the tablet (figure 2). However, the high-viscosity Methocel® K4M made the gel domains more viscous and less susceptible to erosion, even though the high amount of c-DHEA (57.3% w/w) in the formulation could not be ignored and which, after dissolution and therefore leaching of the tablet, could also be responsible for its degradation.

'Binary' tablets were prepared by mixing different amounts of 'fast' and 'gelling' powders or granules with different properties with regard to drug release. They contain the two 'fast' and 'gelling' components at three different weight ratios (table III); it was, therefore, expected that the 'binary' tablets would demonstrate an intermediate behavior with respect to the previously discussed formulations (figure 3).

A very weak control and poor differentiation could be observed in the release profiles for the tablets containing an excess of disintegrants compared to gelling components (series 21; figure

3). The slope of the ascending portions of the release profiles did not differ much; therefore, the controlling behavior of gel-forming components was very limited and only seen in the case of C21 tablets.

In the series 11 and 12 tablets, the increase in the Methocel® K4M component, passing from A to C (in both series), provided increased gel formation inside the tablet and modified the drug release mechanism; therefore, decreases in the rate of drug release were expected. In particular, series 11 tablets offer a profile according to a release mechanism governed by diffusion ( $n$  is very close to 0.5 in all cases; table IV). In the series 12 tablets, the gel-making components were in the range of 10–15% and the release was more regular; it could be suggested that the formation of a gel was balanced by the action of the disintegrant. As the Methocel® K4M component increased, a decrease of the drug release rate was observed; after contact with the aqueous medium, a gel was rapidly formed, increasing the path length for the release of the drug.

The behavior of the series 11 formulations was very interesting. The release profile appears to be divided in steps, each linear with time. It was possible to identify two steps: a first fast release, followed by a slower release. In particular, about 90% of the drug was released within the first 30 minutes in the Aw11 tablets, and the residual 10% within the next 30 minutes (figure 3). These differences were even more marked for Bw11 and Cw11 tablets (figure 3). In the last case almost half of the drug was released in each of the two steps and it was evident that changes in the formulation with respect to Methocel® K4M content could favor one or other of the two steps. Gel formation and swelling determined the second phase of reduced release as the dissolved drug is obliged to diffuse across the forming gel matrix to be released.

When the ratio between 'fast' and 'gelling' powder is 0.5 (series 12), formulations were able to release the drug according to zero-order kinetics; the amount of Methocel® K4M controlled the release rate. The weight ratio also controlled the mode of the release: 0.5 (series 12) led to zero-order kinetics; 2.0 (series 21) led to release controlled by diffusion; and 1.0 (series 11) led to stepwise linear release. The amount of Methocel® K4M controlled the rank order of the rate constant:  $C < B \leq A$ ; the release rate decreased as the Methocel® K4M content increased (table IV). When the whole composition of the tablets was described by a net prevalence of either main component (fast or gelling powder), the mechanism was clearly evident (diffusion or linear release). When the composition was more balanced the mechanism of release was not well defined. Profiles can be read both as two linear steps (of different weights according to the Methocel® K4M amount) or as profile with  $n > 0.5$ , where the mechanism is intermediate between a linear or diffusion-controlled one. Linearity of the plots (simple

or in terms of log/log) was assessed using lack of fit tests; in all cases  $F$  values were below the critical  $F$  value ( $p = 0.05$ ), thus, confirming the appropriateness of the linear model.

## Conclusions

The knowledge of single excipient behavior is important for formulating controlled release systems with different mechanisms and rates. A mixture is expected to display a behavior that is the sum of that of the single components. The composition is thus critical in determining the mechanism and release rate. Complexation with  $\alpha$ -cyclodextrin improved the dissolution of DHEA with respect to pure drug; the presence of disintegrants in 'fast' tablets resulted in the release of c-DHEA within a few minutes. These formulations may be suitable for a sublingual administration or for preparing extemporaneous solutions, for the easy and rapid oral administration of DHEA.<sup>[13,17]</sup> The presence of 'gelling' compounds inside the tablets decreased the release rate compared with 'fast' tablets. Accelerating (disintegrants) or retarding (gel-forming) excipients, suitably coupled in formulations containing c-DHEA, modified the rate and mechanism of the release of this drug. No important differences were found between the method of preparing tablets, by direct compression or by previous wet granulation of the powders. The major advantages of these formulations are the ease of preparation, even at industrial level and their applicability to different type of drugs, with the possibility of slowing the release of hydrophilic drugs or accelerating the release of hydrophobic ones. This study has demonstrated the possibility of achieving different release mechanisms by simply changing the composition of the excipients in the preparation of tablets using common techniques.

## Acknowledgments

This research was partly supported by the PRIN Fund.

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|                                                                                                              |                                                         | WO2009003125                                                                                                                                                        | 1 – 13          | N/A                               |                                                                  |    |
|                                                                                                              |                                                         | The role of excipients in the control of dehydro epiandrosterone inclusion complex delivery. <i>American Journal of Drug Delivery</i> . 2006 vol. 4, no. 2, 105-112 | 1 – 13          | Nivel Inventivo                   | X                                                                |    |
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