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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-090985- -00011-0000

Fecha: 2015-04-23 16:28:07 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 412 REPOSPRESRECU Folios: 25

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Trámite: 11

Evento: 378

Actuación: 412

Re: PI.-ASTRAZENECA AB Y NEKTAR THERAPEUTICS.-Solicitud de Patente de Invención en Fase Nacional PCT para "SALES CRISTALINAS DE OXALATO Y FOSFATO DE mPEG7-O-NALOXOL Y MÉTODO PARA SU PRODUCCIÓN".- Clase A61K 31/485.-Expediente número 13-090.985.-

Yo, **ALICIA LLOREDA RICAURTE**, mayor, vecina de esta ciudad, identificada con la cédula de ciudadanía número 39.690.713 de Usaquén, Representante Legal en Bogotá para todos los asuntos relacionados con la Propiedad Industrial de las sociedades **ASTRAZENECA AB Y NEKTAR THERAPEUTICS**, organizadas y existentes de conformidad con las leyes de Suecia y Estado de Delaware, Estados Unidos de América, y domiciliadas en Södertälje, Suecia y San Francisco, Estado de California, Estados Unidos de América respectivamente, atentamente manifiesto a usted que interpongo **RECURSO DE REPOSICIÓN** contra la Resolución Número **11321** dictada por el señor Superintendente de Industria y Comercio el 13 de Marzo de 2015 y notificada por fijación en lista el 17 de Marzo de 2015, por medio de la cual se niega el privilegio de patente solicitado para la invención contenida en el expediente de la referencia.

I. FUNDAMENTOS DE DERECHO

Como fundamento de mi recurso, me permito manifestar ante ese Despacho que el contenido de la Resolución Número **11321** evidencia que durante el examen técnico realizado a la solicitud denegada se realizó una evaluación incorrecta del objeto de la invención allí reclamada, sin considerarse su real alcance e importancia. En este sentido, no se consideró el verdadero y valioso aporte técnico que representa para el arte en cuestión la sal cristalina de tipo oxalato de mPEG₇-O-naloxol y el correspondiente método para su obtención, revelados en la solicitud denegada.

Es así que, a pesar de los argumentos proporcionados por el solicitante en mi memorial del 19 de noviembre de 2014 (en respuesta al Oficio No. **10463**), en la Resolución impugnada este Despacho mantiene las objeciones frente al Nivel Inventivo de la solicitud, argumentando básicamente que:

"(...) La solución al problema técnico planteado por la invención reclamada se considera obvia porque la anterioridad D2 divulga muchos sólidos con actividad farmacológica pueden exhibir polimorfismo (...) En consecuencia, la formación de sales con finalidad de modificar las propiedades fisicoquímicas y termodinámicas de los compuestos farmacéuticos ya se había discutido en D2 (págs. 79 y 80 (...))."

Además, el señor Examinador resalta que:

"(...) 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 polimorfismo y formación revelados en D2 al compuesto de fórmula (1), con el fin de determinar la existencia de una forma cristalina y amorfa para este compuesto tal como la reivindicada".

En este sentido, concluye que:

"(...) las sales cristalinas de la reivindicación 1 y los cristales de la sal fosfato de la reivindicación 8 junto con sus dependientes y las composiciones que las contienen carecen de nivel inventivo".

Con relación a las reivindicaciones 2 y 3, el señor Examinador afirma que:

"(...) la persona del oficio normalmente versada en la materia, frente a la necesidad de obtener sales del compuesto PEG-naloxol, utilizaría la técnica de formación de sales por reacción ácido base durante la recristalización, como lo sugiere la anterioridad D3, en el compuesto previamente divulgado en D1 para proporcionar así un proceso como el reclamado. En consecuencia, las reivindicaciones 2 y 3 carecen de nivel inventivo".

Por consiguiente, a continuación me permito brindar argumentos técnicos para no sólo demostrar ante ese Despacho que el nuevo capítulo reivindicatorio que se presenta junto con el presente recurso cumple a cabalidad con el nivel inventivo exigido por el artículo 18 de la Decisión 486 de 2000, sino además para establecer que la invención ha sido interpretada de manera errónea a la luz de los documentos del arte previo.

1. MODIFICACIONES AL CAPITULO REINVIDICATORIO.

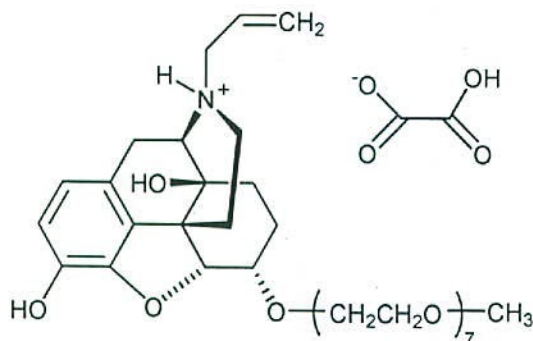
Inicialmente y en razón de defender la patentabilidad de la presente solicitud denegada, me permito manifestar que el solicitante ha decidido **eliminar la reivindicación 8** del capítulo reivindicatorio actualmente modificado. Frente a esto, me permito señalar que dicha modificación cumple con el propósito de restringir el alcance de la materia reclamada y así permitir una mayor diferenciación de la invención de la solicitud denegada con el estado del arte previo.

De acuerdo a lo anterior, el mencionado **capítulo reivindicatorio modificado queda constituido por 7 reivindicaciones**, la cuales no constituyen de ninguna manera una ampliación al alcance de la solicitud original y cuenta con pleno sustento en las enseñanzas de la descripción. Con lo anterior, me permito reiterar que dicho capítulo cumple a cabalidad con las disposiciones de patentabilidad establecidas en el Artículo 34 de la Decisión 486 de 2000.

2. PRINCIPALES CARACTERÍSTICAS DE LA INVENCIÓN DENEGADA.

Con el fin de contextualizar los motivos por los cuales ese Despacho realiza una incorrecta valoración y evaluación del arte previo, me permito señalar a continuación las principales características y ventajas técnicas asociadas a la materia revelada en la solicitud de patente negada.

En vista del capítulo reivindicatorio modificado anexo a este memorial, la presente solicitud reclama de manera específica y exclusiva una sal cristalina de tipo oxalato de mPEG₇-O-naloxol y un método para producir dicha sal, la cual comprende una especie iónica de mPEG₇-O-naloxol y ácido oxálico con la siguiente fórmula:



Con relación a las características esenciales de la sal cristalina reclamada en la Resolución impugnada, considero importante resaltar ante ese Despacho que su caracterización cumple con los requerimientos necesarios para definir las características técnicas de un polimorfo. En este sentido, la reivindicación 1 presenta los valores d (Å) de los picos de difracción de rayos X en polvo (DRXP) de la forma B, los cuales comprenden 13.2; 12.0; 7.9; 7.4; 7.0; 6.6; 6.0; 5.7; 5.6; 5.4; 5.2; 5.1; 4.91; 4.86; 4.78; 4.71; 4.48; 4.44; 4.39; 4.17; 4.09; 3.95; 3.91; 3.88; 3.69; 3.63; 3.43; 3.29; 3.14; y 3.01.

Ahora, con respecto a los beneficios de la presente invención, me permito traer a colación que el descubrimiento de una forma cristalina (*sólida*) del compuesto naloxol tiene un impacto significativo no sólo en la estabilidad y en la vida útil del compuesto sino también en la manufacturabilidad de la sustancia y el producto farmacológico que incluya el compuesto.

Frente a la anterior consideración, es de resaltar que, en los estudios de estabilidad de la forma B de la sal de tipo oxalato de mPEG₇-O-naloxol (*forma cristalina* obtenida) en comparación con la base libre de mPEG₇-O-naloxol, "no se observó ningún cambio de la forma en estado sólido con el tiempo para ninguna de las muestras en polvo" ni se observó que "las impurezas asociadas a la sal aumentarán" (Página 51 de la memoria descriptiva). Lo anterior contribuye a soportar la idea que el polimorfo obtenido presenta una estabilidad adecuada, lo cual lo convierte en un potencial candidato -antagonista opioide- en la terapia eficaz para el control del dolor.

A la luz de las anteriores consideraciones, me permito concluir ante ese Despacho que la sal cristalina de tipo oxalato de mPEG₇-O-naloxol de la solicitud denegada, constituye un novedoso polimorfo que dispone de una forma sólida y termodinámicamente estable al ser expuesto al aire. Dichas características técnicas esenciales de la forma cristalina particular se evidencian a lo largo de la descripción de la solicitud, particularmente en los ejemplos realizados.

3. CONSIDERACIONES TÉCNICAS FRENTE A LAS ENSEÑANZAS DEL ARTE PREVIO

Ahora, teniendo en cuenta el alcance del nuevo capítulo reivindicatorio de la invención en cuestión, me permito manifestar ante ese Despacho que la sal cristalina de tipo oxalato de mPEG₇-O-naloxol y su correspondiente método de obtención en la solicitud de patente denegada presentan un inequívoco nivel inventivo frente a las enseñanzas de los documentos **Eldon et al., "NKTR-118 (Oral PEG-Naloxol), a PEGylated Derivative of Naloxone: Demonstration of Selective Peripheral Opioid Antagonism After Oral Administration in Preclinical Models"** (Poster Presentation, September 2007 (D1), **H.G. Brittain, "Polymorphism in Pharmaceutical Solids", Second Ed., Informa Healthcare, NY, 2009 (D2)** y **Berge, S. M. et al., "Pharmaceutical Salts" (Review Article), Journal of Pharmaceutical Sciences, 66:1, pgs. 2 to 10, 1997 (D3).**

En la Resolución aquí impugnada, el señor Examinador considera que el particular polimorfo reclamado y su correspondiente método de obtención en la solicitud no tienen nivel inventivo puesto que, a la luz de las enseñanzas de los documentos D1, D2 y D3, la persona del oficio normalmente versada en la materia podría derivar de manera evidente el objeto de las reivindicaciones 1, 2 y 3 de la solicitud.

Frente a tal consideración, **me permito sostener que las enseñanzas de los documentos D1, D2 y D3, solas o en combinación, de ninguna manera anticipan o sugieren de manera obvia la sal cristalina de tipo oxalato de mPEG₇-O-naloxol y su correspondiente método de obtención con todas y cada una de las características técnicas estructurales y funcionales, tal y como se reclaman en el capítulo reivindicatorio modificado que se presenta junto con este memorial.**

Con el ánimo de demostrar ante ese Despacho que la anterior afirmación es completamente correcta, a continuación me permito presentar las siguientes consideraciones técnicas:

3.1. La sal cristalina de tipo oxalato del compuesto mPEG₇-O-naloxol y su correspondiente método de obtención de la presente invención constituyen una solución novedosa e inventiva al problema técnico objetivo

De conformidad con lo señalado por el señor Examinador en la Resolución Número **11321**, el documento D1 divulga el compuesto naloxona-PEG, el cual se absorbe rápidamente luego de su administración oral con elevada selectividad periférica antagonista opioide y con adecuada seguridad y perfil farmacocinético.

Específicamente, el documento D1 se relaciona a presentar los resultados de una investigación sobre el potencial antagonista del compuesto NKTR-118 y sobre su rol en el bloqueo del efecto constipativo periférico de la morfina sin afectar el poder analgésico de la misma. Efectivamente, el documento D1 revela que la administración oral de NKTR-118 tiene un perfil seguro y favorable en relación a su farmacocinética en estudios en modelos preclínicos. Asimismo, D1 concluye que futura investigación es necesaria establecer el potencial de la administración oral de NKTR-118 en el tratamiento para constipación inducida por opioides y otras manifestaciones relacionas.

Por otro lado, los documentos D2 y D3 presentan temas relacionados a la naturaleza y métodos de polimorfismos y sales farmacéuticas. Concretamente, el documento D2 demuestra la capacidad de varios compuestos de exhibir polimorfismo, los cuales pueden dar lugar a formas cristalinas con diferentes propiedades fisicoquímicas. Asimismo, dicho documento D2 describe diversas técnicas que permiten la obtención de diversos polimorfos y las tecnologías que permiten su caracterización.

Esencialmente, el documento D3 constituye un artículo de revisión académica que enseña los efectos químicos, biológicos, físicos y económicos que pueden obtenerse al convertir un compuesto farmacéutico en una sal. Dicha revisión analiza la literatura académica de los últimos 25 años y se enfoca en presentar comparaciones entre las propiedades de diferentes formas salinas del mismo compuesto. El documento D3 cumple con presentar una vista generalizada de las propiedades de diferentes sales e incluir información útil para la selección racional de una forma salina apropiada.

Ahora bien, a la luz de las anteriores enseñanzas, el señor Examinador mantiene su opinión sobre la obviedad de la presente invención, argumentando inicialmente que el problema técnico objetivo de esta solicitud consiste en "*¿cómo desarrollar las sales e identificar las formas polimórficas del compuesto mPEG₇-O-naloxol previamente divulgado en D1?*".

En este sentido, el señor Examinador insiste que "(...) las sales cristalinas reivindicadas son el resultado de un trabajo rutinario o habitual, en el cual el cometido inicial del investigador consiste en determinar si el compuesto de la solicitud puede existir en formas salinas con propiedades físicas diferentes y a su vez en otras formas cristalinas, mediante la aplicación de técnicas conocidas como las divulgadas en D2 y D3".

Ante lo anterior, muy amablemente me permito señalar que, contrario a lo que afirma el señor Examinador, el verdadero problema técnico objetivo resuelto por la presente solicitud consiste en proporcionar formas sólidas y estables (sean cristalinas o amorfas) de conjugados de naloxol-polietilenglicol. En este sentido, el problema técnico a superar en ningún momento se refiere a simplemente identificar o caracterizar polimorfos del compuesto en cuestión sino se busca resolver la falta de dichas formas sólidas, lo cual se justifica en la memoria descriptiva de la solicitud de la siguiente manera:

"Se suelen preferir las formas sólidas de una sustancia farmacológica por su comodidad a la hora de formular el producto farmacológico. Hasta la fecha no se dispone de ninguna forma sólida de la sustancia farmacológica mPEG₇-O-naloxol, que actualmente se comercializa y aísla como un aceite en forma de base libre (...) No se ha observado que la forma de base libre de mPEG₇-O-naloxol forme una fase cristalina incluso cuando se enfría hasta -60 °C y se ha observado que existe en forma vítrea con una temperatura de transición de aproximadamente -45 °C. Además, mPEG₇-O-naloxol en su forma de base libre puede sufrir una degradación oxidativa cuando se expone al aire. Se pueden tomar precauciones a la hora de manipular la base libre, por ejemplo, almacenándola en atmósfera de gas inerte, para evitar su degradación. No obstante, sería deseable disponer de una forma sólida de mPEG₇-O-naloxol, preferentemente una que fuera estable cuando se mantuviera expuesta al aire".
(Resaltado fuera del texto - Página 2 de la memoria descriptiva).

Frente a lo anterior, es evidente que existe la necesidad de obtener una forma sólida del compuesto mPEG₇-O-naloxol dado que en el estado no se dispone de ninguna. En realidad, esta consideración abarca de igual manera los documentos D1, D2 y D3 presentados por el señor Examinador, los cuales no divulgan ni sugieren formas sólidas y estables de mPEG₇-O-naloxol o los métodos para su producción.

Ahora, habiendo definido correctamente el problema técnico objetivo a resolver, se puede hacer una valoración adecuada de la solución propuesta por la invención de la solicitud. Respecto a lo anterior, me permito señalar que, en relación con el examen de nivel inventivo de polimorfos, la Guía para Examen de Solicitudes de Patente de Invención y Modelo de Utilidad, en su numeral 3.4.7, establece que "(...) teniendo en cuenta la información incluida en la descripción de la solicitud y la información aportada por el solicitante, se debe verificar que el problema técnico objetivo se resuelve con la obtención de la estructura cristalina del compuesto".

Efectivamente, **la presente solicitud logra proporcionar una estructura cristalina y estable del compuesto mPEG₇-O-naloxol, resolviendo así el problema técnico objetivo y proponiendo una alternativa sólida para su uso en un producto farmacológico útil en el tratamiento y control del dolor junto con analgésicos opioides.**

Contrario al "*trabajo rutinario y habitual*" descrito por el señor Examinador, la obtención de dicho particular polimorfo fue el resultado de la evaluación de más de 40 ácidos, en donde se determinó el contraíón adecuado para producir una formula solida estable del conjugado (Ejemplo 6.1 y Tabla 1, páginas 31 a 39). Es más, usando diferentes disolventes juntos a estos potenciales contraiones, se evaluaron más de 400 combinaciones diferentes de ácido/disolvente en experimentos a pequeña escala y a gran escala (Ejemplos 6.1 y 6.2).

Frente a lo anterior, los resultados de los experimentos a pequeña escala, ilustrados en las Tablas 2 a 4, demuestran que, de lejos, la mayoría de combinaciones de ácido/disolvente fallaron al producir una forma sólida estable y viable del compuesto en cuestión.

Similarmente, se observó que la base libre de mPEG₇-O-naloxol tampoco produjo ninguna forma sólida viable del compuesto (Pág. 35, líneas 5 a 8). En experimentos de escalado (Ejemplo 6.2), de 10 ácidos seleccionados para intentar producir sales cristalinas de mPEG₇-O-naloxol bajo varias condiciones, "*(...) en la mayoría de los casos, la mezcla de mPEG₇-O-naloxol y ácido en el disolvente proporcionó una solución transparente*" (Página 39). Junto con las anteriores consideraciones, dichos resultados demuestran lo impredecible que sería obtener con éxito las formas sólidas del compuesto en cuestión. Además, es pertinente señalar que dichos resultados tampoco hubiesen podido ser predichos por las enseñanzas de los documentos D1, D2 y/o D3.

Ahora bien, a pesar de las dificultades de la preparación de mPEG₇-O-naloxol en forma sólida/cristalina y estable, los estudios de estabilidad descritos en el Ejemplo 6.4 (página 49) y los resultados de dichos estudios ilustrados en la Tabla 8 (página 50) demuestran que **la Forma B de la sal de tipo oxalato de mPEG₇-O-naloxol tiene una estabilidad superior a los compuestos divulgados en el arte previo** dado que produce menos ppm del compuesto glicidaldehído, el cual es un producto propio de la degradación oxidativa.

Consecuentemente, es claro que ninguna de las enseñanzas de los documentos citados en el estado del arte sugiere a la persona medianamente versada en la materia las condiciones específicas para lograr derivar de manera obvia una forma sólida de mPEG₇-O-naloxol. Es así, como los resultados obtenidos, expuestos a lo largo de la memoria descriptiva, demuestran que no es posible obtener de manera evidente una sal viable para

numerosas combinaciones de ácido/disolvente y base libre ensayados, lo que claramente demuestra la imprevisibilidad en la producción de mPEG₇-O-naloxol sólido.

3.2. Las condiciones específicas para la obtención de una forma cristalina y estable del compuesto mPEG₇-O-naloxol, no son reveladas en ninguna de las enseñanzas del estado del arte previo.

Respondiendo a lo sostenido por el señor Examinador en la Resolución aquí impugnada, si bien el documento D2 *"divulga de manera extensiva las técnicas de obtención de sales, cristales y los métodos de caracterización de los mismos (...)"*, D2 en realidad no da información alguna sobre las condiciones específicas para obtener la sal cristalina del compuesto mPEG₇-O-naloxol. Es evidente que las técnicas y los métodos para su obtención son conocidos en el estado anterior de la técnica; sin embargo, las específicas condiciones para la obtención de un sólido estable y viable –las cuales son el aspecto novedoso de la presente invención- no son sugeridas ni mucho menos divulgadas por ningún documento del estado del arte previo.

En la Resolución aquí impugnada, el señor Examinador sostiene que los resultados presentados en la especificación *"no evidencian una ventaja o superioridad real de las formas cristalinas reivindicadas, debido a que los resultados presentados corresponden a la determinación de una propiedad física, como lo es la estabilidad del sólido, lo cual corresponde a parte de los estudios comunes de pre-formulación que buscan identificar las formas cristalinas y polimorfos del producto"*.

Sin embargo, y contrario a lo que sugiere el señor Examinador, los resultados que se incluyen en la descripción de la presente solicitud demuestran ampliamente la existencia de una forma física del compuesto mPEG₇-O-naloxol que no había estado disponible previamente, lo cual, en sí, representa una ventaja inesperada y novedosa. Además, la forma B reivindicada de la sal tipo oxalato, de acuerdo a los resultados del Ejemplo 6.4, es superior con respecto a la estabilidad de la forma base libre del arte previo dado que la forma de la invención es menos susceptible a degradación oxidativa. Todo lo anterior tiene un impacto significativo con relación a su manejo, como por ejemplo al formular un producto farmacéutico.

Por otro lado, el señor Examinador afirma que *"la solución al problema técnico planteado"* se considera obvia porque *"la anterioridad divulga que muchos sólidos con actividad farmacológica que pueden exhibir polimorfismo (...)"* (resaltado fuera del texto). No obstante, me permito sostener que nada en el documento D2 sugiere o revela información relacionada a la solución de obtener, de manera exitosa, una forma sólida y estable de mPEG₇-O-naloxol.

En realidad, cualquier discusión en el documento D2 sobre polimorfismos no es relevante para el examen de patentabilidad de la presente solicitud puesto que la base libre de mPEG₇-O-naloxol es, a temperatura ambiente, un aceite. Ante esto y como se ha explicado anteriormente, la descripción de la presente solicitud se encuentra repleta de ejemplos de contraiones que no son útiles para formar una sal sólida del compuesto en cuestión. Es así que me permito manifestar que se refuta el hecho de que *muchos sólidos* del específico compuesto mPEG₇-O-naloxol pueden presentar polimorfismos (*sales cristalinas, en este caso*).

Ahora, el señor Examinador además afirma que el documento D2 enseña que: a) las sales de medicamentos son usualmente utilizadas para incrementar la solubilidad de los productos farmacéuticos en el agua, b) los agentes formadores de sales se determinan empíricamente, y c), junto al documento D3, *"la lista de sales farmacéuticas aceptadas es ampliamente conocida"*. Ante esto, me permito señalar que cualquier discusión sobre solubilidad en los documentos D2 o D3 no es de particular relevancia para la presente aplicación ya que el compuesto mPEG₇-O-naloxol es fácilmente soluble en agua.

Efectivamente, la tabla I de la página 2 de D3 presenta alrededor de 53 sales aniónicas y 14 sales catiónicas bajo el título de *"FDA-Approved Commercially Marketed Salts"*. Sin embargo, en ningún lugar de esa tabla o en ningún lugar del artículo existe algún indicio o guía sobre cuál combinación de sal y disolvente sería útil para producir una forma sólida de una sustancia que es aceite a temperatura ambiente. Mucho menos, dicho documento D2 divulga dicha información para producir específicamente una forma sólida de mPEG₇-O-naloxol. En realidad, el punto central de la discusión es verificar que exista sugerencia o mención alguna sobre las condiciones exactas para la obtención de la forma sólida del compuesto y el análisis no se debe basar en la existencia de técnicas generalizadas para identificar y caracterizar polimorfos.

Frente a todas las anteriores consideraciones, me permito expresar que es relativamente sencillo producir sales alternativas del compuesto mPEG₇-O-naloxol. No obstante, los numerosos fracasos relacionados a las combinaciones de sal y disolvente, descritas en las Tablas 2 a 4 de la descripción, indican que era impredecible identificar la sal -si alguna- que sería útil para producir una forma sólida de dicho compuesto.

Consecuentemente, **me permito sostener que nada en las enseñanzas de los documentos D1, D2, o D3 habría motivado a la persona versada en la materia para seleccionar específicamente el contraión de oxalato con la razonable expectativa de obtener una forma cristalina de mPEG₇-O-naloxol.**

3.3. Ni la forma sólido del compuesto mPEG₇-O-naloxol, ni el correspondiente método de producción son materia obvia o evidente a la luz de las enseñanzas del arte previo.

En el mismo análisis, el señor Examinador objeta el método de obtención de la sal tipo oxalato de mPEG₇-O-naloxol definido en las reivindicaciones 2 y 3 actualmente presentadas. En este sentido, el señor Examinador revela que *"el problema técnico objetivo que pretende resolver esta invención se puede formular así: ¿cómo aplicar las técnicas de formación de sales divulgadas en el estado de la técnica para identificar las formas salinas alternativas del compuesto PEG-naloxol?"*.

Tal y como se discutió en los anteriores literales, el punto de la presente solicitud no es simplemente identificar o caracterizar formas salinas. En realidad, el problema técnico a resolver con la invención es ¿cómo se pueden obtener formas sólidas de conjugados naloxol-polietileno? Frente a esto, el mismo señor Examinador reconoce que *"las condiciones requeridas para preparar los polimorfos hasta ahora desconocidos de ninguna manera son obvias"*. Consecuentemente, ninguna enseñanza de D1, D2 o D3 sugiere algún método que use contraiones y disolventes, como los definidos en las reivindicaciones 2 y 3, para producir exclusivamente una forma cristalina de mPEG₇-O-naloxol.

Con relación al método de obtención de sales cristalinas, me permito explicar que, mientras bastantes compuestos orgánicos se conocen en su forma cristalina –incluyendo ciertos oploides-, compuesto con un grado alto de libertad molecular (*flexibilidad*) no tienden a ser compuestos cristalinos. La razón de ello es el impedimento termodinámico requerido para impartir suficiente orden en la molécula y asociarla con otras moléculas en de una manera organizada para formar cristales.

Un excelente ejemplo de lo anterior sería la situación con los alcanos de alto grado, los cuales, a pesar de tener pesos moleculares similares a otros compuestos cristalinos, se encuentran generalmente como sustancias aceitosas o ceras. Por ejemplo, el ácido benzoico, de fórmula molecular C₇H₆O₂, es cristalino con un punto de fusión de aproximadamente 123°C. En contraste, el ácido heptanoico, el cual es más pesado (C₇H₁₄O₂) y tiene mayor flexibilidad molecular, es líquido a temperatura ambiente. En el caso de la invención de la solicitud, naloxol es un opioide PEGilado y la adición de la cadena PEG altamente flexible lo convierte en un compuesto no cristalino. Consecuentemente, la base libre de naloxol es un líquido viscoso.

Ahora, se esperaría que, la flexibilidad molecular que determina que la forma no-cristalina de una base libre, también determine que cualquier sal de naloxol se encuentre en forma no-cristalina. Por lo tanto, se esperaría que la probabilidad de encontrar una sal cristalina de naloxol sea razonablemente baja. Lo anterior se evidencia claramente en los ejemplos incluidos en la descripción de la presente solicitud. Como ya se mencionó, un gran

número de sales fueron estudiadas usando una variedad de sales formando ácidos en varios disolventes un con un amplio rango de estequiometría. Con relación a los resultados, se encontró que muy pocas sales fueron exitosamente obtenidas y asiladas en estos experimentos, donde únicamente las sales de tipo oxalato y fosfato mostraron la forma sólida más prometedora.

Frente a la base libre de naloxol, dicho compuesto tiene una propensión a la degradación oxidativa, por lo que se requiere de procedimientos de manufactura y contenedores excepcionales para su manejo y almacenamiento. Es preciso resaltar que dicha inestabilidad oxidativa no es inmediatamente aparente, lo cual requiere experimentación significativa para entenderla. Por lo tanto, es improbable que dicho fenómeno pueda ser predicho por un químico practicante.

Asimismo, la forma física de naloxol presentó desafíos a la manufacturabilidad de tabletas de naloxol dado que operaciones de procesamiento a larga escala con un líquido altamente viscoso son difíciles de realizar. **Es por esto que el descubrimiento y obtención una sal cristalina de naloxol no sólo otorga una estabilidad mejorada al compuesto en cuestión sino también incrementa significativamente la manufacturabilidad de las sustancias y productos farmacológicos.**

En síntesis, me permito expresar que no se puede esperar que todos los compuestos presenten una forma cristalina, en especial aquellos que tienen un grado alto de flexibilidad molecular. Similarmente, tampoco se puede esperar que las sales de moléculas con dicho grado alto de flexibilidad molecular sean cristalinas. Por lo tanto, la obtención de una forma sólida de naloxol –después de una extensa experimentación– representa la superación de dificultades nos resueltas por técnicas rutinarias y la solución al problema técnico con éxito.

Ahora, tal y como expresa la Guía para Examen de Solicitudes de Patente de Invención y Modelo de Utilidad, en su numeral 3.4.7, "(...) *si no hay indicaciones en el estado de la técnica que pudieran inducir a la persona del oficio normalmente versada en la materia técnica, enfrentada al problema técnico de obtener una forma física alternativa de un compuesto conocido o modificar el polimorfo o el producto conocido para lograr un polimorfo tal como el reivindicado, entonces la invención no es obvia (...)*".

Como se ha venido argumentado, en el estado de la técnica anterior se presentan métodos y procedimientos para identificar y caracterizar polimorfos de compuestos conocidos. Sin embargo, no existe indicación alguna sobre las condiciones específicas y necesarias para lograr la forma cristalina y estable del compuesto mPEG₇-O-naloxol. **Siendo que no hay algún conocimiento en el estado de la técnica que pudiera conducir a la persona versada en la materia a la sal cristalina tipo oxalato de dicho compuesto reivindicado, me permito manifestar que el polimorfo tiene nivel inventivo.**

Ahora bien, el punto no es si un experto en la materia podría haber llegado a la invención mediante la adaptación o modificación de las enseñanzas del documento D2 o D3 sino que, si lo hubiera hecho de esa manera, ¿por qué dichas enseñanzas le motivaron a hacerlo con la expectativa de resolver el problema técnico objetivo?

Es más, **¿qué razón tendría la persona versada en la materia para que, a la luz del problema resuelto por la presente invención, decidiera aplicar las técnicas o enseñanzas de D2 y/o D3 de manera que se obtuviera la forma cristalina estable de naloxol, y no otro tipo de polimorfo?**

En conexión con lo anterior, muy respetuosamente me permito señalar que la única motivación que tendría la persona versada en la materia para hacer esta particular modificación sería la revelación hecha por la presente invención, por lo que el análisis de nivel inventivo realizado por el Señor Examinador está enmarcado dentro de lo que en el ámbito de las patentes se conoce como "*hindsight*" o análisis "*Ex post facto*".

En este sentido, vale la pena resaltar que, al tener conocimiento de la invención, es de esperarse que las enseñanzas particulares de D2 y D3, aplicadas a D1, parezcan obvias, toda vez que ya se sabe de antemano que efectivamente estas técnicas resuelven el problema planteado. Sin embargo, la información específica sobre las condiciones para obtener el particular polimorfo no era conocida por el inventor en el momento de desarrollar la invención, por lo que no podría tener certeza de la utilidad de realizar estos pasos.

En vista de este señalamiento, y a la luz de lo discutido en el presente memorial, me permito resaltar que al no "*saltar a la vista de manera clara y directa*" a partir de las enseñanzas de D1, D2 y D3 la sal cristalina de tipo oxalato de mPEG₇-O-naloxol, como la considerada en la presente invención, y al no tenerse "*certeza clara y manifiesta*" de que se obtendría un compuesto cristalino y estable, es claro que los documentos de la anterioridad no pueden de ninguna manera afectar el Nivel Inventivo de la solicitud en estudio.

4. **CONCESIÓN DE LA PRESENTE SOLICITUD POR PARTE DE OTRAS OFICINAS DE PATENTES.**

Finalmente y aparte de lo mencionado hasta el momento en el presente recurso, atentamente me permito resaltar ante ese Despacho que la materia revelada en la solicitud de patente en cuestión, ha sido considerada como materia patentable por parte de los examinadores de la Oficina Americana de Patentes, USPTO, y como consecuencia de ello ha sido concedida la patente US 9,012,469 (El anexo iii) y iv) del presente recurso corresponde a una copia del documento de dicha patente americana cuyo No. Publicación US 2015/0038524- y de la noticia de su concesión- Notice Of Allowance).

En este sentido, considero relevante aclarar que las reivindicaciones patentables en la aplicación americana son sustancialmente idénticas a las reivindicaciones 1 a 14 (*sales de tipo oxalato*) que se presentaron originalmente bajo la Solicitud Internacional No. PCT/SE2011/051161. Por lo tanto, las reivindicaciones de la presente solicitud colombiana están dirigidas al misma materia pero con una considerable restricción a su alcance, tal y como se expuso en el presente memorial.

Así las cosas, considero de gran importancia resaltar el hecho particular de que la patentabilidad de la solicitud ha sido reconocida por los Examinadores de la USPTO, teniendo en cuenta, lo establecido en la Resolución Número 54093 de 2012, la cual en su numeral 1.2.2.5.21, establece el "*Reconocimiento de exámenes de patentabilidad de solicitudes extranjeras*", y de donde se desprende la posibilidad de que a pesar de la independencia con la que cuenta la SIC, ese Despacho ha empezado a darle credibilidad a las decisiones tomadas por las autoridades de Patentes de otros países, a través de la figura del "Patent Prosecution Highway PPH".

En este sentido, Colombia ha firmado el tratado del PPH con Estados Unidos, permitiendo así reconocer que a pesar de la independencia de las Oficinas de Patentes, si una solicitud ha sido reconocida como patentable en dicho país como en el presente caso Estados Unidos, se entiende que la decisión emitida por dicha oficina, tiene más peso y puede ser tenida en cuenta a la hora de revisar la patentabilidad de una solicitud.

Por lo anterior, respetuosamente solicitamos a ese Despacho, que a la hora de revisar este caso, tenga en cuenta el resultado emitido por otra Autoridad de Patente como lo es la USPTO, y que el mismo sea considerado como un indicio fuerte de que la presente solicitud sí cuenta con los requisitos de patentabilidad exigidos por la normativa andina.

II. CONCLUSIÓN

Con base en los argumentos técnicos señalados previamente, me permito manifestar ante ese Despacho que el nuevo capítulo reivindicatorio presentado junto con este memorial goza de un inequívoco carácter inventivo frente a las enseñanzas del documento D1, D2 y D3, razón por la cuales dicha materia es clara merecedora del privilegio de patente solicitado.

Así mismo me permito manifestar que el nuevo capítulo reivindicatorio cumple a cabalidad con las disposiciones de claridad exigidas por el artículo 30 de la Decisión 486 de 2000, respectivamente.

III. PETICIÓN

En vista de todo lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de las modificaciones y argumentaciones presentadas, y proceder a revocar la Resolución Número **11321**, con el fin de que se conceda el privilegio de patente solicitado.

IV. PODER

En este punto me permito mencionar ante ese Despacho, que los documentos de poder, que acredita mi calidad de Representante Legal en Bogotá para asuntos relativos a la Propiedad Industrial de las sociedades peticionarias, fueron presentados junto con la solicitud de patente el 8 de abril de 2013.

V. ANEXOS

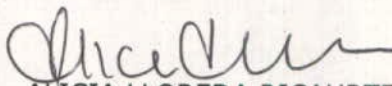
Anexo al presente recurso me permito presentar:

- i) Recibo número 15-007260 expedido por la Superintendencia de Industria y Comercio, que acredita el pago de las modificaciones mencionadas;
- ii) Copia de las páginas **52 a 54** que corresponden al nuevo capítulo reivindicatorio modificado, compuesto por **7** reivindicaciones, tal y como se describe en el numeral 1 del presente memorial;
- iii) Copia del documento de la patente americana US 9,012,469, y
- iv) Copia de la decisión de conceder la patente US 9,012,469 por parte de la USPTO.

VI. DOMICILIO

Mi dirección es Calle 72 No. 5-83, Piso 6º, Bogotá D.C.

Del Señor Superintendente,

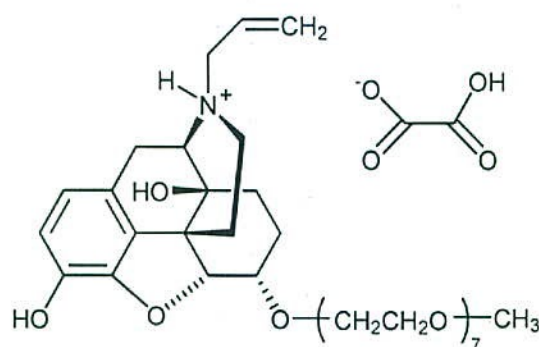

ALICIA LLOREDA RICAURTE

T. P. 53.215

Dirección para Notificaciones: **notificacionespatentes@lloredacamacho.com**

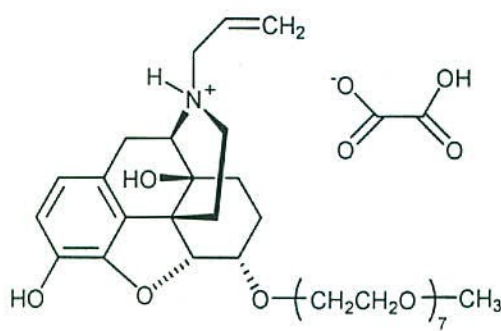
REIVINDICACIONES

1. Una sal cristalina de tipo oxalato de mPEG₇-O-naloxol que presenta los valores d (Å) de los picos de difracción de rayos X en polvo de la forma B comprenden 13.2; 12.0; 7.9; 7.4; 7.0; 6.6; 6.0; 5.7; 5.6; 5.4; 5.2; 5.1; 4.91; 4.86; 4.78; 4.71; 4.48; 4.44; 4.39; 4.17; 4.09; 3.95; 3.91; 3.88; 3.69; 3.63; 3.43; 3.29; 3.14; y 3.01.
2. Un método para producir una sal de tipo oxalato del conjugado de naloxol-polietilenglicol de acuerdo con la reivindicación 1, donde la sal comprende una especie iónica de mPEG₇-O-naloxol y ácido oxálico con la siguiente fórmula:



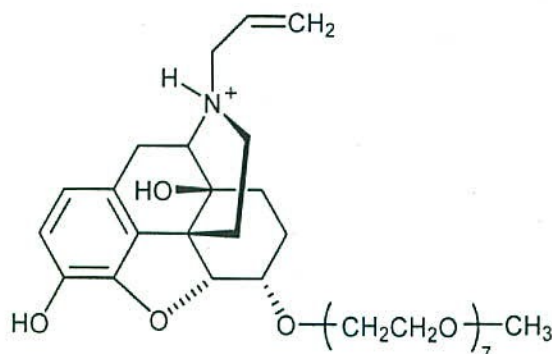
comprendiendo el método:

- a) disolver la base libre de mPEG₇-O-naloxol en 2 volúmenes relativos de acetonitrilo;
 - b) añadir 3 equivalentes de agua a la solución de mPEG₇-O-naloxol disuelto;
 - c) añadir ácido oxálico en acetato de etilo al mPEG₇-O-naloxol disuelto durante un periodo de al menos 2 horas para producir una suspensión; y
 - d) filtrar la suspensión para obtener la sal de tipo oxalato del conjugado de naloxol-polietilenglicol en forma sólida.
3. Un método para producir una sal de tipo oxalato del conjugado de naloxol-polietilenglicol de acuerdo con la reivindicación 1, donde la sal comprende una especie iónica de mPEG₇-O-naloxol y ácido oxálico con la siguiente fórmula:



comprendiendo el método:

- disolver la base libre de mPEG₇-O-naloxol en 2 volúmenes relativos de etanol;
 - añadir 8 volúmenes relativos de éter *t*-butil metílico a la solución de mPEG₇-O-naloxol disuelto;
 - añadir ácido oxálico en éter *t*-butil metílico al mPEG₇-O-naloxol disuelto durante un periodo de al menos 2 horas para producir una suspensión; y
 - filtrar la suspensión para obtener la sal de tipo oxalato del conjugado de naloxol-polietilenglicol en forma sólida.
4. Una sal cristalina de tipo oxalato del conjugado de naloxol-polietilenglicol, que presenta un único pico endotérmico en la calorimetría diferencial de barrido entre temperatura ambiente y aproximadamente 150 °C, donde el máximo del único pico endotérmico se encuentra entre aproximadamente 91 °C y aproximadamente 94 °C, donde el conjugado de naloxol-polietilenglicol donde tiene la siguiente fórmula:



5. La sal de tipo oxalato del conjugado de naloxol-polietilenglicol de la reivindicación 4, donde la forma cristalina presenta valores d (Å) de los picos de difracción de rayos X en polvo de la Forma B que comprenden 13.2; 7.9; 7.0; 6.6; 6.0; 5.7; 5.2; 5.1; 4.44; 4.39; 3.95; 3.88; 3.63 y 3.43, o presenta picos de ángulo 2θ (grados) en: 6.72; 11.24; 12.65; 13.44; 14.72; 15.61; 17.01; 17.34; 19.98; 20.21; 22.50; 22.93; 24.53 y 25.99.
6. Una composición farmacéutica que comprende la sal de tipo oxalato del conjugado de naloxol-polietilenglicol de la reivindicación 4 y un excipiente farmacéuticamente aceptable.
7. La composición farmacéutica de la reivindicación 6 caracterizada porque comprende la sal de tipo oxalato del conjugado de naloxol-polietilenglicol y un excipiente farmacéuticamente aceptable para la administración oral.



US 20150038524A1

11

(19) **United States**(12) **Patent Application Publication**
Aslund et al.(10) Pub. No.: **US 2015/0038524 A1**(43) Pub. Date: **Feb. 5, 2015**(54) **CRYSTALLINE NALOXOL-PEG CONJUGATE****Publication Classification**

(75) Inventors: **Bengt Leonard Aslund**, Macclesfield Cheshire (SE); **Carl-Johan Aurell**, Macclesfield Cheshire (SE); **Martin Hans Bohlin**, Macclesfield Cheshire (SE); **David Richard Jensen**, Waltham, MA (US); **David Thomas Jonaitis**, Waltham, MA (US); **Eric Thomas Healy**, Waltham, MA (US); **Bo Ingvar Ymén**, Macclesfield Cheshire (SE); **Stephan Parent**, Waltham, MA (US); **Tesfai Sebhathu**, Macclesfield Cheshire (SE)

(51) **Int. Cl.**

A61K 47/48 (2006.01)
A61K 31/485 (2006.01)
C07C 55/07 (2006.01)
C07D 489/04 (2006.01)
C07C 51/41 (2006.01)

(52) **U.S. Cl.**

CPC *A61K 47/48215* (2013.01); *C07D 489/04* (2013.01); *C07C 51/41* (2013.01); *C07C 55/07* (2013.01); *A61K 31/485* (2013.01)
USPC 514/282; 546/44

(73) Assignee: **ASTRAZENECA INTELLECTUAL PROPERTY**, Macclesfield (UK)(21) Appl. No.: **13/823,953**(22) PCT Filed: **Sep. 29, 2011**(86) PCT No.: **PCT/SE2011/051161**

§ 371 (c)(1),
(2), (4) Date: **Sep. 4, 2013**

Related U.S. Application Data

(60) Provisional application No. 61/388,501, filed on Sep. 30, 2010.

(57) **ABSTRACT**

Naloxol-polyethylene glycol conjugates of the formula: are provided in oxalate or phosphate salt forms including crystalline forms. Methods of preparing the salt forms and pharmaceutical compositions comprising the salt forms are also provided.

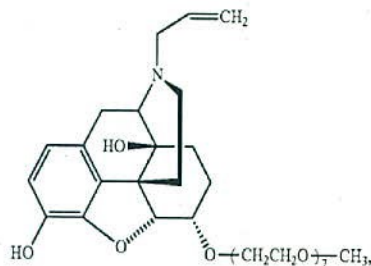


Figure 1

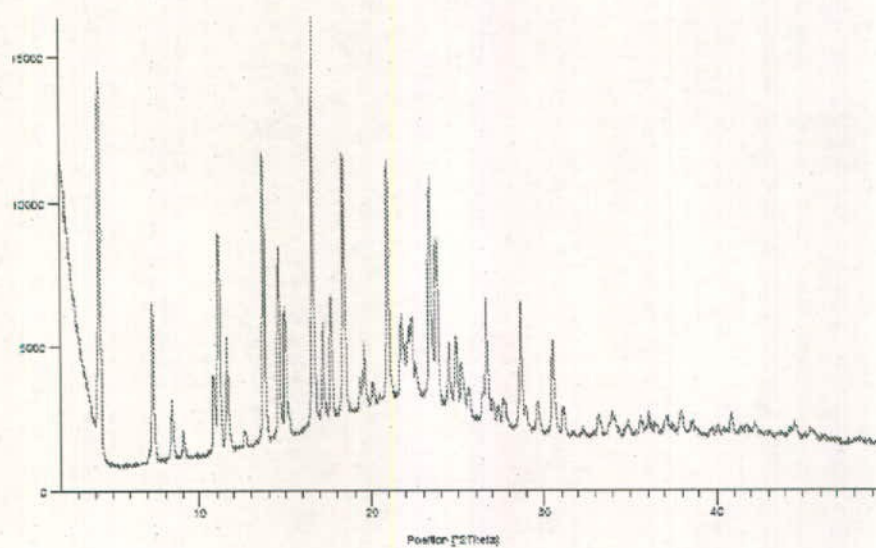


Figure 2

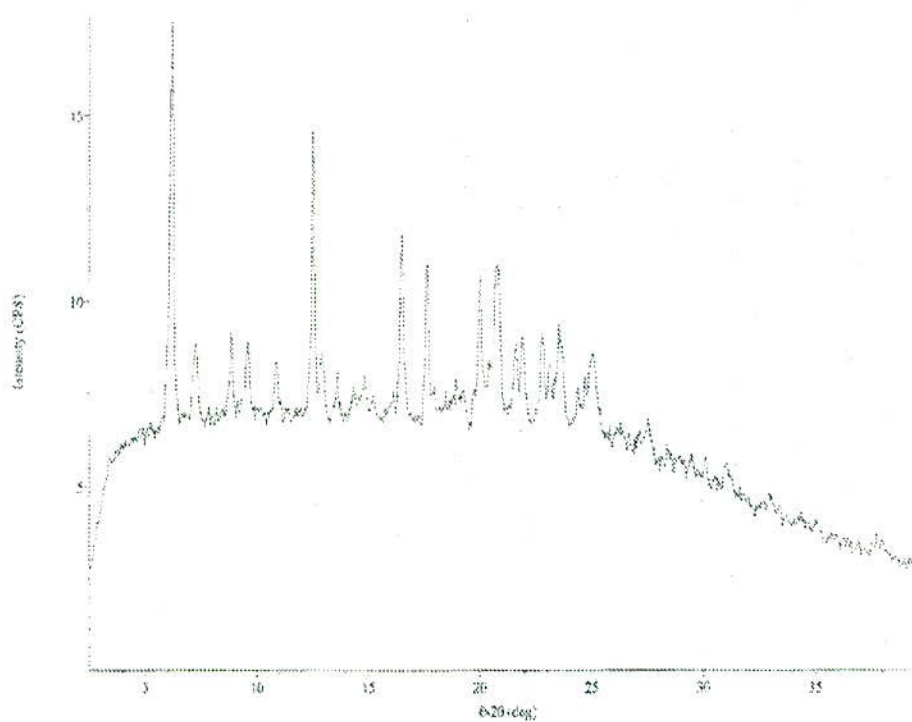
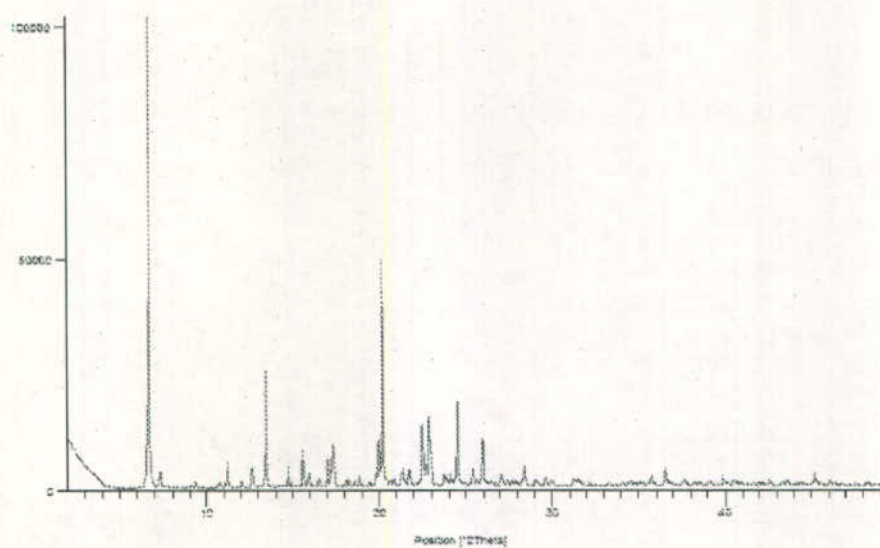


Figure 3



CRYSTALLINE NALOXOL-PEG CONJUGATE

1. RELATED APPLICATION

[0001] This application claims the benefit of priority to U.S. Provisional Patent Application Ser. No. 61/388,501, filed Sep. 30, 2010, which is incorporated herein by reference.

2. TECHNICAL FIELD

[0002] Naloxol-polyethylene glycol conjugates are provided herein in solid phosphate and oxalate salt forms. Methods of preparing the salt forms, and pharmaceutical compositions comprising the salt forms are also provided herein.

3. BACKGROUND

[0003] Effective pain management therapy often calls for an opioid analgesic. In addition to the desired analgesic effect, however, certain undesirable side effects, such as bowel dysfunction, nausea, constipation, among others, can accompany the use of an opioid analgesic. Such side effects may be due to opioid receptors being present outside of the central nervous system, principally in the gastrointestinal tract. Clinical and preclinical studies support the use of mPEG₇-O-naloxol, a conjugate of the opioid antagonist naloxol and polyethylene glycol, to counteract undesirable side effects associated with use of opioid analgesics. When administered orally to a patient mPEG₇-O-naloxol largely does not cross the blood brain barrier into the central nervous system, and has minimal impact on opioid-induced analgesia. See, e.g., WO 2005/058367; WO 2008/057579; Webster et al., "NKTR-118 Significantly Reverses Opioid-Induced Constipation," Poster 39, 20th AAPM Annual Clinical Meeting (Phoenix, Ariz.), Oct. 10, 2009.

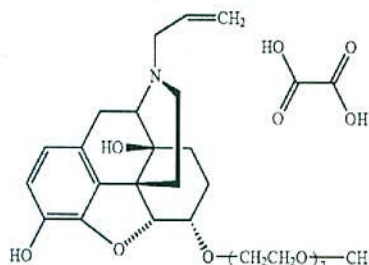
[0004] To move a drug candidate such as mPEG₇-O-naloxol to a viable pharmaceutical product, it is important to understand whether the drug candidate has polymorphic forms, as well as the relative stability and interconversions of these forms under conditions likely to be encountered upon large-scale production, transportation, storage and pre-usage preparation. Solid forms of a drug substance are often desired for their convenience in formulating a drug product. No solid form of mPEG₇-O-naloxol drug substance has been made available to date, which is currently manufactured and isolated as an oil in a free base form. Exactly how to accomplish this is often not obvious. For example the number of pharmaceutical products that are oxalate salts is limited. The free base form of mPEG₇-O-naloxol has not been observed to form a crystalline phase even when cooled to -60° C. and has been observed to exist as a glass with a transition temperature of approximately -45° C. Furthermore, mPEG₇-O-naloxol in its free base form can undergo oxidative degradation upon exposure to air. Care can be taken in handling the free base, for example, storing it under inert gas, to avoid its degradation. However, a solid form of mPEG₇-O-naloxol, preferably one that is stable when kept exposed to air, is desired.

SUMMARY OF THE INVENTION

[0005] In one aspect, provided herein are solid salt forms of mPEG₇-O-naloxol.

[0006] In another aspect, provided herein are methods of producing a naloxol-polyethylene glycol conjugate oxalate

salt, the salt comprising ionic species of mPEG₇-O-naloxol and oxalic acid. The formulas of mPEG₇-O-naloxol and oxalic acid are as follows:



[0007] In certain embodiments, the methods provided comprise dissolving mPEG₇-O-naloxol free base in ethanol; adding methyl t-butyl ether to the dissolved mPEG₇-O-naloxol solution; adding oxalic acid in methyl t-butyl ether to the dissolved mPEG₇-O-naloxol over a period of at least 2 hours to produce a slurry; and filtering the slurry to yield the naloxol-polyethylene glycol conjugate oxalate salt in solid form.

[0008] In certain embodiments, the methods provided comprise dissolving mPEG₇-O-naloxol free base in acetonitrile; adding water to the dissolved mPEG₇-O-naloxol solution; adding oxalic acid in ethyl acetate to the dissolved mPEG₇-O-naloxol over a period of at least 2 hours to produce a slurry; and filtering the slurry to yield the naloxol-polyethylene glycol conjugate oxalate salt in solid form.

[0009] In some embodiments, the solid salt form of mPEG₇-O-naloxol is a crystalline form.

[0010] In certain embodiments a solid crystalline salt provided herein is substantially pure, having a purity of at least about 80%, at least about 85%, at least about 90%, at least about 92%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99%.

[0011] In certain embodiments, the solid salt form of mPEG₇-O-naloxol is a phosphate salt.

[0012] In other embodiments, the solid mPEG₇-O-naloxol salt form is an oxalate salt. For instance, in some embodiments of solid oxalate salt forms provided herein, the solid mPEG₇-O-naloxol oxalate salt form is in Form A, as described herein. As another example, in some embodiments of solid oxalate salt forms provided herein, the solid mPEG₇-O-naloxol oxalate salt form is in Form B, as described herein.

[0013] In yet other embodiments, an oxalate salt of mPEG₇-O-naloxol in solid form prepared according to the methods described herein is provided.

[0014] In yet other embodiments, an dihydrogenphosphate salt of mPEG₇-O-naloxol in solid form prepared according to the methods described herein is provided.

[0015] In certain embodiments of a solid mPEG₇-O-naloxol oxalate salt Form B provided herein, the salt form exhibits a single endothermic peak on differential scanning calorimetry between room temperature and about 150° C. The single endothermic peak can occur, for instance, between about 91° C. to about 94° C. For example, in some embodiments the endothermic peak is at about 92° C., about 92.5° C., or about 93° C.

[0016] In yet other embodiments of a solid mPEG₇-O-naloxol oxalate salt Form A has an XRPD pattern as that in FIG. 2.

[0017] In yet other embodiments of a solid mPEG₇-O-naloxol oxalate salt Form B has an XRPD pattern as that in FIG. 3.

[0018] In yet other embodiments of a solid mPEG₇-O-naloxol dihydrogenphosphate salt it has an XRPD pattern as that in FIG. 1.

[0019] In another aspect, provided herein are pharmaceutical compositions comprising a solid mPEG₇-O-naloxol salt form and a pharmaceutically acceptable excipient. In some embodiments, pharmaceutical compositions provided herein are formulated for oral administration to a subject in a solid form.

4. DESCRIPTION OF THE DRAWINGS

[0020] FIG. 1 provides an X-ray powder diffraction (XRPD) diffractogram of crystalline mPEG₇-O-naloxol dihydrogenphosphate salt.

[0021] FIG. 2 provides an XRPD diffractogram of crystalline mPEG₇-O-naloxol oxalate salt form A.

[0022] FIG. 3 provides an XRPD diffractogram of crystalline mPEG₇-O-naloxol oxalate salt form B.

5. DETAILED DESCRIPTION

[0023] Provided herein are solid forms of an mPEG₇-O-naloxol salt, including, for example, phosphate salt and oxalate salt forms. There are a limited number of oxalate salts as pharmaceutical products. Methods of preparing solid salt forms of mPEG₇-O-naloxol are also provided. The solid salt forms include, for instance, substantially pure crystalline forms. Certain methods of preparing mPEG₇-O-naloxol provided herein can be adapted to manufacturing scale production of mPEG₇-O-naloxol oxalate salt in crystalline form. As demonstrated in the following examples, for instance with a solid oxalate salt form, solid mPEG₇-O-naloxol salt forms can be stable and can produce little or no oxidative degradation product under conditions that produce oxidative degradation product in mPEG₇-O-naloxol free base. The salt formation produces a purer product, which is substantially free from other chemical compounds. Initial crystallization efforts did not yield a pure product and numerous methods were attempted before a successful result was achieved. In addition various acids were attempted before success was achieved with oxalic and phosphoric acids to produce the corresponding salts.

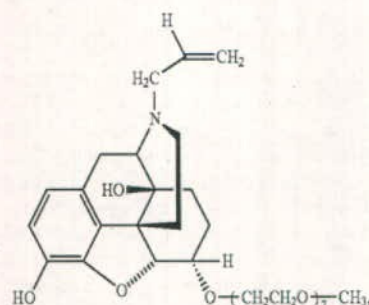
[0024] Furthermore, it is believed that an oxalate salt will increase the likelihood of success for manufacturing purposes. Pharmaceutical compositions comprising the mPEG₇-O-naloxol solid salt forms are also provided herein.

5.1 TERMINOLOGY

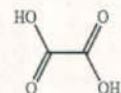
[0025] Abbreviations used herein include the following: DCM, dichloromethane; DMF, dimethylformamide; DSC, differential scanning calorimetry; DVS, dynamic vapor sorption; EtOAc, ethyl acetate; IPA, 2-propanol; IPE, diisopropyl ether; MEK, methyl ethyl ketone; MeOH, methanol; MeTHF, 2-methyltetrahydrofuran; MIBK, methyl isobutyl ketone; MTBE, methyl t-butyl ether; mPEG, methyl-capped polyethylene glycol; PEG, polyethylene glycol; PrCN, n-propyl cyanide; RH, relative humidity; THF, tetrahydrofuran; and XRPD, X-ray powder diffraction.

[0026] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0027] As used herein, the terms "mPEG₇-O-naloxol" "α-6-mPEG₇-O-naloxol" and "α-6-CH₃-(OCH₂CH₂)₇-O-naloxol" are used synonymously to refer to a compound having the formula:

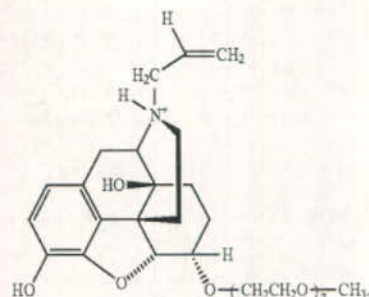


which, unless otherwise stated or apparent from the context in which it is used, means in its free base form. A salt of mPEG₇-O-naloxol, is an ionic form of mPEG₇-O-naloxol that exists with a counterion produced from, in this case, an acid. The counterion produced from the acid is variously referred to herein as an "acid counterion" or just "counterion." When, for example, the acid counterion is that of oxalic acid, the mPEG₇-O-naloxol salt is an oxalate salt. Oxalic acid has the formula:

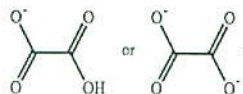


[0028] When, for example, the acid counterion is that of phosphoric acid, the mPEG₇-O-naloxol salt is a phosphate salt. There can be three types of phosphate salts; dihydrogenphosphate; hydrogenphosphate and phosphate. Accordingly, one, two or three hydrogens have been removed.

[0029] Without intending to be limited by any theory or mechanism, it is believed that an ionic species of mPEG₇-O-naloxol may include species where the nitrogen accepts a proton, having the formula:



[0030] Without intending to be limited by any theory or mechanism, it is believed that an ionic species of oxalic acid may include those where one or more hydrogens are removed, for instance:



[0031] As used herein, and unless otherwise specified, the terms "about" and "approximately," when used in connection with doses, amounts, or weight percent of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by those of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. Specifically, the terms "about" and "approximately," when used in this context, contemplate a dose, amount, or weight percent within 15%, within 10%, within 5%, within 4%, within 3%, within 2%, within 1%, or within 0.5% of the specified dose, amount, or weight percent.

[0032] As used herein, and unless otherwise specified, the terms "about" and "approximately," when used in connection with a numeric value or range of values which is provided to describe a particular solid form, e.g., a specific temperature or temperature range, such as, for example, that describing a melting, dehydration, desolvation or glass transition; a mass change, such as, for example, a mass change as a function of temperature (TGA) or humidity (DVS); a solvent or water content, in terms of, for example, mass or a percentage; or a peak position, such as, for example, in analysis by, for example, differential scanning calorimetry (DSC), thermogravimetric analysis or powder X-ray powder diffraction (XRPD); indicate that the value or range of values may deviate to an extent deemed reasonable to one of ordinary skill in the art while still describing the particular solid form. Specifically, the terms "about" and "approximately," when used in this context, indicate that the numeric value or range of values may vary by 5%, 4%, 3%, 2%, 1%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2% or 0.1% of the recited value or range of values while still describing the particular solid form.

[0033] The term "amorphous" or "amorphous form" is intended to mean that the substance, component, or product in question is not substantially crystalline as determined, for instance, by XRPD or where the substance, component, or product in question, for example is not birefringent or cubic when viewed using a polarized light microscope. In certain embodiments, a sample comprising an amorphous form of a substance may be substantially free of other amorphous forms and/or crystalline forms.

[0034] The term "crystalline form" refers to a crystalline solid of a chemical compound, including, but not limited to, a single-component or multiple-component crystal, and/or a polymorph, a solvate, a hydrate, a clathrate, a co-crystal, a salt of a compound, solvates of salts, hydrates of salts. Crystalline forms of a substance can be obtained by a number of methods, as known in the art. Such methods include, but are not limited to, melt crystallization, melt cooling, solvent crystallization, crystallization in confined spaces such as, e.g., in nanopores or capillaries, crystallization on surfaces or templates such as, e.g., on polymers, crystallization in the presence of additives,

such as, e.g., co-crystal counter-molecules, desolvation, dehydration, rapid evaporation, rapid cooling, slow cooling, vapor diffusion, sublimation, reaction crystallization, antisolvent addition, grinding and solvent-drop grinding.

[0035] Techniques for characterizing crystal forms and amorphous forms include, but are not limited to, thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), single crystal X-ray diffractometry, vibrational spectroscopy, e.g., infrared (IR) and Raman spectroscopy, solid-state NMR, optical microscopy, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography and quantitative analysis, particle size analysis (PSA), surface area analysis, solubility studies and dissolution studies.

[0036] As used herein and unless otherwise indicated, the term "hydrate" means a compound or salt thereof, further including a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces. As used herein and unless otherwise indicated, the term "solvate" means a solvate formed from the association of one or more solvent molecules to a compound provided herein. The term "solvate" includes hydrates (e.g., monohydrate, dihydrate, trihydrate, tetrahydrate, and the like).

[0037] The term "pharmaceutically acceptable excipient" refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. In one embodiment, each component is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. See, e.g., *Remington: The Science and Practice of Pharmacy*, 21st ed.; Lippincott Williams & Wilkins: Philadelphia, Pa., 2005; *Handbook of Pharmaceutical Excipients*, 6th ed.; Rowe et al., Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives*, 3rd ed.; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation*, 2nd ed.; Gibson Ed.; CRC Press LLC: Boca Raton, Fla., 2009.

[0038] The term "polymorph" or "polymorphic form" refers to one of two or more crystal forms that comprise the same molecule, molecules or ions. Different polymorphs may have different physical properties such as, for example, melting temperatures, heats of fusion, solubilities, dissolution rates, and/or vibrational spectra as a result of the arrangement or conformation of the molecules or ions in the crystal lattice. The differences in physical properties exhibited by polymorphs may affect pharmaceutical parameters, such as storage stability, compressibility, density (important in formulation and product manufacturing), and dissolution rate (an important factor in bioavailability). Differences in stability can result from changes in chemical reactivity (e.g., differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph), mechanical changes (e.g., tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph), or both (e.g., tablets of one polymorph are more susceptible to breakdown at high humidity). As a result of solubility/dissolution differences, in the extreme case, some polymorphic transitions may result in lack of potency or, at the other extreme,

toxicity. In addition, the physical properties of a crystalline form may be important in processing; for example, one polymorph might be more likely to form solvates or might be difficult to filter and wash free of impurities (e.g., particle shape and size distribution might be different between polymorphs). As used herein and unless otherwise indicated, the term "stereomerically pure" means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound. In certain embodiments stereomerically pure α -6-mPEG₇-O-naloxol or salt thereof is provided herein that is substantially free of other stereoisomers including, for example, β -6-mPEG₇-O-naloxol or salt thereof. In certain embodiments, a stereomerically pure compound or salt thereof comprises greater than about 80 percent by weight of one stereoisomer of the compound and less than about 20 percent by weight of other stereoisomers of the compound, greater than about 90 percent by weight of one stereoisomer of the compound and less than about 10 percent by weight of the other stereoisomers of the compound, greater than about 95 percent by weight of one stereoisomer of the compound and less than about 5 percent by weight of the other stereoisomers of the compound, greater than about 97 percent by weight of one stereoisomer of the compound and less than about 3 percent by weight of the other stereoisomers or greater than about 99 percent by weight of one stereoisomer of the compound and less than about 1 percent by weight of the other stereoisomers of the compound. In certain embodiments, the term "stereomerically pure" mPEG₇-O-naloxol means that the compound is made up of approximately 100% by weight of α -6-mPEG₇-O-naloxol. The above percentages are based on the total amount of combined stereoisomers of the compound.

[0039] As used herein, a crystalline or amorphous form that is "pure," i.e., substantially free of other crystalline or amorphous forms, contains less than about 15 percent by weight of one or more other crystalline or amorphous forms, less than about 10 percent by weight of one or more other crystalline or amorphous forms, less than about 5 percent by weight of one or more other crystalline or amorphous forms, less than about 3 percent by weight of one or more other crystalline or amorphous forms, less than about 1 percent by weight of one or more other crystalline or amorphous forms, or less than about 0.5 percent by weight of one or more other crystalline or amorphous forms. In certain contexts, as used herein, "substantially pure" mPEG₇-O-naloxol salt can mean free of organic impurities, for example, unreacted precursors and side products or oxidative degradation products that might be present in the process for preparing mPEG₇-O-naloxol free base, or formed during storage of mPEG₇-O-naloxol free base. Organic impurities can include, for example, α -6-naloxol, naloxol conjugated to 4, 5, 6 or 8 polyethylene glycol subunits (i.e., ethylene oxide monomers), and so forth. An oxidative degradation product of mPEG₇-O-naloxol free base can, for instance, be glycidaldehyde. In certain embodiments, "substantially pure" means less than 100 ppm, less than 50 ppm, less than 25 ppm, 5 ppm, less than about 2 ppm or less than about 1 ppm of glycidaldehyde. As such, "substantially pure" mPEG₇-O-naloxol salt may comprise, in certain embodiments, less than about 10%, 5%, 3%, 2%, 1%, 0.75%, 0.5%, 0.25%, or 0.1% by weight of one or more other crystal forms and amorphous forms of the compound and/or other chemical compounds. In certain embodiments, a solid form

that is substantially pure is substantially free of one or more other particular crystal forms, amorphous forms, and/or other chemical compounds.

[0040] The terms "subject," "patient" and "individual" as used herein are interchangeable and refer to a living organism suffering from or prone to a condition that can be prevented or treated by administration of a peripherally acting opioid antagonist, and includes both humans and animals. Such a condition can include, for example, an opioid-induced effect, e.g., bowel dysfunction, nausea, pruritis, or constipation. The terms "treat," "treating," and "treatment," as used herein with reference to mPEG₇-O-naloxol, are meant to include alleviating or abrogating one or more opioid-induced effects, e.g., bowel dysfunction, nausea, pruritis, or constipation, in a subject taking one or more opioid analgesics, where the subject taking the one or more opioid analgesics experiences, or continues to experience, opioid-induced analgesia.

[0041] The terms "prevent," "preventing," and "prevention," as used herein with reference to mPEG₇-O-naloxol, are meant to include decreasing a likelihood of occurrence, or of decreasing the severity, of one or more opioid-induced effects, e.g., bowel dysfunction, nausea, pruritis, or constipation, in a subject taking one or more opioid analgesics, where the subject taking the one or more analgesics experiences, or continues to experience, opioid-induced analgesia.

[0042] The term "therapeutically effective amount" is meant to include the amount of mPEG₇-O-naloxol salt that, when administered to a subject, is sufficient to prevent development of, or alleviate to some extent, one or more opioid-induced effects, e.g., bowel dysfunction, nausea, pruritis, or constipation, in the subject when administered one or more opioid analgesics, where the individual taking the one or more analgesics experiences, or continues to experience, opioid-induced analgesia.

[0043] As used herein, it will be understood that reference to a central analgesic effect means the central analgesic effect associated within an opioid-treated subject (i.e., a subject receiving opioid-based analgesia via administration of one or more opioid analgesics). To achieve a central analgesic effect, the subject will typically be administered an opioid agonist. The opioid agonist can be administered to the subject by any suitable means, including, for example, by injection (e.g., intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly or subcutaneously), orally, buccally, nasally, transmucosally, topically, via an ophthalmic preparation, or by inhalation. Administration of the opioid agonist can be achieved via self administration by the subject as well as by another person.

[0044] The therapeutically effective dose (including frequency of dosing) of the opioid agonist will typically be in accordance with conventional administration schemes associated with the specific opioid and available, for example, in *Drug Facts and Comparisons* 2010 (Wolters Kluwer Health/Facts & Comparisons®, St. Louis, Mo., USA).

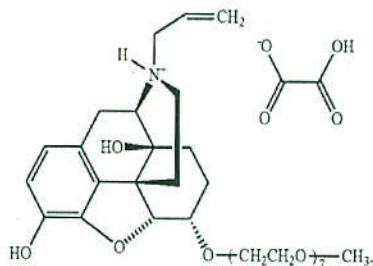
[0045] As used herein, an "opioid agonist" is any natural or synthetic alkaloid or structural derivative of opium that activates one or more opioid receptor types. In some embodiments, an opioid agonist is also an "opioid analgesic," which, as used herein, means an opioid agonist that, when administered to a subject, produces some level of analgesia or relief of pain however short or long lasting for the subject. The opioid agonist can be a natural alkaloid such as penanthrene (e.g., morphine), or benzylisoquinoline (e.g., papaverine), a semi-synthetic derivative (e.g., hydromorphone), or any of various

classes of synthetic derivatives (e.g., phenylpiperidines, benzomorphans, propionanilides, and morphinans). Exemplary opioid agonists include alfentanil, bremazocine, buprenorphine, butorphanol, codeine, cyclazocine, dezocine, diacetylmorphine (i.e., heroin), dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, noscapine, oxycodone, oxymorphone, papaverine, pentazocine, pethidine, phenazocine, propiram, propoxyphene, sufentanil, thebaine and tramadol. Preferably, the opioid agonist is selected from the group consisting of morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl, and tramadol.

5.2 EMBODIMENTS

[0046] In one aspect, a solid salt form of mPEG₇-O-naloxol is provided. In certain embodiments, the solid salt form of mPEG₇-O-naloxol is crystalline. In some embodiments, the solid salt form is an mPEG₇-O-naloxol phosphate salt. In other embodiments, the solid salt form is a mPEG₇-O-naloxol oxalate salt.

[0047] In another aspect, provided herein are methods of producing a naloxol-polyethylene glycol conjugate oxalate salt, wherein the salt comprises ionic species of mPEG₇-O-naloxol and oxalic acid, which have the formula:



[0048] In other embodiments, an mPEG₇-O-naloxol oxalate salt is provided. In some embodiments, the mPEG₇-O-naloxol oxalate salt is in a solid form, which can, for example, be in an amorphous form, single crystalline form, multi-crystalline form, or mixed amorphous and crystalline form. Preferably, the mPEG₇-O-naloxol oxalate salt is in a solid crystalline form.

[0049] In some embodiments, the mPEG₇-O-naloxol oxalate salt crystalline form is in a 1:1 acid to base form.

[0050] In certain embodiments, the methods comprises the steps of dissolving mPEG₇-O-naloxol free base in a first solvent comprising ethanol and methyl t-butyl ether (MTBE), adding oxalic acid in methyl t-butyl ether to the dissolved mPEG₇-O-naloxol, optionally seeding the mixture, to produce a slurry, and filtering the slurry to yield the naloxol-polyethylene glycol conjugate oxalate salt in solid form.

[0051] Typically, the resulting solid is washed and dried, which can be performed according to standard procedures known to those skilled in the art.

[0052] In certain embodiments, dissolving mPEG₇-O-naloxol free base in a solvent comprises dissolving mPEG₇-O-naloxol free base in 1-5 relative volumes of ethanol, preferably 2 relative volumes of ethanol, and adding 5-15 relative volumes of MTBE, preferably 8 relative volumes of MTBE, to the dissolved mPEG₇-O-naloxol in ethanol solution.

[0053] In some embodiments, the oxalic acid, dissolved in 5-15 relative volumes of MTBE, preferably 10 relative volumes, is added to the dissolved mPEG₇-O-naloxol solution over a period of at least 2 hours to produce a slurry. In some embodiments, the oxalic acid is added over a period of at least 5 hours. In some embodiments, the oxalic acid is added at a temperature of between about 0° C. to about 50° C., between about 15° C. to about 30° C., between about 15° C. to about 25° C. or, in some embodiments, at a temperature of about 20° C.

[0054] In certain embodiments, the methods comprises the steps of dissolving mPEG₇-O-naloxol free base in a first solvent comprising acetonitrile and water, adding oxalic acid in ethyl acetate to the dissolved mPEG₇-O-naloxol, optionally seeding the mixture, to produce a slurry, and filtering the slurry to yield the naloxol-polyethylene glycol conjugate oxalate salt in solid form. Typically, the resulting solid is washed and dried, which can be performed according to standard procedures known to those skilled in the art.

[0055] In certain embodiments, dissolving mPEG₇-O-naloxol free base in a solvent comprises dissolving mPEG₇-O-naloxol free base in 1-5 relative volumes of acetonitrile preferably 2 relative volumes of acetonitrile and adding 0.5-8. equivalents of water, preferably 3 equivalents of water, to the dissolved mPEG₇-O-naloxol in the solution.

[0056] In some embodiments, dissolving mPEG₇-O-naloxol free base in 2 relative volumes of acetonitrile and adding 3 equivalents of water to the dissolved mPEG₇-O-naloxol solution; and adding oxalic acid in ethyl acetate to the dissolved mPEG₇-O-naloxol over a period of at least 2 hours to produce a slurry; and filtering the slurry to yield the naloxol-polyethylene glycol conjugate oxalate salt in solid form.

[0057] In some embodiments, the oxalic acid, dissolved in 5-15 relative volumes of ethyl acetate, preferably 11 relative volumes, is added to the dissolved mPEG₇-O-naloxol solution over a period of at least 2 hours to produce a slurry. In some embodiments, the oxalic acid is added over a period of at least 5 hours. In some embodiments, the oxalic acid is added at a temperature of between about 0° C. to about 50° C., between about 15° C. to about 30° C., between about 15° C. to about 25° C. or, in some embodiments, at a temperature of about 20° C.

[0058] In certain embodiments the slurry is produced with seeding. In other embodiments, the slurry is produced without seeding.

[0059] In certain embodiments the slurry is produced with seeding. In other embodiments, the slurry is produced without seeding.

[0060] In some embodiments, the mPEG₇-O-naloxol salt provided is a phosphate salt. In some embodiments, the mPEG₇-O-naloxol phosphate salt is in a crystalline form having an X-ray powder diffraction (XRPD) pattern substantially as that provided in FIG. 1.

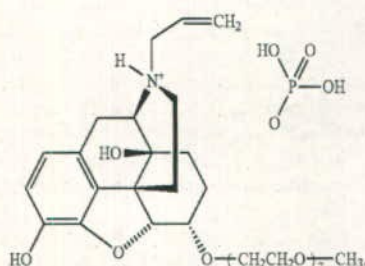
[0061] In some embodiments, a crystalline mPEG₇-O-naloxol phosphate salt is provided having XRPD d values (Å) comprising 21.0 (s); 12.1 (s); 7.9 (s); 6.5 (s); 5.3 (s); 4.83 (s); 4.24 (s); 3.81 (s); and 3.75 (s).

[0062] In certain embodiments, the crystalline mPEG₇-O-naloxol phosphate salt XRPD d values (Å) comprise 21.0 (s); 12.1 (s); 10.5 (m); 8.2 (m); 7.9 (s); 7.6 (m); 6.5 (s); 6.1 (m); 5.9 (m); 5.3 (s); 5.2 (m); 5.0 (m); 4.83 (s); 4.54 (w); 4.24 (s); 3.81 (s); 3.75 (s); 3.35 (m); and 3.12 (m). In yet other embodiments, the mPEG₇-O-naloxol phosphate salt XRPD d values

(Å) are 21.0 (s); 12.1 (s); 10.5 (m); 9.8 (w); 8.2 (m); 7.9 (s); 7.6 (m); 6.5 (s); 6.1 (m); 5.9 (m); 5.3 (s); 5.2 (m); 5.0 (m); 4.83 (s); 4.54 (w); 4.24 (s); 4.09 (w); 4.02 (w); 3.98 (w); 3.81 (s); 3.75 (s); 3.64 (w); 3.58 (w); 3.53 (w); 3.35 (m); and 3.12 (m).

[0063] In some embodiments, a crystalline mPEG₇-O-naloxol phosphate salt is provided having XRPD 2θ peak (°) values at 4.20 (s); 7.29 (s); 8.42 (m); 10.83 (m); 11.13 (s); 11.63 (m); 13.71 (s); 14.58 (m); 14.96 (m); 16.59 (s); 17.18 (m); 17.62 (m); 18.37 (s); 23.38 (s); 23.75 (s); 26.64 (m); and 28.61 (m). In certain embodiments, the crystalline mPEG₇-O-naloxol phosphate salt XRPD 2θ peak (°) values are 4.20 (s); 7.29 (s); 8.42 (m); 9.03 (w); 10.83 (m); 11.13 (s); 11.63 (m); 13.71 (s); 14.58 (m); 14.96 (m); 16.59 (s); 17.18 (m); 17.62 (m); 18.37 (s); 19.55 (w); 20.94 (s); 21.73 (w); 22.14 (w); 22.34 (w); 23.38 (s); 23.75 (s); 24.47 (w); 24.87 (w); 25.20 (w); 26.64 (m); and 28.61 (m).

[0064] In another aspect, provided herein are methods of producing a naloxol-polyethylene glycol conjugate phosphate salt, wherein the salt comprises ionic species of mPEG₇-O-naloxol and phosphoric acid, which have the formula:



[0065] In other embodiments, an mPEG₇-O-naloxol phosphate salt is provided. In some embodiments, the mPEG₇-O-naloxol phosphate salt is in a solid form, which can, for example, be in an amorphous form, single crystalline form, multi-crystalline form, or mixed amorphous and crystalline form. Preferably, the mPEG₇-O-naloxol phosphate salt is in a solid crystalline form.

[0066] In some embodiments, the mPEG₇-O-naloxol phosphate salt crystalline form is in a 1:1 acid counterion to mPEG₇-O-naloxol cation form.

[0067] In another aspect, a method of preparing an mPEG₇-O-naloxol phosphate salt is provided herein. For instance, an mPEG₇-O-naloxol phosphate salt can be prepared by dissolving mPEG₇-O-naloxol free base in ethanol and adding MTBE to the dissolved mPEG₇-O-naloxol free base. Phosphoric acid in MTBE is added to the dissolved mPEG₇-O-naloxol free base. Optionally, the dissolved mPEG₇-O-naloxol solution may be seeded. Typically, the phosphoric acid is added slowly over a period of about 2 hours, more typically over 5 or more hours. Once the phosphoric acid is added, the mixture is allowed to stand at 10° C. for over 2 hours, producing a slurry. The slurry is filtered to yield the mPEG₇-O-naloxol conjugate phosphate salt in solid form. Typically, the resulting solid is washed and dried, which can be performed according to standard procedures known to those skilled in the art.

[0068] In certain embodiments, the mPEG₇-O-naloxol free base is dissolved in 2 relative volumes of ethanol and 8 relative volumes of MTBE prior to addition of the phosphoric

acid. In certain embodiments, 1.01 equivalents of phosphoric acid are added to the dissolved mPEG₇-O-naloxol free base.

[0069] In some embodiments, an mPEG₇-O-naloxol salt crystalline form provided herein (for example, a phosphate or an oxalate salt) is in a hydrate form. In other embodiments, the mPEG₇-O-naloxol salt crystalline form is in a non-solvated (e.g., non-hydrated) form. In some embodiments, the mPEG₇-O-naloxol salt crystalline form is a solvate or a hydrate.

[0070] In certain embodiments, a naloxol-polyethylene glycol conjugate (e.g., mPEG₇-O-naloxol) oxalate salt prepared according to the methods described herein is provided.

[0071] In some embodiments, solid salt forms of mPEG₇-O-naloxol, including its phosphate or oxalate salt forms, provided herein can be prepared using techniques other than those provided herein, such as those techniques as known in the art, including, but not limited to, melt cooling, rapid melt cooling, freeze drying, spray drying, roller drying, lyophilization, quench cooling the melt, rapid solvent evaporation, slow solvent evaporation, solvent crystallization, slurry recrystallization, melt crystallization, desolvation, sublimation, recrystallization in confined spaces (e.g., in nanopores or capillaries), recrystallization on surfaces or templates (e.g., on polymers), recrystallization in the presence of additives (e.g., co-crystal counter-molecules), dehydration, rapid cooling, slow cooling, vapor diffusion, grinding, cryo-grinding, solvent-drop grinding, microwave-induced precipitation, ultrasonication-induced precipitation, laser-induced precipitation, reaction crystallization, antisolvent addition and precipitation from a supercritical fluid.

[0072] In some embodiments of a solid mPEG₇-O-naloxol salt provided herein (e.g., a phosphate or an oxalate salt), the salt is in a substantially pure crystalline form.

[0073] For instance, in various subembodiments, a crystalline mPEG₇-O-naloxol salt can have a purity of at least about 84%, at least about 85%, at least about 90%, at least about 95%, at least about 97%, at least about 98%, at least about 99%, at least about 99.2%, at least about 99.5%, at least about 99.6%, at least about 99.7% or at least about 99.8% by weight of a single crystalline form, the remainder of the total weight which may be other crystalline or amorphous forms and/or other compounds (such as, for example, an oxidative degradation product).

[0074] In certain embodiments, the crystalline mPEG₇-O-naloxol salt is substantially free of glycidaldehyde. In some embodiments, the crystalline mPEG₇-O-naloxol salt has less than about 100 ppm, less than about 50 ppm, less than about 25 ppm, less than about 5 ppm, less than about 2 ppm or less than about 1 ppm, of glycidaldehyde, for instance, when the crystalline mPEG₇-O-naloxol salt is stored at 40° C. for 4 weeks. In various embodiments, the crystalline mPEG₇-O-naloxol salt substantially free of glycidaldehyde provided herein is stable. "Stable" as used herein, means that the crystalline mPEG₇-O-naloxol salt comprises less than about 100 ppm, less than about 50 ppm, less than about 25 ppm, less than about 5 ppm, less than about 2 ppm, less than about 1 ppm, or is substantially free of glycidaldehyde when the crystalline mPEG₇-O-naloxol salt is stored at 40° C. for 4 or more weeks.

[0075] In certain embodiments, an mPEG₇-O-naloxol oxalate salt is provided, wherein the salt is in crystalline Form A. mPEG₇-O-naloxol oxalate salt of Form A exhibits an XRPD pattern substantially such as that shown in FIG. 2.

[0076] In certain embodiments, an mPEG₇-O-naloxol oxalate salt is provided, wherein the salt is in crystalline Form

B. mPEG₇-O-naloxol oxalate salt of Form B exhibits an XRPD pattern such as that shown in FIG. 3.

[0077] In some embodiments, a crystalline mPEG₇-O-naloxol oxalate salt is provided having XRPD d values (Å) comprising 13.2 (s); 6.6 (s); and 4.39 (s).

[0078] In certain embodiments, the crystalline mPEG₇-O-naloxol oxalate salt XRPD d values (Å) comprise 13.2 (s); 7.9 (m); 7.0 (m); 6.6 (s); 6.0 (m); 5.7 (m); 5.2 (m); 5.1 (m); 4.44 (m); 4.39 (s); 3.95 (m); 3.88 (m); 3.63 (m); and 3.43 (m). In yet other embodiments, the crystalline mPEG₇-O-naloxol oxalate salt XRPD d values (Å) are 13.2 (s); 12.0 (w); 9.7 (w); 9.4 (w); 8.3 (w); 8.2 (w); 7.9 (m); 7.4 (w); 7.0 (m); 6.6 (s); 6.0 (m); 5.7 (m); 5.6 (w); 5.4 (w); 5.2 (m); 5.1 (m); 4.91 (w); 4.86 (w); 4.78 (w); 4.71 (w); 4.48 (w); 4.44 (m); 4.39 (s); 4.17 (w); 4.09 (w); 3.95 (m); 3.91 (w); 3.88 (m); 3.69 (w); 3.63 (m); 3.43 (m); 3.29 (w); 3.14 (w); and 3.01 (w).

[0079] In some embodiments, a crystalline mPEG₇-O-naloxol oxalate salt is provided having XRPD 2θ peak (°) values at 6.72 (s); 11.24 (m); 12.65 (m); 13.44 (s); 14.72 (m); 15.61 (m); 17.01 (m); 17.34 (m); 19.98 (m); 20.21 (s); 22.50 (m); 22.93 (m); 24.53 (m); and 25.99 (m). In certain embodiments, the crystalline mPEG₇-O-naloxol oxalate salt XRPD 2θ peak (°) values are 0.6.72 (s); 7.35 (w); 9.13 (w); 9.37 (w); 10.72 (w); 10.82 (w); 11.24 (m); 12.02 (w); 12.65 (m); 13.44 (s); 14.72 (m); 15.61 (m); 15.95 (w); 16.53 (w); 17.01 (m); 17.22 (w); 17.34 (m); 18.06 (w); 18.25 (w); 18.56 (w); 18.86 (w); 19.81 (w); 19.98 (m); 20.21 (s); 21.33 (w); 21.75 (w); 22.50 (m); 22.72 (w); 22.93 (m); 24.14 (w); 24.53 (m); 25.99 (m); 27.07 (w); 28.40 (w); and 29.64 (w).

[0080] In certain embodiments, a crystalline mPEG₇-O-naloxol oxalate salt is provided exhibiting a single endothermic peak on a differential scanning calorimeter between room temperature and about 150° C., wherein the single endothermic peak maximum occurs between about 84° C. to about 96° C. In certain embodiments, the endothermic peak is between about 89° C. to about 95° C., between about 92° C. to about 93° C. or at about 89° C., about 90° C., about 91° C., about 92° C., about 92.5° C., or at about 93° C., and its ΔH is between about 84 J/gram to about 97 J/gram, or at about 96.1 J/gram.

[0081] It will be recognized that, in their solid forms, mPEG₇-O-naloxol salts provided herein (e.g., oxalate salts) can exhibit desirable characteristics for the preparation, processing and/or storage of a pharmaceutical composition or drug product. As such, in another aspect, pharmaceutical compositions are provided that comprise an mPEG₇-O-naloxol salt. In some embodiments, a pharmaceutical composition is provided comprising an mPEG₇-O-naloxol salt and a pharmaceutically acceptable excipient and/or carrier. The choice of excipient, to a large extent, depends on factors, such as the particular mode of administration, the effect of the excipient on the solubility and stability of the active ingredient, and the nature of the dosage form.

[0082] Exemplary solids include granules, pellets, beads, powders, which can be administered "as is" or formulated into one or more of the following for administration to a patient: a tablet; a capsule; a caplet; a suppository; and a troche. Preferably, the composition will be in a unit dosage form to thereby provide a unit dosage suitable for single administration of a dosage of mPEG₇-O-naloxol in the unit dosage form. Suitable pharmaceutical compositions and dosage forms may be prepared using conventional methods known to those in the field of pharmaceutical formulation and described in the pertinent texts and literature, e.g., *Remington*:

The Science and Practice of Pharmacy, 21st edition (Lippincott Williams & Wilkins, Philadelphia, Pa., 2005).

[0083] Oral dosage forms are preferred and include, for instance, tablets and capsules. Tablets can be manufactured using standard tablet processing procedures and equipment. Preferred techniques for forming tablets include direct compression and granulation. In addition to mPEG₇-O-naloxol salt, tablets will generally contain inactive, pharmaceutically acceptable carrier materials such as binders, lubricants, disintegrants, fillers, stabilizers, surfactants, coloring agents, and the like. Binders are used to impart cohesive qualities to a tablet, and thus ensure that the tablet remains intact. Suitable binder materials include, but are not limited to, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, waxes, and natural and synthetic gums, e.g., *acacia* sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, microcrystalline cellulose, ethyl cellulose, hydroxyethyl cellulose, and the like), and Veegum. Lubricants are used to facilitate tablet manufacture, promoting powder flow and preventing particle capping (i.e., particle breakage) when pressure is relieved. Useful lubricants are magnesium stearate, calcium stearate, and stearic acid. Disintegrants are used to facilitate disintegration of the tablet, and are generally starches, clays, celluloses, algin, gums, or crosslinked polymers. Fillers include, for example, materials such as silicon dioxide, titanium dioxide, alumina, talc, kaolin, powdered cellulose, and microcrystalline cellulose, as well as soluble materials such as mannitol, urea, sucrose, lactose, dextrose, sodium chloride, and sorbitol. Stabilizers, as well known in the art, are used to inhibit or retard drug decomposition reactions that include, by way of example, oxidative reactions.

[0084] In some instances, the tablet can be in the form of a uniform tablet. In uniform tablets, the formulation used in preparing the tablet is a substantially homogenous mixture of one or more active agents and one or more pharmaceutical excipients (e.g., diluent). The formulation is then used to make tablets using a suitable tableting process to thereby result in a tablet that is substantially homogenous throughout the tablet.

[0085] In still other instances, the tablet can also take the form of a layered tablet (of one, two, three or more layers). The method for manufacturing the layered tablet can include combining two different formulations (e.g., one formulation containing an opioid agonist and another containing the mPEG₇-O-naloxol salt) and compressing the two together to form the tablet. Multiple layered tablets of three or more layers are also possible and can be formed, for example, in a similar manner by combining three or more distinct formulations and followed by compression. Capsules are also suitable oral dosage forms, in which case the mPEG₇-O-naloxol salt may be encapsulated in a semi-solid or solid form (including particulates such as granules, beads, powders or pellets). Suitable capsules may be either hard or soft, and are generally made of gelatin, starch, or a cellulosic material, with gelatin capsules preferred. Two-piece hard gelatin capsules are preferably sealed, such as with gelatin bands or the like. See, for example, *Remington: The Science and Practice of Pharmacy*, supra, which describes materials and methods for preparing encapsulated pharmaceuticals.

[0086] Exemplary excipients include, without limitation, those selected from the group consisting of carbohydrates,

inorganic salts, antimicrobial agents, antioxidants, surfactants, buffers, acids, bases, and combinations thereof.

[0087] An antioxidant can be present in the preparation as well. Antioxidants are used to prevent oxidation, thereby preventing the deterioration of the conjugate or other components of the preparation. Suitable antioxidants for use in the present invention include, for example, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, propyl gallate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite, and combinations thereof.

[0088] A surfactant may be present as an excipient. Exemplary surfactants include: polysorbates, such as TWEEN 20 and TWEEN 80, and PLURONICS such as F68 and F88 (both of which are available from BASF, Mount Olive, N.J.); sorbitan esters; lipids, such as phospholipids such as lecithin and other phosphatidylcholines, phosphatidylethanolamines (although preferably not in liposomal form), fatty acids and fatty esters; steroids, such as cholesterol; and chelating agents, such as EDTA, zinc and other such suitable cations.

[0089] In addition to mPEG₇-O-naloxol salt, the pharmaceutical composition may comprise an opioid agonist. The amount of the active agents (i.e., opioid agonist and mPEG₇-O-naloxol salt) in the composition will vary depending on a number of factors, but will optimally be a therapeutically effective dose of each active agent when the composition is stored in a unit dose form. A therapeutically effective dose for each active agent can be determined experimentally by repeated administration of increasing amounts of the active agent in order to determine which amount produces a clinically desired endpoint.

[0090] In other embodiments, the unit dose form will comprise both the mPEG₇-O-naloxol salt and the opioid agonist, wherein the mPEG₇-O-naloxol salt is present in an amount such that significant inhibition of the central analgesic effect of said opioid does not occur when the composition is administered to a subject.

[0091] The amount of any individual excipient in the composition will vary depending on the activity of the excipient and particular needs of the composition. Typically, the optimal amount of any individual excipient is determined through routine experimentation, i.e., by preparing compositions containing varying amounts of the excipient (ranging from low to high), examining the stability and other parameters, and then determining the range at which optimal performance is attained with no significant adverse effects. Exemplary excipients are described, for instance, in *Handbook of Pharmaceutical Excipients*, 5th Edition (Rowe et al., editors; American Pharmaceutical Association Publications, Washington D.C., 2005).

[0092] In another aspect, provided herein is a method for administering a composition as provided herein to a patient suffering from a condition that is responsive to treatment with an opioid agonist. Preferably, this method comprises administering a unit dosage form as described herein. The method of administering may be used to treat any condition that can be remedied or prevented by administration of the opioid agonist (e.g., moderate to severe pain). Those of ordinary skill in the art appreciate which conditions an opioid agonist can effectively treat. The actual dose to be administered will vary depend upon the age, weight, and general condition of the subject as well as the severity of the condition being treated, the judgment of the health care professional, and the active agent being administered. Therapeutically effective amounts

are known to those skilled in the art and/or are described in the pertinent reference texts and literature. Generally, a therapeutically effective amount will range from about 0.001 mg to 100 mg, preferably in doses from 0.01 mg/day to 75 mg/day, and more preferably in doses from 0.10 mg/day to 50 mg/day. [0093] It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the foregoing description as well as the experimental that follow are intended to illustrate and not limit the scope of the invention.

6. EXAMPLES

[0094] Methods and Procedures.

[0095] Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wis., USA). Solutions of oxalic acid were prepared from oxalic acid dihydrate. Routine chemical and physicochemical analyses were conducted following standard operating procedures known to those skilled in the art. For example, certain analyses were performed as described in the following paragraphs.

[0096] XRPD.

[0097] In microplate experiments described below, XRPD patterns were collected with BRUKER D-8 DISCOVER diffractometer with BRUKER'S GENERAL AREA DIFFRACTION DETECTION SYSTEM (GADDS, v. 4.1.20). An incident beam of CuK radiation was produced using a fine-focus tube (40 kV, 40 mA), a Goebel mirror and a 0.5 mm double-pinhole collimator. Diffraction patterns were collected using a HI-STAR area detector located 15 cm from the sample and processed using GADDS. The intensity in the GADDS image of the diffraction pattern was integrated using a step size of 0.04° 2θ. Prior to analysis a silicon standard was analyzed to verify the Si 111 peak positions.

[0098] In other instances XRPD analysis were performed on an INEL SRG-3000 diffractometer, equipped with a curved position-sensitive detector with a 2θ range of 120°. Real time data was collected using CuK radiation at a resolution of 0.03° 2θ. The tube voltage and amperage were set to 40 kV and 30 mA, respectively. Instrument calibration was performed daily using a silicon reference standard.

[0099] In yet other instances, XRPD patterns were collected on an PANALYTICAL X'PERT PRO MPD THETA-THETA system (PANalytical B.V., Almelo, Netherlands) using long-fine-focus Cu Kα-radiation, wavelength of X-rays 1.5418 Å, at 45 kV and 40 mA. A programmable divergence slit and a programmable anti-scatter slit giving an irradiated length of 10 mm were used. 0.02 radian Soller slits were used on the incident and on the diffracted beam path. A 20 mm fixed mask was used on the incident beam path and a nickel-filter was placed in front of a PIXCEL detector using 255 active channels. Thin flat samples were prepared on flat zero background plates made of silicon using a spatula. The plates were mounted in sample holders and rotated in a horizontal position during measurement. Diffraction patterns were collected between 2° 2θ and 50° 2θ in a continuous scan mode. Total time for a scan between 2 and 50° 2θ was approximately 26 minutes. Six scans were collected and a merged scan was calculated by adding the separate scans.

[0100] DSC.

[0101] Differential scanning calorimetric analyses were carried out on a TA INSTRUMENTS differential scanning calorimeter Q1000. The instrument was calibrated using indium as the reference material. The sample was placed into a

standard aluminum DSC pan with a non-crimped lid configuration, and the weight recorded. The sample cell was equilibrated at 25° C. and heated under a nitrogen purge at a rate of 10° C./min.

[0102] TGA.

[0103] Thermogravimetric analyses were performed on a TA INSTRUMENTS 2950 thermogravimetric analyzer. The calibration standards were nickel and ALUMEL. Each sample was placed in an aluminum pan and inserted into the furnace. Samples were started at 25° C. and heated under a stream of nitrogen at a heating rate of 10° C./min.

6.1 Small Scale Experiments

[0104] Results of the following small scale experiments exemplify the difficulties in preparing mPEG₇-O-naloxol in a solid form. In the small scale experiments explained below, mixtures of mPEG₇-O-naloxol and solvent were prepared and assessed for solid formation under various conditions. Potential counterions of a number of acids were tested to assess whether they might form a solid salt with mPEG₇-O-naloxol. Over 400 different of acid/solvent combinations were tested in small scale experiments. Table 1 summarizes the acid counterions tested in the small scale experiments. In Table 1, acid counterions indicated with superscript were also tested in scaled up salt experiments. As explained in Section 6.2 below, when scaling up from the small scale experiments to larger scale experiments, it was only possible to isolate solid forms of the phosphate and oxalate salts.

TABLE 1

Acids Used in Small Scale Salt Experiments			
Acetic	Gentisic	Malonic ¹	Pantoic ¹
Adipic ¹	Glutaric	Methanesulfonic ¹	Phosphoric ¹
Benzenesulfonic	Glycolic	1,5-Naphthalenedisulfonic	Pyroglutamic
Benzoic	Hexanoic	2-Naphthalenesulfonic	Succinic
Camphoric	Hippuric	1-Hydroxy-2-Naphthoic	Stearic
Citric	Hydrobromic	3-Hydroxy-2-Naphthoic	Sulfuric
Decanoic ¹	Hydrochloric	Nicotinic	D-Tartaric ¹
Ethanesulfonic ¹	α -Ketoglutaric	Octanoic	L-Tartaric
1,2-Ethanedisulfonic	Maleic ¹	Orotic	Toluenesulfonic ¹
Formic	D-Malic	Oxalic ¹	Trifluoroacetic
Fumaric ¹	L-Malic ¹	Palmitic	

¹Also tested in scaled up salt experiments.

[0105] Manual Experiment #1.

[0106] Using MICROSCREEN™ technology (SSCI, a division of Aptuit, West Lafayette, Ind., USA), mixtures were made by adding an acid counterion to a small amount of mPEG₇-O-naloxol in one of five solvents (acetone, DCM, EtOAc, MeOH or THF) to wells of a microplate. The mixtures had a 1:1 molar ratio of mPEG₇-O-naloxol to acid. Thirteen acid counterions were assessed in at least one of the solvents (e.g., pyroglutamic acid was tested in MeOH; benzoic acid was tested in each of the five solvents), where most of the counterions were tested in at least three different solvents. Clear solutions were observed in each well after adding the counterion indicating that no immediate solid precipitation was produced. One of two wells containing the same solvent/counterion combination was subjected to fast evaporation conditions and the other well to slow evaporation conditions. In each well, after allowing evaporation, only oils were observed. A different set of acid counterions were tested in manual experiment #2, described below.

[0107] Manual Experiment #2.

[0108] A set of 13 acid counterions was assessed in a manual microplate method using SSCI's MICROSCREEN™ technology in which wells contained mPEG₇-O-naloxol in one of the following five solvents: acetone, EtOAc, MeOH, THF and diethyl ether. Certain wells of the microplate containing mPEG₇-O-naloxol and solvent did not have any acid counterion added. In wells to which acid was added, each acid was tested in combination with acetone, MeOH and THF. Some acids were also added to wells containing EtOAc or ether. Except for one well, clear solutions were observed in the wells. The exception was a cloudy mixture produced when maleic acid was added to well containing ether and mPEG₇-O-naloxol. After the contents of the wells were allowed to evaporate, however, only oils were observed. Thereafter, solvent was added to each well and the mixtures sonicated. The mixtures were sonicated in two second bursts and allowed to rest for 50 seconds. A total of 20 sonication cycles were completed.

[0109] Sonication did not result in formation of solids. The mixtures were allowed to evaporate under fast evaporation conditions, and again, only oils were observed. Next, the contents of the microplate were exposed to 45° C., under vacuum, for approximately 20 hours. Oil was observed in each well, however, in about 70 out of the 95 wells there also appeared to be small particles suspended in oil. The entire plate was analyzed by XRPD. No crystalline reflections were observed. *Automated Experiments.* mPEG₇-O-naloxol was dissolved in methanol to provide a 0.1 M solution. Selected

acids were dissolved in methanol to provide 0.1 M solutions. Using four 96-well microplates prepared within an automated platform (Symyx Technologies, Inc., Santa Clara, Calif., USA) specified amounts of mPEG₇-O-naloxol and stoichiometric amounts of acid counterion were distributed into about 70 wells in each of the sealed microplates. The same set of 34 acids was added to wells on each of the four microplates. Methanol was then removed from the microplates using a centrifugal vacuum evaporator at room temperature for approximately 30 minutes. Microplates were examined under a light microscope for the presence of solids. Selected solvents or solvent mixtures were then autodispensed into appropriate wells of the microplates.

[0110] On microplates 1-3, each acid was tested with in combination with at least one solvent, most against 3 or 4 solvents selected from THF, 2-propanol, 1,4-dioxane, propionitrile, ethanol, 1-butanol and methanol. Microplates 1-3 were sealed and heated in an oven at 40° C. for approximately 30 minutes. The microplates were then agitated at ambient

conditions on an orbital shaker for approximately 1 hour. Contents of microplate 1 were subject to fast evaporation by placing the microplate in a fume hood, and solvent allowed to evaporate under ambient conditions.

[0111] Contents of microplate 2 were subject to slow evaporation by applying an adhesive backed aluminum foil cover (one pin hole per well) to the top of the microplate, placing the microplate in a fume hood, and allowing the solvent to evaporate under ambient conditions. Contents of microplate 3 were subject to sonication, then the solvent allowed to evaporate under slow evaporation conditions explained for microplate 2.

[0112] On microplate 4, the acids were tested in combination with 30 μ l of solvent which was isopropyl ether in one well and, in another well, acetonitrile. Contents on microplate 4 were subject sonication and then subject to slow evaporation, as previously described.

[0113] Wells of microplates 1-4 were examined under light microscope for presence of solids. A large majority of wells on microplates 1-4 did not appear to contain any viable candidate solid salt forms. This observation was also made for wells containing mPEG₇-O-naloxol free base and solvent to which no acid counterion was added. However, in a few of the wells where phosphoric, oxalic or pamoic acids were added, solids appeared to be present.

[0114] Experiments with 1-propanol, ethyl acetate or THF/water (9:1).

[0115] In small vials, the oil of mPEG₇-O-naloxol free base (100 mg) was dissolved in 1 ml of 1-propanol, ethyl acetate or THF/water (9:1). The counter ions were added to the vials, which were stirred by magnetic bars at room temperature for at least one week. The vials were observed from time to time and if a precipitate appeared the vial was sampled and analyzed by XRPD. Slurry tests were run in three series as provided in Tables 2-4. In these tables, "no reaction observed" means any of unsolved starting material, amorphous material or clear solution; "clear solution" means that no solids were observed and "gel (amorphous)" means that while solids were observed in the slurry produced, the solids were amorphous as determined by XRPD.

TABLE 2

Results Using Acid:Base Ratio of 1:1			
Acid	1-Propanol	Ethyl Acetate	THF/Water (9:1)
L-Tartaric acid	No reaction observed	No reaction observed	clear solution
D-Tartaric acid	Gel (amorphous)	No reaction observed	clear solution
Fumaric acid	No reaction observed	Counter ion	clear solution
Maleic acid	No reaction observed	Gel (amorphous)	clear solution
Succinic acid	No reaction observed	Counter ion	clear solution
DL-Malic acid	No reaction observed	Counter ion	clear solution
Orotic acid	Counter ion	Counter ion	Counter ion
Pamoic acid	No reaction observed	Sticky matter	clear solution
Malonic acid	No reaction observed	No reaction observed	clear solution
L-Malic acid	No reaction observed	No reaction observed	clear solution
D-Malic acid	No reaction observed	No reaction observed	clear solution
Adipic acid	No reaction observed	Sticky matter	clear solution
Citric acid	No reaction observed	No reaction observed	clear solution

Counter ion - The solid form is the counter ion itself.

TABLE 3

Results Using Acid:Base Ratio of 2:1	
Acid	Ethyl Acetate
L-Tartaric acid	Sticky matter
D-Tartaric acid	Sticky matter
Fumaric acid	Sticky matter
Maleic acid	Clear solution + single particles
DL-Malic acid	Precipitate
Orotic acid	Sticky matter
Pamoic acid	Counter ion
Malonic acid	clear solution
D-Malic acid	Sticky matter
Adipic acid	Precipitate
Citric acid	Sticky matter

TABLE 4

Acid	Acid:Base	Ethyl Acetate
Phosphoric acid	1:1	Gel (amorphous)
Phosphoric acid	2:1	Gel (amorphous) (1:1 salt)
Sulfuric acid	1:1	Sticky matter
Sulfuric acid	2:1	Sticky matter
Acetic acid	1:1	Clear solution
Formic acid (>90%)	1:1	Clear solution
Methanesulfonic acid	1:1	Clear solution
Benzenesulfonic acid	1:1	Clear solution + single particles
Hydrobromic acid (48%) aq	1:1	Amorphous precipitate
Hydrochloric acid, aq	1:1	Clear solution
1,2-Ethanedisulfonic acid	1:1	Gel amorph (less viscous than phosphate)
1,2-Ethanedisulfonic acid	2:1	Gel amorph (less viscous than phosphate)
Stearic acid	1:1	Counter ion

[0116] As indicated in Tables 2-4, in most of the vials either the acid itself crystallized or there was no crystallization. In some vials a gel was formed. In two of these cases, with D-tartaric acid and 1,2-ethanedisulfonic acid, crystalline material may have been formed based on observation by microscopy but became a liquid when isolated from scaled up tests.

[0117] After one week the vials with no precipitate were left to slowly evaporate. No crystalline phase was observed, other than that observed with phosphoric acid.

[0118] Experiments with mPEG₇-O-Naloxol Free Base.

[0119] mPEG₇-O-naloxol was dissolved in each of the solvents, ethyl acetate, 1-propanol and THF/water (9:1) in concentrations of 100 mg/ml and 500 mg/ml. No crystallization was observed for 3 weeks at 20° C. The samples were then treated with sonification, evaporation, antisolvent addition and put into freezer, without result. The free base was also tested in heptane, toluene and hexane by allowing the solvents to evaporate, with the result that no crystallization was observed.

[0120] Results of small scale experiments indicated that, by far, the large majority of combinations of different solvents, potential acid counterions and conditions tested would not produce a solid form of mPEG₇-O-naloxol. A few of the acids, at least in certain combinations, suggested that a solid salt form might be possible. These acids were tested in scaled up experiments to assess their potential for forming a solid mPEG₇-O-naloxol salt form.

6.2 Scaled Up Experiments

[0121] Several acids, including adipic, decanoic, fumaric, maleic, malonic, methanesulfonic, oxalic, pamoic, phosphoric and toluenesulfonic, were chosen for scale-up attempts for producing mPEG₇-O-naloxol salts at approximately 30 mg each. Solvents used in these experiments included THF, n-hexanes, cyclohexane, EtOAc, ether, DCM, IPE, acetonitrile, MeOH, PrCN, butanol, acetone, and mixtures thereof. In most instances, the mixture of mPEG₇-O-naloxol and acid in solvent produced a clear solution. Some exceptions, were, for example, where mixtures included L-malic acid or malonic acid and EtOAc, toluene-sulfonic acid and hexanes, and oxalic in some solvents. The mixtures were subject to various conditions intended to assist in producing a precipitate, which are briefly described in the following paragraphs.

[0122] Crash Cool—

[0123] Saturated solutions were filtered through a 0.2 µm nylon filter into a vial. Vials were then either left at ambient temperature or placed in the refrigerator.

[0124] Fast Evaporation—

[0125] Solutions were sonicated between aliquot additions to assist in dissolution. Once a mixture reached dissolution, as judged by visual inspection, the solution was filtered through a 0.2 µm nylon filter. The filtered solution was allowed to evaporate at ambient temperature in an uncapped vial.

[0126] Slow Cool—

[0127] Saturated solutions were filtered through a 0.2 µm nylon filter into a vial. In vials where there were no solids present, or if the amount of solids was judged too little for XRPD analysis, the vial was placed in a refrigerator.

[0128] Following refrigeration, in those vials where no solids were observed, the vial was placed in a freezer. Any solids that formed during the procedures were isolated by filtration and allowed to dry prior to analysis.

[0129] Although results of small scale experiments hinted that maleic, pamoic, D-tartaric and 1,2-ethanedithiolonic acids might form solid salt forms, in the scaled up experiments only an oil was produced with these potential acid counterions, or, when any precipitate was present, the precipitate dissolved or melted when isolated. It was not possible to measure XRPD or confirm salt formation for these potential acid counterions.

[0130] The results of the scaled up salt experiments were that, of the potential acid counterions tested, only the phosphoric and oxalic acids were found to produce a solid form that could be characterized. Efforts were directed to determining exemplary preparations of solid phosphate and oxalate salt forms, which are provided below, together with a characterization of each of the solid forms produced.

6.3 Preparation and Characterization of mPEG₇-O-Naloxol Solid Forms

[0131] The following examples provide exemplary preparations and a characterization of phosphate salt and oxalate salt forms of mPEG₇-O-naloxol.

[0132] 6.3.1 Solid mPEG₇-O-Naloxol Phosphate Salt Form

[0133] A single solid mPEG₇-O-naloxol phosphate salt form was obtained using the following procedures.

[0134] Toluene/Heptane Method.

[0135] Salt was formed in a mixture of toluene and heptane by addition of 85% w/w (aq.) phosphoric acid in equivalent amount to the free base at about 20° C. In this method, the crystals were small and the filtration time was long. The procedure of solvent addition and the composition of toluene to heptane was difficult to balance. In some experiments oil was formed.

[0136] Ethanol/MTBE Method.

[0137] In a number of separate preparations, mPEG₇-O-naloxol was dissolved in ethanol and MTBE and then phosphoric acid dissolved in MTBE was added to it. The solutions were allowed to evaporate, which in some of the preparations, produced some crystalline phosphate salt. In other preparations an oil formed, which may be due to adding the phosphoric acid solution too fast. Using crystals from these preparations as seeds, the following steps were taken to prepare crystalline mPEG₇-O-naloxol phosphate salt: (1) free base (1 gram) was dissolved in 2 relative volumes of ethanol (2 ml) at 20° C.; (2) 8 rel. vol. (8 ml) MTBE was added to the solution; (3) a phosphoric acid solution was prepared by dissolving 1.01 eq. of the phosphoric acid (99% w/w) in 10 rel. vol. MTBE (10 ml); (4) 3% of the phosphoric acid solution (0.3 rel. vol) was added to the free base solution over 10 minutes at 20° C.; (5) seeds (1% w/w) were added and the solution allowed to stand for at least 30 minutes; (6) the remaining acid solution was added over 5 hours; (7) the solution was cooled to 10° C. over 2 hours, and kept at that temperature for at least 12 hours; (8) the slurry was then filtered; (9) the solid material was washed with MTBE, 10 rel. vol. and dried under vacuum at 20° C. The yield was about 90%. This method was scaled up to 10 L using about 400 grams of mPEG₇-O-naloxol resulting in a yield of 94%.

[0138] Characterization of Solid State of mPEG₇-O-Naloxol Phosphate.

[0139] It is an 1:1 salt and only one crystal modification has been observed. The crystallinity of the salt is good as shown by the XRPD (FIG. 1). XRPD pattern data are provided in Table 5.

TABLE 5

XRPD values mPEG ₇ -O-Naloxol Phosphate Salt			
2θ Angle, °	d value, Å	Relative Intensity, %	
4.20	21.0	40	s
7.29	12.1	25	s

TABLE 5-continued

XRPD values mPEG ₇ -O-Naloxol Phosphate Salt				
2θ Angle, °	d value, Å	Relative Intensity, %		
8.42	10.5	10	m	
9.03	9.8	5	w	
10.83	8.2	15	m	
11.13	7.9	40	s	
11.63	7.6	25	m	
13.71	6.5	65	s	
14.58	6.1	45	m	
14.96	5.9	30	m	
16.59	5.3	100	s	
17.18	5.2	30	m	
17.62	5.0	35	m	
18.37	4.83	70	s	
19.55	4.54	30	w	
20.94	4.24	75	s	
21.73	4.09	35	w	
22.14	4.02	35	w	
22.34	3.98	35	w	
23.38	3.81	70	s	
23.75	3.75	60	s	
24.47	3.64	30	w	
24.87	3.58	30	w	
25.20	3.53	25	w	
26.64	3.35	45	m	
28.61	3.12	45	m	

[0140] As determined by DSC, the melting onset of mPEG₇-O-naloxol phosphate salt is 107.3° C. and the heat of fusion is 33.3 J/g, although the peak is broad. The isotherm curve from the DVS shows continuous (exponential) moisture uptake from the start. The desorption curve is close to the adsorption curve (no hysteresis). Scanning electron microscopy revealed that the solid is composed of small aggregated needles.

[0141] When analyzed by NMR, it was observed that chemical shifts with the solution ¹H-NMR spectra are consistent with salt formation. Proton NMR with an internal standard (sodium formate) indicated that the phosphate salt is an unsolvated mono-phosphate (1:1) salt. Summary of NMR assignments for mPEG₇-O-naloxol phosphate salt were as follows.

[0142] ¹H NMR, ppm (multiplicity, number of H, coupling constants in Hz if possible): 1.34 (m, 1H), 1.54-1.67 (m, 2H), 1.73 (dd, 1H, 4, 14), 1.77-1.85 (m, 1H), 2.48 (dt, 1H, 5, 14), 2.89 (dt, 1H, 4, 13), 3.08 (dd, 1H, 7, 20), 3.22 (dd, 1H, 5, 13), 3.35 (s, 3H), 3.38 (d, 1H, 20), 3.50-3.90 (m, 31H), 4.01 (m, 1H), 4.91 (d, 1H, 5), 5.60 (d, 1H, 10), 5.61 (d, 1H, 17), 5.87 (m, 1H), 6.73 (d, 1H, 8), 6.82 (d, 1H, 8).

[0143] ¹³C NMR, ppm: 20.1, 23.0, 27.2, 29.1, 45.3, 45.8, 55.7, 58.0, 62.4, 69.1, 69.4, 69.51-69.54 (multiple of signals), 69.6, 69.8, 70.5, 70.9, 74.1, 87.2, 118.3, 119.6, 122.3, 125.8, 126.2, 129.2, 137.7, 145.3.

[0144] 6.3.2 Solid mPEG₇-O-Naloxol Oxalate Salt Forms
[0145] The following examples describe the preparation and characterization of solid state mPEG₇-O-naloxol oxalate salt forms.

[0146] Form A.

[0147] In scaled-up experiments, summarized in Section 6.2 above, it was noted that a combination of oxalic acid and EtOAc produced a white solid that appeared to be hygroscopic that deliquesced upon filtration. The solid was successfully isolated when filtered under dry nitrogen and characterized by XRPD as provided in FIG. 2. This form was termed mPEG₇-O-naloxol oxalate salt solid "Form A."

[0148] Form B.

[0149] In scaled-up experiments, summarized in Section 6.2 above, it was noted that combinations of oxalic acid with IPE or with MTBE produced a white solid. These observations were reproduced when scaling up from the 30 mg amounts previously used (see Section 6.2, above) to amounts indicated in Table 6. XRPD and other analysis, discussed below, confirmed that the solid form of mPEG₇-O-naloxol made from the combinations provided in Table 6 were in a form, termed "Form B," which was different than Form A produced with the combination of oxalic acid and EtOAc.

TABLE 6

Production of Solid State mPEG ₇ -O-Naloxol Oxalate Salt Form B			
Solvent	Approximate Scale	Description	XRPD Result
IPE	150 mg	White solid	Form B
	1.5 g (92% yield)	White solid	Form B
MTBE	2.2 g (84% yield)	White solid	Form B

[0150] Using small amounts of the mPEG₇-O-naloxol oxalate salt Form B from preparations such as those summarized in Table 6 for seeding, Form B was produced following these steps: (1) dissolve the free base (1 gram) in 2 relative volumes of ethanol (2 ml) at 20° C.; (2) add 8 rel. vol. (8 ml) MTBE to the solution; (3) dissolve 1.01 equivalents of the oxalic acid (98%) in 10 rel. vol. MTBE (10 ml); (4) add 10% of the oxalic acid solution to the free base solution over 5-10 minutes at 20° C. (1.0 rel. vol.); (5) Add seeds, 1% w/w and wait for at least 30 minutes; (5) start the addition of the remaining acid solution over 2 hrs.; (6) after additional ageing for at least 2 hrs., filtrate the slurry; (7) wash with MTBE, 10 rel. vol.; and (8) dry at vacuum and at 20° C. Using the same method, scaled up, Form B was produced with a yield of 93%, with formation of about 400 gram oxalate salt.

[0151] In another example form B was produced following the steps: (1) dissolve the free base (400 gram) in 2 relative volumes of acetonitrile (800 ml) and 3.0 equivalents (32.3 ml) water at 20° C.; (2) dissolve 1.01 equivalents (55.46 gram) of oxalic acid (98%) in 11 relative volumes (4400 ml) of ethyl acetate; (3) add 60% of the oxalic acid solution to the free base solution over about 30 minutes at 20° C.; (4) Add seeds, 1% w/w and wait for at least 30 minutes; (5) Start the addition of the remaining acid solution over 2 hrs. at 20° C.; (6) Cool to 10° C. over 1 hr. (7) after additional ageing for at least 1 hr. filter the slurry; (8) wash with a mixture of acetonitrile (1 rel. vol. 400 ml) and ethyl acetate (5.5 rel. vol. 2200 ml) at 10° C.; (9) wash with 2.5 rel. vol. (1000 ml) ethyl acetate at 20° C.; (10) dry at vacuum and 40° C.

[0152] The crystallinity of the salt was good as demonstrated by XRPD (FIG. 3). XRPD pattern data for Form B are provided in Table 7.

TABLE 7

XRPD Values for mPEG ₇ -O-Naloxol Oxalate Salt Form B			
2θ Angle, °	d value, Å	Relative Intensity, %	
6.72	13.2	100	s
7.35	12.0	5	w

TABLE 7-continued

XRPD Values for mPEG ₇ -O-Naloxol Oxalate Salt Form B			
2θ Angle, °	d value, Å	Relative Intensity, %	
9.13	9.7	<5	w
9.37	9.4	<5	w
10.72	8.3	<5	w
10.82	8.2	<5	w
11.24	7.9	10	m
12.02	7.4	5	w
12.65	7.0	5	m
13.44	6.6	40	s
14.72	6.0	10	m
15.61	5.7	15	m
15.95	5.6	10	w
16.53	5.4	5	w
17.01	5.2	15	m
17.22	5.1	10	w
17.34	5.1	20	m
18.06	4.91	5	w
18.25	4.86	5	w
18.56	4.78	5	w
18.86	4.71	5	w
19.81	4.48	10	w
19.98	4.44	25	m
20.21	4.39	100	s
21.33	4.17	10	w
21.75	4.09	10	w
22.50	3.95	35	m
22.72	3.91	10	w
22.93	3.88	40	m
24.14	3.69	5	w
24.53	3.63	50	m
25.99	3.43	30	m
27.07	3.29	5	w
28.40	3.14	15	w
29.64	3.01	5	w

[0153] Further analysis of Form B by DSC showed a sharp endothermic peak at 92.5° C. (ΔH is 96.1 J/g), which was

[0154] Thermogravimetric analysis showed negligible weight loss (~0.3%) up to 90° C. Scanning electron microscopy visualization indicated that the isolated material is composed of aggregates of small crystalline thin plates.

[0155] When analyzed by NMR, it was observed that chemical shifts within the solution ¹H-NMR spectra are consistent with salt formation. Proton NMR with an internal standard (sodium formate) indicated that Form B is an unsolvated mono-oxalate (1:1) salt. Summary of NMR assignments for mPEG₇-O-naloxol oxalate salt were as follows.

[0156] ¹H NMR, ppm (multiplicity, number of H, coupling constants in Hz if possible): 1.35 (m, 1H), 1.55-1.67 (m, 2H), 1.74 (dd, 1H, 4, 14), 1.77-1.85 (m, 1H), 2.49 (dt, 1H, 5, 14), 2.90 (dt, 1H, 4, 13), 3.09 (dd, 1H, 7, 20), 3.23 (dd, 1H, 5, 13), 3.36 (s, 3H), 3.39 (d, 1H, 20), 3.51-3.90 (m, 31H), 4.01 (m, 1H), 4.92 (d, 1H, 5), 5.60 (d, 1H, 10), 5.61 (d, 1H, 17), 5.88 (m, 1H), 6.73 (d, 1H, 8), 6.83 (d, 1H, 8).

[0157] ¹³C NMR, ppm: 20.0, 23.0, 27.2, 29.1, 45.3, 45.8, 55.7, 58.0, 62.4, 69.1, 69.4, 69.5-69.5 (multiple of signals), 69.6, 69.8, 70.5, 70.9, 74.1, 87.2, 118.3, 119.6, 122.3, 125.8, 126.2, 129.2, 137.7, 145.3, 165.8.

[0158] 6.4 Stability Studies on mPEG₇-O-Naloxol Oxalate Salt Form B

[0159] Stability of mPEG₇-O-naloxol oxalate salt form B under different storage conditions was assessed by storing individual samples at a temperature ranging from about 5° C. to about 70° C., with varying relative humidity ("RH"), for 2 or 4 weeks, using unsealed bottles without added anti-oxidants. After storage, the samples were visually inspected, its solid state form analyzed by XRPD, and then chemically analyzed by tandem gas chromatography/mass spectrometry (starting samples) or liquid chromatography/mass spectrometry (all other samples) for impurities including glycylaldehyde, as summarized in Table 8. In Table 8, concentrations of glycylaldehyde, an oxidative degradation product of mPEG₇-O-naloxol free base, are provided in parts per million (ppm).

TABLE 8

Stability of mPEG ₇ -O-Naloxol Oxalate Salt Form B As Compared to mPEG ₇ -O-Naloxol Free Base				
Condition, Time Period	Appearance	Organic Impurities (area %)	XRPD	Glycylaldehyde (ppm)
Oxalate salt				
Salt, 0 weeks	White powder	1.74	Form B	<1.2
25° C., 60% RH, 2 weeks	White powder	1.63	Form B	<5
25° C., 60% RH, 4 weeks	White powder	1.62	Form B	<5
40° C., 75% RH, 2 weeks	Pale yellow liquid	1.60	(liquid)	<5
40° C., 75% RH, 4 weeks	Pale yellow liquid	1.67	(liquid)	<5
5° C., 4 weeks	White powder	1.63	Form B	<5
40° C., 2 weeks	White powder	1.57	Form B	<5
40° C., 4 weeks	White powder	1.67	Form B	<5
70° C., 2 weeks	Pale yellow powder	1.64	Form B	<5
70° C., 4 weeks	Pale yellow powder	1.95	Form B	<5
Free Base				
Free base, 0 weeks	Yellow to brown liquid	2.4	(oil)	1.6
40° C., 4 weeks	Dark yellow liquid	3.74	(oil)	440

confirmed as the melt by hot stage microscopy. Moisture uptake by DVS showed a minor uptake below 70% relative humidity (RH). Above 70% RH there is moisture uptake indicating deliquescence. There was hysteresis during desorption.

[0160] The results in Table 8 show that at high relative humidity (75% RH), the salt liquefies which, consistent with the DVS analysis of form B (see subsection 6.3.2, above), is likely due to moisture uptake. The impurities associated in the salt were not observed to increase. Unlike the free base in

which the concentration of glycidaldehyde increased from 1.6 ppm to about 440 ppm when stored at 40° C., glycidaldehyde was below 5 ppm in all salt samples. No change to the solid state form was observed over time for any of the powder samples.

6.5 Exemplary Pharmaceutical Formulations

[0161] Prophetic pharmaceutical formulations comprising solid B mPEG₇-O-naloxol oxalate salt form B for oral administration are provided below.

[0162] Exemplary Capsule Formulation for Oral Administration.

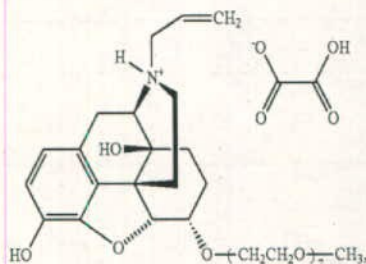
[0163] Ingredients of 30 mg mPEG₇-O-naloxol oxalate salt Form B, 50 mg Lactose, 50 mg Starch, 2 mg Talc and 10 mg magnesium stearate, in proper quantity, are mixed, and filled in a gelatin capsule according to conventional preparation for capsules known to those skilled in the art to give a capsule.

[0164] Modifications and variations in the subject matter set forth in the above illustrative examples are expected to occur to those skilled in the art. Only such limitations as appear in the appended claims should be placed on any claimed invention.

[0165] All publications including books, patents, patent applications and published patent applications cited herein are hereby incorporated by reference in their entireties for all purposes.

1. A crystalline oxalate salt of mPEG₇-O-naloxol.

2. A method of producing a naloxol-polyethylene glycol conjugate oxalate salt, wherein the salt comprises an ionic species of mPEG₇-O-naloxol and oxalic acid having the formula:



the method comprising:

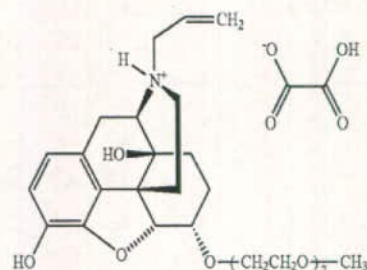
dissolving mPEG₇-O-naloxol free base in 2 relative volumes of acetonitrile;

adding 3 equivalents of water to the dissolved mPEG₇-O-naloxol solution;

adding oxalic acid in ethyl acetate to the dissolved mPEG₇-O-naloxol over a period of at least 2 hours to produce a slurry; and

filtering the slurry to yield the naloxol-polyethylene glycol conjugate oxalate salt in solid form.

3. A method of producing a naloxol-polyethylene glycol conjugate oxalate salt, wherein the salt comprises an ionic species of mPEG₇-O-naloxol and oxalic acid having the formula:



the method comprising:

dissolving mPEG₇-O-naloxol free base in 2 relative volumes of ethanol;

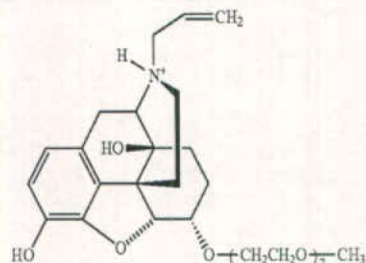
adding 8 relative volumes of methyl t-butyl ether to the dissolved mPEG₇-O-naloxol solution;

adding oxalic acid in methyl t-butyl ether to the dissolved mPEG₇-O-naloxol over a period of at least 2 hours to produce a slurry; and

filtering the slurry to yield the naloxol-polyethylene glycol conjugate oxalate salt in solid form.

4. A naloxol-polyethylene glycol conjugate oxalate salt prepared according to the method of claim 2.

5. A naloxol-polyethylene glycol conjugate oxalate salt, wherein the naloxol-polyethylene glycol conjugate has the formula:



6. The naloxol-polyethylene glycol conjugate oxalate salt of claim 5, wherein the salt is in a substantially pure crystalline form.

7. The naloxol-polyethylene glycol conjugate oxalate salt of claim 5 wherein the crystalline form exhibits Form A X-ray powder diffraction pattern substantially as that shown in FIG. 2.

8. The naloxol-polyethylene glycol conjugate oxalate salt of claim 5 wherein the crystalline form exhibits Form B X-ray powder diffraction peak d values (Å) comprising 13.2; 7.9; 7.0; 6.6; 6.0; 5.7; 5.2; 5.1; 4.44; 4.39; 3.95; 3.88; 3.63; and 3.43.

9. The naloxol-polyethylene glycol conjugate oxalate salt of claim 8, wherein X-ray powder diffraction peak d values (Å) comprise 13.2; 12.0; 9.7; 9.4; 8.3; 8.2; 7.9; 7.4; 7.0; 6.6; 6.0; 5.7; 5.6; 5.4; 5.2; 5.1; 4.91; 4.86; 4.78; 4.71; 4.48; 4.44; 4.39; 4.17; 4.09; 3.95; 3.91; 3.88; 3.69; 3.63; 3.43; 3.29; 3.14; and 3.01.

10. The naloxol-polyethylene glycol conjugate oxalate salt of claim 6 wherein the crystalline form exhibits Form B X-ray

powder diffraction 2θ angle peaks at (degrees): 6.72; 11.24; 12.65; 13.44; 14.72; 15.61; 17.01; 17.34; 19.98; 20.21; 22.50; 22.93; 24.53; and 25.99.

11. The naloxol-polyethylene glycol conjugate oxalate salt of claim 6 having a purity of at least about 90%.

12. The naloxol-polyethylene glycol conjugate oxalate salt of claim 6, wherein the salt exhibits a single endothermal peak on differential scanning calorimetry between room temperature and about 150° C., wherein the single endothermal peak maximum occurs between about 91° C. to about 94° C.

13. A pharmaceutical composition comprising the naloxol-polyethylene glycol conjugate oxalate salt of claim 6 and a pharmaceutically acceptable excipient.

14. The pharmaceutical composition of claim 13 formulated for oral administration to a subject.

15. (canceled)

* * * * *



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PAPER NUMBER

1625

DATE MAILED: 01/08/2015

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/823,953	09/04/2013	Bengt Leonard Aslund	104068USPCT(12745-23-999)	4418

TITLE OF INVENTION: CRYSTALLINE NALOXOL-PEG CONJUGATE

APPL. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$960	\$0	\$0	\$960	04/08/2015

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/823,953	09/04/2013	Bengt Leonard Aslund	104068USPCT(12745-23-999)	4418

TITLE OF INVENTION: CRYSTALLINE NALOXOL-PEG CONJUGATE

APPL.N. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$960	\$0	\$0	\$960	04/08/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
AULAKH, CHARANJIT	1625	514-282000

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NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/823,953	09/04/2013	Bengt Leonard Aslund	104068USPCT(12745-23-999)	4418
20583	7590	01/08/2015	EXAMINER	
JONES DAY 222 EAST 41ST ST NEW YORK, NY 10017			AULAKH, CHARANJIT	
			ART UNIT	PAPER NUMBER
			1625	
DATE MAILED: 01/08/2015				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.** Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 13/823,953	Applicant(s) ASLUND ET AL.	
	Examiner Charanjit Aulakh	Art Unit 1625	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to Paper filed on 18 December 2014.
☐ A declaration(s)/affidavit(s) under 37 CFR 1.130(b) was/were filed on _____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 1-14. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some *c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has **THREE MONTHS FROM THE "MAILING DATE"** of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in **ABANDONMENT** of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892) 2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date <u>12/18/14</u> 3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material 4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____	5. ☐ Examiner's Amendment/Comment 6. ☐ Examiner's Statement of Reasons for Allowance 7. ☒ Other <u>The drawings are accepted.</u>
--	---

/Charanjit Aulakh/
 Primary Examiner, Art Unit 1625

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	13823953
Filing Date	2013-09-04
First Named Inventor	Bengt Leonard Aslund
Art Unit	1625
Examiner Name	Charanjit Aulakh
Attorney Docket Number	104068USPCT (12745-23-999)

U.S. PATENTS

Examiner Initial*	Cite No.	Patent Number	Kind Code ¹	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/CA/	1	8,067,431	B2	2011-11-29	FISHBURN et al.	
/CA/	2	8,440,687	B2	2013-05-14	RIGGS-SAUTHIER et al.	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number	Kind Code ¹	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/CA/	1	2006/0182692	A1	2006-08-17	FISHBURN et al.	
/CA/	2	2010/0210676	A1	2010-08-19	FISHBURN et al.	
/CA/	3	2012/0264775	A1	2012-10-18	RIGGS-SAUTHIER et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number ¹	Country Code ²	Kind Code ⁴	Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ³
/CA/	1	2003/084504	WO	A2	2003-10-16	EURO-CELTIQUE S.A. [LU]		☐

NON PATENT LITERATURE DOCUMENTS

Examiner Initial*	Cite No.	Include name of the author (in CAPITAL LETTERS), (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ³
/CA/	1	BERGE et al., "Pharmaceutical Salts," J. Pharm. Sci. (January 1977), pp. 132-150, Vol. 66, No. 1.	☐
/CA/	2	BRITAIN et al., "Polymorphism in Pharmaceutical Solids", Second Ed., (2009), pp. 334-335, Informa Healthcare, New York.	☐
/CA/	3	EUROPEAN SEARCHING AUTHORITY, "Supplementary Search Report for International Application No. EP 11829686," (August 18, 2014), 10 pages.	☐
/CA/	4	INTERNATIONAL CENTRE FOR TRADE AND SUSTAINABLE DEVELOPMENT (ICTSD) et al., "Guidelines for the examination of pharmaceutical patents: developing a public health perspective - A Working Paper, by C. Correa, (January 2007), 56 pages, available at http://ictsd.org/i/publications/11393/?view=document	☐
/CA/	5	LAHIANI-SKIBA et al., "Solubility and dissolution rate of progesterone-cyclodextrin-polymer systems," Drug Dev. Ind. Pharm., (2006), pages 1043-1058, Vol. 32, No.9.	☐
/CA/	6	ODINEES et al., "NKTR-118, An Oral 15 Peripheral Opioid antagonist, Has Low Potential for Drug-Drug Interactions," Journal of Clinical Pharmacology, (September 13-15, 2009), page 1123, Vol. 49, No. 9, Post 28, 38 th Annual Meeting of the American-College-of-Clinical-Pharmacology, San Antonio, TX.	☐
/CA/	7	ODINEES, A., et al., "Comparative 15 Bioavailability of NKTR-118 Tablets and Solution: A Case of Bioequivalence Between Dosage Forms for a Rapidly Absorbed Drug," Journal of Clinical Pharmacology, (September 13-15, 2009), page 1123, Vol. 49, No. 9, Post 27, 38 th Annual Meeting of the American-College-of-Clinical-Pharmacology, San Antonio, TX	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	13823953
Filing Date	2013-09-04
First Named Inventor	Bengt Leonard Aslund
Art Unit	1625
Examiner Name	Charanjit Aulakh
Attorney Docket Number	104068USPCT (12745-23-999)

NON PATENT LITERATURE DOCUMENTS

Examiner Initial*	Cite No.	Include name of the author (in CAPITAL LETTERS), (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
/CA/	8	Water-Insoluble Drug Formulation, 2nd Edition, R. Liu (editor), CRC Press/Taylor & Francis Group, Boca Raton, Florida USA (2008), pages 166-168.	☐

EXAMINER SIGNATURE

Examiner Signature	/Charanjit Aulakh/	Date Considered	12/23/2014
--------------------	--------------------	-----------------	------------

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	13823953
Filing Date	2013-09-04
First Named Inventor	Bengt Leonard Aslund
Art Unit	1625
Examiner Name	Charanjit Aulakh
Attorney Docket Number	104068USPCT (12745-23-999)

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

- ☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

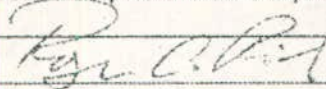
OR

- ☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

- ☐ See attached certification statement.
- ☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.
- ☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature		Date (YYYY-MM-DD)	2014-12-18
Name/Print	Roger C. Rich for Anthony Insogna, Reg. No. 35,203	Registration Number	54,398

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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*** Soporte del Pago ***

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RECIBO DE CA	999999999	5875	20/01/2015		24.945.000.00
RECIBO DE CA	999999999	7174	20/01/2015		1.054.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICACIONES	EN CREACION CORRECCION A SOLICITUD EN TRAMITE / MODIFICA	132.000.00	132.000.00
				\$132.000.00

SON: **CIENTO TREINTAY DOS MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-090985- -00011-0000

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Act. 412 REPOSPRESRECU Folios: 25

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