JOSE LLOREDA CAMACHO & CO.
ABOGADOS

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Seæor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO E. S. D.

SUPERtNTENDbNCtA Ob INDUSI RIA Y CQMERCO

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No. 02-091153-.00019-0000
- cl 20004 1 40 09 Dsp. 2020 NUECREACIONE
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HL1 00EOS 116

Re: P1.-JAGOTEC AG.-Solictud de Patente de Invención para "FORMULACIÔN DE DOSIFICACION EN MATRIZ POLIMERICA HIDROFfLICA/LIPOFfLICA".-Clase A61K 9/24.-Expediente nómero 02-091.153.-

1. Yo, ALICIA LLOREDA RIcAURTE, mayor, vedria de Østa ciudad, identificada con la cØdula de ciudadanIa nómero 39.690.713 de UsaquØn y la Tarjeta Profesional 53.215 del Consejo Superior de la Judicatura, Representante Legal en Bogota para todos los asuntos relativos a la Propiedad Industrial de la sociedad JAGOTEC AG, organizada y existente de conformidad con las [eyes de Suiza y domiciliada en Muttenz, Suiza, atentamente manifiesto a usted que interpongo Recurso de Reposición contra la Resolución ntmero 10129, por medio de la cual se niega la presente solicitud de patente, dictada por el seæor Superintendente de Industria y Comercio el 31 de Marzo de 2008 y notificada por Edicto ntmero 5672, fijado el 10 de AbnI de 2008 y desfijado el 23 de Abril del mismo aæo.

2. ACLARACIÔN PREVIA

En el considerando OCTAVO de la Resolución nümero 10129 que se impugna
se afirma equivocadamente que el capItulo reivindicatorio de la presente solicitud estÆcompuesto por 31 reivindicaciones.

Solicito al seæorSuperintendente de Industria y Comercio tener en cuenta que
el capItulo reivindicatorio que se debe tener en cuenta para el anÆlisis de patentabilidad de la presente invención se compone solo de 30 reivindicaciones y fue debidamente aportado como una modificación voluntaria el pasado 23 de Enero de 2008, en la cual se procedió a cancelar la reivindicación 22 original.

Para su pronta referenda me permito aportar como anexo (a copia de ml memorial de 23 de Enero de 2008, junto con sus anexos de formulario, recibo de pago de tasa, y copia de las pÆginas 71 a 77 que se incluyeron coma nuevo capItulo reivindicatorio. (Anexo a)

3. FUNDAMENTOS DEL REcuRso

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(a) Con base en el contenido de la Resolución nmero 10129 de 31 de Marzo de Z0-D,% mediante la cual se niega el privilegio de patente para
las reivindicaciones 1 a 30 de la presente solicitud, es evidente que de ninguna manera se consideraron la importancia, alcance y objeto de la presente invención en su verdadera dimension, esto es, no se consideró el valioso aporte tØcnico que representa al arte en cuestión la materia revelada en la presente solicitud de patente, la cual bÆsicamente proporciona una novedosa tableta multicapa de liberación controlada que comprende una matriz mixta de componentes hidrofIlicos y lipofIlicos capaz de controlar de manera efectiva la velocidad de liberación de ropinirol de cualquiera de sus sales farmacØuticamente aceptables, cuando dicho compuesto activo es administrado oralmente a pacientes que asI Ic requieran.

En efecto, a pesar de los argumentos proporcionados por el solicitante en respuesta al Concepto TØcnico publicado por ese Despacho el 12 de Enero de 2007, en la Resolución impugnada se mantienen las objeciones frente al nivel inventivo de la invenciOn, argumentando bÆsicamente que "...el objeto inventivo de la presente solicitud no es materia diferente al de las anterioridades, ya que no hay un aporte real al acervo tecnológico, ni se observa el salto cualitativo a la regla tØcnica, o el efecto inesperado de las comün y universalmente conocidas tabletas multicapa de liberación modificada, pues el simple hecho de tomar composiciones de tableta multicapa conocidas (donde la Onica diferencia tØcnica real es el nombre del principio activo), y colocar ahora el nombre particular de un principio activo, de ninguna manera le confieren nivel inventivoTM.

Por consiguiente, a continuación me permito demostrar ante ese Despacho que la presente invención si cumple con el requisito de nivel inventivo exigido por el ArtIculo 18 de la Decision 486 de 2000, toda vez que la formulación revelada en la solicitud de patente en cuestión
(en conjunto con sus componentes especIficos y las ventajas proporcionadas por la misma) tal comoha sido descrita en la solicitud denegada, de ninguna manera puede ser predicha por una persona versada en la materia que se base en las enseæanzas encontradas dentro del estado de la tØcnica en cuestión.

(b) En conexión con el punto anterior, inicialmente me permito realizar un resumen de las principales caracterIsticas y ventajas tØcnicas de la

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invención en estudio, tal como ha sido enseæado en la memoria descriptiva proporcionada por el solicitante, y tat como ha sido reclamado en las reivindicaciones 1 a 30 actualmente presentadas.

De conformidad con lo anterior, la presente invención enseæa una novedosa tableta multicapa de liberación controlada comprendida por: (a) una capa activa que contiene, I) 0.05% a 20% en peso de ropinirol o sales farmacØuticamente aceptables del mismo; ii) sustancias polimØricas hidrofIlicas que se hinchan y/o gelifican y/o erosionan al contacto con lIquidos acuosos; iii) sustancias lipofIlicas (en donde la relación en peso de las sustancias polimØricas hidrofIlicas y las sustancias lipofIlicas contenidas en dicha capa activa se encuentra en el rango entre 7:1 y 1:1); y, iv) 5%-50% en peso de sustancias excipientes; y, (b) una o mÆs capas de barrera que limitan la superficie de liberación de la capa activa y que contienen una o mØs de: sustancias polimØricas hidrofIlicas las cuales se hinchan yb gelifican y/o erosionan al contacto con lIquidos acuosos, sustancias lipofIlicas y sustancias excipientes.

Dichas tabletas multicapa preparadas en concordancia con la presente invención exhiben la capacidad de proporcionar una cinØtica de liberación muy similar cuando se formula una misma sustancia activa pero en cantidades diferentes dentro de la capa activa en la tableta multicapa. En otras palabras, el solicitante de la invención en cuestión ha encontrado de manera sorprendente que con la utilización de la forma farmacØutica revelada en la presente solicitud de patente, es posible obtener una velocidad de liberación de ropinirol similar o idØntica, aiin si dicha tableta contiene cantidades muy diferentes de la misma sustancia activa.

Lo anterior resulta ser de gran utilidad en diferentes modelos patológicos en donde cobra importancia la necesidad de contar con formas farmacØuticas que presenten un contenido de principio activo variable (para favorecer, por ejemplo, Ia personalización de la posologIa), pero que sin embargo tengan la capacidad de liberar dicho principio activo con un perfil cinØtico idØntico (o al menos similar) independientemente de la cantidad de sustancia activa transportada.

De otro lado, las tabletas de dosificación de la presente solicitud de patente se caracterizan porque en tØrminos estructurales, la(s) capa(s)

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que dicha sustancia activa sea liberada tThicamente a travØs de la superficie no cubierta que es capaz de entrar en contacto con el medio de disolución (ver, por ejemplo, las figuras 1 a 9 de la memoria descriptiva de la presente solicitud).

Asimismo, las tabletas de dosificación de la presente solicitud de patente se caracterizan porque en tØrminos de composición, el ropinirol representa entre un 0,05% y un 20% en peso de la capa activa. Adicionalmente, dicha capa activa contiene substancias polimØricas hidrofIlicas naturales o sintØticas, las cuales deben ser materiales biocompatibles, biodegradables y farmacØuticamente aceptables, tales como la polivi nil pirrolidona, la hid roxipropilmetilcelulosa (HMPC) y la carboximetilcelulosa sódica, destacÆndose que la combinación preferida en la presente invención comprende HMPC y carboximetilcelulosa sódica. Finalmente, la capa activa de las tabletas de la presente invención contienen sustancias lipofIlicas (por ejemplo, aceite de ricino hidrogenado y estearato de magnesio), de manera que la proporción en peso entre el contenido de sustancias polimØricas hidrofIlicas versus las sustancias lipofIlicas en la capa que contiene la sustancia activa se sitta entre 7:1 y 1:1.

Finalmente, las tabletas de formulación de la presente invención incluyen excipientes o auxiliares de formulación normalmente usados
en la tecnologIa farmacØutica, como por ejemplo, diluyentes, aglutinantes, lubricantes, deslizantes y agentes anti-pegado.

(c) Teniendo en cuenta las caracterIsticas tØcnicas previamente mencionadas, atentamente me permito manifestar que las formulaciones de dosificación para la liberación controlada de ropinirol reveladas en la presente solicitud de patente no podrIan de ninguna manera ser sugeridas de manera evidente por una persona versada en
la materia que tuviera acceso a los siguientes documentos mencionados en la Resolución ntmero 10129: (Dl) WO 97 03670, (1132) WO 9800115, (D3) US 5,326,570, (1134) US 5,422,121, (D5) US 5,510,114 y (1136) US 6,027,748. Adicionalmente, en dicha Resolución se hace referenda al documento "Sustained Release Dosage Forms", que corresponde at capItulo 14 del libro titulado "The Theory and Practice of Industrial Pharmacy". Por to tanto, en el presente recurso se harÆ mención a dicho documento con el tØrmino (1137).

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las enseæanzas de las anterioridades antes mencionadas, a
continuación me permito realizar un anÆlisis comparativo entre la
materia revetada en la presente solicitud y las enseæanzas de los
documento Dl a D7.

En primer lugar, inicialmente me permito seæalar la existencia de
notables diferencias en tØrminos estructurales entre las tabletas multicapas de liberación controlada reveladas en la presente invención y las formulaciones de liberación controlada enseæadas en las anterioridades citadas en Ia Resolución nÆmero10129.

En efecto, las reivindicaciones de la presente solicitud de patente estân dirigidas a proteger una tableta caracterizada porque contiene una capa activa y una o mÆs capas de barrera. Sin embargo, en la pÆgina 8 (lIneas 5 a 11) de la memoria descriptiva de la presente solicitud se establece claramente que dicha(s) capa(s) de barrera no cubre(n) completamente la capa activa, de manera que la oresente solicitud de oatente no se encuentra dirialda a proteger fprmulaciones en las cuales la(s) capa(s) de barrera rodee(n) totalmente Ia capa activa. Ahora bien, en Ia presente solicitud se
ha establecido que la tableta entera, esto es, la capa activa y todas
las capas de barrera, pueden estar opcionalmente cubiertas, tat y
como se ilustra a continuación:

Capa de barrera F Capa activa va
Capa ac,

Capa de barrera Capa de barrera ------
Recubrimiento opcional Recubrimiento opcional

Figura 1. Estructura general de las tabletas de liberación controlada de ropinirol reveladas en la presente solicitud de patente.

Contrario a to anterior, los documentos D2, D3 y D5 enseæan
pellets en los cuales un nücleo que contiene el compuesto activo
estÆ completamente recubierto por una 0 mÆs capas, mientras que
el documento D4 inicamente enseæa una tableta monocapa o una tableta totalmente recubierta, tat y como se ilustra a continuación:

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D2 recubrmento(s) D3

Capa activa

D4 D5

Figura 2. Estructura general de las formas de liberaciOn controlada reveladas en los documentos 02, 03, 04 y D5.

Por lo tanto, es totalmente clara que ninguno de los documentos D2
a D5 enseæan una tableta multicapa en la cual una o mÆs capas de barrera cubran parcialmente la capa activa.

Ahora bien, aparte de las diferencias estructurales previamente seæaladas, resulta de gran importancia resaltar las diferencias existentes entre Ia composición de la capa activa de las tabletas de la presente invención y la composición de la capa activa de las formulaciones enseæadas en los documentos Dl y D6. En este sentido, del atento anÆlisisde las formulaciones ejempllficadas en el documento Dl puede establecerse que dichas formulaciones no contienen la misma relación ense?Sada en la presente solicitud de patente entre las substancias polimØricas hidrofIlicas y las substancias lipofIlicas que conforman la capa activa. En este sentido, el ejemplo 8 de dicho documento Dl claramente enseæa una formulación cuya capa activa comprende Metocel KM4 y polivinilpirrolidona como sustancias polimØricas hidrofIlicas, y estearato de magneslo coma sustancia lipofIlica, las cuales se encuentran en una relación en peso (sustancias polimØricas hidrofIlicas:sustancias lipofIlicas) de 18:1, por lo cual a partir de las enseæanzas de este documento es evidente aue no se habrIa ood.do Ileaar a las enseæanzas de Ia oresente solicitud, en donde claramente se establece que la relación en peso de las sustancias polimØncas hidrofIlicas y las sustancias lipofIlicas contenidas en la capa activa estÆ en el rango entre 7:1 y 1:1. De otro [ado, de la atenta lectura del documento D6 es clara que las formulaciones alli ejemplificadas comprenden mÆs de un 20% de compuesto activo, mientras que las novedosas tabletas multicapas

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reveladas en la solicitud de patente en cuestión ünicamente comprenden entre el 0.05% y el 20% de ropinirol o una de sus sales farmacØuticamente aceptables.

De otro lado, tal como ha sido adecuadamente seæalado por la Superintendencia de Industria y Comercio en la Resolución nmero 10129, el capItulo reivindicatorio de la presente invención se encuentra dirigido a proteger novedosas formulaciones de dosificación para la liberación controlada de ropinirol o sus sales farmacØuticamente aceptables. Sin embargo, contrario a dichas enseæanzas, las formulaciones reveladas en los documentos Dl a D6 no se encuentran diseæadas nara la liberación controlada de comDuestos activos con caracterIsticas fisicopuImicas similares a las del ropinirol, haciendo evidente pue las tabletas multicapas de la presente solicitud no pueden ser eciuivalentes a las formulaciones de dosificación enseæadasen el arte previo.

Para clarificar lo manifestado en el pÆrrafoanterior, inicialmente me permito resaltar que en el documento D7 se enseæa que: "la selección de una forma de dosis particular puede estar limitada por las propiedades especIficas de dicha droga, por ejemplo, solubilidad, constante de disociación, estabilidad, etc" (pÆrrafo 3, columna 1, pÆgina 19 del documento D7). En otras palabras, es claro que los agentes activos difieren en sus propiedades fisicoquImicas, y dichas propiedades fisicoqulmicas afectan no solamente la velocidad de liberación de una formulación, sino que tambiØn afectan su mecanismo de liberación, ya que por ejemplo resulta bien conocido para una persona experta en la materia tØcnica en cuestión que las drocias solubles son princilpalmente liberadas oor difusión, mientras pue las droaas insolubles son principalmente liberaclas por erosion de las formulación.

En vista de lo anterior, es claro que los agentes activos que presentan propiedades fisicoquImicas diferentes no pueden ser considerados equivalentes y, por lo tanto, una formulación que ha sido empleada para la Iiberación controlada de un agente activo en particular no puede ser usada para lograr un perfil de liberación adecuado de otro agente activo con propiedades fisicoquImicas diferentes. En otras palabras, si dos compuestos activos que

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compuestos, con plena certeza, exhibirlan perfiles de liberación

diferentes.

Por lo tanto, es claro que una persona experta en la materia no puede de ninguna manera considerar gue una formulación de dosificación gue haya permitido la liberación controlada de una drocia en particular, permita necesariamente lograr un pertH de liberaci6n similar de una drocia con propiedades fisicoguImicas diferentes.

Ahora bien, tal como se comentó previamente es claro que el ropinirol es un compuesto activo con propiedades fisicoquImicas muy diferentes a las exhibidas por los compuestos activos para los cuales fueron diseæadas las formulaciones de liberación controlada reveladas en los documentos Dl a D6.

Para demostrar lo anterior, resulta de gran importancia tener en cuenta que: I) el ropinirol es una molØcula muy soluble en agua, esto es, presenta una solubilidad de 133 gIL (pÆgina 11, lInea 3 de la descripción) y, ii) en el estado de la tØcnica era conocida la dificultad de controlar la velocidad de Iiberación de medicamentos muy solubles en aqua debido a su rÆpida difusión. AsI, por ejemplo, en el documento US 5,126,145 (columna 1, lIneas 23 a 30) se establece de manera clara la dificultad para controlar la velocidad de liberación de medicamentos altamente solubles en agua a partir de tabletas de dosificación que contienen hid roxipropilmetilcelulosa (HPMC). En este sentido, resulta ótil aclarar que una persona experta que pretendiera desarrollar una formulación de ropinirol de liberación controlada, tendrIa que tener en cuenta el estado del arte que haga alusión especIfica al problema de lograr la liberación controlada de medicamentos solubles en agua, tal como lo hace, por ejemplo, el documento US 5,126,145 (Anexo b).

Ahora bien, contrario a lo anterior, considero de gran importancia hacer notar que los documentos Dl a D6 no proporcionan ninguna enseæanza para lograr Ia Iiberación controlada de medicamentos solubles, toda vez que ninguno de dichos documentos proporciona ejemplos de un medicamento con solubilidad en agua alta, tal y como se demuestra a continuación:

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I En el documento Dl, la substancia farmacØutica formulada en
las tabletas descritas es cloruro de paroxetina, la cual es considerada liqeramente soluble ya que tiene una solubilidad de 5,4 g/L en agua, siendo por lo tanto cerca de 24 veces menos soluble en agua que el ropinirol. (Información obtenida de la pÆgina de Internet http://us.gsk.com/products/›assets/us paxil. pdf (Anexo C).

I En D2, los ejemplos se refieren a formulaciones de omeprazol
y diclofenaco, los cuales tienen solubilidades de 823 mq/L y 8,2 mq/L en aqua, respectivamente, y son considerados prÆcticamente insolubles. Dichos agentes activos, son por 10 tanto, 1600 veces menos solubles en agua que el ropinirol. (Información obtenida de http://www.drugbank.ca/cqi-
bin/cietCard.cqi?QARD=DB00338 y http://www.drugbank.ca/cgi-
bin/QetCard.cqi?QARD=DB00586 (Anexo c).

I El documento D3 estÆ relacionado ünicamente con
formulaciones de carbamazepina, substancia que tiene una solubilidad de 17,7 mg/L en aqua y es considerado prÆcticamente insoluble. Dicho compuesto activo es cerca de 7500 veces menos soluble que el ropinirol. (Información obtenida de http://www.drugbank.ca/cqi-bin/getCard.cqi?CARD=DB00564
(Anexo c).

I Por su parte, el documento D4 no contiene ninauna enseiianza
respecto a formulaciones de aaentes activos altamente solubles en aqua. En este sentido, es notorio que los ejemplos allI revelados contienen sustancias no activas 6 prednosolona y teofilina, las cuales tienen solubilidades en agua de 0.223 g/L y 1-5 g/L, respectivamente. Por lo tanto, dichos compuestos son al menos 26 veces menos solubles en agua que el ropinirol. (Información obtenida de las pginas de Internet http://www.drugbank.ca/cgi-
bin/QetCard.cgi?CARD= DB00860 y http://www.druabank.cgLML
bin/aetCard.cgi?QARQ=QB00277 (Anexo c).

/ El documento D5 describe formulaciones de Æcidos biliares. Los ejemplos describen una formulación de Æcido ursodeoxicólico, el cual tiene una solubilidad en agua de 0.02 g/L, de forma tal que es 6600 veces menos soluble en agua que el ropinirol. (Información
rip ht-rrllwww driinhriLr rIe-rti_

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/ Finalmente, los ejemplos del documento D6 describen
formulaciones de liberación controlada de ketoprofeno y
nifedipina, los cuales se consideran como prÆcticamente
* insolubles en aqua. EspecIficamente, la solubilidad en agua del
ketoprofeno es 51 mg/L, mientras que la solubilidad en agua de la
nifedipina es 0,58 mg/L. Por 10 tanto, dichas drogas son cerca de
2000 veces menos solubles en agua que el ropinirol. (Información
obtenida de la version electrónica del documento titulado
"Martindale: The Complete Drug Reference" (Anexo C).

Ahora bien, teniendo en cuenta las consideraciones tØcnicas planteadas hasta el momento para demostrar las evidentes diferencias existentes entre las tabletas multicapas de la presente solicitud de patente y las formulaciones de dosificación de los documentos Dl a D6, atentamente me permito manifestar queuna persona experta en el arte interesada en oroclucir una formulación de rooinirol no encontrarIa sucierencias ütiles dentro de los documentos Dl a

 . AdemÆs, queda claro que el simple reemplazo del aciente activo ejemplificado en cada uno de dichos documentos por ropinirol, resultarIa en una formulaciôn que no contiene uno 0 mÆs de las caracterIstucas reivindicadas como parte de las tabletas multicapas de la oresente invención.

En este sentido, el Ænico documento citado en Ia Resolución nÆmero 10129 que se refiere a la Iiberación controlada de medicamentos solubles en aaua es D7. Dicho documento enseæa que la solubilidad de drogas es un factor a tener en cuenta a la hora de seleccionar una formulación de liberación controlada (pârrafo 3, columna 1, pÆgina 19), y enseæaque la mejor formulación para drogas solubles en agua es el empleo de una matriz insoluble (pÆrrafo 3, columna 1, pÆgina 28). En vistade estas enseæanzas,es claro que una persona experta en la materia considerarIa el uso de una matriz insoluble al momento de intentar la formulación de ropinirol. En particular, no hay ninguna motivación para proporcionar una formulación que tenga una o mÆs capas de barrera, 0 tampoco para proporcionar una formulación que contenga substancias polimØricas hidrofIlicas y substancias lipofIlicas en Ia capa activa en una relación como la reivindicada en la presente solicitud de patente. Por tnto, el lector experto nunca llegarIa a la tableta multicapas

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Aparte de to planteado hasta el momento, me permito resaltar que las tabletas multicapa reveladas en la presente solicitud de patente se caracterizan por exhibir un excelente perfil de liberación controlada de ropinirol. En este sentido, me permito Ilamar la atención de esa Superintendencia hacia las formulaciones ejemplificadas en el capItulo descriptivo de la solicitud de patente en cuestión, en donde se observa la efectiva obtención de un perfil de Iiberación controlada in vitro de ropinirol de orden cero a partir de las formulaciones de dosificación reveladas (ver por ejemplo los resuttados del ejemplo 24 y las figuras 10 a 13), hecho que, por ejemplo, demuestra la ausencia de un paso inicial de liberación rÆpida que frecuentemente se presenta en diferentes formulaciones de liberación controlada conocidas en el estado de la tØcnica.

En conexión con to anterior, dicho perfil de liberación controlada de orden cero exhibido por las formulaciones de la presente solicitud, permite, por un lado, disminuir la necesidad de una dosificación frecuente de ropinirol por parte del paciente en necesidad de Øste, mientras que por otro lado, permite evitar el rÆpido aumento de la concentración de ropinirol en et plasma, y por ende evitar la generación de efectos secundarios asociados con las terapias dopaminØrgicas (por ejemplo, terapias con ropinirol).

De otro lado, de manera enfÆtica me permito resaltar una vez mÆs que el perfil de liberación exhibido por una formulación en particular se encuentra completamente determinado por la composición de dicha formulación y por las propiedades fisicoquImicas del agente activo, lo cual hace realmente complejo la predicción de dicho perfil de liberación. En consecuencia, Si bien los documentos seæalados en Ia Resolución nÆmero 1.0129 revelan Ia efectiva liberaclØn de los acientes activos esDecIficamente mencionados en dichos documentos mediante las formulaciones alII descritas, es claro que de ninauna manera es posible predecir Si dichas formulaciones Dueden ser usadas satisfactoriamente para controlar Ia Iiberación de otros acientes activos ciue presenten propiedades fisicociuImicas diferentes, asI como tamoco es posible predecir los parÆmetros pue eventualmente deben ser modificados en dichas formulaciones con el fin de locirar el perfil de Iiberación deseado.

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Por 6itimo, atentamente me permito resaltar una vez mÆs en el
presente recurso que antes de Ia Dresentación de Ia presente
- - solicitud de patente existIa en el estado del arte Ia necesidad de obtener una forma de dosificación de Iiberación controlada
capaz de liberar un aciente activo con una cinØtica
independiente de Ia cantidad de principio activo
transportado.

En este sentido, el documento D7 (prrafo 2, columna 1, pÆgina 17)
claramente enseæa que para el caso de drogas con alta solubilidad en el medlo de elusion (por ejemplo, el ropinirol), la velocidad de liberación a partir de una matriz insoluble debe ser directamente proporcional a la cantidad de la droga transportada. En otras palabras, lo anterior significa que normalmente Ia velocidad de hberacion de un compuesto activo altamente soluble desde una matriz insoluble incrementa a medida pue Ia cantidad de compuesto activo tambiØn incrementa.

Pese a 10 anterior, las formulaciones reveladas en los ejemplos 18 a 21 y 24 de la presente invención sorprendentemente exhiben una cinØtica de liberación in vitro que resulta ser ampliamente independiente de la cantidad de ropinirol transportado, dentro del rango de concentración estudiado. Dicho comportamiento sorprendente es claramente mostrado en la figura 13 de la descripción, en la cual se compara la cinØtica de liberación in vitro de ropinirol a partir de tabletas conteniendo 0,75 mg, 6 mg y 12 mg
- de dicho compuesto activo.

En conexión con lo anterior, es evidente que dicho comportamientonopudo haber sido predecido a oartir de las enseæanzas de cualciuiera de los documentos citados en Ia Resolución impugnada, toda vez gue ninciuno de dichos documentos proporciona o all menos sucilere formulaciones caracterizadas por presentar un mismo perfil de Iiberación de medicarnento independientemente de Ia cantidad de medicamento transportado.

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Con base en lo anteriormente planteado, es claro que, contrario a 10 afirmado por ese Despacho en la Resolución nUmero 10129, materia revelada en Ia presente solicitud de oatente oresenta

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satisfactoria con las disposiciones establecidas en el ArtIculo
18 de Ia Decision 486 de 2000.

(d) De conformidad con los anteriores argumentos, me permito seæalar ante ese Despacho que las afirmadones presentadas en la Resolución impugnada carecen de toda relevancia para desvirtuar la altura inventiva de la presente solicitud, tal como me permito seæalar brevemente a continuación:

> Inicialmente, de la lectura de la Resolución nOmero 10129 es claro
que ese Despacho asegura que la presente solicitud de patente no es inventiva frente a las enseæanzas de los documentos Dl a D6, asI como tampoco /0 es frente a las enseIianzas del capItulo 14 del libro titulado "Sustained Release Dosage Forms" (D7), el cual fue citado en la oposición interpuesta por la sociedad Procaps S.A.

De acuerdo con ese Despacho, la Onica diferencia tØcnica real entre las formulaciones reveladas en los documentos citados y las tabletas multicapa de liberación controlada reivindicadas en la solicitud de patente en cuestión es el hecho de que el agente activo ha sido reemplazado con ropinirol o una sal farmacØuticamente aceptable del mismo, de tal suerte que dicho reemplazo de n/nguna manera le confiere el carÆcter inventivo requerido para que la solicitud de patente sea aceptada.

En respuesta a la anterior afirmación, me permito insistir una vez mÆs en el presente recurso que, de manera totalmente contraria a lo afirmado por ese Despacho, las tabletas multicapa de liberación controlada reveladas en la presente solicitud de Datente presentan evidentes diferencias en estructura, composición y funcionamiento (perfil de Iiberación) con respecto a las formulaciones enseæadas en el estado de Ia tØcnica, diferencias pue claramente van mucho mÆs aIlÆ deun simple reemplazo del compuesto activo.

En efecto, a lo largo del presente escrito se ha reiterado que la capa activa de las tabletas de la presente invención se encuentra limitada

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por las capas de barrera, de forma tal que dichas capas de barrera no rodean completamente a la capa activa (ver, por ejemplo, las figuras 1 a 9 del capItulo descriptivo originalmente presentado). Contrarlo a

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una capa activa no recubierta 6 recubierta completamente por
capas de barrera.

Asimismo, en el presente recurso se ha insistido en que los
documentos Dl y D6 enseæan formulaciones de liberación
controlada en donde Ia composición de Ia capa activa es muv
diferente a Ia composición de la capa activa de las tabletas reveladas en la solicitud de patente en cuestión, esto es, tanto en la cantidad de aqente activo transportado, como tamblØn en la relación en peso entre las sustancias polimØricas hidrofIlicas y las sustancias lipofIlicas.

De otro lado, se ha aclarado que no es posible suponer que una formulación empleada para la liberación controlada de un agente activo en particular pueda permitir la obtención de un perfil de liberación similar pero de otro tipo de compuesto activo cuyas propiedades fisicoquImicas difieran de las propiedades fisicoquImicas del agente activo inicial. En este sentido, previamente en el presente memorial se demostró que los documentos Dl a D6 estÆn diriciidos a proporcionar formulaciones de liberación controlada Para aqentes activos insolubles o muy poco solubles en aqua, mientras que las tabletas multicapa de la presente invención han demostrado ser efectivas en Ia liberación de ropinirol, el cual es un aqente activo altamente soluble en aqua. Adicionalmente, se ha resaltado que el documento D7 seæalado por ese Despacho claramente enseæa que la selección de una forma de dosificación en particular se encuentra limitada a las propiedades fisicoquImicas del agente activo que se pretende transportar, toda vez que, por ejemplo, mientras un medicamento soluble es liberado bÆsicamentepor difusión, un medicamento insoluble es liberado principalmente por erosion de Ia formulación de dosificación.

Finalmente, previamente en el presente documento se ha seæalado que las formulaciones reveladas en la presente invención exhiben, de manera sorprendente, una cinØtica de liberación in vitro que es independiente de la cantidad de ropinirol transportado (dentro del rango de concentración estudiado), haciendo Ønfasis en que dicho comportamiento no pudo haber sido predecido a partir de las enseæanzas de cualquiera de los documentos citados en la Resolución impugnada, toda vez que ninguno de ellos proporciona, o al menos

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Iiberación de un medicamento independientemente de la cantidad de medicamento transportado.

En vista de todo lo anterior, me permito reiterar ante ese Despacho que NO ES CIERTO gue la Ænica diferencia tØcnica existente entre las tabletas multicana de la presente solicitud de natente y las formulaciones de dosificación enseæadas en los documentos Dl a D7 sea el aaente activo utilizado en cada caso, v pue contrario a eso. la materia revelada en la presente invención proporciona una novedosa tableta multicapa capaz de controlar de manera efectiva la velocidad de Iiberación de ropinirol 6 de cualpuiera de sus sales farmacØuticamente acentables, donde dicha tableta nresenta marcadas diferencias en estructura, composición y funcionamiento, ciue le confieren un inepulvoco carÆcter inventivo frente a las enseæanzas conocidas hasta el momento en el estado de la tØcnica.

> De otro lado, en la Resolución nÆmero 10129 ese Despacho aclaró at solicitante que no resulta sufic/ente que una /nvención tenga una diferencia cuatquiera para cumpl/r con los requisitos de patentabiidad, tal y como sucede en et presente caso, donde segOn se describe en dicha Reso/ución, bÆsicamente se argumenta que ahora es diferente a lo existente deb/do a que el nombre del principio activo no estÆ dado en el estado de la tØcnica citado y que por ello esa diferencia imp//ca un avance o progreso significativo.

En este sent/do, ese Despacho concluye entonces que con la materia revelada en la presente solicitud no se estÆ real/zando ningQnaporte en el camino trilado de las formas de presentación multicapa, razón por la cual dicha materia no cumpie con el requ/sito de n/vet inventivo exigido por el ArtIculo 18 de la Decision 486 de 2000.

La anterior afirmación evidencia una vez mâs que el examen de patentabilidad realizado nor la Superintendencia de Industria y Comercio a la materia revelada en la presente solicitud de patente no es correcto, toda vez que de ninguna manera se consideró el alcance de la presente invención en su verdadera dimension, esto es, no se tuvieron en cuenta las novedosas e inventivas caracterIsticas tØcnicas que nresenta la invención en cuestión (ampliamente analizadas en el presente recurso), y por ende,

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en cuestión Ia materia revelada en la presente solicitud de patente.

En efecto, es claro que dicho examen de patentabilidad se enfocó exclusivamente en la comnaración del nombre del agente activo utilizado en las tabletas multicapa de la presente invención, y en las formulaciones enseæadas en los documentos Dl a 1136, desconociendo nor lo tanto las demÆs diferencias en estructura, composición y funcionamiento existentes entre la materia revelada en dichos documentos, y peor aÆn, dandoa entender de manera totalmente errónea gue Para una persona versada en la materia todos los aaentes activos existentes son eciuivalentes. y pue nor ende, es nerfectamente factible suponer pue una formulación aue ha sido empleada para Ia Iiberación controlada de un aciente activo en particular puede ser utilizada de manera exitosa para locirar un perfil de liberación similar de otro aciente activo, sin ciue importen las propiedades fisicociuImicas ciue cada uno de estos acientes presenten.

En conexión con to anterior, adicionalmente me permito resaltar la ligereza con la cual se realizó el examen de patentabilidad a la presente solicitud, toda vez que los argumentos tØcnicos empleados nor ese Despacho nara desvirtuar el nivel inventivp de Ia materia revelada con respecto a las enseæanzas de los documentos Dl a D6 evidencian no

solamente el dØbil anÆlisistØcnico realizado (se ha demostrado reiteradamente en el Dresente escrito aue no se tuvieron en cuenta todas las caracterIsticas novedosas e inventivas de Ia presente solicitud de natente), sing tambiØn la negativa, nor parte del Examinador encarciado del caso, de realizar el esfuerzo intellectual de colocarse en Ia situación aue ha tenido aue afrontar el tØcnico con conocimientos medios en la materia en un momento en aue la invención no era conocida, es decir antes de Ia invención. En este sentido, me permito manifestar que la correcta posición del Examinador durante el caso en cuestión debió incluir el estudio de la patentabilidad de la invención sobre el anâlisis de lo que una persona experta en la materia hubiera hecho al momento de enfrentarse al problema de intentar proporcionar una formulación de Iiberación controlada de medicamentos altamente solubtes en agua (tat como el ropinirol). A este respecto, debido a que

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formulación de Iiberación controlada de medicamentos solubles
en aqua, es claro que una persona experta en el arte no habrIa considerado ninquno de dichos documentos all momento de desarrollar una formulación de liberación controlada de ropinirol o sales farmacØuticamente acetables del mismo.

(e) Finalmente, de la manera ms atenta me permito resaltar ante ese Despacho que la solicitud de patente en cuestión ha sido aceptada hasta el momento por las Oficinas de Propiedad Intelectual de los siguientes paIses: Australia, China, Mexico, Nueva Zelandia, Singapur, Taiwan, Surâfrica y Corea del Sur, asI como tambiØn ha sido aceptada por la Oficina de Patentes Europea. En este sentido, anexo al presente recurso me permito presentar copias de los capItulos reivindicatorios aceptados en cada uno de dichos paIses y regiones (Anexo d).

Ante todo, con el anterior comentario de ninguna manera pretendo desconocer la independencia de la que goza la Superintendencia de Industria y Comercio al momento de analizar los mØritos de patentabilidad de una solicitud, de acuerdo con las disposiciones que para el efecto contempla la legislación andina en su Regimen de Propiedad Industrial.

Sin embargo, sí considero de gran importancia resaltar el hecho de que la materia tØcnica revelada en la solicitud de patente en cuestión ha sido cataloqada como novedosa, inventiva e industrialmente aplicable oor los Examinadores de las oficinas de propiedad intelectual de los paIses y regiones previamente mencionados; en este sentido, si bien es cierto que existen claras diferencias en la normatividad vigente en materia de propiedad intelectual entre dichos paIses o regiones y la Comunidad Andina de Naciones, tales diferencias no incluyen de ninguna manera los requisitos de novedad, nivel inventivo y aplicabilidad industrial, cuyo cumplimiento es condicio sine qua non a nivel mundial.

De manera especIfica, me permito poner en consideración de ese Despacho la especial importancia que adquiere el reconocimiento del nivel inventivo de una solicitud de patente por parte de otras oficinas de propiedad intelectual a nivel mundial durante el examen de patentabilidad realizado por los Examinadores de la Superintendencia de Industria y Comercio, toda vez que resulta de vital importancia

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de la materia revelada en una solicitud de patente, recaiqa en apreciaciones personales por parte del Examinador encaroado
del caso.

- 4. CONCLUSION

Con base en los argumentos tØcnicos mostrados previamente, me permito manifestar ante ese Despacho que la materia revelada en la presente solicitud de patente presenta una evidente altura inventiva frente a las enseæanzas de los documentos citados en la Resolución nümero 10129 aquI impugnada, cumpliendo de esta manera con las disposiciones establecidas en el ArtIculo 18 de la Decision 486 de 2000, y por lo tanto demostrando ser merecedora del privilegio de patente requerido.

En efecto, se ha demostrado de manera contundente que existen claras diferencias tØcnicas entre el objeto de la presente invención y las enseæanzas de las referencias citadas, incluyendo diferencias estructurales (ubicación de las capas de barrera con respecto a Ia capa activa al interior de las tabletas multicapa reveladas), diferencias en la composición (componentes de la capa activa, asI como tipo y concentración del agente activo transportado), y finalmente, diferencias en el perfil de Iiberación obtenido (perfil de liberación independiente de la concentración de ropinirol al interior de la capa activa).

Adicionalmente, se aclaró que no es posible suponer que una formulación empleada para la liberación controlada de un agente activo en particular pueda permitir la obtención de un perfil de liberación similar de otro compuesto activo cuyas propiedades fisicoquImicas difieran de las propiedades fisicoquImicas del agente activo inicial. En este sentido, se demostró que ninquno de los documentos citados en la Resolución nümero 10129 describe una formulación de liberación controlada para medicamentos solubles en aqua, de manera que una persona experta en la materia tØcnica en cuestión no podrIa basarse en la información revelada en dichos documentos para loprar una formulación de Iiberación controlada efectiva para aqentes activos altamente solubles en aqua, como 10 es el ropinirol.

En vista de lo anterior, es posible concluir que si una persona experta en
el arte pretendiera obtener una formulación de Iiberación controlada de ropinirol, y se basara en los documentos Dl a D7 seæalados por ese Desacho (lo cual resulta tØcnicamente inadecuado debido a que ninauno de dichos documentos or000rciona enseæanza aiquna con respecto a la

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patente, toda vez ciue la simple sustitución del aaente activo empleado en las formulaciones de dichas anterioridades por el ropinirol, resultarIa en una formulación gue no contiene una o mÆsde las caracterIsticas de las tabletas multicapas de Ia presente invención, y peor aün, dicha persona experta en el arte no podrIa haber supuesto el perfil de liberación obtenido para el ropinirol bajo dichas condiciones.

En consecuencia, es claro que la presente invención si posee el nivel inventivo requerido con respecto a las enseæanzas de las referencias citadas, toda vez que dichos documentos no le permitirIan a una persona versada en la materia Ilegar de manera evidente a las tabletas multicapas tal como han sido reivindicadas por el solicitante, y mucho menos le permitirIan suponer las ventajas tØcnicas ofrecidas por dicha novedosa formulación de liberación controlada de ropinirol.

5. PETIcIÔN

En consecuencia, atentamente solicito a ese Despacho considerar los argumentos expuestos anteriormente y revocar en su totalidad la Resolución nimero 10129 impugnada, para conceder el privilegio de patente solicitado.

6. ANEXOS

(a) Copia de ml memorial de 23 de Enero de 2008, junto con sus anexos
de formulario, recibo de pago de tasa, y copia de las pÆginas 71 a 77
que se incluyeron como nuevo capItulo reivindicatorio.

(b) Copia del documento US 5,126,145 que hace alusión especIfica at
probtema de lograr la liberación controlada de medicamentos solubtes
en agua.

(c) Información tØcnica de documentos Dl a D6 obtenida de Internet.

(d) Copia de los capItulos reivindicatorios concedidos por las Oficinas de
Propiedad Intelectual de Australia, China, Mexico, Nueva Zelanda, Singapur, Taiwan, SudÆfrica y Corea del Sur, y la Oficina de Patentes Europea.

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7. El documento que acredita ml caHdad de Representante Legal en Bogota para asuntos relativos a la Propiedad Industrial de la sociedad peticionaria, fue presentadot

mi memorial de 8 de Noviembre de 2004 a Tt ’-,
w

8 Mi direccion es Calle 72 No 5-83, Piso 60, Bogota D.C.

Del Seæor Superintendente,

ICI LLOREDA RICAURTE
T.P. 53.125

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A. A LLOREDA RICAURTE
C.C. No. 39.690.713 de UsaquØn

JOSE LLOREDA CAMACHO & CO.
ABOGADOS

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A
SUPERINTENDENCIA DE INDUSTRIA V COMERCIO

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Seæor No. 02-091153-.00015.0000

Fecha: 2008-01 -23 16:27:10 Dep. 2020 NUECREACIONE

Tra. 11 PATENTEIYII Eve; 379 FASENACIONALII SUPERINTENDENTE DE INDUSTRIA Y COME Act. 329 CTOINFORMACION Folios; 10
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: P1.-JAGOTEC AG.-Solicitud de Patente de Invención en Fase Nacional
PCT rara "FORMULACION DE DOSIFICACION EN MATRIZ POLIMERICA HIDROFILICA/ LIPOF–LICA".-Clase A61K 9124.-
Expediente nümero 02-091.153.-

1. Me refiero a ml memorial de 17 de Mayo de 2007.

2. Por medio del presente, me permito manifestar a ese Despacho que
debidamente autorizado por ml representado se ha modificado el capItulo reivindicatorio presentado con ml memorial de 17 de Mayo de 2007.

Dicha modificación consiste en la cancelación actual de la reivindicación 22, dado que como esta enunciada resulta rebundante frente a la reivindicación 21. El capitulo reivindicatorlo fue renumerado, y las dependencias correspondientes modificadas, con et fin de dare coherencia a las mismas. En consecuencia, el nuevo capItulo reivindicatonio que se debe tener en cuenta para estudlo consta de 30 reivindicaciones.

Finalmente, me permito manifestar a ese Despacho que la anterior modificación no constituyen de ninguna manera una ampliación all alcance de la presente invención, toda vez que la modificación anterior encuentra pleno sustento en la descripción de la presente solicitud.

3. Anexo me permito presentar:

(a) Formularlo Cinico de modificaciones y correcciones.

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- (b) Recibo ntmero 08-1.403, expedidO por la SuperintendenCia de
Industria y ComerCiO, que acredita el pago de la modificaciófl
mencionada; y

(c) Copia de las pÆginas 71 a 77, que corresponde al nuevo capitulo
reivindicatoriO, en el cual se han realizado las modificaciofleS
mencionadas anteriormente.

4. En vista de todo lo anterior, ruego a usted proceder a estudiar nuevamente la
solicitud a la Iuz de las modificacioneS realizadas y conceder el privileglo de patente
sol i citad0.

SeæorSuperintendente,

ALICIA LLOREDA RICAURTE
T.P. 53.215

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Espaclo reseado para el adhesivo de radicaciOn

Industria Comercio

SUPERINTENDENCIA

FORMULARIO

1JNICO DE CORRECCIONES Y MODIFICACIONES.
2000-10

0 SOLICITUD DE

CorrecciOn de Error Material. ModificaciOn a una Solicitüd.

Nombre: JAGOTEC AG, sociedad existente
2 organizada de conformidad con las leyes de Suiza. IDENTIFICACION

SOLICITANTE Direccion: Eptingerstrasse 51, CH -4132 Muttenz, C, C. NIT
Suiza

Telefono 3264270 Fax 6069701 CE Otro

E-mail: jllcco@lloredacamacho.com
Nümero
Dornicillo: Muttenz, Suiza.

Nombre: ALICIA LLOREDA RICAURTE IDENTIFICACION

C. C. NIT REPRESENTANTE DirecciOn: Calle 72 No.5-83 50 Piso
o APODERADO

TelØfono: C.E. Otro 3 264270 Fax: 2 126426

NUmero 39.690.713 TP 53.215

E-mail: jIlcco'lloredacamacho.com

Nümero de expediente:
02-091.153

Descripcion de la correccion o modificacion solicitada modificaciÆnal capitulo reivindicatorio

Comprobante de pago No 08-1.403 Fecha 04-01-08

Anexos:

23 Comprobante de pago de la tasa.
E Poderes, si fuere el caso.
Certificado de existencia representación legal de las partes, cuando sean personas jurIdicas.

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REIVINDICACIONES

1. Una tableta multicapa de liberación controlada que comprende:

(a) una capa activa que contiene:
(I) 0.05 a 20°h en peso de ropinirol o inclusive de sales farmacØuticamente aceptables del mismo,
(ii) sustancias polimØricas hidrofIlicas las cuales se hinchan yb gelifican y/o erosionan al contacto con lIquidos acuosos,
(iii) sustancias lipofIlicas, y
(iv) 5-50% en peso de sustancias excipientes,
en donde la relación en peso de las sustancias polimØricas hidrofIlicas y las sustancias lipofIlicas contenidas en dicha capa activa se encuentra en el rango entre 7:1 y 1:1; y

b) una mÆs capas de barrera que limitan la superficie de liberación
de la capa activa, las cuales contienen una mÆsde las
sig uientes:
sustancias polimØricas hidrofIlicas las cuales se hinchan yb
gelifican y/o erosionan al contacto con lIquidos acuosos, sustancias lipofIlicas, y sustancias excipientes;
en donde la tableta se encuentra opcionalmente recubierta.

2. Una tableta multicapa de liberaciOn controlada acorde con la
ReivindicaciOn 1, en donde la sustancia activa es clorhidrato de ropini roI.

3. Una tableta multicapa de liberación controlada acorde con la
Reivindicación 1, en donde dichas sustancias polimØricas hidrofIlicas (ii) estÆn contenidasen un porcentaje entre 30% y 75%, respecto del peso de la capa activa.

4. Una tableta multicapa de liberación controlada acorde con la
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contenidas en un porcentaje entre 5% y 55% respecto del peso de la capa activa.

S. Una tableta multicapa de liberación controlada acorde con la
Reivindicación 1, en donde dichas sustancias excipientes (iv) estÆn contenidas en un porcentaje entre 10% a 40%, respecto del peso de la capa activa.

6. Una tableta multicapa de Iiberación controlada acorde con la ReivindicaciÆn 1, en donde dichas sustancias polimØricas hidrofIlicas comprenden un material farmacØuticamente aceptable biocompatible y/o biodegradable, incluyendo polivinilpirrolidona no entrecruzada, hidroxipropilcelulosa con un peso molecular de 100 000 a 4 000 000, carboximetilcelulosa sódica, carboximetilalmidón, copolImero metacrilato de potasio-divinilbenceno, hidroxipropilmetilcelulosa de peso molecular entre 2 000 Y 4 000 000, un polietilenglicol de peso molecular entre 200 y 15 000, un polioxietileno con peso molecular de hasta 20 000 000, un carboxivinilpolImero, un poloxÆmero (copolImero polioxietileno-polioxipropileno), un polivinilalcohol, un glucano (glucan), una carragenina, un escleroglucano (escleroglucan), un manano, un galactomanano, gelanos, xantanos, âcido algInico y/o un derivado de Øste, poliaminoÆcidos, copolImero metilvinil ØterI anhIdrido maleico, carboximetilcelulosa y/o un derivado de Østa, etilcelulosa, metilcelulosa, almidón, un derivado del almidón, alfa-, beta-, gama ciclodextrina y/o un derivado de Ia dextrina.

7. Una tableta multicapa de liberación controlada acorde con la Reivindicación 6, en donde las sustancias polimØricas hidrofIlicas en la capa activa comprenden:

(a) una o mÆs de las siguientes: hidroxipropilcelulosa con un peso molecular de 100 000 a 400 000, hidroxipropilmetilcelulosa (HPMC) de peso molecular entre 2 000 V 4 000 000, etilcelulosa 0

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- (b) carboximetilcelulosa sódica, carboximetilcelulosa o sus derivados, hidroxipropilcelulosa de peso molecular entre 100
- 000 y 4 000 000, un carboxivinil polImero, una carragenina,
un xantano, Æcido alginico o un derivado, etilcelulosa,
metilcelulosa, dextrina y/o maltodextrina.

S. Una tableta multicapa de Iiberación controlada acorde con Ia
Reivindicación 7, en donde las sustancias polimØricas hidrofIlicas
en la capa activa incluyen: hidroxipropilmetilcelulosa y carboximetilcelulosa sódica.

9. Una tableta multicapa de Iiberación controlada, acorde con la
Reivindicación 6, en donde las sustancias polimØricas hidrofIlicas
en Ia capa activa comprenden: hidroxipropilmetilcelulosa de peso molecular en el rango de 20 000 a 500 000 o una viscosidad at 2% en el rango de 80 000 a 120 000 mPa.seg

10. Una tableta multicapa de liberación controlada acorde con la
Reivindicación 9, en donde las sustancias polimØricas hidrofIlicas
en la capa activa incluyen: hidroxipropilmetilcelulosa de peso molecular 250 000.

11. Una tableta multicapa de Iiberación controlada acorde con la
Reivindicación 6, en donde la hidroxipropilmetilcelulosa en la capa
activa es una hidroxipropilmetilcelulosa gelificable.

12. Una tableta multicapa de Iiberación controlada, acorde con la Reivindicación 1, en donde las sustancias lipofIlicas incluyen una grasa natural ya sea como tal total 6 parcialmente hidrogenada, cera de abejas, cera de abejas polietoxilada, un glicØrido mono-, bi- O tri-sustituido, palmitoestearato de glicerilo, behenato de glicerilo, palmitoestearato de dietilenglicol, un estearato de rrIi4-i Inn riIjrrI urn naImiMPctPeireitn ri

monopalmitoestearato de glicerilo, palmitato de cetilo, palmitoestearato de polietilenglicol, mono di-behenato de glicerilo, un alcohol graso asociado con un alcohol graso polietoxilado, alcohol cetIlico, Æcido esteÆrico, un âcido graso saturado insaturado un derivado hidrogenado de Øste, yb aceite de ricino hidrogenado.

13. Una tableta multicapa de Iiberación controlada acorde con la Reivindicación 12, en donde la sustancia lipofIlica presente en la capa activa se selecciona entre aceite de ricino hidrogenado y behenato de glicerilo.

14. Una tableta multicapa de liberación controlada acorde con la Reivindicación 1, en donde la sustancia activa es ropinirol, inclusive sales farmacØuticamente aceptables del mismo, contenido en un porcentaje de 0.05°Io a 20% en peso de la capa activa, (ii) I sustancia polimØrica hidrofIlica comprende hidroxipropilmetilcelulosa, carboximetilcelulosa sódia o carboximetilcelulosa cälcica, (iii) la sustancia lipofIlica comprende aceite de ricino hidrogenado o behenato de glicerilo, y (iv) las sustancias excipientes estân contenidas en un porcentaje de 5% a 50% en peso de la capa activa, y la relación en peso de las sustancias polimØricas hidrofIlicas y las sustancias lipofIlicas contenidas en la capa activa se encuentra en el rango de 7:1 a 1:1.

15. Una tableta multicapa de liberación controlada acorde con la Reivindicación 1, en donde la proporción en peso de las sustancias polimØricas hidrofIlicas hinchables y/o gelificables yb erosionables y las sustancias lipofIlicas contenidas en Ia capa de barrera se encuentra en el rango de 1:1 a 7,5:1.

16. Una tableta multicapa de liberación controlada acorde con la
- ;,;r#-1;,-,-;An 1 tn rinn(ip In cnt-kii rip rnninirnl nrcnf

- inclusive de sales farmacØuticamente aceptables del mismo, es
- hasta 12.0 mg, medida como la cantidad de ropinirol base presente.

17. Una tableta multicapa de liberación controlada acorde con la
Reivindicación 16 en donde la cantidad de ropinirol presente, o
inclusive de sales farmacØuticamente aceptables del mismo, es de 0.75
mg a 12 mg, medida como la cantidad de ropinirol base presente.

18. Una tableta multicapa de liberación controlada acorde con la Reivindicación 1, en donde dicha capa mÆs capas de barrera se aplican sobre una o ambas superficies (bases) de la capa activa.

19. Una tableta multicapa de Iiberación controlada acorde con la Reivindicación 18, en donde se aplica una capa de barrera sobre ambas superficies (bases) de la capa activa.

20. Una tableta multicapa de Iiberación controlada acorde con la ReMndicación 1, en donde la liberación de ropinirol durante la primera hora despuØs de la administración oral o inmersión en lIquidos acuosos, ocurre sustancialmente solo desde la superficie de la tableta no recubierta con una o mâs capas de barrera.

21. Una tableta multicapa de Iiberación controlada acorde con la Reivindicación 1, que consiste de una capa activa y dos capas de barrera, estando una capa de barrera aplicada en cada superficie (base) de la capa activa, en donde la capa activa pesa 150 mg y consiste esencialmente de hasta 12 mg de ropinirol HCI (medido como la cantidad de ropinirol base presente), 41% de HPMC tipo 2208 (100 000 cps), 10% de carboximetilcelulosa sódica, 5% de maltodextrina, lOs/a de aceite de ricino hidrogenado, l% de estearato de magneslo, 0.6% de dióxido de silicio coloidal y cantidad suficiente de lactosa monohidrato, en donde las capas de barrera tienen un peso entre 120 y 171 -- xf rnncicfPn esendlmente rip 2360/n rip manil-nL 7ç% rit-

behenato de glicerilo, 5% de polivinilpirrolidona, 1% de estearato de magneslo, 0.4% de dióxido de siliclo coloidal, HPMC tipo 2208 (100 000 cps) y opcionalmente un agente colorante en cantidad suficiente, en donde dicha tableta de liberación controlada estÆopcionalmente recubierta con una pelIcula con 13.8 mg de un agente de recubrimiento.

22. Una tableta multicapa de liberación controlada acorde con la Reivindicación 21, en donde una de [as capas de barrera pesa 170 mg y la otra capa de barrera pesa 140 mg.

23. Una tableta multicapa de Iiberación controlada acorde con la
Reivindicación 22, en donde dicha tableta estÆ recubierta con una
pelIcula con 13.80 mg de agente de recubrimiento.

24. Una tableta multicapa de Iiberación controlada acorde con la Reivindicación 21, en donde una capa de barrera pesa 130 mg y la otra capa de barrera pesa 120 mg.

25. Una tableta multicapa de liberación controlada acorde con la Reivindicación 24, en donde dicha tableta no estÆ recubierta.

26. Una tableta multicapa de liberación controlada acorde con la
Reivindicación 21, en donde dichas capas de barrera contienen un
agente colorante.

27. Una tableta multicapa de Iiberación controlada acorde con la
Reivindicación 26, en donde dicho agente colorante es óxido fØrrico
a mar11 10.

28. Una tableta multicapa de Iiberación controlada acorde con la ReivindicaciOn 21, en donde la cantidad de ropinirol HCI en la capa activa es 0.75-12 mg, medida como la cantidad de ropinirol base libre

- 29. Una tableta multicapa de liberación controlada acorde con la Reivindicación 1, la cual no estÆ recubierta con una pelIcula de material
polimØrico gastrointestinal y enterosoluble.

30. Una tableta multicapa de liberación controlada acorde con la
Reivindicación 1, en donde la preparación de la tableta se lieva a cabo
mediante compresión de la mezcla en polvo o granular y trabajar entre
1 000 Y 5 000 kg/cm2.

1111)1 111111111111111111111111111111111 11111 11111 11111 gill llIll 1111111111(1111111 US005126145A United States Patent [19] (II) Patent Number: 59126,145

Evenstad et al. (45) Date of Patent: Jun. 30, 1992

(54) CONTROLLED RELEASE TABLET
CONTAINING WATER SOLUBLE
MEDICAMENT

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[211 Appl. No.: 536,184

[22] Filed: Jun. 13, 1990

Related U.S. Application Data

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doned.

[SI) lit. CI........................... A6IK 9/20: A61 9/22
[52] U.S. Cl..................................... 424/465; 424/468;
424/469;424/470:424/48&-424/499,424/502: 5)4/960; 514/964
[58] Field of Search...............424/488. 469, 470. 465,
424/489

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Primary ExaminerThurman K. Page
Assistant ExaminerJames M. Spear

(57] ABSTRACT
A sustained or controlled release tablet is disclosed. The tablet comprises a water soluble medicament. a bydrox-ypropyi methylcellulose having sustaining action, a pharmaceutical binding agent, and a hydrophobic com-ponent.

TIME I24HOURS

24 ClaIms, 2 Drawing Sheets

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U.S. Patent June 30, 1992 Sheet 1 of 2 5,1261145

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FIG. I

TIME (24HOURS
C

PERCENT DISSOLUTION

i’1’9ZI’Sz J° z)3qs Z661 ’oc

N

3U3d Sul

IWO

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CONTROLLED RELEASE TABLET CONTAINING WATER SOLUBLE MEDICAMENT

This is a Continuation of application Set. No. 07/337,460, filed Apr. 13. 1989 now abandoned. This, invention relates to a controlled release tablet comprising hydroxypropyl methylcellulose. a binding agent. an internal hydrophobic component, and water soluble medicament. The tablet can be formed by wet granulation techniques.

BACKGROUND OF THE INVENTION

Sustained or controlled release products for oral ad-ministration are known and widely used. Hydroxypro-pyl inethylcellulose has been used in such products. It is believed that hydroxypropyl methylcellulose in such tablets partially hydrates on the tablet surface to form a gel layer. The rate of hydration and gelling of the hy-droxypropyl methylcellulose tablet surface affects the drug release from the tablet and contributes signifi. cantiv to the sustained release aspect of such products. However, it has been difficult to formulate controlled release tablets of soluble medicaments and hydroxypro-pyl methylcellulose. First, it has been difficult to achieve the desired dissolution profiles or to control the rate of release ofsoluble to freely soluble medicaments. This may be due to leaching of the medicament from the tablet before hydration and gelling of the hydroxy. propyl methylcellulose occurs. Second, known tablet. ing techniques such as direct compression and granula. tion may fail when a high proportion ofsoluble medics-meat is required regardless of its degree of solubility. Dead coating technology can be used to form sus-tained release products Them products typically com-prise hard gelatin capsules containing coated beads of medicament. Soluble medicaments are available in con-trolled release capsules of this type. However, tablets have certain advantages over capsules and these advan-tages are lost with the use of capsules for sustained release of soluble therapeutic agents.
Tablets have several advantages over capsules. For some drugs, it is recommended that the patient begin taking a smaller dose and gradually over time increase the dose to the desired level. This can help avoid unde-sirable side effects. Tablets can be preferable to capsules in this regard because a scored tablet easily can be bro-ken to form a smaller dose.
In addition, tableting processes such as wet granula-tion are generally simpler and less expensive than bead coating and capsule formation. Further, tablets can be safer to use because they may be less subject to tamper-ing.
Accordingly, a need exists for a controlled release product of more soluble medicaments, combining the advantages of hydroxypropyl methylcellulose in sus-taining and controlling the release rate, the relative ease and low cost of wet granulation, and the other advan-tages of the tablet form over capsules.

BRIEF DESCRIPTION OF THE INVENTION

We have discovered a sustained release tablet com-prising hydroxypropyl mechylcellulose with sustaining properties but negligible binding properties, in an amount effective 10 produce a desired release rate,suffi-cient water soluble pharmaceutical binder to permit wet granulation, an amount of internal hydrophobic compo-

nent effective to permit wet granulation, and a water soluble medicament.

BRIEF DESCRIPTION OF THE DRAWINGS

5 FIG. 1 is a graph showing an average dissolution
profile of 750 mg. niacin tablets made in accordance with the invention.
FIG. 2 is a graph comparing the average dissolution profiles of niacin (500 mg) tablets made in accordance 10 with the invention and a commercially available extend-ed-release niacin (500 mg) capsule.

DETAILED DESCRIPTION OF THE E
INVENTION

15 The controlled release tablet includes a medicament
and a hydrophilic polymer matrix for achieving con-trolled or sustained or extended release of the medica-Incnt. The tablet can include a high proportion of water soluble medicament and can be prepared by standard 20 wet granulation techniques. A desirable dissolution profile can be achieved. The tablet can be scored to permit easy titration up to the desired dose.
The medicament can be any suitable water soluble therapeutically active material which is commonly ad-25 ministered orally. The medicaments that we believe will benefit most from the invention are those that appear to be too soluble for ready inclusion in an effective con-trolled release tablet utilizing hydroxypropyl methyl-cellulose. The solubility ofthe medicaments could from 30 about 0.1 to 30% (at 25’ C.). This includes slightly soluble to freely soluble compounds, according to the definitions provided by Remington Pharmaceutical Sciences.

The minimum amount of medicament or active drug
35 in the tablets of the invention will typically be about 30% by weight based on the weight of the tablet and can range up to about 90%. Within this range, generally it is possible to incorporate a greater amount of a less soluble medicament.

40 Niacin, with a water solubility of about 1.67 g/lOOml
(25’ C.), is a medicament falling within the scope of the invention. Niacin has the chemical formula CóHNO2 and is also known as nicotinic acid, it is commercially available as fine white crystals or white crystalline pow-45 der, From sources such as Lotus and Ashland Chemical. It will typically be present at a level of from 50-85% by weight ofthe tablet. Other therapeutically active mate-rials suitable for use in the invention include morphine sulfate. chlorpbcniramine hydrochloride. pseudoephed-50 tine, codeine sulfate and dlltiazein hydrochloride, aspi-rin, acetaminophen, and liaproxen.
The hydrophiflic polymer matrix of the,tablets ofthe invention is a dynamic system involving hydroxypropyl inethylccllulose wetting, hydration, and dissolution.
3 Other soluble excipienis or drugs also wet, dissolve, and diffuse out of the matrix while insoluble materials are held in place until the surrounding polymer/excipient/- drug complex erodes or dissolves away.
The most significant mechanism by which drug re-
60 lease is controlled is through the use of hydroxypropyl metbylcellulose. The hydroxypropyl methylcellulose, present throughout the tablet, partially hydrates on the tablet surface to form a gel layer. Overall dissolution rate and drug availability are dependent on the rate of 65 soluble drug diffusion through the wet gel and the rate of tablet erosion. Hydroxypropyl niethylcellulose with substitution rates of about 7-30% for the mechoxyl group and greater than 7% or about 7-20% for the

hydroxypropoxyl group are preferred for formation of this gel layer. More preferred are substitution rates of 19-30% for the methoxyl group and -12% for the hydroxypropyl group.
Hydroxypropyl roethylcelluloses vary in their viscos-ity. rnethoxy content, and hydroxypropoxyl content. Properties also vary. Some have more sustaining prop-erties or the ability to achieve conrolled release of medi-caments. Others have good binding properties and are less desirable for sustained properties. By "binding properties" we are referring to the ability to act as a binding agent for tablet production by wet granulation, for example, incorporating the hydroxypropyl methyl-cellulose into aqueous solution in order to spray onto the dry powders. Hydroxypropyl methylcelluloses with good sustaining properties are too viscous for use as the binder in wet granulation techniques.
The tablets of the invention comprise about 5-30 percent by weight hydroxypropyl methylcellulose with sustaining properties and negligible binding properties. Such hydroxypropyl methylcelluloses generally have a viscosity of no less than about 1000 centipoises. More typically, the viscosity will be no less than about 4000 cps. For improved performance, the tablet will comprise about 5-20 weight percent, or, more pref. crably. about 8-12 percent hydroxypropyl methylcellu-lose with sustaining characteristics.
A preferred hydroxypropyl methylcellulose with sustaining properties is a hydroxypropyl methylcellu-lose with substitution type 2208, with a nominal viscos-

ity. 2% aqueous, of about 100,000 cps, a melhoayl con-
tent of about 19-24, and a liydroaypropoxyl content of about 7-12%. A "controlled release" grade is pre-ferred, with a particle size where at least 90% passes through a #100 USS mesh screen. A commercially-available hydroxypropyl methylcellulose meeting these specifications is the Methocel KIOOMCR, from The Dow Chemical Company.
The tablet further comprises or includes about 2-15 weight percent water soluble pharmaceutical binder. The binder or binding agent aids in tablet production by wet granulation, serving as an adhesive and adding strength to the tablet.
Many suitable binders are known. They include poly-vinyl pyrollidone, starch, gelatin, sucrose, lactose, methylcellulose, hydroxypropyl methylcellulose, and the like. For good binding action without excess bind-ing agent, we prefer the use of about 2-8% by weight. or more preferably, particularly where the preferred binding agent is used, about 2-5% by weight.
The preferred water soluble pharmaceutical binder for use in this invention is hydroxypropyl methylcellu-lose having binding properties. Such hydroxypropyl methylcelluloses typically have a much lower viscosity than the bydroxypropyl methylcelluloses that have good sustaining characteristics. Generally, the viscosity of a 2% aqueous solution will be less than about 1000 cps. More typically, it will be less than 100 cps,
A preferred bydroxypropyl methylcellulose for use as a binding agent in the context of the invention has a nominal viscosity, 2% aqueous, of about 13, a methozy content of about 28-30%, a hydroxypropyl content of
about 7-12%, and a particle size of 100% through USS
30 mesh screen and 99% through USS 40 mesh screen. Hydroxypropyl methylcellulose 2910, Methocel ElS
from The Dow Chemical Company meets these stan-
dards and is a preferred binder.

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Other suitable binding hydroxypropyl methylcel-lulss include Methocel ESLVP, Methocel ESOLVP. and Methocel K3P. The methylcellulose Methocel AISLVP can also be used.
Another binder we recommend is polyvinyl pyrolli-done, also known as polyvidone, povidone, and PVP. Typical properties of commercially available PVP’s include density between 1.17 and 1.18 g/rrd and an average molecular weight ranging from about 10,000 to 360,000. Generally, the higher molecular weight PVP’s would be more suitable for use in this inventIon. Suppli-ers include BASF Wyandotte and GAP.
An essential component of the invention is what we refer to as the hydrophobic component. This compo-nent permits wet granulation of soluble medicaments with hydroxypropyl methylcellulose where it would not otherwise be easily accomplished using standard wet granulation techniques. In the absence of this com-ponent, we have found that the hydroxypropyl methyl-cellulose/medicament mixture tends to become "doughy" and granules or powder cannot easily be obtained.

The hydrophobic component comprises a wax-like material. The was-like material comprises a solid gener-ally Insoluble substance having a waxy consistency. It 5hould, ofcourse, be ingestible. Many such materials are known and include waxes such as beeswax. carnauba wax, candclilla wax, Japan wax, paraffin, hydrogenated castor oil, higher fatty acids, such as palmitic acid, stea-ric acid, and mynstic acid, esters of such higher fatty acids such as substituted mono-, di-. and tri-glycerides. acetylated monoglycerides. glyceryl monostearate, glyceryl tristearate. cetyl palmitate, glycol alcaraic. glyceryl tri.myristate, higher fatty alcohols such as cetyl alcohol. stearyl alcohol, and myristyl alcohol, and mixtures thereof.

Two wax-like materials are preferred in view of their ready availability in powdered form, reasonable cost. ease of handling, and their effectiveness in the context or this invention. These waxy materials are hydroge-nated vegetable oil and stearic acid. Hydrogenated vegetable oil generally consists mainly of the triglycer. ides of stearic and palmitic acids, and is readily commer-cially available. A preferred hydrogenated vegetable oil for use in this invention is available through Edward Mendell, Co., Inc., of N.Y., under the trademark Lu-britab fi. The Lubntab fi product has a bulk density of 0.48-0.56 grams per milliliter, a melting point of from 61’-66’ C, a saponification value of 188-198. 0.8 maxi-mum ussszponifiable matter, and a typical particle size distribution of 15 percent maximum on 100 meals USS screen, 35 percent maximum through 200 mesh USS screen. An advantage ofthis product is its availability in powder form. A similar hydrogenated vegetable oil is available from Durkec, under the trademark Durstex. Stearic or octadecanoic acid is typically manufac-tured from fats and oils derived from edible sources, and commercial stearic acid is typically a mixture of stearic acid (CiHöOz) and palmitic acid C16H3202). Siearic acid is available from many chemical suppliers, includ-ing Emery Industries and Mallinckrodt, Inc.
The powdered stearic acid NP available from Mal-linckrodt contains not less than 40.0 percent C35H3602 and not less than 40.0 percent C1eH2O2; the sum of these two components is not less than 90.0 percent. The congealing temperature is not lower than 54’, and the iodine value is not more than 4.

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The hydrophobic component should be present in an
amount effective to permit wet granulation of the con-trolled release tablet. Such an amount is commonly
2-20 percent by weight of the tablet depending on the solubility of the medicament. Higher concentrations
will be required for more soluble medicaments. Prefera-bly. for good granulating results and sustained release, it will be present at from 5-15 percent of the total tablet weight, or more preferably, 6-12 percent by weight. Other components commonly used in tablet forma-tion, such as external lubricants, dyes, fillers and exten-ders, may also be used as desired. External lubricants or tableting aids can include calcium stcarate, stearic acid. hydrogenated vegetable oils, talc, corn starch, colloidal silicone dioxide, magnesium stearatc and glyccryl be-henate. We have found that a combination of glyceral behenaic, magnesium slcarate, and colloidal silicon di-oxide is particularly effective as a tableting aid.
The external lubricants, typically added to the dried granules before tableting, if used, can be present at up to about 5 percent ofthe total tablet weight. More prefera-bly. they will be present at 0.5-4 percent, or for im-proved tableting. 1-3 percent of the tablet weight. Dyes can, of course, be used for a more pleasing tablet appearance. Many suitable ingestible dyes for tablets are known and are widely available.
Fillers or extenders can be used if needed or desired. When a tablet containing a 250, 500. or 750 tug. dose of niacin is formed, fillers or extenders typically would not be used because the medicament itself supplies sufficient volume to the tablet. However, fillers or extenders may be desirable where a lower dose of medicament is used. Many fillers or extenders are known and are readily available, including calcium sulfate. dicalciurn phos-phate. iricalcium phosphate, lactose, sucrose, starch dextrose, and microcrystalline cellulose.
The methodsof forming the tablets of the invention are typical wet granulation methods, either conven. tional or fluid bed. A uniform blend of the hydrophobic component (flakes or powder) and dye, if used, is fanned. The binding agent is dissolved in water to form a binding agent solution. The hydrophobic component blend, the sustaining hydroxypropyl metbylcellulose, and the medicament are granulated using the binding agent solution to a final moisture level of less than about 7 percent, preferably less than about 5 percent. In the conventional process, the granulation is removed from the mixer and oven dried. External lubricating agents are then mixed in and the mixture is tablcted. As would be understood by one of skill in the art, fluid bed pro-cessing would not require the oven drying step; instead the components would be granulated and dried in one procedure.
Where niacin is the medicament, useful tablets in-elude doses of 250. 500. and 750 mg. High doses such as 750 mg. can cause side effects such as uncomfortable flushing and nausea unless treatment begins with smaller doses. Tablets can be scored to permit dasy breakage into smaller doses for titration up to the stan-dard 750 mg. dose given twice daily. Titration, particu-larly with sustained release tablets, has been shown to help avoid side effects of niacin therapy.
Tablets made according to the invention can have desirable dissolution profiles mimicking zero order ab-sorption characteristics or constant rate of release over time. Niacin tablets in accordance with the invention show dissolution profiles of 10-35% in 2 hours after ingestion, 40-7(% in 8 hours, and at least 90% dissolu-

tion in 24 hours. Even more preferably, the profile of the niacin tablets is 10-30% release in 2 hours, 40-60% in S hours, and complete dissolution in 24 hours, and tablets in accordance with the invention have shown
5 this profile.
The invention will be further understood by refer-ence to the following Examples which include pre-ferred embodiments.

10 1

EXAMPLE[

750 tu& niacin tablets were formed having the fol-lowing components:

IS by Weight Mg.Priblei
Niacin (L.oxza) 73.07 750.0
Hydrosypeopyt 2.50 25.7
Mdbylcsllulasc 2910

(Meikocel EISLV, Dow) Itydrosypeopyl 9.74 100.0

20 klctbykcllulosc 220$

Methocet KIOOMC&, Dow) Hydrogenated Vegetable 11.36 111.7

Oil (Lubntab, McndclIt
Glycaryl Behenite 0.50 5.1
(Compn.OI $15)

25 M.ancsium Sicarate t.50 154

(M&fltacktodt)
FD&C Red 040 Lake Dye (40%) 0.13 1.3
(Colorcon)
Colloidal S$iccn Dioxide 1.00 10.3
(Sylold 244)

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To form the tablest, 16 liters of water was heated to
95’ C. in a stainless steel container. The Methocel EISLV powder was slowly added while mixing until a homogenous suspension was obtained. The impeller 33 speed was adjusted to avoid excessive air from entering the solution through the vortex.
48 liters of very cold water was slowly added and the mixture was mixed thoroughly until a clear solution was obtained and the temperature was below 20’ C. Mixing 40 continued for an additional 20 minutes.
The hydrogenated vegetable oil was sized through a USS No. 16 screen and added to a mixer. The dye was added to the mixer and mixed until the color distribu-tion was uniform, about 5 minutes. The color mix was 45 then transferred to a ribbon blender. The niacin powder was added to the ribbon blender and mixed for about 10 minutes. The Methocel KIOOMCR was then added and mixed for an additional 10 minutes.
The Methocel EI5LV solution was sprayed in and
50 then mixed for I minute. The resulting wet granulation was then sized through a USS No. 16 screen.
The sized Wet granulation was spread lightly on trays, it approximately 2 kilograms per tray. The granu-lation was dried in an oven at 230’ F. to a moisture 55 content of less than 5 percent. The oven dried granula-tion was then sized through a USS No. 12 screen. After sizing, the granulation was collected in double poly-lined drums.

Three approximately 200 kilogram batches were
60 formed in the above manner, each utilizing 149.06 kilo-grams niacin, 3.97 kilograms Methocel EISLV. 19.87 kilograms Methocci KIOOMCR, 24.84 kilograms Lu-britab hydrogenated vegetable oil, and 0.26 kilograms FD&C Red Dye #40 Lake 40% pure dye. These 63 batches were weighed, and combined in a ribbon blender. 3.0 kilograms glyceryl behenate and 3.0 kilo. grams magnesium stearate were then added to the rib-bon blender and the mixture was mixed for 5 minutes.

- - S

5,126,145

The resulting product was tableted using a standard rotary press into tablets of 750 milligrams niacin.

EXAMPLE 11

750 milligram niacin tablets were formed as follows:

MiIhgram/
Per Pan Tablet Kilograms Used

Niacin (Loessa) 750.00 332.500
Hydrorsypropyl 24.00 10.000
Mcthykelluloc 2900
(Methocel E15LV. Dow)
Rydroayp,opyt 94.10 39.20)
Methytcallnlose 2201
(Meihocel 1(IOO4CR. Dow)
Hydrogenated Vegetable 6240 26.00
Oil (Lubfltab, Mendell)
F13&C Red 440 Lake Dye (40%0 0.70 0.30D
(Colorcon)

The niacin tablets of Example 11 were formulated by the fluid bed process. Half of the above quantities were used for the first granulation. In this granulation. 33.000 kilograms deionized water were added to a stainless steel steam kettle and heated to 95’ C. While mixing (but avoiding excess roarningl the Methocel EI5LV and dye were added to the water. 67.000 kilograms cold deionized water were then added and mixing continued for about 20 minutes. The mixture was cooled to 21 C. To the fluid bed container were added the niacin.

Methocel I(IOOMCR. and Lubritab hydrogenated veg-etable oil. These three components were granulated with the Methocel EISLV solution. After exhausting the granulating solution. the material in the fluid bed containers was dried to less than 1% moisture.
The dried material was transferred to clean polylined containers. Using the Sweco Sifter, fitted with a 12 mesh screen, the granulation was sized into clean poiyl. med drums.

A second batch of granulation was formed in an iden-tical manner using the remaining half of the compo-nents. The two granulations were then added to a rib-bon blender. These components were blended for 5 minutes. 6.000 kilograms magnesium stearate. 2.000 kilogram glyceral behenate, and 4.000 kilograms colloi-dal silicon dioxide were added to the ribbon blender and mixed for 5 minutes. The material was transferred to clean poly-lined drums and later tableted into tablets containing 750.00 milligrams niacin.
Two other formulations are shown below.

EXAMPLE Ill

Cbem,cal Name MilIi4ra.ns ’Tab Percent
Niacin 130.0 71.125
Meihocel EISLV 24.0 230
(hydrosypropyl zncthylcettulonc)
Methocel KI00MCR 94.1 9.10

(bydrooypeopyl methylcellutcac)
Lubriiab 62.4 6.30
(hydrogenated vegetable oil)
I’DICC Red 040 dye 0.7 0.073
Magnesium Sovaraic 04.4 1.50
Compntol 4.1 0.50
(glyceryl behenate)
Syloid 244 9.6 1.00
(cotlo.daJ suI.con dicside)

Tablets having the formulation of example III were made using conventional and fluid bed granulating techniques in a production mode.
FIG. I shows the average dissolution pattern of six
5 tablets having the formula shown in Example 113. Tablest were dissolved using a Hanson Dissolution Apparatus with a U.S.?. rotating bracket at 100 rpm in 900 ml. water at 37 C. Samples were taken from each dissolution vessel at 1, 2, 4, S. 12, and 24 hours, and 10 analyzed by UV for nicotinic acid content. The results show a desirable release pattern.

Chemical Name MtlhpsmsfTab Percent
IS Niacin 750.0 16.220
Meibocci EISLV 24.0 2.439
(bydroaypropyl incthylcellutoee)
Mctbocel ItIOOMCR 94.1 9.501
(hydrcaypropyl methylcetlalosc)
Lubnieb 16.4 1710

20 (hYdo$eiiied ve$4iable oil)
FOaC Red #40 dye 0.7 0.073
Magnesium Slearstc 14.4 1.46)
Ccmpfliot .1.0 0414
lgtvccry) bcl’cnaI)
Syloid 144 9.6 0.976
25 (colloidal silicon dioxide)

Tablets having the formulation of Example IV were made using conventional granulating techniques in the laboratory.
30

Chemical Nam B Weight rd ms./Tablet
NIacin 73.07 50000
Methocci EISLV 2.50 17.11

(hydroxypropyl methylccllutose) 35 Meihocel ICI00MCR 9.74 66.65
(hydrosypropyl meihylccllulosel
Lubncab 11.56 79.10
(hydrogenated vegetable oil)
Coinpneol III 0.30 3.42
(glyccryI bchcnmc)
40 Magnesium S,earale iSO 10.26
’FD&C Red #4odye 0.13 .19
Syloid 244 i.bo 6.14
(colloidal silicon dioxide)

45 Tablets having the composition shown in Example V were made using conventional and fluid bed techniques. The dissolution pattern of tablets made in accordance with the formula of Example V was compared with the dissolution pattern of a typical commercially available So ectended release capsule.. 50D mg. niacin. Six samples of each product were dissolved using a Hanson Dissolu-tion Apparatus with a U.S.?. rotating basket at 100 rpm in 900 ml. of water it 37* C. Samples were t.qken from each dissolution vessel over a 24-hour period, and ana-55 by UV for nicotinic acid content. As shown in
110. 3, the tablets of the invention followed by similar profile to the commercially available extended release capsules, 500 Ms. niacin.

60 By Weight
Chemical Man" Total MgTable.
Niacin 13.07 250.0)
Methocet EISLV 2.50 5.35
(hydrosypropyl meihylcellulose)
65 Methocel KIOOMCR ’-3 3332
(hydrosypeopyl nncthylcclhrlose)
Lubnc.b 11.35 39.55

(hydrogenated vegetable oil)
Compniol 145 0.50 1.71

Martindale - The Complete Drug Reference - Monographs

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Document Outline

Adverse Effects
Treatment of Adverse Effects
Precautions
Interactions
Pharmacokinetics
Uses and Administration

Nifedipine (9263-k)

Nifedipine (BAN USAN, rINN)
Chemical Name: Dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate
Chemical Formula: C17H18N206
Molecular Weight: 346.3
CAS Number: 21829-25-4

Synonyms: Bay-a-1040; Nifedipina; NifØdipine; Nifedipino; Nifedipinum Pharmacopoeias: In Chin., Eur. (see About Martindale), Int., Jpn, and US. Ph. Eur. 5.4 (Nifedipine). A yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone. When exposed to daylight or to certain wavelengths of artificial light it is converted to a nitrosophenylpyridine derivative, while exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Solutions should be prepared in the dark or under light ofwavelength greater than 420 nm, immediately before use. Protect from light. USP 29 (Nifedipine). A yellow powder. Practically insoluble in water; soluble 1 in 10 of acetone. When exposed to daylight or to certain wavelengths of artificial light it is converted to a nitrosophenylpyridine derivative, while exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Store in airtight containers. Protect from light.
Indications: Calcium-channel blocker
Revision Date: 20051121

Preparations

Adalat (Bayer, Am.) Adalat (Bayer, Austral.) Adalat (Bayer, Austria)
Adalat (Bayer, BeIg.) Adalat (Bayer, Braz,) Adalat (Bayer, Canad.)
Adalat (Bayer, Chile) Adalat (Bayer, Cz.) Adalat (Bayer, Denrn.)
Adalat (Bayer. Fin.) Adalat (Bayer, Ger.) Adalat (Bayer, Gr.)
Adalat (Bayer. Hong Kong) Adalat (Bayer, Hung.) Adalat (Bayer. itt.)

Martindale - The Complete Drug Reference - Monographs

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Document Outline

Adverse Effects and Precautions
Interactions
Pharmacokinetics
Uses and Administration

Ketoprofen (2662-f)
Ketoprofen (BAN, USAN, rINN)
Chemical Name: (RS)-2-(3-Benzoylphenyl)propionic acid
Chemical Formula: C16H1403
Molecular Weight: 254.3
CAS Number: 22071-15-4 (ketoprofen); 57469-78-0 (ketoprofen lysine); 57495-14-4 (ketoprofen sodium)
Synonyms: KØtoprofŁne;Ketoprofeno; Ketoprofenum; RP-19583 Pharmacopoeias: In Chin., Eur. (see About Martindale), Jpn, Pol., and US. Ph. Eur. 5.4 (Ketoprofen). A white or almost white, crystalline powder. M.p. 94° to 97°. Practically insoluble in water; freely soluble in alcohol, in acetone, and in dichioromethane. USP 29 (Ketoprofen). Store in airtight containers.
Indications: Analgesic; anti-inflammatory; antipyretic; NSAID
Revision Date: 20051121

Preparations

Actron (Bayer. Austria)
Algiprofen (Eurofarma,
Braz.)

Alrheurnat (Bayer, UK)

Apo-Keto (Apotex. Hong
Kong)

Arcental (F5 Profas. Spain)

Bibix (Lernery, Mex.)

Bi-Profenid (Aventis, Fr.)

Dexal (Pulitzer. Ital.)
Dolo-Ketazon (Recalcine,
Chile)

Actron (Bayer, USA) Actroneffix (Bayer. Fr.)

Alket (Difass. Ital.) Airheumat (Bayer. fri.)

Airheurnun (Teofarma, Apo-Keto (Apotex, Canad.)

Apo-Keto (Apotex. Apo-Keto (Apotex.
Malaysia) Singapore)

Arthril (Sons. Mex.) Artrinid (Uniao Ouimica,

Braz.)
Bi-Profenid (Aventis, Braz.) Bi-Profenid (Aventis, Cz.)

Birofenid (Aventis, Beig.) Ceprofen (Neo Quimica,

Braz.)
Dolgosin (Pulitzer, Ital.) Dolofar (Medipharm, Chile)

Efiken (Kendrick, Mex.) Euketos (CT, Ital.)

PRESCRIBING INFORMATION

PAXILfi
(paroxetine hydrochloride)
Tablets and Oral Suspension

SuicidaUty and Antidepressant Drugs
Antidepressants increased the risk compared to placebo ofsuicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of PAX1L or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk ofsuicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidailty, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PAXIL is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

DESCRIPTION
PAXIL (paroxetine hydrochloride) is an orally administered psychotropic drug. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4’- fluorophenyl)-3S-[(3’,4’-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula ofC9H20FN03.HCl.1/2H20. The molecular weight is 374.8 (329.4 as free base). The structural formula ofparoxetine hydrochloride is:

Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of
120° to 138°C and a solubility of 5.4 mg/mL in water.
Tablets: Each film-coated tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 10 mgyellow (scored); 20 mgpink (scored); 30 mgblue, 40 mggreen. Inactive ingredients consist of dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide, and I or more of

DrugBafllc: DB00333 (Omepazoe)

Home Browse PharmaBrowse ChemQuery Text Query SeqSearch Data Extractor Download and Stats

Search DrugBank for: [_
IZI Common Name ZI Synonym and Brand Name DAli Text Fields

Showing card for Omeprazole (DB00338)

for I Approved Drugs

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Primary Accession l00338

’Secondary Accession?JAPRD00446

fOmeprazolo
T Small Molecule
I!IVi"

Ir*ipiaMk..

Approved
Investigational

highly effective inhibitor of gastric acid secretion used in the therapy of stomach ulcers and zollinger-ellison syndrome. The drug inhibits the H(+)-K(+)-ATPase (H(+)-K(+)- exchanging ATPase) in the proton pump of gastric parietal cells. [PubChem]

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DgBank: DB00338 (OnxprazoJe)

Predicted Water

I.1I!15fr.W,IeT! ilTTSolubility R14

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Dn3gBank DB00586 (Diclofenac)

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El Common Name 123 Synonym and Brand Name 0All Text Fields

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Update Date 12007-12-13 18:05:09
Primary Accession ME
I DBOO586 Number

flcIofenac
Small Molecule

1 Approved
Investigational

IA non-steroidal anti-inflammatory agent (NSAID) with antipyretic and analgesic actions. It is
II*(sIISft1]i 1pnmarily available as the sodium salt. [PubChem]

I 1. Diclofenac Sodium I 2. Diclofenac Potassium

1 Diclofenac Acid
(I o(43)23V4/2008 L43I:2

DrugBank DB00586 (Diclofenne)
PDRhealth Link 1INot, Availabl
Wikipedia Link II
FDA Label CORMXne zoo -0 of
Material Safety Data
Sheet (MSDS)
Synthesis Reference TW11NK
Average Molecular
Weight I=
Monoisotopic Molecular
Weight?F.0167 g1mol
Melting Point

Experimental Water
Solubility

Predicted Water mg/mL Solubility
State

Experimental LogP/ IIe________

t Hydrophobicity

Predicted LogP/
Hydrophobicity
Experimental LogS Not Available

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DrugBank: DB00564 (Carbamazepinc)

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Secondary Accession PRD00337

If1ui: Carbamazepine
Small Molecule
Approved
Investigational

An anticonvulsant used to control grand mal and psychomotor or focal seizures. Its mode of action is not fully understood, but some of its actions resemble those of phenytoin; although there is little chemical resemblance between the two compounds, their three-dimensional structure is similar. [PubChem]
(Carbamezepine

http://www.drugbank.ca/cgi-bn/geLCard.CgiCARDDROO564 (1 of 35)2342009 14:29:49

Dnigliank: DB00564 (Carbarnazcpine)

Average Molecular
Weight
Monoisotopic Molecular
Weight
Melting Point EIIJ1I

Experimental Water
Solubility Label]

Predicted Water
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Hydrophobicity Label]

Predicted LogPI [ALOGPS] Hydrophobicity 12.10
Experimental LogS ’NotAvailable

Experimental Caco2 Available Permeability IFot

pKa/lsoelectric PointIWV1k
Mass Spectrum Click Here for Mass Spectrum

MOL File Image [LTj
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DrtigBank: D800860 (Prednisolone)

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DB00860

APR000I 97

Prednisolone
Small Molecule
Approved

glucocorticoid with the general properties of the corticosteroids. It is the drug of choice for I conditions in which routine systemic corticosteroid therapy is indicated, except adrenal ficiency states. [PubChem]

http:l/www.dnigbank.ca/cgi-binlge(Csrd.CgI7CARD=D300860 (1 of 19)23/0412008 14:27:24

DrugBank: DB00860 (Ptcdnisolofle)

Average Molecular
Weight

Monoisotopic Molecular 360.1937 g/mol

Melting Point

Experimental Water

Solubility jI111iT3

FAUO Predicted Water Solubility
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Permeability
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DngBank DB00277 (rheophyllinc)

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Showing card for Theophylline (DB00277)

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for lApproved Drugs

Secondary Accession
Number

Small Molecule
Approved

methyl xanthine derivative from tea with diuretic, smooth muscle relaxant, bronchial
lation, cardiac and central nervous system stimulant activities. Theophylline inhibits the ,5’-cyclic nucleotide phosphodiesterase that degrades cyclic AMP thus potentiates the
tions of agents that act through adenylate cyclase and cyclic AMP. [PubChem]

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DjagBank: DB00277 (TheophyUine)

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PubChem Compound 41
PubChem Substance ’LK
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PharmGKB ID
HETID Il.
GenBank ID

Drug ID Number [DIN] II$Ii[I
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PDRhealth Link IIiTTlIiIi:
Wikipedia Link iTheophylline
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Synthesis Reference
Average Molecular
Weight

Monoisotopic Molecular EiI1I1T4 Weight
Melting Point

Experimental Water

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DrugBank DB01586 (Ursodeoxycholic acid)

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’update Date 12007-12-13 18:20:06

Primary Acces§ion 1131301586 Number
,Secondary Accession
?Number ’I

Not Available

Ursodeoxycholic acid
Small Molecule

Approved Drug Type Investigational -Al

Ursodeoxycholic acid is an epimer of chenodeoxycholic acid. It is a mammalian bile acid

found first in the bear and is apparently either a precursor or a product of - I-Il chenodeoxycholate. Its administration changes the composition of bile and may dissolve
gallstones. It is used as a cholagogue and choleretic.

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lUrsodeoxycholic acid
IClick for FDA Label (pdf)

Material Safety Data 1Ick for MSDS (pdf)

Available

Average Molecular f392.5720 glmol Iu!1I1

,Monoisotopic Molecular F92.2927 glmol?Weight
ILWITh1 1203 °C
10.02 mg/mL at 20

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11.97e02 mg/mL [ALOGPS] Water

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Experimental LogPI [RODA, [FDA
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TX 523 656 epmu d
FAX +4989 2399-4465

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London WC1R 4
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Europäisches
Patentamt

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European Office europØen
Patent Office des brevets

Directorate General 2 Direction GenØrale 2

Application No. Ref. Date
01 921 605.0 - 2108 P32315EP-K,NCB 16.08.2007

Applicant
JAGOTEC AG

Communication under Rule 51(4) EPC

You are informed that the Examining Division intends to grant a European patent on the basis of the above application with the text and drawings as indicated below:

In the text for the Contracting States:
AT BE CH CY DE DK ES Fl FR GB GR lE IT LI LU MC NL PT SE TA

Description, Pages

1,2,4-60 as published

3, 3a filed with telefax on 16.03.2006

Claims, Numbers

1-34 filed with telefax on 11.05.2007

Drawings, Sheets

1i5-5i5 as published

A copy of relevant documents is enclosed

The title of the invention in the three official languages of the European Patent Office, the international patent classification, the designated Contracting States, the registered name of the applicant and the bibliographic data are shown on the attached EPO Form 2056.

You are requested within a non-extendable period of four months of notification of this communication

Registered Letter EPO Form 2004 01.O6CSX

j Date 16.08.2007 Sheet 2 Application No.: 01 921 605.0
to file 1 set of translations of the claim (s) in the two other EPO official languages;

EUR

2a. to pay the fee for grant including the fee for printing up to and including 35 pages;
Reference 007 750.00

2b. to pay the printing fee for the 36th and each additional page;
number of pages: 37
Reference 008 407.00

3. to pay the additional claim fee(s) (Rule 51(7) EPC);
number of claims fees payable: 1
Reference 016 45.00

Total amount 1202.00

Concerning the possibility of a request for accelerated grant pursuant to Article 97(6) EPC, reference is made to OJ EPO 2001, 459.

If you do not approve the text intended for grant but wish to request amendments or corrections, the procedure described in Rule 51(5) EPC is to be followed.

If this communication is based upon an auxiliary request, and you reply within the time limit set that you maintain the main or a higher ranking request which is not allowable, the application will be refused (Article 97(1) EPC, see also Legal Advice 15,05 (rev. 02), OJ 612005, 357).

If the enclosed claims contain amendments proposed by the Examining Division, and you reply within the time limit set that you cannot accept these amendments, refusal of the application under Article 97(1) EPC would result in the case that agreement cannot be reached on the text for grant.

In all cases except those of the previous two paragraphs, if the grant, printing or claims fees are not paid, or the translations not filed, in due time, the European patent application will be deemed to be withdrawn (Rule 51(8) EPC).

For all payments you are requested to use EPO Form 1010 or to refer to the relevant reference number.

After publication, the European patent specification can be downloaded free of charge from the EPO

publication server https:/4ublications.european-patent-office.orq or ordered only from the Vienna sub- office upon payment of a fee (OJ EPO 2005, 126).
Upon request in writing each proprietor will receive the certificate for the European patent together with one copy of the patent specification only if the request is filed within the time limit of Rule 51(4) EPC. If such request has been previously filed, it has to be confirmed within the time limit of Rule 51(4) EPC. The requested copy is free of charge. If the request is filed after expiry of the Rule 51(4) EPC time limit, the certificate will be delivered without a copy of the patent specification.

Translation of the priority document(s)

If the translation of the priority document(s), as required by Article 88(1) EPC, or the declaration according to Rule 38(5) EPC has not yet been tiled, Form 2530 will be despatched separately. The translation is to be filed within the above mentioned time limit (Rule 38(5) EPC).

Note on payment of renewal fees

Registered Letter EPO Form 2004 01 OGCSX

j Date 16.08.2007 Sheet 3 Application No.: 01 921 605.0
If a renewal fee falls due between notification of the present communication and the proposed date of publication of the mention of the grant of the European patent, publication will be effected only after the
renewal fee and any additional fee have been paid (Rule 51(9) EPC).

Under Article 86(4) EPC, renewal fees are payable to the European Patent Office until the year in which
the mention of the grant of the European patent is published.

Filing of translations in the Contracting States

Pursuant to Article 65(1) EPC the following Contracting States require a translation of the specification of the European patent in their/one of their official language(s) (Rule 51 (10) EPC), insofar this specification will not be published in their/one of their official language(s)

within three months of publication of the mention of such decision:

AT AUSTRIA FR FRANCE
BE BELGIUM GB UNITED KINGDOM
CH SWITZERLAND /LIECHTENSTEIN GR GREECE
CY CYPRUS IT ITALY
DE GERMANY NL NETHERLANDS
DK DENMARK PT PORTUGAL
ES SPAIN SE SWEDEN
Fl FINLAND TR TURKEY

within six months of publication of the mention of such decision:

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The date on which the European Patent Bulletin publishes the mention of the grant of the European patent will be indicated in the decision on the grant of the European patent (EPO Form 2006).

In case of a valid extension the following Extension States require a translation of the claims in their official language within three months after publication of the mention of the grant of the European patent:

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The translation must be filed with the national Patent Offices of the Contracting or Extension States in

accordance with the provisions applying thereto in the State concerned. Further details (e.g. appointment of a national representative or indication of an address for service within the country) are given in the

EPO information brochure "National law relating to the EPC", and in the supplementary information published in the Official Journal of the EPO, or available on the EPO website.

Failure to supply such translation to the Contracting and Extension States in time and in accordance with the requirements may result in the patent being deemed to be void ab initio in the State concerned.

Note to users of the automatic debiting procedure

Unless the EPO receives prior instructions to the contrary, the fee(s) will be debited on the last day of th

period of payment. For further details see the Arrangements for the automatic debiting procedure (see Supplement to OJ EPO 2, 2002).

Registered Letter EPO Form 2004 01 O6CSX

jDate16.08.2007 Sheet 4

Examining Division:

Chairman: VILLA RIVA, A
2nd Examiner: Felder, Christian
1st Examiner: Schifferer, Hermann

ONes Patent,,

CP111) O./17Q 30

HANRIEDER-KREUZER, K
For the Examining Division
Tel. No.: +49 89 2399 - 8081

Enclosure(s): Form 2056
72 Copies of the relevant documents

Application No.: 01 921 605.0

Registered Letter FF0 Form 2004 01.O6CSX

Europaisches P2 itamt European Patent Office

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Annex to EPO Form 2004, Communication under Rule 51(4) EPC

Bibliographical data of European patent application No. 01 921 605.0

For the intended grant of a European patent, the bibliographical data are set out below, for information:

Title of invention: Ropinirol enthaltende Darreichungsform mit einer hydrophilenAipophilen Matrix

Ropinirole-containing hydrophilicAiphilic polymeric matrix dosage
formulation

Forme posologique comprenant ropinirole a matrice polymŁrehydrophile/
lipophile

Classification: INV. A61 K9i24 A61 K31/4045 A61 P25/16

Date of filing: 12.04.2001

Priority claimed: IT 14.04.2000 1TAMI200852
IT /07.09.2000 /ITAMI2O1 963

Contracting States*
for which fees have
been paid: AT BE CH CY DE DK ES Fl FR GB OR IE IT LI LU MC NL PT SE TR

Extension States*
for which fees have
been paid: SI

Applicant(s)**: JAGOTEC AG
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Via Treviglio, 6
1-21052 Busto Arsizio
IT

EPO Form 2056(Sheetl) 04OOCSX

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) In case the time limits pursuant to Article 79(2) and Rule 85a EPC have not yet expired, all

Contracting StatesiExtension States have been mentioned. **) In case two or more applicants have designated different Contracting States, this is indicated

here.

EPO Form 2056 SFee2) 04 OOCSX

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CLAIMS

I. A multi-layer controlled release tablet consisting of:

5 (a) one active layer which consists of: (1) 0.05-20% by weight of ropinirole,
inclusive of pharmaceutically acceptable salts thereof, (ii) hydrophilic
polymeric substances which swell and/or gel and/or erode upon contact with
aqueous liquids, (iii) lipophilic substances, and (iv) 5-50% by weight of
adjuvant substances, wherein the weight ratio of the hydrophilic polymeric
10 substances to the lipophilic substances contained in said active layer is in the
range of 7:1 to 1:1; and

(b) one or more barrier layers which limit the release surface of the active
layer, which barrier layers contain one or more of: hydrophilic polymeric
15 substances which swell and/or gel and/or erode upon contact with aqueous
liquids, lipophilic substances, and adjuvant substances, which tablet is
optionally coated.

2. A multi-layer controlled release tablet according to claim 1, wherein the active
20 substance is ropinirole hydrochloride.

3. A multi-layer controlled release tablet 1 or claim 2, in
which said hydrophilic polymeric substances (ii) are contained in a percentage between 30% and 15% of the weight of the active layer.
25

4. A multi-layer controlled release tablet according to any one of claims 1 to 3, in
which said lipophilic substances (iii) are contained in a percentage between 5% and
55% of the weight of the active layer.

30 5. A multi-layer controlled release tablet according to any one of claims 1 to 4, in
which said adjuvant substances (iv) are contained in a percentage between 10% to
40% of the weight of the active layer.

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6. A multi-layer controlled release tablet according to any preceding claim, in
which said hydrophilic polymeric substances comprise a pharmaceutically acceptable biocornpatible and/or biodegradable material, including non-cross-linked
5 polyvinylpyrrolidone, hydroxypropylcellulose with a molecular weight of 100,000 to
4,000,000, sodium carboxymethylcellulose, carboxymethylstaich, potassium methacrylate-divinylbenzene copolymer, hydroxypropylmethylcellulose of molecular weight between 2,000 and 4,000,000, a polyethyleneglycol of molecular weight between 200 and 15,000, a polyoxyethylene with molecular weight of up to
10 20,000,000, a carboxyvinylpolymer, a poloxamer (polyoxyethylene-polyoxypropylcne
copolymer), a polyvinylalcohol, a glucane (glucan), a carrageenan, a scleroglucane (scieroglucan), a mannan, a galactomannan, gellans, xanthans, alginic acid and/or a derivative thereof, polyaminoacids, methyl vinyl ether maleic anhydride copolymer, carboxymethylcellulose and/or a derivative thereof, ethylcellulose, methylcellulose,
15 starch, a starch derivative, alpha, beta, or gamma cyclodextnn and/or a dextrin
derivative.

7. A multi-layer controlled release tablet according to claim 6, wherein the
hydrophilic polymeric substances in the active layer comprise:
20 (a) one or more of the following; hydroxypropylcellulose with a molecular weight
between 100,000 and 4,000,000, hydroxypropylmethycellulose (HPMC) with a molecular weight between 2,000 and 4,000,000, ethylcellulose or methylcellulose; and
(b) sodium carboxymethylcellulose, carboxymethyicelhulose or derivatives,
hydroxypropylcellulose with a molecular weight of from 100,000 to 4,000,000, a
25 carboxyvinyl polymer, a carrageenan, a xanthan, alginic acid or a derivative,
ethylcellulose, inethylcellulose, dextrin and/or maltodextrin.

8. A multi-layer controlled release tablet according to claim 7, wherein the
hydrophilic polymeric substances in the active layer include
30 hydroxypropyl.rnechylcellulose and sodium carboxymethylcellulose.

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9. A multi-layer controlled release tablet according to any one of claims 6 to 8,
wherein the hydrophilic polymeric substances in the active layer comprise hydroxypropylmethylcellulose having a molecular weight in the range 20,000 and
500,000 or a 2% viscosity in the range of 80,000 to 120,000 mPa.sec.

5

10. A multi-layer controlled release tablet according to claim 9, wherein the
hydrophilic polymeric substances in the active layer comprise hydroxypropylmethylcellulose having a molecular weight of about 250,000.

10 11. A multi-layer controlled release tablet according to any one of claims 6 to 10,
wherein the hydroxypropylmethylceliulose in the active layer is a gellable hydroxypropylmethylcellulose.

12. A multi-layer controlled release tablet according to any preceding claim, in
15 which said lipophilic substances include a natural fat as such or totally or partially
hydrogenated, beeswax, polyethoxylated beeswax, a mono-, bi- or tn-substituted
glyceride, glyceryl palmitostearate, glyceryl behenate, diethyleneglycol
palmitostearate, a polyethyleneglycol stearate, a polyoxyethyleneglycol
palmitostearate, glyceryl monopalmitostearate, cetyl palmitate, polyethyleneglycol
20 palmitostearate, mono- or di-glyceryl behenate, a fatty alcohol associated with a
polyethoxylate fatty alcohol, cetyl alcohol, stearic acid, a saturated or unsaturated fatty
acid or a hydrogenated derivative thereof, and/or hydrogenated castor oil.

13. A multi-layer controlled release tablet according to claim 12, in which the
25 lipophilic substance present in the active layer is selected from hydrogenated castor oil
and glyceryl behenate.

14. A multi-layer controlled release tablet according to any preceding claim, in
which the active substance is ropinirole inclusive of pharmaceutically acceptable salts
30 thereof contained in a percentage of 0.05% to 20% by weight of the active layer, (ii)
the hydrophilic polymeric substance comprises hydroxypropylmethylceilulose, sodium
carboxymethykellulose or calcium carboxymethyLcdllulose, (iii) the lipophilic

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substance comprises hydrogenated castor oil or glyceryl behenate, and (iv) the
adjuvant substances are contained in a percentage of 5% to 50% by weight of the
active layer, and the weight ratio of the hydrophilic polymeric substances to the
lipophilic substances contained in the active layer is in the range of from 7:1 to 1:1.

5

15. A multi-layer controlled release tablet according to any preceding claim, in
which the weight ratio of hydrophilic swelling and/or gelling and/or erodible polymeric substances to lipophilic substances contained in the barrier layer is in the range of 1:1 to 7.5:1.
10

16. A multi-layer controlled release tablet according to any preceding claim, in
which the amount of ropinirole present, inclusive of pharmaceutically acceptable salts thereof, is up to 12.0 mg, measured as the amount of ropinirole base present.

15 17. A multi-layer controlled release tablet according to claim 16, in which the
amount of ropinirole present, inclusive of pharmaceutically acceptable salts thereof, is
from 0.75mg to 12 mg, measured as the amount of ropinirole base present.

18. A multi-layer controlled release tablet according to any preceding claim, in
20 which said one or more barrier layers are applied to one or both surfaces (bases) of the active layer.

19. A multi-layer controlled release tablet according to claim 18, wherein a barrier
layer is applied to both surfaces (bases) of the active layer.
25

20. A multi-layer controlled release tablet according to any preceding claim,
wherein release of ropinirole during the first hour after oral administration or immersion in aqueous liquids occurs substantially only from the surface of the tablet
not covered by the one or more barrier layers.
30

21. A multi-layer controlled release tablet according to claim 1, which consists of
an active layer and two barrier layers, one bather layer being applied to each surface

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(base) of the active layer, wherein the active layer weighs about 150 mg and consists essentially of up to 12 mg ropinirole HO (measured as the amount of ropinirole base present), 4101b HPMC type 2208 (100,000cps), 10% carboxymethylcellulose sodium,
5% maftodextrin, 100/c hydrogenated castor oil, 1% magnesium stearate, 0.6%
5 colloidal silicon dioxide and lactose monohydrate quantum sufficiat, and wherein the
barrier layers weigh between 120-170 mg, the barrier layers consisting essentially of
23.6% mannitol, 25% glyceryl behenate. 5% polyvinyipyrrolidone, 1% magnesium
stearate, 04% colloidal silicon dioxide, HPMC type 2208 (100,000cps) and optionally
a colouring agent aria quantum sufficiat, wherein said controlled release tablet is
10 optionally film coated with about 13.80 mg of a coating agent.

A-,. 22. A multi-layer controlled release tablet according to claim 21, wherein the
active layer weighs 150 mg and consists of up to 12 mg ropinirole HO (measured as
the amount of ropinirole base present), 41% HPMC type 2208 (100,000cps), 10%
15 carboxymethylcelluiose sodium, 5% maltodextrin, 10% hydrogenated castor oil, 1%
magnesium stearate, 0.6% colloidal silicon dioxide and lactose monohydrate quantum
sufficial, and wherein the barrier layers weigh between 120-170 mg, the barrier layers
consisting of 23.6% mannitol, 25% glyceryl behenate, 5% polyvinylpyrrolidonc, 1% magnesium stearate, 0,4% colloidal silicon dioxide, HPMC type 2208 (100,000cps)
20 and optionally a colouring agent ana quantum sufficiat, wherein said controlled release
tablet is optionally film coated with about 13.80 mg of a coating agent.

23. A multi-layer controlled release tablet according to claim 21 or claim 22,
wherein one barrier layer weighs about 170 mg and the other barrier layer weighs
25 about 140 mg.

24. A multi-layer controlled release tablet according to claim 23, wherein one
barrier layer weighs 170 mg and the other barrier layer weighs 140 mg.

30 25. A multi-layer controlled release tablet according to claim 23 or claim 24,
wherein said tablet is film coated with 13.80 mg of a coating agent.

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26. A multi-layer controlled release tablet according to claim 21 or claim 22,
wherein one barrier layer weighs about 130 mg and the other barrier layer weighs
about 120 mg.

5 27. A multi-layer controlled release tablet according to claim 26, wherein one
barrier layer weighs 130 mg and the other barrier layer weighs 120 mg.
4

28. A multi-layer controlled release tablet according to claim 26 or claim 27,
wherein said tablet is uncoated.
10

29. A multi-layer controlled release tablet according to any one of claims 21 to 28,
wherein said barrier layers contain a colouring agent.

30. A multi-layer controlled release tablet according to claim 29, wherein said
15 colouring agent is yellow ferric oxide.

31. A multi-layer controlled release tablet according to any one of claims 21 to 30,
wherein the amount of ropinirole HC1 in the active layer is 0.75-12 mg, measured as
the amount of ropinirole free base present.
20

32. A multi-layer controlled release tablet according to any preceding claim, in
which the tablet preparation is carried out by compression of the powder or granular mixture and working between 1000 and 5000 Kg/cm2.

25 33 Use of ropinirole in the manufacture of a multi-layer controlled release
tablet as defined in any one of claims 1 to 32 for the treatment of Parkinson’s Disease.

34. Use according to claim 33, in which a single multi-layer controlled release
tablet is administered once per day to a human in need of such treatment.

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Delivery No.: 9-5-2008-007536702 Delivery Date: February 14, 2008

NOTICE OF DECISION FOR PATENT

Applicant(s): JAGOTEC AG
Eptingerstrasse 51
CH-4132 Muttenz
SWITZERLAND

Attorney(s): Lee International

Inventor(s): 1) VERGNAULT, Guy
2) GRENIER, Pascal
3) MAGGI, Lauretta
4) CONTE, Ubaldo

Application No.: 10-2002-7013768

’ For: HYDROPHILIC/LIPOPHILIC POLYMERIC MATRIX DOSAGE
FORMULATION

Number of Claims: 11

The original decision for rejection dated September 7, 2007 of the above-referenced application
has been revoked; therefore, the subject application is allowed for issuance as a patent according
to Article 66 ofthe Patent Law.

Acknowledgement is made of a claim for priority as follows:
Country: IT Number: MI2000A000852 Date: April 14, 2000
Country: IT Number: M12000A001963 Date: September 7, 2000

Reference Materials
1. US patent application publication no. 6027748

This 14th day of February, 2008

Patent Examiner (sealed)
Pharmaceutical Chemistry Examination Team
Chemistry & Biotechnology Examinations Bureau Korean Intellectual Property Office

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Commonwealth
of Australia

Letters patent

Patents Act 1990

STANDARD PATENT

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I, Fatima Beattie, Commissioner of Patents, grant a Standard Patent with the following particulars: Name and Address of Patentee:

Jagotec AG, Eptingerstrasse 51, CH-4132 Muttenz, Switzerland
Names of Actual Inventors: Guy Vergnault; Pascal Grenier; Lauretta Maggi and Ubaldo Conte
Title of Invention: Hydrophilic/lipophilic polymeric matrix dosage formulation
Application Number: 48576/01
Term of Letters Patent: Twenty years from 12 April 2001
Priority Details:
Number Date Flied with
,-, M1200A000852 14 April 2000 ITALY
M1200A001963 7 September 2000 ITALY

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AUSTRALIA

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Dated this 2 day of June 2005

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COMMISSIONER OF PATENTS

Letters patent No.
of Australia

No.
Act 1990
Commonwealth 779623 c3\\

STANDARD PATENT

I, Fatima Beattie, Commissioner of Patents, grant a Standard Patent with the following particulars:

Name and Address of Patentee:
Jagotec AG, Eptingerstrasse 51, CH-4132 Muttenz, Switzerland
Names of Actual Inventors Guy Vergnault Pascal Grenier Lauretta Maggi and Ubaldo Conte
Title of Invention Hydrophilic/lipophiiic polymeric matrix dosage formulation
Application Number: 48576/01
Term of Letters Patent: Twenty years from 12 April 2001
Priority Details:
Number Date Flied with
M1200A000852 14 April 2000 ITALY
M1200A001963 7 September 2000 ITALY

Dated this 2 day of June 2005

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COMMISSIONER OF PATENTS

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CLAIMS

1. A multi-layer controlled-release tablet comprising:

5 (a) one active layer containing: (i) an active substance, (ii) hydrophilic
polymeric substances which swell and/or gel and/or erode upon contact with
aqueous liquids, (in) lipophilic substances, and (iv) adjuvant substances,
wherein the weight ratio of the hydrophilic polymeric substances to the
lipophilic substances contained said active layer is in the range of 10:1 to
10 0.5:1; and

, (b) one or more barrier layers containing one or more of: hydrophilic polymeric
substances which swell and/or gel and/or erode upon contact with aqueous
liquids, lipophilic substances, and adjuvant substances.

15

2. A multi-layer tablet as claimed in claim 1, in which the weight ratio of the
hydrophilic polymeric substances to the lipophilic substances contained in said active
layer is in the range of7:1 to 1:1

20 3. A multi-layer tablet as claimed in claim 1 or claim 2, in which said hydrophilic
polymeric substances (ii) are contained in a percentage between 1% and 75%, preferably between 5% and 65%, ofthe weight ofthe active layer.

4. A multi-layer tablet as claimed in any one of claims I to 3, in which said
25 lipophilic substances (iii). are contained in a percentage between 1% and 70%,
preferably between 5 and 55% ofthe weight ofsaid active layer.

5. A multi-layer tablet as claimed in any one of claims I to 4, in Which said
adjuvants (iv) are contained in a percentage between 5% 501/9, preferably from 10%
30 to 400/9, ofthe weight ofsaid active layer.

6. A multi-layer tablet as claimed in any one of claims 1 to 5, in which the weight

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een said active substance (1) and said adjuvant substances (iv) in the active
in the range of 0.001:1 to 4:1, preferably from 0.003:1 to 3:1.

7. A multi-layer tablet as claimed in any preceding claim, in which said one or
5 more barrier layers are applied to one or both surfaces (bases) ofthe active layer.

8. A multi-layer tablet as claimed in any preceding claim, in which the weight
ratio of hydrophilic swelling and/or gelling and/or erodible polymeric substances to lipophilic substances contained in the barrier layer is in the range of 1l to 7.5:1,
10 suitably, from 1.5:1 to 4:1, and preferably between 2:l and 3.5:1.

9. A multi-layer tablet as claimed in any preceding claim, in which the actii’e
substance (I) is contained in a weight percentage between 0.01% to 70%, preferably
between 0.05% to 50% by weight ofthe active layer.
15

10. A multi-layer tablet as claimed in claim 9, in which the active substance (i) is
contained in a percentage of0.05% to 20% by weight ofthe active layer.

11. A multi-layertablet as claimed in any preceding claim, in which the active
20 layer contains polymeric material with slow swelling and/or gelification and/or erosion
and/or solubility properties.

12. A multi-layer tablet as claimed in any preceding claim, in which the active
layer farther contains polymeric substances of a lipophilic nature.

25 -

13. A multi-layer tablet as claimed in any preceding claim, in which said
hydrophilic polymeric substances comprise a pharmaceutically acceptable
biocoinpatible and/or biodegradable material, including non-cross-’linked polyvinylpyrrolidone, hydroxypropylcellulose with a molecular weight of 100,000 to
30 4,000,000, sodium carboxymethylcellulose, carboxymethylstarch, potassium
niethacrylate-divinylbenzene copolymer, hydroxypropyirnethylceUulose ofmolecular weight between 2,000 and 4,000,000, a polyethyleneglycol ofmolecular weight

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ietween 200 and 15,000, a polyoxyethylene with molecular weight ofup to

f 20,000,000, a carboxyvmylpolymer, a poloxarner (polyoxyethylene-po]yoxypropylene copolymer), a polyvrnylalcohol, a glucane(glucan), a carrageenan, a scieroglucane (sclemglucan) a mannan, a galactomannan,.gellans, xanthans, alginic acid and/or a
5 derivative,thereof, polyaminoacids, methyl vinyl ether / maleic anhydzide copolymer,
- carboxymethylcellulose and/or a derivative thereof, ethylcellulose, methylcellulose,
- starch, a starch derivative, alpha, beta, or gamma cyclodextrin and/or a dextrin.
derivative.

10 14. A multi-layer tablet as claimed in any preceding claim, in which said lipophilic
substances include a natural fat (for example coconut, soya, cocoa) as such or totally
or partially hydrogenated, beeswax, polyethoxylated beeswax, a mono-, bi- or ti-
substituted glyceride, glyceryl pakriitostearate, glyceryl behenate, diethyleneglycol palmitostearate, a polyethyleneglycol stearate, a polyoxyethyleneglycol
15 painiitostearate, glyceryl monopalmitostearate, cetyl pabnitate, polyethyleneglycol
palmitostearate, mono- or di-glyceryl behenate, a fatty alcohol associated with a polyethoxylate fatty alcohol, cetyl alcohol, stearic acid, a saturated or unsaturated fatty
acid or a hydrogenated ’derivative thereof, and/or hydrogenated castor oil.

20 15. A multi-layer tablet as claimed in any preceding claim, in which the active
substance(s) are therapeutic agents for the treatment of chronic diseases, for example
drugs acting on the cardiovascular system, anti-arrhythmics, cardiac stimulants, vasodilators, anti-hypertensives, anti-adrenergiŁsubstances of central and peripheral
action or substances acting on the arteriolar musculature, substances acting on the
’ 25 renin-angiotensin ystcin, anti-hypertensives and diuretics in association, anti-
Parkinson’s Disease ’agents, diuretics and drags for thC treatment of Alzheimer’s
disease;

16. A multi-layer tablet as claimed in any preceding claim, in which the active
30 substance(s) is selected from: propranolol, atenolol, pindolol, ropinirole, pra70s1fl,
ramipril, spirapril; spironolactone, metipranolol, rnolsidoinine, moxonidina, nadolol,

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xo101, levodopa, metoprolol, or timolol, inclusive ofpharmaceutically acceptable

thereof.

! 17. A multi-layertablet as claimed in any preceding claim, in which the tablet
5 preparation is carried out by compression ofthe powder or granular mixture and
working between 1000 and 5000 Kg/cm2.

18.. A multi-layer tablet as claimed in any preceding claim, in which the lipophilic
substance present in the active layer is selected from hydrogenated castor oil and
10 glyceryl behenate.

15

19. A multi-layer tablet as claimed in any preceding claim, in which the active
substance comprises or is ropinirole, inclusive ofpharmaceutically acceptable salts
thereof.

20. Aniulti-layer tablet as claimed in claim 19, in which the amount ofropinirole
present, inclusive of pharmaceutically acceptable salts thereof; is up to 12.0mg, measured as the amount ofropinirole base present.

20 21. A multi-layer tablet as claimed in claim 19, in which the amount ofropinirole
present, inclusive of pharmaceutically acceptable salts thereof; is from 0.75mg to 12.0mg, measured as the amount ofropinirole base present

22.. A multi-layer tablet as claimed in any preceding claim, in which the active
25 layer consists of components (i) to (iv) wherein the active substance is contained in a
percentage of 0.05% to 20% by weight ofthe active layer, the adjuvant substances are contained in a percentage of 5% to 50% by weight ofthe active layer, and the weight
ratio ofthe hydrophilic po1ymeri substances to the lipophilic substances contained in
the active layer is in the range offrom 7:1 to 1:1.
30

23. A multi-layer tablet as claimed in any preceding claim, in which the active
layer consists essentially of components (i) to (iv) wherein the active substance is.

- - - - Page 66 of 76

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contained in a percentage of0.05% to 20% by weight ofthe active layer, the adjuvant substances are contained in a percentage of 5% to 50% by weight ofthe active layer,

V, and the weight ratio ofthe hydrophilic polymeric substances to the lipophilic

substances contained in Ilie active layer is in the range offrom 7:1 to 1:1.

5

24. A multi-layer tablet as claimed in any preceding claim, in which the
hydrophilic polymeric substance comprises hydroxypropylmethylcellulose of molecular weight 2,000 to 4,000,000, sodium carboxymethylcellulose or calcium carboxymethylcelhilose.
10

25. A multi-layer tablet as claimed in any preceding claim, in which (i) the active
substance is ropinirole contained in a percentage of 0.05% to 20% by weight of the active layer, (ii) the hydrophilic polymeric substance comprises hydroxypropylinethylcellulose, sodium carboxyniethylcellulose or calcium
15 carboxymethylcellulose, (iii) the lipophilic substance comprises hydrogenated castor
oil or glyceryl behenate, and (iv) the adjuvant substances are contained in a percentage
of 5% to 50% by weight of the active layer, and the weight ratio of the hydrophilic polymeric substances to the lipophilic substances contained in the active layer is in the range offrom 7:1 to 1:1.
20

26. A multi-layer tablet as claimed in any preceding claim, wherein the active
substance is ropinirole contained in a percentage of 0.05 to 20% by weight of the
active layer, and wherein the hydrophilic polymeric substances in the active layer comprise hydroxypropylmethylceliulose and sodium carboxymethylcellulose.
25

27. A multi-layer tablet as claimed in any preceding claim, in which the active
layer consists ofcomponents (i) to (iv) wherein:
- the active substance is ropinirole contained in a percentage of 0.05% to 20% by weight ofthe active layer,. -
30 - the adjuvant substances are contained in a percentage of5% to 500% by weight ofthe
active layer,
-the hydrophilic polymeric substances in the active layer comprise hydroxypropyl-

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jy1ce1lulose and sodium carboxymethylcellulose, and
the weight ratio ofthe hydrophilic polymeric substances to the lipophilic substances contained in the active layer is in the range offrom 7:1 to 1:1.

5 28. A method oftreating Parkinson’s Disease comprising administering to a human,
in need of such treatment one or more multi-layer tablets as defined in any one of claims 19 to 27.

29. A method as claimed in claim 28, in which one or more multi-layer tablets as
10 defined in ay one ’ofclaims 19 to 27 are administered once per day to the human in need ofsuch treatment.

30. A method as claimed in claim 28, in which a single multi-layer tablet as
defined in any one ofclaims 19 to 27 is administered once per day.’
15,
31. A multi-layer tablet as claimed in any one of claims 1 to 27, in which’
the one or more barrier layers:
- are applied to one or both surfaces (bases) ofthe active layer,
- contain hydrophilic polymeric substances which swell and/or gel and/or
20 erode upon contactwith aqueous liquids, as defined in claim 13, and
- contain lipophilic substances.

32. A multi-layer tablet as claimed in any one ofclaims I to 27 or 31, in
which the one or more barrier layers:
25 - are applied to one or both surfaces (bases) ofthe active layer,
- contain hydrophilic polymeric substances which swell and/or gel and/or
erode upon contact with aqueous liquids, as well as lipophilic substances,
and

- are such that during the first hour after oral administration or
30 . immersion in aqueous liquids (e.g. water), release ofthe active substance
occurs.substantially only from the surface ofthe tablet not covered by the
one or more barrier layers.

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33. A multi-layer tablet as claimed in any once of claims ito 27 or 31 to 32 wherein a
barrier layer is applied to both surfaces (bases) of the active layer.
34. A multi-layer controlled-release tablet substantially as hereinbefore described.
35. A multi-layer controlled-release tablet substantially as hereinbefore described with
5 reference to the drawings.

Date. 8 December 2004

Fatent Attorneys for the Applicant
BLAKE DAWSOW WALDRON PKIT.Nf SERVICES

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ANtq4 instituto

Mexicano

de la Propledad
Industrial

TITULO DEPATENTE NO 234153

Titular(es): - JAGOTEC AG

Domicflio(s) Eptingerstrasse 51, CH-4132, Muttenz, SUIZA

Denominación: FORMULACION DE DOSIFICACION DE MATRIZ POLIMERICA
HIDROFILICNLIPOFILICA.

Clasificación: Int.CL6: A61 K31/4045; A61 K9/24; A61 P25/16

Inventories): GUY VERGNAULT; PASCAL GRENIER; LAURETTA MAGGI; UBALDO CONTE

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ESTA PATENTE:.
DEL INVENTO R
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Fecha de presentación intemaj

51 .. 12 de AbrU de 2001

PRIORIDAD,

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Fecha de expedición: 3 de febrero de 2006

DE PATENTES

SALAZAR GARCIA

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TITULO DEPATENTENO 234153

Tltular(es): JAGOTEC AG

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Denominaciôn: FORMULACION DE DOSIFICACION DE MATRIZ POLIMERICA
HIDROFILICA/LIPOFILICA.

Claslficaciôn: mt. CI.6: A61 K31/4045; A61 K9124; A61 P25/16

Inventor(es): GUY VERGNAULT: PASCAL GRENIER; LAURETTA MAGGI; UBALDO CONTE

SOLICITUD

Nümero: Fecha de presentac,ôn internaclonal:

PNa/2002/010151 12 deAbril de 2001

PRIORIDAD

Pals: Fecha: NUmoro:

IT 14 de abril do 2000 M1000A000852
IT L ptiembre de 2000 r112000A00163

ESTA PATENTECONCEDE A SU TITULAR EL DERECHO EXCLUSIVO DE EXPLOTACION DEL INVENTO RECLAMADO EN EL CAPITULO REIINDICATORIO Y TIENE UNA VIGENCIA IMPRORROGABLE DE VEINTE AfOS CONTADOS A PARTIR DE LA FEC HA DE PRESENTACIONINTERNACIONAL DE LA soLIcrrub:

Fecha de expedición: 3 de febrero de 2006

EL DIRECTOR flSFItIAL DE PATENTES

SALAZAR GARCIA

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CAPITUL0D: NO

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HablØndose descrito la invención como anMexne

do la Propiedad
reclama como propiedad 10 contenido en las
5 reivindicaciones

1. Una tableta de liberación controlada de capas
multiples, caracterizada porque comprende:
(a) una capa activa que contiene: (i) 0.05-20% en
10 peso de ropinirol, inclusive de sales farmacØuticamente
aceptables de los mismos, (ii) sustancias polimØricas
hidrofIlicas, las cuales se hinchan y/o gelifican y/o se
erosionan tras el contacto con lIquidos acuosos, (iii)
sustancias lipofIlicas, y (iv) 5-50% en peso de sustancias
15 adyuvantes, donde la relación en peso de las sustancias
polimØricas hidrofIlicas a las sustancias lipofIlicas contenidas en la capa activa estÆ en el intervalo de 7:1 a
1:1; y
(b) una o ma’s capas de barrera que limitan la
20 superficie de liberación de la capa activa que contienen una
o mÆs de: Sustancias polimØricas hidrofIlicas, las cuales se
hinchan y/o gelifican yb se erosionan tras el contacto con
lIquidos acuosos, sustancias lipofIlicas y sustancias adyuvantes.

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2. La tableta de liberación
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multiples de conformidad con la reiv a
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caracterizada porque la sustancia activa es

ropinirol. de la Propiedad

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5 3. La tableta de liberación controlada de capas
multiples de conformidad con la reivindicación 1 6 2, caracterizada porque las sustancias polImØricas hidrofIlicas
(ii) estÆn contenidas en un porcentaje de entre el 30% y el
75% del peso de la capa activa.
10 4. La tableta de liberación controlada de capas
multiples de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizada porque las sustancias lipofIlicas (iii) estÆn contenidas en un porcentaje de entre
el 5% y el 55%, del peso de la capa activa.
15 5. La tableta de liberación controlada de capas
multiples de conformidad con cualquiera de las reivindicac i ones 1 a 4, caracterizada porque los adyuvantes
(iv) estÆn contenidos en un porcentaje de entre el 10% al
40%, del peso de la capa activa.
20 6. La tableta de liberación controlada de capas
multiples de conformidad con cualquiera de las reivindicaciones precedentes, caracterizada porque las sustancias polimØricas hidrofIlicas comprenden un material biocompatible y/o biodegradable farmacØuticamente aceptable,
25 incluyendo polivinilpirrolidona no reticulada,

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hidroxipropilcelulosa con un peso molecu1ar0a 4,000,000, carboximetilcelulosa sódica, carb ___
copoilmero de metacrilato de potasio_divinjt, hidroxipropilmetilcelulosa con un peso mole ueitPIP1e4ie lfloustr,*I
2,000 y 4,000,000, un polietilenglicol con un peso molecular de entre 200 y 15,000, un polioxieti].eno con un peso molecular de hasta 20,000,000, un polImero de carboxivinilo, un poloxÆmero (copoilmero de polioxietileno-polioxipropileno), un alcohol polivinIlico, un glucano (glucano), una carragenina, un escleroglucano (escieroglucano), un manano, un glactomanano, gelificantes, xantanas, Æcido algInico y/o un derivado de los mismos, poliaminoÆcidos, copolirnero de metil vinil Øter/anhIdrido maleico, carboximetilcelulosa y/o derivados de los mismos, etilcelulosa, metilcelulosa, almidón, derivados de almidón, alfa, beta o gama ciclodextrina y/o un derivado de dextrina.
7. La tableta de liberación controlada de capas milltiples de conformidad con la reivindicación 6, caracterizada porque las sustancias polimØricas hidrofIlicas en la capa activa comprenden: (a) uno mÆs de lo siguiente: hidroxipropilcelulosa con un peso molecular de 100,000 y 4,000,000, hidroxipropilmetilcelulosa (HPMC) con un peso molecular de entre 2,000 y 400,000, etilcelulosa o metilcelulosa.; y (b) carboximetilcelulosa sód.ica, carboximetilcelulosa o derivados, hidroxipropilcelulosa con

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un peso molecular de 100,000 a 4,000,000,uIim
carboxivinhlo, una carragenina, xantanas, un Æc 1
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un derivado, etilcelulosa, metilcelulosa, ;g,I8C,

de la Propiedad inaltodextrina. Industrial
5 B. La tableta de liberación controlada de capas
multiples de conformidad con la rivindicación 7, caracterizada porque las sustancias polimØricas hidrofIlicas
en la capa activa incluye hidroxipropilmetilcelulosa y carboximetilcelulosa sódica.
9. La tableta de liberación controlada de capas
multiples de conformidad con cualq:uiera de las reivindicaciones 6 a 8, en donde las substancias polimØricas hidrofIlicas en la capa activa comprenden hidroxipropilmetilcelulosa con un peso molecular en el
15 intervalo de 20,000 y 500,000 o una viscosidad al 2 % en el
intervalo de 80,000 a 120,000 mPa.sec.
10. La tableta de liberación controlada de capas
multiples de conformidad con la reivindicación 9, caracterizada porque las sustancias polimØricas hidrofIlicas
20 en la capa activa incluye hidroxipropilmetilcelulosa con mi
peso molecular de 250,000.
11. La tabletade liberación controlada de capas
multiples de conformidad con cualquiera de las reivindicaciones 6 a 10, en donde la

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gelificable

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hidroxipropilmetilcelulosaa . Instftuto
12. La tableta de liberación controiaMeagjas
delaPropiedad
mi.iltiples de conformidad con cualquiera JnjtrjaLas
reivindicaciones anteriores, en donde las substancias lipofIlicas incluyen una grasa natural como tal o total o parcialmente hidrogenada, cera de abejas, cera de abejas polietoxilada, glicØridos mono, bi y trisustituido, palmitoestearato de glicerilo, behenato de glicerilo, palmitoestearato de dietilenglicol, un estearato de
polietilenglicol, un palmitoestearato de polioxietilenglicol,
monopalmitoestearato de glicerilo, palmitato de cetilo, palmitoestearato de polietilenglicol, behenato de mono o diglicerilo, un alcohol graso asociado con un alcohol graso polietoxilado, alcohol cetlilco, Æcido esteÆrico, un Æcido graso saturado o insaturado o un derivado hidrogenado del mismo, y/o aceite de ricino hidrogenado.
13. La tableta de liberación controlada de capas
multiples de conformidad con la reivindicación 12, caracterizada porque la sustancia lipofIlica presente en la capa activa se selecciona de aceite de ricino hidrogenado y behenato de glicerilo.
14. La tableta de liberación controlada de capas
mi1tiples de conformidad con cualquiera de las reivindicacjones anteriores, en donde la sustancia activa es

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ropinirol, inclusive de sales farmacØuticam de

los mismos contenidos en un porcentaje de 0.15Reso

i nst;tuto
de la capa activa, (ii) la sustancia polimØrica MIŁica

de Ia PrQoiedad coinprende hidroxipropilnietilcelulosa, carboximJ.osa
sódica o carboximetilcelulosa cÆlcica, (iii) la sustancia lipofIlica comprende aceite de ricino hidrogenado o behenato de glicerilo y, (iv) las sustancias adyuvantes estÆn contenidas en un porcentaje del 5% al 50% en peso de la capa activa, y la relación en peso de las sustancias polimØricas hidrofIlicas a las sustancias lipofIlicas contenidas en la capa activa estÆ en el intervalo de 7:1 a 1:1.
15. La tableta de liberación controlada de capas
multiples de conformidad con cualquiera de las
reivindicaciones anteriores, en donde la relación en peso de
las sustancias polimØricas hidrofilicas las cuales se hinchan
y/o gelifican y/o se erosionan a las substaricias lipofIlicas contenidas en la capa de barrera estÆn en el intervalo de 1:1
a 7.5:1.

16. La tableta de liberación controlada de capas
20 multiples de conformidad con cualquiera de las reivindicaciones anteriores, caracterizada porque la cantidad
de ropinirol presente, inclusive sales farrnacØuticamente aceptables del mismo, puede ser de hasta 12.0 mg, medida de acuerdo a la cantidad de ropinirol base presen’ce.

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17. La tableta deliberac–ón co tpr pas
multiples de conformidad con la reivindiLIfl3itJtO 16,
Mexicano
caracterizada porgue la cantidad de ro*poPdadnte, 1dustrIaI
inclusive sales farmacØuticamente aceptables del mismo, puede
5 ser de 0.75 rag hasta 12.0 rag, medida de acuerdo a la cantidad
de ropinirol base presente.
18. La tableta de liberación controlada de capas
multiples de conformidad con cualquiera de las
reivindicaciones precedentes, en la cual una o mÆs capas de
10 barrera es aplicada a una o ambas superficies (bases) de la
capa activa.
19. La tableta de liberación controlada de capas
multiples de conformidad con la reivindicación 18, en donde
la capa de barrera es aplicada a axnbas superficies(bases) de
15 la capa activa.
20. La tableta de liberación controlad.a de capas
multiples de conformidad con cualquiera de las reivindicaciones anteriores, en donde la liberación de ropinirol durante la prirnera hora despuØs de la
20 administración oral o inmersión en lIquidos acuosos ocurre
substancialmente solo a partir de la superficie de. la tableta
no cubierta por una o mÆs capas de barrera.
21. La tableta de liberación controlada de capas
multiples de conformidad con cualquiera de las

reivindicaciones anteriores, caracterizada porque la

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preparación de la tableta se lieva a cabo poe1
polvo o mezcla granular y trabajando ent 00
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Kg/cm2. Mexicano

delaPropiedad 22. Uso de ropirinol en la preparacijdUft.j31,na
5 tableta de liberación controlada de capas multiples de conformidad con cualquiera de las reivindicaciones 1 a 22, para tratar la enfermedad de Parkinson.
23. Uso de conformidad con la reivindicación 22,
en la cual una sola tableta de liberación controlada de capas
0 multiples es administrada una vez por dIa a un humano en
necesidad de dicho tratamiento.

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Development Mantü Ohga

LETTERS PATENT
Number 521902
ELIZABETH THE SECOND by the Grace of God Queen of New Zealand and Her Other Realms and Territories, Head of the Commonwealth Defender of the Faith To all to whom these presents shall come Greeting
WHEREAS pursuant to the Patents Act 1953 an application has been made for a patent of an invention for Hydrophilic/lipophilic polymeric matrix dosage formulation
(more particularly described in the complete specification relating to the application)

AND WHEREAS
Jagotec AG, Eptingerstrasse 51, CH-4132 Muttenz, Switzerland
(hereinafter together with his or their successors and assigns or any of them called "the patentee") is entitled to be registered as the proprietor of the patent hereinafter granted:
Address for service: BALDWINS, Level 14, NCR House, 342 Lambton Quay, Wellington, New Zealand
NOW, THEREFORE, We by these letters patent give and grant to the patentee our special licence, full power, sole

privilege and authonty, that the patentee by himself, his agents or licensees and no others may subject to the provisions of any statute or regulation for the time being in force make use exercise and vend the said invention within New Zealand
and its dependencies during a term of twenty years from 12 April 2001 and that the patentee shall have and enjoy the whole profit and advantage from time to time accruing by reason of the said invention during the said term:
AND WE strictly command all our subjects whomsoever within New Zealand and its dependencies that they do not at

any time during said term either directly or indirectly make use of or put into practice the said invention nor in any way imitate the said invention without the consent licence or agreement of the patentee in writing under his hand on pain of

incurring such penalties as are prescribed by law and of being answerable to the patentee according to law for his damages thereby occasioned:
PROVIDED ALWAYS:

(1) That these letters patent shall determine and become void if the patentee does not from time to time pay the renewal fees prescribed by law in respect of the patent:

(2) That these letters patent are revocable on any of the grounds prescribed by the Patents Act 1953 as grounds for revoking letters patent:
(3) That nothing in these letters patent shall prevent the granting of licences in the manner in which and for the considerations
on which they may by law be granted
(4) That these letters patent shall be construed in the most beneficial sense for the advantage of the patentee

IN WITNESS whereof We have caused these letters patent to be signed and sealed on 5 July 2004 with effect from 12 April 2001.

co

)co) Neville Harris
Commissioner of Patents Trade Marks and Designs

330 High Stinet, Lower Hull and 17 Toop Street, Seaview

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CLAIMS

1. A multi-layer controlled-release tablet comprising:

5 (a) one active layer containing: (i) an active substance, (ii) hydrophilic
polymeric substances which swell and/or gel and/or erode upon contact with
aqueous liquids, (iii) lipophilic substances, and (iv) adjuvant substances,
wherein the weight ratio of the hydrophilic polymeric substances to the
lipophilic substances contained in said active layer is in’ the range of 10:1 to
10 0.5:l;and
/

(b) one or more barrier layers containing one or more of: hydrophilic polymeric
substances winch swell and/or gel and/or erode upon contact with aqueous
liquids, lipophilic subs:ances, and adjuvant substances.

2. A multi-layer tablet as claimed in claim 1, in which the weight ratio of the
hydrophilic polymeric substances to the lipophilic substances contained in said active
layer is in the range of 7:1 to 1:1

20 3. A multi-layer tablet as claimed in claim 1 or claim 2, in which said hydrophilic
polymeric substances (ii) are contained in a percentage between 1% and 75% of the weight of the active layer.

4. A multi-layer tablet as claimed in claim 3, in which said hydrophilic polymeric
25 substances (ii) are contained in a percentage between 5% and 65% of the weight of
said active layer.

5. A multi-layer tablet as claimed in any one of claims 1 to 4, in which said
lipophilic substances (iii) are contained in a percentage between 1% and 70% of the
30 weight ofsaid active layer.

6. A multi-layer tablet as claimed in claim 5, in which said lipophilic substances

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(iii) are contained in a percentage between 5 and 55% of the weight of said active
- - layer.

7. A multi-layer tablet as claimed in any one of claims 1 to 6, in which said
5 adjuvants (iv) are contained in a percentage between 5% to 50% of the weight of said
active layer.

8. A multi-layer tablet as claimed in claim 7, in which said adjuvants (iv) are
contained in a percentage between 10% to 40% ofthe weight ofsaid active layer.
10

9. A multi-layer tablet as claimed in any one of claims 1 to 8, in which the weight
ratio between said active substance (i) and said adjuvant substances (iv) in the active
layer is in the range of 0.001:1 to 4:1.

15 10 A multi-layer tablet as claimed in claim 9, in which the weight ratio between
- said active substance (i) and said adjuvant substances (iv) in the active layer is in the
range of 0.003:1 to 3:1.

11. A multi-layer tablet as claimed in any preceding claim, in which said one or
20 more barrier layers are applied to one or both surfaces (bases) ofthe active layer.

25

12. A multi-layer tablet as claimed in any preceding claim, in which the weight
ratio of hydrophilic swelling and/or gelling and/or erodible polymeric substances to lipophilic substances contained in the barrier layer is in the range of 1:1 to 7.5:1.

13. A multi-layer tablet as claimed in claim 12, in which the weight ratio of
hydrophilic swelling and/or gelling and/or erodible polymeric substances to lipophilic substances contained in the barrier layer is in the range of 1.5:1 to 4:1.

30 14. A multi-layer tablet as claimed in claim 12 or claim 13, in which the weight
ratio of hydrophilic swelling and/or gelling and/or erodible polymeric substances to lipophilic substances contained in the barrier layer is in the range of 2:1 and 3.5:1.

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- 15. A multi-layer tablet as claimed in any preceding claim, in which the active
substance (i) is contained in a weight percentage between 0.0 1% to 70% by weight of
the active layer.

16. A multi-layer tablet as claimed in claim 15, in which the active substance (i) is
contained in a percentage between 0.05% to 50% by weight ofthe active layer.

17. A multi-layer tablet as claimed in claim 15 or claim 16, in which the active
10 substance (i) is contained in a percentage of 0.05% to 20% by weight ofthe active
layer.

18. A multi-layer tablet as claimed in any preceding claim, in which the active
layer contains polymeric material with SlOW swelling and’or gelification and/or erosion
15 and/or -solubility properties.

19. A multi-layer tablet as claimed in any preceding claim, in which the active
layer further contains polymeric substances of a lipophilic nature.

20 20. A multi-layer tablet as claimed in any preceding claim, in which said
hydrophilic polymeric substances comprise a pharmaceutically acceptable
biocompatible and/or biodegradable material, including non-cross-linked polyvinylpyrrolidone, hydroxypropylcellulose with a molecular weight of 100,000 to 4,000,000, sodium carboxymethylcellulose, carboxymethylstarch, potassium
25 methacrylate-divinylbenzene copolymer, hydroxypropylmethylcellulose ofmolecular
weight between 2,000 and 4,000,000, a polyethyleneglycol ofmolecular weight
between 200 and 15,000, a polyoxyethylene with molecular weight of up to
20,000,000, a carboxyvinylpolymer, a poloxamer (polyoxyethylene-polyoxypropylene copolymer), a polyvinylalcohol, a glucane(glucan), a carrageenan, a scieroglucane
30 (scieroglucan), a mannan, a galactomannan, gellans, xanthans, alginic acid and/or a
derivative thereof, polyaminoacids, methyl vinyl ether / inaleic anhydride copolymer, carboxymethylcellulose and/or a derivative thereof, ethylcellulose, methylcellulose,

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starch, a starch derivative, alpha, beta, or gamma cyclodextrin and/or a dextrin

- derivative.

21. A multi-layer tablet as claimed in any preceding claim, in which said lipophilic
5 substances include a natural fat (for example coconut, soya, cocoa) as such or totally
or partially hydrogenated, beeswax, polyethoxylated beeswax, a mono-, bi- or tn-
substituted glyceride, glyceryl palmitostearate, glyceryl behenate, diethyleneglycol palmitostearate, a polyethyleneglycol stearate, a polyoxyethyleneglycol
palmitostearate, glyceryl monopalmitostearate, cetyl palmitate, polyethyleneglycol
10 palmitostearate, mono- or di-glyceryl behenate, a fatty alcohol associated with a
polyethoxylate fatty alcohol, cetyl alcohol, stearic acid, a saturated or unsaturated fatty
acid or a hydrogenated derivative thereof, and/or hydrogenated castor oil.

22. A multi-layer tablet as claimed in any preceding claim, in which the active
15 substance(s) are therapeutic agents for the treatment of chronic diseases.

23. A multi-layer tablet as claimed in claim 22, wherein said therapeutic agents
comprise drugs acting on the cardiovascular system, anti-arrhythmics, cardiac
stimulants, vasodilators, anti-hypertensives, anti-adrenergic substances of central and
20 peripheral action or substances acting on the arteriolar musculature, substances acting
on the renin-angiotensin system, anti-hypertensives and diuretics in association, anti-Parkinson’s Disease agents, diuretics and drugs for the treatment of Alzheimer’s
disease.

25 24. A multi-layer tablet as claimed in any preceding claim, in which the active
substance(s) is selected from: propranolol, atenolol, pindolol, ropinirole, prazosin,
rarnipril, spirapril; spironolactone, metipranolol, molsidomine, moxonidina, nadolol, nadoxolol, levodopa, metoprolol, or timolol, inclusive ofpharmaceutically acceptable

salts thereof.
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25. A multi-layer tablet as claimed in any preceding claim, in which the tablet
preparation is carried out by compression ofthe powder or granular mixture and
working between 1000 and 5000 Kg/cm2.

5 26. A multi-layer tablet as claimed in any preceding claim, in which the lipophilic
substance present in the active layer is selected from hydrogenated castor oil and
glyceryl behenate.

27. A multi-layer tablet as claimed in any preceding claim, in which the active
10 substance comprises or is ropinirole, inclusive of pharmaceutically acceptable salts
thereof.

28. A multi-layer tablet as claimed in claim 27, in which the amount of ropinirole
present, inclusive of phan-r1aceuticaj1y acceptable salts thereof, is up to 12.0mg.
15 measured as the amount ofropinirole base present.

29. A multi-layer tablet as claimed in claim 27, in which the amount ofropinirole
present, inclusive of pharmaceutically acceptable salts thereof, is from 0.75mg to
12.0mg, measured as the amount ofropinirole base present.

20

30. A multi-layer tablet as claimed in any preceding claim, in which the active
Slayer consists of components (i) to (iv) wherein the active substance is contained in a percentage of 0.05% to 20% by weight ofthe active layer, the adjuvant substances are
contained in a percentage of 5% to 50% by weight of the active layer, and the weight
25 ratio of the hydrophilic polymeric substances to the lipophilic substances contained in
the active layer is in the range offrom 7:1 to 1:1.

31. A multi-layer tablet as claimed in any preceding claim, in which the active
layer consists essentially of components (i) to (iv) wherein the active substance is
30 contained in a percentage of 0.05% to 20% by weight ofthe active layer, the adjuvant
substances are contained in a percentage of 5% to 50% by weight of the active layer,

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and the weight ratio ofthe hydrophilic polymeric substances to the lipophilic
substances contained in the active layer is in the range offrom 7:1 to 1:1.

32. A multi-layer tablet as claimed in any preceding claim, in which the
5 hydrophilic polymeric substance comprises hydroxypropylmethylcellulose of
molecular weight 2,000 to 4,000,000, sodium carboxymethylcellulose or calcium carboxymethylcellulose.

33. A multi-layer tablet as claimed in any preceding claim, in which (i) the active
10 substance is ropinirole contained in a percentage of 0.05% to 20% by weight of the
active layer, (ii) the hydrophilic polymeric substance comprises hydroxypropylmethylcellulose, sodium carboxymethylcellulose or calcium carboxymethylcellulose, (iii) the lipophilic substance comprises hydrogenated castor
Oil or glyceryl behenate, and (iv) the adjuvant substances are contained in a percentage
15 of 5% to 50% by weight of the active layer, and the weight ratio of the hydrophilic
polymeric substances to the lipophilic substances contained in the active layer is in the range of from 7:1 to 1:1.

34. A multi-layer tablet as claimed in any preceding claim, wherein the active
20 substance is ropinirole contained in a percentage of 0.05 to 20% by weight of the
active layer, and wherein the hydrophilic polymeric substances in the active layer comprise hydroxypropylmethylcellulose and sodium carboxymethylcellulose.

35. A multi-layer tablet as claimed in any preceding claim, in which the active
25 layer consists of components (i) to (iv) wherein:
- the active substance is ropinirole contained in a percentage of 0.05% to 20% by weight ofthe active layer,
- the adjuvant substances are contained in a percentage of 5% to 50% by weight ofthe
active layer,
30 - the hydrophilic polymeric substances in the active layer comprise hydroxypropyl-
methylcellulose and sodium carboxymethylcellulose, and
- the weight ratio of the hydrophilic polymeric substances to the lipophilic substances

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contained in the active layer is in the range offrom 7:1 to 1:1.

36. A multi-layer tablet as claimed in any preceding claim, in which the one or more
barrier layers:
5 - are applied to one or both surfaces (bases) ofthe active layer,
- contain hydrophilic polymeric substances which swell and/or gel and/or
erode upon contact with aqueous liquids, as defined in claim 13, and
- contain lipophilic substances.

10 37. A multi-layer tablet as claimed in any preceding claim, in which the one or more
barrier layers:
- are applied to one or both surfaces (bases) ofthe active layer,
- contain hydrophilic polymeric substances which swell and/or gel and/or
erode upon contact with aqueous liquids, as well as lipophilic substances,
15 and

20

- are such that during the first hour after oral administration or
immersion in aqueous liquids (e.g. water), release ofthe active substance
occurs substantially only from the surface ofthe tablet not covered by the
one or more barrier layers.

38. A multi-layer tablet as claimed in any preceding claim, wherein a barrier layer is applied to both surfaces (bases) ofthe active layer.

39. Use of the active substance in the manufacture of a medicament wherein said
25 medicament is a multi-layer controlled release tablet as claimed in any one of claims
1-38 for treating Parkinson’s disease.

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40. A multi-layer tablet as claimed in any one of claims 1 to 38, substantially as
herein described with reference to figures 1 to 13 and/or examples 1 to 24.

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THE PATENTS ACT

(CHAPTER 22 1)

CERTIFICATE OF GRANT OF PATENT

In accordance with section 35 of the Patents Act, it is hereby certified that a patent having the P-No. 92249 [WO 01/78688] has been granted in respect of an invention having the following particulars:

Title

Application Number

Date of Filing

Priority Data

Name ofInventor(s)

Name(s)
and Address(es) of
Proprietor(s) of Patent

Date of Grant

HYDROPHILIC/LIPOPHILIC POLYMERIC MATRIX DOSAGE FORMULATION

200206101-8

12 April 2001

14 April 2000 - PATENT APPLICATION NO. M12000A000852 (ITALY)

7 September 2000 - PATENT APPLICATION NO. MI2000A001 963 (ITALY)

VERGNAULT, GUY; GRENIER, PASCAL;
MAGGI, LAUREYFA; CONTE, UBALDO

JAGOTEC AG
EPTINGERSTRASSE 51, CH-4132, MUTTENZ SWITZERLAND

30 September 2005

Dated this 30th day of September 2005.

Wong Sheng "KKwai (Mr

Acting Registrar of Patents,
Singapore

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THE REGISTRY OF PATENTS SINGAPORE

THE PATENTS ACT

(CHAPTER 221)

CERTIFICATE OF GRANT OF PATENT

In accordance with section 35 of the Patents Act, it is hereby certified that a patent having the P -No. 92249 [WO 01/78688] has been granted in respect of an invention having the following particulars:

Title : HYDROPHILIC/LIPOPHILIC POLYMERIC
MATRIX DOSAGE FORMULATION

Application Number: 200206101-8

Date of Filing : 12 April 2001

Priority Data : 14 April 2000 - PATENT APPLICATION NO.
M12000A000852 (ITALY)

7 September 2000 - PATENT APPLICATION NO.
M12000A001963 (ITAL))

Name ofInventor(s) \ERGNAULT, GUY; GRENIER, PASCAL;
MAGGI, LAUREUFA; CONTE, UBALDO

Name(s) JAGOTEC AG
and Address(e) of EPTINGERSTRASSE 51, CH-4132, MtJYFENZ
Proprietor(s) of Patent: SWITZERLAND

Date of Grant : 30 September 2005

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CLAIMS

5 1. A multi-layer controlled-release tablet comprising:

(a) one active layer containing: (i) an active substance which is ropinirole or a pharmaceutically acceptable salt thereof, (ii) hydrophilic polymeric substances
which swell and/or gel and/or erode upon contact with aqueous liquids, (iii)
10 lipophilic substances, and (iv) adjuvant substances, wherein the weight ratio of
the hydrophilic polymeric substances to the lipophilic substances contained in
said active layer is in the range of 10:1 to 0.5:1; and

(b) one or more barrier layers containing one or more of: hydrophilic polymeric
15 substances which swell and/or gel and/or erode upon contact with aqueous
liquids, lipophilic substances, and adjuvant substances.

2. A multi-layer tablet as claimed in claim 1, in which the weight ratio of the
hydrophilic polymeric substances to the lipophilic substances contained in said active
20 layeris in th.e range of 7:1 to 1:1

25

3. A multi-layer tablet as claimed in claim 1 or claim 2, in which said hydrophilic
polymeric substances (ii) are contained in a percentage between 5% and 65%, of the weight ofthe active layer.

4. A multi-layer tablet as claimed in any one of claims 1 to 3, in which said
lipophilic substances (iii) are contained in a percentage between 5% and 55% of the weight ofsaid active layer..

30 5. A multi-layer tablet as claimed in any one of claims I to 4, in which said
adjuvants (iv) are contained in a percentage between 10% to 40% of the weight ofsaid active layer.

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6. A multi-layer tablet as claimed in any one of claims ito 5, in which the weight
ratio between said active substance i) and said adjuvant substances (iv) in the active
layer is in the range of 0.003:1 to 3:1.

7. A multi-layer tablet as claimed in any preceding claim, in which said one or
more barrier layers are applied to one or both surfaces (bases) ofthe active layer.

8. A multi-layer tablet as claimed in any preceding claim, in which the weight
10 ratio of hydrophilic swelling and/or gelling and/or erodible polymeric substances to
lipophilic substances contained in the barrier layer is in the range of 2:1 to 3.5:1.

9. A multi-layer tablet as claimed in any preceding claim, in which the active
substance (i) is contained in a weight percentage between 0.05% to 50% by weight of
15 the active layer.

10. A multi-layer tablet as claimed in claim 9, in which the active substance (1) is
contained in a percentage of 0.05% to 20% by weight of the active layer.

20 11. A multi-layer tablet as claimed in any preceding claim, in which the active
layer contains polymeric material with slow swelling and/or geification and/or erosion and/or solubility properties.

12. A multi-layer tablet as claimed in any preceding claim, in which the active
25 layer further contains polymeric substances of a lipophilic nature.

13. A multi-layer tablet as claimed in any preceding claim, in which said
hydrophilic polymeric substances comprise a pharmaceutically acceptable
biocompatible and/or biodegradable material, including non-cross-linked
30 polyvinylpyrrolidone, hydroxypropylcellulose with a molecular weight of 100,000 to
4,000,000, sodium carboxymethylcellulose, carboxymethylstarch, potassium methacrylate-divinylbcflZene copolymer, hydroxypropylmethylcelluloSe of molecular

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weight between 2,000 and 4,000,000, a polyethyleneglycol ofmolecular weight
between 200 and 15,000, a polyoxyethylene with molecular weight of up to
20,000,000, a carboxyvinylpolymer, a poloxamer (polyoxyethylene-polyoxypropylene copolymer), a polyvinylalcohol, a glucane(glucan), a carrageenan, a scieroglucane
5 (scleroglucan), a mannan, a galactomannan, gellans, xanthans, alginic acid and/or a
derivative thereof, polyaminoacids, methyl vinyl ether /maleic anhydride copolymer, carboxymethylcellulose and/or a derivative thereof, ethylcellulose, methylcel.lulose,
starch, a starch derivative, alpha, beta, or gamma cyclodextrin and/or a dextrin
derivative.
10

14. A multi-layer tablet as claimed in any preceding claim, in which said lipophilic
substances include a natural fat (for example coconut, soya, cocoa) as such or totally
or partially hydrogenated, beeswax, polyethoxylated beeswax, a mono-, bi- or tn-
substituted glyceride, glyceryl palmitostearate, glyceryl behenate, diethyleneglycol
15 palmitostearate, a polyethyleneglycol stearate, a polyoxyethyleneglycol
palmitostearate, glyceryl monopalmitostearate, cetyl palmitate, polyethyleneglycol palmitostearate, mono- or di-glyceryl behenate, a fatty alcohol associated with a polyethoxylate fatty alcohol, cetyl alcohol, stearic acid, a saturated or unsaturated fatty
acid or a hydrogenated derivative thereof, and/or hydrogenated castor oil.

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15. A multi-layer tablet as claimed in any preceding claim, in which the tablet
preparation is carried out by compression of the powder or granular mixture and
working between 1000 and 5000 Kg/cm.

25 16. A multi-layer tablet as claimed in any preceding claim, in which the lipophilic
substance present in the active layer is selected from hydrogenated castor oil and
glyceryl behenate.

17. A multi-layer tablet as claimed in claim 1, in which the amount of ropinirole
30 present, inclusive of pharmaceutically acceptable salts thereof, is up to 12.0mg,
measured as the amount ofropinirole base present.

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PW 18. A multi-layer tablet as claimed in claim 1, in which the amount of ropinirole
present, inclusive of pharmaceutically acceptable salts thereof, is from 0.75mg to
12.0mg, measured as the amount ofropinirole base present.

5 19. A multi-layer tablet as claimed in any preceding claim, in which the active
.layer consists of components (i) to (iv) wherein the active substance is contained in a
percentage of 0.05% to 20% by weight of the active layer, the adjuvant substances are
contained in a percentage of 5% to 50% by weight of the active layer, and the weight
ratio of the hydrophilic polymeric substances to the lipophilic substances contained in
10 the active layer is in the range offrom 7:1 to 1:1.

20. A multi-layer tablet as claimed in any preceding claim, in which the
hydrophilic polymeric substance comprises hydroxypropyhnethylcellulose of molecular weight 2,000 to 4,000,000, sodium carboxymethylcellulose or calcium.
15 carboxymethylcellulose.

21. A multi-layer tablet as claimed in any preceding claim, in which (i) the active
substance is ropinirole contained in a percentage of 0.05% to 20% by weight of the
active layer, (ii) the hydrophilic polymeric substance comprises
20 hydroxypropylmethylcellulose, sodium carboxymethylcellulose or calcium
carboxymethylcellulose, (iii) the lipophilic substance comprises hydrogenated castor
oil or glyceryl behenate, and (iv) the adjuvant substances are contained in a percentage
of 5% to 50% by weight of the active layer, and the weight ratio of the hydrophilic polymeric substances to the lipophilic substances contained in the active layer is in the
25 range of from 7:1 to 1:1.

22. A multi-layer tablet as-claimed in any preceding claim, wherein the active
substance is ropinirole contained in a percentage of 0.05 to 20% by weight of the active layer, and wherein the hydrophilic polymeric substances in the active layer
30 comprise hydroxypropylmethylcellulose and sodium carboxymethylcellulose.

23. A multi-layer tablet as claimed in any preceding claim, in which the active

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layer consists of components (i) to (iv) wherein:
- the active substance is ropinirole contained in a percentage of 0.05% to 20% by weight ofthe active layer,
- the adjuvant substances are contained in a percentage of 5% to 50% by weight ofthe
5 active layer,
the hydrophilic polymeric substances in the active layer comprise hydroxypropyl-methylcellulose and sodium carboxymethylcellulose, and
- the weight ratio of the hydrophilic.polymeric substances to the lipophilic substances contained in the active layer is in the range offrom 7:1 to 1:1.
10

24. The use of one or more multi-layer tablets as defined in any one of claims 1 to
23 in the preparation of a medicament for the treatment of Parkinson’s Disease.

25. A use as claimed in claim 24, in which the one or more multi-layer tablets as
15 defined in any one of claims 1 to 23 are suitable for administration once per day.

26. A use as claimed in claim 24, in which the medicament comprises a single
multi-layer tablet as defined in any one of claims 1 to 23 which is uitable for administration once per day.
20

27. A multi-layer tablet as claimed in any one of claims I to 23, in which
the one or more barrier layers:
- are applied to one or both surfaces (bases) ofthe active layer,
- contain hydrophilic polymeric substances which swell and/or gel and/or
25 erode upon contact with aqueous liquids, as defined in claim 13, and
- contain lipophilic substances.

28. A multi-layer tablet as claimed in any one of claims 1 to 23 or 27, in
which the one or more barrier layers:
30 - are applied to one or both surfaces (bases) of the active layer,
contain hydrophilic polymeric substances which swell and/or gel and/or
erode upon contact with aqueous liquids, as well as lipophilic substances,

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and

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- are such that during the first hour after oral administration or
immersion in aqueous liquids (e.g. water), release of the active substance
occurs substantially only from the surface ofthe tablet not covered by the
S one or more batherlayers.

29. A multi-layer tablet as claimed in any one of claims 1 to 23 or 27 to 28 wherein a barrier layer is applied to both surfaces (bases) of the active layer.

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PATENTS ACT, 1978

CERTIFICATE

ction 44 (1) of the Patents Act, No. 57 of 1978, it is hereby certified that JAGOTEC AG

patent in respect of an invention described and claimed in complete cation deposited at the Patent Office under the number
2002/9226

iplete specification is annexed, together with the relevant Form P2.

the seal of the Patent Office has been affixed at Pretoria with effect the 31st day of December 2003

Registrar ofPatents

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CLAIMS

1. A multi-layer controlled-release tablet comprising:

(a) one active layer containing: (i) an active substance, (ii) hydrophilic polymeric substances which swell and/or gel and/or erode upon contact with aqueous liquids, (iii) lipophilic substances, and (iv) adjuvant substances, wherein the weight ratio of the hydrophilic polymeric substances to the lipophilic substances contained in said active layer is in the range of 10:1 to 0.5:1; and

(b) one or more barrier layers containing one or more of hydrophilic polymeric substances which swell and/or gel and/or erode upon contact with aqueous liquids, lipophilic substances, and adjuvant substances.

2. A multi-layer tablet as claimed in claim 1, in which the weight ratio of the
hydrophilic polymeric substances to the lipophilic substances contained in said active layer is in the range of 7:1 to 1:1.

3. A multi-layer tablet as claimed in claim 1 or claim 2, in which said hydrophilic
polymeric substances (ii) are contained in a percentage between 1% and 75% of the weight of the active layer.

4. A multi-layer tablet as claimed in claim 3, wherein the hydrophilic polymeric
substances (ii) are contained in a percentage between 5% and 65% of the weight of the active layer.

5. A multi-layer tablet as claimed in any one of claims 1 to 4, in which said
lipophilic substances (iii) are contained in a percentage between 1% and 70% of the weight of said active layer.

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6. A multi-layer tablet as claimed in claim 5, wherein the lipophilic substances
(iii) are contained in a percentage between 5% and 55% of the weight of the active layer.

7. A multi-layer tablet as claimed in any one of claims 1 to 6, in which said
adjuvants (iv) are contained in a percentage between 5% to 50% of the weight of said active layer.

8. A multi-layer tablet as claimed in claim 7, wherein the adjuvants (iv) are
contained in a percentage between 10% and 40% ofthe weight of the active layer.

9. A multi-layer tablet as claimed in any one of claims 1 to 8, in which the weight

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ratio between said active substance (i) and said adjuvant substances (iv) in the active layer is in the range of 0.001:1 to 4:1, preferably from 0.003:1 to 3:1.

10. A multi-layer tablet as claimed in claim 9, wherein the weight ratio between
the active substances (i) and the adjuvant substances (iv) in the active layer is in the range of 0.003:1 to 3:1.

11. A multi-layer tablet as claimed in any one of the preceding claims, in which said
one or more barrier layers are applied to one or both surfaces (bases) ofthe active layer.

12. A multi-layer as claimed in any one ofthe preceding claims, in which the
weight ratio of hydrophilic swelling and/or gelling and/or erodible polymetic substances to lipophilic substances contained in the barrier layer is in the range of 1:1 to 7.5:1.

13. A multi-layer tablet as claimed in claim 12, wherein the weight ratio of
hydrophilic swelling and/or gelling and/or erodible polymeric substances to lipophilic substances contained in the barrier layer is in the range of 1.5:1 to 4:1.

14. A multi-layer tablet as claimed in claim 13, wherein the weight ratio of
hydrophilic swelling and/or gelling and/or erodible polymeric substances to lipophilic substances contained in the barrier layer is in the range of 2:1 to 3.5:1.

15. A multi-layer tablet as claimed in any one ofthe preceding claims, in which
the active substance (i) is contained in a weight percentage between 0.01% to 70% by weight of the active layer.

16. A multi-layer tablet as claimed in claim 15, wherein the active substance (i) is
contained in a weight percentage between 0.05% and 50% of the weight of the active layer.

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17. A multi-layer tablet as claimed in claim 15, in which the active substance (i) is
contained in a percentage of 0.05% to 20% by weight of the active layer.

18. A multi-layer tablet as claimed in any one of the preceding claims, in which
the active layer contains polymeric material with slow swelling and/or gelification and/or erosion and/or solubility properties.

19. A multi-layer tablet as claimed in any one of the preceding claims, in which
the active layer further contains polymeric substances of a lipophilic nature.

20. A multi-layer tablet as claimed in any one ofthe preceding claims, in which
said hydrophilic polymeric substances comprise a pharmaceutically acceptable biocompatible and/or biodegradable material, including non-cross-linked polyvinylpyrrolidone, hydroxypropylcellulose with a molecular weight of 100,000 to 4,000,000, sodium carboxymethylcellulose, carboxymethylstarch, potassium methacrylate-divinylbenzene copolymer, hydroxypropylmethylcellulose of molecular weight between 2,000 and 4,000,000, a polyethyleneglycol of molecular weight

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between 200 and 15,000, a polyoxyethylene with molecular weight of up to
20,000,000, a carboxyvinylpolymer, a poioxamer (polyoxyethylene-polyoxypropyl ene
copolymer), a polyvinyl alcohol, a glucane(glucan), a carrageenan, a scieroglucane
(scieroglucan), a mannan, a galactomannan,, gellans, xanthans, alginic acid and/or a
derivative thereof, poiyaminoacids, methyl vinyl ether/maleic anhydride copolymer, carboxymethylcellulose and/or a derivative thereof, ethylcellulose, methylcellulose,
ft starch, a starch derivative, alpha, beta, or gamma cyclodextrin and/or a dextrin derivative.

21. A multi-layer tablet as claimed in any one of the preceding claims, in which
said lipophilic substances include a natural fat (for example coconut, soya, cocoa) as such
a totally or partially hydrogenated, beeswax, polyethoxylated beeswax, a mono-, bi- or
tn-substituted glyceride, glyceryl palmitostearate, glyceryl behenate, diethyleneglycol
palmitostearate, a polyethyleneglycol stearate, a polyoxyethyleneglycol palmitostearate, glyceryl monopalmitostearate, cetyl palmitate, polyethyleneglycol palmitostearate, mono- or di-glyceryl behenate, a fatty alcohol associated with a polyethoxylate fatty alcohol, cetyl alcohol, stearic acid, a saturated or unsaturated fatty acid or a hydrogenated derivative thereof, and/or hydrogenated castor oil.

22. A multi-layer tablet as claimed in any one ofthe preceding claims, in which
the active substance(s) are therapeutic agents for the treatment of chronic diseases, for example drugs acting on the cardiovascular system, anti-arrhythmics, cardiac stimulants, vasodilators, anti-hypertensives, anti-adrenergic substances of central and peripheral action or substances acting on the arteriolar musculature, substances acting on the rennin-angiotensin system, anti-hypertensives and diuretics in association, anti-Parkinson’s Disease agents, diuretics and drugs for the treatment of Alzheimer’s disease.

23. A multi-layer tablet as claimed in any one ofthe preceding claims, in which the
active substance(s) is selected from: propranolol, atenolol, pindolol, ropinirole, prazosin, ramipril, spirapril; spironolactone, metipranolol, molsidomine, moxonidina, nadolol,

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nadoxolol, levodopa, metoprolol, or timolol, inclusive of pharmaceutically acceptable salts thereof.

24. A multi-layer tablet as claimed in any one of the preceding claims, in which
the tablet preparation is carried out by compression of the powder or granular mixture
- and working between 1000 and 5000 Kg/cm2.

25. A multi-layer tablet as claimed in any one of the preceding claims, in which
the lipophilic substance present in the active layer is selected from hydrogenated castor oil and glyceryl behenate.

26. A multi-layer tablet as claimed in any one ofthe preceding claims, in which
the active substance comprises or is ropinirole, inclusive of pharmaceutically acceptable salts thereof.

27. A multi-layer tablet as claimed in claim 26, in which the amount ofropinirole
present, inclusive of pharmaceutically acceptable salts thereof, is up to 12.0mg, measured as the amount of ropinirole base present.

28. A multi-layer tablet as claimed in claim 26, in which the amount of ropinirole
present, inclusive of pharmaceutically acceptable salts thereof, is from 0.75mg to 12.0mg, measured as the amount ofropinirole base present.

29. A multi-layer tablet as claimed in any one of the preceding claims, in which
the active layer consists of components (i) to (iv) wherein the active substance is contained in a percentage of 0.05% to 20% by weight of the active layer, the adjuvant substances are contained in a percentage of 5% to 50% by weight of the active layer, and the weight ratio of the hydrophilic polymeric substances to the lipophilic substances contained in the active layer is in the range of from 7:1 to 1: 1.

30. A multi-layer tablet as claimed in any one ofthe preceding claims, in which the
active layer consists essentially of components (i) to (iv) wherein the active substance is

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contained in a percentage of 0.05% to 20% by weight of the active layer, the adjuvant substances are contained in a percentage of 5% to 50% by weight of the active layer, and the weight ratio of the hydrophilic polymeric substances to the lipophilic substances contained in the active layer is in the range of from 7:1 to 1:1.

31. A multi-layer tablet as claimed in any one of the preceding claims, in which
the hydrophilic polymeric substance comprises hydroxypropylmethyl cell ul ose of molecular weight 2,000 to 4,000,000, sodium carboxymethylcellulose or calcium carboxymethylcellulose.

32. A multi-layer tablet as claimed in any one of the preceding claims, in which (i)
the active substance is ropinirole contained in a percentage of 0.05% to 20% by weight of the active layer, (ii) the hydrophilic polymeric substance comprises hydroxypropylmethylcellulose, sodium carboxymethylcellulose or calcium carboxymethylcellulose, (iii) the lipophilic substance comprises hydrogenated castor oil or glyceryl behenate, and (iv) the adjuvant substances are contained in a percentage of 5% to 50% by weight of the active layer, and the weight ratio of the hydrophilic polymeric substances to the lipophilic substances contained in the active layer is in the range of from 7:1 to 1:1.

33. A multi-layer tablet as claimed in any one of the preceding claims, wherein the
active substance is ropinirole contained in a percentage of 0.05 to 20% by weight of the active layer, and wherein the hydrophilic polymeric substances in the active layer comprise hydroxypropylmethylcellulose and sodium carboxymethyl cellulose.

34. A multi-layer tablet as claimed in any one of the preceding claims, in which
the active layer consists of components (i) to (iv) wherein:
- the active substance is ropinirole contained in a percentage of 0.05% to 20% by weight of the active layer,
- the adjuvant substances are contained in a percentage of 5% to 50% by weight of the active layer,
- the hydrophilic polymeric substances in the active layer comprise hydroxypropyl-

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methylcellulose and sodium carboxymethylcellulose, and
- the weight ratio of the hydrophilic polymeric substances to the lipophilic substances
contained in the active layer is in the range of from 7:1 to 1:1.

35. A multi-layer tablet as claimed in any one of claims 26 to 34 for use in the
treatment of Parkinson’s Disease comprising administering to a human in need of such treatment one or more multi-layer tablets.

36. A multi-layer tablet as claimed in claim 35, in which one or more multi-layer
tablets as defined in any one of claims 26 to 34 are administered once per day to the human in need of such treatment.

37. A multi-layer tablet as claimed in claim 35, in which a single multi-layer tablet as
defined in any one of claims 26 to 34 are administered once per day.

38. A multi-layer tablet as claimed in any one of claims 1 to 34, in which the one
or more barrier layers:
- are applied to one or both surfaces (bases) of the active layer,
- contain hydrophilic substances which swell and/or gel and/or erode upon contact with aqueous liquids, as defined in claim 20, and
- contain lipophilic substances.

39. A multi-layer tablet as claimed in any one of claims 1 to 34 and 38, in which
the one or more barrier layers:

and

- are applied to one or both surfaces (bases) of the active layer,
- contain hydrophilic substances which swell and/or gel and/or
erode upon contact with aqueous liquids, as well as lipophilic substances,

- are such that during the first hour after oral administration or immersion in aqueous liquids (e.g. water), release of the active substance occurs substantially only from the surface of the tablet not covered by the one or more barrier layers.

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40. A multi-layer tablet as claimed in any one of claims ito 34 and 38 to 39
wherein a barrier layer is applied to both surfaces (bases) of the active layer.

41. A multi-layer controlled-release tablet as claimed in any one of claims 1 to 40,
substantially as hereinbefore described and exemplified.

42. A multi-layer controlled-release tablet including any new and inventive integer
or combination of integers, substantially as herein described.