G A R A N T Í A D E C A L I D A D

D E M E D I C A M E N T O S

Anexo
Trabajo práctico Nº 1

BIBLIOGRAFÍA

Año 2026

Descripción de la Monografía de Paracetamol de la Farmacopea Argentina

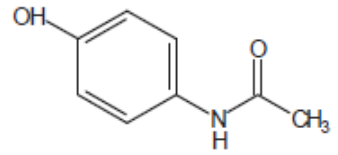
Cuando se conoce la composición química de una sustancia oficial, se especifica a título informativo la fórmula molecular, el peso molecular y el número CAS (Chemical Abstracts Service).
Esta información se refiere a la sustancia químicamente pura y no se considera un indicador de la pureza del material oficial.
Cuando se especifica la configuración estereoquímica absoluta, se emplean los sistemas de designación propuestos por la Unión Internacional de Química Pura y Aplicada (IUPAC) R/S y E/Z. El nombre químico será otorgado según las reglas propuestas por la Unión Internacional de Química Pura y Aplicada (IUPAC).

Requerimiento de Pureza: 98,0 - 101,0 %. Será determinado mediante el ensayo de valoración.

Caracteres Generales

Los términos como inodoro, prácticamente inodoro, con un débil olor característico o expresiones semejantes, se aplican al examen después de la exposición al aire durante 15 minutos de un envase recientemente abierto del producto (envases que contengan no más de 25 g) o de una porción de aproximadamente 25 g del producto (en caso de envases más grandes) que haya sido trasladada de su envase a un cristalizador, con una capacidad de aproximadamente 100 mL. Solo se hará mención a este tipo de características cuando la misma sea un elemento relevante en la descripción del principio activo.

PARACETAMOL



$C_8H_9NO_2$ PM: 151,2 *103-90-2*

Sinonimia - Acetaminofeno.

Definición - Paracetamol es *N*-(4-Hidroxifenil)acetamida. Debe contener no menos de 98.0 por ciento y no más de 101.0 por ciento de $C_8H_9NO_2$, calculado sobre la sustancia anhidra y debe cumplir con las siguientes especificaciones.

Caracteres generales - Polvo cristalino blanco, inodoro. Fácilmente soluble en alcohol; soluble en agua hirviendo e hidróxido de sodio 1 N; moderadamente soluble en agua; muy poco soluble en cloruro de metileno y éter.
Presenta polimorfismo.

Sustancia de referencia - Paracetamol SR-FA.

CONSERVACIÓN

En envases inactínicos de cierre perfecto.

Consideraciones para su conservación evaluando su estabilidad a la humedad, luz y temperatura entre otras.

Solubilidad

La solubilidad indicada no debe ser considerada en el sentido estricto de constante física, sino que complementa con los demás ensayos, pudiendo tener un valor definitivo en caso de que la sustancia no presente la solubilidad mínima exigida, principalmente cuando el solvente es agua.
Las indicaciones sobre la solubilidad a la cual se hace referencia son realizadas a la temperatura de 25 ± 5 ºC.
La expresión *partes* se refiere al número de mililitros de solvente por gramo de sólido a disolver.
Las solubilidades aproximadas establecidas en las monografías son designadas en términos escriptivos cuyos significados están relacionados en la tabla a continuación:

Término descriptivo	*Volúmenes aproximados de solvente en mililitros por gramo de sustancia*
Muy soluble	Inferior a 1
Fácilmente soluble	De 1 a 10 partes
Soluble	De 10 a 30 partes
Moderadamente soluble	De 30 a 100 partes
Poco soluble	De 100 a 1.000 partes
Muy poco soluble	De 1.000 a 10.000 partes
Prácticamente insoluble	Más de 10.000 partes

Miscibilidad

El término miscible se emplea para describir un líquido o un gas que produce una mezcla homogénea al mezclarse en cualquier proporción con el solvente indicado en el mismo estado físico.

ENSAYOS

Identificación

A - Absorción infrarroja <460>. *En fase sólida.*

B - Absorción ultravioleta <470>

Solvente: ácido clorhídrico 0,1 N en metanol 1 en 100.

Concentración: 5 µg por ml.

C - Aplicar la siguiente técnica cromatográfica.

Fase estacionaria - Emplear una placa para cromatografía en capa delgada (ver *100. Cromatografía*) recubierta con gel de sílice para cromatografía con indicador de fluorescencia, de 0,25 mm de espesor.

Fase móvil - Cloruro de metileno y metanol (4:1).

Solución estándar - Preparar una solución de Paracetamol SR-FA en metanol de aproximadamente 1 mg por ml.

Solución muestra - Preparar una solución de Paracetamol en metanol de aproximadamente 1 mg por ml.

Procedimiento - Aplicar por separado sobre la placa 10 µl de la *Solución muestra* y 10 µl de la *Solución estándar*. Dejar secar las aplicaciones y desarrollar los cromatogramas hasta que el frente del solvente haya recorrido aproximadamente tres cuartas partes de la longitud de la placa. Retirar la placa de la cámara, marcar el frente del solvente y dejar secar. Examinar la placa bajo luz ultravioleta a 254 nm. El valor de R_f de la mancha principal en el cromatograma obtenido a partir de la *Solución muestra* debe ser similar al obtenido con la *Solución estándar*.

Solventes y soluciones de una monografía

Cuando no se menciona explícitamente el solvente, se entiende que la muestra es disuelta en agua.

Agua: la expresión agua, empleada sin otra calificación significa *Agua purificada.*

Cuando no se menciona explícitamente la normalidad (N) ni concentración del solvente, se entiende que debe emplearse el solvente concentrado.

La expresión *10:6:1* significa que los números respectivos de partes, en volumen, de los líquidos señalados deberán mezclarse, a menos que se indique de otro modo.

Identificación

Los ensayos de la Farmacopea que figuran después del subtítulo *Identificación* no están destinados a proporcionar una confirmación completa de la estructura química o composición del producto; su objeto es confirmar que el producto se ajusta a la descripción dada en el rótulo del envase. Cuando un producto no satisface los requisitos de un ensayo de identificación descripto, indica que el mismo no cumple con las especificaciones. Otros ensayos o especificaciones en la monografía a menudo contribuyen a establecer o confirmar la identidad del producto ensayado.

A menos que se indique lo contrario en la monografía individual, todos los ensayos identificatorios son de carácter obligatorio y por ende, necesarios para demostrar que el producto cumple con la descripción dada en el rótulo.

Determinación del punto de fusión <260>
Entre 168 y 172 °C.

Determinación de agua <120>
Titulación volumétrica directa. No más de 0,5 %.

Límite de cloruro y sulfato <560>
Cloruro - Agitar 1,0 g de Paracetamol con 25 ml de agua, filtrar y agregar 1 ml de ácido nítrico 2 N y 1 ml de nitrato de plata (SR): el filtrado no debe presentar más cloruro que el equivalente a 0,20 ml de ácido clorhídrico 0,020 N (0,014 %).
Sulfato - Agitar 1,0 g de Paracetamol con 25 ml de agua, filtrar y agregar 2 ml de ácido acético 1 N. A continuación, agregar 2 ml de cloruro de bario (SR): la mezcla no debe presentar más sulfato que el equivalente a 0,20 ml de ácido sulfúrico 0,020 N (0,02 %).

Sulfuro
Transferir 2,5 g de Paracetamol a un vaso de precipitados de 50 ml. Agregar 5 ml de alcohol y 1 ml de ácido clorhídrico 3 N. Humedecer en agua una tira de papel indicador de acetato de plomo (ver *Papeles y Papeles indicadores* en *Reactivos y Soluciones*) y fijarla sobre la cara inferior de un vidrio de reloj. Cubrir el vaso de precipitados con el vidrio de reloj, de modo que parte del papel indicador de acetato de plomo quede suspendido cerca del pico vertedor del vaso de precipitados. Calentar el contenido del vaso de precipitados sobre una placa calefactora hasta ebullición. No deben aparecer manchas o coloración en el papel indicador.

***p*-Aminofenol libre**
Diluyente - Agua y metanol (1:1).
Solución alcalina de nitroferricianuro de sodio - Disolver 1 g de nitroferricianuro de sodio y 1 g de carbonato de sodio anhidro en 100 ml de agua.
Solución muestra - Transferir 5,0 g de Paracetamol a un matraz aforado de 100 ml y disolver con aproximadamente 75 ml de *Diluyente*. Agregar 5,0 ml de *Solución alcalina de nitroferricianuro de sodio*, completar a volumen con *Diluyente*, mezclar y dejar en reposo durante 30 minutos.
Solución estándar - Emplear una solución recientemente preparada de *p*-aminofenol de aproximadamente 2,5 µg por ml, preparada según se indica en *Solución muestra*.

Procedimiento - Determinar las absorbancias de la *Solución muestra* y la *Solución estándar* en celdas de 1 cm, a la longitud de onda de máxima absorción, aproximadamente a 710 nm, con un espectrofotómetro, empleando 5,0 ml de *Solución alcalina de nitroferricianuro de sodio* diluida a 100 ml con *Diluyente* como blanco: la absorbancia de la *Solución muestra* no debe ser mayor que la absorbancia de la *Solución estándar* (0,005 %).

Límite de *p*-Cloroacetanilida
Fase estacionaria - Emplear una placa para cromatografía en capa delgada (ver *100. Cromatografía*) recubierta con gel de sílice para cromatografía con indicador de fluorescencia, de 0,25 mm de espesor.
Fase móvil - Éter de petróleo y acetona (75:25).
Solución estándar - Preparar una solución de *p*-cloroacetanilida en éter de aproximadamente 10 µg por ml.
Solución muestra - Transferir 1,0 g de Paracetamol a un tubo de centrífuga de 15 ml provisto de un tapón de vidrio y agregar 5,0 ml de éter. Agitar mecánicamente durante 30 minutos y centrifugar a 1.000 rpm durante 15 minutos o hasta obtener una separación neta, emplear la solución sobrenadante.
Procedimiento - Aplicar por separado sobre la placa 200 µl de la *Solución muestra* (en porciones de 40 µl, de manera de obtener una única mancha de no más de 10 mm de diámetro) y 40 µl de la *Solución estándar*. Dejar secar las aplicaciones y desarrollar los cromatogramas en una cámara no saturada hasta que el frente del solvente haya recorrido aproximadamente tres cuartas partes de la longitud de la placa. Retirar la placa de la cámara, marcar el frente del solvente y dejar evaporar. Examinar bajo luz ultravioleta a 254 nm: la mancha obtenida en el cromatograma de la *Solución muestra*, con valor de R_f correspondiente a la mancha principal obtenida con la *Solución estándar*, no debe ser mayor en tamaño o intensidad a la mancha principal obtenida con la *Solución estándar* (0,001 %).

Ensayo de sustancias fácilmente carbonizables <350>
Disolver 0,50 g de Paracetamol en 5 ml de ácido sulfúrico (SR): el color de la solución no debe ser más intenso que el de la *Solución de comparación A*.

Impurezas orgánicas volátiles <520>
Método III.
Solvente: dimetilsulfóxido.

Límite de metales pesados <590>
Método II. No más de 0,001 %.

Determinación del residuo de ignición <270>
No más de 0,1 %.

En la monografía se listan un total de 11 pruebas de Pureza

- **Punto de Fusión**
- **Limites de impureza comunes** (agua, cloruro, sulfato, sulfuro, metales pesados ,sustancias fácilmente carbonizables (determina impurezas orgánicas), impurezas orgánicas volátiles y residuo de ignición (determina impurezas inorgánicas))
- **Limites de impurezas especificas al principio activo** (p-aminofenol libre y p-cloroacetanilida)

Comparación de color: cuando se indique una *comparación visual de color o de turbidez*, deberán emplearse tubos de comparación de fondo plano (tubos de Nessler) cuyas medidas internas se correspondan lo más estrechamente posible. Para la comparación del color, los tubos en posición vertical deberán ser observados longitudinalmente a lo largo del tubo con una fuente de luz difusa sobre un fondo blanco, mientras que para la comparación de turbidez deberán ser observados transversalmente, colocados sobre un fondo oscuro, con ayuda de una fuente luminosa que los ilumine lateralmente.

VALORACIÓN

Preparación muestra - Pesar exactamente alrededor de 120 mg de Paracetamol, transferir a un matraz aforado de 500 ml, disolver con 10 ml de metanol, completar a volumen con agua y mezclar. Transferir 5,0 ml de esta solución a un matraz aforado de 100 ml, completar a volumen con agua y mezclar.

Preparación estándar - Emplear una solución de Paracetamol SR-FA de aproximadamente 12 µg por ml, preparada según se indica en *Preparación muestra*.

Procedimiento - Determinar las absorbancias de la *Preparación muestra* y la *Preparación estándar* en celdas de 1 cm, a la longitud de onda de máxima absorción, aproximadamente 244 nm, con un espectrofotómetro, empleando agua como blanco. Calcular la cantidad de $C_8H_9NO_2$ en la porción de Paracetamol en ensayo.

Se emplea una valoración mediante espectrofotometría ultravioleta

Ensayos y valoraciones

Los ensayos y las valoraciones descriptas en esta Farmacopea constituyen los métodos oficiales de análisis. Se podrán emplear ensayos alternativos, previamente validados (ver *1130. Validación de métodos analíticos*), si éstos demuestran otorgar ventajas desde el punto de vista de la exactitud, precisión, sensibilidad, selectividad o simplifican el procedimiento sin modificar los atributos anteriores. Sin embargo, en caso de indecisión o litigio, los ensayos descriptos en esta Farmacopea serán los definitivos. La concentración de impurezas establecida en ciertos ensayos se expresa entre paréntesis como porcentaje o partes por millón (ppm). En el caso que corresponda, el cumplimiento de este ensayo será necesario para establecer la conformidad de un producto.

Los materiales volumétricos, pesas y balanzas deberán ajustarse a las especificaciones establecidas en los capítulos *<620>. Materiales volumétricos* y *<690>. Pesas y balanzas.*

Procedimientos

En todos los ensayos descriptos en esta Farmacopea, se deberá cumplir estrictamente con las Buenas Prácticas de Laboratorio (BPL).

La utilización de las siguientes expresiones se refieren a:

Blanco: cuando se indique que se deben hacer las correcciones necesarias por medio de una determinación con un control, tal determinación se hará empleando las mismas cantidades de los reactivos tratados de igual manera que la solución o mezcla que contiene la sustancia bajo valoración o ensayo, pero omitiendo dicha sustancia.

EJERCITACIÓN FARMACOPEAS

Farmacopea es el texto oficial que codifica los principios activos, excipientes y productos farmacéuticos y contiene las especificaciones que éstos deben cumplir para demostrar su calidad y resguardar la salud de la población.

Proceder a la lectura del TP1 de la guía previamente. Adjunto encontraran las monografías de Hidrocortisona de cada farmacopea para realizar la ejercitación.

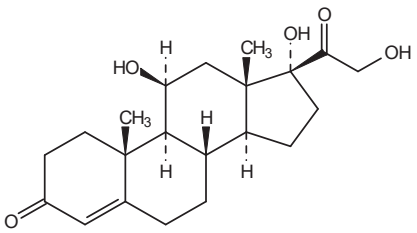
Tabla a completar:

FARMACOPEA	Farmacopea Argentina	Farmacopea Brasilera	USP 30- NF 25	Farmacopea Europea	Farmacopea Británica
a) INFORMACION ADICIONAL					
b) PRUEBAS DE IDENTIFICACIÓN					
c) PRUEBAS DE PUREZA					
d) ENSAYO DE VALORACIÓN					

Aclaraciones:

a) Opciones: Conservación, caracteres generales, acción farmacológica o clase terapéutica, PM, n° CAS (número que identifica un principio activo y es específico para cada fármaco).
b) Nombrar las pruebas. Ejemplo: espectroscopia Infrarroja, prueba de desarrollo de color, etc.
c) Nombrar las pruebas. Ejemplo: perdida por secado, residuo de ignición, límite de cloruro, etc.
d) Tipo de ensayo de valoración empleado. Ejemplo: Volumetría acido-base, Cromatografía liquida, etc.

HIDROCORTISONA



$C_{21}H_{30}O_5$ PM: 362,5 *50-23-7*

Definición - Hidrocortisona es (11*β*)11,17,21-Trihidroxi-pregn-4-eno-3,20-diona. Debe contener no menos de 97,0 por ciento y no más de 102,0 por ciento de $C_{21}H_{30}O_5$, calculado sobre la sustancia seca y debe cumplir con las siguientes especificaciones.

Caracteres generales - Polvo cristalino blanco o casi blanco. Inodoro. Funde aproximadamente a 215 ºC, con descomposición. Moderadamente soluble en acetona y alcohol; poco soluble en cloroformo; muy poco soluble en agua y éter.

Presenta polimorfismo.

Sustancias de referencia - Hidrocortisona SR-FA. Prednisolona SR-FA

CONSERVACIÓN

En envases bien cerrados.

ENSAYOS

Identificación

A - Absorción infrarroja <460>. *En suspensión*.

B - Absorción ultravioleta <470>

Solvente: metanol.

Concentración: 10 µg por ml.

Las absortividades a 242 nm, calculadas sobre la sustancia seca, no deben diferir en más de 2,5 %.

Determinación de rotación óptica <170>

Rotación específica: Entre + 150º y + 156º.

Solución muestra: 10 mg por ml, en dioxano.

Determinación del residuo de ignición <270>

Inapreciable, determinado sobre 100 mg.

Pureza cromatográfica

Sistema cromatográfico y *Fase móvil* - Proceder según se indica en *Valoración.*

Solución muestra - Pesar exactamente alrededor de 25 mg de Hidrocortisona, transferir a un matraz aforado de 10 ml y disolver en 2 ml de tetrahidrofurano. Completar a volumen con agua para obtener una solución de aproximadamente 2,5 mg por ml y homogeneizar.

Solución estándar - Diluir 1 ml de *Solución muestra* a 100 ml con *Fase móvil*.

Solución de resolución - Disolver cantidades exactamente pesadas de Hidrocortisona SR-FA y Prednisolona SR-FA en *Fase móvil* para obtener una solución de aproximadamente 20 µg de cada una por ml.

Aptitud del sistema (ver *100. Cromatografía*) - Cromatografiar la *Solución de resolución* y registrar las respuestas de los picos según se indica en *Procedimiento*: los tiempos de retención relativos deben ser aproximadamente 1,0 para prednisolona y 1,5 para hidrocortisona; la resolución *R* entre los picos de hidrocortisona y del estándar interno no debe ser menor de 2,2.

Procedimiento - Inyectar por separado en el cromatógrafo volúmenes iguales (aproximadamente 20 µl) de la *Solución estándar*, la *Solución muestra*, la *Solución de resolución* y *Fase móvil* como blanco, registrar los cromatogramas y medir las respuestas de todos los picos. Cromatografiar la *Solución muestra* durante aproximadamente cuatro veces el tiempo de retención del pico principal. A excepción del pico principal en el cromatograma obtenido a partir de la *Solución muestra*, la respuesta de ningún pico debe ser mayor que la mitad del pico principal obtenido con la *Solución estándar* (0,5 %) y la suma de las respuestas de todos los picos, a excepción del pico principal, no debe ser mayor que 1,5 veces la respuesta del pico principal obtenido con la *Solución estándar* (1,5 %). Ignorar la respuesta de cualquier pico en el cromatograma obtenido a partir del blanco y cualquier pico con una respuesta menor de 0,05 veces la respuesta del pico principal obtenido con la *Solución estándar.*

Pérdida por secado <680>

Secar a 105 °C durante 3 horas: no debe perder más de 1,0 % de su peso.

Impurezas orgánicas volátiles <520>

Método II.

VALORACIÓN

Sistema cromatográfico - Emplear un equipo para cromatografía de líquidos con un detector ultravioleta ajustado a 254 nm y una columna de 25 cm × 4,6 mm con fase estacionaria constituida por partículas de octadecilsilano totalmente ligada, de 5 µm de diámetro. Mantener la columna aproximadamente a 45 °C. El caudal debe ser aproximadamente 1,0 ml por minuto.

Fase móvil - Transferir 220 ml de tetrahidrofurano a un matraz de 1 litro, agregar 700 ml de agua, mezclar y dejar equilibrar. Completar a volumen

con agua y mezclar nuevamente. Filtrar y desgasificar. Hacer los ajustes necesarios (ver *Aptitud del sistema* en *100. Cromatografía*).

Preparación estándar - Disolver una cantidad exactamente pesada de Hidrocortisona SR-FA en metanol para obtener una solución de aproximadamente 0,1 mg por ml.

Preparación muestra - Disolver una cantidad exactamente pesada de Hidrocortisona en metanol para obtener una solución de aproximadamente 0,1 mg por ml.

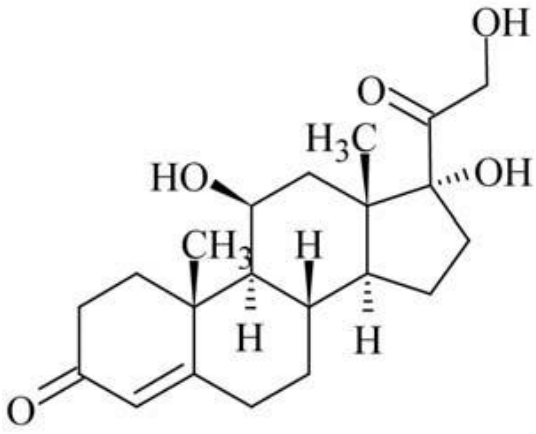
Solución de resolución - Disolver cantidades exactamente pesadas de Hidrocortisona SR-FA y Prednisolona SR-FA en metanol para obtener una solución de aproximadamente 20 µg de cada una por ml.

Aptitud del sistema (ver *100. Cromatografía*) - Cromatografiar la *Solución de resolución* y registrar las respuestas de los picos según se indica en *Procedimiento*: la resolución *R* entre los picos de hidrocortisona y prednisolona no debe ser menor de 2,2; la desviación estándar relativa para inyecciones repetidas no debe ser mayor de 2,0 %.

Procedimiento - Inyectar por separado en el cromatógrafo volúmenes iguales de la *Preparación estándar* y la *Preparación muestra*, registrar los cromatogramas y medir las respuestas de los picos principales. Calcular la cantidad en mg de $C_{21}H_{30}O_5$ en la porción de Hidrocortisona en ensayo.

HIDROCORTISONA

Hydrocortisonum



$C_{21}H_{30}O_5$; 362,47
hidrocortisona; 04664
(11β)-11,17,21-Tri-hidroxipregn-4-eno-3,20-diona
[*50-23-7*]

Contém, no mínimo, 97,0% e, no máximo, 102,0% de $C_{21}H_{30}O_5$, em relação à substância dessecada.

DESCRIÇÃO

Características físicas. Pó cristalino branco ou quase branco.

Constantes físico-químicas.

Faixa de fusão **(5.2.2)**: 214 °C a 215 °C, com decomposição.

Rotação óptica **(5.2.8)**: +150° a +156°, em relação à substância dessecada. Determinar em solução a 1% (p/v) em dioxano.

IDENTIFICAÇÃO

A. No espectro de absorção no infravermelho **(5.2.14)** da amostra dessecada, dispersa em brometo de potássio, há máximos de absorção somente nos mesmos comprimentos de onda e com as mesmas intensidades relativas daqueles observados no espectro de hidrocortisona SQR, preparado de maneira idêntica.

B. No espectro de absorção no ultravioleta **(5.2.14)**, na faixa de 200 nm a 400 nm, de uma solução a 0,0002% (p/v) em álcool etílico, há máximos idênticos aos observados no espectro da solução preparada de maneira similar de hidrocortisona SQR.

ENSAIOS DE PUREZA

Substâncias relacionadas. Proceder conforme descrito em *Cromatografia em camada delgada* **(5.2.17.1)**, utilizando sílica-gel G 60, como suporte, e mistura de clorofórmio e álcool etílico (85:15), como fase móvel. Aplicar, separadamente, à placa, 10 µL de cada uma das soluções descritas a seguir:

Solução (1): dissolver cerca de 20 mg da amostra em 10 mL de mistura de clorofórmio-álcool metílico (9:1).

Solução (2): pipetar 1 mL da *Solução (1)* para um balão volumétrico de 50 mL e completar o volume com mistura de clorofórmio e álcool metílico (9:1).

Desenvolver o cromatograma. Remover a placa, deixar secar ao ar e examinar a placa sob luz ultravioleta (254 nm). Nenhuma mancha secundária obtida com a *Solução (1)* é mais intensa que a mancha principal obtida com a *Solução (2)* (2,0%).

Perda por dessecação (5.2.9.1). Determinar em 1 g de amostra. Dessecar em estufa a 105 °C, por três horas. No máximo, 1,0%.

Resíduo por incineração (5.2.10). Determinar em 100 mg de amostra. No máximo, 0,1%.

TESTES DE SEGURANÇA BIOLÓGICA

Contagem do número total de micro-organismos mesofílicos (5.5.3.1.2). Cumpre o teste.

Pesquisa de micro-organismos patogênicos (5.5.3.1.3). Cumpre o teste.

DOSEAMENTO

A. Proceder conforme descrito em *Espectrofotometria de absorção no ultravioleta* **(5.2.14)**. Transferir, quantitativamente, 20 mg de amostra para um balão volumétrico de 100 mL, completar o volume com álcool etílico e agitar. Transferir 5 mL dessa solução para um balão volumétrico de 100 mL e completar o volume com álcool etílico. Preparar solução de hidrocortisona SQR na mesma concentração, utilizando os mesmos solventes. Medir as absorvâncias das soluções resultantes em 242 nm, utilizando álcool etílico para ajuste do zero. Calcular a quantidade de $C_{21}H_{30}O_5$ a partir das leituras obtidas.

B. Proceder conforme descrito em *Cromatografia a líquido de alta eficiência* **(5.2.17.4)**. Utilizar cromatógrafo provido de detector ultravioleta a 254 nm; coluna de 150 mm de comprimido e 4,6 mm de diâmetro interno, empacotada com sílica quimicamente ligada a grupo octadecilsilano (5 µm) e fluxo da *Fase móvel* de 1,0 mL/minuto.

Fase móvel: mistura de água, acetonitrila e álcool metílico (50:25:25).

Diluente: mistura de álcool metílico e água (1;1).

Solução padrão interno: preparar solução de propilparabeno a 1 mg/mL em álcool metílico.

Solução amostra: pesar, com exatidão, cerca de 50 mg de amostra e transferir para balão volumétrico de 50 mL. Dissolver e diluir com álcool metílico até completar o volume e homogeneizar. Transferir 2,0 mL dessa solução e 2,0 mL de *Solução padrão interno* para um balão volumétrico de 50 mL. Completar o volume com *Diluente* e homogeneizar.

Solução padrão: pesar, com exatidão, cerca de 25 mg hidrocortisona SQR e transferir para balão volumétrico de 25 mL. Dissolver em álcool metílico, completar o volume e homogeneizar de modo a obter uma solução com concentração aproximada de 1 mg/mL. transferir 2,0 mL dessa solução e 2,0 mL de S*olução padrão interno* para balão volumétrico de 50 mL. Completar o volume com *Diluente* e homogeneizar.

Injetar replicatas de 10 µL da *Solução padrão*. A eficiência da coluna é, no mínimo, 3000 pratos teóricos para hidrocortisona. Os tempos de retenção relativos são cerca de 1,0 para hidrocortisona e 1,8 para propilparabeno . O fator de cauda é, no máximo, 1,2. A resolução entre propilparabeno e hidrocortisona é, no mínimo, 9,0. O desvio padrão relativo das áreas de replicatas sob os picos registrados é, no máximo, 2,0%.

Procedimento: injetar, separadamente, 10 µL da *Solução padrão* e da *Solução amostra*, registrar os cromatogramas e medir as áreas sob os picos correspondentes à hidrocortisona e ao propilparabeno. Calcular a quantidade de $C_{21}H_{30}O_5$ a partir das respostas obtidas para a relação hidrocortisona/propilparabeno com a *Solução padrão* e a *Solução amostra*.

EMBALAGEM E ARMAZENAMENTO

Em recipientes bem fechados, protegidos da luz.

ROTULAGEM

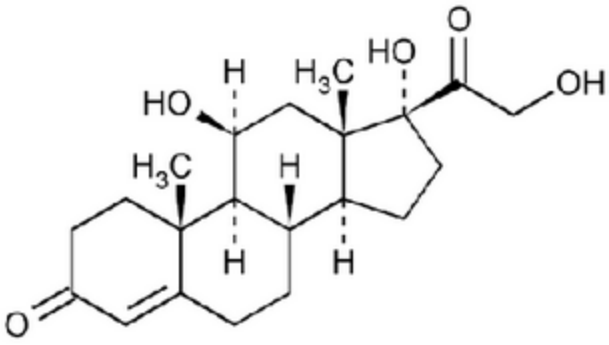
Observar a legislação vigente.

CLASSE TERAPÊUTICA

Anti-inflamatório.

Hydrocortisone

Hydrocortisone



$C_{21}H_{30}O_5$ -----362.46

Pregn-4-ene-3,20-dione, 11,17,21-trihydroxy-, (11β)-.
Cortisol ---[*50-23-7*].

» Hydrocortisone contains not less than 97.0 percent and not more than 102.0 percent of $C_{21}H_{30}O_5$, calculated on the dried basis.

Packaging and storage— Preserve in well-closed containers. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩ **—**
USP Hydrocortisone RS.

Identification—

A: *Infrared Absorption* ⟨197M⟩.

B: *Ultraviolet Absorption* ⟨197U⟩ —

Solution: 10 µg per mL.

Medium: methanol.

Absorptivities at 242 nm, calculated on the dried basis, do not differ by more than 2.5%.

Specific rotation ⟨781S⟩ **:** between +150° and +156°.

Test solution: 10 mg per mL, in dioxane.

Loss on drying ⟨731⟩ **—** Dry it at 105° for 3 hours: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩ **:** negligible, from 100 mg.

Chromatographic purity—

Mobile phase— Prepare a filtered and degassed mixture of butyl chloride, tetrahydrofuran, methanol, glacial acetic acid, and water (890:56:28:24:0.4), and sonicate to dissolve. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluting solution— Prepare a solution of butyl chloride, tetrahydrofuran, methanol, and glacial acetic acid (81.5:10:8:0.5).

Standard solution— Prepare a solution in *Diluting solution* containing 40 µg of *USP Hydrocortisone RS* per mL. Sonicate for about 5 minutes.

Test solution— Transfer 20 mg of Hydrocortisone to a 10-mL volumetric flask, dissolve in *Diluting solution,* add *Diluting solution* to volume to obtain a solution having a known concentration of about 2.0 mg per mL, and sonicate for about 5 minutes.

Chromatographic system (see *Chromatography* ⟨621⟩)— The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 3-µm packing L3. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 5%.

Procedure— Separately inject equal volumes (about 5 µL) of the *Standard solution,* the *Diluting solution,* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all the peaks, ignoring artifact peaks. Calculate the percentage of impurities in the portion of Hydrocortisone taken by the formula:

$$1000(C/W)(r_i / r_s)$$

in which C is the concentration, in mg per mL, of *USP Hydrocortisone RS* in the *Standard solution;* W is the weight, in mg, of Hydrocortisone taken; r_i is the response of each individual impurity peak in the *Test solution;* and r_s is the response of the major peak obtained from the *Standard solution:* not more than 0.5% of any individual impurity and not more than 2.0% of total impurities is found.

Organic volatile impurities, *Method IV* ⟨467⟩ **:** meets the requirements.

(Official until July 1, 2007)

Assay—

Mobile phase— Prepare a filtered and degassed mixture of water, acetonitrile, and methanol (50:25:25). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent— Prepare a mixture of methanol and water (1:1).

Internal standard solution— Prepare a solution of propylparaben in methanol having a

concentration of about 1 mg per mL.

Standard stock solution— Dissolve an accurately weighed quantity of *USP Hydrocortisone RS* in methanol to obtain a solution having a known concentration of about 1 mg per mL.

Standard preparation— Transfer 2.0 mL of *Standard stock solution* and 2.0 mL of *Internal standard solution* to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Assay preparation— Transfer about 50 mg of Hydrocortisone, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix. Transfer 2.0 mL of this solution and 2.0 mL of *Internal standard solution* to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)— The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.8 for propylparaben and 1.0 for hydrocortisone; the resolution, *R,* between the hydrocortisone and propylparaben peaks is not less than 9.0; the column efficiency is not less than 3000 theoretical plates for hydrocortisone; the tailing factor is not more than 1.2; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure— Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{21}H_{30}O_5$ in the portion of Hydrocortisone taken by the formula:

$$1250C(R_U / R_S)$$

in which *C* is the concentration, in mg per mL, of *USP Hydrocortisone RS* in the *Standard preparation;* and R_U and R_S are the ratios of the peak response of hydrocortisone to that of propylparaben obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Auxiliary Information— *Staff Liaison* : Daniel K. Bempong, Ph.D., Senior Scientist

Expert Committee : (MDPS05) Monograph Development-Pulmonary and Steroids

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and *methanol R*, using sonication if necessary, and dilute to 100.0 ml with *phosphate buffer solution pH 3.2 R1*. Dilute 5.0 ml to 100.0 ml with the solvent solution.

Reference solution (b). Dilute 1.0 ml of the test solution to 50.0 ml with the solvent solution. Dilute 5.0 ml of this solution to 20.0 ml with the solvent solution.

The chromatographic procedure may be carried out using:

– a stainless steel column 0.1 m long and 4.6 mm in internal diameter packed with *octadecylsilyl silica gel for chromatography R* (3 µm),

– as mobile phase at a flow rate of 0.8 ml/min:

Mobile phase A. To 940 ml of *phosphate buffer solution pH 3.2 R1* add 60.0 ml of *methanol R* and 10.0 ml of *tetrahydrofuran R* and mix,

Mobile phase B. To a mixture of 500 ml of *methanol R* and 500 ml of *phosphate buffer solution pH 3.2 R1* add 50.0 ml of *tetrahydrofuran R* and mix,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Comment
0 - 17	100 → 55	0 → 45	linear gradient
17 - 30	55	45	isocratic
30 - 35	55 → 100	45 → 0	linear gradient
35 - 50	100	0	isocratic
50 = 0	100	0	return to initial eluent composition

– as detector a spectrophotometer set at 224 nm.

Equilibrate the column for at least 20 min with mobile phase A. Adjust the sensitivity of the system so that the height of the principal peak in the chromatogram obtained with 10 µl of reference solution (b) is at least 50 per cent of the full scale of the recorder.

Inject 10 µl of reference solution (a). When the chromatogram is recorded in the prescribed conditions, the retention times are: chlorothiazide about 7 min and hydrochlorothiazide about 8 min. The test is not valid unless the resolution between the peaks corresponding to chlorothiazide and hydrochlorothiazide is at least 2.5. If necessary, adjust slightly the composition of the mobile phase or the time programme of the linear gradient.

Inject separately 10 µl of the solvent solution as a blank, 10 µl of the test solution and 10 µl of reference solution (b). In the chromatogram obtained with the test solution: the area of any peak, apart from the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent); the sum of the areas of all peaks, apart from the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent). Disregard any peak due to the solvent solution and any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b).

Chlorides (*2.4.4*). Dissolve 1.0 g in 25 ml of *acetone R* and dilute to 30 ml with *water R*. 15 ml complies with the limit test for chlorides (100 ppm). Prepare the standard using 5 ml of *acetone R* containing 15 per cent *V/V* of *water R* and 10 ml of *chloride standard solution (5 ppm Cl) R*.

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 100 °C to 105 °C.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

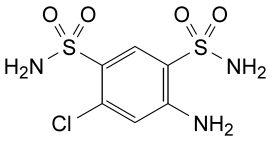
ASSAY

Dissolve 0.120 g in 50 ml of *dimethyl sulphoxide R*. Titrate with *0.1 M tetrabutylammonium hydroxide in 2-propanol*, determining the end-point potentiometrically (*2.2.20*) at the second point of inflexion. Carry out a blank titration.

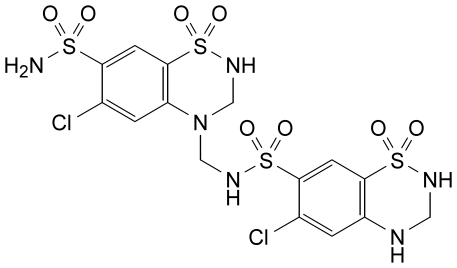
1 ml of *0.1 M tetrabutylammonium hydroxide in 2-propanol* is equivalent to 14.88 mg of $C_7H_8ClN_3O_4S_2$.

IMPURITIES

A. chlorothiazide,



B. 4-amino-6-chlorobenzene-1,3-disulphonamide (salamide),

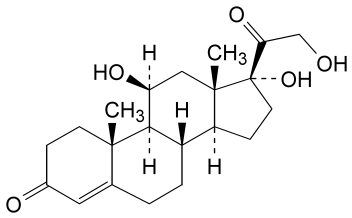


C. 6-chloro-*N*-[(6-chloro-7-sulphamoyl-2,3-dihydro-4*H*-1,2,4-benzothiadiazin-4-yl 1,1-dioxide)methyl]-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

01/2005:0335

HYDROCORTISONE

Hydrocortisonum



$C_{21}H_{30}O_5$ M_r 362.5

DEFINITION

Hydrocortisone contains not less than 97.0 per cent and not more than the equivalent of 103.0 per cent of 11β,17,21-trihydroxypregn-4-ene-3,20-dione, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, practically insoluble in water, sparingly soluble in acetone and in alcohol, slightly soluble in methylene chloride.

It shows polymorphism.

IDENTIFICATION

First identification: A, B.

Second identification: C, D.

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *hydrocortisone CRS*. If the spectra obtained in the solid state show differences, dissolve the substance to be

examined and the reference substance separately in the minimum volume of *acetone R*, evaporate to dryness on a water-bath and record new spectra using the residues.

B. Examine by thin-layer chromatography (*2.2.27*), using as the coating substance a suitable silica gel with a fluorescent indicator having an optimal intensity at 254 nm.

Test solution. Dissolve 10 mg of the substance to be examined in a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R* and dilute to 10 ml with the same mixture of solvents.

Reference solution (a). Dissolve 20 mg of *hydrocortisone CRS* in a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R* and dilute to 20 ml with the same mixture of solvents.

Reference solution (b). Dissolve 10 mg of *prednisolone CRS* in reference solution (a) and dilute to 10 ml with reference solution (a).

Apply to the plate 5 µl of each solution. Prepare the mobile phase by adding a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*. Develop over a path of 15 cm. Carry out a second development over a path of 15 cm using a mixture of 5 volumes of *butanol R* saturated with *water R*, 15 volumes of *toluene R* and 80 volumes of *ether R*. Allow the plate to dry in air. Examine in ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a). Spray with *alcoholic solution of sulphuric acid R*. Heat at 120 °C for 10 min or until the spots appear. Allow to cool. Examine the chromatograms in daylight and in ultraviolet light at 365 nm. The principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows two clearly separated spots.

C. Examine by thin-layer chromatography (*2.2.27*), using as the coating substance a suitable silica gel with a fluorescent indicator having an optimal intensity at 254 nm.

Test solution (a). Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 ml with the same solvent. This solution is also used to prepare test solution (b). Dilute 2 ml of the solution to 10 ml with *methylene chloride R*.

Test solution (b). Transfer 0.4 ml of the solution obtained during preparation of test solution (a) to a glass tube 100 mm long and 20 mm in diameter and fitted with a ground-glass stopper or a polytetrafluoroethylene cap and evaporate the solvent with gentle heating under a stream of *nitrogen R*. Add 2 ml of a 15 per cent *V/V* solution of *glacial acetic acid R* and 50 mg of *sodium bismuthate R*. Stopper the tube and shake the suspension for 1 h in a mechanical shaker, protected from light. Add 2 ml of a 15 per cent *V/V* solution of *glacial acetic acid R* and filter into a 50 ml separating funnel, washing the filter with two quantities, each of 5 ml, of *water R*. Shake the clear filtrate with 10 ml of *methylene chloride R*. Wash the organic layer with 5 ml of *1 M sodium hydroxide* and two quantities, each of 5 ml, of *water R*. Dry over *anhydrous sodium sulphate R*.

Reference solution (a). Dissolve 25 mg of *hydrocortisone CRS* in *methanol R* and dilute to 5 ml with the same solvent. This solution is also used to prepare reference solution (b). Dilute 2 ml of the solution to 10 ml with *methylene chloride R*.

Reference solution (b). Transfer 0.4 ml of the solution obtained during preparation of reference solution (a) to a glass tube 100 mm long and 20 mm in diameter and fitted with a ground-glass stopper or a polytetrafluoroethylene cap and evaporate the solvent with gentle heating under a stream of *nitrogen R*. Add 2 ml of a 15 per cent *V/V* solution of *glacial acetic acid R* and 50 mg of *sodium bismuthate R*. Stopper the tube and shake the suspension for 1 h in a mechanical shaker protected from light. Add 2 ml of a 15 per cent *V/V* solution of *glacial acetic acid R* and filter into a 50 ml separating funnel, washing the filter with two quantities, each of 5 ml, of *water R*. Shake the clear filtrate with 10 ml of *methylene chloride R*. Wash the organic layer with 5 ml of *1 M sodium hydroxide* and two quantities, each of 5 ml, of *water R*. Dry over *anhydrous sodium sulphate R*.

Apply to the plate 5 µl of test solution (a), 5 µl of reference solution (a), 25 µl of test solution (b) and 25 µl of reference solution (b), applying the latter two in small quantities to obtain small spots. Prepare the mobile phase by adding a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*. Develop over a path of 15 cm. Carry out a second development over a path of 15 cm using a mixture of 5 volumes of *butanol R* saturated with *water R*, 15 volumes of *toluene R* and 80 volumes of *ether R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. The principal spot in each of the chromatograms obtained with the test solutions is similar in position and size to the principal spot in the chromatogram obtained with the corresponding reference solution. Spray with *alcoholic solution of sulphuric acid R* and heat at 120 °C for 10 min or until the spots appear. Allow to cool. Examine the plate in daylight and in ultraviolet light at 365 nm. The principal spot in each of the chromatograms obtained with the test solutions is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with the corresponding reference solution. The principal spots in the chromatograms obtained with test solution (b) and reference solution (b) have an R_f value distinctly higher than that of the principal spots in the chromatograms obtained with test solution (a) and reference solution (a).

D. Add about 2 mg to 2 ml of *sulphuric acid R* and shake to dissolve. Within 5 min, an intense brownish-red colour develops with a green fluorescence which is particularly intense when examined in ultraviolet light at 365 nm. Add the solution to 10 ml of *water R* and mix. The colour fades and a clear solution remains. The fluorescence in ultraviolet light does not disappear.

TESTS

Specific optical rotation (*2.2.7*). Dissolve 0.250 g in *dioxan R* and dilute to 25.0 ml with the same solvent. The specific optical rotation is + 150 to + 156, calculated with reference to the dried substance.

Related substances. Examine by liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 25.0 mg of the substance to be examined in 2 ml of *tetrahydrofuran R* and dilute to 10.0 ml with *water R*.

Reference solution (a). Dissolve 2 mg of *hydrocortisone CRS* and 2 mg of *prednisolone CRS* in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with the mobile phase.

The chromatographic procedure may be carried out using:

– a stainless steel column 0.25 m long and 4.6 mm in internal diameter packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm),

– as mobile phase at a flow rate of 1 ml/min a mixture prepared as follows: in a 1000 ml volumetric flask mix 220 ml of *tetrahydrofuran R* with 700 ml of *water R* and allow to equilibrate; dilute to 1000 ml with *water R* and mix again,

– as detector a spectrophotometer set at 254 nm,

maintaining the temperature of the column at 45 °C.

Equilibrate the column with the mobile phase at a flow rate of 1 ml/min for about 30 min.

Adjust the sensitivity of the system so that the height of the principal peak in the chromatogram obtained with 20 µl of reference solution (b) is at least 50 per cent of the full scale of the recorder.

Inject 20 µl of reference solution (a). When the chromatograms are recorded in the prescribed conditions, the retention times are: prednisolone about 14 min and hydrocortisone about 15.5 min. The test is not valid unless the resolution between the peaks due to prednisolone and hydrocortisone is at least 2.2. If necessary, adjust the concentration of *tetrahydrofuran R* in the mobile phase.

Inject separately 20 µl of the solvent mixture of the test solution as a blank, 20 µl of the test solution and 20 µl of reference solution (b). Continue the chromatography of the test solution for four times the retention time of the principal peak. In the chromatogram obtained with the test solution: the area of any peak, apart from the principal peak, is not greater than half the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent): the sum of the areas of all the peaks, apart from the principal peak, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent). Disregard any peak obtained with the blank run and any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b).

Loss on drying (*2.2.32*). Not more than 1.0 per cent, determined on 0.500 g by drying in an oven at 100 °C to 105 °C.

ASSAY

Dissolve 0.100 g in *alcohol R* and dilute to 100.0 ml with the same solvent. Dilute 2.0 ml of the solution to 100.0 ml with *alcohol R*. Measure the absorbance (*2.2.25*) at the maximum at 241.5 nm.

Calculate the content of $C_{21}H_{30}O_5$ taking the specific absorbance to be 440.

STORAGE

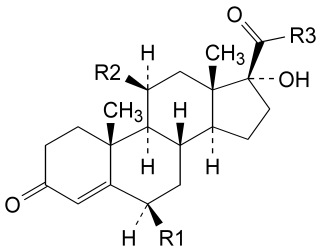
Store protected from light.

IMPURITIES

A. prednisolone,

B. cortisone,

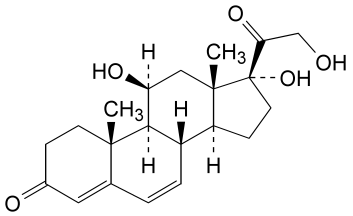
C. hydrocortisone acetate,



D. R1 = R2 = OH, R3 = CH_2OH: 6β,11β,17,21-tetrahydroxypregn-4-ene-3,20-dione (6β-hydroxyhydrocortisone),

F. R1 = R2 = H, R3 = CH_2OH: 17,21-dihydroxypregn-4-ene-3,20-dione (Reichstein's substance),

G. R1 = H, R2 = OH, R3 = CHO: 11β,17-dihydroxy-3,20-dioxopregn-4-en-21-al,

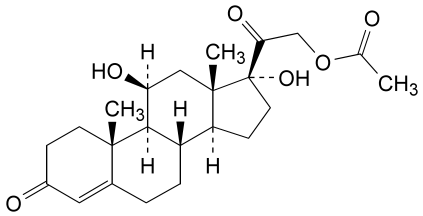


E. 11β,17,21-trihydroxypregna-4,6-diene-3,20-dione (Δ6-hydrocortisone).

01/2005:0334

HYDROCORTISONE ACETATE

Hydrocortisoni acetas



$C_{23}H_{32}O_6$ M_r 404.5

DEFINITION

Hydrocortisone acetate contains not less than 97.0 per cent and not more than the equivalent of 103.0 per cent of 11β,17-dihydroxy-3,20-dioxopregn-4-en-21-yl acetate, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, practically insoluble in water, slightly soluble in ethanol and in methylene chloride.

It melts at about 220 °C, with decomposition.

IDENTIFICATION

First identification: A, B.

Second identification: C, D, E.

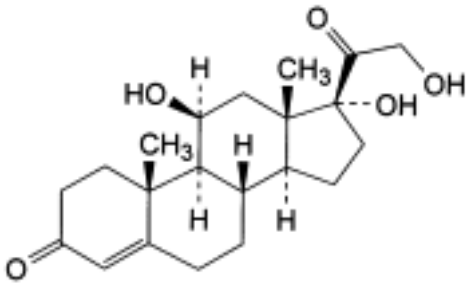
A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *hydrocortisone acetate CRS*.

B. Examine by thin-layer chromatography (*2.2.27*), using as the coating substance a suitable silica gel with a fluorescent indicator having an optimal intensity at 254 nm.

Hydrocortisone

General Notices

(Ph Eur monograph 0335)



$C_{21}H_{30}O_5$ 362.5 *50-23-7*

Action and use

Corticosteroid.

Preparations

Hydrocortisone Cream

Hydrocortisone and Clioquinol Cream

Hydrocortisone and Neomycin Cream

Hydrocortisone Ointment

Hydrocortisone and Clioquinol Ointment

Ph Eur

DEFINITION

Hydrocortisone contains not less than 97.0 per cent and not more than the equivalent of 103.0 per cent of 11β,17,21-trihydroxypregn-4-ene-3,20-dione, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, practically insoluble in water, sparingly soluble in acetone and in alcohol, slightly soluble in methylene chloride.

It shows polymorphism.

IDENTIFICATION

First identification A, B.

Second identification C, D.

A. Examine by infrared absorption spectrophotometry *(2.2.24)*, comparing with the spectrum obtained with *hydrocortisone CRS*. If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *acetone R*, evaporate to dryness on a water-bath and record new spectra using the residues.

B. Examine by thin-layer chromatography *(2.2.27)*, using as the coating substance a suitable silica gel with a fluorescent indicator having an optimal intensity at 254 nm.

Test solution Dissolve 10 mg of the substance to be examined in a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R* and dilute to 10 ml with the same mixture of solvents.

Reference solution (a) Dissolve 20 mg of *hydrocortisone CRS* in a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R* and dilute to 20 ml with the same mixture of solvents.

Reference solution (b) Dissolve 10 mg of *prednisolone CRS* in reference solution (a) and dilute to 10 ml with reference solution (a).

Apply to the plate 5 µl of each solution. Prepare the mobile phase by adding a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*. Develop over a path of 15 cm. Carry out a second development over a path of 15 cm using a mixture of 5 volumes of *butanol R* saturated with *water R*, 15 volumes of *toluene R* and 80 volumes of *ether R*. Allow the plate to dry in air. Examine in ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a). Spray with *alcoholic solution of sulphuric acid R*. Heat at 120 °C for 10 min or until the spots appear. Allow to cool. Examine the chromatograms in daylight and in ultraviolet light at 365 nm. The principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows two clearly separated spots.

C. Examine by thin-layer chromatography *(2.2.27)*, using as the coating substance a suitable silica gel with a fluorescent indicator having an optimal intensity at 254 nm.

Test solution (a) Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 ml with the same solvent. This solution is also used to prepare test solution (b). Dilute 2 ml of the solution to 10 ml with *methylene chloride R*.

Test solution (b) Transfer 0.4 ml of the solution obtained during preparation of test solution (a) to a glass tube 100 mm long and 20 mm in diameter and fitted with a ground-glass stopper or a polytetrafluoroethylene cap and evaporate the solvent with gentle heating under a stream of *nitrogen R*. Add 2 ml of a 15 per cent *V/V* solution of *glacial acetic acid R* and 50 mg of *sodium bismuthate R*. Stopper the tube and shake the suspension for 1 h in a mechanical shaker, protected from light. Add 2 ml of a 15 per cent *V/V* solution of *glacial acetic acid R* and filter into a 50 ml separating funnel, washing the filter with two quantities, each of 5 ml, of *water R*. Shake the clear filtrate with 10 ml of *methylene chloride R*. Wash the organic layer with 5 ml of *1 M sodium hydroxide* and two quantities, each of 5 ml, of *water R*. Dry over *anhydrous sodium sulphate R*.

Reference solution (a) Dissolve 25 mg of *hydrocortisone CRS* in *methanol R* and dilute to 5 ml with the same solvent. This solution is also used to prepare reference solution (b). Dilute 2

ml of the solution to 10 ml with *methylene chloride R*.

Reference solution (b) Transfer 0.4 ml of the solution obtained during preparation of reference solution (a) to a glass tube 100 mm long and 20 mm in diameter and fitted with a ground-glass stopper or a polytetrafluoroethylene cap and evaporate the solvent with gentle heating under a stream of *nitrogen R*. Add 2 ml of a 15 per cent *V/V* solution of *glacial acetic acid R* and 50 mg of *sodium bismuthate R*. Stopper the tube and shake the suspension for 1 h in a mechanical shaker protected from light. Add 2 ml of a 15 per cent *V/V* solution of *glacial acetic acid R* and filter into a 50 ml separating funnel, washing the filter with two quantities, each of 5 ml, of *water R*. Shake the clear filtrate with 10 ml of *methylene chloride R*. Wash the organic layer with 5 ml of *1 M sodium hydroxide* and two quantities, each of 5 ml, of *water R*. Dry over *anhydrous sodium sulphate R*.

Apply to the plate 5 µl of test solution (a), 5 µl of reference solution (a), 25 µl of test solution (b) and 25 µl of reference solution (b), applying the latter two in small quantities to obtain small spots. Prepare the mobile phase by adding a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*. Develop over a path of 15 cm. Carry out a second development over a path of 15 cm using a mixture of 5 volumes of *butanol R* saturated with *water R*, 15 volumes of *toluene R* and 80 volumes of *ether R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. The principal spot in each of the chromatograms obtained with the test solutions is similar in position and size to the principal spot in the chromatogram obtained with the corresponding reference solution. Spray with *alcoholic solution of sulphuric acid R* and heat at 120 °C for 10 min or until the spots appear. Allow to cool. Examine the plate in daylight and in ultraviolet light at 365 nm. The principal spot in each of the chromatograms obtained with the test solutions is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with the corresponding reference solution. The principal spots in the chromatograms obtained with test solution (b) and reference solution (b) have an R_f value distinctly higher than that of the principal spots in the chromatograms obtained with test solution (a) and reference solution (a).

D. Add about 2 mg to 2 ml of *sulphuric acid R* and shake to dissolve. Within 5 min, an intense brownish-red colour develops with a green fluorescence which is particularly intense when examined in ultraviolet light at 365 nm. Add the solution to 10 ml of *water R* and mix. The colour fades and a clear solution remains. The fluorescence in ultraviolet light does not disappear.

TESTS

Specific optical rotation *(2.2.7)*

Dissolve 0.250 g in *dioxan R* and dilute to 25.0 ml with the same solvent. The specific optical rotation is + 150 to + 156, calculated with reference to the dried substance.

Related substances

Examine by liquid chromatography *(2.2.29)*. *Prepare the solutions immediately before use*.

Test solution Dissolve 25.0 mg of the substance to be examined in 2 ml of *tetrahydrofuran R* and dilute to 10.0 ml with *water R*.

Reference solution (a) Dissolve 2 mg of *hydrocortisone CRS* and 2 mg of *prednisolone CRS* in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution (b) Dilute 1.0 ml of the test solution to 100.0 ml with the mobile phase.

The chromatographic procedure may be carried out using:

—a stainless steel column 0.25 m long and 4.6 mm in internal diameter packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm),

—as mobile phase at a flow rate of 1 ml/min a mixture prepared as follows: in a 1000 ml volumetric flask mix 220 ml of *tetrahydrofuran R* with 700 ml of *water R* and allow to equilibrate; dilute to 1000 ml with *water R* and mix again,

—as detector a spectrophotometer set at 254 nm,

maintaining the temperature of the column at 45 °C.

Equilibrate the column with the mobile phase at a flow rate of 1 ml/min for about 30 min.

Adjust the sensitivity of the system so that the height of the principal peak in the chromatogram obtained with 20 µl of reference solution (b) is at least 50 per cent of the full scale of the recorder.

Inject 20 µl of reference solution (a). When the chromatograms are recorded in the prescribed conditions, the retention times are: prednisolone about 14 min and hydrocortisone about 15.5 min. The test is not valid unless the resolution between the peaks due to prednisolone and hydrocortisone is at least 2.2. If necessary, adjust the concentration of *tetrahydrofuran R* in the mobile phase.

Inject separately 20 µl of the solvent mixture of the test solution as a blank, 20 µl of the test solution and 20 µl of reference solution (b). Continue the chromatography of the test solution for four times the retention time of the principal peak. In the chromatogram obtained with the test solution: the area of any peak, apart from the principal peak, is not greater than half the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent): the sum of the areas of all the peaks, apart from the principal peak, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent). Disregard any peak obtained with the blank run and any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b).

Loss on drying *(2.2.32)*

Not more than 1.0 per cent, determined on 0.500 g by drying in an oven at 100 °C to 105 °C.

ASSAY

Dissolve 0.100 g in *alcohol R* and dilute to 100.0 ml with the same solvent. Dilute 2.0 ml of the solution to 100.0 ml with *alcohol R*. Measure the absorbance *(2.2.25)* at the maximum at 241.5 nm.

Calculate the content of $C_{21}H_{30}O_5$ taking the specific absorbance to be 440.

STORAGE

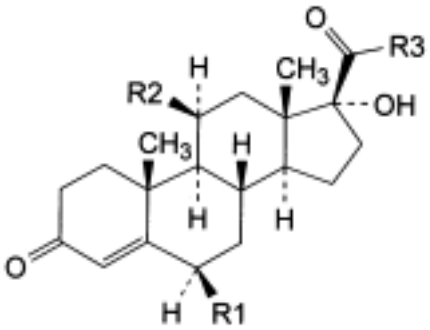
Store protected from light.

IMPURITIES

A. prednisolone,

B. cortisone,

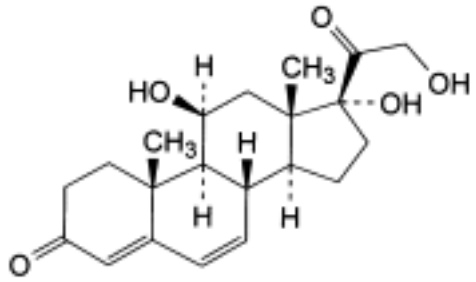
C. hydrocortisone acetate,



D. R1 = R2 = OH, R3 = CH_2OH: 6β,11β,17,21-tetrahydroxypregn-4-ene-3,20-dione (6β-hydroxyhydrocortisone),

F. R1 = R2 = H, R3 = CH_2OH: 17,21-dihydroxypregn-4-ene-3,20-dione (Reichstein's substance),

G. R1 = H, R2 = OH, R3 = CHO: 11β,17-dihydroxy-3,20-dioxopregn-4-en-21-al,



E. 11β,17,21-trihydroxypregna-4,6-diene-3,20-dione (Δ6-hydrocortisone).

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Ejercitación búsqueda de articulo científico

Elegir uno de los fármacos que se listan a continuación para completar la ejercitación de la guía (Punto 4 de la página 3 de la guía). Encontraran toda la información necesaria en el abstract del trabajo.

Lista de Fármacos:

- Codeína (en inglés, codeine). **Comisión 1**
- Paracetamol. **Comisión 2**
- Ranitidina (en inglés, ranitidine). **Comisión 3**
- Carbamazepina (en inglés, carbamazepine). **Comisión4**
- Pseudoefedrina (en inglés, pseudoephedrine). **Comisión 5**

Ejemplo:

Título: Determination of meloxicam in bulk and pharmaceutical formulations Autores: N.H Zawilla, M Abdul-Azim Mohammad, N.M El kousy, S.M El-Moghazy Aly

Nombre de la revista: Journal of Pharmaceutical and Biomedical Analysis

Información bibliográfica adicional: Vol 32; Año 2003; Páginas 1135-1144.

Método: Cromatográfico (CLAE) y espectroscópico (UV-Vis)

Matriz: principio activo puro y producto formulado

Finalidad: determinación del tenor del principio activo

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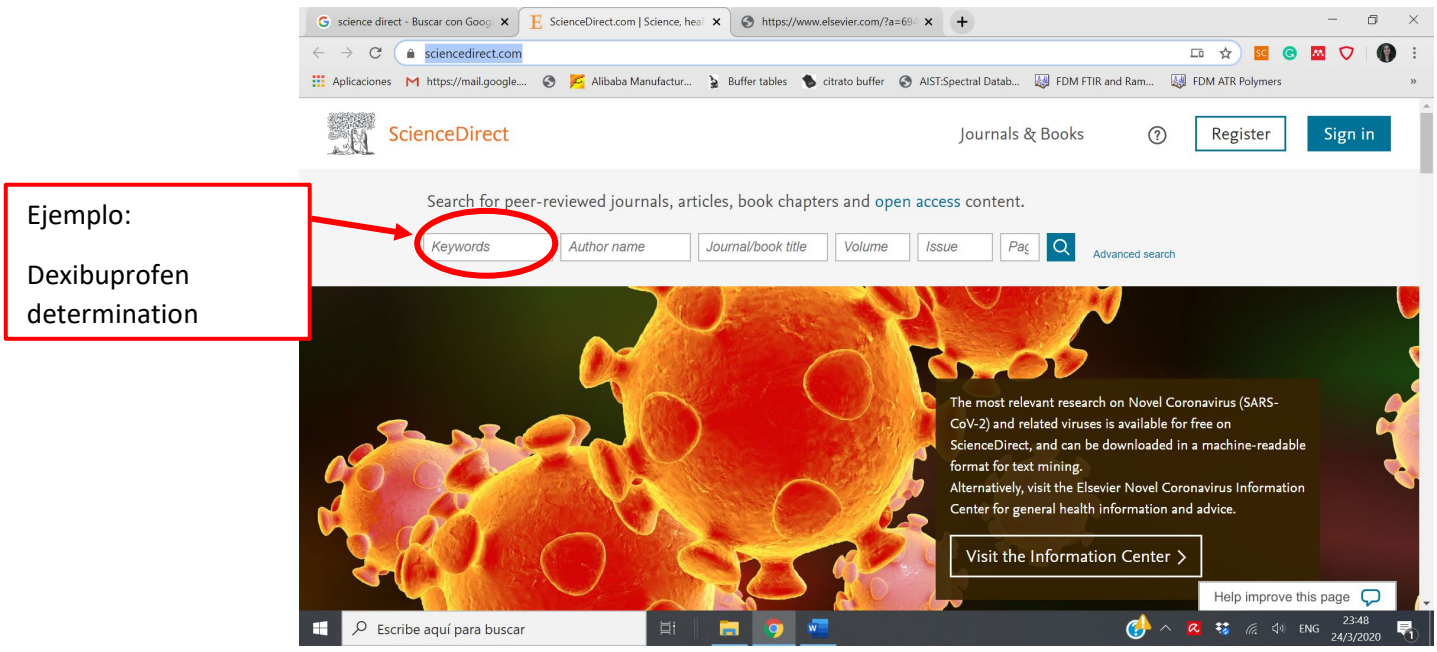

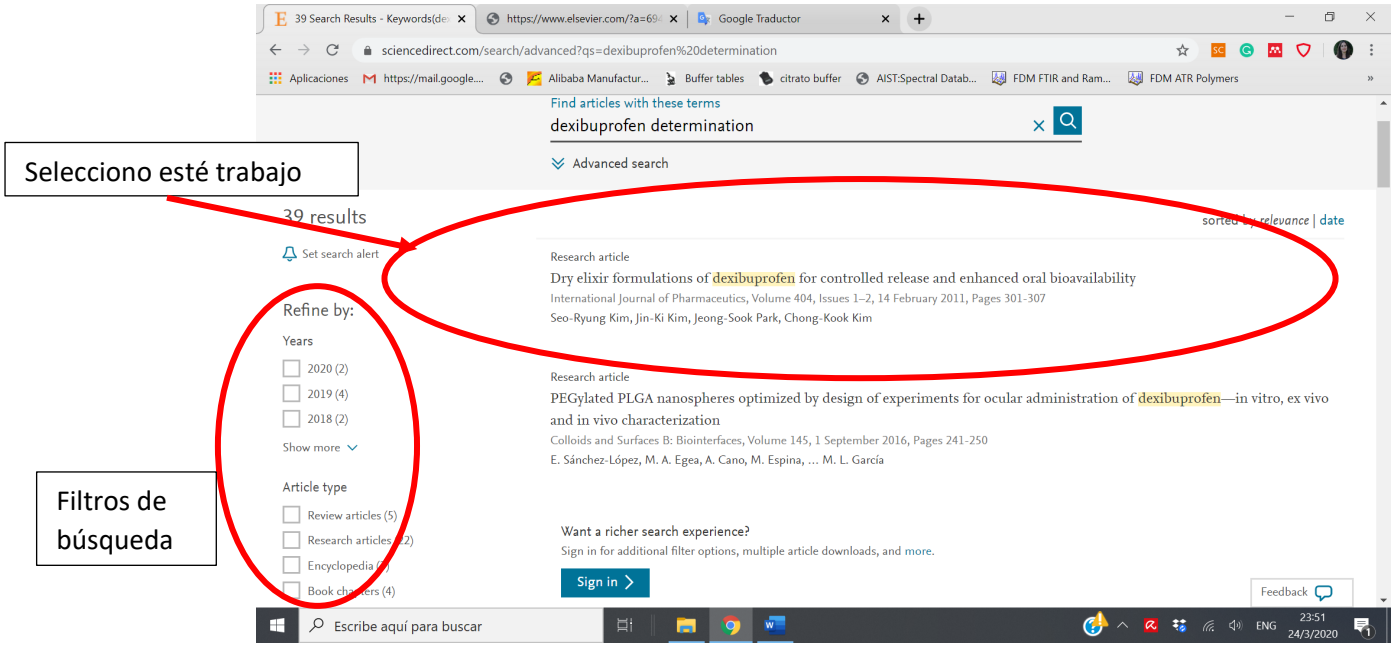
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International Journal of Pharmaceutics, Volume 404, Issues 1–2, 14 February 2011, Pages 301-307
Seo-Ryung Kim, Jin-Ki Kim, Jeong-Sook Park, Chong-Kook Kim
Research article
PEGylated PLGA nanospheres optimized by design of experiments for ocular administration of dexibuprofen—in vitro, ex vivo and in vivo characterization
Colloids and Surfaces B: Biointerfaces, Volume 145, 1 September 2016, Pages 241-250
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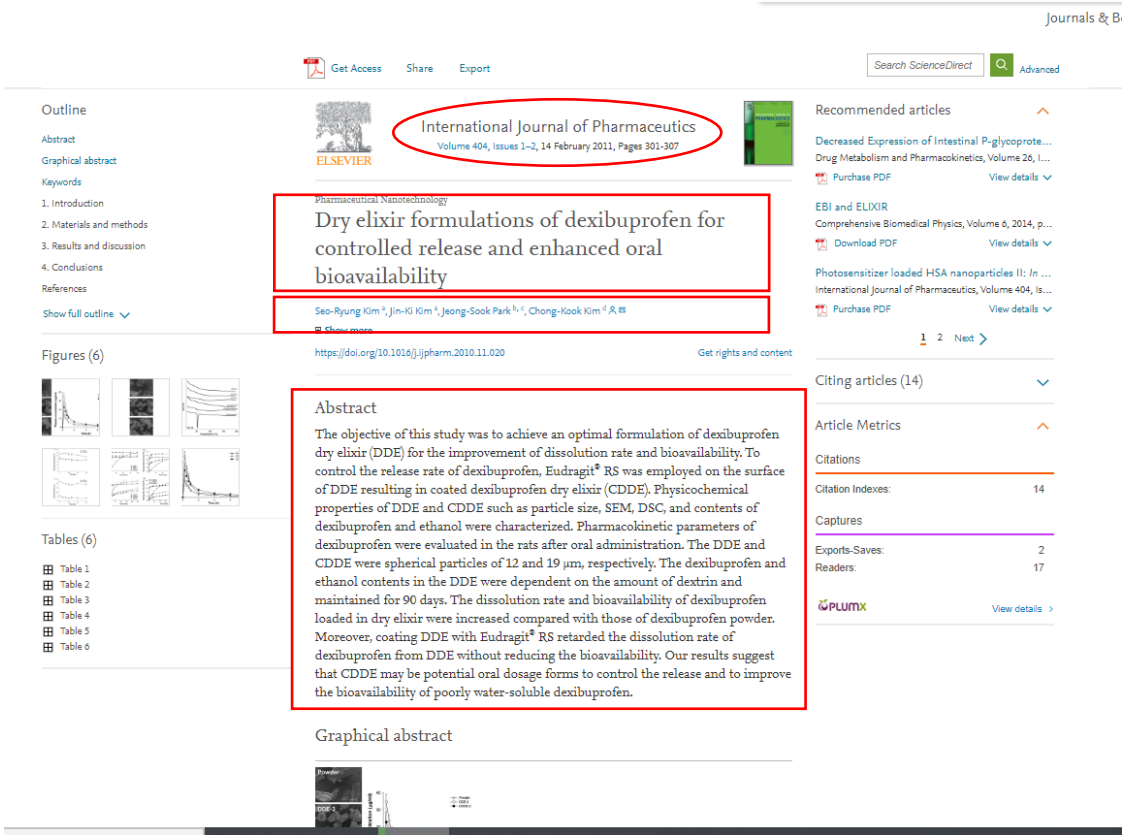
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International Journal of Pharmaceutics
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Pharmaceutical Nanotechnology
Dry elixir formulations of dexibuprofen for controlled release and enhanced oral bioavailability
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Abstract
The objective of this study was to achieve an optimal formulation of dexibuprofen dry elixir (DDE) for the improvement of dissolution rate and bioavailability. To control the release rate of dexibuprofen, Eudragit® RS was employed on the surface of DDE resulting in coated dexibuprofen dry elixir (CDDE). Physicochemical properties of DDE and CDDE such as particle size, SEM, DSC, and contents of dexibuprofen and ethanol were characterized. Pharmacokinetic parameters of dexibuprofen were evaluated in the rats after oral administration. The DDE and CDDE were spherical particles of 12 and 19 μm, respectively. The dexibuprofen and ethanol contents in the DDE were dependent on the amount of dextrin and maintained for 90 days. The dissolution rate and bioavailability of dexibuprofen loaded in dry elixir were increased compared with those of dexibuprofen powder. Moreover, coating DDE with Eudragit® RS retarded the dissolution rate of dexibuprofen from DDE without reducing the bioavailability. Our results suggest that CDDE may be potential oral dosage forms to control the release and to improve the bioavailability of poorly water-soluble dexibuprofen.
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