C

Señor Superintendente
SUPERINTENDENCIA DE INDUSTRIA Y COME
E. S. D.

Trámite : 011
Evento : 378
Actuación : 412

Referencia : Expediente No. **11.067.790**
Asunto : Solicitud de patente para: **CLORHIDRATO DE NALMEFENO DIHIDRATO**
Solicitante : H. LUNDBECK A/S y BIOTIE THERAPIES CORP.
Fecha de solicitud : 01 de Junio de 2011

I. RECURSO VÍA GUBERNATIVA

Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad **H. LUNDBECK A/S y BIOTIE THERAPIES CORP.** solicitante de la patente de la referencia, por el presente escrito atentamente manifiesto a usted que debidamente notificada de la Resolución No. **60094** del 17 de Octubre de 2013, interpongo en su contra el recurso de **REPOSICIÓN**, para que sea revocada y en consecuencia se conceda el privilegio de patente de invención para **"CLORHIDRATO DE NALMEFENO DIHIDRATO"** a favor de **LUNDBECK A/S y BIOTIE THERAPIES CORP.**

II. OPORTUNIDAD DE LA IMPUGNACIÓN

La Resolución No. **60094** del 17 de Octubre de 2013, con fecha de publicación listado el 22 de Octubre de 2013, fecha de vencimiento el 22 de Noviembre de 2013, y fecha del término legal el 29 de Noviembre de 2013.

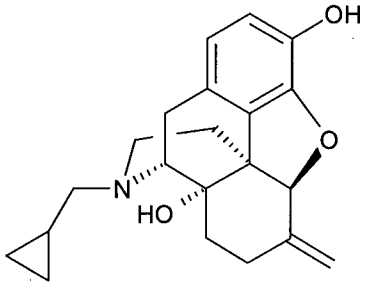
III. LA DECISIÓN RECURRIDA

3.1 Mediante la Resolución objeto de la presente impugnación, el Superintendente de Industria y Comercio decidió:

3.1.1 Denegar la patente de invención a la creación titulada: **"CLORHIDRATO DE NALMEFENO DIHIDRATO"**

3.2 En la parte motiva de la providencia, se mencionaron los siguientes fundamentos:

3.2.1 Las características esenciales de la invención de la reivindicación 1 habían sido derivadas de manera evidente previamente en los documentos D3 y D4, los cuales dan a conocer un compuesto representado mediante la fórmula



$.HCl.2H_2O$

3.2.2 "El análisis de nivel inventivo del producto reclamado se realizó mediante la aproximación problema-solución en polimorfos (Patenting Polymorphs at the European Patent Office) posición que adoptada por la Superintendencia de Industria y Comercio para efectos del análisis de la patentabilidad de las formas polimórficas."

3.2.3 "Determinación del estado de la técnica más cercano:
El documento D3 se considera el estado de la técnica cercano a la invención definida en la reivindicación 4 porque divulga el compuesto clorhidrato de Nalmefeno (pág. 1180, col. Derecha, en: "treatment and assessments")."

3.2.4 "Determinación de las diferencias técnicas de la invención con respecto al estado del estado de la técnica más cercano:
La diferencia entre la invención definida en la reivindicación 1 y el compuesto del documento D3, consiste en que revela una forma cristalina de dihidrato de Nalmefeno HCl, que está caracterizada por un espectro de difracción de rayos X en polvo en valores 2e utilizando radiación Cu Kal que tiene pico en 8.99 y además en uno o más de 10.63, 15.24, 16.55 y/o 17.20."

3.2.5 "Determinación del efecto técnico obtenido por las diferencias técnicas de la invención con respecto al estado de la técnica más cercano:
Según la descripción de la solicitud, el efecto técnico que logra la forma cristalina de Nalmefeno dihidrato HCl es que las propiedades físicas pueden ser fácilmente controladas, que además se evitan problemas que se presentan con grupos higroscópicos como el uso de cámaras de humedad controlada para el almacenamiento y el procesamiento del producto y que no se presentan problemas de estabilidad dados por la humedad que debe controlarse en los compuestos higroscópicos (capítulo descriptivo pág. 6 líneas 8 — 21)."

3.2.6 "Establecimiento del problema técnico objetivo a solucionar con base en el estado de la técnica más cercano:
El problema técnico objetivo que pretende resolver esta invención se puede formular como la necesidad de obtener una forma cristalina de clorhidrato de Nalmefeno para pacientes que presenten problemas con el manejo del alcoholismo.

3.2.7 "Comprobación de la solución al problema técnico objetivo de la solicitud:
De acuerdo con la información suministrada en la descripción de la solicitud (pág. 7), en donde se mencionan las características de la forma cristalina dihidrato de Nalmefeno HCl, se encuentra en forma resumida que:
Aunque la solicitante presenta métodos para obtención por recristalización en solución acuosa de la forma cristalina dihidrato de clorhidrato de Nalmefeno, y señala en la página 7 datos de reflexión de rayos X indicados en ángulos 8.99 y además en uno o más de 10.63, 15.24, 16.55 y/o 17.20 en 20, no se evidencian propiedades fisicoquímicas ventajosas tales como, por ejemplo, velocidad de disolución (relacionada con la biodisponibilidad), estabilidad térmica y mecánica realmente demostrada, una higroscopicidad ventajosa frente a la forma monohidrato del Nalmefeno HCl, solubilidad, entre otras, que indiquen que las formas cristalinas puedan tener un efecto técnico superior respecto del compuesto Nalmefeno I-ICI ya conocido en el estado de la técnica cercano.
Por lo tanto se puede concluir que no existe un efecto técnico probado, porque no se demuestra las ventajas en las propiedades fisicoquímicas de la forma cristalina del dihidrato de Nalmefeno HCl reclamado en la presente solicitud, con respecto al compuesto Nalmefeno HCl divulgado en D3."

3.2.8 "Evaluar si habría sido obvio solucionar el problema técnico objetivo por la invención reivindicada:
De tal manera que la solución al problema técnico planteado por la invención reclamada se considera obvia porque la anterioridad D4, ya divulga que las diferentes formas cristalinas para un mismo compuesto difieren en sus propiedades fisicoquímicas tales como la solubilidad, estabilidad, velocidad de disolución, higroscopicidad, biodisponibilidad entre otras, y es además una práctica habitual en estudios de preformulación dentro de los cuales se incluyen rigurosos trabajos para determinar su presencia en los medicamentos con el fin de evitar su inestabilidad o falta de efectividad. Dentro de estos estudios, se investiga habitualmente (i) la cantidad de polimorfos que existen, (ii) el grado relativo de estabilidad de los diversos polimorfos, (iii) las gamas de estabilidad térmica de cada polimorfo, (iv) solubilidades,(v) método de preparación de cada forma, (vi) efecto de la micronización o tableteado e interacción con los componentes de la formulación (página 1913 ambas columnas), y una vez establecido que el compuesto (en este caso aplicable al compuesto Nalmefeno HCl) presenta polimorfismo, existen procedimientos con los cuales el preformulador puede preparar las diversas formas en cantidades más grandes para su evaluación adicional y adecuarlas para incorporar en las formas posológicas (página 1915 columna izquierda)."

3.2.9 "También es conocido en el campo técnico que los polimorfos son diferentes arreglos estructurales dentro de un cristal de una misma molécula o sustancia, por lo tanto una persona del oficio normalmente versada en la materia, conociendo que en D3 ya se divulgo el compuesto Nalmefeno HCl, y que en D4 se conoce que el fenómeno de polimorfismo se da ampliamente en los medicamentos de uso farmacéutico, esta persona se encontraría motivada a utilizar métodos como los revelados en D4 para identificar las formas polimórficas de la molécula en cuestión, que además pueden ser analizadas por métodos de cristalografía conocidos (pág. 1915 — 1917). De tal manera, no es posible concluir que la identificación de la forma cristalina reclamada en la actual solicitud envuelvan actividad inventiva, como quiera que la molécula misma ya era conocida con anterioridad; es decir, la identificación de las forma cristalina reclamada y caracterizadas mediante la técnica de DRX, no representa un avance técnico real y tampoco un salto cualitativo a la regla técnica porque el efecto asociado no fue demostrado en la descripción de la solicitud, comoquiera que no se encontró alguna prueba o ensayo que permitiera determinar las

ventajas reales de las forma dihidrato de Nalmefeno HCl, con respecto al compuesto conocido con anterioridad (D3) que permita probar, un efecto realmente inesperado asociado con sus propiedades fisicoquímicas."

3.2.10 "En consecuencia, una persona del oficio normalmente versada en la materia, encontraría la sugerencia o motivación suficiente aplicando los métodos y conocimientos que se tiene sobre el polimorfismo revelados en D4, al clorhidrato de Nalmefeno divulgado en D3, con el fin de determinar la existencia de la forma dihidrato del Nalmefeno HCL, tal como se reclama en la presente solicitud."

3.2.11 "De acuerdo con lo expuesto, la reivindicación 1 y sus dependientes 27 — 32 no cumplen con el requisito de nivel inventivo (Art. 18)."

3.2.12 "La reivindicación 2 consiste en un método para obtener un compuesto de acuerdo con la reivindicación 1, que comprende los pasos de:

3.2.13 "(1) mezclar el clorhidrato de Nalmefeno (clorhidrato de 17-(ciclopropilmetil)-4,5-alfa-epoxi-6-metilenmorfinan-3,14-diol) y solución acuosa tal como agua, (2) opcionalmente, calentar la mezcla, (3) opcionalmente, destilar la mezcla, (4) agitar la mezcla hasta completarse la transformación, y (5) aislar el sólido formado. (Ver pág. 10 del radicado No 11-067790-00007-0000)."

3.2.14 "El documento D3 se considera el estado de la técnica cercano a la invención definida en la reivindicación 2 porque divulga el compuesto Nalmefeno Clorhidrato."

3.2.15 "La diferencia entre la invención definida en la reivindicación 2 y el documento D3, consiste en que menciona la forma dihidrato de Nalmefeno HC1 y define los pasos llevados a cabo para obtener por recristalización tal compuesto."

3.2.16 "El efecto que logra incluir esta característica es que proporciona un método de obtención de la forma cristalina dihidrato de Nalmefeno HCl."

3.2.17 "Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular como la necesidad de suministrar métodos de obtención de la forma cristalina dihidrato de Nalmefeno HCl."

3.2.18 "Sin embargo, como se mencionó en el examen de fondo, es de conocimiento común de la persona del oficio normalmente versada en la materia que una forma de obtener polimorfos consiste en el empleo de técnicas de cristalización y re-cristalización, que se basan ya sea en la disolución de la molécula en diferentes solventes (entre los más usados encuentran las mezclas agua) y/o en cambios de temperatura (por calentamiento y remoción del solvente donde la agitación es necesaria y es un factor que determina la obtención de las formas cristalinas). Las técnicas de recristalización permiten además obtener compuestos con una pureza incrementada y que dependiendo de parámetros como el calentamiento, el tiempo de destilación o la agitación se pueden obtener sólidos resultantes de tal técnica."

3.2.19 "En consecuencia, la reivindicación 2 es obvia, porque la persona del oficio normalmente versada en la materia enfrentada al problema de suministrar métodos de obtención formas cristalinas de Nalmefeno HCl dihidrato, habría podido utilizar técnicas de cristalización y re-cristalización basadas en la disolución de la molécula en diferentes solventes y/o la remoción del solvente por agitación y calentamiento tal como lo establece la bibliografía básica utilizada por el técnico medio, por lo que resulta obvio diseñar una secuencia de cristalización — re-cristalización y/o la remoción del solvente por agitación y calentamiento en diferentes solventes o estos mismos en diferentes proporciones, con el ánimo de obtener los polimorfos de interés, más aún si se conoce el fundamento teórico para la obtención de cristales por diferencias en solubilidad y modificando parámetros adicionales como temperatura, velocidad de enfriamiento, agitación, presión, evaporación, con la expectativa razonable de encontrar los ordenamientos cristalinos reivindicados."

3.2.20 "Lo anterior aplica para las reivindicaciones 3 — 26 cuyo objeto a reclamar es en esencia el mismo de la reivindicación 2."

3.2.21 "Por lo anterior, las reivindicaciones 2 — 26 no cumplen con el requisito de nivel inventivo (Art. 18)."

3.2.22 "La solicitante argumenta en su oficio bajo el radicado No 11-067790-00007-0000, que el nivel inventivo de la presente invención se encuentra sustentado en que el clorhidrato de Nalmefeno dihidrato no es higroscópico y es estable en contenido acuoso y que a partir de los ejemplos 1.2 y 2.2 por experimentos DVS

se demuestran tales propiedades y que eran imprevisibles a partir del arte previo."

3.2.23 "Frente a estos argumentos esta Superintendencia se permite precisar a la solicitante que lo que se evidencia es que la solicitante realiza una modificación estructural en una sal de principio activo conocido como lo es el clorhidrato de Nalmefeno, incluyendo en tal sal dos moléculas de agua, para obtener la forma dihidratada de la misma. Lo anterior se señala porque cuando se observa el capítulo descriptivo, no se encuentra que tal modificación estructural conceda a la sal propiedades fisicoquímicas ventajosas tales como, por ejemplo, velocidad de disolución (relacionada con la biodisponibiliclad), estabilidad térmica y mecánica realmente demostrada, una higroscopicidad ventajosa frente a la forma monohidrato del Nalmefeno HCl, solubilidad, entre otras, que indiquen que las formas cristalinas puedan tener un efecto técnico superior respecto del compuesto Nalmefeno FICI ya conocido en el estado de la técnica cercano. La solicitante puede realizar una correcta caracterización de la forma cristalina del clorhidrato de Nalmefeno dihidrato pero esto debe ir acompañado de sustento técnico que evidencia la ventaja sustancial de la misma y por lo tanto la solicitante falla al demostrar esto. Una invención de este tipo no puede encontrar nivel inventivo en simples modificaciones y condiciones que se deben tener en cuenta para la obtención de una forma cristalina de un principio activo ya conocido, pues para cualquier persona del oficio normalmente versada en la materia una forma de obtener polimorfos (formas cristalinas) consiste en el empleo de técnicas tales como por ejemplo su obtención por cristalización o re-cristalización, que se basan ya sea en la disolución de la molécula en diferentes solventes y/o en cambios de temperatura (por calentamiento y remoción del solvente para la obtención de las formas cristalinas deseadas) y el control de la velocidad de agitación, lo cual no constituye nivel inventivo alguno sino que por el contrario tales métodos son tan comunes en el campo químico-farmacéutico que prácticamente constituyen los métodos de obtención más deseados por su economía y conveniencia."

IV. OBJETO DEL RECURSO

De acuerdo con los argumentos que expongo a continuación, solicito atentamente a su Despacho lo siguiente:

1. Revocar la Resolución No. **60094** del 17 de Octubre de 2013.

2. Conceder el privilegio de patente de invención para **"CLORHIDRATO DE NALMEFENO DIHIDRATO"** a favor de **H. LUNDBECK A/S y BIOTIE THERAPIES CORP.**

V. FUNDAMENTOS DEL RECURSO

Respetuosamente me permito disentir de lo expuesto por ese Despacho en la Resolución objeto del presente recurso, toda vez que la presente solicitud sí cumple con los requerimientos de novedad y nivel inventivo exigidos en la Decisión 486, como se demostrará a continuación:

5.1 La presente solicitud sí tiene nivel inventivo

El artículo 18 de la Decisión 486 señala lo siguiente:

> *"**Artículo 18.-** Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."*

Consecuentemente, una invención se considerará inventiva si la misma no hubiese resultado obvia a partir del arte previo, para una persona del oficio normalmente versada en la materia. Esto a su vez implica que el Examinador a cargo de esta evaluación debe colocarse en el momento exacto en el que el inventor buscaba resolver el problema técnico contemplado en la solicitud y para el cual poseía la literatura y el conocimiento disponibles en dicho momento.

Siguiendo entonces los lineamientos de la Jurisprudencia aplicable al análisis del nivel inventivo de una solicitud de patente, se considera que una anterioridad o una combinación de dos anterioridades puede afectar dicho requerimiento de patentabilidad, si una persona medianamente versada en la materia encuentra enseñanzas o sugerencias claras que, a partir de un conocimiento medio en dicho campo, le permitan llegar de manera obvia a la invención reivindicada. Adicionalmente se considera que una mejora

sustancial, un efecto inesperado o una ventaja con respecto al arte previo es un indicio de nivel inventivo, por cuanto aporta un salto tecnológico en la regla técnica.

Respecto a lo anterior, el Tribunal de Justicia de la Comunidad Andina ha expuesto en la Interpretación Prejudicial del proceso 13-IP-2010:

> *"En este orden de ideas, se puede concluir que una invención goza de nivel inventivo cuando a los ojos de un experto medio en el asunto de que se trate, se necesita algo más que la simple aplicación de los conocimientos técnicos en la materia para llegar a ella, es decir, que de conformidad con el estado de la técnica el invento no es consecuencia clara y directa de dicho estado".*
> [señalado fuera del texto]

Por lo anterior, se entiende que para que una persona medianamente versada en la materia pudiera derivar de manera obvia una invención, requeriría simplemente aplicar sus conocimientos técnicos. En contraste, todo aquello que va más allá de la simple aplicación de los conocimientos técnicos y que no ha sido revelado en el estado de la técnica, debe ser considerado inventivo.

A este respecto, respetuosamente manifestamos nuestro desacuerdo con el análisis llevado a cabo por el Examinador y con las conclusiones del mismo y solicitamos atentamente la reconsideración de las razones por las cuales se decidió negar la patente, con base en la siguiente información:

El Examinador objetó la reivindicación 4 en vista de los documentos D3 y D4 y de acuerdo al Examinador no hay ningún efecto técnico comprobado entre el compuesto de la presente invención el cual es clorhidrato de Nalmefeno dihidratado comparado con el clorhidrato de nalmefeno descrito en el arte previo. Sin embargo, tal como se mencionó en la en la respuesta a la Acción Oficial No. 9662 radicada ante su Despacho el 8 de Octubre de 2013, el documento D3 no menciona en ninguna parte el dihidrato del clorhidrato de nalmefeno y solo se refiere al clorhidrato de nalmefeno como tal. A la fecha de la presentación de la solicitud internacional de esta invención, la única forma conocida del Clorhidrato de nalmefeno era la forma monohidrato (descripción de la presente solicitud, pág. 2, líneas 11 a 15, referencia a Brittain).

Por lo tanto, se reitera a su Despacho que tal como se establece en la descripción de la presente solicitud en la página 2, líneas 18 a 20, los inventores encontraron que

contrariamente a lo expuesto en la bibliografía técnica, el clorhidrato de nalmefeno es higroscópico. Luego en la página 6, líneas 21 a 24 se establece que el clorhidrato de Nalmefeno dihidratado se caracteriza por ser no higroscópico y estable en su contenido acuoso. El compuesto no absorbe o pierde agua cuando se expone a una humedad relativa (HR) de entre 10% y 95%; esto es demostrado en los ejemplos 1.2 y 2.2 de la presente solicitud.

El Ejemplo 1.2 demuestra las propiedades de clorhidrato de Nalmefeno dihidratado por experimentos DVS, mostrando que el dihidrato es retenido a una humedad relativa de 10-95% y adsorción a la superficie a una humedad relativa alta es menos de 0.2%. El Ejemplo 2.2 demuestra las propiedades de clorhidrato de Nalmefeno monohidratado conocidas del arte previo, en donde los experimentos de DVS muestran que el contenido de agua del monohidrato cambian con respecto a la humedad relativa. Estas propiedades mejoradas del de dihidratado comparadas con el clorhidrato de Nalmefeno monohidratado conocido eran imprevisibles a la fecha de la solicitud de esta invención. Por ende la presente solicitud si tiene demuestra en la presente solicitud las ventajas y el efecto asociado al clorhidrato de Nalmefeno dihidratado sobre un clorhidrato de nalmefeno como el que se divulga en el documento D3.

Adicionalmente, el Examinador establece que la persona versada en la materia encontraría sugerencias y motivaciones para aplicar los métodos y los conocimientos de los polimorfos que se divulga en el documento D4 al clorhidrato de Nalmefeno divulgado en el documento D3. Respetuosamente estamos en desacuerdo con este argumento ya que no era predecible a la fecha de presentación de la solicitud y por ende era inesperado que clorhidrato de nalmefeno existiera en una forma de dihidrato. No existe ninguna expectativa razonable a la fecha de prioridad de que una forma de clorhidrato de Nalmefeno dihidratado se pudiera obtener.

Con respecto a la objeción de falta de nivel inventivo de las reivindicaciones de método originales 7-14, 15-25 y 26 a 31, se desea establecer que también tienen nivel inventivo ya que se divulga los procesos por el cual se obtiene el compuesto de clorhidrato de Nalmefeno dihidratado, el cual no era esperado. Específicamente en estas tres reivindicaciones independientes y en sus dependientes se están divulgando unas etapas y condiciones específicas que seleccionaron cuidadosamente y específicamente para poder obtener el clorhidrato de Nalmefeno dihidratado y que no se deben considerar como obvias ya que su resultado fue inesperado y con una ventaja mejorada, como se

demostró anteriormente. Al respecto el "INSTRUCTIVO EXAMEN DE SOLICITUDES DE PATENTES DE INVENCIÓN Y MODELO DE UTILIDAD" de su Despacho, establece que una selección no es obvia y por tanto inventiva cuando "La invención involucra una selección especial en un proceso de condiciones operativas particulares (por ejemplo temperatura y presión) dentro de un rango conocido, tal selección produce efectos inesperados en el funcionamiento del proceso o en las propiedades del producto resultante.". De esta manera es claro y se ha comprobado que la presente solicitud tanto el compuesto como los métodos y la composición farmacéutica son novedoso e inventivas con respecto al estado técnico citado.

Adicionalmente, a continuación presentamos argumentos adicionales, los cuales demuestran y soportan el nivel inventivo de la presente invención. Veamos:

El Examinador impugna el efecto técnico superior del nalmefeno dihidrato HCl. Sin embargo, como se demuestra en la solicitud de patente mediante los Ejemplos 1.2, el nalmefeno dihidrato HCl no absorbe ni pierde agua cuando se expone a una humedad relativa (HR) de entre 10% y 95%, es decir, el nalmefeno dihidrato HCl no es higroscópico y estable en su contenido de agua. En contraste con lo anterior, para el nalmefeno dihidrato HCl los cambios en el contenido de agua con la humedad relativa como se demuestra en el Ejemplo 2.2. En la página 6 líneas 6-19 de la presente solicitud de patente se enumeran una serie de ventajas que tienen una forma no higroscópica de un compuesto farmacéutico. En general, por tener una forma no higroscópica las propiedades físicas se pueden controlar más fácilmente, lo cual es de gran importancia en la preparación de formas de dosificación sólidas, tales como formas administrables por vía oral. Si una forma higroscópica se utiliza en un proceso farmacéutico, esto implicaría el uso de cámaras de humedad controladas tanto para el almacenamiento, así como para el propio proceso. Por otra parte, los productos higroscópicos terminados deberán empacarse en blisters sellados con el fin de evitar problemas de estabilidad debido a la humedad. Estas desventajas se evitan mediante el uso de nalmefeno HCl en forma de dihidrato no higroscópico.

Adicionalmente, el señor Examinador presenta que para cualquier persona del oficio normalmente versada en la materia una manera de obtener polimorfos consiste en el empleo de técnicas que no impliquen nivel inventivo, pero son muy comunes en el campo de la química farmacéutica. Con respecto a esto se debe decir que, incluso si esto es cierto y fuera considerado un asunto de rutina para la detección de polimorfos e hidratos etc., la persona versada en la materia no sería capaz de predecir que pudiera

existir una cierta forma polimorfa o hidrato. En particular, para el nalmefeno HCl, el estado de la técnica enseña que la recristalización del nalmefeno HCl a partir de agua, inevitablemente, da nalmefeno monohidrato HCl que ha sido descrito como forma no higroscópica. Con este conocimiento, la persona versada en la materia estaría muy vacilante al buscar una nueva forma de hidrato de nalmefeno HCl y ciertamente no esperaría encontrar que el monohidrato de hecho es higroscópico y que una forma no higroscópica más estable, es decir, el dihidrato podría ser recristalizado a partir de agua. En consecuencia, esto fue altamente impredecible y no es un resultado que se derive a partir de las enseñanzas del estado de la técnica y que se pueda predecir sin experimentación alguna.

Considerando los nuevos descubrimientos sorprendentes en el que el monohidrato es higroscópico y que una nueva forma de dihidrato no higroscópico puede ser aislada, y combinando estos hechos con los efectos técnicos obtenidos por el uso del dihidrato en vez del monohidrato, atentamente afirmamos que la invención posee nivel inventivo.

Por lo tanto, un técnico con conocimientos medios en la materia no estaba en condiciones de plantearse el problema, tampoco de resolverlo en la forma en que se reivindica y tampoco de prever el resultado, por lo que la presente solicitud posee la altura inventiva para que se le conceda el privilegio solicitado.

En consecuencia de lo anterior, la invención de la presente invención tiene nivel inventivo en vista de los documentos D3 y D4 del estado de la técnica citados por el Examinador.

Conclusión

El documento D3, el documento D4, o su combinación no resulta anterioridad válida capaz de afectar el nivel inventivo de la invención de la presente solicitud.

En consecuencia, el mérito investigativo de la presente invención ha sido reconocido por otras oficinas de patentes del mundo, las cuales han otorgado patentes para invenciones equivalentes. Tal es el caso de Europa, Eurasia, Canadá, Israel, México, Malasia, Nueva Zelanda, Singapur, Ucrania, Estados Unidos de América y Sudáfrica.

Si bien es cierto que cada país es autónomo en conceder o negar el privilegio de patente para una solicitud, también es cierto que los requisitos de concesión de dichos privilegios son universales, esto es, novedad, nivel inventivo y aplicación industrial, como también la forma de evaluarlos. Así las cosas, el hecho de que la misma solicitud cumpla con los mencionados requisitos en diferentes países, como se mencionó anteriormente, es un claro indicio del merecimiento de la patente en Colombia.

Por todo lo anterior, consideramos que la presente solicitud cumple a cabalidad con los requerimientos de patentabilidad exigidos por la legislación actual, por lo que atentamente solicitamos en consideración lo siguiente:

VI. PETICIÓN

Por todo lo anterior, solicito a ese Despacho lo siguiente:

6.1 Que al considerar las razones precedentes se revoque la decisión contenida en la Resolución No. **60094** del 17 de Octubre de 2013, en cuanto resuelve negar el privilegio de patente de invención.

6.2. Que se otorgue el privilegio de patente de invención para **"CLORHIDRATO DE NALMEFENO DIHIDRATO"** a favor de **H. LUNDBECK A/S y BIOTIE THERAPIES CORP.**

VII. NOMBRE Y DIRECCIÓN

El nombre y la dirección del solicitante recurrente son los siguientes:

H. LUNDBECK A/S
Ottiliavej 9,
DK-2500 Valby,
Dinamarca

y

14

BIOTIE THERAPIES CORP.
Tykistökatu 6,
FI-20520 Turku,
Finlandia

IX. ANEXOS

- Copia de la patente concedida en Estados Unidos de América
- Copia de la patente concedida en Europa

X. NOTIFICACIONES

Atentamente manifiesto a usted que recibiré notificaciones en la Secretaria de su Despacho o en mi oficina de abogada situada en la Carrera 4ª. No. 72-35, piso 4°, de esta ciudad de Bogotá, D.C.

Señor Superintendente,

LUZ CLEMENCIA DE PÁEZ
C.C. 35.456.344 de Usaquén
T.P.A. No. 23.555

COLO-18424-0841-001-3
SGD\SGD\ID-255646\WPC18424
No. M-2013-255646\SGD

The United States of America

The Director of the United States Patent and Trademark Office

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person(s) having title to this patent the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States of America or importing the invention into the United States of America, and if the invention is a process, of the right to exclude others from using, offering for sale or selling throughout the United States of America, or importing into the United States of America, products made by that process, for the term set forth in 35 U.S.C. 154(a)(2) or (c)(1), subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b). See the Maintenance Fee Notice on the inside of the cover.

Teresa Stanek Rea

Acting Director of the United States Patent and Trademark Office

US008530495B2

(12) **United States Patent**
Lopez de Diego et al.

(10) **Patent No.: US 8,530,495 B2**
(45) **Date of Patent: Sep. 10, 2013**

(54) **NALMEFENE HYDROCHLORIDE DIHYDRATE**

(75) Inventors: **Heidi Lopez de Diego**, Naerum (DK); **Carla de Faveri**, Farra di Soligo (IT); **Florian Anton Martin Huber**, Bolzano Vicentino (IT)

(73) Assignees: **H. Lundbeck A/S**, Valby (DK); **Bioei Therapies Corp**, Turku (FI)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 247 days.

(21) Appl. No.: **13/132,494**

(22) PCT Filed: **Dec. 4, 2009**

(86) PCT No.: **PCT/DK2009/050320**

§ 371 (c)(1),
(2), (4) Date: **Jun. 22, 2011**

(87) PCT Pub. No.: **WO2010/063292**

PCT Pub. Date: **Jun. 10, 2010**

(65) **Prior Publication Data**

US 2011/0251228 A1 Oct. 13, 2011

Related U.S. Application Data

(60) Provisional application No. 61/120,132, filed on Dec. 5, 2008.

(30) **Foreign Application Priority Data**

Dec. 5, 2008 (DK) 2008 01729

(51) **Int. Cl.**
A61K 31/485 (2006.01)
C07D 489/08 (2006.01)

(52) **U.S. Cl.**
USPC **514/282**; 546/44

(58) **Field of Classification Search**
USPC 514/282; 546/44
See application file for complete search history.

(56) **References Cited**

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Primary Examiner — Charanjit Aulakh
(74) *Attorney, Agent, or Firm* — Mary Catherine Di Nunzio; Vineet Kohli

(57) **ABSTRACT**

The present invention relates to the Nalmefene hydrochloride dihydrate, methods of manufacturing Nalmefene hydrochloride dihydrate, a pharmaceutical composition comprising Nalmefene hydrochloride dihydrate and a method of treatment comprising administering Nalmefene hydrochloride dihydrate.

15 Claims, 6 Drawing Sheets

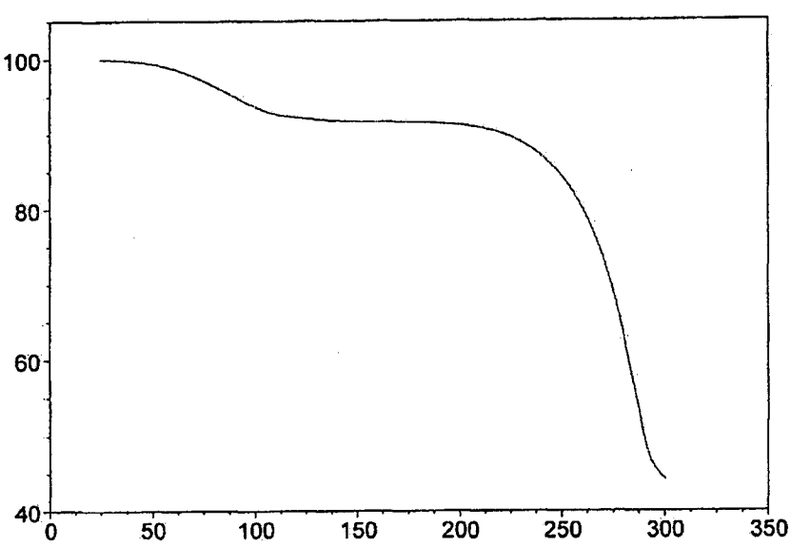

Figure 1

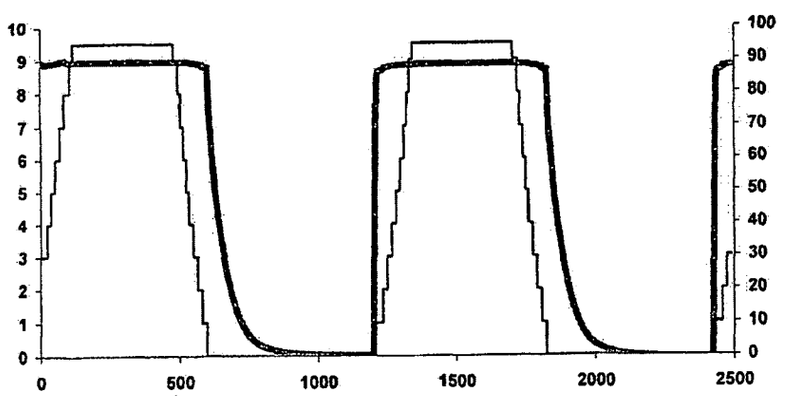
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Figure 2

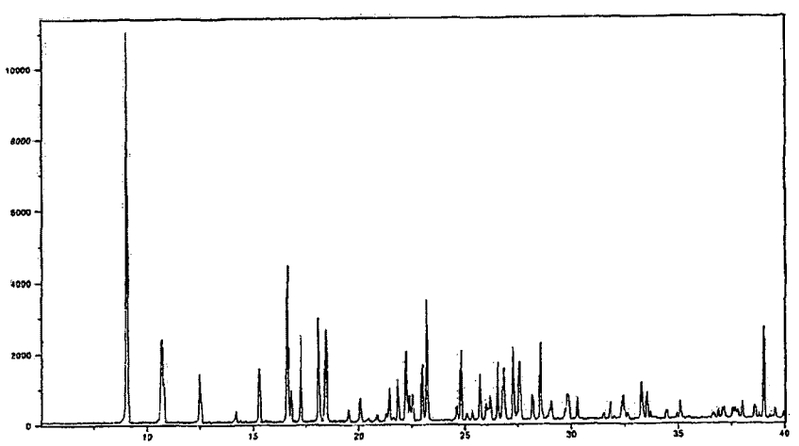

Figure 3

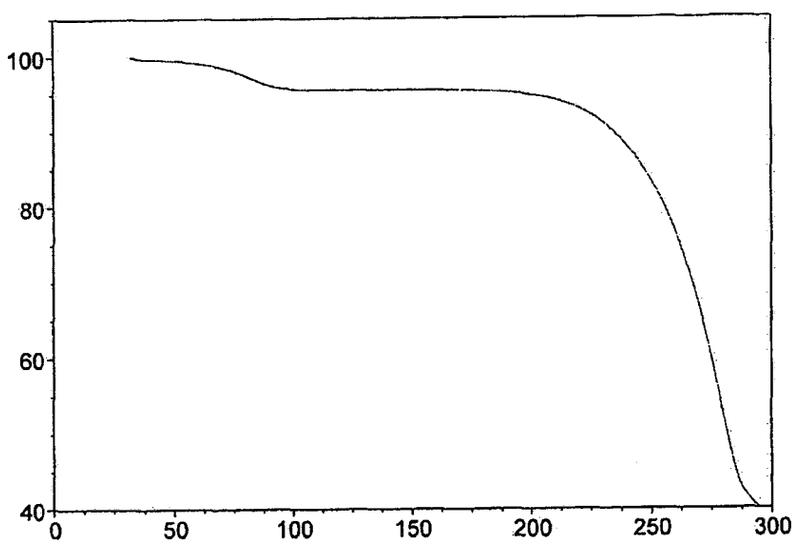

Figure 4

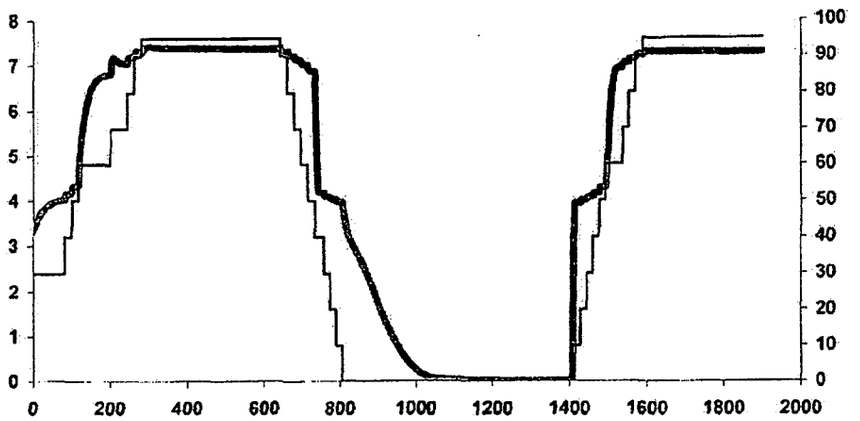
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Figure 5

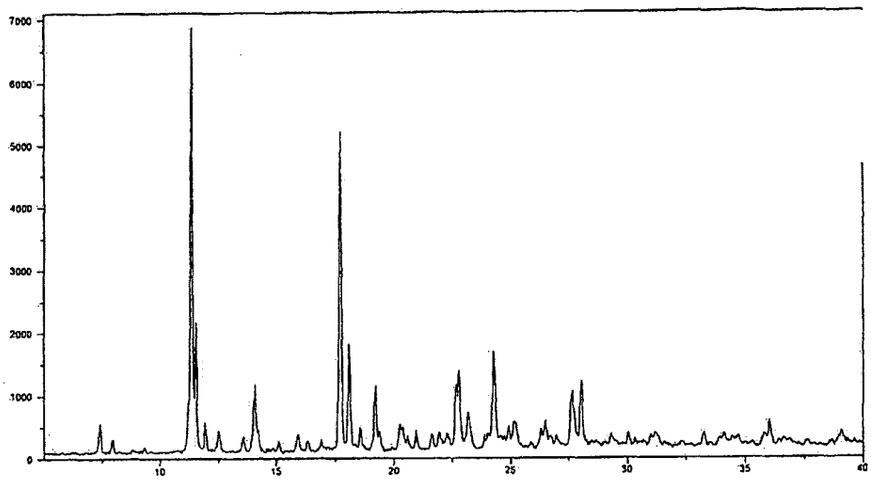


Figure 6

NALMEFENE HYDROCHLORIDE DIHYDRATE

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a §371 U.S. National Stage Application of International Application No. PCT/DK2009/050320, filed Dec. 4, 2009, which claims priority of U.S. Provisional Application No. 61/120,132, filed Dec. 5, 2008 and Danish Application No. PA. 200801729 filed Dec. 5, 2008. Each of these applications is hereby incorporated by reference in its entirety.

The present invention relates to a novel non-hygroscopic form of Nalmefene Hydrochloride, namely Nalmefene hydrochloride dihydrate, in particular for oral dosage forms, and methods for its production.

BACKGROUND

Nalmefene is a known opioid receptor antagonist which can inhibit pharmacological effects of both administered opioid agonists and endogenous produced agonists from the opioid system. The clinical usefulness of Nalmefene as an antagonist comes from its ability to promptly (and selectively) reverse the effects of these opioid agonists, including the often observed depressions in the central nervous system and the respiratory system.

Nalmefene has primarily been developed for use in the management of alcohol dependence, where it has shown good effect in doses of 10 to 40 mg taken when the patient believed drinking to be imminent (about 1-2 hours before drinking) (Karhuvaara et al., *Alcohol. Clin. Exp. Res.*, (2007), Vol. 31 No. 7. pp 1179-1187). Additionally, Nalmefene has also been investigated for the treatment of other addictions such as pathological gambling and addiction to shopping. In these developmental programs and testing, Nalmefene has been used, for example as a parental solution (Revex™).

Nalmefene is an opiate derivative similar in structure to the opiate antagonist Naltrexone. Advantages of Nalmefene relative to Naltrexone include longer half-life, greater oral bio availability and no observed dose-dependent liver toxicity.

Nalmefene differs from Naltrexone by substitution of the ketone group at the 6-position of Naltrexone with a methylene (CH_2) group, which considerably increases binding affinity to the μ-opioid receptor. Nalmefene also has high affinity for the other opioid receptors (κ and δ receptors), and is known as a "universal antagonist" for its ability to block all three.

Nalmefene can be produced according to the method described by Hanh et al., (*J. Med. Chem.*, 18, 259-262 (1975), Mallinckrodt (U.S. Pat. No. 4,751,307), and Meltzner et al., (U.S. Pat. No. 4,535,157).

By using the above-mentioned methods, the free base of Nalmefene is obtained, which subsequently can be converted into the hydrochloride salt, by use of conventional methods.

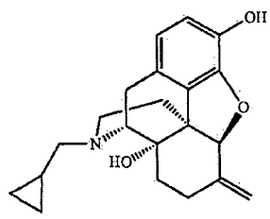
According to Brittain, (*Analytical Profiles of Drug Substances and Excipients* (1996), Vol 24, pp. 351-395) Nalmefene hydrochloride can be recrystallized from water, giving a pure drug substance, which inevitably consists of a monohydrate crystal phase. In the same review the monohydrate phase of Nalmefene hydrochloride is described as essentially non-hygroscopic since it can only sorb up to 1% of adventitious moisture.

The inventors of the present invention have found that, contrary to the literature, Nalmefene hydrochloride as a monohydrate is hygroscopic.

There is therefore a need for providing a novel, stable and non-hygroscopic hydrate form of Nalamefene and methods for its manufacturing.

SUMMARY OF THE INVENTION

The present invention relates to Nalmefene hydrochloride dihydrate represented by the formula



$\cdot HCl \cdot 2H_2O$

preferably in a crystalline form. Said Nalmefene hydrochloride dihydrate is non-hygroscopic

The invention further relates to two methods of producing Nalmefene hydrochloride dihydrate:

Method (I): transformation of Nalmefene hydrochloride into Nalmefene hydrochloride dihydrate by re-slurry in aqueous solution, exemplified by water, such as pure water, and

Method (II): recrystallisation of Nalmefene hydrochloride in aqueous solution, exemplified by water, such as pure water.

The re-slurry method (Method I) comprises the steps of:

(1) mixing Nalmefene Hydrochloride (17-(cyclopropylmethyl)-4,5-α-epoxy-6-methylenemorphinan-3,14-diol hydrochloride) and aqueous solution, exemplified by water, such as pure water,

(2) optionally, heating the mixture,

(3) optionally, distilling the mixture,

(4) stirring the mixture until transformation is complete, such as less than 1 hour, such as about 1 hour, such as for at least 1 hour, and

(5) isolating the formed solid.

The re-crystallisation method (Method II) comprises the steps of:

(a) mixing Nalmefene hydrochloride (17-(cyclopropylmethyl)-4,5-α-epoxy-6-methylenemorphinan-3,14-diol hydrochloride) and aqueous solution, exemplified by water, such as pure water,

(b) heating of the mixture to obtain a substantially homogenous solution,

(c) optionally, distillation of the mixture obtained in (b),

(d) cooling of the solution obtained in step (b) or (c), subsequently seeding with Nalmefene hydrochloride, and

(e) isolation of the formed solid.

A further aspect of the present invention (Method III) is a method to recover any unused Nalmefene from the methods I and II, comprising the steps of:

(i) optionally, distillation of mother liquors obtained from method (I) or (II)

(ii) basification of the mother liquors obtained in step (i), or from the methods (I) or (II),

(iii) extracting the mixture with a suitable organic solvent,

(iv) adding hydrogen chloride, and

(v) isolating the formed solid

The invention further relates to pharmaceutical compositions comprising Nalmefene hydrochloride dihydrate, the use of Nalmefene hydrochloride dihydrate in medicine, and in particular the use of Nalmefene hydrochloride dihydrate for the treatment of alcohol dependency.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** Shows TGA thermogram of the Nalmefene hydrochloride dihydrate. The y-axis shows the percentage in mass, and the X-axis shows temperatures (° C.).

FIG. **2** Shows DVS experiments performed at 40° C. of Nalmefene hydrochloride dihydrate (dry plot). The first y-axis (left) show the change in mass relative to anhydrous (%), and the other y-axis (right) displays the targeted relative humidity (RH)(%), while the x-axis show the time in minutes. The thin line shows the changes in target RH, and the bold line the changes in relation to mass.

FIG. **3** Shows X-ray powder diffractogram of the Nalmefene hydrochloride dihydrate. The y-axis shows the intensity (counts), and the x-axis shows the 2Theta angle (°).

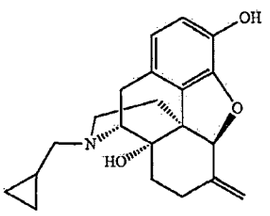
FIG. **4** Shows TGA thermogram of the Nalmefene hydrochloride monohydrate. The y-axis shows the percentage in mass, and the x-axis shows temperatures (° C.).

FIG. **5** Shows DVS experiments performed at 40° C. of Nalmefene hydrochloride monohydrate (dry plot). The first y-axis (left) show the change in mass relative to anhydrous (%), and the other y-axis (right) displays the targeted relative humidity (RH)(%), while the x-axis show the time in minutes. The thin line shows the changes in target RH, and the bold line the changes in relation to mass.

FIG. **6** Shows X-ray powder diffractogram of the Nalmefene hydrochloride monohydrate. The y-axis shows the intensity (counts), and the x-axis shows the 2Theta angle (°).

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to Nalmefene hydrochloride dihydrate represented by the below formula



$\cdot HCl \cdot 2H_2O$

The dihydrate form of Nalmefene hydrochloride is particular advantageous in that it is non-hygroscopic. As a result of this non-hygroscopic feature, the physical properties can more easily be controlled. This is of great importance when preparing solid dosage forms such as orally administrable forms, including solid unit dosage forms e.g. tablets or chewable tablet and capsules.

As is well known within the pharmaceutical industry, processing of hygroscopic products entails the use of controlled humidity chambers both for storage and for the processing itself. Moreover, the finished hygroscopic products must be packed in sealed blisters in order to avoid stability problems due to humidity. These disadvantages are avoided by using Nalmefene hydrochloride as the non-hygroscopic dihydrate.

Nalmefene hydrochloride dihydrate is characterized by being non-hygroscopic and stable in its water content. The compound does not absorb or lose water when exposed to a relative humidity (RH) of between 10% and 95%.

As shown in Example 1 of the present invention, DVS (Dynamic Vapour Sorption) experiments were performed at 25° C. and at 40° C. The results showed that no water was absorbed by Nalmefene hydrochloride dihydrate even at 95% RH. In contrast hereto, as shown in Example 2, Nalmefene hydrochloride as monohydrate absorbed about 2.5% water when exposed to 95% RH and 40° C.

Furthermore, the result in Example 2 showed that in contrast to the dihydrate, the monohydrate form changes in the water content with the surrounding humidity, and at RH above 50% the monohydrate form changed into a new structure with higher water content.

It is therefore an important characteristic of Nalmefene hydrochloride dihydrate that it is non-hygroscopic, as defined above. Thus the present invention relates to Nalmefene hydrochloride dihydrate which is non-hygroscopic, meaning that less than 1%, such as less than 0.5%, such as less than 0.3% moisture is absorbed when exposed to 95% RH at 25° C.

Nalmefene hydrochloride dihydrate is a crystalline solid characterized by X-ray reflections at angles 8.99, 10.63, 15.24, 16.55 and 17.20° 2θ (±0.1° 2θ) as measured using $CuK_{\alpha 1}$ radiation, and having water content of about 8 to about 9%, such as about 8.7%, while the monohydrate of Nalmefene hydrochloride is a crystalline solid characterized by X-ray reflections at angles 7.39, 11.33, 11.52, 17.70 and 24.27° 2θ (±0.1° 2θ) and water content of 4-7% depending on the relative humidity of the surroundings.

The present invention also relates to the use of Nalmefene hydrochloride dihydrate in the manufacturing of a medicament.

In particular, the invention is related to the use of Nalmefene hydrochloride dihydrate in the manufacturing of a medicament, wherein Nalmefene hydrochloride dihydrate comprises at least 5% (w/w), such as at least 10% (w/w), at least 30%, at least 50% (w/w), such as at least 70% (w/w), at least 90% (w/w), at least 95% (w/w), at least 99% (w/w), or 100% of the pharmaceutical dosage form, particularly a oral dosage form, e.g. a single unit solid dosage form such as a tablet. Nalmefene hydrochloride dihydrate is in particular related to the use in the manufacturing of a medicament for the treatment alcohol dependency.

In a further embodiment, the present invention relates to a method for treating alcohol dependency comprising administering a therapeutically effective amount of Nalmefene hydrochloride dihydrate, e.g. in a pharmaceutical composition (such as a solid dosage form, e.g. tablet for oral administration) to a patient in the need thereof.

By the term "therapeutically effective amount" is referred to the amount/dose of a compound or pharmaceutical composition that is sufficient to produce an effective response (i.e., a biological or medical response of a tissue, system, animal or human sought by a researcher, veterinarian, medical doctor or other clinician) upon administration to a patient. The "therapeutically effective amount" will vary depending on inter alia the disease and its severity, and the age, weight, physical condition and responsiveness of the patient to be treated. Furthermore the "therapeutically effective amount" may vary if the compound of the invention is combined with one or more compounds, in such a case the amount of a given compound might be lower, such as a sub-effective amount.

The term 'distil' refers to a method of separating mixtures based on differences in their volatilities in a boiling liquid mixture. Application of vacuum such as partial vacuum is an example of such separation method.

The term 'chemical purity' is given its normal meaning within the art and thus refers to the degree to which an obtained compound is contaminated with impurities. Accordingly, an obtained compound which is at least 98% chemically pure comprises at most 2% of impurities. The chemical purity may be measured by e.g. HPLC.

The term 'assay' refers to the effective content of the desired substance expressed as a weight by weight percentage (w/w %).

The term 'extraction' refers to a liquid-liquid extraction in which the free Nalmefene base is transferred from an aqueous phase to an organic phase.

The term 're-slurry' refers to a process wherein the crystalline material is suspended in a solvent or a solvent mixture at an appropriate temperature whereby the crystalline material partially dissolves and partially crystallises again thus permitting its transformation into the desired form and/or its purification.

KF refers to 'Karl Fisher titration'.

TGA refers to 'Thermo-Gravimetric Analysis'.

DVS refers to 'Dynamic Vapour Sorption'

In the present invention, the term "substantially homogenous solution" is intended to mean a liquid mixture free of visible undissolved material.

In the present invention, the term "seeding" is intended to mean the addition of a small amount of crystals to initiate the precipitation of the product.

In the present context the term "non-hygroscopic" is intended to mean that less than 1%, such as less than 0.5%, such as less than 0.3% w/w of moisture is absorbed when exposed to 95% RH at 25° C.

In the present context, particle sizes are determined by Laser Diffraction using a Malvern Mastersizer S instrument as disclosed in details in the introductory part of the experimental section.

Preferably the amount of Nalmefene hydrochloride dihydrate in a pharmaceutical composition is in an amount from about 10 mg to about 100 mg, such as about 10 mg to about 60 mg, about 10 mg to about 40 mg, or about 20 mg.

The term "alcohol dependency" is a commonly known term for a skilled person which, in the revised 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IVTR) (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition text revision, American Psychiatric Publishing, 2000), is defined as the presence of three or more of the seven areas of life impairment related to alcohol in the same 12-month period. These impairments include tolerance, evidence of a withdrawal syndrome when alcohol is discontinued or intake is decreased, potential interference with life functioning associated with spending a great deal of time using alcohol and returning to use despite evidence of physical or psychological problems.

The pharmaceutical composition comprising Nalmefene hydrochloride dihydrate may further comprise one or more pharmaceutically acceptable carriers.

Methods for the preparation of solid pharmaceutical preparations are well known in the art. See, e.g., Remington: The Science and Practice of Pharmacy, 21st ed., Lippincott Williams & Wilkins (2005). Solid preparations, such as tablets, may be prepared by mixing the active ingredients with an ordinary carrier, such as an adjuvant and/or diluent, and subsequently compressing the mixture in a tabletting machine. Non-limiting examples of adjuvants and/or diluents include: corn starch, lactose, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive such as colourings, aroma, and preservatives may also be used provided that they are compatible with the active ingredients. The pharmaceutical compositions of the invention thus typically comprise an effective amount of Nalmefene hydrochloride dihydrate and one or more pharmaceutically acceptable carriers.

According to the present invention, it is envisaged that Nalmefene hydrochloride dihydrate may be administered in any suitable way, e.g., orally or parenterally, and it may be presented in any suitable form for such administration, e.g., in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. In an embodiment, Nalmefene hydrochloride dihydrate is preferably administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule.

A further aspect of the present invention relates to methods for obtaining Nalmefene hydrochloride dihydrate. Nalmefene hydrochloride dihydrate may be obtained by any of the methods (I) and (II), as will be outlined below.

Method (I) transformation of Nalmefene hydrochloride into Nalmefene hydrochloride dihydrate by re-slurry in aqueous solution, such as water, such as pure water and

Method (II) re-crystallization of Nalmefene hydrochloride in aqueous solution, such as water, such as pure water

According to one aspect of the invention, the re-slurry method (Method (I)) comprises the steps of:

(1) mixing Nalmefene Hydrochloride (17-(cyclopropylmethyl)-4,5-α-epoxy-6-methylenemorphinan-3,14-diol hydrochloride) and aquous solution, such as water, such as pure water

(2) optionally, heating the mixture,

(3) optionally, distilling the mixture

(4) stirring the mixture, and

(5) isolating the formed solid.

In one embodiment of Method (I), Nalmefene hydrochloride is transformed into Nalmefene hydrochloride dihydrate by re-slurry in aqueous solution. In another embodiment Nalmefene hydrochloride is transformed into Nalmefene hydrochloride dihydrate by re-slurry in water. In yet another embodiment Nalmefene hydrochloride is transformed into Nalmefene hydrochloride dihydrate by re-slurry in pure water.

The ratio of aqueous solution such as water, such as pure water, used in step (1) may range from about 0.5 ml to about 4 ml aqueous solution/nalmefene hydrochloride (g), such as from about 1 ml to about 2 ml aqueous solution/nalmefene hydrochloride (g), more preferably about 1.5 ml aqueous solution/nalmefene hydrochloride (g). The Nalmefene hydrochloride used can be selected from any hydrated or solvated form of Nalmefene or mixtures of hydrated and/or solvated forms with or without solvents. In one embodiment Nalmefene hydrochloride as monohydrate is used. In another embodiment of Method (I), Nalmefene hydrochloride is used in hydrated form. In another embodiment, Nalmefene hydrochloride is used in solvated form. In yet another embodiment, Nalmefene hydrochloride is used in a mixture of hydrated solvated form.

In an embodiment of Method (I), solvents comprised in said hydrated and/or solvated forms are selected from the group consisting of acetone, n-propanol, isopropanol, dichloromethane and water. In one embodiment said solvent is acetone. In another embodiment said solvent is n-propanol. In yet another embodiment said solvent is isopropanol. In yet another embodiment said solvent is dichloromethane. In yet another embodiment said solvent is water.

Heating in step (2) is an optional step, which may under some conditions be beneficial in order to increase the dissolution rate of the mixture obtained in step (b). The heating temperature may depend on the circumstances. Under some circumstances the mixing will be efficiently performed at room temperature (20-25° C.). It is envisaged that in one embodiment heating in step (2) is to about 50° C. In another embodiment, heating in step (2) is to 50° C. or less. In another embodiment heating to in step (2) is to about 20° C. to about 40° C. In yet another embodiment heating in step (2) is to about 30° C.

Step (2) and step (3) may be performed with or without stirring.

The distillation in step (3) may be performed to remove organic solvents if present in the mixture. The distillation may be performed by applying Vacuum.

The stirring in step (4) may be performed at a temperature of about 0° C. to about 50° C., such as 45° C., such as from 20° C. to about 40° C. In one embodiment, the mixture is stirred for less than one hour. In another embodiment the mixture is stirred for about one hour. In yet another embodiment the mixture is stirred for at least one hour.

The solid can be isolated at a temperature within the range of about 0-25° C. such as 0-20° C. and more preferably in the range of 0-5° C. in order to lower the solubility of the product, such as in water, and to increase the yield. The solid may be isolated by filtration and washed with a suitable solvent. Solvents for washings include water and mixtures of water/organic solvents or pure organic solvents. Preferably water is used and in a further embodiment pre-cooled water is preferred. When organic solvents are used, Class 2 or 3 solvents (ICH Q3C(R4) guidelines) are preferred. In one embodiment, class 3 solvents such as acetone and ethyl acetate are used. In one embodiment acetone is used. In another embodiment ethyl acetate is used.

The product can be dried under vacuum below 40° C. and more preferably at a temperature in the range 25-35° C.

It is envisaged that the obtained compound is at least 98% chemically pure, such as at least 99% chemically pure, or at least 99.5% chemically pure.

According to one aspect of the invention, the re-crystallization method (Method (II)) comprises the steps of:

(a) mixing Nalmefene hydrochloride (17-(cyclopropylmethyl)-4,5-α-epoxy-6-methylenemorphinan-3,14-diol hydrochloride) and aqueous solution, such as water, such as pure water,

(b) heating the mixture to obtain a substantially homogenous solution,

(c) optionally, distillation of mixture obtained in step (b),

(d) cooling of the solution obtained in step (b) or (c), subsequently seeding with Nalmefene hydrochloride, and

(e) isolation of the formed solid.

In one embodiment of Method (II), Nalmefene hydrochloride is transformed into Nalmefene hydrochloride dihydrate by re-crystallization in aqueous solution. In another embodiment Nalmefene hydrochloride is transformed into Nalmefene hydrochloride dihydrate by re-slurry in water. In yet another embodiment Nalmefene hydrochloride is transformed into Nalmefene hydrochloride dihydrate by re-slurry in pure water.

The amount of aqueous solution, such as water, such as pure water, which is used in step (a) may range from about 0.9 ml to about 4 ml aqueous solution/Nalmefene hydrochloride (g), such as from about 1 ml to about 2 ml aqueous solution/Nalmefene hydrochloride (g), or about 1.5 ml aqueous solution/Nalmefene hydrochloride (g). The Nalmefene hydrochloride used can be selected from any hydrated or solvated form of Nalmefene or mixtures of hydrated and/or solvated forms with or without solvents.

In one embodiment of Method (II), Nalmefene hydrochloride is used in hydrated form. In another embodiment, Nalmefene hydrochloride is used in solvated form. In yet another embodiment, Nalmefene hydrochloride is used in a mixture of hydrated solvated form.

In an embodiment of Method (II), solvents comprised in said hydrated and/or solvated forms are selected from the group consisting of acetone, n-propanol, isopropanol, dichloromethane and water. In one embodiment said solvent is acetone. In another embodiment said solvent is n-propanol. In yet another embodiment said solvent is isopropanol. In yet another embodiment said solvent is dichloromethane. In yet another embodiment said solvent is water.

The suspension may be heated until a substantially homogenous solution is obtained, i.e. a solution. The heating in step (b) may be performed to reach a temperature of about 50° C. to about 100° C., such as about 50° C. to about 90° C., or about 70° C. to about 85° C.

Partial vacuum may then applied to remove traces of organic volatiles, if present, in step (c).

The solution obtained either from step (b) or step (c) may optionally be filtered (e.g. through a 0.65 μm cartridge) to remove foreign matters before proceeding to step (d).

In step (d) the solution may be cooled to a temperature between 40° C. to about 50° C. and seeded. In one embodiment of the invention, the seeding is performed at a temperature between 40° C. and 50° C. The seeding is performed with Nalmefene hydrochloride dihydrate crystals. The Nalmefene seeding material may, in one embodiment of the invention, be obtained by the re-slurry method (I) described above.

The amount of seed crystal added in step (d) may be from about 1/2000 (w/w) of seed crystal of Nalmefene hydrochloride/Nalmefene hydrochloride added in step (a), such as from about 1/1000 (w/w) of seed crystal or 1/200 of seed crystal of Nalmefene hydrochloride/Nalmefene hydrochloride added in step (a).

An appropriate cooling ramp, such as a fast cooling ramp, and an appropriate stirring, such as a vigorous stirring, impede the crystals already formed to grow further and help to provide a product with a well defined, narrow and relatively small particle size. The cooling from seeding temperature to isolation temperature may be accomplished within a few hours and more preferably within 1 hour. The seeded mixture obtained in step (d) may therefore further be subjected to a cooling, such as a fast cooling, which comprises the steps of:

(d') a further cooling of the mixture to a temperature of about 0-5° C. such as over a time period of about 45 minutes or more, and

(d") thereafter the mixture may be maintained at a temperature of about 0-5° C. for e.g. about 45 minutes or more before isolating the formed solid according to step (e).

The solid formed in step (e) may be isolated. The solid can be isolated at a temperature within the range of about 0-20° C. and more preferably in the range of 0-5° C. in order to lower the solubility of the product in water and thereby increase the yield. The solid may be isolated by filtration and washed with a suitable solvent. Solvents for washings include water and mixtures of water/organic solvents or pure organic solvents. In one embodiment solvents for washing are selected from the group consisting of acetone and water. In one embodiment acetone is used. In another embodiment a mixture of acetone and water. In yet another embodiment water is used. In a further embodiment the water used is pre-cooled water. When organic solvents are used for washing, Class 2 or 3 solvents

(ICH Q3C(R4) guidelines) are preferred, more preferably class 3 solvents such as acetone and ethyl acetate. In one embodiment ethyl acetate is used.

The product can be dried under vacuum below 40° C. and more preferably at a temperature in the range 25-35° C.

It is envisaged that the obtained compound is at least 98% chemically pure, such as at least 99% chemically pure, or at least 99.5% chemically pure.

It is further envisaged that the Nalmefene hydrochloride dihydrate obtained by the above method (II) has the following particle size distribution: D90 equal to or below 400 μm and D50 equal to or below 200 μm, and D10 equal to or below 50 μm, and with ratio D90/D50 equal to or below 2.5, wherein D"XX" (XX is given as 10, 50 or 90) is defined as the value for which an "XX percentage" (given in volumes) of the particles have a diameter under the indicated value. Thus for D10, 10 percentage of the particle size (in volume) has a diameter equal to or below 50 μm.

Recovery of Nalmefene hydrochloride from mother liquors (Method III):

Nalmefene hydrochloride is highly soluble in aqueous solutions such as water, such as pure water, and therefore a part of this material is lost in the mother liquors. To recover any unused Nalmefene hydrochloride from the methods I or II, outlined above, a method for the recovery has been developed that comprises

(i) optionally, distillation of mother liquors obtained from method (I) or (II)

(ii) basification of the mother liquors obtained in step (i), or from the methods (I) or (II),

(iii) extracting the mixture with a suitable organic solvent,

(iv) adding hydrogen chloride, and

(v) isolating the formed solid

The basification in step (ii) is performed to bring the pH in the range of 8-10, such as 8-9 using an organic or inorganic base. In an embodiment of method (III), the basification in step (ii) is performed with ammonium hydroxide.

In the extraction step (iii) the organic solvent may be selected from the group comprising halogenated hydrocarbons, ethers, esters, ketones, and preferably dichloromethane, 2-methyl-tetrahydrofurane, ethyl acetate, 2-butanone, even more preferably dichloromethane. In one embodiment the organic solvent is halogenated hydrocarbons. In another embodiment the organic solvent is ethers. In another embodiment the organic solvent is selected from the group of esters. In another embodiment the organic solvent is selected from the group of ketones. In another embodiment the organic solvent is dichloromethane. In another embodiment the organic solvent is 2-methyl-tetrahydrofurane. In another embodiment the organic solvent is ethyl acetate. In another embodiment the organic solvent is 2-butanone.

The solution of nalmefene base in an organic solvent obtained in step (iii) is treated with hydrogen chloride to precipitate nalmefene hydrochloride.

The amount of hydrogen chloride added in step (iv) depends on different factors such as the amount of nalmefene in mother liquors used, and will be apparent to a person skilled in the art. After hydrochloric acid is added to the mixture in step (iv) the product is allowed to precipitate.

The precipitated solid may be isolated as described for methods I and II.

It is envisaged that the obtained compound is at least 98% chemically pure, such as at least 99% chemically pure, or at least 99.5% chemically pure.

EXAMPLES

In the present contest, chemical purity is measured by HPLC using the below conditions:

Chromatographic Conditions:

Column:	YMC Basic B-03-5, 5 μm, 250 × 4.6 mm or equivalent
Mobile Phase A:	Buffer
Mobile Phase B:	Methanol
Buffer:	Dissolve 1.1 g of Sodium Octansulfonate (FW 216.28) in 1 L of water. Adjust the pH to 3.8 with diluted H_3PO_4.
Column Temperature:	35° C.
Detector:	UV at 230 nm
Flow:	1.5 ml/min
Injection volume:	20 μl
Time of Analysis:	50 minutes

Time (min)	Mobile Phase A	Mobile Phase B
0	90	10
10	70	30
25	50	50
40	20	80
50	20	80

In the present context, particle sizes are determined by Laser Diffraction using a Malvern Mastersizer S instrument made up of a laser transmitter (LASER HELIUM-NEON—wavelength 632 nm), an optical system (300 F lens, range 0.5-900 μm), a measurement cell for suspension (beam length 2.4 mm) and a photodiode detector. The sample is analysed using mineral oil (CAS 8042-47) as dispergent.

Example 1

1.1a Preparation of the Dihydrate

Dihydrate was prepared as follows:

20 g of crude Nalmefene Hydrochloride (chemical purity 99.26%, assay 92.9%) was suspended in 24 ml of water. The mixture was heated up and the solid dissolved completely at 60-65° C. The solution was heated up to 70° C. and maintained at that temperature for 15 minutes. The solution was cooled down from 70° C. to 20° C. in 3 hours using a linear ramp.

At 50° C., Nalmefene Hydrochloride was added as seeding. The seed did not dissolve and Nalmefene started to crystallize. When the cooling ramp was terminated the suspension was maintained under stirring at 20° C. for 2.5 days. The solid was filtered and washed with acetone (50 ml). The wet product was dried overnight under vacuum at 40° C. yielding 13.2 g of Nalmefene hydrochloride dihydrate (chemical purity 99.74%, water content 8.54% w/w as measured by Karl Fisher titration).

1.1b Preparation of the Dihydrate

20 g of crude Nalmefene Hydrochloride (chemical purity 97.2%, assay 82.6%) was suspended in 30 ml of water. The mixture was heated up and the solid dissolved completely at 80° C. Organic volatiles were removed by vacuum distillation. The solution was cooled down to 50° C.

At 50° C., Nalmefene Hydrochloride dihydrate was added as seeding. The mixture was maintained at 50° C. for 3 hours and then allowed to cool down to 20° C. The suspension was maintained under stirring at 20° C. for around 2.5 days. The solid was filtered and washed with acetone (20 ml). The wet product was dried overnight under vacuum at 30° C. yielding

11.5 g of Nalmefene hydrochloride dihydrate (chemical purity 99.78%, water content 8.78% w/w as measured by Karl Fisher titration).

1.2 Properties of the Dihydrate

In the TGA (FIG. 1) about 10 mg of sample was heated 10°/min in an open pan under nitrogen flow. The thermogram shows a weigh-loss of about 8.5% starting at 0, room temperature and ending at 125-150° C.

DVS experiments were performed at 25° C. and at 40° C. The shape of the curves were the same at the two temperatures; the curve at 40° C. is shown in FIG. 2. The dihydrate is retained at relative humidity of 10-95%. Adsorbtion to the surface at high relative humidity is less than 0.2%. Desorption of the crystal water occurs slowly under 10% RH. The DVS-curve however shows complete rehydration after drying at 0% RH, thus the crystal lattice is retained by this treatment.

X-ray powder diffractogram for Nalmefene hydrochloride.dihydrate as obtained using Cu $K_{\alpha 1}$ radiation is shown in FIG. 3. The diffractogram is measured in reflection mode in the range 5-40° 2θ. It is characterised by XRPD reflections at 8.99, 10.63, 15.24, 16.55 and 17.20° 2θ (±0.1° 2θ).

Example 2

2.1a Preparation of the Monohydrate

25 g of Nalmefene hydrochloride (chemical purity 99.24, assay 84.1) was suspended in 32 ml of water. The mixture was heated up to 80° C. Vacuum was applied to distill low boiling organic solvents. The solution was cooled down to 20° C. in one hour using a linear ramp. The suspension was maintained under stirring for two hours and then further cooled to 4° C. in one hour and maintained under stirring at this temperature for one additional. The solid was filtered and washed with 25 ml of acetone. The wet solid was dried overnight under vacuum at 30° C. yielding 13.5 g of Nalmefene hydrochloride monohydrate (water content 4.74% w/w as measured by Karl Fisher titration, yield 61%).

2.1b Preparation of the Monohydrate

In a jacketed reactor nalmefene hydrochloride (72.3 g) and water (100 ml) were charged. The suspension was heated up to 85° C. obtaining a solution. Nitrogen flow was applied. The solution was cooled down to 60° C. in around 50 minutes and then kept at this temperature for 10 minutes. The product started to precipitate at 60° C. The suspension was further cooled to 55° C. and maintained at 55° C. for 10 minutes. The suspension was cooled to 8° C. in around one hour and maintained at that temperature for 30 minutes before isolation. The solid was filtered and washed with 83 ml of acetone. The solid was dried yielding 48.6 g of nalmefene hydrochloride monohydrate.

2.2 Properties of the Monohydrate

In the TGA (FIG. 4) about 5 mg of sample was heated 10°/min in an open pan under nitrogen flow. The thermogram showed a weigh-loss of about 4% starting at room temperature and ending at 100-110° C.

DVS experiments were performed at 25° C. and at 40° C. The shape of the curves was the same, only the curve at 40° C. is shown (FIG. 5).

Most of the water of hydration (4%) was absorbed at 10% RH. Then the weight stepwise increased with the humidity up to 4.3% at 50% RH, but at 60% RH it suddenly increased to 6.9% and then again stepwise increased to 7.3% at 95% RH. The amounts here are given as % weigh increase relative to dry, thus the weight gain corresponding to monohydrate was 4.8% and a 1.5 hydrate corresponds to a gain of 7.2%. The curve therefore showed that the water content of the monohydrate was not constant but changes with the relative humidity.

X-ray powder diffractogram (FIG. 6) for Nalmefene hydrochloride monohydrate as obtained using Cu Kα1 radiation is shown in FIG. 6. The diffractogram is measured in reflection mode in the range 5-40° 2θ. It is characterised by XRPD reflections at 7.39, 11.33, 11.52, 17.70 and 24.27° 2θ (±0.1° 2θ).

Example 3

Preparation of Namlefene Hydrochloride Dihydrate

Crude Nalmefene hydrochloride (7.67 Kg, assay 93.9%) and water (8.6 liter) were charged into a suitable reactor. The suspension was heated up to 80° C. until the substrate completely dissolved. Vacuum was then applied to remove organic solvents. The resulting solution was then filtered through a 0.65 μm cartridge and then diluted with water (2.1 liter) used to rinse the reactor and pipelines. The solution was cooled down to 50° C. and 7 g of Nalmefene hydrochloride dihydrate seeding material was added. The mixture was cooled down to 0-5° C. in one hour under efficient stirring and then maintained under stirring for one additional hour. The solid was filtered and washed with acetone. The wet product was dried at 25° C. under vacuum to provide Nalmefene hydrochloride dihydrate (5.4 Kg; yield 73%) with a chemical purity of 99.89% (HPLC).

The particle size of the so obtained Nalmefene hydrochloride dihydrate was determined by Laser Diffraction using a Malvern Mastersizer S instrument. Particle size distribution is reported in the table below:

D10	D50	D90
14 μm	122 μm	287 μm

Example 4

Recovery of Nalmefene Hydrochloride

The mother liquors obtained in Example 3 were concentrated under vacuum. Ammonium hydroxide was added till pH 8-9. The mixture was extracted with dichloromethane at a temperature of 30-35° C. The organic phase was separated and cooled down to 25° C. Concentrated hydrochloric acid was added and the product was allowed to precipitate. The solid was filtered and washed with dichloromethane thus giving 1.35 Kg of Nalmefene HCl with a chemical purity of 98.9%, which can be transformed into the dihydrate applying the procedure described in Example 3.

Example 5

Transformation of Nalmefene HCl into Nalmefene HCl Dihydrate by Re-Slurry

50 g Nalmefene HCl (mixture of monohydrate, acetone solvate and dihydrate) was suspended in 50 ml of water at room temperature. Vacuum was applied for one hour in order to remove acetone. The suspension was further stirred at room temperature for two hours. The solid was filtered and dried under vacuum at 30° C. obtaining 39.9 g of pure Nalmefene HCl dihydrate (water content 8.76% w/w as measured by Karl Fisher titration).

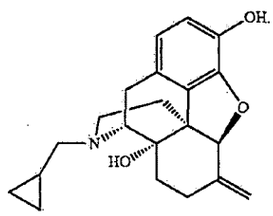
Example 6

Transformation of Nalmefene HCl into Nalmefene HCl Dihydrate by Re-Slurry

3.6 g of Nalmefene HCl monohydrate was suspended at room temperature in 5 ml of water. The suspension was stirred at room temperature. The conversion to dihydrate was completed after 1.5 hours.

The invention claimed is:

1. A compound represented by the formula



$\cdot HCl \cdot 2H_2O$

2. A compound according to claim **1**, wherein the compound is Nalmefene HCl dihydrate.

3. A compound according to claim **1**, wherein the compound is in a crystalline form.

4. A compound according to claim **3**, wherein the compound in a crystalline form is characterized by an X-ray powder diffraction spectrum in 2θ values using Cu $K_{\alpha 1}$ radiation having a peak at 8.99.

5. A compound according to claim **4**, wherein the compound in a crystalline form is further characterized by an X-ray powder diffraction spectrum in 2θ values using Cu $K_{\alpha 1}$ radiation having a peak at one or more of 10.63, 15.24, 16.55, and/or 17.20.

6. A compound according to claim **1**, wherein said compound is non-hygroscopic and less than 1% w/w of moisture is absorbed when exposed to 95% RH at 25° C.

7. A compound according to claim **1**, wherein the water content is from about 8% to about 9% in a relative humidity of about 10% to about 95%.

8. A pharmaceutical composition comprising a compound of claim **1**.

9. A pharmaceutical composition according to claim **8**, wherein Nalmefene hydrochloride dihydrate comprises at least 5% (w/w) of the pharmaceutical dosage form.

10. A pharmaceutical composition according to claim **9**, further comprising one or more pharmaceutically acceptable carriers.

11. A pharmaceutical composition according to claim **8**, in a solid dosage form for oral administration.

12. A pharmaceutical composition according to claim **8** comprising said compound in an amount of about 10 mg to about 100 mg.

13. A method for treating alcohol dependency comprising administering a therapeutically effective amount of a compound according to claim **1** to a patient in the need thereof.

14. A compound according to claim **1**, wherein said compound is non-hygroscopic and less than 0.5% w/w of moisture is absorbed when exposed to 95% RH at 25° C.

15. A compound according to claim **1**, wherein said compound is non-hygroscopic and less than 0.3% w/w of moisture is absorbed when exposed to 95% RE at 25° C.

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(54) **NALMEFENE HYDROCHLORIDE DIHYDRATE**

NALMEFEN-HYDROCHLORID-DIHYDRAT

CHLORHYDRATE DE NALMEFENE DIHYDRATÉ

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Description

[0001] The present invention relates to a novel non-hygroscopic form of Nalmefene Hydrochloride, namely Nalmefene hydrochloride dihydrate, in particular for oral dosage forms, and methods for its production.

Background

[0002] Nalmefene is a known opioid receptor antagonist which can inhibit pharmacological effects of both administered opioid agonists and endogenous produced agonists from the opioid system. The clinical usefulness of Nalmefene as an antagonist comes from its ability to promptly (and selectively) reverse the effects of these opioid agonists, including the often observed depressions in the central nervous system and the respiratory system.

[0003] Nalmefene has primarily been developed for use in the management of alcohol dependence, where it has shown good effect in doses of 10 to 40 mg taken when the patient believed drinking to be imminent (about 1-2 hours before drinking) (Karhuvaara et al., Alcohol. Clin. Exp. Res., (2007), Vol. 31 No. 7. pp 1179-1187). Additionally, Nalmefene has also been investigated for the treatment of other addictions such as pathological gambling and addiction to shopping. In these developmental programs and testing, Nalmefene has been used, for example as a parental solution (Revex™).

[0004] Nalmefene is an opiate derivative similar in structure to the opiate antagonist Naltrexone. Advantages of Nalmefene relative to Naltrexone include longer half-life, greater oral bioavailability and no observed dose-dependent liver toxicity.

[0005] Nalmefene differs from Naltrexone by substitution of the ketone group at the 6-position of Naltrexone with a methylene (CH_2) group, which considerably increases binding affinity to the μ-opioid receptor. Nalmefene also has high affinity for the other opioid receptors (κ and δ receptors), and is known as a "universal antagonist" for its ability to block all three.

[0006] Nalmefene can be produced according to the method described by Hanh et al., (J. Med. Chem., 18, 259-262 (1975), Mallinckrodt (US 4,751,307), and Meltzner et al., (US patent No. 4,535,157).

[0007] By using the above-mentioned methods, the free base of Nalmefene is obtained, which subsequently can be converted into the hydrochloride salt, by use of conventional methods.

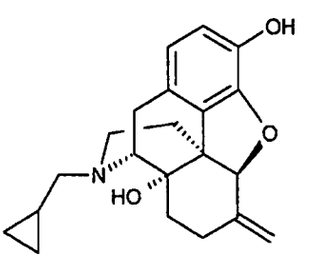
[0008] According to Brittain, (Analytical Profiles of Drug Substances and Excipients (1996), Vol 24, pp. 351-395) Nalmefene hydrochloride can be recrystallized from water, giving a pure drug substance, which inevitably consists of a monohydrate crystal phase. In the same review the monohydrate phase of Nalmefene hydrochloride is described as essentially non-hygroscopic since it can only sorb up to 1% of adventitious moisture.

[0009] The inventors of the present invention have found that, contrary to the literature, Nalmefene hydrochloride as a monohydrate is hygroscopic.

[0010] There is therefore a need for providing a novel, stable and non-hygroscopic hydrate form of Nalamefene and methods for its manufacturing.

Summary of the invention

[0011] The present invention relates to Nalmefene hydrochloride dihydrate represented by the formula



$.HCl.2H_2O$

preferably in a crystalline form. Said Nalmefene hydrochloride dihydrate is non-hygroscopic

[0012] The invention further relates to two methods of producing Nalmefene hydrochloride dihydrate:

Method (I): transformation of Nalmefene hydrochloride into Nalmefene hydrochloride dihydrate by re-slurry in aqueous solution, exemplified by water, such as pure water, and

Method (II): recrystallisation of Nalmefene hydrochloride in aqueous solution, exemplified by water, such as pure

water.

[0013] The re-slurry method (Method I) comprises the steps of:

(1) mixing Nalmefene Hydrochloride (17-(cyclopropylmethyl)-4,5-α-epoxy-6-methylenemorphinan-3,14-diol hydrochloride) and aqueous solution, exemplified by water, such as pure water,
(2) optionally, heating the mixture,
(3) optionally, distilling the mixture,
(4) stirring the mixture until transformation is complete, such as less than 1 hour, such as about 1 hour, such as for at least 1 hour, and
(5) isolating the formed solid.

[0014] The re-crystallisation method (Method II) comprises the steps of:

(a) mixing Nalmefene hydrochloride (17-(cyclopropylmethyl)-4,5-α-epoxy-6-methylenemorphinan-3,14-diol hydrochloride) and aqueous solution, exemplified by water, such as pure water,
(b) heating of the mixture to obtain a substantially homogenous solution,
(c) optionally, distillation of the mixture obtained in (b),
(d) cooling of the solution obtained in step (b) or (c), subsequently seeding with Nalmefene hydrochloride, and
(e) isolation of the formed solid.

[0015] A further aspect of the present invention (Method III) is a method to recover any unused Nalmefene from the methods I and II, comprising the steps of:

(i) optionally, distillation of mother liquors obtained from method (I) or (II)
(ii) basification of the mother liquors obtained in step (i), or from the methods (I) or (II),
(iii) extracting the mixture with a suitable organic solvent,
(iv) adding hydrogen chloride, and
(v) isolating the formed solid

[0016] The invention further relates to pharmaceutical compositions comprising Nalmefene hydrochloride dihydrate, the use of Nalmefene hydrochloride dihydrate in medicine, and in particular the use of Nalmefene hydrochloride dihydrate for the treatment of alcohol dependency.

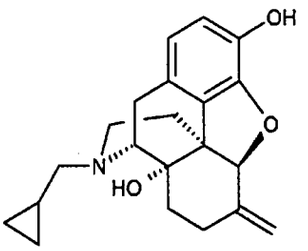
Brief description of the drawings

[0017]

Figure 1 Shows TGA thermogram of the Nalmefene hydrochloride dihydrate. The y-axis shows the percentage in mass, and the X-axis shows temperatures (°C).
Figure 2 Shows DVS experiments performed at 40°C of Nalmefene hydrochloride dihydrate (dry plot). The first y-axis (left) show the change in mass relative to anhydrous (%), and the other y-axis (right) displays the targeted relative humidity (RH)(%), while the x-axis show the time in minutes. The thin line shows the changes in target RH, and the bold line the changes in relation to mass.
Figure 3 Shows X-ray powder diffractogram of the Nalmefene hydrochloride dihydrate. The y-axis shows the intensity (counts), and the x-axis shows the 2Theta angle (°).
Figure 4 Shows TGA thermogram of the Nalmefene hydrochloride monohydrate. The y-axis shows the percentage in mass, and the x-axis shows temperatures (°C).
Figure 5 Shows DVS experiments performed at 40°C of Nalmefene hydrochloride monohydrate (dry plot). The first y-axis (left) show the change in mass relative to anhydrous (%), and the other y-axis (right) displays the targeted relative humidity (RH)(%), while the x-axis show the time in minutes. The thin line shows the changes in target RH, and the bold line the changes in relation to mass.
Figure 6 Shows X-ray powder diffractogram of the Nalmefene hydrochloride monohydrate. The y-axis shows the intensity (counts), and the x-axis shows the 2Theta angle(°).

Detailed description of the invention

[0018] The present invention relates to Nalmefene hydrochloride dihydrate represented by the below formula



.HCl.2H_2O

[0019] The dihydrate form of Nalmefene hydrochloride is particular advantageous in that it is non-hygroscopic. As a result of this non-hygroscopic feature, the physical properties can more easily be controlled. This is of great importance when preparing solid dosage forms such as orally administrable forms, including solid unit dosage forms e.g. tablets or chewable tablet and capsules.

[0020] As is well known within the pharmaceutical industry, processing of hygroscopic products entails the use of controlled humidity chambers both for storage and for the processing itself. Moreover, the finished hygroscopic products must be packed in sealed blisters in order to avoid stability problems due to humidity. These disadvantages are avoided by using Nalmefene hydrochloride as the non-hygroscopic dihydrate.

[0021] Nalmefene hydrochloride dihydrate is characterized by being non-hygroscopic and stable in its water content. The compound does not absorb or lose water when exposed to a relative humidity (RH) of between 10% and 95%.

[0022] As shown in Example 1 of the present invention, DVS (Dynamic Vapour Sorption) experiments were performed at 25°C and at 40°C. The results showed that no water was absorbed by Nalmefene hydrochloride dihydrate even at 95% RH. In contrast hereto, as shown in Example 2, Nalmefene hydrochloride as monohydrate absorbed about 2.5% water when exposed to 95% RH and 40°C.

[0023] Furthermore, the result in Example 2 showed that in contrast to the dihydrate, the monohydrate form changes in the water content with the surrounding humidity, and at RH above 50% the monohydrate form changed into a new structure with higher water content.

[0024] It is therefore an important characteristic of Nalmefene hydrochloride dihydrate that it is non-hygroscopic, as defined above. Thus the present invention relates to Nalmefene hydrochloride dihydrate which is non-hygroscopic, meaning that less than 1%, such as less than 0.5%, such as less than 0,3% moisture is absorbed when exposed to 95% RH at 25°C.

[0025] Nalmefene hydrochloride dihydrate is a crystalline solid characterized by X-ray reflections at angles 8.99, 10.63, 15.24, 16.55 and 17.20°2θ (±0.1°2θ) as measured using $CuK_{\alpha 1}$ radiation, and having water content of about 8 to about 9 %, such as about 8.7%, while the monohydrate of Nalmefene hydrochloride is a crystalline solid characterized by X-ray reflections at angles 7.39, 11.33, 11.52, 17.70 and 24.27°2θ (±0.1°2θ) and water content of 4-7% depending on the relative humidity of the surroundings.

[0026] The present invention also relates to the use of Nalmefene hydrochloride dihydrate in the manufacturing of a medicament.

[0027] In particular, the invention is related to the use of Nalmefene hydrochloride dihydrate in the manufacturing of a medicament, wherein Nalmefene hydrochloride dihydrate comprises at least 5% (w/w), such as at least 10% (w/w), at least 30%, at least 50% (w/w), such as at least 70% (w/w), at least 90% (w/w), at least 95% (w/w), at least 99% (w/w), or 100% of the pharmaceutical dosage form, particularly a oral dosage form, e.g. a single unit solid dosage form such as a tablet. Nalmefene hydrochloride dihydrate is in particular related to the use in the manufacturing of a medicament for the treatment alcohol dependency.

[0028] In a further embodiment, the present invention relates to a method for treating alcohol dependency comprising administering a therapeutically effective amount of Nalmefene hydrochloride dihydrate, e.g. in a pharmaceutical composition (such as a solid dosage form, e.g. tablet for oral administration) to a patient in the need thereof. By the term "therapeutically effective amount" is referred to the amount/dose of a compound or pharmaceutical composition that is sufficient to produce an effective response (i.e., a biological or medical response of a tissue, system, animal or human sought by a researcher, veterinarian, medical doctor or other clinician) upon administration to a patient. The "therapeutically effective amount" will vary depending on inter alia the disease and its severity, and the age, weight, physical condition and responsiveness of the patient to be treated. Furthermore the "therapeutically effective amount" may vary if the compound of the invention is combined with one or more compounds, in such a case the amount of a given compound might be lower, such as a sub-effective amount.

[0029] The term 'distil' refers to a method of separating mixtures based on differences in their volatilities in a boiling liquid mixture. Application of vacuum such as partial vacuum is an example of such separation method.

[0030] The term 'chemical purity' is given its normal meaning within the art and thus refers to the degree to which an obtained compound is contaminated with impurities. Accordingly, an obtained compound which is at least 98% chemically pure comprises at most 2% of impurities. The chemical purity may be measured by e.g. HPLC.

[0031] The term 'assay' refers to the effective content of the desired substance expressed as a weight by weight percentage (w/w%).

[0032] The term 'extraction' refers to a liquid-liquid extraction in which the free Nalmefene base is transferred from an aqueous phase to an organic phase.

[0033] The term 're-slurry' refers to a process wherein the crystalline material is suspended in a solvent or a solvent mixture at an appropriate temperature whereby the crystalline material partially dissolves and partially crystallises again thus permitting its transformation into the desired form and/or its purification.

[0034] KF refers to 'Karl Fisher titration'.

[0035] TGA refers to 'Thermo-Gravimetric Analysis'.

[0036] DVS refers to 'Dynamic Vapour Sorption'

[0037] In the present invention, the term "substantially homogenous solution" is intended to mean a liquid mixture free of visible undissolved material.

[0038] In the present invention, the term "seeding" is intended to mean the addition of a small amount of crystals to initiate the precipitation of the product.

[0039] In the present context the term "non-hygroscopic" is intended to mean that less than 1%, such as less than 0.5%, such as less than 0,3% w/w of moisture is absorbed when exposed to 95% RH at 25°C.

[0040] In the present context, particle sizes are determined by Laser Diffraction using a Malvern Mastersizer S instrument as disclosed in details in the introductory part of the experimental section.

[0041] Preferably the amount of Nalmefene hydrochloride dihydrate in a pharmaceutical composition is in an amount from about 10 mg to about 100 mg, such as about 10 mg to about 60 mg, about 10 mg to about 40 mg, or about 20 mg.

[0042] The term "alcohol dependency" is a commonly known term for a skilled person which, in the revised 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IVTR) (Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision, American Psychiatric Publishing, 2000), is defined as the presence of three or more of the seven areas of life impairment related to alcohol in the same 12-month period. These impairments include tolerance, evidence of a withdrawal syndrome when alcohol is discontinued or intake is decreased, potential interference with life functioning associated with spending a great deal of time using alcohol and returning to use despite evidence of physical or psychological problems.

[0043] The pharmaceutical composition comprising Nalmefene hydrochloride dihydrate may further comprise one or more pharmaceutically acceptable carriers.

[0044] Methods for the preparation of solid pharmaceutical preparations are well known in the art. See, e.g., Remington: The Science and Practice of Pharmacy, 21st ed., Lippincott Williams & Wilkins (2005). Solid preparations, such as tablets, may be prepared by mixing the active ingredients with an ordinary carrier, such as an adjuvant and/or diluent, and subsequently compressing the mixture in a tabletting machine. Non-limiting examples of adjuvants and/or diluents include: corn starch, lactose, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive such as colourings, aroma, and preservatives may also be used provided that they are compatible with the active ingredients. The pharmaceutical compositions of the invention thus typically comprise an effective amount of Nalmefene hydrochloride dihydrate and one or more pharmaceutically acceptable carriers.

[0045] According to the present invention, it is envisaged that Nalmefene hydrochloride dihydrate may be administered in any suitable way, e.g., orally or parenterally, and it may be presented in any suitable form for such administration, e.g., in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. In an embodiment, Nalmefene hydrochloride dihydrate is preferably administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule.

[0046] A further aspect of the present invention relates to methods for obtaining Nalmefene hydrochloride dihydrate. Nalmefene hydrochloride dihydrate may be obtained by any of the methods (I) and (II), as will be outlined below.

Method (I) transformation of Nalmefene hydrochloride into Nalmefene hydrochloride dihydrate by re-slurry in aqueous solution, such as water, such as pure water and
Method (II) re-crystallization of Nalmefene hydrochloride in aqueous solution, such as water, such as pure water

[0047] According to one aspect of the invention, the re-slurry method (Method (I)) comprises the steps of:

(1) mixing Nalmefene Hydrochloride (17-(cyclopropylmethyl)-4,5-α-epoxy-6-methylenemorphinan-3,14-diol hydrochloride) and aquous solution, such as water, such as pure water
(2) optionally, heating the mixture,
(3) optionally, distilling the mixture

(4) stirring the mixture, and
(5) isolating the formed solid.

[0048] In one embodiment of Method (I), Nalmefene hydrochloride is transformed into Nalmefene hydrochloride dihydrate by re-slurry in aqueous solution. In another embodiment Nalmefene hydrochloride is transformed into Nalmefene hydrochloride dihydrate by re-slurry in water. In yet another embodiment Nalmefene hydrochloride is transformed into Nalmefene hydrochloride dihydrate by re-slurry in pure water.

[0049] The ratio of aqueous solution such as water, such as pure water, used in step (1) may range from about 0.5 ml to about 4 ml aqueous solution /nalmefene hydrochloride (g), such as from about 1 ml to about 2 ml aqueous solution /nalmefene hydrochloride (g), more preferably about 1.5 ml aqueous solution / nalmefene hydrochloride (g). The Nalmefene hydrochloride used can be selected from any hydrated or solvated form of Nalmefene or mixtures of hydrated and/or solvated forms with or without solvents., In one embodiment Nalmefene hydrochloride as monohydrate is used. In another embodiment of Method (I), Nalmefene hydrochloride is used in hydrated form. In another embodiment, Nalmefene hydrochloride is used in solvated form. In yet another embodiment, Nalmefene hydrochloride is used in a mixture of hydrated solvated form.

[0050] In an embodiment of Method (I), solvents comprised in said hydrated and/or solvated forms are selected from the group consisting of acetone, n-propanol, isopropanol, dichloromethane and water. In one embodiment said solvent is acetone. In another embodiment said solvent is n-propanol. In yet another embodiment said solvent is isopropanol. In yet another embodiment said solvent is dichloromethane. In yet another embodiment said solvent is water.

[0051] Heating in step (2) is an optional step, which may under some conditions be beneficial in order to increase the dissolution rate of the mixture obtained in step (b). The heating temperature may depend on the circumstances. Under some circumstances the mixing will be efficiently performed at room temperature (20-25°C). It is envisaged that in one embodiment heating in step (2) is to about 50°C. In another embodiment, heating in step (2) is to 50°C or less. In another embodiment heating to in step (2) is to about 20 °C to about 40 °C. In yet another embodiment heating in step (2) is to about 30°C.

[0052] Step (2) and step (3) may be performed with or without stirring.

[0053] The distillation in step (3) may be performed to remove organic solvents if present in the mixture. The distillation may be performed by applying Vacuum.

[0054] The stirring in step (4) may be performed at a temperature of about 0°C to about 50°C, such as 45°C, such as from 20°C to about 40°C. In one embodiment, the mixture is stirred for less than one hour. In another embodiment the mixture is stirred for about one hour. In yet another embodiment the mixture is stirred for at least one hour.

[0055] The solid can be isolated at a temperature within the range of about 0-25°C such as 0-20°C and more preferably in the range of 0-5°C in order to lower the solubility of the product, such as in water, and to increase the yield. The solid may be isolated by filtration and washed with a suitable solvent. Solvents for washings include water and mixtures of water/organic solvents or pure organic solvents. Preferably water is used and in a further embodiment pre-cooled water is preferred. When organic solvents are used, Class 2 or 3 solvents (ICH Q3C(R4) guidelines) are preferred. In one embodiment, class 3 solvents such as acetone and ethyl acetate are used. In one embodiment acetone is used. In another embodiment ethyl acetate is used.

[0056] The product can be dried under vacuum below 40°C and more preferably at a temperature in the range 25-35°C.

[0057] It is envisaged that the obtained compound is at least 98% chemically pure, such as at least 99% chemically pure, or at least 99.5% chemically pure.

[0058] According to one aspect of the invention, the re-crystallization method (Method (II)) comprises the steps of:

(a) mixing Nalmefene hydrochloride (17-(cyclopropylmethyl)-4,5-α-epoxy-6-methylenemorphinan-3,14-diol hydrochloride) and aqueous solution, such as water, such as pure water,
(b) heating the mixture to obtain a substantially homogenous solution,
(c) optionally, distillation of mixture obtained in step (b),
(d) cooling of the solution obtained in step (b) or (c), subsequently seeding with Nalmefene hydrochloride, and
(e) isolation of the formed solid.

[0059] In one embodiment of Method (II), Nalmefene hydrochloride is transformed into Nalmefene hydrochloride dihydrate by re-crystallization in aqueous solution. In another embodiment Nalmefene hydrochloride is transformed into Nalmefene hydrochloride dihydrate by re-slurry in water. In yet another embodiment Nalmefene hydrochloride is transformed into Nalmefene hydrochloride dihydrate by re-slurry in pure water.

[0060] The amount of aqueous solution, such as water, such as pure water, which is used in step (a) may range from about 0.9 ml to about 4 ml aqueous solution /Nalmefene hydrochloride (g), such as from about 1 ml to about 2 ml aqueous solution /Nalmefene hydrochloride (g), or about 1.5 ml aqueous solution /Nalmefene hydrochloride (g). The Nalmefene hydrochloride used can be selected from any hydrated or solvated form of Nalmefene or mixtures of hydrated and/or

solvated forms with or without solvents.

[0061] In one embodiment of Method (II), Nalmefene hydrochloride is used in hydrated form. In another embodiment, Nalmefene hydrochloride is used in solvated form. In yet another embodiment, Nalmefene hydrochloride is used in a mixture of hydrated solvated form.

[0062] In an embodiment of Method (II), solvents comprised in said hydrated and/or solvated forms are selected from the group consisting of acetone, n-propanol, isopropanol, dichloromethane and water. In one embodiment said solvent is acetone. In another embodiment said solvent is n-propanol. In yet another embodiment said solvent is isopropanol. In yet another embodiment said solvent is dichloromethane. In yet another embodiment said solvent is water.

[0063] The suspension may be heated until a substantially homogenous solution is obtained, i.e. a solution. The heating in step (b) may be performed to reach a temperature of about 50°C to about 100 °C, such as about 50 °C to about 90 °C , or about 70 °C to about 85°C.

[0064] Partial vacuum may then applied to remove traces of organic volatiles, if present, in step (c).

[0065] The solution obtained either from step (b) or step (c) may optionally be filtered (e.g. through a 0.65 μm cartridge) to remove foreign matters before proceeding to step (d).

[0066] In step (d) the solution may be cooled to a temperature between 40°C to about 50°C and seeded. In one embodiment of the invention, the seeding is performed at a temperature between 40°C and 50°C. The seeding is performed with Nalmefene hydrochloride dihydrate crystals. The Nalmefene seeding material may, in one embodiment of the invention, be obtained by the re-slurry method (I) described above.

[0067] The amount of seed crystal added in step (d) may be from about 1/2000 (w/w) of seed crystal of Nalmefene hydrochloride / Nalmefene hydrochloride added in step (a), such as from about 1/1000 (w/w) of seed crystal or 1/200 of seed crystal of Nalmefene hydrochloride / Nalmefene hydrochloride added in step (a).

[0068] An appropriate cooling ramp, such as a fast cooling ramp, and an appropriate stirring, such as a vigorous stirring, impede the crystals already formed to grow further and help to provide a product with a well defined, narrow and relatively small particle size. The cooling from seeding temperature to isolation temperature may be accomplished within a few hours and more preferably within 1 hour. The seeded mixture obtained in step (d) may therefore further be subjected to a cooling, such as a fast cooling, which comprises the steps of:

(d') a further cooling of the mixture to a temperature of about 0-5°C such as over a time period of about 45 minutes or more, and

(d") thereafter the mixture may be maintained at a temperature of about 0-5°C for e.g. about 45 minutes or more before isolating the formed solid according to step (e).

[0069] The solid formed in step (e) may be isolated. The solid can be isolated at a temperature within the range of about 0-20°C and more preferably in the range of 0-5°C in order to lower the solubility of the product in water and thereby increase the yield. The solid may be isolated by filtration and washed with a suitable solvent. Solvents for washings include water and mixtures of water/ organic solvents or pure organic solvents. In one embodiment solvents for washing are selected from the group consisting of acetone and water. In one embodiment acetone is used. In another embodiment a mixture of acetone and water. In yet another embodiment water is used. In a further embodiment the water used is pre-cooled water. When organic solvents are used for washing, Class 2 or 3 solvents (ICH Q3C(R4) guidelines) are preferred, more preferably class 3 solvents such as acetone and ethyl acetate. In one embodiment ethyl acetate is used.

[0070] The product can be dried under vacuum below 40°C and more preferably at a temperature in the range 25-35°C.

[0071] It is envisaged that the obtained compound is at least 98% chemically pure, such as at least 99% chemically pure, or at least 99.5% chemically pure.

[0072] It is further envisaged that the Nalmefene hydrochloride dihydrate obtained by the above method (II) has the following particle size distribution: D90 equal to or below 400 μm and D50 equal to or below 200 μm, and D10 equal to or below 50 μm, and with ratio D90/D50 equal to or below 2.5, wherein D"XX" (XX is given as 10, 50 or 90) is defined as the value for which an "XX percentage" (given in volumes) of the particles have a diameter under the indicated value. Thus for D10, 10 percentage of the particle size (in volume) has a diameter equal to or below 50 μm.

[0073] Recovery of Nalmefene hydrochloride from mother liquors (Method III):

Nalmefene hydrochloride is highly soluble in aqueous solutions such as water, such as pure water, and therefore a part of this material is lost in the mother liquors. To recover any unused Nalmefene hydrochloride from the methods I or II, outlined above, a method for the recovery has been developed that comprises

(i) optionally, distillation of mother liquors obtained from method (I) or (II)
(ii) basification of the mother liquors obtained in step (i), or from the methods (I) or (II),
(iii) extracting the mixture with a suitable organic solvent,
(iv) adding hydrogen chloride, and

(v) isolating the formed solid

[0074] The basification in step (ii) is performed to bring the pH in the range of 8-10, such as 8-9 using an organic or inorganic base. In an embodiment of method (III), the basification in step (ii) is performed with ammonium hydroxide.

[0075] In the extraction step (iii) the organic solvent may be selected from the group comprising halogenated hydrocarbons, ethers, esters, ketones, and preferably dichloromethane, 2-methyl-tetrahydrofurane, ethyl acetate, 2-butanone, even more preferably dichloromethane. In one embodiment the organic solvent is halogenated hydrocarbons. In another embodiment the organic solvent is ethers. In another embodiment the organic solvent is selected from the group of esters. In another embodiment the organic solvent is selected from the group of ketones. In another embodiment the organic solvent is dichloromethane. In another embodiment the organic solvent is 2-methyl-tetrahydrofurane. In another embodiment the organic solvent is ethyl acetate. In another embodiment the organic solvent is 2-butanone.

[0076] The solution of nalmefene base in an organic solvent obtained in step (iii) is treated with hydrogen chloride to precipitate nalmefene hydrochloride.

[0077] The amount of hydrogen chloride added in step (iv) depends on different factors such as the amount of nalmefene in mother liquors used, and will be apparent to a person skilled in the art. After hydrochloric acid is added to the mixture in step (iv) the product is allowed to precipitate.

[0078] The precipitated solid may be isolated as described for methods I and II.

[0079] It is envisaged that the obtained compound is at least 98% chemically pure, such as at least 99% chemically pure, or at least 99.5% chemically pure.

Examples

[0080] In the present contest, chemical purity is measured by HPLC using the below conditions:

Chromatographic conditions:

[0081]

Column:	YMC Basic B-03-5, 5 μm, 250 × 4.6 mm or equivalent
Mobile Phase A:	Buffer
Mobile Phase B:	Methanol
Buffer:	Dissolve 1.1 g of Sodium Octansulfonate (FW 216.28) in 1 L of water. Adjust the pH to 3.8 with diluted H_3PO_4.
Column Temperature:	35°C
Detector:	UV at 230 nm
Flow:	1.5 ml/min
Injection volume:	20 μl
Time of Analysis:	50 minutes

Time (min)	Mobile Phase A	Mobile PhaseB
0	90	10
10	70	30
25	50	50
40	20	80
50	20	80

[0082] In the present context, particle sizes are determined by Laser Diffraction using a Malvern Mastersizer S instrument made up of a laser transmitter (LASER HELIUM-NEON - wavelength 632 nm), an optical system (300 F lens, range 0.5 - 900 μm), a measurement cell for suspension (beam length 2.4 mm) and a photodiode detector. The sample is analysed using mineral oil (CAS 8042-47) as dispergent.

Example 1

1.1a Preparation of the dihydrate

[0083] Dihydrate was prepared as follows:

[0084] 20 g of crude Nalmefene Hydrochloride (chemical purity 99.26%, assay 92.9%) was suspended in 24 ml of water. The mixture was heated up and the solid dissolved completely at 60-65°C. The solution was heated up to 70°C and maintained at that temperature for 15 minutes. The solution was cooled down from 70 °C to 20°C in 3 hours using a linear ramp.

[0085] At 50°C, Nalmefene Hydrochloride was added as seeding. The seed did not dissolve and Nalmefene started to crystallize. When the cooling ramp was terminated the suspension was maintained under stirring at 20°C for 2.5 days. The solid was filtered and washed with acetone (50 ml). The wet product was dried overnight under vacuum at 40°C yielding 13.2 g of Nalmefene hydrochloride dihydrate (chemical purity 99.74%, water content 8.54 % w/w as measured by Karl Fisher titration).

1.1b Preparation of the dihydrate

[0086] 20 g of crude Nalmefene Hydrochloride (chemical purity 97.2%, assay 82.6%) was suspended in 30 ml of water. The mixture was heated up and the solid dissolved completely at 80°C. Organic volatiles were removed by vacuum distillation. The solution was cooled down to 50°C.

[0087] At 50°C, Nalmefene Hydrochloride dihydrate was added as seeding. The mixture was maintained at 50°C for 3 hours and then allowed to cool down to 20°C. The suspension was maintained under stirring at 20°C for around 2.5 days. The solid was filtered and washed with acetone (20 ml). The wet product was dried overnight under vacuum at 30°C yielding 11.5 g of Nalmefene hydrochloride dihydrate (chemical purity 99.78%, water content 8.78 % w/w as measured by Karl Fisher titration).

1.2 Properties of the dihydrate

[0088] In the TGA (figure 1) about 10 mg of sample was heated 10°/min in an open pan under nitrogen flow. The thermogram shows a weigh-loss of about 8.5% starting at 0,room temperature and ending at 125-150°C.

[0089] DVS experiments were performed at 25°C and at 40°C. The shape of the curves were the same at the two temperatures; the curve at 40°C is shown in figure 2. The dihydrate is retained at relative humidity of 10-95%. Adsorbtion to the surface at high relative humidity is less than 0.2%. Desorption of the crystal water occurs slowly under 10%RH. The DVS-curve however shows complete rehydration after drying at 0%RH, thus the crystal lattice is retained by this treatment.

[0090] X-ray powder diffractogram for Nalmefene hydrochloride.dihydrate as obtained using Cu $K_{\alpha 1}$ radiation is shown in figure 3. The diffractogram is measured in reflection mode in the range 5-40°2θ. It is characterised by XRPD reflections at 8.99, 10.63, 15.24, 16.55 and 17.20°2θ (±0.1°2θ).

Example 2

2.1a Preparation of the monohydrate

[0091] 25 g of Nalmefene hydrochloride (chemical purity 99.24, assay 84.1) was suspended in 32 ml of water. The mixture was heated up to 80°C. Vacuum was applied to distill low boiling organic solvents. The solution was cooled down to 20°C in one hour using a linear ramp. The suspension was maintained under stirring for two hours and then further cooled to 4°C in one hour and maintained under stirring at this temperature for one additional. The solid was filtered and washed with 25 ml of acetone. The wet solid was dried overnight under vacuum at 30°C yielding 13.5 g of Nalmefene hydrochloride monohydrate (water content 4.74% w/w as measured by Karl Fisher titration, yield 61 %).

2.1b Preparation of the monohydrate

[0092] In a jacketed reactor nalmefene hydrochloride (72.3 g) and water (100 ml) were charged. The suspension was heated up to 85°C obtaining a solution. Nitrogen flow was applied. The solution was cooled down to 60°C in around 50 minutes and then kept at this temperature for 10 minutes. The product started to precipitate at 60°C. The suspension was further cooled to 55°C and maintained at 55°C for 10 minutes. The suspension was cooled to 8°C in around one hour and maintained at that temperature for 30 minutes before isolation. The solid was filtered and washed with 83 ml of acetone. The solid was dried yielding 48.6g of nalmefene hydrochloride monohydrate.

2.2 Properties of the monohydrate

[0093] In the TGA (Figure 4) about 5 mg of sample was heated 10°/min in an open pan under nitrogen flow. The thermogram showed a weigh-loss of about 4% starting at room temperature and ending at 100-110°C.

[0094] DVS experiments were performed at 25°C and at 40°C. The shape of the curves was the same, only the curve at 40°C is shown (Figure 5).

[0095] Most of the water of hydration (4%) was absorbed at 10%RH. Then the weight stepwise increased with the humidity up to 4.3% at 50%RH, but at 60%RH it suddenly increased to 6.9% and then again stepwise increased to 7.3% at 95%RH. The amounts here are given as % weigh increase relative to dry, thus the weight gain corresponding to monohydrate was 4.8% and a 1.5 hydrate corresponds to a gain of 7.2%. The curve therefore showed that the water content of the monohydrate was not constant but changes with the relative humidity.

[0096] X-ray powder diffractogram (Figure 6) for Nalmefene hydrochloride monohydrate as obtained using Cu Kα1 radiation is shown in figure 6. The diffractogram is measured in reflection mode in the range 5-40°2θ. It is characterised by XRPD reflections at 7.39, 11.33, 11.52, 17.70 and 24.27°2θ (±0.1°2θ).

Example 3

Preparation of Namlefene hydrochloride dihydrate

[0097] Crude Nalmefene hydrochloride (7.67 Kg, assay 93.9%) and water (8.6 liter) were charged into a suitable reactor. The suspension was heated up to 80°C until the substrate completely dissolved. Vacuum was then applied to remove organic solvents. The resulting solution was then filtered through a 0.65 μm cartridge and then diluted with water (2.1 liter) used to rinse the reactor and pipelines. The solution was cooled down to 50°C and 7 g of Nalmefene hydrochloride dihydrate seeding material was added. The mixture was cooled down to 0-5°C in one hour under efficient stirring and then maintained under stirring for one additional hour. The solid was filtered and washed with acetone. The wet product was dried at 25°C under vacuum to provide Nalmefene hydrochloride dihydrate (5.4 Kg; yield 73%) with a chemical purity of 99.89% (HPLC).

[0098] The particle size of the so obtained Nalmefene hydrochloride dihydrate was determined by Laser Diffraction using a Malvern Mastersizer S instrument. Particle size distribution is reported in the table below:

D10	D50	D90
14 μm	122 μm	287 μm

Example 4

Recovery of Nalmefene hydrochloride

[0099] The mother liquors obtained in Example 3 were concentrated under vacuum. Ammonium hydroxide was added till pH 8-9. The mixture was extracted with dichloromethane at a temperature of 30-35°C. The organic phase was separated and cooled down to 25°C. Concentrated hydrochloric acid was added and the product was allowed to precipitate. The solid was filtered and washed with dichloromethane thus giving 1.35 Kg of Nalmefene HCl with a chemical purity of 98.9%, which can be transformed into the dihydrate applying the procedure described in Example 3.

Example 5

Transformation of Nalmefene HCl into Nalmefene HCl dihydrate by re-slurry

[0100] 50 g Nalmefene HCl (mixture of monohydrate, acetone solvate and dihydrate) was suspended in 50 ml of water at room temperature. Vacuum was applied for one hour in order to remove acetone. The suspension was further stirred at room temperature for two hours. The solid was filtered and dried under vacuum at 30°C obtaining 39.9 g of pure Nalmefene HCl dihydrate (water content 8.76% w/w as measured by Karl Fisher titration).

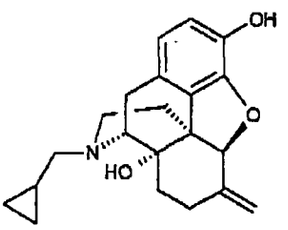
Example 6

Transformation of Nalmefene HCl into Nalmefene HCl dihydrate by re-slurry

[0101] 3.6 g of Nalmefene HCl monohydrate was suspended at room temperature in 5 ml of water. The suspension was stirred at room temperature. The conversion to dihydrate was completed after 1.5 hours.

Claims

1. A compound represented by the formula



$.HCl.2H_2O$

2. A compound according to claim 1, wherein the compound is in a crystalline form.

3. A compound according to claim 2, wherein the compound in a crystalline form is **characterized by** an X-ray powder diffraction spectrum in 2θ values using Cu $K_{\alpha 1}$ radiation having a peak at 8.99.

4. A compound according to claim 3, wherein the compound in a crystalline form is further **characterized by** an X-ray powder diffraction spectrum in 2θ values using Cu $K_{\alpha 1}$ radiation having a peak at one or more of 10.63, 15.24, 16.55, and/or 17.20.

5. A compound according to any one of the preceding claims being non-hygroscopic and thus less than 1%, such as less than 0.5%, such as less than 0.3% w/w of moisture is absorbed when exposed to 95% RH at 25°C.

6. A compound according to any one of the preceding claims, wherein the water content is from about 8% to about 9% in a relative humidity of about 10% to about 95%.

7. A method for obtaining a compound according to any one of claims 1-6, comprising the steps of:

   (1) mixing Nalmefene Hydrochloride (17-(cyclopropylmethyl)-4,5-α-epoxy-6-methylenemorphinan-3,14-diol hydrochloride) and aqueous solution such as water,
   (2) optionally, heating the mixture,
   (3) optionally, distilling the mixture,
   (4) stirring the mixture until transformation is complete, and
   (5) isolating the formed solid.

8. A method according to claim 7 wherein the mixture in (4) is stirred for at least 1 hour

9. A method according to any one of claims 7 and 8, wherein the ratio of aqueous solution such as water used in step (1) ranges from about 0.9 ml to about 4 ml aqueous solution /Nalmefene Hydrochloride (g), such as from about 1 ml to about 2 ml aqueous solution /Nalmefene Hydrochloride (g), more preferably 1.5 ml aqueous solution / Nalmefene Hydrochloride (g).

10. A method according to any one of claims 7-9, wherein Nalmefene Hydrocloride used in step (1) is in a hydrated form such as monohydrate form.

11. A method according to any one of claims 7-9, wherein Nalmefene Hydrocloride used in step (1) is in a solvated form

or a mixture of hydrated and solvated forms.

12. A method according to any one of claims 7-11, wherein stirring is performed in step (2) and/or (3).

13. A method according to any one of claims 7-12, wherein the stirring in step (4) is performed at a temperature of about 0°C to about 45°C, such as from 20°C to about 40°C.

14. A method according to any one of claims 7-13, wherein the formed solid in step (5) is isolated at a temperature from about 0 °C to about 20°C, such as from about 0°C to about 5°C.

15. A method for obtaining a compound according to any one of claims 1-6, comprising the steps of

(a) mixing Nalmefene hydrochloride (17-(cyclopropylmethyl)-4,5-α-epoxy-6-methylenemorphinan-3,14-diol hydrochloride) and aqueous solution such as water,
(b) heating of the mixture to obtain a substantially homogenous solution,
(c) optionally, distillation of the mixture obtained in (b),
(d) cooling of the solution obtained in step (b) or (c), subsequently seeding with Nalmefene hydrochloride, and
(e) isolation of the formed solid.

16. A method according to claim 15, wherein the amount of aqueous solution such as water used in step (a) ranges from about 0.9 ml to about 4 ml aqueous solution /Nalmefene hydrochloride (g), such as from about 1 ml to about 2 ml aqueous solution /Nalmefene hydrochloride (g), or about 1.5 ml aqueous solution / Nalmefene hydrochloride (g).

17. A method according to any one of claims 15-16, wherein heating in step (b) is performed to reach a temperature of about 50°C to about 100 °C, such as at about 50 °C to about 90 °C, or at about 70 °C to about 85°C.

18. A method according to any one of claims 15-17, wherein the solution in step (d) is cooled to a temperature between 40 to 50°C and seeding is performed at that temperature.

19. A method according to any one of claims 15-18, wherein the amount of seed crystal added in step (d) is from about 1/2000 (w/w) of seed crystal of Nalmefene hydrochloride / Nalmefene hydrochloride added in step (a), such as from about 1/1000 (w/w) of seed crystal or 1/200 of seed crystal of Nalmefene hydrochloride / Nalmefene hydrochloride added in step (a).

20. A method according to any one of claims 15-19, wherein the Nalmefene used for seeding is Nalmefene hydrochloride dihydrate.

21. A method according to any one of claims 15-20, wherein the seed crystal added in step (d) is obtained by a method according to claims 7-14.

22. A method according any one of claims 15-21, wherein the mixture obtained in step (d) comprising the seed crystal (s), is further subjected to:

(d') further cooling the mixture to temperature of about 0-5°C over a time period of about 45 minutes or more, and
(d") thereafter maintaining the mixture at a temperature of about 0-5°C for about 45 minutes or more,

before isolating the formed solid according to step (e) of claim 18.

23. A method according to any one of claims 15-22, wherein the solid formed is isolated at temperature of about 0-5°C in step (e) of claim 16.

24. A method according to any of claim 15-23, wherein the obtained compound has the following particle size distribution: D90 equal to or below 400 μm, D50 equal to or below 200 μm, D10 equal to or below 50 μm, with ratio D90/D50 equal to or below 2.5; as measured under the conditions given herein.

25. A method according to any one of claims 7-14 and 15-24, to obtain a compound as defined in any one of claims 1-6 for use in a pharmaceutical composition.

26. A method according any of claims 7-25, further comprising the steps of:

(i) optionally distillation of mother liquors obtained from the method defined in claim 7 or 15,
(ii) basification of the mother liquors obtained in step (i), or from the method defined in claim 7 or 15,
(iii) extracting the mixture with a suitable organic solvent,
(iv) adding hydrogen chloride, and
(v) isolating the formed solid.

27. A method according to claim 26 wherein the basification in step (ii) is performed until pH is in the range 8-10

28. A method according to claim 27, wherein the basification in step (ii) is performed until pH is in the range 8-9.

29. A method according to any one of claims 27-28, wherein the basification in step (ii) is performed with ammonium hydroxide.

30. A method according to any one of claims 27-29, wherein the solvents used in the extraction step (iii) are selected from the group comprising halogenated hydrocarbons, ethers, esters, ketones, more preferably dichloromethane, 2-methyl-tetrahydrofurane, ethyl acetate, 2-butanone, and more preferably dichloromethane

31. A method according to any one of claims 7-14, 15-25 and 26-30, wherein the obtained compound is at least 98% chemically pure, such as at least 99% chemically pure or at least 99.5% chemically pure.

32. A pharmaceutical composition comprising a compound as defined in any of claims 1-6.

33. A pharmaceutical composition according to claim 32, wherein Nalmefene hydrochloride dihydrate comprises at least 5% (w/w), such as at least 10% (w/w), at least 30%, at least 50% (w/w at least 70% (w/w), at least 90% (w/w), at least 95% (w/w), at least 99% (w/w), or 100% of the pharmaceutical dosage form.

34. A pharmaceutical composition according to any one of claims 32 or 33, further comprising one or more pharmaceutically acceptable carriers.

35. A pharmaceutical composition according to any one of claims 32-34, in a solid dosage form, such as a tablet, for oral administration.

36. A pharmaceutical composition according to any one of claims 32-35, comprising a compound according to any one of claims 1-6 in a therapeutically effective amount.

37. A pharmaceutical composition according to any one of claims 32-36 comprising a compound according to any one of claims 1-6 in an amount of about 10 mg to about 100 mg, such as about 10 mg to about 60 mg, about 10 mg to about 40 mg, or about 20 mg.

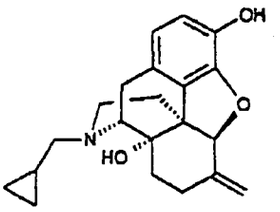
38. A method for producing a pharmaceutical composition according to any one of claims 32-37, comprising a method according to any one of claims 8-14 or 15-31.

39. A compound according to any of claims 1-6, for use in medicine.

40. A compound according to any one of claims 1-6, or a pharmaceutical composition according to any one of claims 32-37, for use in treatment of alcohol dependency.

Patentansprüche

1. Verbindung, dargestellt durch die Formel



$.HCl.2H_2O$

2. Verbindung nach Anspruch 1, wobei die Verbindung in kristalliner Form vorliegt.

3. Verbindung nach Anspruch 2, wobei die Verbindung in kristalliner Form durch ein Röntgenpulverdiffraktogramm in 2θ-Werten unter Verwendung von Cu $K_{\alpha 1}$-Strahlung mit einem Höchstwert bei 8,99 gekennzeichnet ist.

4. Verbindung nach Anspruch 3, wobei die Verbindung in kristalliner Form ferner durch ein Röntgenpulverdiffraktogramm in 2θ-Werten unter Verwendung von Cu $K_{\alpha 1}$-Strahlung mit einem Höchstwert bei einem oder mehreren von 10,63, 15,24, 16,55 und/oder 17,20 gekennzeichnet ist.

5. Verbindung nach einem der vorangehenden Ansprüche, die nichthygroskopisch ist, so dass weniger als 1 %, wie z. B. weniger als 0,5 %, wie z. B. weniger als 0,3 %, (Gew./Gew.) Feuchtigkeit absorbiert wird, wenn sie bei 25 °C einer relativen Feuchte von 95 % ausgesetzt ist.

6. Verbindung nach einem der vorangehenden Ansprüche, wobei bei einer relativen Feuchte von ca. 10 % bis ca. 95 % der Wassergehalt ca. 8 % bis ca. 9 % beträgt.

7. Verfahren zum Erhalt einer Verbindung nach einem der Ansprüche 1-6, das folgende Schritte umfasst:

   (1) Mischen von Nalmefenhydrochlorid (17-(cyclopropylmethyl)-4,5-α-epoxy-6-methylenmorphinan-3,14-diol-hydrochlorid) und wässriger Lösung wie z. B. Wasser,
   (2) optional, Erhitzen des Gemisches,
   (3) optional, Destillieren des Gemisches,
   (4) Rühren des Gemisches, bis die Umwandlung abgeschlossen ist, und
   (5) Isolieren des gebildeten Feststoffs.

8. Verfahren nach Anspruch 7, wobei das Gemisch bei (4) mindestens 1 Stunde lang gerührt wird.

9. Verfahren nach einem der Ansprüche 7 und 8, wobei das Verhältnis von wässriger Lösung wie z. B. Wasser, die in Schritt (1) verwendet wird, im Bereich von ca. 0,9 ml bis ca. 4 ml wässrige Lösung / Nalmefenhydrochlorid (g), wie z. B. von ca. 1 ml bis ca. 2 ml wässrige Lösung / Nalmefenhydrochlorid (g), bevorzugter 1,5 ml wässrige Lösung / Nalmefenhydrochlorid (g), liegt.

10. Verfahren nach einem der Ansprüche 7-9, wobei Nalmefenhydrochlorid, das in Schritt (1) verwendet wird, in hydratisierter Form wie z. B. Monohydrat-Form vorliegt.

11. Verfahren nach einem der Ansprüche 7-9, wobei Nalmefenhydrochlorid, das in Schritt (1) verwendet wird, in solvatisierter Form vorliegt oder ein Gemisch aus hydratisierten und solvatisierten Formen ist.

12. Verfahren nach einem der Ansprüche 7-11, wobei in Schritt (2) und/oder (3) gerührt wird.

13. Verfahren nach einem der Ansprüche 7-12, wobei das Rühren in Schritt (4) bei einer Temperatur von ca. 0 °C bis ca. 45 °C, wie z. B. von 20 °C bis ca. 40 °C, erfolgt.

14. Verfahren nach einem der Ansprüche 7-13, wobei der gebildete Feststoff in Schritt (5) bei einer Temperatur von ca. 0 °C bis ca. 20 °C, wie z. B. von ca. 0 °C bis ca. 5 °C, isoliert wird.

15. Verfahren zum Erhalt einer Verbindung nach einem der Ansprüche 1-6, das folgende Schritte umfasst

(a) Mischen von Nalmefenhydrochlorid (17-(cyclopropylmethyl)-4,5-α-epoxy-6-methylenmorphinan-3,14-diol-hydrochlorid) und wässriger Lösung wie z. B. Wasser,
(b) Erhitzen des Gemisches zum Erhalt einer im Wesentlichen homogenen Lösung,
(c) optional, Destillieren des bei (b) erhaltenen Gemisches,
(d) Kühlen der in Schritt (b) oder (c) erhaltenen Lösung, anschließend Impfen mit Nalmefenhydrochlorid, und
(e) Isolieren des gebildeten Feststoffs.

16. Verfahren nach Anspruch 15, wobei die Menge an wässriger Lösung wie z. B. Wasser, die in Schritt (a) verwendet wird, im Bereich von ca. 0,9 ml bis ca. 4 ml wässrige Lösung / Nalmefenhydrochlorid (g), wie z. B. von ca. 1 ml bis ca. 2 ml wässrige Lösung / Nalmefenhydrochlorid (g) oder ca. 1,5 ml wässrige Lösung / Nalmefenhydrochlorid (g), liegt.

17. Verfahren nach einem der Ansprüche 15-16, wobei das Erhitzen in Schritt (b) erfolgt, um eine Temperatur von ca. 50 °C bis ca. 100 °C, wie z. B. bei ca. 50 °C bis ca. 90 °C oder bei ca. 70 °C bis ca. 85 °C, zu erreichen.

18. Verfahren nach einem der Ansprüche 15-17, wobei die Lösung in Schritt (d) auf eine Temperatur zwischen 40 bis 50 °C abgekühlt wird und das Impfen bei dieser Temperatur erfolgt.

19. Verfahren nach einem der Ansprüche 15-18, wobei die Menge an Impfkristall, das in Schritt (d) zugegeben wird, ab ca. 1/2000 (Gew./Gew.) an Impfkristall aus Nalmefenhydrochlorid / Nalmefenhydrochlorid, das in Schritt (a) zugegeben wird, wie z. B. ab ca. 1/1000 (Gew./Gew.) an Impfkristall oder 1/200 an Impfkristall aus Nalmefenhydrochlorid / Nalmefenhydrochlorid, das in Schritt (a) zugegeben wird, beträgt.

20. Verfahren nach einem der Ansprüche 15-19, wobei das zum Impfen verwendete Nalmefen Nalmefenhydrochlorid-dihydrat ist.

21. Verfahren nach einem der Ansprüche 15-20, wobei der Impfkristall, der in Schritt (d) zugegeben wird, durch ein Verfahren nach den Ansprüchen 7-14 erhalten wird.

22. Verfahren nach einem der Ansprüche 15-21, wobei das in Schritt (d) erhaltene Gemisch, das den/die Impfkristall (e) umfasst, ferner wie folgt behandelt wird:

(d') weiteres Abkühlen des Gemisches auf eine Temperatur von ca. 0-5 °C über einen Zeitraum von ca. 45 Minuten oder mehr, und
(d") danach Halten des Gemisches bei einer Temperatur von ca. 0-5 °C für ca. 45 Minuten oder mehr,

bevor der gebildete Feststoff gemäß Schritt (e) von Anspruch 18 isoliert wird.

23. Verfahren nach einem der Ansprüche 15-22, wobei der gebildete Feststoff in Schritt (e) von Anspruch 16 bei einer Temperatur von ca. 0-5 °C isoliert wird.

24. Verfahren nach einem der Ansprüche 15-23, wobei die erhaltene Verbindung die folgende Teilchengrößenverteilung aufweist: D90 gleich oder unter 400 μm, D50 gleich oder unter 200 μm, D10 gleich oder unter 50 μm, mit einem Verhältnis D90/D50 gleich oder unter 2,5, gemessen unter den hierin angegebenen Bedingungen.

25. Verfahren nach einem der Ansprüche 7-14 und 15-24 zum Erhalt einer Verbindung wie in einem der Ansprüche 1-6 definiert zur Verwendung in einer pharmazeutischen Zusammensetzung.

26. Verfahren nach einem der Ansprüche 7-25, das ferner folgende Schritte umfasst:

(i) optional, Destillieren von Mutterlaugen, die aus dem Verfahren erhalten werden, das in Anspruch 7 oder 15 definiert ist,
(ii) Basischstellen der in Schritt (i) oder aus dem in Anspruch 7 oder 15 definierten Verfahren erhaltenen Mutterlaugen,
(iii) Extrahieren des Gemisches mit einem geeigneten organischen Lösungsmittel,
(iv) Zugeben von Chlorwasserstoff, und
(v) Isolieren des gebildeten Feststoffs.

27. Verfahren nach Anspruch 26, wobei das Basischstellen in Schritt (ii) erfolgt, bis der pH-Wert im Bereich von 8-10 liegt.

28. Verfahren nach Anspruch 27, wobei das Basischstellen in Schritt (ii) erfolgt, bis der pH-Wert im Bereich von 8-9 liegt.

29. Verfahren nach einem der Ansprüche 27-28, wobei das Basischstellen in Schritt (ii) mit Ammoniumhydroxid erfolgt.

30. Verfahren nach einem der Ansprüche 27-29, wobei die im Extraktionsschritt (iii) verwendeten Lösungsmittel ausgewählt sind aus der Gruppe umfassend halogenierte Kohlenwasserstoffe, Ether, Ester, Ketone, bevorzugter Dichlormethan, 2-Methyltetrahydrofuran, Ethylacetat, 2-Butanon und bevorzugter Dichlormethan.

31. Verfahren nach einem der Ansprüche 7-14, 15-25 und 26-30, wobei die erhaltene Verbindung mindestens zu 98 % chemisch rein, wie z. B. mindestens zu 99 % chemisch rein oder mindestens zu 99,5 % chemisch rein, ist.

32. Pharmazeutische Zusammensetzung, die eine Verbindung wie in einem der Ansprüche 1-6 definiert umfasst.

33. Pharmazeutische Zusammensetzung nach Anspruch 32, wobei Nalmefenhydrochloriddihydrat mindestens 5 % (Gew./Gew.), wie z. B. mindestens 10 % (Gew./Gew.), mindestens 30 %, mindestens 50 % (Gew./Gew.), mindestens 70 % (Gew./Gew.), mindestens 90 % (Gew./Gew.), mindestens 95 % (Gew./Gew.), mindestens 99 % (Gew./Gew.), oder 100 % der pharmazeutischen Arzneiform umfasst.

34. Pharmazeutische Zusammensetzung nach einem der Ansprüche 32 oder 33, die ferner einen oder mehrere pharmazeutisch akzeptable Träger umfasst.

35. Pharmazeutische Zusammensetzung nach einem der Ansprüche 32-34 in einer festen Arzneiform, wie z. B. als Tablette, zur oralen Verabreichung.

36. Pharmazeutische Zusammensetzung nach einem der Ansprüche 32-35, die eine Verbindung nach einem der Ansprüche 1-6 in einer therapeutisch wirksamen Menge umfasst.

37. Pharmazeutische Zusammensetzung nach einem der Ansprüche 32-36, die eine Verbindung nach einem der Ansprüche 1-6 in einer Menge von ca. 10 mg bis ca. 100 mg, wie z. B. ca. 10 mg bis ca. 60 mg, ca. 10 mg bis ca. 40 mg oder ca. 20 mg, umfasst.

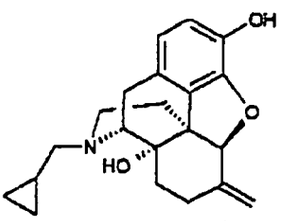
38. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung nach einem der Ansprüche 32-37, das ein Verfahren nach einem der Ansprüche 8-14 oder 15-31 umfasst.

39. Verbindung nach einem der Ansprüche 1-6 zur Verwendung in der Medizin.

40. Verbindung nach einem der Ansprüche 1-6 oder pharmazeutische Zusammensetzung nach einem der Ansprüche 32-37 zur Verwendung bei der Behandlung von Alkoholabhängigkeit.

Revendications

1. Composé représenté par la formule suivante :



$.HCl.2H_2O$

2. Composé selon la revendication 1, dans lequel le composé est sous forme cristalline.

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3. Composé selon la revendication 2, dans lequel le composé sous forme cristalline est **caractérisé par** un spectre de diffraction des rayons X sur poudre dont les valeurs 2θ, en utilisant la raie $K_{\alpha 1}$ du Cu, présentent un pic à 8,99.

4. Composé selon la revendication 3, dans lequel le composé sous forme cristalline est encore **caractérisé par** un spectre de diffraction des rayons X sur poudre dont les valeurs 2θ, en utilisant la raie $K_{\alpha 1}$ du Cu, présentent un pic à une ou plusieurs des valeurs 10,63, 15,24, 16,55 et/ou 17,20.

5. Composé selon l'une quelconque des revendications précédentes, présentant un caractère non hygroscopique de sorte qu'une quantité inférieure à 1 %, comme par exemple inférieure à 0,5 %, par exemple inférieure à 0,3 % p/p d'humidité est absorbée sous une exposition à une HR de 95 % à 25 °C.

6. Composé selon l'une quelconque des revendications précédentes, dans lequel la teneur en eau est d'environ 8 % à environ 9 % sous une humidité relative d'environ 10 % à environ 95 %.

7. Procédé pour obtenir un composé selon l'une quelconque des revendications 1 à 6, comprenant les étapes consistant à :

(1) mélanger du chlorhydrate de nalméfène (chlorhydrate de 17-(cyclopropylméthyl)-4,5-α-époxy-6-méthylènemorphinan-3,14-diol) et une solution aqueuse, comme de l'eau,
(2) éventuellement, chauffer le mélange,
(3) éventuellement, distiller le mélange,
(4) agiter le mélange jusqu'à ce que la transformation soit complète, et
(5) isoler le solide formé.

8. Procédé selon la revendication 7, dans lequel le mélange du point (4) est agité pendant au moins 1 heure.

9. Procédé selon l'une quelconque des revendications 7 et 8, dans lequel le rapport de la solution aqueuse, comme l'eau utilisée à l'étape (1), se situe dans la plage d'environ 0,9 ml à environ 4 ml de solution aqueuse/chlorhydrate de nalméfène (g), comme par exemple environ 1 ml à environ 2 ml de solution aqueuse/chlorhydrate de nalméfène (g), de préférence 1,5 ml de solution aqueuse/chlorhydrate de nalméfène (g).

10. Procédé selon l'une quelconque des revendications 7 à 9, dans lequel le chlorhydrate de nalméfène utilisé à l'étape (1) est sous forme hydratée, comme la forme monohydratée.

11. Procédé selon l'une quelconque des revendications 7 à 9, dans lequel le chlorhydrate de nalméfène utilisé à l'étape (1) est sous forme solvatée ou sous forme d'un mélange de formes hydratée et solvatée.

12. Procédé selon l'une quelconque des revendications 7 à 11, dans lequel l'agitation est effectuée à l'étape (2) et/ou (3).

13. Procédé selon l'une quelconque des revendications 7 à 12, dans lequel l'agitation à l'étape (4) est effectuée à une température d'environ 0 °C à environ 45 °C, comme par exemple de 20 °C à environ 40 °C.

14. Procédé selon l'une quelconque des revendications 7 à 13, dans lequel le solide formé à l'étape (5) est isolé à une température d'environ 0 °C à environ 20 °C, comme par exemple d'environ 0 °C à environ 5 °C.

15. Procédé pour obtenir un composé selon l'une quelconque des revendications 1 à 6, comprenant les étapes consistant à :

(a) mélanger du chlorhydrate de nalméfène (chlorhydrate de 17-(cyclopropylméthyl)-4,5-α-époxy-6-méthylènemorphinan-3,14-diol) et une solution aqueuse, telle que de l'eau,
(b) chauffer le mélange pour obtenir une solution sensiblement homogène,
(c) éventuellement, distiller le mélange obtenu au point (b),
(d) refroidir la solution obtenue à l'étape (b) ou (c), puis ensemencer celle-ci avec du chlorhydrate de nalméfène, et
(e) isoler le solide formé.

16. Procédé selon la revendication 15, dans lequel la quantité de solution aqueuse, comme l'eau utilisée à l'étape (a), se situe dans la plage d'environ 0,9 ml à environ 4 ml de solution aqueuse/chlorhydrate de nalméfène (g), comme

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par exemple d'environ 1 ml à environ 2 ml de solution aqueuse/chlorhydrate de nalméfène (g), ou d'environ 1,5 ml de solution aqueuse/chlorhydrate de nalméfène (g).

17. Procédé selon l'une quelconque des revendications 15 à 16, dans lequel le chauffage à l'étape (b) est effectué de manière à atteindre une température d'environ 50 °C à environ 100 °C, comme par exemple d'environ 50 °C à environ 90 °C, ou d'environ 70 °C à environ 85 °C.

18. Procédé selon l'une quelconque des revendications 15 à 17, dans lequel la solution de l'étape (d) est refroidie à une température comprise entre 40 et 50 °C et l'ensemencement est effectué à cette température.

19. Procédé selon l'une quelconque des revendications 15 à 18, dans lequel la quantité de cristal d'ensemencement ajouté à l'étape (d) représente environ 1/2000 (p/p) de cristal d'ensemencement de chlorhydrate de nalméfène/chlorhydrate de nalméfène ajouté à l'étape (a), comme par exemple environ 1/1000 (p/p) de cristal d'ensemencement ou 1/200 de cristal d'ensemencement de chlorhydrate de nalméfène/chlorhydrate de nalméfène ajouté à l'étape (a).

20. Procédé selon l'une quelconque des revendications 15 à 19, dans lequel le nalméfène utilisé pour l'ensemencement est un chlorhydrate de nalméfène dihydraté.

21. Procédé selon l'une quelconque des revendications 15 à 20, dans lequel le cristal d'ensemencement ajouté à l'étape (d) est obtenu par un procédé selon les revendications 7 à 14.

22. Procédé selon l'une quelconque des revendications 15 à 21, dans lequel le mélange obtenu à l'étape (d) comprenant le ou les cristaux d'ensemencement est également soumis à des étapes consistant à :

(d') refroidir encore le mélange à une température d'environ 0 à 5 °C sur une période de temps d'environ 45 minutes ou plus, et
(d") maintenir ensuite le mélange à une température d'environ 0 à 5 °C pendant environ 45 minutes ou plus,

avant d'isoler le solide formé selon l'étape (e) de la revendication 18.

23. Procédé selon l'une quelconque des revendications 15 à 22, dans lequel le solide formé est isolé à une température d'environ 0 à 5 °C à l'étape (e) de la revendication 16.

24. Procédé selon l'une quelconque des revendications 15 à 23, dans lequel le composé obtenu présente la distribution de taille particulaire suivante : D90 égal ou inférieur à 400 μm, D50 égal ou inférieur à 200 μm, D10 égal ou inférieur à 50 μm, avec un rapport D90/D50 égal ou inférieur à 2,5 ; comme mesuré dans les conditions mentionnés ici.

25. Procédé selon l'une quelconque des revendications 7 à 14 et 15 à 24, pour obtenir un composé tel que défini dans l'une quelconque des revendications 1 à 6 pour une utilisation dans une composition pharmaceutique.

26. Procédé selon l'une quelconque des revendications 7 à 25, comprenant en outre les étapes consistant à :

(i) distiller éventuellement les liqueurs mères obtenues selon le procédé défini dans la revendication 7 ou 15,
(ii) basifier les liqueurs mères obtenues à l'étape (i), ou issues du procédé défini à la revendication 7 ou 15,
(iii) extraire le mélange avec un solvant organique approprié,
(iv) ajouter du chlorure d'hydrogène, et
(v) isoler le solide formé.

27. Procédé selon la revendication 26, dans lequel la basification à l'étape (ii) est effectuée jusqu'à ce que le pH se situe dans la plage de 8 à 10.

28. Procédé selon la revendication 27, dans lequel la basification à l'étape (ii) est effectuée jusqu'à ce que le pH se situe dans la plage de 8 à 9.

29. Procédé selon l'une quelconque des revendications 27 à 28, dans lequel la basification à l'étape (ii) est effectuée avec de l'hydroxyde d'ammonium.

30. Procédé selon l'une quelconque des revendications 27 à 29, dans lequel les solvants utilisés à l'étape d'extraction

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(iii) sont sélectionnés dans le groupe comprenant des hydrocarbures halogénés, des éthers, des esters, des cétones, mieux encore le dichlorométhane, le 2-méthyl-tétrahydrofurane, l'acétate d'éthyle, la 2-butanone et, bien mieux encore, le dichlorométhane.

31. Procédé selon l'une quelconque des revendications 7 à 14, 15 à 25 et 26 à 30, dans lequel le composé obtenu est chimiquement pur à au moins 98 %, comme par exemple chimiquement pur à au moins 99 % ou chimiquement pur à au moins 99,5 %.

32. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 6.

33. Composition pharmaceutique selon la revendication 32, dans laquelle le chlorhydrate de nalméfène dihydraté constitue au moins 5 % (p/p), comme par exemple au moins 10 % (p/p), au moins 30 %, au moins 50 % (p/p), au moins 70 % (p/p), au moins 90 % (p/p), au moins 95 % (p/p), au moins 99 % (p/p) ou 100 % de la forme de dosage pharmaceutique.

34. Composition pharmaceutique selon l'une quelconque des revendications 32 ou 33, comprenant encore un ou plusieurs véhicules acceptables au plan pharmaceutique.

35. Composition pharmaceutique selon l'une quelconque des revendications 32 à 34, sous la forme d'un dosage solide, comme un comprimé, pour une administration orale.

36. Composition pharmaceutique selon l'une quelconque des revendications 32 à 35, comprenant un composé selon l'une quelconque des revendications 1 à 6 en quantité efficace au plan thérapeutique.

37. Composition pharmaceutique selon l'une quelconque des revendications 32 à 36 comprenant un composé selon l'une quelconque des revendications 1 à 6 en quantité d'environ 10 mg à environ 100 mg, comme par exemple d'environ 10 mg à environ 60 mg, d'environ 10 mg à environ 40 mg ou d'environ 20 mg.

38. Procédé pour produire une composition pharmaceutique selon l'une quelconque des revendications 32 à 37, comprenant un procédé selon l'une quelconque des revendications 8 à 14 ou 15 à 31.

39. Composé selon l'une quelconque des revendications 1 à 6, pour une utilisation en médecine.

40. Composé selon l'une quelconque des revendications 1 à 6, ou composition pharmaceutique selon l'une quelconque des revendications 32 à 37, pour une utilisation dans le traitement de la dépendance à l'alcool.

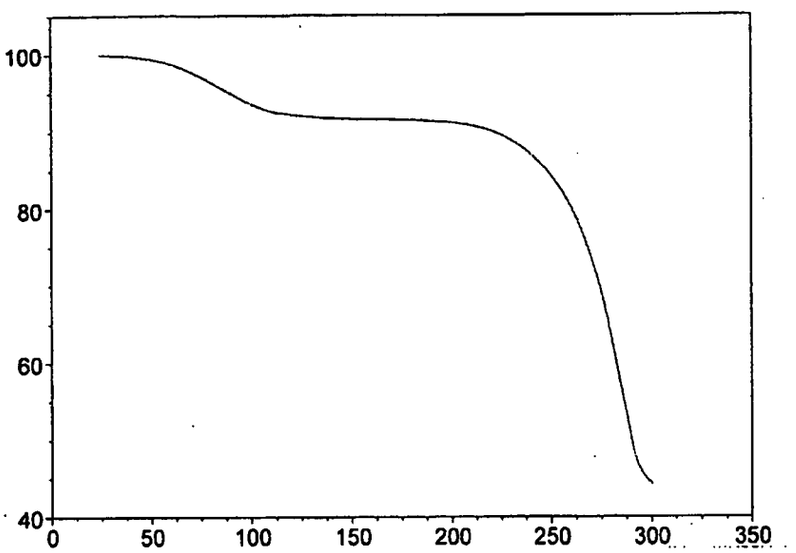

Figure 1

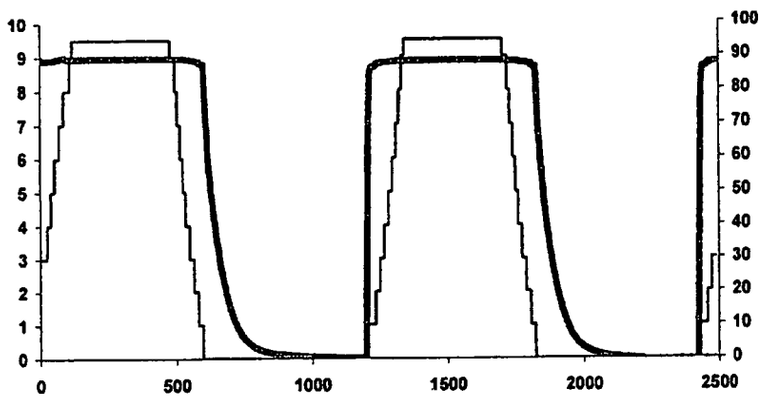
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Figure 2

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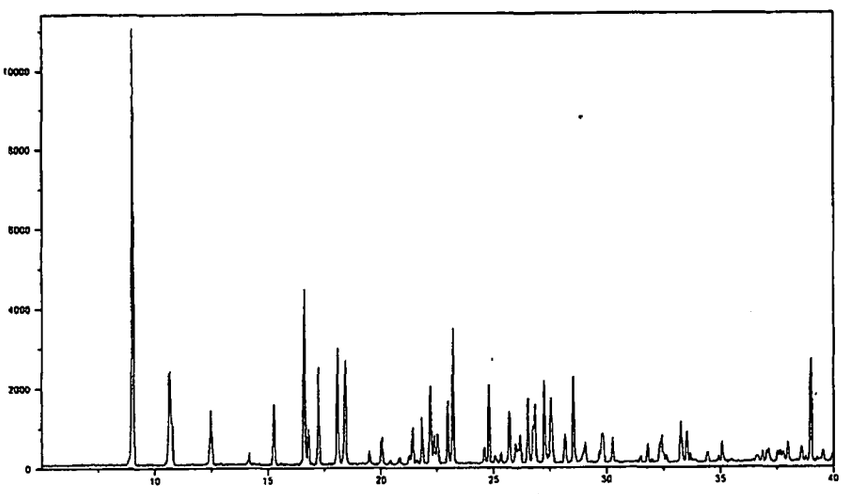

Figure 3

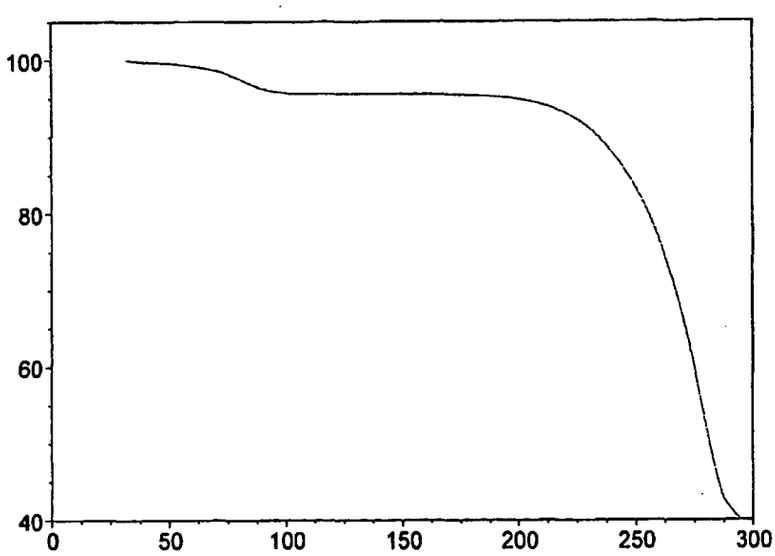

Figure 4

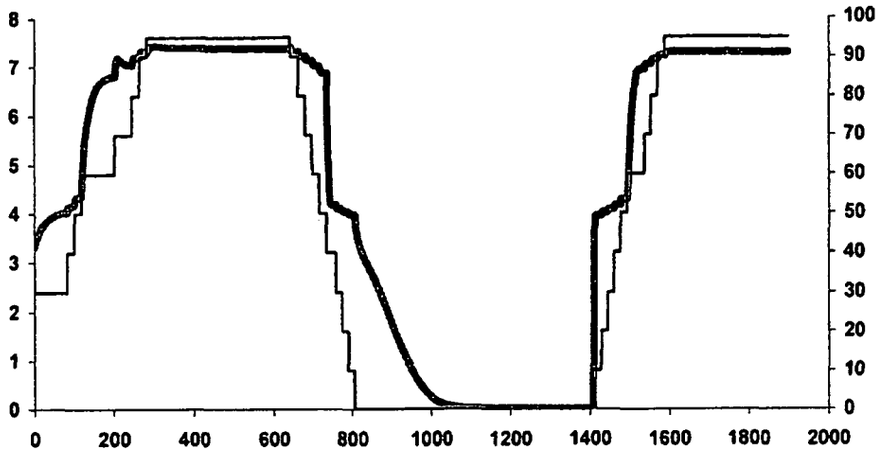
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Figure 5

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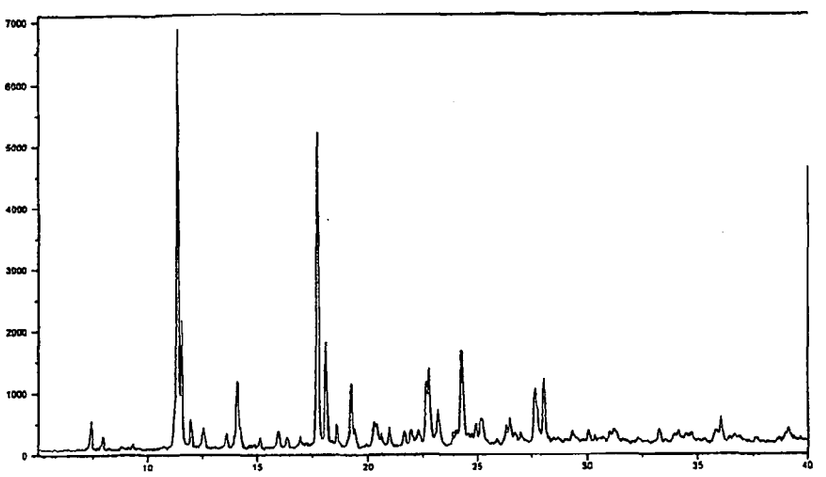

Figure 6

REFERENCES CITED IN THE DESCRIPTION

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