

POSSE
HERRERA
RUIZ

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 14-045641- -00000-0000

Fecha: 2014-03-04 14:29:05 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 166



Industria y Comercio
SUPERINTENDENCIA

DELEGATURA DE NUEVAS CREACIONES

SOLICITUD
FASE NACIONAL -PCT

21. EXPEDIENTE No. _____

54. TITULO: NUEVA COMPOSICIÓN FARMACÉUTICA
RESISTENTE AL ABUSO PARA EL TRATAMIENTO DE
LA DEPENDENCIA DE OPIOIDES

51. CLASIFICACION INTERNACIONAL:

A61K 9/00 (2006.01) A61K 31/485 (2006.01)

71. SOLICITANTE:

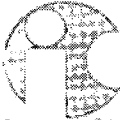
OREXO AB

DOMICILIO:

PO Box 303, SE-751 05 Uppsala SUECIA

74. APODERADO: HELENA CAMARGO WILLIAMSON

22. BOGOTÁ D.C., MARZO 4 DE 2014

 Industria y Comercio SUPERINTENDENCIA	SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  No. 14-045641- -00000-0000 Fecha: 2014-03-04 14:29:05 Tra. 11 PATENTEIYII Act. 411 PRESENTACION Dep. 2020 DIR.NUEVASCR Eve: 379 FASENACIONALII Folios: 100 170 radicación
---	---

DIRECCIÓN DE NUEVAS CREACIONES
SOLICITUD FASE NACIONAL –PCT

1	TIPO DE SOLICITUD	☒ Patente de invención ☐ Capítulo I	☐ Patente de Modelo de Utilidad ☒ Capítulo II
2	DATOS SOLICITUD INTERNACIONAL PCT (86)		
Solicitud Internacional No.		PCT/GB2012/052303	Fecha 18/09/2012
Publicación Internacional No.		WO 2013/041851 A1	Fecha 28/03/2013
3	TÍTULO DE LA INVENCIÓN (200 caracteres o espacios máximos)		
NUEVA COMPOSICIÓN FARMACÉUTICA RESISTENTE AL ABUSO PARA EL TRATAMIENTO DE LA DEPENDENCIA DE OPIOIDES			
4	CLASIFICACIÓN INTERNACIONAL (CIP)		
A61K 9/00 (2006.01)		A61K 31/485 (2006.01)	
SOLICITANTE (S) Esta persona también es inventor. Para datos adicionales utilizar hoja de información complementaria			
APELLIDOS O RAZÓN SOCIAL		NOMBRE	IDENTIFICACIÓN TIPO
OREXO AB			
6	DATOS DEL SOLICITANTE		
DIRECCIÓN		PO Box 303, SE-751 05 Uppsala	
CIUDAD			
DEPARTAMENTO/ESTADO			
PAÍS DE RESIDENCIA		SUECIA	
No. TELÉFONO			
CORREO ELECTRÓNICO			
NACIONALIDAD O LUGAR DE CONSTITUCIÓN		SUECIA	
7	INVENTOR (ES) Para datos adicionales utilizar hoja de información complementaria		
APELLIDOS		NOMBRES	NACIONALIDAD
1. FISCHER		1. Andreas	1. SUECIA
DIRECCIÓN DE CORREO ELECTRÓNICO:			
8	DATOS INVENTOR (ES)		
PAÍS RESIDENCIA		DEPARTAMENTO/ESTADO	CIUDAD DIRECCIÓN
1. SUECIA			1. Uppsala 1. Orexo AB, PO Box 303, SE-751 05
OTRO(S) SOLICITANTE(S) Y/O (OTRO(S)) INVENTOR(ES)			
☐ Los demás solicitantes y/o (demás) inventores se indican en una hoja a continuación.			
9	☐ REPRESENTANTE LEGAL ☒ APODERADO		
APELLIDOS		NOMBRES	IDENTIFICACIÓN
CAMARGO WILLIAMSON		HELENA	C.C 35.455.268 Bta. T.P 76985
DIRECCIÓN		CARRERA 7 N° 71 – 52, TORRE A, PISO 5	
CIUDAD		BOGOTÁ	
PAÍS		COLOMBIA	
No. TELÉFONO		3257300	
CORREO ELECTRÓNICO		helena.camargo@phrlegal.com	
No. RADICACIÓN DE PROTOCOLO DE PODER GENERAL			
10	DECLARACIONES DE PRIORIDAD ☒ SI ☐ NO		
(33) PAÍS DE ORIGEN		CÓDIGO PAÍS	(31) NÚMERO (32) FECHA (AAAA/MM/DD)
1. ESTADOS UNIDOS DE AMERICA			61/536,180 19/09/2011

2

11

DECLARACIÓN SOBRE USO DE RECURSOS GENÉTICOS O BIOLÓGICOS

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de recursos genéticos o biológicos de los que cualquiera de los países miembros de la Comunidad Andina es país de origen.

☐ SI

☒ NO

Nota: En caso afirmativo deberá anexar copia del contrato de acceso de recursos genéticos o productos derivados, o certificado o número de registro, expedido por la Autoridad competente.

12

DECLARACIÓN SOBRE USO DE CONOCIMIENTOS TRADICIONALES

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de conocimientos tradicionales de comunidades indígenas, afroamericanas o locales de países miembros de la Comunidad Andina.

☐ SI

☒ NO

Nota: En caso afirmativo deberá anexar la licencia o autorización de uso de conocimiento tradicional, o certificado, o número de registro expedido por la Autoridad competente.

13

REDUCCIÓN DE TASAS

Declaro que carezco de medios económicos para presentar la solicitud de patente.

☐ SI

☒ NO

Nota: En caso de ser persona natural y carecer de medios económicos, y por lo tanto, aplique la reducción de tasas a que se refiere la resolución vigente en tarifas, debe firmar la presente solicitud bajo la gravedad de juramento.

Micro, pequeñas y medianas empresas

Universidades públicas o privadas

Entidades sin ánimo de lucro

☐

☐

☐

Debe aportar los documentos que se indican en el numeral 17 de anexos

14

AUTORIZACIÓN DE NOTIFICACIÓN EN LÍNEA

☒ SI

☐ NO

Manifiesto que he leído y entendido perfectamente los términos y condiciones de uso de medios electrónicos para las notificaciones en línea a través de Internet de los actos administrativos proferidos por la Superintendencia de Industria y Comercio que deben ser notificados personalmente y, en consecuencia, autorizo el servicio de notificación a través de internet.

15

COMPROBANTE DE PAGO O PAGO ELECTRÓNICO

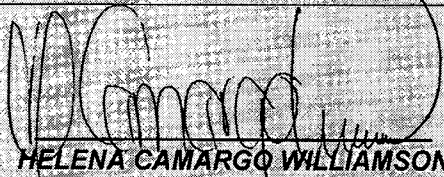
N°

Fecha

16

FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL

Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)


HELENA CAMARGO WILLIAMSON

17

ANEXOS

Documentación Técnica

Solicitud Internacional en castellano

1.

☒ Descripción

N° de folios:

2.

☒ Reivindicaciones

N° Reivindicaciones:

3.

☒ Dibujos y/o figuras

N° folios:

4.

☒ Resumen.

5.

☐ Certificado de depósito de material biológico si fuera el caso.

6.

☐ Listado de secuencias de nucleótidos y/o aminoácidos en forma digital si fuera el caso.

7.

☐ Arte final 12 x 12.

8.

☐ Anexo formato digital.

Documentación Jurídica

9.

☐ Poderes, si fuera el caso,

10.

☐ Documento que legalmente pruebe la cesión del inventor al solicitante o a su causante.

11.

☐ Copia del contrato de acceso de recursos genéticos o productos derivados, certificado o número de registro, si fuera el caso.

12.

☐ Copia de la licencia o autorización de Conocimientos Tradicionales, certificado o número de registro, si fuera el caso.

13.

Reducción de tasas

Micro, pequeñas o medianas empresas

☐ Copia simple de la declaración de renta del año inmediatamente anterior, o en su defecto prueba documental idónea.

☐ Documento de constancia de cumplimiento con lo establecido en la ley 905 de 2004.

Universidades públicas o privadas

☐ Copia acto de reconocimiento institucional emitido por el Ministerio de Educación

Entidades sin ánimo de lucro

☐ Copia de registro vigente en Cámara de comercio.

☐ Hoja de información complementaria.

☐ Otros, especificar

14.

☒ Comprobante de pago de la tasa de presentación de la solicitud.

15.

☐ Comprobante de pago por reivindicación de prioridad.

16.

☐ Comprobante de pago de la tasa por concepto de excedente de palabras en la publicación.

17.

☒ Comprobante de pago por reivindicación adicional a 10.

PI02-F06 vr4 (2012-04-19)

NUEVA COMPOSICIÓN FARMACÉUTICA RESISTENTE AL ABUSO PARA EL TRATAMIENTO DE LA DEPENDENCIA DE OPIOIDES

La presente invención se refiere a nuevas composiciones farmacéuticas que
5 comprenden opioides que son útiles en el tratamiento de la dependencia de
opioides/opiáceos y/o del dolor, composiciones que pueden ser resistentes al
abuso y que se pueden administrar por vía transmucosa y, en particular,
sublingual.

Los opioides se usan ampliamente en medicina como analgésicos. De
10 hecho, en la actualidad se ha aceptado que, en el alivio del dolor más grave, no
existen agentes terapéuticos más eficaces.

Los analgésicos agonistas de opioides se usan para tratar el dolor por cáncer
crónico de moderado a grave, a menudo en combinación con fármacos
antiinflamatorios no esteroideos (AINE), así como el dolor agudo (es decir, durante
15 la recuperación de la cirugía y del dolor intercurrente. Además, su uso es cada vez
mayor en la gestión del dolor no maligno crónico.

No obstante, un problema perenne con potentes agonistas opioides es el de
su abuso por los drogadictos. La drogadicción es un problema mundial del que la
dependencia de los opioides, principalmente la heroína, es un componente
20 principal. La Organización Mundial de la Salud (OMS) estima que existen
aproximadamente 4,3 millones de adictos a los opioides a nivel mundial, con
aproximadamente 0,7 millones en Europa y 0,2 millones en EE.UU. y Canadá.

La dependencia de los opioides es un importante problema de salud y el uso
de la heroína a largo plazo está relacionado con un riesgo sustancialmente mayor
25 de muerte prematura por sobredosis de drogas, violencia y suicidio. Además,
compartir agujas entre los adictos contribuyen a la diseminación de infecciones de
sangre potencialmente mortales tales como VIH y hepatitis C. Además, la
dependencia de opioides a menudo conduce a dificultades en las relaciones
sociales, incapacidad para manejar un trabajo normal y aumento de la criminalidad

para financiarse la adicción, con implicaciones graves para la persona dependiente de opioides y su familia.

Los adictos a los opioides no solo alimentan su adicción mediante la adquisición directa de opioides “en la calle”, normalmente en forma de polvos con base de opioide (como heroína), sino que también consiguen formulaciones farmacéuticas destinadas al tratamiento de, por ejemplo, el dolor. Dichos individuos a menudo aplican innovadoras técnicas en su abuso de dichas formulaciones, por ejemplo extrayendo una gran cantidad de principios activos de dicha formulación en solución, que después se inyecta por vía intravenosa. Con la mayoría de las formulaciones farmacéuticas disponibles en el comercio, esto se puede realizar relativamente fácilmente, lo que las hace inseguras o “de las que se puede abusar”. Por tanto, existe la necesidad general de formulaciones farmacéuticas de las que no se pueda abusar que comprendan agonistas de opioides.

Los adictos a los opioides a menudo se tratan a modo de terapia “de sustitución”, en la que principalmente los opioides “de la calle” de potencia y pureza desconocidos son sustituidos por opioides de calidad farmacéutica con una duración de acción más prolongada, tal como buprenorfina.

Además, durante la última década ha comenzado a aparecer una nueva cohorte de individuos dependientes de opioides, en particular en EE.UU., es decir, los denominados adictos de “cuello blanco”, que se han convertido en dependientes tras serles prescritos opioides, normalmente iniciados para el tratamiento del dolor. También se requiere terapia de sustitución para este grupo creciente de pacientes.

Los antagonistas de opioides se usan para invertir los efectos farmacológicos de los opioides. Los antagonistas selectivos de los opioides, tales como la naloxona, pueden usarse para tratar la sobredosis por fármacos narcóticos o para diagnosticar una sospecha de adicción a opioides. La naloxona, en particular, tiene una mala biodisponibilidad cuando se administra por vía transmucosa, pero

se hace completamente biodisponible cuando se administra mediante inyección.

Un simple comprimido de combinación en mezcla que comprende el agonista parcial de opioides buprenorfina y naloxona en una proporción de 4:1 para administración sublingual está disponible como la marca registrada Suboxone®.

- 5 (Esta y otras formulaciones que contienen opioides resistentes al abuso se recapitulan en Fudula y Johnson in Drug and Alcohol Dependence, 83S, S40 (2006). Véase, también, las solicitudes de patente de EE.UU. US 2003/0124061 y US 2003/0191147.).

- 10 Dada la mala biodisponibilidad transmucosa de la naloxona, si Suboxone se toma por vía sublingual, como se ha indicado, la pequeña cantidad de naloxona que se absorbe no debería interferir en los efectos deseados de la buprenorfina.

- Por otro lado, si un adicto disuelve e inyecta Suboxone con la idea de tener un “viaje”, la mayor disponibilidad de la naloxona por vía parenteral deberá servir para antagonizar los efectos de la buprenorfina, al mismo tiempo que
15 desencadena desagradables síntomas de abstinencia de opioides en un individuo físicamente dependiente de opioides.

- No obstante, cuando se administra por vía parenteral, el bloqueo funcional por la naloxona de la acción de la buprenorfina también tiene una naturaleza solo parcial y de vida corta. A la luz de esto, con frecuencia se ha notificado la diversión
20 y el uso ilícito de Suboxone, en especial en poblaciones escondidas como encarcelados y drogadictos activos (véase, por ejemplo, Alho et al, Drug and Alcohol Dependence, 88, 75 (2007), Monte et al, Journal of Addictive Diseases, 28, 226 (2009), Stimmel, ibid., 26, 1 (2007) and Smith et al, ibid., 26, 107, 2007). De hecho, en un estudio reciente de adictos a drogas intravenosas sin tratar en
25 Finlandia, se reveló que el 68% había notificado abuso de Suboxone. Además, el 66% de los que habían abusado del fármaco una vez admitió que también habían abusado del mismo al menos una vez después o incluso con regularidad (véase, Ahlo et al, supra).

Además, también se ha informado de que Suboxone tiene otras varias

limitaciones significativas. Por ejemplo, los comprimidos son grandes y se disgregan lentamente. La biodisponibilidad de la buprenorfina también es significativamente menor que para una solución sublingual (véase Compton et al, Drug and Alcohol Dependence, 82, 25 (2006)). Además, el gusto no es bien tolerado por todos los pacientes y el comprimido tienen una sensación en boca arenosa desagradable. Un producto a base de película se ha desarrollado recientemente para contrarrestar estos problemas, pero la formulación pelicular tampoco se disuelve particularmente rápidamente. Además, de forma simultánea solo se puede administrar una máximo de solo dos películas (con dosis de 2 mg y 8 mg de buprenorfina). Por tanto, se requiere la administración secuencial para dosis (de administración habitual) superiores a 10 mg o a 16 mg de buprenorfina, respectivamente.

Por tanto, existe una necesidad clínica actualmente no satisfecha de un producto resistente al abuso para usar en la terapia de sustitución de la adicción de opioides, pero que no posea las limitaciones mencionadas anteriormente. En particular, si fuera posible idear una formulación que fuera capaz de incrementar significativamente la biodisponibilidad de la buprenorfina, podría ser posible reducir la cantidad de este ingrediente farmacéutico activo, dando lugar a menos opioide en la formulación y, de este modo, reducir la cantidad disponible para inyectar por diversión mediante abuso intravenoso.

Las solicitudes de patente internacionales WO 00/16751, WO 2004/067004, WO 2006/103418 and WO 2008/068471 divulgan todas ellas sistemas de liberación de fármacos para el tratamiento de, por ejemplo, el dolor agudo mediante administración sublingual, aplicando el principio de la mezcla interactiva, en el que el ingrediente activo en forma de micropartículas se adhiere a las superficies de partículas vehículo más grandes en presencia de un agente estimulante bioadhesivo y/o mucoadhesivo. En particular, el documento WO 2008/068471 divulga una formulación que comprende partículas de fármacos agonistas opioides sobre las superficies de partículas vehículo que comprenden

un antagonista de opioides, tal como naloxona.

Los documentos de la técnica anterior, incluidas las solicitudes de patente internacional WO 03/005944, WO 02/067903, WO 2007/141328, WO 2010/132605, WO 01/30288 y la solicitud de patente de EE.UU. 2009/0263476 A1
5 usan agentes modificadores del pH para estimular la disolución y/o la absorción de ingredientes activos.

Los inventores han descubierto ahora que aplicando un principio de formulación específico a una combinación de ingredientes activos, buprenorfina y naloxona, los inventores han proporcionado un producto con propiedades clínicas y farmacéuticas inesperadas y significativamente mejoradas.
10

De acuerdo con un primer aspecto de la invención se proporciona una composición farmacéutica que comprende micropartículas de una cantidad farmacológicamente eficaz de buprenorfina o una sal farmacéuticamente aceptable de la misma, en mezcla asociativa con partículas que comprenden un ácido débil o partículas que comprenden materiales formadores de tampón débilmente ácido. Dichas composiciones se denominan en el presente documento "las composiciones de la invención".
15

Se prefiere que las composiciones farmacéuticas que comprenden buprenorfina, o una sal farmacéuticamente aceptable de la misma, se presenten mezcladas (p. ej., en mezcla simple) con un disgregante.
20

A este respecto, se proporciona además una composición farmacéutica que comprende:

- (i) una composición de la invención como se ha definido anteriormente en el presente documento ("Componente (i)"); y
- 25 (ii) un disgregante (en lo sucesivo en el presente documento "Componente (ii)").

Las composiciones que comprenden los Componentes (i) y (ii) también se denominan en lo sucesivo en el presente documento composiciones de la invención.

También se prefiere que las composiciones farmacéuticas que comprenden buprenorfina, o una sal farmacéuticamente aceptable de la misma, se presenten mezcladas (p. ej., en mezcla simple) con un disgregante y naloxona.

5 A este respecto, se proporciona además una composición farmacéutica que comprende:

(a) una composición de la invención que comprende los Componentes (i) y/o (ii) como se ha definido anteriormente en el presente documento; y

(b) partículas de una cantidad terapéuticamente eficaz de un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo (en lo sucesivo en el presente documento "Componente (iii)").

Las composiciones que comprenden el Componente (iii) formulado junto con los Componentes (i) y/o (ii) también se denominan en lo sucesivo en el presente documento composiciones de la invención.

La buprenorfina y sus sales farmacéuticamente aceptables se presentan en las composiciones de la invención en forma de micropartículas. La naloxona y sus sales farmacéuticamente aceptables también pueden (p. ej., preferentemente) presentarse en las composiciones de la invención en forma de micropartículas. Las micropartículas poseen, preferentemente, un diámetro medio en base al peso, un diámetro medio en base al número y/o un diámetro medio en base al volumen de entre aproximadamente 0.5 μm y aproximadamente 15 μm , tal como aproximadamente 1 μm y aproximadamente 10 μm . Como se usa en el presente documento, el experto en la técnica entenderá que la expresión "diámetro medio en base al peso" incluye que el tamaño promedio de la partícula se caracteriza y define a partir de una distribución del tamaño de la partícula en peso, es decir una distribución en la que la fracción existente (cantidad relativa) en cada clase de tamaño se define como la fracción en peso, obtenida mediante, por ejemplo, tamizado (p.ej, tamizado en húmedo). Como se usa en el presente documento, el experto en la técnica entenderá que la expresión "diámetro medio en base al número" incluye que el tamaño promedio de la partícula se caracteriza y define a

d

partir de una distribución del tamaño de la partícula en número, es decir una distribución en la que la fracción existente (cantidad relativa) en cada clase de tamaño se define como la fracción en número, medida mediante, por ejemplo, microscopia. Como se usa en el presente documento, el experto en la técnica entenderá que la expresión "diámetro medio en base al volumen" incluye que el tamaño promedio de la partícula se caracteriza y define a partir de una distribución del tamaño de la partícula en volumen, es decir una distribución en la que la fracción existente (cantidad relativa) en cada clase de tamaño se define como la fracción en volumen, medida mediante, por ejemplo, difracción láser.

10 Las micropartículas de ingredientes activos se pueden preparar mediante técnicas de micronización estándar, tales como trituración, molturación en chorro, molturación en seco, molturación en húmedo, precipitación etc. Un procedimiento de elutriación en aire se puede usar después para preparar fracciones de tamaño específicos, en caso necesario.

15 Sales preferidas de buprenorfina and naloxona incluyen sales clorhidrato.

La buprenorfina y sus sales farmacéuticamente aceptables se formulan juntas en mezcla asociativa con partículas de un ácido débil o con o partículas de materiales formadores de tampón débilmente ácido, para proporcionar composiciones de la invención (o Componente (i) o composiciones de la invención.

20 Materiales débilmente ácidos que se pueden mencionar incluyen aquellos que, cuando se proporcionan en una composición de la invención, permiten la provisión cuando la composición está disuelta en agua y/o saliva (p. ej., en el lugar de administración de composiciones de la invención) de un pH de entre aproximadamente 4,0 y aproximadamente 6.5 (p. ej., aproximadamente 6.25), y están presentes en una cantidad suficiente para permitir el mantenimiento del pH dentro de este intervalo durante un periodo de tiempo adecuado (p. ej., aproximadamente 30 segundos, tal como aproximadamente 1 minuto) a aproximadamente 3 minutos (p. ej., aproximadamente 2 minutos, tal como

aproximadamente 1,5 minutos) para facilitar la disolución de, en particular, las micropartículas de buprenorfina y/o absorción de buprenorfina en la mucosa sublingual a continuación. Para los fines de la presente invención, el término incluye sustancias que son seguras para usar en mamíferos e incluye ácidos débiles, derivados de ácidos débiles y otras sustancias químicas que se convierten en ácidos débiles in vivo (p. ej., precursores que se convierten en ácidos in vivo, por ejemplo, siendo secuencialmente activados de acuerdo con las propiedades del ambiente local). Los pKa típicos de los ácidos débiles están en el intervalo de entre aproximadamente -1,5 (p. ej., aproximadamente -1,74) y aproximadamente 16 (p. ej., aproximadamente 15,74) (p. ej., véase Vollhardt, Organic Chemistry (1987). Un intervalo preferido está entre aproximadamente 1 y aproximadamente 10. Más preferentemente, el material débilmente ácido comprende un ácido débil que es seguro para consumo humano, por ejemplo un ácido alimentario, tal como ácido málico, ácido fumárico, ácido adípico, ácido succínico, ácido láctico, ácido acético, ácido oxálico, ácido maleico, cloruro amónico, preferentemente ácido tartárico, y, más preferentemente, ácido cítrico o una combinación de dichos ácidos. El experto en la técnica apreciará que, cuando se usan ácidos débiles que no son sólidos (y, por tanto, no son partículas) en o alrededor de la temperatura atmosférica y a presión atmosférica, se pueden adsorber en un material vehículo particulado (como sílice coloidal) con el fin de proporcionar partículas que comprenden el material débilmente ácido.

Los materiales formadores de tampón débilmente ácido, cuando se proporcionan en una composición de la invención, proporcionan un sistema tampón débilmente ácido cuando la composición está disuelta en agua y/o saliva (p. ej., en el lugar de administración de composiciones de la invención) lo que permite aportar un pH de entre aproximadamente 4,0 y aproximadamente 6,5 (p. ej., aproximadamente 6,25), y están presentes en una cantidad suficiente para permitir el mantenimiento del pH dentro de este intervalo durante un periodo de tiempo adecuado (p. ej., aproximadamente 30 segundos, tal como

- aproximadamente 1 minuto) a aproximadamente 3 minutos (p. ej., aproximadamente 2 minutos, tal como aproximadamente 1,5 minutos) para facilitar la disolución de, en particular, las micropartículas de buprenorfina y/o absorción de buprenorfina en la mucosa sublingual a continuación. Por tanto, materiales
- 5 formadores de tampón incluyen combinaciones de ácido débil y sal de ácido débil, tal como combinaciones de los ácidos mencionados anteriormente con sales alcalinas de dichos ácidos, incluyendo citrato sódico, citrato potásico, tartrato sódico, tartrato potásico y similares. Materiales formadores de tampón preferidos son ácido cítrico y citrato sódico. El experto en la técnica apreciará que, cuando se
- 10 usan materiales que no son sólidos (y, por tanto, no son partículas) en o alrededor de la temperatura atmosférica y a presión atmosférica, se pueden adsorber en un material vehículo particulado (como sílice coloidal) con el fin de proporcionar partículas que comprenden los materiales formadores de tampón débilmente ácido.
- 15 Tamaños de partículas adecuados de materiales débilmente ácidos, o formadores de tampón débilmente ácido, se encuentran en el intervalo de aproximadamente 1 μm y aproximadamente 1000 μm (p. ej., aproximadamente 800 μm , tal como aproximadamente 750 μm), y, preferentemente entre aproximadamente 40 (tal como aproximadamente 50 μm) y aproximadamente 600
- 20 μm . Cantidades adecuadas de materiales débilmente ácidos que permiten el mantenimiento del pH dentro de los intervalos mencionados anteriormente tras la administración oral como se ha descrito en el presente documento anteriormente están en el intervalo de al menos aproximadamente 1% a aproximadamente 10% en peso de la formulación total. Cantidades totales adecuadas de materiales
- 25 formadores de tampón débilmente ácido que permiten el mantenimiento del pH dentro de los intervalos mencionados anteriormente tras la administración oral como se ha descrito en el presente documento anteriormente están en el intervalo de al menos aproximadamente 1% a aproximadamente 15% en peso de la formulación total.

El disgregante o "agente disgregante" que se puede usar como, o como parte del, Componente (ii) en las composiciones de la invención se puede definir como cualquier material que es capaz de acelerar hasta un grado mensurable la disgregación/dispersión de una composición de la invención.

- 5 Por tanto, el disgregante puede proporcionar un tiempo de disgregación in vitro de aproximadamente 30 segundos o menos, medido de acuerdo con el procedimiento estándar de ensayo de disgregación de la Farmacopea de EE.UU. (USP) estándar (véase FDA Guidance for Industry: Orally Disintegrating Tablets; December 2008). Esto se puede conseguir, por ejemplo, si el material es capaz de
- 10 hincharse, absorber humedad y/o deformarse cuando entra en contacto con agua y/o moco (p. ej., saliva), causando, de este modo, que las formulaciones en comprimidos se disgreguen cuando están humedecidas.

- Disgregantes adecuados (como se define en, por ejemplo, Rowe et al, Handbook of Pharmaceutical Excipients, 6ª ed. (2009)) incluyen derivados de
- 15 celulosa tales como hidroxipropilcelulosa (HPC), HPC de baja sustitución, metilcelulosa, etilhidroxietilcelulosa, carboximetilcelulosa cálcica, carboximetilcelulosa sódica, celulosa microcristalina, goma de celulosa modificada; derivados de almidón tales como almidón moderadamente reticulado, hidroxipropilalmidón y almidón pregelatinizado; y otros disgregantes tales como
- 20 alginato cálcico, ácido alginico, quitosano, dióxido de silicio coloidal, docusato sódico, goma guar, silicato de magnesio aluminio, polacrilinpotasio y polivinilpirrolidona. Se pueden usar combinaciones de dos o más disgregantes.

- Disgregantes preferidos incluyen los denominados "superdisgregantes" (como se define en, por ejemplo, Mohanachandran et al, International Journal of
- 25 Pharmaceutical Sciences Review and Research, 6, 105 (2011)), tal como polivinilpirrolidona reticulada, glicolato de almidón sódico y croscarmelosa sódica. Se pueden usar combinaciones de dos o más superdisgregantes.

Los disgregantes también se pueden combinar con superdisgregantes en las composiciones de la invención.

Los disgregantes y/o superdisgregantes se usan, preferentemente, en una cantidad (p. ej., total) de entre 0,5 y 15% en peso en base al peso total de la composición. Un intervalo preferido es de 1 a 8%, tal como de aproximadamente 2 a aproximadamente 7% (p. ej., aproximadamente 5%, tal como aproximadamente 4%) en peso.

Las composiciones de la invención se pueden formular juntas (junto con cualquier otro material que pueda estar presente) mediante simples técnicas de mezclado estándar o mediante granulación.

Los gránulos se pueden preparar mediante un procedimiento de granulación en seco, granulación en húmedo, peletización termoplástica, granulación por pulverización o extrusión/esferonización.

Las técnicas de granulación en húmedo son bien conocidas para los expertos en la materia e incluyen cualquier técnica que implique el amasado de una mezcla de partículas de polvo primario seco usando un fluido de granulación, en la que el fluido comprende un disolvente inerte volátil, tal como agua, etanol o isopropanol, solo o en combinación, y, opcionalmente, en presencia de un aglutinante o agente aglutinante. La técnica puede implicar forzar una masa húmeda a través de un tamiz para producir gránulos húmedos que después se secan, preferentemente hasta una pérdida por desecación de menos de aproximadamente un 3% en peso.

Las técnicas de granulación en seco también son bien conocidas por los expertos en la materia e incluyen cualquier técnica en la que las partículas de polvo primario se agreguen a presión alta, incluyendo precompresión y compactación en rodillo, por ejemplo como se describe en el presente documento.

Los expertos en la materia conocerán que la granulación en fusión incluye cualquier técnica en la que los gránulos se obtengan mediante la adición de un aglutinante fundido o un aglutinante sólido que se funde durante el procedimiento. Después de la granulación, el aglutinante se solidifica a temperatura ambiente. Se sabe que la peletización termoplástica es similar a la granulación en húmedo, pero

se usan propiedades plásticas del aglutinante. En ambos procedimientos, los aglomerados (gránulos) obtenidos comprenden una estructura de matriz.

Los expertos en la materia conocerán que la granulación por pulverización incluye cualquier técnica que implique desecación de líquidos (soluciones, suspensiones, fundidos) al mismo tiempo que se generan simultáneamente los gránulos en un lecho fluidizado. Por tanto, el término incluye procedimientos en los que se proporcionan semillas extrañas (gérmenes) con las que se generan gránulos, así como aquellos en los que se forman semillas inherentes (gérmenes) en el lecho fluidizado debido a abrasión y/o fractura, además de, generalmente, cualquier técnica de granulación con recubrimiento por pulverización. El líquido pulverizado recubre los gérmenes y ayuda a la aglomeración adicional de las partículas. Después se seca para formar gránulos en forma de una matriz.

Los expertos en la técnica sabrán que la extrusión/esferonización incluye cualquier procedimiento que implique la mezcla en seco de ingredientes, el amasado en húmedo junto con un aglutinante, la extrusión, la esferonización del extrudido en esferoides de tamaño uniforme, y la desecación.

En particular, las micropartículas de buprenorfina o una sal de la misma y partículas de materiales débilmente ácidos, formadores de tampón débilmente ácidos, se presentan en mezcla asociativa entre sí en las composiciones de la invención. Por "mezcla asociativa" los inventores quieren decir que si el Componente (i) se formule o no después junto con los Componentes (ii) y (iii) como se ha definido anteriormente en el presente documento, tiene lugar alguna forma de etapa de mezclado (mezclado simple, granulación como se ha descrito en el presente documento anteriormente, o lo contrario) como entre las micropartículas de buprenorfina/sal y partículas de materiales débilmente ácidos, formadores de tampón débilmente ácidos, haciendo que entren en contacto íntimo.

Para evitar dudas, por "contacto íntimo" los inventores incluyen que las micropartículas de buprenorfina o una sal de la misma y partículas de materiales débilmente ácidos, formadores de tampón débilmente ácido, se presentan en

mezcla asociativa entre sí en las composiciones de la invención en cualquier forma en la que estén, al menos en parte, en contacto íntimo entre sí. Esto incluye la posibilidad de la inclusión de recubrimientos de disolución rápida en uno u otro, o ambos, conjuntos de partículas.

5 A este respecto, el Componente (i) se presenta, preferentemente, como, o como parte de, una composición de la invención en forma de una mezcla interactiva que comprende al menos una población de partículas vehículo sobre cuyas superficies se presentan (p. ej., adheridas) las micropartículas de buprenorfina o una sal farmacéuticamente aceptable de la misma.

10 Los expertos en la técnica entenderán que el término mezcla “interactiva” incluye el término mezcla “ordenada” y que indica una mezcla en la cual las partículas no aparecen como unidades únicas, como en las mezclas aleatorias, sino en las que partículas más pequeñas (p. ej., micropartículas de, por ejemplo, buprenorfina) están unidas a (es decir, adheridas a o asociadas con) las
15 superficies de las partículas vehículo más grandes. Dichas mezclas se caracterizan por fuerzas interactivas (por ejemplo fuerzas de van der Waals, fuerzas electrostáticas o de Coulomb y/o puentes de hidrógeno) entre el vehículo y las partículas asociadas a la superficie (véase, por ejemplo, Staniforth, Powder Technol., 45, 75 (1985)). En mezclas finales, y composiciones que comprenden
20 dichas mezclas, las fuerzas interactivas tienen que ser lo bastante fuertes como para mantener las partículas adherentes en la superficie del vehículo.

 Cuando se usan mezclas interactivas como el principio de la formulación por la cual el componente (i) particulado se presenta en una composición de la invención, estas están hechas, preferentemente, con partículas vehículo que son
25 de un tamaño (diámetro medio o promedio en base al peso y/o al volumen, véase anteriormente) que está entre aproximadamente 30 μm y aproximadamente 1000 μm (p. ej., aproximadamente 800 μm , tal como aproximadamente 750 μm), y preferentemente entre aproximadamente 40 (tal como aproximadamente 50 μm) y aproximadamente 600 μm .

Las partículas vehículo pueden comprender sustancias farmacéuticamente aceptables que son hidrosolubles, tales como hidratos de carbono, por ejemplo azúcares, tales como lactosa y alcoholes de azúcar, tal como manitol, sorbitol y xilitol, sales inorgánicas farmacéuticamente aceptables, tal como cloruro sódico.

- 5 Las partículas vehículo hidrosolubles pueden comprender también materiales débilmente ácidos, y/o formadores de tampón débilmente ácido, mencionados en el presente documento anteriormente (tal como ácido cítrico y/o citrato sódico). Como alternativa, las partículas vehículo pueden comprender sustancias farmacéuticamente aceptables que sean insolubles o poco solubles en agua, tales como fosfato dicálcico anhidrato, fosfato dicálcico dihidrato, fosfato tricálcico, carbonato cálcico y sulfato de bario, almidón y almidón pregelatinizado, materiales bioadhesivo y mucoadhesivo, tal como polivinilpirrolidona reticulada y croscarmelosa sódica; y otros polímeros, tales como celulosa microcristalina, celulosa y; o mezclas de los mismos.

- 15 En "soluble en agua" se incluye que el material tenga una solubilidad en agua que sea superior a 33,3 mg/ml a presión atmosférica (p. ej., 100 kPa) y a temperatura ambiente (p. ej., 21°C). Por otro lado, la expresión "escasamente soluble o insoluble en agua" incluye materiales que tienen una solubilidad en agua que es inferior a 33,3 mg/ml en las mismas condiciones. Materiales de partículas
- 20 vehículo solubles preferidas incluyen alcoholes de azúcar, tal como sorbitol, xilitol y particularmente manitol. Materiales de partículas vehículo hidrosolubles o insolubles en agua preferidos incluyen celulosa y almidones, tales como celulosa microcristalina.

- 25 Se prefiere que la buprenorfina o su sal farmacéuticamente aceptable se presente sobre las superficies de partículas vehículo hidrosolubles.

A este respecto, como se ha indicado anteriormente, los materiales débilmente ácidos y/o materiales formadores de tampón débilmente ácidos también pueden funcionar como materiales de partículas vehículo hidrosolubles. Por tanto, la mezcla asociada de dichos materiales con buprenorfina/sal de la

misma puede significar que lo anterior comprende partículas vehículo sobre las cuales se presentan micropartículas del último. En dichos casos, dichos materiales se pueden presentar al menos como partículas vehículo hidrosolubles adicionales, además de la presencia de otras partículas vehículo hidrosolubles sobre cuyas superficies se presentan micropartículas de burprenorfina.

Cuando las partículas vehículo comprenden dichos materiales débilmente ácidos/formadores de tampón, se pueden proporcionar compuestos de dichos materiales con otros materiales de partículas vehículo hidrosolubles (tales como los descritos en el presente documento anteriormente). Dichos materiales se pueden preparar mediante compresión directa o granulación, por ejemplo. Como alternativa, las partículas vehículo pueden estar constituidas esencialmente por un material débilmente ácido y/o uno o más materiales que, cuando se disuelven en saliva, dan lugar a un sistema tampón débilmente ácido. Por “constituido esencialmente por” de dichos materiales los inventores quieren decir que, excluyendo la posible presencia de agua (véase más adelante), las partículas vehículo comprenden al menos aproximadamente 95%, tal como al menos aproximadamente 98%, más preferentemente más de aproximadamente 99%, y particularmente al menos aproximadamente 99,5% en peso (en base al peso total de la partícula vehículo) de dichos materiales. Estos porcentajes excluyen la presencia de cantidades resto de agua (p. ej., agua cristalina o agua unida a las superficies externas de los materiales) y/o cualquier impureza que pueda estar presente en dichos materiales, impurezas que pueden surgir tras la producción de dichos materiales, bien por un tercero suministrador comercial o no comercial o por un experto en la técnica que fabrica una composición de la invención.

Como alternativa (y/o además), en el Componente (i), las partículas de material débilmente ácido y/o de materiales formadores de tampón débilmente ácido, se pueden presentar, al menos en parte, sobre las superficies, y/o entre ellas, de las partículas vehículo. En dichos casos, los tamaños de partícula adecuados de dichos materiales son los presentados en el presente documento

para principios activos y/o disgregantes

Cuando se usan en composiciones de la invención, los Componentes (ii) e (iii) se formulan, preferentemente, juntos, por ejemplo para formar partículas que comprendan naloxona o una sal de la misma y el disgregante, antes de mezclar con el Componente (i). Como alternativa, las partículas de material débilmente ácido, y/o de materiales formadores de tampón débilmente ácido, se pueden formular junto con los Componentes (ii) y/o (iii) antes de mezclar con micropartículas de buprenorfina, pudiéndose presentar las últimas micropartículas en forma de mezclas interactivas con partículas vehículo como se ha descrito anteriormente en el presente documento. Los materiales débilmente ácidos, y/o los materiales formadores de tampón débilmente ácido, pueden, de este modo, formularse en mezcla asociativa con micropartículas de buprenorfina como se ha definido anteriormente en el presente documento) de este modo.

Además, en el Componente (iii), las partículas de naloxona, o sales farmacéuticamente aceptables de la misma, también se pueden presentar sobre las superficies de, y/o entre ellas, las partículas vehículo en las composiciones de la invención, pero esto no es esencial. Dichas partículas vehículo pueden ser hidrosolubles (como se ha definido anteriormente en el presente documento), o pueden (preferentemente) ser partículas vehículo insolubles / escasamente solubles en agua.

Los materiales disgregantes y/o superdisgregantes también se pueden presentar, al menos en parte, como partículas sobre las superficies de, y/o entre ellas, las partículas vehículo que pueden o no portar también naloxona o sales de la misma. Si se usan en forma particulada, las partículas de disgregantes y/o superdisgregantes se pueden presentar con un tamaño de partícula (diámetro medio o promedio basado en peso y/o en volumen, véase anteriormente) de entre aproximadamente 0,1 y aproximadamente 100 μm (p. ej., aproximadamente 1 y aproximadamente 50 μm).

Como alternativa, los disgregantes y/o superdisgregantes también pueden

estar presentes como un constituyente en excipientes compuestos. Los excipientes compuestos se pueden definir como mezclas de excipientes coprocesados. Ejemplos de excipientes compuestos que comprenden superdisgregantes son Parteck® ODT, Ludipress® y Prosolv® EASYtab.

- 5 También se pueden presentar en las composiciones de la invención materiales bio/mucoadhesivos. Dichos materiales se pueden presentar sobre (p. ej., adheridos) las superficies de partículas vehículo cuando componentes de composiciones de la invención se presentan en forma de mezclas interactivas.

- Las composiciones de la invención se pueden usar en el tratamiento de la
- 10 dependencia de y/o adicción a opioides como se ha descrito anteriormente en el presente documento, por ejemplo en programas de terapia de sustitución. La dependencia y/o adicción de opioides se puede definir de numerosas formas (véase, por ejemplo, www.who.int/substance_abuse/terminology/definition1), pero se puede caracterizar por, por ejemplo, fenómenos fisiológicos, conductuales y
- 15 cognitivos en los que el uso de una sustancia o una clase de sustancias toma una prioridad mucho mayor para un individuo dado que otros comportamientos que una vez tuvieron mayor valor y/o se caracteriza por un deseo (a menudo fuerte y en ocasiones abrumador, de tomar opioides y/u opiáceos (que pueden o no haberse prescrito médicamente). Es particularmente preferido que las
- 20 composiciones de la invención que comprenden naloxona se usen en el tratamiento de la dependencia y/o adicción a opioides.

- La buprenorfina es un agonista parcial en el receptor de opioides μ y un antagonista en el receptor de opioides κ . Posee una afinidad alta en ambos receptores y compite con otros agonistas, como la metadona, la heroína
- 25 (diamorfina) y la morfina, en el receptor de opioides μ . Los efectos del agonista de opioides buprenorfina son menos que los efectos máximos de otros agonistas "completos" de opioides, tales como morfina, y están limitados por un efecto de "techo". Por tanto, el fármaco produce un grado menor de dependencia física que otros agonistas de opioides, tales como la heroína, la morfina o la metadona y, por

consiguiente, es particularmente útil en terapias de sustitución.

La expresión "cantidad farmacológicamente eficaz" hace referencia a una cantidad de un ingrediente activo, que es capaz de conferir un efecto terapéutico deseado sobre un paciente tratado, se administre solo o en combinación con otro
5 ingrediente activo. Dicho efecto terapéutico puede ser objetivo (es decir, medible mediante alguna prueba o marcador) o subjetivo (es decir, un sujeto da un indicación o siente un efecto).

Por tanto, las cantidades farmacológicamente eficaces adecuadas de buprenorfina (o una sal de la misma) incluyen las que son capaces de producir y/o
10 contribuir a la producción del efecto terapéutico deseado, a saber, menos ansias por opioides y/u opiáceos y/o menor uso ilícito del fármaco, cuando se administran por vía transmucosa, mientras que cantidades farmacológicamente eficaces adecuadas de naloxona (o una sal de la misma) cuando se usan deben ser
15 suficientes para no competir con el efecto farmacológico mencionado anteriormente de la buprenorfina presente en la composición de la invención tras su administración transmucosa, pero para antagonizar el efecto de la buprenorfina y desencadenar síntomas de abstinencia si se realiza un intento por parte de un individuo adicto a los opioides de inyectarse una composición de la invención.

Por consiguiente, el experto en la técnica puede determinar las cantidades
20 de ingredientes activos que se pueden usar en las composiciones de la invención en relación con lo que será más adecuado para un paciente individual. Esto es probable que varíe con la vía de administración, el tipo y la gravedad de la afección que se va a tratar, así como la edad, el peso, el sexo, la función renal, la función hepática y la respuesta del paciente concreto que se va a tratar.

25 La cantidad total de buprenorfina/sal de la misma que se puede usar en una composición de la invención puede estar en el intervalo de aproximadamente 0,1%, tal como aproximadamente 1%, a aproximadamente 20%, tal como aproximadamente 10%, en peso en base al peso total de la composición. La cantidad de este ingrediente activo también se puede expresar como la cantidad

en una forma de dosificación unitaria (p. ej., un comprimido). En tal caso, la cantidad de buprenorfina/sal que puede estar presente puede ser suficiente para proporcionar una dosis de buprenorfina (calculada como la base libre) por forma farmacéutica unitaria que está en el intervalo de entre aproximadamente 0,1 mg, tal como aproximadamente 1 mg y aproximadamente 50, por ejemplo 30, tal como aproximadamente 20 mg (p. ej., aproximadamente 15 mg, p. ej., aproximadamente 12 mg, tal como aproximadamente 10 mg). Intervalos preferidos para el tratamiento del dolor son de aproximadamente 0,1 mg a aproximadamente 4 mg. Intervalos preferidos para la terapia de sustitución son de aproximadamente 0,5 mg a aproximadamente 50 mg, tal como aproximadamente 0,75 mg, (p. ej., aproximadamente 1 mg) a aproximadamente 12 mg, tal como aproximadamente 10 mg (p. ej., aproximadamente 7 mg). Las dosis de buprenorfina individuales por comprimido que se puede mencionar incluyen aproximadamente 11,4 mg, aproximadamente 8,6 mg, aproximadamente 5,7 mg, aproximadamente 2,9 mg y aproximadamente 1,4 mg.

Cuando se usa, la cantidad total de naloxona/sal de la misma que se puede usar en una composición de la invención puede estar en el intervalo de aproximadamente 0,125%, tal como aproximadamente 0,25%, a aproximadamente 5%, tal como aproximadamente 2,5%, en peso en base al peso total de la composición. La cantidad de este principio activo también se puede expresar como la cantidad en una forma farmacéutica unitaria (p. ej., un comprimido). En tal caso, la cantidad de naloxona/sal que puede estar presente puede ser suficiente para proporcionar una dosis de naloxona (calculada como la base libre) por forma farmacéutica unitaria que está en el intervalo de entre aproximadamente 0,125 mg y aproximadamente 12,5 mg, tal como aproximadamente 0,19 mg (p. ej., aproximadamente 0,25 mg) a aproximadamente 3 mg, tal como aproximadamente 2,5 mg (p. ej., aproximadamente 1,75 mg). Las dosis de naloxona individual por comprimido que se puede mencionar incluyen aproximadamente 2,9 mg, aproximadamente 2,2 mg, aproximadamente 1,4 mg, aproximadamente 0,7 mg y

aproximadamente 0,4 mg.

Aunque para las composiciones de la invención que contienen naloxona se prefiere que la proporción de la dosis de buprenorfina:naloxona se mantenga en aproximadamente 4:1, las dosis mencionadas anteriormente son ejemplos del caso medio; por supuesto, puede haber casos individuales en los que se prefieran dosis mayores o menores y estas están dentro del alcance de la presente invención.

Las composiciones de la invención, una vez preparadas, se comprimen/compactan directamente en formas farmacéuticas unitarias (p. ej., comprimidos) para administrar a pacientes mamíferos (p. ej., seres humanos), por ejemplo como se ha descrito anteriormente en el presente documento.

Las composiciones de la invención pueden estar en forma de polvos o, más preferentemente, comprimidos para, p. ej., administración sublingual. Los comprimidos también pueden comprender un aglutinante. Un aglutinante se puede definir como un material que es capaz de actuar como un potenciador de la formación de ligazón, facilitando la compresión de la masa en polvo en compactos consistentes. Aglutinantes adecuados incluyen goma de celulosa y celulosa microcristalina. Si están presentes, los disgregantes y/o superdisgregantes se usan, preferentemente, en una cantidad de entre 0,5 y 20% en peso en base al peso total de la formulación del comprimido. Un intervalo preferido es de 1 a 15%, tal como de aproximadamente 2,0 a aproximadamente 12% (p. ej., aproximadamente 10%) en peso.

Aditivos y/o excipientes adicionales adecuados que se pueden usar en las composiciones de la invención, en particular aquellas en forma de comprimidos para, por ejemplo, administración sublingual, pueden comprender:

(a) lubricantes (tales como estearato de magnesio, o, preferentemente, fumarato de estearilo sódico);

(b) aromatizantes (p. ej., limón, polvo de menta piperita o, preferentemente, mentol), edulcorantes (p. ej., neohesperidina, acesulfamo K o,

preferentemente, sucralosa) y colorantes.

- (c) antioxidantes, que pueden ser de origen natural o, de otro modo (p. ej., hidroxitolueno butilado (BHT), vitamina C, vitamina E, β -caroteno, ácido úrico, uniuion, superóxido dismutasa (SOD), glutatión peroxidasa o peroxidasa catalasa); y/o

(d) otros ingredientes, tales como agentes vehículo, conservantes y agentes deslizantes (p. ej., sílice coloidal).

Las composiciones de la invención pueden prepararse mediante técnicas estándar y usando equipos estándar, conocidos para los expertos en la técnica.

- 10 Cuando se presentan en forma de mezclas interactivas, partículas de, p. ej., buprenorfina/sal pueden mezclarse en seco con partículas vehículo adecuadas durante un periodo de tiempo que sea lo suficientemente largo como para permitir que cantidades adecuadas de los respectivos ingredientes activos se adhieran a la superficie de las partículas vehículo. Esto también se puede aplicar a otros
- 15 principios activos y/o excipientes definidos anteriormente en el presente documento.

- El experto apreciará que, con el fin de obtener una formulación en polvo seco en forma de una mezcla interactiva, las partículas vehículo más grandes deben ser capaces de ejercer una fuerza suficiente como para romper los aglomerados de
- 20 partículas más pequeñas. Esta capacidad se determinará principalmente mediante la densidad de partícula, la aspereza de la superficie, la forma, la fluidez y, en particular, los tamaños relativos de las partículas.

- A este respecto se puede usar equipo de mezclado estándar. Es probable que el periodo de tiempo de la mezcla varíe de acuerdo con el equipo usado y el
- 25 experto no tendrá dificultades para determinar mediante experimentación rutinaria un tiempo de mezclado adecuado para una combinación dada del ingrediente activo y el o los materiales de partículas vehículo.

Las mezclas interactivas también se pueden proporcionar usando técnicas distintas del mezclado en seco, que los expertos en la materia conocerán bien.

Como alternativa se pueden incorporar otros ingredientes mediante mezclado estándar u otros principios de formulación.

Las composiciones de la invención pueden administrarse por vía transmucosa, tal como bucal, rectal, nasal o preferentemente, sublingual, mediante los medios de dosificación adecuados conocidos para los expertos. Un comprimido sublingual se puede colocar debajo de la lengua y los principios activos se absorben a través de las membranas mucosas circundantes.

A este respecto, las composiciones de la invención se pueden incorporar en varias clases de preparaciones farmacéuticas destinadas para administración transmucosa (p. ej., sublingual) usando técnicas estándar (véase, por ejemplo, Lachman et al, "The Theory and Practice of Industrial Pharmacy", Lea & Febiger, 3ª edición (1986) and "Remington The Science and Practice of Pharmacy", Gennaro (ed.), Philadelphia College of Pharmacy & Sciences, 19ª edición (1995)).

Las preparaciones farmacéuticas para administración sublingual se pueden obtener combinando las composiciones de la invención con aditivos y/o excipientes farmacéuticos convencionales usados en la técnica para dichas preparaciones y, después, preferentemente, comprimirse/compactarse directamente en formas farmacéuticas unitarias (p. ej., comprimidos). (Véase, por ejemplo, Pharmaceutical Dosage Forms: Tablets. Volumen 1, 2ª Edición, Lieberman et al (eds.), Marcel Dekker, New York and Basel (1989) p. 354-356 y los documentos citados en los mismos.) Equipo de compactación adecuado incluye máquinas de formación de comprimidos estándar, tales como Kilian SP300, el Korsch EK0, el Korsch XP1, the Korsch XL100 o el Korsch PharmaPress 800

Los pesos de los comprimidos sublinguales finales adecuados están en el intervalo de aproximadamente 30 a aproximadamente 400 mg, tal como aproximadamente 40 (p. ej., aproximadamente 50) a aproximadamente 300 mg (p. ej., aproximadamente 250 mg, tal como aproximadamente 200 mg), por ejemplo aproximadamente 50 (p. ej., aproximadamente 60) a 180 mg, más

preferentemente entre aproximadamente 60 (p. ej., aproximadamente 70) and aproximadamente 160 mg. Diámetros de comprimidos finales adecuados están en el intervalo de aproximadamente 3 a aproximadamente 12 mm, por ejemplo aproximadamente 4 a aproximadamente 10 mm, y más preferentemente aproximadamente 5 a aproximadamente 9 mm. Espesores de comprimidos finales adecuados están en el intervalo de aproximadamente 0,5 mm a aproximadamente 4 mm, tal como aproximadamente 1,5 mm a aproximadamente 3 mm. Son posibles varias formas de comprimidos (p. ej., circular, triangular, cuadrada, romboide, poligonal u ovalada). Durezas adecuadas de los comprimidos incluyen resistencias a la rotura por compresión en el intervalo de aproximadamente 10N a aproximadamente 100N, por ejemplo aproximadamente 15N a aproximadamente 50N (dependiendo del tamaño y/o el peso del comprimido), de acuerdo con el procedimiento <1217> de la Farmacopea USP.

Con independencia de lo anterior, las composiciones de la invención que comprenden disgregantes (u otros excipientes que funcionan mediante hinchamiento) deben carecer esencialmente (p. ej., menos de aproximadamente 20% en peso en base al peso total de la formulación) de agua. Será evidente para el experto que la hidratación "prematura" disminuirá espectacularmente el rendimiento de una formulación en comprimido en uso y puede dar lugar a la disolución prematura de los ingredientes activos.

Siempre que la palabra "aproximadamente" se usa en el presente documento en el contexto de las dimensiones (p. ej., tamaños y pesos de los comprimidos, tamaños de las partículas etc.), cobertura de la superficie (p. ej., de las partículas vehículo por las partículas de los ingredientes activos), cantidades (p. ej., cantidades relativas de constituyentes individuales en una composición o componente de una composición y dosis absolutas (incluyendo las proporciones de ingredientes activos), temperaturas, presiones, tiempos, valores de pH, concentraciones, se apreciará que dichas variables son aproximadas y como tal pueden variar en un $\pm 10\%$, por ejemplo $\pm 5\%$ y preferentemente $\pm 2\%$ (p. ej., $\pm$

1%) de los números especificados en el presente documento. Siempre que la palabra “aproximadamente” se usa en el presente documento en el contexto de las propiedades farmacocinéticas (C_{max} , t_{max} , AUC), etc., se apreciará que dichas variables son aproximadas y como tal pueden variar en un $\pm 15\%$, tal como $\pm 10\%$.

5 Las composiciones de la invención pueden administrarse mediante medios de dosificación adecuados conocidos para los expertos en la técnica. Por ejemplo, un comprimido sublingual se puede colocar debajo de la lengua y los ingredientes activos se absorben a través de las membranas mucosas circundantes.

Los inventores han encontrado que las composiciones de la invención, sorprendentemente, dan lugar a una biodisponibilidad significativamente mejorada para buprenorfina en comparación con las formulaciones disponibles comercialmente en la técnica anterior. Esto significa que formulaciones con dosis unitarias menores de buprenorfina se pueden administrar mediante las composiciones de la invención, de modo que reduciendo el “valor de la calle” a un solo comprimido cuando comprende una composición de la invención, siendo necesarios más de uno de estos comprimidos para proporcionar el mismo efecto cuando se administran ilegalmente por vía parenteral (es decir, en términos “de la calle”, el mismo “chute”). Esto significa que es menos probable que se abuse de las composiciones de la invención que de las formulaciones comercialmente disponibles de la técnica anterior (véase Comer et al, *Addiction*, 105, 709–718 (2010)).

Adicionalmente, los inventores han encontrado que las composiciones de la invención que comprenden naloxona, sorprendentemente, también dan lugar a una biodisponibilidad significativamente (y simultáneamente con la buprenorfina) mejorada para naloxona en comparación con las formulaciones disponibles comercialmente en la técnica anterior.

Por tanto y sorprendentemente, las composiciones de la invención que comprenden naloxona dan lugar a grados de biodisponibilidad mejorada similares y casi paralelos para buprenorfina y naloxona, lo que significa que la proporción

“óptima” entre buprenorfina y naloxona, a la que se ha llegado para reducir el potencial de abuso (véase, por ejemplo, Mendelson and Jones, Drug and Alcohol Dependence, 70, 829 (2003)), se puede mantener y, por tanto, se pueden disminuir las dosis de ambos ingredientes activos en un grado equivalente para
5 conservar la misma proporción.

De acuerdo con un aspecto adicional de la invención se proporciona un procedimiento de tratamiento de la dependencia de y/o adicción a los opioides en un ser humano,

- procedimiento que comprende la administración sublingual a un paciente
10 humano que sufre dependencia y/o adicción de opioides de

- al menos una dosis unitaria de una composición farmacéutica (p. ej., un comprimido) que comprende buprenorfina o una sal farmacéuticamente aceptable de la misma, en combinación con naloxona o una sal farmacéuticamente aceptable de la misma, en aproximadamente una proporción de la dosis de
15 buprenorfina:naloxona de 4:1 (calculada como bases libres),

- en el que dicha composición de dosis unitaria comprende una dosis de buprenorfina que es aproximadamente un 75% de la de un comprimido de mezcla aleatoria comprimida (RMC) que comprende buprenorfina, y

- procedimiento que alcanza, tras una dosis inicial en un programa
20 terapéutico dado, un perfil concentración en plasma - tiempo para buprenorfina (y/o naloxona) que es esencialmente equivalente al/los exhibidos por dichos comprimidos RMC.

"Comprimidos RMC" incluyen, entre otros, el producto en comprimidos comercialmente disponible Suboxone® (NDA No. 20-733, fecha de autorización 8
25 de octubre de 2002; buprenorfina, concentración de 2 mg (nº de producto 001; peso real aproximadamente 100 mg) y 8 mg (nº de producto 002; peso real aproximadamente 400 mg)). Los comprimidos de 8 mg (al menos) tienen una resistencia media a la rotura por compresión (procedimiento <1217> de la Farmacopea de EE.UU.) de aproximadamente 127 N. Por tanto, las resistencias

de los comprimidos RMC están en el intervalo de aproximadamente 80 a aproximadamente 180 N. Los comprimidos RMC se forman mediante compresión de una mezcla aleatoria, preparada mediante granulación en húmedo, de una mezcla estándar que comprende buprenorfina clorhidrato, naloxona clorhidrato dihidrato, lactosa monohidrato, manitol, almidón de maíz, povidona K30, ácido cítrico (anhidro granular), citrato sódico, aroma a limón natural y lima, acesulfamo potásico y estearato de magnesio.

Por un "perfil concentración en plasma - tiempo para buprenorfina y/o naloxona que es esencialmente equivalente al/los exhibidos por dichos comprimidos RMC", los inventores incluyen que, tras una dosis en un programa terapéutico dado, uno o más de:

- (i) la concentración máxima en plasma (C_{max}); y/o
- (ii) el tiempo hasta la concentración máxima en plasma (t_{max}); y/o
- (iii) el área total bajo la curva concentración en plasma – tiempo desde el tiempo cero al tiempo de la última concentración en plasma medida (AUC_t); y/
- (iv) el área bajo la curva concentración en plasma – tiempo desde el tiempo cero al tiempo de la última concentración extrapolada al infinito en base a la velocidad de eliminación constante (AUC_{inf}),

medidos por medios de seguimiento farmacocinético estándar, p. ej., como se describe en el Ejemplo 2 más adelante en el presente documento, para naloxona y/o, más preferentemente, para buprenorfina, está entre aproximadamente 80% y aproximadamente 125% de los valores correspondientes obtenidos para los comprimidos RCM mencionados anteriormente.

Por tanto, tras una dosis inicial en un programa terapéutico dado, para los comprimidos que comprenden una dosis de buprenorfina que es aproximadamente un 75% de un comprimido RMC que comprende 8 mg de buprenorfina puede haber

- (i) una C_{max} de entre aproximadamente 3,0 ng/ml y aproximadamente 5,6 (tal como aproximadamente 4,5) ng/ml; y/o

(ii) un tmax que es menor de aproximadamente 3 horas, preferentemente menor de aproximadamente 2 horas; y/o

(iii) una AUCinf que es menor de aproximadamente 25 ng.h/ml a aproximadamente 40 ng.h/ml, tal como aproximadamente 28 ng.h/ml a 5 aproximadamente 36 ng.h/m,

para buprenorfina; y/o

(a) una Cmax de entre aproximadamente 150 pg/ml y aproximadamente 300 (tal como aproximadamente 250) pg/ml; y/o

10 (b) un tmax que es inferior a aproximadamente 1 hora, para naloxona.

De acuerdo con un aspecto adicional de la invención se proporciona un procedimiento de tratamiento de la dependencia y/o adicción a los opioides en un ser humano,

- procedimiento que comprende la administración sublingual a un paciente 15 humano que sufre dependencia y/o adicción de opioides de

- al menos una dosis unitaria de una composición farmacéutica (p. ej., un comprimido) que comprende buprenorfina o una sal farmacéuticamente aceptable de la misma, en combinación con naloxona o una sal farmacéuticamente aceptable de la misma, en aproximadamente una proporción de la dosis de 20 buprenorfina:naloxona de 4:1 (calculada como bases libres),

- en el que dicha composición de dosis unitaria comprende una dosis de buprenorfina que es aproximadamente un 75% la de un comprimido RMC como se ha definido anteriormente en el presente documento, y

- procedimiento que alcanza, tras una dosis inicial en un programa 25 terapéutico dado, una biodisponibilidad media relativa en comparación con dichos comprimidos RMC que es:

(A) de aproximadamente 1,2 a aproximadamente 1,6 para buprenorfina; y/o

(B) de aproximadamente 1,2 a aproximadamente 2,0 para naloxona.

De acuerdo con un aspecto adicional de la invención se proporciona un

procedimiento de tratamiento de la dependencia y/o adicción de opioides en un ser humano, comprendiendo el procedimiento la administración sublingual a un paciente humano que sufre dependencia de y/o adicción a opioides de al menos una dosis unitaria de una composición farmacéutica (p. ej., un comprimido) que comprende buprenorfina o una sal farmacéuticamente aceptable de la misma, en combinación con naloxona o una sal farmacéuticamente aceptable de la misma, en el que dicho comprimido comprende una dosis de buprenorfina o sal de la misma que es de aproximadamente 6 mg o aproximadamente 1,5 mg, y la proporción de la dosis de buprenorfina:naloxona es de aproximadamente 4:1 (calculado como la base libre).

Las composiciones de la invención también pueden dar lugar a una proporción norbuprenorfina:buprenorfina menor en plasma en comparación con las formulaciones disponibles comercialmente de la técnica anterior. Una proporción norbuprenorfina:buprenorfina menor también se observa tras la administración sublingual de una solución en etanol en comparación con una formulación en comprimido (véase Harris et al, Clin. Pharmacokinet., 43, 329 (2004)) a medida que la dosis se incrementa, lo que sugiere que se está tragando menos buprenorfina. Además, se encuentra menos norbuprenorfina en el plasma tras la administración parenteral en comparación con la administración sublingual (Sigmon et al, Addiction, 101, 420 (2005)), lo que avala la idea de que la norbuprenorfina se forma a partir de buprenorfina ingerida mediante el metabolismo de primer paso por el hígado. Por tanto, la menor proporción norbuprenorfina:buprenorfina notificada en el presente documento puede ser un reflejo del hecho de que se absorbe más buprenorfina por la mucosa sublingual (y, por tanto, se ingiere menos) que con las formulaciones (p. ej., comprimido RMC) comercialmente disponibles de la técnica anterior. También puede haber beneficios de la reducción de la proporción norbuprenorfina:buprenorfina per se, tal como menor depresión respiratoria (véase Megarbane et al, Toxicology and Applied Pharmacology, 212, 256 (2006)).

De acuerdo con un aspecto adicional de la invención, también se proporciona un procedimiento de tratamiento de la dependencia de y/o adicción a opioides en un ser humano, comprendiendo el procedimiento la administración sublingual de una composición farmacéutica que comprende buprenorfina o una sal farmacéuticamente aceptable de la misma en combinación con naloxona o una sal farmacéuticamente aceptable de la misma en una proporción de buprenorfina:naloxona de aproximadamente 4:1 (calculada como la base libre), en el que dicha composición comprende una dosis de buprenorfina que es aproximadamente un 75% de la del comprimido RMC como se ha definido anteriormente en el presente documento, a un paciente humano que sufre dependencia de y/o adicción a opioides, en el que dicha formulación alcanza, tras una dosis inicial en un programa terapéutico dado, una proporción de concentraciones en plasma de norbuprenorfina/buprenorfina inferior a aproximadamente 0,8 en base a AUC₂₄₄:1 (calculado como la base libre).

Dichos procedimientos pueden comprender la administración de una composición de la invención como se ha definido en el presente documento.

Por "un programa terapéutico dado", los inventores quieren decir cualquier curso de tratamiento de un paciente con una composición de la invención.

Sin desear quedar limitado por la teoría, se entiende que las composiciones de la invención dan lugar a dicha sorprendentemente incrementada biodisponibilidad cuando se comparan con las formulaciones comercialmente disponibles de la técnica anterior, p. ej., comprimidos RMC, tales como Suboxone, por el efecto de tiempo sobre el pH, en el que el pH se disminuye como se ha descrito anteriormente en el presente documento durante un periodo de tiempo corto (p. ej., entre aproximadamente 1 y aproximadamente 3 minutos) tras la administración sublingual, lo que tiene como resultado una disolución más rápida y/o mejorada de micropartículas de burprenorfina. Aunque dicha disolución podría esperarse que mejorara disminuyendo el pH, lo que es completamente inesperado es que el grado de absorción por la mucosa sublingual no parece disminuir. Cabría

esperar que la disminución del pH local diera lugar a la presencia de más buprenorfina en estado ionizado en el lugar de la absorción, lo que a su vez se esperaba que disminuyera el grado de absorción a través de la mucosa sublingual. El hecho de que la biodisponibilidad es mejor por dosis unitaria de buprenorfina para las composiciones de la invención que para las composiciones de la técnica anterior es, de hecho, muy importante.

De acuerdo con un aspecto adicional de la invención, se proporciona una composición farmacéutica que comprende micropartículas de buprenorfina o una sal farmacéuticamente aceptable de la misma y partículas de un ácido débil o de materiales formadores de tampón débilmente ácido, que se caracteriza porque la composición exhibe en un procedimiento de disolución en embudo de volumen pequeño in vitro, por ejemplo como se describe en el Ejemplo 5 más adelante en el presente documento:

- a) un descenso de pH de aproximadamente 0,5 a aproximadamente 5 unidades de pH;
- b) un descenso máximo de pH en aproximadamente 1 minuto desde el inicio del procedimiento; y
- c) un retorno al pH inicial (± 0.5) en aproximadamente 3 minutos.

De acuerdo con un aspecto adicional más de la invención, se proporciona una composición farmacéutica que comprende micropartículas de buprenorfina o una sal farmacéuticamente aceptable de la misma, y partículas de un ácido débil o partículas de materiales formadores de tampón débilmente ácido, que se caracteriza porque la composición permite la provisión (en el lugar de la administración) de un pH entre aproximadamente 4,0 y aproximadamente 6,5 (p. ej., menos de aproximadamente 6,25), y el mantenimiento del pH dentro de este intervalo durante un periodo de tiempo adecuado (p. ej., aproximadamente 30 segundos, tal como aproximadamente 1 minuto) a aproximadamente 3 minutos (p. ej., aproximadamente 2 minutos, tal como aproximadamente 1,5 minutos), para facilitar la disolución de, en particular, las micropartículas de buprenorfina, y/o la

absorción de buprenorfina a través de la mucosa sublingual después.

Sorprendentemente, las composiciones de la invención que comprenden naloxona dan lugar a grados de biodisponibilidad mejorada similares y casi paralelos para buprenorfina y naloxona, lo que significa que la proporción “óptima” entre buprenorfina y naloxona, a la que se ha llegado para reducir el potencial de abuso (véase, por ejemplo, Mendelson and Jones, Drug and Alcohol Dependence, 70, 829 (2003)), se puede mantener y, por tanto, se pueden disminuir las dosis de ambos ingredientes activos en un grado equivalente para conservar la misma proporción.

10 Las composiciones de la invención son útiles en el tratamiento de la dependencia de y/o adicción a opioides. Las composiciones de la invención también pueden ser útiles en el tratamiento del dolor (incluyendo el dolor leve, moderado y grave).

De acuerdo con tres aspectos más de la invención, se proporciona:

- 15 (i) un procedimiento de tratamiento de la dependencia y/o adicción a los opioides;
- (ii) un procedimiento de tratamiento del dolor; y
- (iii) un procedimiento de tratamiento tanto del dolor como de la dependencia y/o adicción de/a los opioides;

20 procedimientos que comprenden la administración de una composición de la invención a una persona que sufre las afecciones correspondientes, o que es propensa a las mismas.

Las composiciones de la invención también se pueden administrar en la fase de inducción (es decir, el inicio) del tratamiento con buprenorfina, administrándose la buprenorfina una vez que un individuo adicto a los opioides se ha abstenido de usar opioides durante aproximadamente 12–24 horas y está en las etapas tempranas de la abstinencia de los opioides.

De acuerdo con un aspecto adicional de la invención se proporciona un procedimiento de tratamiento de la dependencia de y/o adicción a opioides,

comprendiendo el procedimiento la administración de una composición de la invención a un individuo que se ha abstenido de usar opioides durante al menos aproximadamente 12 horas y/o está en las etapas tempranas de la abstinencia de opioides.

- 5 Por "tratamiento" del dolor, los inventores incluyen el tratamiento terapéutico, así como el tratamiento sintomático y paliativo de la afección. No obstante, por "tratamiento" de la dependencia y/o adicción de/a los opioides, los inventores incluyen también la profilaxis o el diagnóstico de la afección relevante además del
- 10 usando buprenorfina en el tratamiento del dolor, las composiciones de la invención pueden prevenir el desarrollo de dependencia y/o adicción de/a los opioides.

Las composiciones de la invención permiten la producción de formas de farmacéuticas unitarias que son fáciles y baratas de fabricar y que permiten la rápida liberación y/o la rápida captación de los ingredientes activos usados a

15 través de la mucosa, tal como la mucosa oral, de modo que se permite el alivio rápido de los síntomas, como los descritos anteriormente en el presente documento.

Las composiciones de la invención también tienen la ventaja de que, si se las inyecta un adicto a los opioides, no producen los efectos eufóricos que busca el adicto y, de hecho, inducen síntomas de abstinencia de los opioides.

20

Las composiciones de la invención también pueden tener la ventaja de que se pueden preparar usando procedimientos de procesamiento farmacéuticos establecidos y usan materiales que están aprobados para usar en alimentos o sustancias farmacéuticas o de estado regulador similar.

25 Las composiciones de la invención también pueden tener la ventaja de que son más eficaces, menos tóxicas y de acción más prolongada, más potentes, producen menos efectos secundarios, se absorben más fácilmente, poseen una mejor aceptabilidad por el paciente, tienen un perfil farmacocinético mejor y/o tienen otras propiedades farmacológicas, físicas o químicas más útiles que las

composiciones farmacéuticas conocidas de la técnica anterior, sea para usar en el tratamiento de la adicción a opioides o del dolor o de otras cosas.

La invención se ilustra mediante los siguientes ejemplos con referencia a las figuras adjuntas en las que los perfiles concentración en plasma-tiempo del analito se presentan en gráficas de escala lineal para buprenorfina (Figura 1), norbuprenorfina (Figura 2) y naloxona (Figura 3) tras la administración sublingual de comprimidos que comprenden una composición de la invención (rombos) y el comparador comercialmente disponible, Suboxone® (cuadrados); la Figura 4 muestra un perfil de pH sublingual in vivo obtenido para una composición placebo (análoga a la preparada de acuerdo con la invención); la Figura 5 muestra los perfiles comparativos del pH in vitro para la composición de la invención frente a Suboxone y otros comparadores en un ensayo de disolución en embudo de volumen pequeño; las Figuras 6 y 7 muestran la liberación de buprenorfina y naloxona, respectivamente, de las composiciones a las que se hace referencia en la Figura 5; la Figura 8 muestra perfiles de pH comparativos in vitro pH para las composiciones de la invención frente a otros comparadores en un ensayo de disolución en embudo de volumen pequeño; y la Figura 9 muestra la liberación de buprenorfina de las composiciones a las que se hace referencia en la Figura 8.

Ejemplo 1

Comprimidos sublinguales de buprenorfina/naloxona I

Naloxona clorhidrato dihidrato (Macfarlan Smith, Edinburgo, RU) y buprenorfina clorhidrato (Macfarlan Smith, Edinburgo, RU) se micronizaron usando un molino de chorro de aire (Pilotmill-1/Food and Pharma Systems, Italia). El tamaño de partícula media en base al volumen (diámetro) de la buprenorfina fue de 3,4 μm y el de la naloxona fue de 4,6 μm .

Se mezclaron 9,15 g de la naloxona clorhidrato dihidrato micronizada junto con celulosa microcristalina (47,50 g; Avicel™ PH102 (tamaño medio de partícula

100 µm), FMC Biopolymer, Cork, Irlanda) y croscarmelosa sódica (18,00 g; AcDiSolTM, FMC Biopolymer) en un mezclador de tambor (Turbula, WAG, Suiza) durante 40 horas.

5 Se mezclaron 32,40 g de la buprenorfina clorhidrato micronizada junto con manitol (314,20 g; PearlitolTM 200SD, Roquette, Lestrem, Francia), ácido cítrico tamizado (15,00 g; gránulos finos de calidad 16/40, DSM, Suiza, Basilea) y citrato sódico tamizado (para evitar la aglomeración) (48,75 g) EmproveTM cryst., Merck, Darmstadt, Alemania) en un mezclador de tambor durante 40 horas.

10 Se machacó mentol (5,00 g; EmproveTM cryst., Merck) en mortero hasta que se formó un polvo fino. Este y también acesulfamo potásico (5,00 g; Sunett Pharma D, Nutrinova, Kelsterbach, Alemania) y sílice coloidal anhidra (5,00 g; AerosilTM 200 Pharma, Evonik Degussa, Hanau-Wolfgang, Alemania) se añadieron tamizando a la mezcla previa de buprenorfina, junto con la premezcla de naloxona y todo se mezcló en un mezclador de tambor durante 1 hora.

15 Después se añadió fumarato de estearilo y sodio (10,00 g; PruvTM, JRS Pharma, Polanco, Swain) tamizando a esta mezcla y continuó el mezclado en el mezclador de tambor durante 5 minutos.

20 Después, la mezcla en polvo final se comprimió formando comprimidos en una máquina para ello (Korsch XP1) equipada con punzones redondos de 7 mm de cara plana con cortes radiales en el borde obteniendo un peso del comprimido de 102 mg y una resistencia a la rotura por compresión del comprimido de 35 N.

Ejemplo 2

Ensayo clínico

25 Los comprimidos del ejemplo 1 se administraron por vía sublingual en un estudio de grupos cruzados abierto y de 2 periodos con una secuencia de tratamiento aleatorizado.

El estudio comprendió una visita de selección realizada 28 días antes del

primer tratamiento, dos periodos de tratamiento, cada uno de 4 días de duración (día -1 a día 3) y un periodo de lavado de al menos 10 días entre periodos de tratamiento. Durante los periodos de tratamiento, los sujetos ingresaron en la unidad clínica por la mañana antes de la primera dosis (día -1) y permanecieron allí hasta la finalización de los procedimientos del día 3. Se realizó una visita de seguimiento de 5 a 10 días después de la finalización de la segunda administración del producto médico en investigación (PMI).

Los PMI eran comprimidos sublinguales preparados de acuerdo con el ejemplo 1 (6 mg de buprenorfina/1,5 mg de naloxona; en lo sucesivo “formulación de la invención”) y, como producto de referencia, Suboxone comprimidos sublinguales (8 mg de buprenorfina/2 mg de naloxona; Reckitt Benckiser Healthcare Ltd, Hull, UK). El tratamiento con la formulación de la invención, o Suboxone (1 comprimido) en periodos alternos fue abierto y se administró el día 1 en cada periodo de tratamiento.

Los comprimidos de naltrexona (Nalorex®, 50 mg, Bristol-Myers Squibb Pharmaceuticals Ltd; Uxbridge, RU) se administraron por vía oral (un comprimido de 50 mg), a -24 a -16 horas, -1 hora (± 5 minutos) y +24 horas (± 1 hora) en relación con la administración del PEI, como un bloque de naltrexona en el estudio (con el fin de aliviar los efectos secundarios de los opioides durante el estudio).

Se reclutó a dieciocho voluntarios masculinos sanos de edades comprendidos entre los 18 y los 50 años de edad. Estos recibieron ambos tratamientos y fueron evaluados. La media de edad era de 29,8 años y las edades variaban entre los 19 y los 49 años. Todos los sujetos eran caucásicos. El peso medio era de 78,16 kg y variable de 63,0 a 93,5 kg, El índice de masa corporal medio de los sujetos fue 25,05 kg/m² y varió de 20,7 a 28,9 kg/m².

Todos los sujetos (a excepción de uno) comunicaron un uso de alcohol actual que variaba de 1 a 20 unidades a la semana. Ninguno de los sujetos era fumador actual. Todos los sujetos notificaron el uso actual de cafeína de 1 a 5 tazas o latas al día. Ningún sujeto había sido tratado con opioides en el año

anterior a la selección.

Ningún sujeto notificó ninguna medicación previa al estudio (tomada en las 2 semanas anteriores a la selección). Un sujeto notificó el uso en curso de antihistamínicos para uso sistémico mediante comprimido o cápsula oral para
5 tratar la rinitis alérgica estacional.

La medicación del ensayo se administró en el ambulatorio bajo la supervisión del personal médico.

Todos los sujetos reclutados en el estudio y que recibieron al menos una dosis de medicación del estudio. Todos los sujetos aleatorizados que recibieron al
10 menos un tratamiento, tenían al menos un perfil plasmático evaluable y no tenían ninguna desviación importante del protocolo que pudiera tener un efecto sustancial sobre el perfil de concentración plasmática de la buprenorfina, norbuprenorfina o naloxona, tal como:

- deglución de la medicación del estudio (se aplica a la formulación de la
15 invención y a Suboxone)

- vómitos en las 4 horas posteriores a la administración de cualquiera de los tipos de comprimido

- tener una concentración cuantificable predosis que sea $> 5\%$ de la C_{max} de un sujeto

20 Todos los sujetos aleatorizados que recibieron al menos un tratamiento y tenían datos de disgregación o aceptabilidad de al menos un tratamiento.

Las variables farmacocinéticas (FC) se basaron en las concentraciones plasmáticas de buprenorfina, norbuprenorfina (un metabolito de la buprenorfina) y naloxona y se calcularon usando procedimientos no compartimentales estándar. El
25 análisis FC no compartimental se realizó usando WinNonlin™ Professional versión 5.2. Cuando los datos lo permitieron, se determinaron los parámetros siguientes:

- $t_{retardo}$ tiempo de retardo antes del inicio de la absorción.
- $C_{máx}$ concentración plasmática máxima
- $t_{máx}$ tiempo transcurrido hasta la concentración plasmática máxima

• AUC_{0-t} área total bajo la curva concentración en plasma – tiempo desde el tiempo cero al tiempo de la última concentración en plasma cuantificable

• AUC_{0-48} área bajo la curva concentración plasmática desde el tiempo cero a las 48 horas después de la dosis

5 • IM Índice metabólico

Además, la biodisponibilidad relativa (F_{rel}) de la formulación de la invención a Suboxone se obtuvo en base a los datos FC ajustados según la dosis.

Los sujetos se clasificaron como evaluables o no evaluables con respecto a la evaluación FC por el farmacocinetista después de explorar los perfiles FC de los sujetos y teniendo en cuenta las desviaciones con respecto a los indicados anteriormente. Los análisis FC basados en la población FC incluyeron solo a los sujetos con datos FC evaluables.

10

Los tiempos de obtención de muestras de sangre reales para buprenorfina, norbuprenorfina y naloxona se convirtieron en un tiempo desde la dosis (tiempo transcurrido). Los tiempos transcurridos fueron enumerados por el sujeto para cada tratamiento, junto con las concentraciones de buprenorfina, norbuprenorfina y naloxona individuales. Los tiempos transcurridos se usaron en el análisis FC.

15

Las concentraciones de buprenorfina, norbuprenorfina y naloxona se resumieron mediante estadística descriptiva del número de muestras que faltaban, el número de muestras menores que el límite de cuantificación inferior ($<LOQ$), n , la media aritmética, SD, CV(%), la media geométrica, los intervalos de confianza del 95% (IC) para la media aritmética, la mediana, el mínimo y el máximo. Todas las concentraciones de buprenorfina, norbuprenorfina y naloxona $<LOQ$ se fijaron en cero para el fin de calcular la estadística descriptiva. Si en algún punto de tiempo 1/3 o más de los sujetos tenían valores $<LOQ$ no se calculó la estadística descriptiva.

20

25

Los parámetros FC C_{max} , AUC_{0-t} y AUC_{0-48} de buprenorfina, norbuprenorfina y naloxona se compararon entre los tratamientos usando un análisis de efectos mixtos de la varianza (ANOVA).

La media aritmética (+SEM) y los perfiles de concentración en plasma-tiempo del analito se presentan en gráficos a escala lineal para cada analito en las Figuras 1 (buprenorfina), 2 (norbuprenorfina) y 3 (naloxona) con ambos tratamientos incluidos en cada gráfico. En estas figuras se puede ver que tanto la buprenorfina como la norbuprenorfina tras la administración de la formulación de la invención (rombos) y Suboxone (cuadrados), las concentraciones en plasma de los tres analitos aumentaban a un máximo y después disminuían de un modo bifásico.

En relación con otros parámetros FC:

10 (i) De media, el tiempo de retardo fue ligeramente más corto después del tratamiento con la formulación de la invención en comparación con Suboxone en 15% para buprenorfina, 29% para norbuprenorfina y 34% para naloxona.

(ii) El intervalo de los tiempos a los que se alcanzaron las concentraciones máximas (t_{max}) fue similar entre los tratamientos para todos los analitos. La mediana de los valores de t_{max} fue inferior o igual a 1 hora para buprenorfina y naloxona, lo que indica una rápida absorción sublingual tras la administración de la formulación de la invención y Suboxone. Para norbuprenorfina, el t_{max} fue generalmente similar al de la buprenorfina después de ambos tratamientos, lo que indica que el metabolismo de la de buprenorfina a norbuprenorfina era rápido.

(iii) Las proporciones medias de los metabolitos superaban 0,5, lo que indica una extensa conversión metabólica de buprenorfina a norbuprenorfina, siendo la conversión del 31% inferior tras la administración de la formulación de la invención en comparación con Suboxone. Este resultado es significativo, ya que significa que se absorbe más buprenorfina por vía sublingual en el caso de la formulación de la invención;

(iv) las dosis de buprenorfina y naloxona fueron menores en la formulación de la invención, pero la exposición sistémica media, en términos de C_{max} y AUC, de buprenorfina y naloxona fue superior cuando se comparó a la de

Suboxone, y, como se ha indicado anteriormente, los valores fueron menores para norbuprenorfina; y

(v) Las biodisponibilidades relativas medias de la formulación de la invención, respecto a Suboxone fueron 1,659 y 2,056 para buprenorfina y naloxona respectivamente, lo que indica que la exposición sistémica normalizada por la dosis era más alta tras la administración de la formulación de la invención. Para norbuprenorfina la exposición sistémica normalizada por la dosis pareció similar entre tratamientos con una biodisponibilidad relativa media de 1,084 El resultado de la buprenorfina es sorprendente. La biodisponibilidad relativa notificada de una solución en etanol administrada por vía sublingual que comprende buprenorfina (estando las condiciones optimizadas teóricamente para su absorción rápida por la mucosa sublingual) comparada con Suboxone se notificó que era 1,5 (véase Compton et al, Drug and Alcohol Dependence, 82, 25 (2006)). El hecho de que el número relativo notificado en este estudio para un comprimido sublingual sólido fuera incluso mayor que el indicado para una solución es importante.

El tiempo de disgregación de los comprimidos lo evaluó una enfermera o un médico mediante inspecciones bucales y también fue comunicado por los sujetos, a los que se les proporcionaron instrucciones detalladas de los procedimientos de dosificación antes de la dosis el día 1 en ambos periodos de tratamiento, incluidos los procedimientos para las evaluaciones de la disgregación realizadas por el observador y del sujeto. Los sujetos debían informar sobre cualquier ingesta prematura.

El espacio sublingual y los comprimidos se examinaron para determinar el tiempo hasta la disgregación. Los residuos de los comprimidos se caracterizaron como "íntactos", "fragmentos", "residuo de tipo pasta" o "disueltos". Las inspecciones se llevaron a cabo cada 2 minutos y los hallazgos se registraron hasta que el comprimido se disgregó completamente. Además, se instruyó al sujeto que indicara cuándo pensaba que el PMI se había disuelto levantando su

mano o que indicara si se había tragado el comprimido antes de su disolución. Se registró el tiempo de disolución o de deglución.

La mediana del tiempo hasta los comprimidos no intactos fue de 2 minutos para la formulación de la invención y fue de 8 minutos para Suboxone.

5

Resumen y Conclusiones

Las proporciones de los parámetros indicados anteriormente sugieren que la formulación de la invención tuvieron como resultado concentraciones plasmáticas de buprenorfina y naloxona ligeramente mayores y concentraciones plasmáticas de norbuprenorfina ligeramente inferiores que las del comparador. El resultado anterior es a pesar de que la dosis inicial es menor, lo que indica que puede ser posible reducir la dosis todavía más. Los comprimidos que comprenden formulaciones de la invención también se disgregaron más rápidamente que el comparador.

15

Ejemplo 3

Comprimidos sublinguales de buprenorfina/naloxona II

Se mezclaron 3,97 g de la naloxona clorhidrato dihidrato micronizada junto con celulosa microcristalina (20,00 g; AvicelTM PH102 (tamaño medio de partícula 100 µm), FMC Biopolymer, Cork, Irlanda) y croscarmelosa sódica (7,20 g; AcDiSolTM, FMC Biopolymer) en un mezclador de tambor (Turbula, WAG, Suiza) durante 40 horas.

Se mezclaron 14,04 g de buprenorfina clorhidrato micronizada junto con manitol (130,30 g; PearlitolTM 200SD, Roquette, Lestrem, Francia), ácido cítrico tamizado (6,00 g; gránulos finos de calidad 16/40, DSM, Suiza, Basilea) y citrato sódico tamizado (para evitar la aglomeración) (19,50 g) EmproveTM cryst., Merck, Darmstadt, Alemania) y se mezclaron en un mezclador de tambor durante 42 horas.

Se machacó mentol (2,00 g; EmproveTM cryst., Merck KGaA, Darmstadt,

Alemania) en mortero hasta que se formó un polvo fino y se mezcló con dióxido de silicio coloidal (0,20 g; Aerosil™ 200 Pharma), (1:1 proporción en volumen).

5 A la premezcla de buprenorfina se añadió sucralosa (6,00 g, Merck KGaA, Darmstadt, Alemania). La premezcla de naloxona y el resto del dióxido de silicio coloidal (2,80 g) se añadieron mediante co-tamizado a la premezcla de buprenorfina. La mezcla de mentol-dióxido de silicio se añadió mediante tamizado a la premezcla de buprenorfina y todos los ingredientes se mezclaron durante 1 hora.

10 Después se añadió fumarato de estearilo y sodio (8,00 g; Pruv™, JRS Pharma, Polanco, España) tamizando a esta mezcla y continuó el mezclado en el mezclador de tambor durante 10 minutos.

Después, la mezcla en polvo final se comprimió formando comprimidos en una máquina para ello (Korsch EK0) equipada con punzones redondos de 7 mm de cara plana con cortes radiales en el borde obteniendo un peso del comprimido de 110 mg y una resistencia a la rotura por compresión del comprimido de 30-35 N.

Ejemplo 4

Experimento in vivo

20 Los comprimidos de placebo preparados de acuerdo con el procedimiento descrito en el Ejemplo 1 anterior (excluyendo buprenorfina, pero incluyendo naloxona) se administraron primero por vía sublingual.

Se midió el pH de la saliva sublingual in vivo usando un medidor de pH Schott CG 842P unido a un electrodo Schott Flatrode™ (pH 0-14,0-60°C). El Flatrode™ tiene una membrana superplana para las mediciones de superficie y un eje de plástico sólido con un diafragma anular, lo que garantiza una rápida respuesta mediante el contacto potenciado entre la muestra y la referencia. El diámetro de la superficie plana del electrodo es de 6,0 mm, dando una superficie de medida de 0,28 cm².

El Flatrode se colocó (con un ángulo en la boca abierta de 45°) suavemente detrás de los dientes inferiores, justo al lado del comprimido en la boca. Se aplicó una presión muy suave con el fin de medir el pH en la saliva en lugar del pH en sangre venosa (normalmente pH 7,4).

- 5 El pH se midió a intervalos de tiempo de 0, 30, 60 y 90 segundos (en 5 segundos hasta que se observó un valor estable). Se tomaron precauciones para evitar la retirada accidental de polvo disuelto por el electrodo. La boca se cerró entre mediciones sin deglución activa.

- 10 Se realizaron ciclos por triplicado para garantizar un perfil de pH fiable. Entre ciclos, la boca se lavó exhaustivamente con agua y el pH se midió antes de la administración para obtener un nuevo valor de cero.

- 15 Los resultados indicaron que la disminución del pH fue máxima a aproximadamente 35-40 segundos. En la Figura 4 se puede ver que el cuerpo compensa rápidamente el pH modificado y también sobrecompensa ligeramente y que la ventana de oportunidad (es decir, el intervalo de tiempo con una disminución del pH de 0,5 unidades (al menos) comparado con el pH en reposo) para el incremento de la solubilidad de buprenorfina es solo aproximadamente de 80 segundos, a partir de 10 segundos (n= 4).

20 **Ejemplo 5**

Experimento comparativo de disolución en embudo de volumen pequeño in vitro I

- 25 Además de los comprimidos sublinguales descritos en el ejemplo 3 anterior, se prepararon otros dos lotes identificables de los comprimidos sublinguales usando la misma metodología, excepto que, en un caso, la buprenorfina clorhidrato no se micronizó y, en el otro, no se incluyeron ácido cítrico y citrato sódico (en su lugar, se incluyeron 12,75 mg por comprimido de manitol).

Los comprimidos forman los tres lotes de comprimidos mencionados anteriormente, así como comprimidos Suboxone (buprenorfina 8 mg/naloxona 2

mg; Reckitt Benckiser Healthcare Ltd, Hull, RU) se colocaron encima de un filtro de sílice de diámetro 120 mm en un embudo de vidrio de 55 mm (diámetro interno superior).

Se dejó gotear tampón de fosfato potásico con un pH 6,8 (USP/NF), que imita a la saliva) por un tubo de plástico blando de PVC con un diámetro interno de 3 mm sobre los comprimidos a una velocidad, fijada con una bomba peristáltica (Flocon 1003), de 2 ml por minuto. La distancia entre el fin del tubo de plástico y el filtro de sílice en el embudo se fijó a aproximadamente 7,5 cm, para, junto con la tasa de goteo, corresponder a una fuerza similar a la presión del lateral inferior de la lengua. Las pequeñas cantidades de agua implicadas intentan imitar las bajas cantidades de agua disponibles in vivo en la lengua humana.

El pH se midió a lo largo del tiempo usando un electrodo Mettler Toledo InLab Expert Pro (pH 0-14; 0-100°C) unido a un medidor del pH estándar Mettler Toledo 340 colocado en la salida del embudo de cristal.

Para medir la liberación de los ingredientes farmacéuticos activos a lo largo del tiempo desde los comprimidos, un vaso de precipitados de vidrio equipado con un agitador magnético que contenía 490 ml de tampón de fosfato potásico de pH 6,8 (USP/NF) recolectó las gotas desde el embudo.

Se extrajeron muestras de 800 µl del vaso de precipitados usando una micropipeta calibrada a intervalos de 0,5, 1,0, 1,5, 2,0, 2,5, 3,0, 3,5, 4,0, 4,5, 5,0, 10,0, 15,0 y 20,0 minutos. Estas muestras se vaciaron en viales de 1 ml que ya contenían 200 µl de ácido fosfórico diluido. No se añadió tampón adicional al vaso de precipitados de recolección para compensar. Comenzó con un volumen de 490 ml y finalizó con un volumen de 520 ml (la diferencia ente 40 ml añadidos al vaso de precipitados durante 20 minutos y 10,4 ml extraídos en total (13 x 0,8 ml) fue de 29,6 ml (es decir, aproximadamente 30 ml)). Se decidió comenzar a 490 ml en lugar de 485 ml para estar más cerca de 500 ml durante un periodo lo más largo posible. Los volúmenes individuales exactos fueron calculados para cada muestra.

Tres comprimidos de cada uno de los cuatro lotes de comprimidos en el

ensayo se analizaron como las muestras de ensayo de liberación. Las cantidades de buprenorfina y naloxona se midieron usando HPLC Agilent 1000; detector de matriz de diodos, bomba de gradiente, inyector automático de muestras, horno de columna), con un procedimiento de gradiente con detección UV a 210 nm.

- 5 El pH se representó frente al tiempo para los siguientes cuatro lotes de comprimidos y los resultados se muestran en la Figura 5 (comprimidos preparados de acuerdo con el Ejemplo 3 (cuadrados); equivalentes de buprenorfina no micronizada (cruces); equivalentes sin ácido cítrico/citrato sódico (rombos); y Suboxone (triángulos)). La línea discontinua en la Figura 5 es el perfil superpuesto
- 10 in vivo de la Figura 4.

- Los perfiles de liberación de fármaco durante los primeros 5 minutos para buprenorfina y naloxona se presentan en las Figuras 6, y 7, respectivamente. Aunque Suboxone tiene una carga de fármaco un 23% superior a la de los demás comprimidos, produce una liberación de buprenorfina tras 20 minutos a través del
- 15 embudo de solo un 75% de la de los comprimidos de acuerdo con la invención. La diferencia es más notable durante los primeros 5 minutos.

Ejemplo 6

Comprimidos sublinguales de buprenorfina/naloxona III

- 20 Se mezclaron 336,0 g de naloxona clorhidrato dihidrato micronizada junto con celulosa microcristalina (2.000,0 g; Avicel™ PH102 (tamaño medio de partícula 100 µm), FMC Biopolymer, Cork, Irlanda) y croscarmelosa sódica (720,0 g; AcDiSol™, FMC Biopolymer Wallington, Little Island, Co. Cork, Irlanda) en un mezclador de doble cono de 12 l (Sewin, Zickert systems, Kungsbacka, Suecia)
- 25 durante 3 horas.

Se desaglomeraron conjuntamente ácido cítrico (600,0 g; fino granular de calidad 16/40, DSM, Suiza, Basilea), citrato sódico (1950,0 g Emprove™ cryst., Merck, Darmstadt, Alemania) y dióxido de silicio coloidal (480,0 g Aerosil™ 200 Pharma, Evonik Degussa GmbH, Rheinfelden, Alemania) con un aparato Quadro

comil (Quadro Engineering, Ontario, Canadá) y se premezclaron con dos tercios de una cantidad premedida de manitol (8737,3 g; PearlitolTM 200SD, Roquette, Lestrem, Francia) en un mezclador de cono doble de 60 l (Sewin, Zickert systems, Kungsbacka, Suecia) durante 5 minutos.

- 5 Se añadieron a la premezcla 1188,0 g de buprenorfina clorhidrato micronizada y el otro tercio de manitol (4368,7 g) se añadió encima de la buprenorfina clorhidrato y todos los ingredientes se mezclaron durante 3 horas.

Se molió mentol (200,0 g; EmproveTM cryst., Merck KGaA, Darmstadt, Germain) con Quadro comill. Se procesaron dióxido de silicio coloidal (20,0 g) y el

- 10 mentol molido (proporción en volumen 1:1) con Quadro comill con el fin de desaglomerar el dióxido de silicio (coloidal).

Se añadieron a la premezcla de buprenorfina sucralosa (600,0 g, Merck KGaA, Darmstadt, Alemania), la premezcla de naloxona y la mezcla de dióxido de silicio-mentol y todos los ingredientes se mezclaron durante 1 hora.

- 15 Se desaglomeró fumarato de estearilo y sodio (800,0 g; PruvTM, JRS Pharma, Polanco, España) con Quadro comil y se añadió a un mezclador de doble cono y se mezclaron durante 10 minutos.

Después, la mezcla en polvo final se comprimió formando comprimidos en una máquina para ello (Korsch XL100, Korsch AG, Berlín, Alemania) equipada con punzones redondos de 7 mm de cara plana con cortes radiales en el borde obteniendo un peso del comprimido de 110 mg y una resistencia a la rotura por compresión del comprimido de 30-35 N.

- 20

Ejemplo 7

- 25 Comprimidos sublinguales de buprenorfina/naloxona IV

Se prepararon 200.000 comprimidos de 100 mg de buprenorfina/naloxona (proporción de la dosis de 4:1) que comprendían una dosis de 1,4 mg de buprenorfina (calculada como la base libre) usando el mismo procedimiento que se ha descrito en el Ejemplo 6.

48

Ejemplo 8

Comprimidos sublinguales de buprenorfina/naloxona V

- Se prepararon 200.000 comprimidos de 110 mg de buprenorfina/naloxona (proporción de la dosis de 4:1) que comprendían una dosis de 5,7 mg de buprenorfina (calculada como la base libre) usando el mismo procedimiento que se ha descrito en el Ejemplo 6.

Ejemplo 9

- 10 Experimento comparativo de disolución en embudo de volumen pequeño in vitro II

Usando el procedimiento de disolución en embudo de volumen pequeño in vitro descrito en el Ejemplo 5, se obtuvieron los perfiles del pH (medición del pH a lo largo del tiempo) para:

- 15 (a) comprimidos sublinguales de buprenorfina/naloxona preparados como se describe en el Ejemplo 8;

- (b) comprimidos sublinguales de buprenorfina/naloxona preparados esencialmente como se describe en el Ejemplo 8, excepto que el ácido cítrico y el citrato sódico se incluyeron durante la etapa de mezclado en la que los dos PAF se mezclan entre sí;

- (c) comprimidos sublinguales de buprenorfina/naloxona preparados esencialmente como se describe en el Ejemplo 8, pero sin ácido cítrico (es decir, solo citrato sódico);

- 25 (d) comprimidos sublinguales de buprenorfina/naloxona preparados esencialmente como se describe en el Ejemplo 8, pero sin citrato sódico (es decir, solo ácido cítrico);

- (e) comprimidos sublinguales de buprenorfina/naloxona preparados esencialmente como se describe en el Ejemplo 8, excepto que se usó ácido tartárico (Sigma-Aldrich) en lugar de ácido cítrico y citrato sódico; y

(f) película de Suboxone® (8 mg de buprenorfina/2 mg de naloxona; Reckitt Benckiser Healthcare Ltd, Hull, RU).

En el caso de los comprimidos (c) y (d), se usó una cantidad equivalente de manitol en lugar del ácido cítrico y el citrato sódico, respectivamente, que se excluyó. En el caso de los comprimidos (e), se usaron 2 mg (por comprimido) de ácido tartárico y 10,75 mg adicionales (por comprimido) de manitol.

Los resultados se muestran en la Figura 8 (comprimidos a) – rombos; comprimidos (b) – cuadrados de color gris claro; comprimidos (c) – triángulos; comprimidos (d) – cuadrados negros; comprimidos (e) – cuadrados de color gris medio; y películas de Suboxone (f) – círculos). En la Figura 8 también están superpuestos:

- (i) el perfil in vivo de la Figura 4 (línea discontinua); y
- (ii) el perfil de pH in vitro previamente obtenido para los comprimidos de Suboxone® (línea continua; inicialmente presentada en la Figura 5).

Los perfiles de liberación/disolución del fármaco en los primeros 5 minutos para buprenorfina se presentan en la Figura 9. Claramente se puede ver en las Figuras 8 y 9 en conjunto que la disolución del fármaco se correlaciona fuertemente con cuánto disminuye el pH durante el primer 1 minuto a los 2 minutos después del inicio del experimento (correspondiente a la administración sublingual in vivo). También se puede ver que el mayor descenso del pH y la velocidad de disolución más alta se obtuvieron cuando se usó solo ácido cítrico.

REIVINDICACIONES

1. Una composición farmacéutica que comprende micropartículas de una cantidad farmacológicamente eficaz de buprenorfina o una sal farmaceuticamente aceptable de la misma, en mezcla asociativa con partículas que comprenden un ácido débil o partículas que comprenden materiales formadores de tampón débilmente ácido.
2. Una composición de acuerdo con la reivindicación 1, en la que las micropartículas de buprenorfina tienen un diámetro medio en base al peso inferior a aproximadamente 15 μm .
3. Una composición de acuerdo con la reivindicación 1 o la reivindicación 2, en la que el material débilmente ácido comprende ácido cítrico, ácido tartárico, ácido málico, ácido fumárico, ácido adípico, ácido succínico, ácido láctico, ácido acético, ácido oxálico, ácido maleico, cloruro amónico o una combinación de los mismos.
4. Una composición de acuerdo con la reivindicación 1 o la reivindicación 2, en la que los materiales formadores de tampón comprenden una combinación de un material débilmente ácido y una sal de un material débilmente ácido.
5. Una composición de acuerdo con la reivindicación 4, en la que el material débilmente ácido es como se ha definido en la reivindicación 3.
6. Una composición de acuerdo con la reivindicación 4 o la reivindicación 5, en la que la sal es citrato sódico, citrato potásico, tartrato sódico o tartrato potásico.
7. Una composición de acuerdo con una cualquiera de las reivindicaciones

precedentes, en la que el sistema tampón es ácido cítrico/citrato sódico.

8. Una composición de acuerdo con una cualquiera de las reivindicaciones precedentes, que se presenta como una mezcla interactiva que comprende
5 micropartículas de buprenorfina o una sal farmacéuticamente aceptable de la misma presentada sobre las superficies de partículas vehículo.

9. Una composición de acuerdo con la reivindicación 8, en la que las partículas vehículo son de un tamaño que está entre aproximadamente 100 y
10 aproximadamente 800 μm .

10. Una composición de acuerdo con la reivindicación 8 o la reivindicación 9, en la que las partículas vehículo son hidrosolubles.

11. Una composición de acuerdo con una cualquiera de las reivindicaciones 8 a 10, en la que las partículas vehículo comprenden manitol.

12. Una composición de acuerdo con una cualquiera de las reivindicaciones 8 a 11, en la que las partículas de ácido débil, o de materiales formadores de
20 tampón débilmente ácido, se presentan y actúan como partículas vehículo.

13. Una composición farmacéutica de acuerdo con una cualquiera de las reivindicaciones precedentes, que además comprende un disgregante.

14. Una composición de acuerdo con la reivindicación 13, en la que el
25 disgregante es un superdisgregante seleccionado de croscarmelosa sódica, glicolato de almidón sódico, polivinilpirrolidona reticulada o una mezcla de los mismos.

15. Una composición farmacéutica de acuerdo con una cualquiera de las reivindicaciones precedentes, que además comprende una cantidad farmacológicamente eficaz de naloxona, o una sal farmacéuticamente aceptable de la misma.

5

16. Una composición farmacéutica acuerdo con la reivindicación 15, en la que la composición comprende partículas que comprenden naloxona o una sal de la misma y un disgregante.

10

17. Una composición de acuerdo con una cualquiera de las reivindicaciones precedentes, que está en forma de un comprimido adecuado para administración sublingual.

15

18. Un procedimiento para la preparación de una composición como se ha definido en una cualquiera de las reivindicaciones 8 a 17, que comprende mezclar en seco las partículas vehículo con buprenorfina o una sal de la misma.

20

19. Un procedimiento para la preparación de una composición como se ha definido en una cualquiera de las reivindicaciones 15 a 17, que comprende un procedimiento de acuerdo con la reivindicación 18, seguido de la mezcla con partículas que comprenden naloxona o una sal de la misma y un disgregante.

25

20. Un procedimiento para la preparación de un comprimido sublingual como se ha definido en la reivindicación 17, que comprende comprimir o compactar directamente una composición como se ha definido en una cualquiera de las reivindicaciones 1 a 16.

21. Un procedimiento de tratamiento de la dependencia y/o adicción de opioides, y/o el dolor, comprendiendo el procedimiento la administración de una

53

composición como se ha definido en una cualquiera de las reivindicaciones 1 a 7 a una persona que sufre la o las afecciones correspondientes o que es propensa a ellas.

- 5 22. Una composición como se ha definido en una cualquiera de las reivindicaciones 1 a 17 para usar en un procedimiento de tratamiento de la dependencia de y/o adicción a opioides, y/o del dolor.

- 10 23. El uso de una composición como se ha definido en una cualquiera de las reivindicaciones 1 a 17 para la fabricación de un medicamento para un procedimiento de tratamiento de la dependencia de y/o adicción a opioides, y/o del dolor.

RESUMEN

Se proporcionan composiciones farmacéuticas para el tratamiento de, por ejemplo, la dependencia de opioides, que comprende micropartículas de una cantidad farmacológicamente eficaz de buprenorfina o una sal farmaceuticamente aceptable de la misma, en mezcla asociativa con partículas que comprenden un ácido débil o partículas que comprenden materiales formadores de tampón débilmente ácido. La composición puede comprender además un disgregante y/o partículas de una cantidad farmacológicamente eficaz de naloxona, o una sal farmacéuticamente aceptable de la misma. Las composiciones son útiles en el tratamiento de la dependencia/adicción de/a los opioides y/o el dolor.

SS

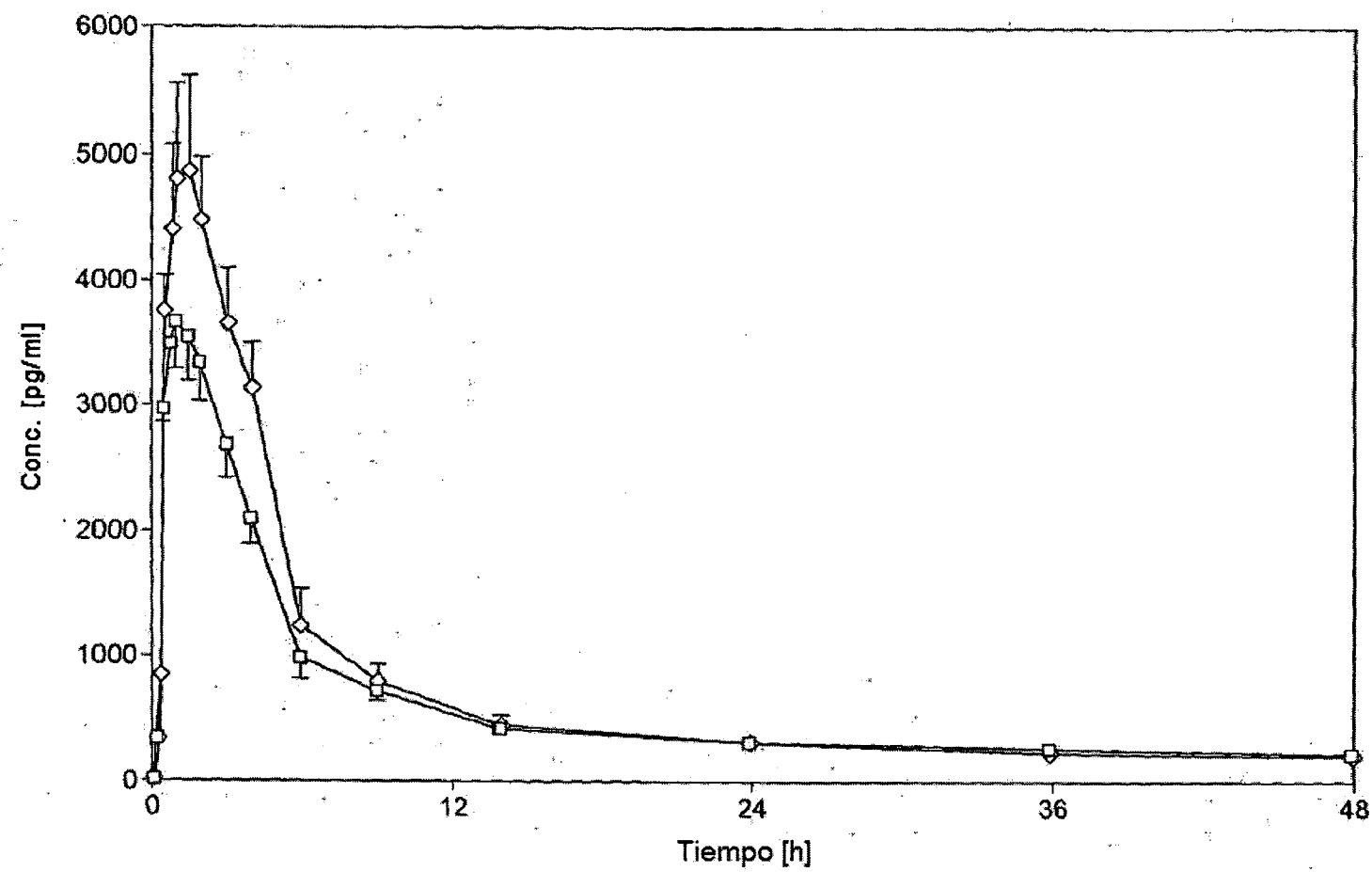


FIG. 1

Handwritten signature or mark.

58

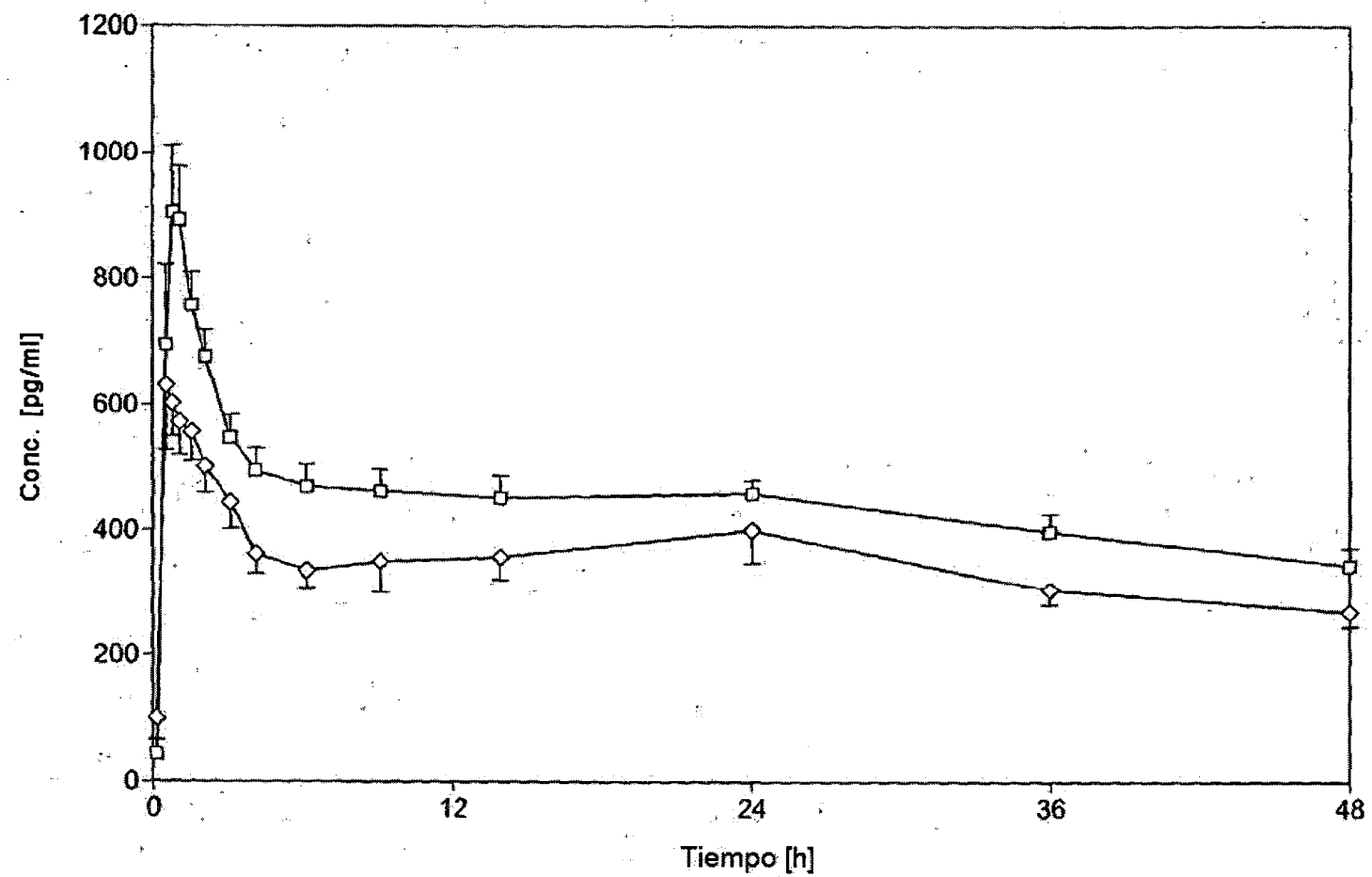


FIG. 2

56

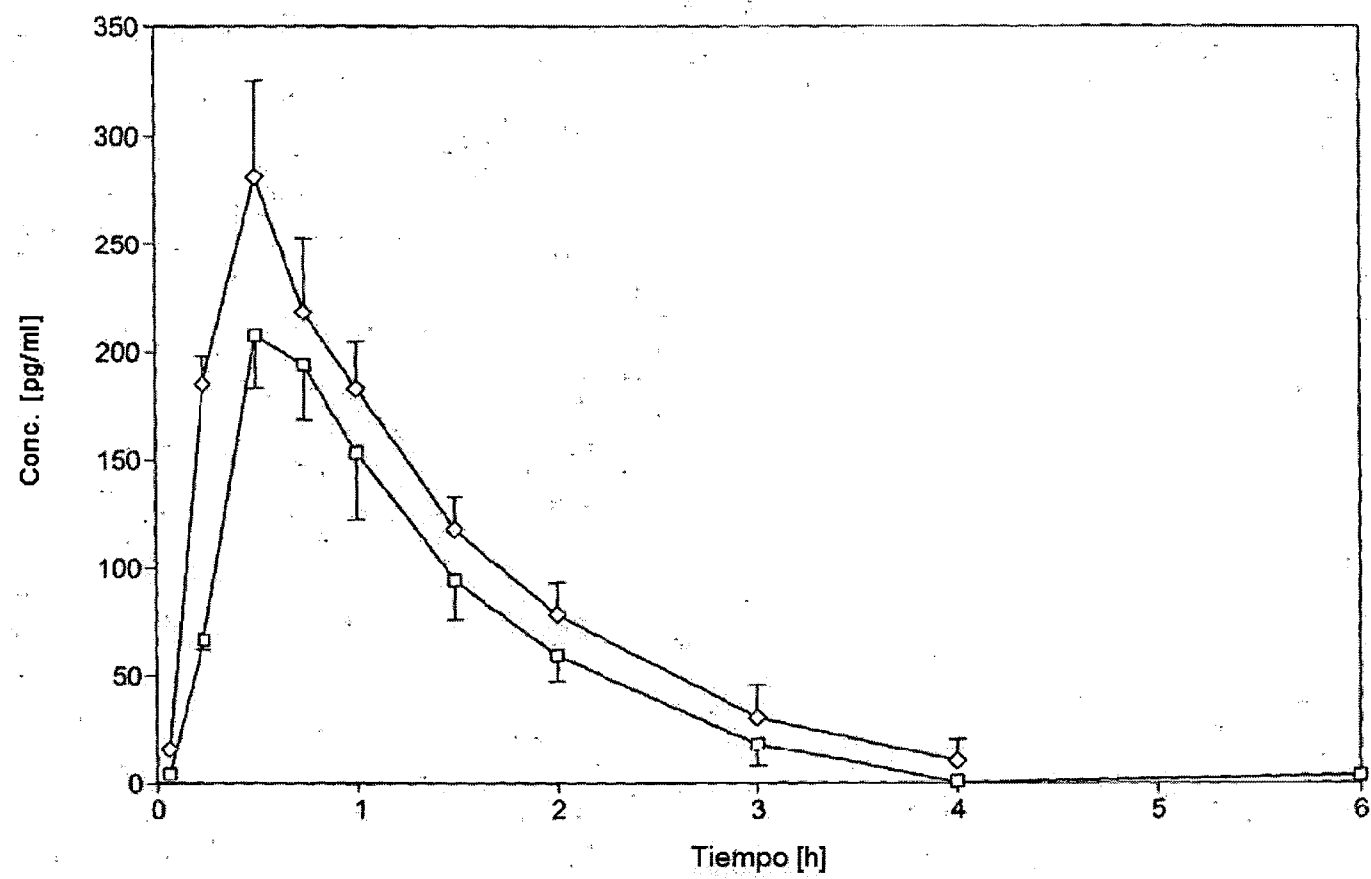


FIG. 3

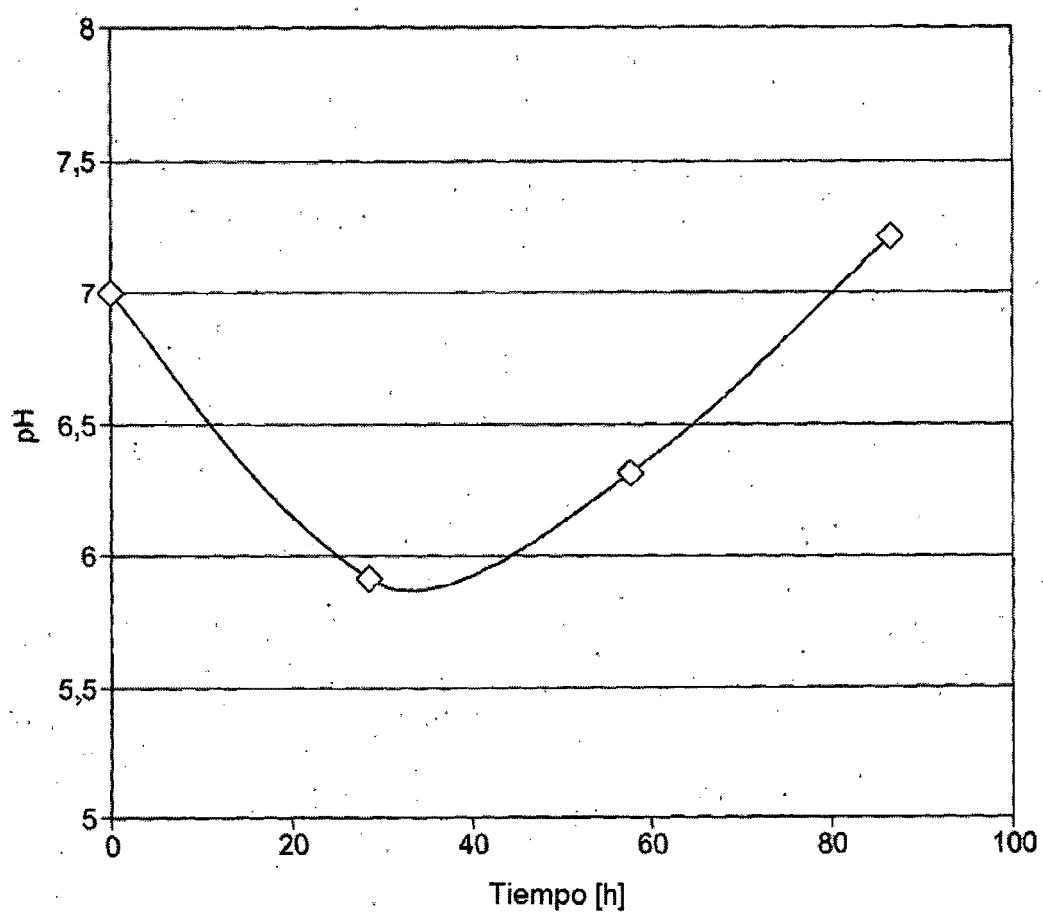


FIG. 4

59

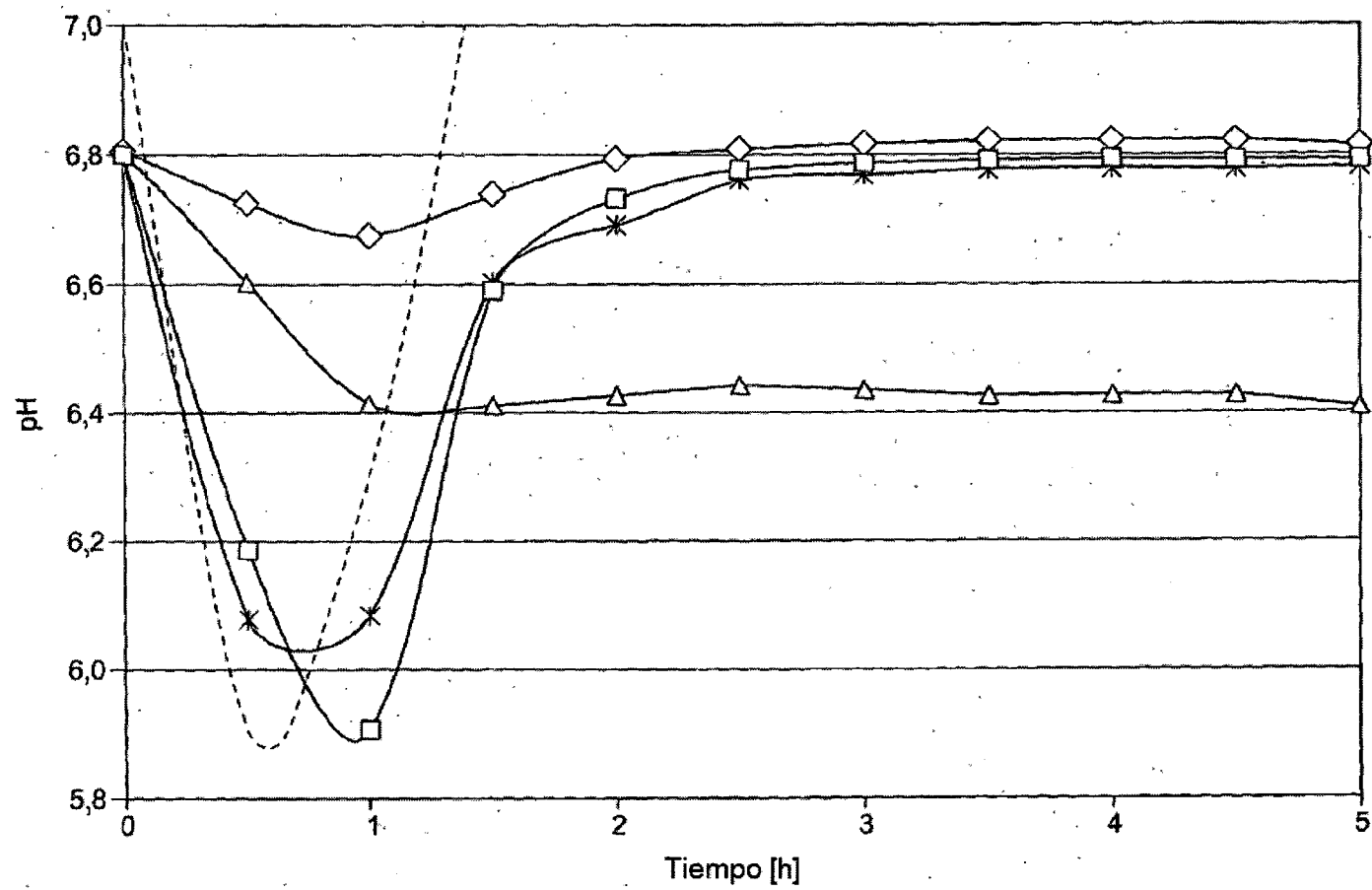


FIG. 5

59

60

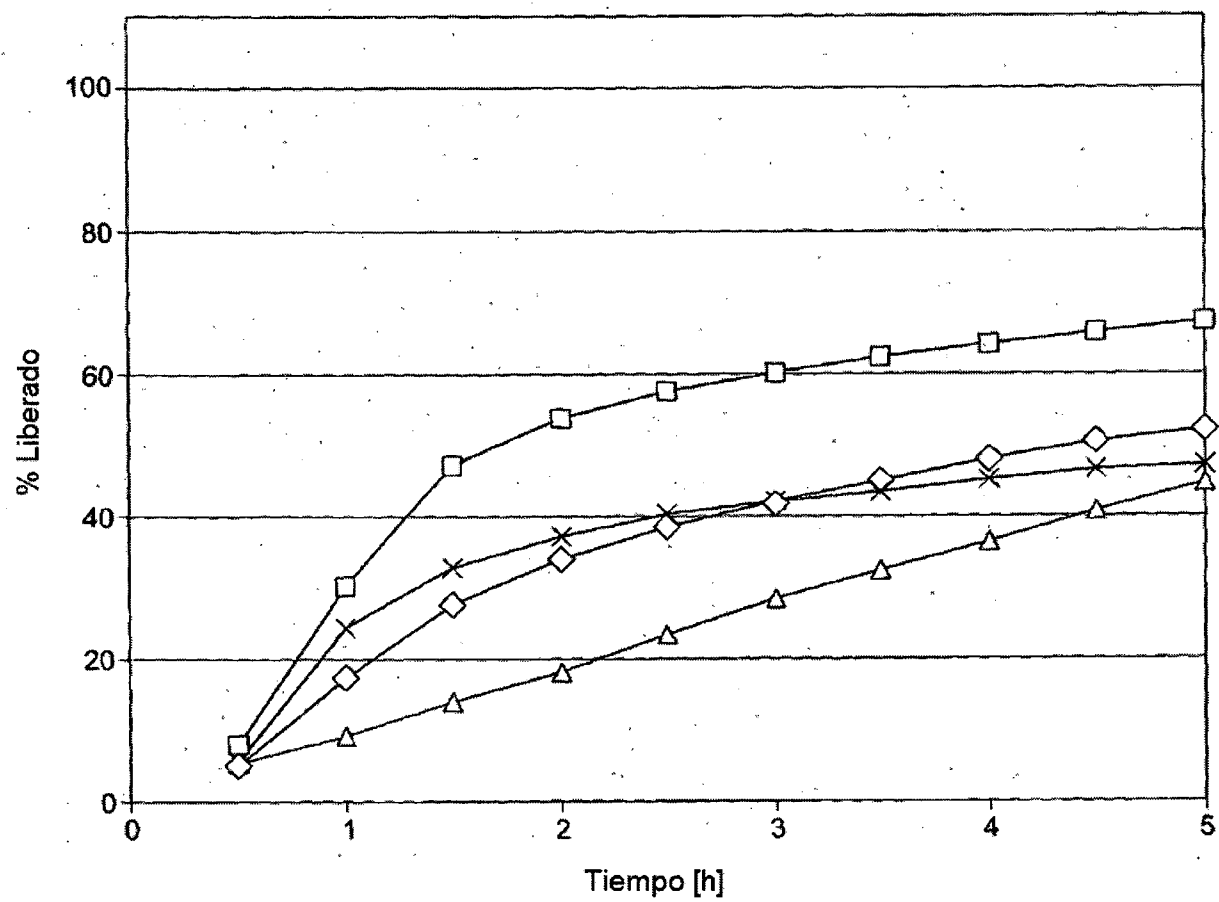


FIG. 6

60

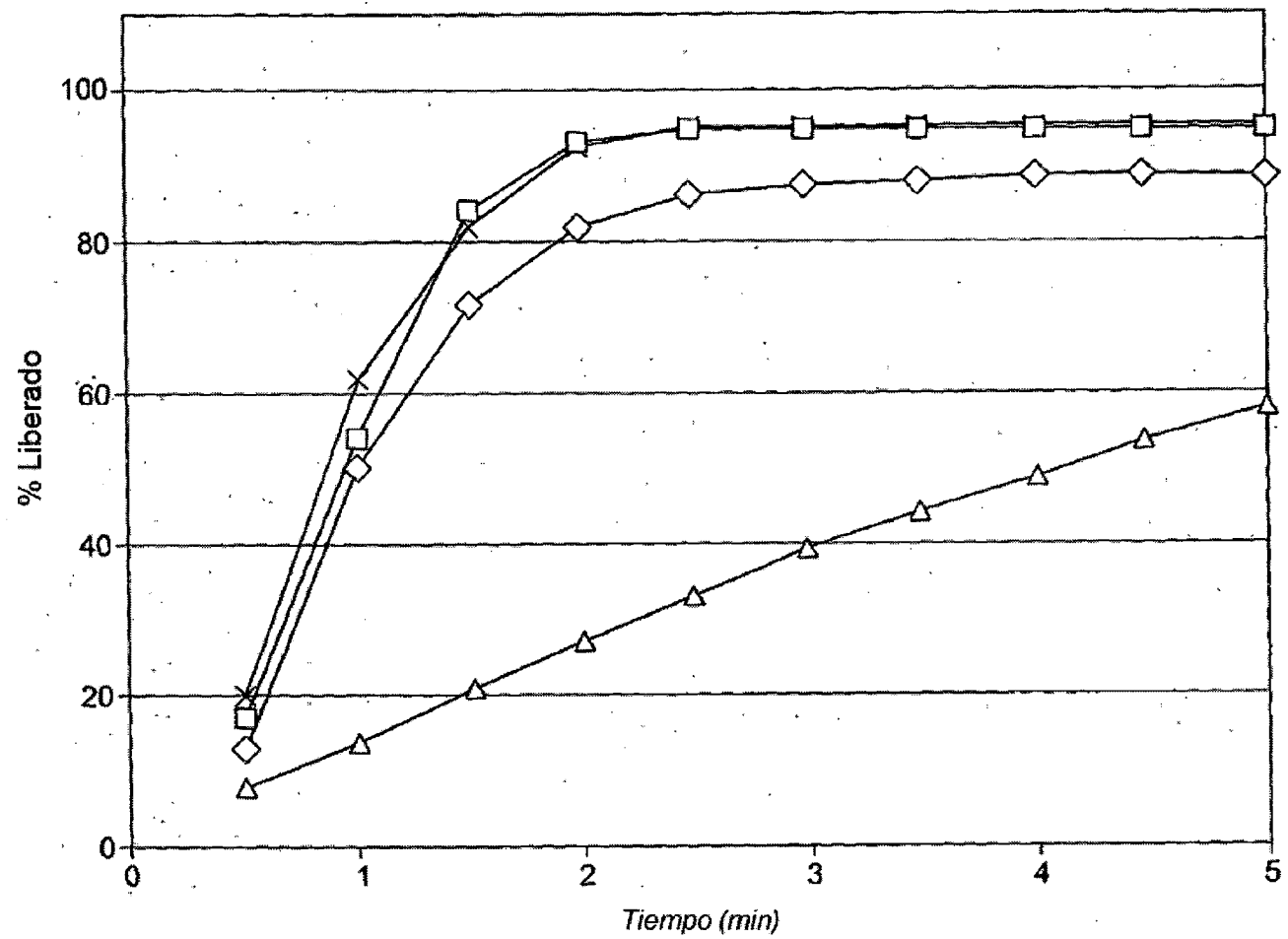


FIG. 7

62

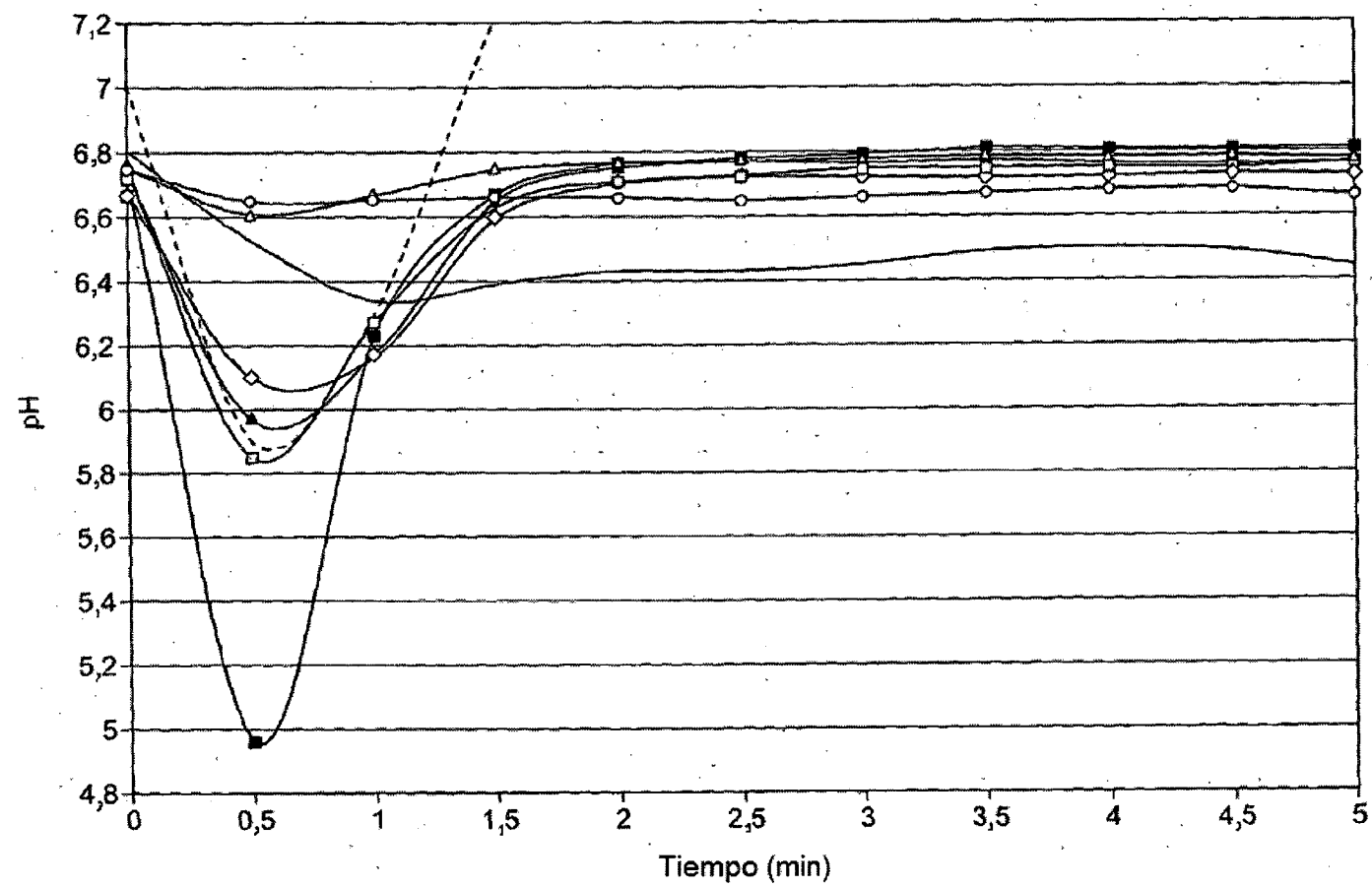


FIG. 8

60

62

63

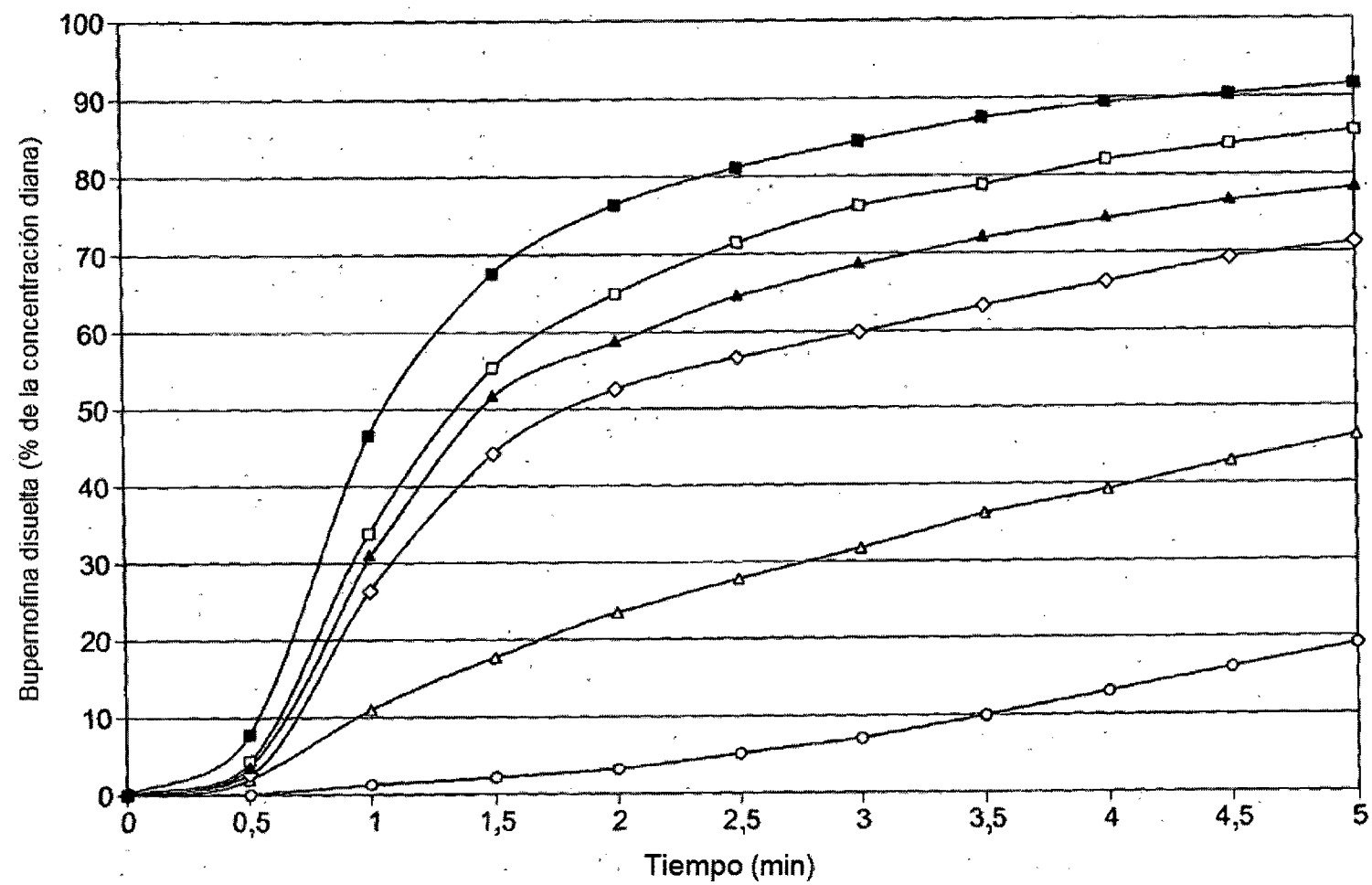


FIG. 9

61

63

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(10) International Publication Number
WO 2013/041851 A1

(43) International Publication Date
28 March 2013 (28.03.2013)

- (51) International Patent Classification:
A61K 9/00 (2006.01) A61K 31/485 (2006.01)
- (21) International Application Number:
PCT/GB2012/052303
- (22) International Filing Date:
18 September 2012 (18.09.2012)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
61/536,180 19 September 2011 (19.09.2011) US
- (71) Applicant: OREXO AB [SE/SE]; PO Box 303, SE-751 05 Uppsala (SE).
- (72) Inventor: FISCHER, Andreas; Orexo AB, PO Box 303, SE-751 05 Uppsala (SE).
- (74) Agent: MCNEENEY, Stephen Phillip; Park View House, 58 The Ropewalk, Nottingham, Nottinghamshire NG1 5DD (GB).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report (Art. 21(3))



WO 2013/041851 A1

(54) Title: NEW ABUSE-RESISTANT PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF OPIOID DEPENDENCE

(57) Abstract: There is provided pharmaceutical compositions for the treatment of e.g. opioid dependency comprising micro-particles of a pharmacologically-effective amount of buprenorphine, or a pharmaceutically-acceptable salt thereof, in associative admixture with particles comprising a weak acid, or particles comprising weakly- acidic buffer forming materials. The composition may further comprise a disintegrant and/or particles of a pharmacologically-effective amount of naloxone, or a pharmaceutically-acceptable salt thereof. The compositions are useful in the treatment of opioid dependency/addiction and/or pain.

NEW ABUSE-RESISTANT PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF OPIOID DEPENDENCE

This invention relates to new pharmaceutical compositions comprising opioids
5 that are useful in the treatment of opioid/opiate dependency and/or pain, which
compositions may be abuse-resistant, and may be administered transmucosally
and, in particular, sublingually.

Opioids are widely used in medicine as analgesics. Indeed, it is presently
10 accepted that, in the palliation of more severe pain, no more effective therapeutic
agents exist.

Opioid agonist analgesics are used to treat moderate to severe, chronic cancer
pain, often in combination with non-steroidal anti-inflammatory drugs (NSAIDs),
15 as well as acute pain (e.g. during recovery from surgery and breakthrough pain).
Further, their use is increasing in the management of chronic, non-malignant
pain.

A perennial problem with potent opioid agonists however is one of abuse by drug
20 addicts. Drug addiction is a worldwide problem of which opioid dependence,
notably of heroin, is a major component. The World Health Organisation (WHO)
estimates that there are approximately 4.3 million opioid addicts globally, with
approximately 0.7 million in Europe and 0.3 million in the US and Canada.

Opioid dependence is a major health problem and long-term heroin use is
connected to a substantially increased risk of premature death from drug
overdoses, violence and suicide. Furthermore, sharing of needles among addicts
contribute to the spreading of potentially fatal blood infections such as HIV, and
hepatitis C. In addition, opioid dependence often leads to difficulties with social
30 relations, inability to manage a normal job and increased criminality to finance
addiction, with severe implications for the opioid dependent person and his/her
family.

Opioid addicts not only feed their addition by direct purchase of opioids "on the
35 street", typically in the form of opioid-based powders (such as heroin), but may

also get hold of pharmaceutical formulations intended for the treatment of e.g. pain. Such individuals then often apply innovative techniques in their abuse of such formulations, for example by extracting a large quantity of active ingredient from that formulation into solution, which is then injected intravenously. With
5 most commercially-available pharmaceutical formulations, this can be done relatively easily, which renders them unsafe or "abusable". Thus, there is a general need for non-abusable pharmaceutical formulations comprising opioid agonists.

10 Opioid addicts are often treated by way of "substitution" therapy, in which mainly "street" opioids of unknown strength and purity are replaced by pharmaceutical-grade opioids with a longer duration of action, such as buprenorphine.

Further, a new cohort of opioid-dependent individuals has begun to emerge in the
15 last decade, particularly in the US, namely so-called "white collar" addicts, who have become dependent upon prescription opioids, typically initiated for the treatment of pain. Substitution therapy is also required for this growing group of patients.

20 Opioid antagonists are used to reverse the pharmacological effects of opioids. Selective opioid antagonists, such as naloxone, may therefore be used to treat narcotic drug overdose or to diagnose suspected opioid addiction. Naloxone in particular has a poor bioavailability when administered transmucosally but is rendered fully bioavailable when administered by injection.

25 A simple mixture combination tablet comprising the opioid partial agonist buprenorphine and naloxone in a 4:1 ratio for sublingual administration is available under the trademark Suboxone®. (This and other abuse-resistant opioid-containing formulations are reviewed by Fudula and Johnson in *Drug and*
30 *Alcohol Dependence*, 83S, S40 (2006). See also US patent applications US 2003/0124061 and US 2003/0191147.)

Because of naloxone's poor transmucosal bioavailability, if Suboxone is taken sublingually, as directed, the small amount of naloxone that is absorbed should
35 not interfere with the desired effects of buprenorphine.

On the other hand, if Suboxone is dissolved and injected by an addict with a view to achieving a "high", the increased availability of naloxone *via* the parenteral route should serve to antagonize the effects of buprenorphine, at the same time
5 as precipitating unpleasant opioid withdrawal symptoms in an individual physically dependent on opioids.

Nonetheless, when administered parenterally, naloxone's functional blockade of buprenorphine's action is also only partial and is short-lived in its nature. In view
10 of this, diversion and illicit use of Suboxone has frequently been reported, especially in hidden populations such as incarcerated and active drug abusers (see, for example, Alho *et al*, *Drug and Alcohol Dependence*, **88**, 75 (2007), Monte *et al*, *Journal of Addictive Diseases*, **28**, 226 (2009), Stimmel, *ibid.*, **26**, 1 (2007) and Smith *et al*, *ibid.*, **26**, 107, 2007). Indeed, a recent study of untreated
15 intravenous abusers in Finland revealed that 68% reported abuse of Suboxone. Moreover, 66% of those that had abused the drug once admitted that they had abused it at least once subsequently, or even regularly thereafter (see Ahlo *et al*, *supra*).

Further, Suboxone has also been reported to have several other significant limitations. For example, the tablets are large and disintegrate slowly. The bioavailability of buprenorphine is also significantly lower than for a sublingual solution (see Compton *et al*, *Drug and Alcohol Dependence*, **82**, 25 (2006)). Moreover, the taste is not well tolerated by all patients and the tablet has an
25 unpleasant gritty mouthfeel. A film-based product has recently been developed to counteract these problems, but the film formulation also does not dissolve particularly quickly. Furthermore, a maximum of only two films (with doses of 2 mg and 8 mg of buprenorphine) may be administered simultaneously. Sequential administration is thus required for (commonly administered) doses in excess of
30 10 mg or 16 mg of buprenorphine, respectively.

There is thus a presently unmet clinical need for an abuse-resistant product for use in opioid addiction substitution therapy, but which does not possess the afore-mentioned limitations. In particular, if it were possible to devise a
35 formulation that was capable of significantly increasing the bioavailability of

buprenorphine, it might be possible to reduce the amount of this active pharmaceutical ingredient, giving rise to less opioid in the formulation and so reducing the amount available for injection if diverted by way of intravenous abuse.

5

International patent applications WO 00/16751, WO 2004/067004, WO 2006/103418 and WO 2008/068471 all disclose drug delivery systems for the treatment of e.g. acute pain by sublingual administration, applying an interactive mixture principle, in which the active ingredient in microparticulate form is
10 adhered to the surfaces of larger carrier particles in the presence of a bioadhesive and/or mucoadhesive promoting agent. WO 2008/068471 in particular discloses a formulation comprising particles of opioid agonist drug upon the surfaces of carrier particles comprising an opioid antagonist, such as naloxone.

15

Prior art documents, including international patent applications WO 03/005944, WO 02/067903, WO 2007/141328, WO 2010/132605, WO 01/30288 and US patent application US 2009/0263476 A1 employ pH modifying agents to promote dissolution and/or absorption of active ingredients.

20

We have now found that, by applying a specific formulation principle to a combination of specific active ingredients, buprenorphine and naloxone, we have provided a product with unexpected, significantly improved pharmaceutical and clinical properties.

25

According to a first aspect of the invention there is provided a pharmaceutical composition comprising microparticles of a pharmacologically-effective amount of buprenorphine, or a pharmaceutically-acceptable salt thereof, in associative admixture with particles comprising a weak acid, or particles comprising weakly-
30 acidic buffer forming materials. Such compositions are referred to hereinafter as "the compositions of the invention".

It is preferred that the pharmaceutical compositions comprising buprenorphine, or a pharmaceutically-acceptable salt thereof, are presented in admixture (e.g. in
35 simple mixture) together with a disintegrant.

69

In this respect, there is further provided a pharmaceutical composition comprising:

- (i) a composition of the invention as hereinbefore defined ("Component (i)"); and
- (ii) a disintegrant (hereinafter "Component (ii)").

Compositions comprising Components (i) and (ii) are also referred to together hereinafter as compositions of the invention.

- It is further preferred that the pharmaceutical compositions comprising buprenorphine, or a pharmaceutically-acceptable salt thereof, are presented in admixture (e.g. in simple mixture) together with a disintegrant and naloxone.

In this respect, there is further provided a pharmaceutical composition comprising:

- (a) a composition of the invention comprising Components (i) and/or (ii) as hereinbefore defined; and
- (b) particles of a pharmacologically-effective amount of naloxone, or a pharmaceutically-acceptable salt thereof (hereinafter "Component (iii)").

Compositions comprising Component (iii) formulated together with Components, (i) and/or (ii) are also referred to together hereinafter as compositions of the invention.

- Buprenorphine and pharmaceutically-acceptable salts thereof are presented in the compositions of the invention in the form of microparticles. Naloxone and pharmaceutically-acceptable salts thereof may also (e.g. preferably) be presented in compositions of the invention in the form of microparticles. Microparticles preferably possess a weight based mean diameter, number based mean diameter and/or a volume based mean diameter of between about 0.5 μm and about 15 μm , such as about 1 μm and about 10 μm . As used herein, the term "weight based mean diameter" will be understood by the skilled person to include that the average particle size is characterised and defined from a particle size distribution by weight, i.e. a distribution where the existing fraction (relative amount) in each size class is defined as the weight fraction, as obtained by e.g.

sieving (e.g. wet sieving). As used herein, the term "number based mean diameter" will be understood by the skilled person to include that the average particle size is characterised and defined from a particle size distribution by number, i.e. a distribution where the existing fraction (relative amount) in each size class is defined as the number fraction, as measured by e.g. microscopy. As used herein, the term "volume based mean diameter" will be understood by the skilled person to include that the average particle size is characterised and defined from a particle size distribution by volume, i.e. a distribution where the existing fraction (relative amount) in each size class is defined as the volume fraction, as measured by e.g. laser diffraction.

Microparticles of active ingredients may be prepared by standard micronisation techniques, such as grinding, jet milling, dry milling, wet milling, precipitation, etc. An air elutriation process may be utilised subsequently to prepare specific size fractions, if required.

Preferred salts of buprenorphine and naloxone include hydrochloride salts.

Buprenorphine and pharmaceutically-acceptable salts thereof are formulated together in associative admixture with particles of a weak acid, or with particles of weakly-acidic buffer forming materials, to provide compositions of the invention (or Component (i) of compositions of the invention).

Weakly acidic materials that may be mentioned include those that, when provided in a composition of the invention, enable the provision when the composition is dissolved in water and/or saliva (e.g. at the site of administration of compositions of the invention) of a pH of between about 4.0 and about 6.5 (e.g. about 6.25), and are present in a sufficient amount to enable the maintenance of pH within this range for an appropriate length of time (e.g. about 30 seconds, such as about 1 minute) to about 3 minutes (e.g. about 2 minutes, such as about 1.5 minutes) to facilitate dissolution of, particularly, the buprenorphine microparticles, and/or absorption of buprenorphine across the sublingual mucosa thereafter. For the purpose of this invention, the term includes substances that are safe for use in mammals, and includes weak acids, weak acid derivatives and other chemicals that convert to weak acids *in vivo*

71

(e.g. precursors that convert to acids *in vivo*, by for example being sequentially activated in accordance with properties of the local environment). Typical pKas of weak acids are in the range of between about -1.5 (e.g. about -1.74) and about 16 (e.g. about 15.74) (e.g. see Vollhardt, *Organic Chemistry* (1987). A preferred range is between about 1 and about 10. More preferably, the weakly acidic material comprises a weak acid that is safe for human consumption, for example a food acid, such as malic acid, fumaric acid, adipic acid, succinic acid, lactic acid, acetic acid, oxalic acid, maleic acid, ammonium chloride, preferably tartaric acid, and more preferably citric acid, or a combination of such acids. The skilled person will appreciate that, when weak acids are employed which are not solids (and therefore not particulate) at or around room temperature and atmospheric pressure, they may be adsorbed into a particulate carrier material (such as colloidal silica) in order to provide particles comprising the weakly acidic material.

15

Weakly-acidic buffer forming materials include materials that, when provided in a composition of the invention, provide a weakly acidic buffer system when the composition is dissolved in water and/or saliva (e.g. at the site of administration of compositions of the invention), enabling the provision of a pH of between about 4.0 and about 6.5 (e.g. about 6.25), and are present in a sufficient amount to enable the maintenance of pH within this range for an appropriate length of time (e.g. about 30 seconds, such as about 1 minute) to about 3 minutes (e.g. about 2 minutes, such as about 1.5 minutes) to facilitate dissolution of, particularly, the buprenorphine microparticles, and/or absorption of buprenorphine across the sublingual mucosa thereafter. Buffer forming materials thus include combinations of weak acid and salt of weak acid, such as combinations of the aforementioned acids with alkaline salts of those acids, including sodium citrate, potassium citrate, sodium tartrate, potassium tartrate and the like. Preferred buffer forming materials are citric acid and sodium citrate. The skilled person will appreciate that, when materials are employed which are not solids (and therefore not particulate) at or around room temperature and atmospheric pressure, they may be adsorbed into a particulate carrier material (such as colloidal silica) in order to provide particles comprising the weakly-acidic buffer forming materials.

35

Suitable particles sizes of weakly acidic, or weakly-acidic buffer forming, materials are in the range about 1 μm and about 1000 μm (e.g. about 800 μm , such as about 750 μm), and preferably between about 40 (such as about 50 μm) and about 600 μm . Suitable amounts of weakly acidic materials that enable the maintenance of pH within the aforementioned ranges after oral administration as hereinbefore described are in the range of at least about 1% to about 10% by weight of the total formulation. Suitable total amounts of weakly-acidic buffer forming materials that enable the maintenance of pH within the aforementioned ranges after oral administration as hereinbefore described are in the range of at least about 1% to about 15% by weight of the total formulation.

The disintegrant or "disintegrating agent" that may be employed as, or as part of, Component (ii) in compositions of the invention may be defined as any material that is capable of accelerating to a measurable degree the disintegration/dispersion of a composition of the invention. The disintegrant may thus provide for an *in vitro* disintegration time of about 30 seconds or less, as measured according to e.g. the standard United States Pharmacopeia (USP) disintegration test method (see *FDA Guidance for Industry: Orally Disintegrating Tablets*; December 2008). This may be achieved, for example, by the material being capable of swelling, wicking and/or deformation when placed in contact with water and/or mucous (e.g. saliva), thus causing tablet formulations to disintegrate when so wetted.

Suitable disintegrants (as defined in, for example, Rowe *et al*, *Handbook of Pharmaceutical Excipients*, 6th ed. (2009)) include cellulose derivatives such as hydroxypropyl cellulose (HPC), low substituted HPC, methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, microcrystalline cellulose, modified cellulose gum; starch derivatives such as moderately cross-linked starch, modified starch, hydroxylpropyl starch and pregelatinized starch; and other disintegrants such as calcium alginate, sodium alginate, alginic acid, chitosan, colloidal silicon dioxide, docusate sodium, guar gum, magnesium aluminium silicate, polacrilin potassium and polyvinylpyrrolidone. Combinations of two or more disintegrants may be used.

73

Preferred disintegrants include so-called "superdisintegrants" (as defined in, for example, Mohanachandran *et al*, *International Journal of Pharmaceutical Sciences Review and Research*, 6, 105 (2011)), such as cross-linked polyvinylpyrrolidone, sodium starch glycolate and croscarmellose sodium.

5 Combinations of two or more superdisintegrants may be used.

Disintegrants may also be combined with superdisintegrants in compositions of the invention.

10 Disintegrants and/or superdisintegrants are preferably employed in an (e.g. total) amount of between 0.5 and 15% by weight based upon the total weight of a composition. A preferred range is from 1 to 8%, such as from about 2 to about 7% (e.g. about 5%, such as about 4%) by weight.

15 Compositions of the invention may be formulated together (along with any other materials that may be present) by standard simple mixing techniques or by way of granulation.

Granules may be prepared by a process of dry granulation, wet granulation, melt
20 granulation, thermoplastic pelletising, spray granulation or extrusion/spheronisation.

Wet granulation techniques are well known to those skilled in the art and include any technique involving the massing of a mix of dry primary powder particles
25 using a granulating fluid, which fluid comprises a volatile, inert solvent, such as water, ethanol or isopropanol, either alone or in combination, and optionally in the presence of a binder or binding agent. The technique may involve forcing a wet mass through a sieve to produce wet granules which are then dried, preferably to a loss on drying of less than about 3% by weight.

30

Dry granulation techniques are also well known to those skilled in the art and include any technique in which primary powder particles are aggregated under high pressure, including slugging and roller compaction, for example as described hereinafter.

35

Melt granulation will be known by those skilled in the art to include any technique in which granules are obtained through the addition of a molten binder, or a solid binder which melts during the process. After granulation, the binder solidifies at room temperature. Thermoplastic pelletising will be known to be similar to melt
5 granulation, but in which plastic properties of the binder are employed. In both processes, the agglomerates (granules) obtained comprise a matrix structure.

Spray granulation will be known by those skilled in the art to include any technique involving the drying of liquids (solutions, suspensions, melts) while
10 simultaneously building up granulates in a fluid bed. The term thus includes processes in which foreign seeds (germs) are provided upon which granules are built up, as well as those in which inherent seeds (germs) form in the fluid bed due to abrasion and/or fracture, in addition to any spray coating granulation technique generally. The sprayed liquid coats the germs and assists further
15 agglomeration of particles. It is then dried to form granules in the form of a matrix.

Extrusion/spheronisation will be well known to those skilled in the art to include any process involving the dry mixing of ingredients, wet massing along with a
20 binder, extruding, spheronising the extrudate into spheroids of uniform size, and drying.

In particular, microparticles of buprenorphine or salt thereof and particles of weakly acidic, weakly-acidic buffer forming, materials are presented in
25 associative admixture with each other in compositions of the invention. By "associative admixture" we mean that whether or not Component (i) is subsequently formulated along with Components (ii) and (iii) as hereinbefore defined, some form of mixing step (simple mixing, granulation as described hereinbefore, or otherwise) takes place as between the buprenorphine/salt
30 microparticles and particles of weakly acidic, weakly-acidic buffer forming, materials, rendering them in intimate contact with each other.

For the avoidance of doubt, by "intimate contact", we include that microparticles of buprenorphine or salt thereof, and particles of weakly acidic, weakly-acidic
35 buffer forming, materials, are presented in compositions of the invention in any

75

form in which they are, at least in part, in intimate contact with each other. This includes the possibility of the inclusion of quickly dissolving coatings on one or other, or both, sets of particles.

5 In this respect, Component (i) is preferably presented as, or as part of, a composition of the invention in the form of a interactive mixture comprising at least one population of carrier particles upon the surfaces of which are presented (e.g. adhered) microparticles of buprenorphine or a pharmaceutically acceptable salt thereof.

10

The term "interactive" mixture will be understood by those skilled in the art to include the term "ordered" mixture, and to denote a mixture in which particles do not appear as single units, as in random mixtures, but rather where smaller particles (e.g. microparticles of, for example, buprenorphine) are attached to (i.e. 15 adhered to or associated with) the surfaces of larger carrier particles. Such mixtures are characterised by interactive forces (for example van der Waals forces, electrostatic or Coulomb forces, and/or hydrogen bonding) between carrier and surface-associated particles (see, for example, Staniforth, *Powder Technol.*, **45**, 75 (1985)). In final mixtures, and compositions comprising such 20 mixtures, the interactive forces need to be strong enough to keep the adherent particles at the carrier surface.

When interactive mixtures are employed as the formulation principle by which the particulate Component (i) is presented in a composition of the invention, these 25 are made, preferably, with carrier particles that are of a size (weight and/or volume based average or mean diameter, *vide supra*) that is between about 30 μm and about 1000 μm (e.g. about 800 μm , such as about 750 μm), and preferably between about 40 (such as about 50 μm) and about 600 μm .

30 Carrier particles may comprise pharmaceutically-acceptable substances that are soluble in water, such as carbohydrates, e.g. sugars, such as lactose, and sugar alcohols, such as mannitol, sorbitol and xylitol; pharmaceutically-acceptable inorganic salts, such as sodium chloride. Water soluble carrier particles may also comprise the weakly acidic, and/or weakly acidic buffer forming materials, 35 mentioned hereinbefore (such as citric acid and/or sodium citrate). Alternatively,

carrier particles may comprise pharmaceutically-acceptable substances that are insoluble or sparingly soluble in water, such as dicalcium phosphate anhydrate, dicalcium phosphate dihydrate, tricalcium phosphate, calcium carbonate, and barium sulphate; starch and pre-gelatinised starch; bioadhesive and
5 mucoadhesive materials, such as crosslinked polyvinylpyrrolidone and croscarmellose sodium; and other polymers, such as microcrystalline cellulose, cellulose and; or mixtures thereof.

By "soluble in water" we include that the material has a solubility in water that is
10 greater than 33.3 mg/mL at atmospheric pressure (e.g. 1 bar) and room temperature (e.g. 21°C). On the other hand, the term "sparingly soluble or insoluble in water" includes materials that have a solubility in water that is less than 33.3 mg/mL under the same conditions. Preferred soluble carrier particle materials include sugar alcohols, such as sorbitol, xylitol and particularly
15 mannitol. Preferred sparingly water-soluble or water-insoluble carrier particle materials include cellulose and starches, such as microcrystalline cellulose.

It is preferred that buprenorphine or pharmaceutically acceptable salt thereof is presented on the surfaces of water-soluble carrier particles.

20

In this respect, as stated above, weakly acidic materials, and/or weakly-acidic buffer forming materials, may also function as water-soluble carrier particle materials. Therefore, the associated admixture of such materials with buprenorphine/salt thereof may mean the former comprise carrier particles upon
25 which microparticles of the latter are presented. In such cases, such materials may be presented at least as further water-soluble carrier particles, in addition to the presence of other water-soluble carrier particles, upon the surfaces of both of which are presented burprenorphine microparticles.

30 When carrier particles comprise such weakly acidic/buffer forming materials, composites of such materials with other water-soluble carrier particle materials (such as those described hereinbefore) may be provided. Such materials may be prepared by direct compression or granulation, for example. Alternatively, carrier particles may consist essentially of a weakly acidic material and/or one or more
35 materials that, when dissolved in saliva, give rise to a weakly acidic buffer

77

system. By "consisting essentially" of such materials, we mean that, excluding the possible presence of water (*vide infra*), the carrier particles comprise at least about 95%, such as at least about 98%, more preferably greater than about 99%, and particularly at least about 99.5% by weight (based on the total weight of the carrier particle) of such materials. These percentages exclude the presence of trace amounts of water (e.g. crystal water or water bound to external surfaces of materials), and/or any impurities that may be present in such materials, which impurities may arise following the production of such materials, either by a commercial or non-commercial third party supplier, or by a skilled person making a composition of the invention.

Alternatively (and/or in addition), in Component (i), particles of weakly acidic material, and/or of weakly-acidic buffer forming materials, may be presented, at least in part, upon the surfaces of, and/or between, carrier particles. In such cases, suitable particle sizes of such materials are as presented herein for active ingredients and/or disintegrants.

When employed in compositions of the invention, Components (ii) and (iii) are preferably formulated together, for example to form particles comprising naloxone or salt thereof and the disintegrant, prior to mixing with Component (i). Alternatively, particles of weakly acidic material, and/or of weakly-acidic buffer forming materials, may be formulated along with Components (ii) and/or (iii) prior to mixing with buprenorphine microparticles, which latter microparticles may be presented in the form of interactive mixtures with carrier particles as hereinbefore described. Weakly acidic, and/or weakly-acidic buffer forming, materials may thus be formulated in associative admixture with buprenorphine microparticles (as hereinbefore defined) in this way.

Furthermore, in Component (iii), particles of naloxone, or pharmaceutically-acceptable salts thereof, may also be presented upon the surfaces of, and/or between, carrier particles in compositions of the invention, but this is not essential. Such carrier particles may be water-soluble (as hereinbefore defined), or may (preferably) be water-insoluble/sparingly soluble carrier particles.

Disintegrant and/or superdisintegrant materials, may also be presented, at least in part, as particles upon the surfaces of, and/or between, carrier particles, which may or may not also carry naloxone or salt thereof. If employed in particulate form, particles of disintegrants and/or superdisintegrants may be presented with a particle size (weight and/or volume based average or mean diameter, *vide supra*) of between about 0.1 and about 100 µm (e.g. about 1 and about 50 µm).

Alternatively, disintegrants and/or superdisintegrants may also be present as a constituent in composite excipients. Composite excipients may be defined as co-processed excipient mixtures. Examples of composite excipients comprising superdisintegrants are Parateck® ODT, Ludipress® and Prosolv® EASYtab.

Bio/mucoadhesive materials may also be presented in compositions of the invention. Such materials may be presented upon (e.g. adhered to) the surfaces of carrier particles when components of compositions of the invention are presented in the form of interactive mixtures.

Compositions of the invention may be employed in the treatment of opioid dependency and/or addiction as described hereinbefore, for example in substitution therapy programs. Opioid dependency and/or addiction may be defined in numerous ways (see, for example, www.who.int/substance_abuse/terminology/definition1), but may be characterized for example by physiological, behavioural, and cognitive phenomena wherein the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value, and/or characterised by a desire (often strong, and sometimes overpowering) to take opioids and/or opiates (which may or may not have been medically prescribed). It is particularly preferred that compositions of the invention comprising naloxone are used in the treatment of opioid dependency and/or addiction.

Buprenorphine is a partial agonist at the µ-opioid receptor and an antagonist at the κ-opioid receptor. It has high binding affinity at both receptors and competes with other agonists, such as methadone, heroin (diamorphine) and morphine, at the µ-opioid receptor. Opioid agonist effects of buprenorphine are less than the maximal effects of other, "full" opioid agonists, such as morphine, and are limited

by a "ceiling" effect. The drug thus produces a lower degree of physical dependence than other opioid agonists, such as heroin, morphine or methadone and is therefore particularly useful in substitution therapy.

- 5 The term "pharmacologically effective amount" refers to an amount of an active ingredient, which is capable of conferring a desired therapeutic effect on a treated patient, whether administered alone or in combination with another active ingredient. Such an effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of, or feels, an effect).

10

- Thus, appropriate pharmacologically effective amounts of buprenorphine (or salt thereof) include those that are capable of producing, and/or contributing to the production of, the desired therapeutic effect, namely decreased opioid and/or opiate craving and/or decreased illicit drug use, when administered
- 15 transmucosally, whereas appropriate pharmacologically effective amounts of naloxone (or salt thereof) when employed must be sufficient so as not to compete with the above-mentioned pharmacological effect of the buprenorphine present in the composition of the invention upon transmucosal administration, but to antagonize the effect of the buprenorphine and precipitate withdrawal symptoms
- 20 if an attempt is made by an opioid-addicted individual to inject a composition of the invention.

- The amounts of active ingredients that may be employed in compositions of the invention may thus be determined by the skilled person, in relation to what will be
- 25 most suitable for an individual patient. This is likely to vary with the route of administration, the type and severity of the condition that is to be treated, as well as the age, weight, sex, renal function, hepatic function and response of the particular patient to be treated.

- 30 The total amount of buprenorphine/salt thereof that may be employed in a composition of the invention may be in the range of about 0.1%, such as about 1%, to about 20%, such as about 10%, by weight based upon the total weight of the composition. The amount of this active ingredient may also be expressed as the amount in a unit dosage form (e.g. a tablet). In such a case, the amount of
- 35 buprenorphine/salt that may be present may be sufficient to provide a dose of

buprenorphine (calculated as the free base) per unit dosage form that is in the range of between about 0.1 mg, such as about 1 mg and about 50, for example about 30, such as about 20 mg (e.g. about 15 mg, e.g. about 12 mg, such as about 10 mg). Preferred ranges for the treatment of pain are about 0.1 mg to about 4 mg. Preferred ranges for substitution therapy are about 0.5 mg to about 50 mg, such as about 0.75 mg, (e.g. about 1 mg) to about 12 mg, such as about 10 mg (e.g. about 7 mg). Individual buprenorphine doses per tablet that may be mentioned include about 11.4 mg, about 8.6 mg, about 5.7 mg, about 2.9 mg and about 1.4 mg.

10

When employed, the total amount of naloxone/salt thereof that may be employed in a composition of the invention may be in the range about 0.125%, such as about 0.25% to about 5%, such as about 2.5%, by weight based upon the total weight of the composition. The amount of this active ingredient may also be expressed as the amount in a unit dosage form (e.g. a tablet). In such a case, the amount of naloxone/salt that may be present may be sufficient to provide a dose of naloxone (calculated as the free base) per unit dosage form that is in the range of between about 0.125 mg and about 12.5 mg, such as about 0.19 mg (e.g. about 0.25 mg) to about 3 mg, such as about 2.5 mg (e.g. about 1.75 mg). Individual naloxone doses per tablet that may be mentioned include about 2.9 mg, about 2.2 mg, about 1.4 mg, about 0.7 mg and about 0.4 mg.

15

Although, for compositions of the invention containing naloxone, it is preferred that the dose ratio of buprenorphine:naloxone is maintained at about 4:1, the above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

20

Compositions of the invention, once prepared, are preferably directly compressed/compacted into unit dosage forms (e.g. tablets) for administration to mammalian (e.g. human) patients, for example as described hereinafter.

25

Compositions of the invention may be in the form of powders or, more preferably, tablets for e.g. sublingual administration. Tablets may also comprise a binder. A binder may be defined as a material that is capable of acting as a bond formation

30

enhancer, facilitating the compression of the powder mass into coherent compacts. Suitable binders include cellulose gum and microcrystalline cellulose. If present, binder is preferably employed in an amount of between 0.5 and 20% by weight based upon the total weight of the tablet formulation. A preferred range
5 is from 1 to 15%, such as from about 2.0 to about 12% (e.g. about 10%) by weight.

Suitable further additives and/or excipients that may be employed in compositions of the invention, in particular those in the form of tablets for e.g. sublingual
10 administration may comprise:

- (a) lubricants (such as magnesium stearate or, preferably, sodium stearyl fumarate);
- (b) flavourings (e.g. lemon, peppermint powder or, preferably, menthol), sweeteners (e.g. neohesperidin, acesulfame K or, preferably, sucralose)
15 and dyestuffs;
- (c) antioxidants, which may be naturally occurring or otherwise (e.g. butylated hydroxytoluene (BHT), vitamin C, vitamin E, β -carotene, uric acid, uniquest, superoxide dismutase (SOD), glutathione peroxidase or peroxidase catalase); and/or
- 20 (d) other ingredients, such as carrier agents, preservatives and gliding agents (e.g. colloidal silica).

Compositions of the invention may be prepared by standard techniques, and using standard equipment, known to the skilled person.

25 When presented in the form of interactive mixtures, particles of e.g. buprenorphine/salt may be dry mixed with relevant carrier particles over a period of time that is sufficiently long to enable appropriate amounts of respective active ingredients to adhere to the surface of the carrier particles. This may also apply
30 to other active ingredients and/or excipients defined hereinbefore.

The skilled person will appreciate that, in order to obtain a dry powder formulation in the form of an interactive mixture, larger carrier particles must be able to exert enough force to break up agglomerates of smaller particles. This ability will

primarily be determined by particle density, surface roughness, shape, flowability and, particularly, relative particle sizes.

Standard mixing equipment may be used in this regard. The mixing time period
5 is likely to vary according to the equipment used, and the skilled person will have no difficulty in determining by routine experimentation a suitable mixing time for a given combination of active ingredient and carrier particle material(s).

Interactive mixtures may also be provided using techniques other than dry mixing,
10 which techniques will be well known to those skilled in the art.

Other ingredients may alternatively be incorporated by standard mixing or other formulation principles.

15 The compositions of the invention may be administered transmucosally, such as buccally, rectally, nasally or preferably sublingually by way of appropriate dosing means known to the skilled person. A sublingual tablet may be placed under the tongue, and the active ingredients absorbed through the surrounding mucous membranes.

20 In this respect, the compositions of the invention may be incorporated into various kinds of pharmaceutical preparations intended for transmucosal (e.g. sublingual) administration using standard techniques (see, for example, Lachman *et al*, "*The Theory and Practice of Industrial Pharmacy*", Lea & Febiger, 3rd edition (1986)
25 and "*Remington: The Science and Practice of Pharmacy*", Gennaro (ed.), Philadelphia College of Pharmacy & Sciences, 19th edition (1995)).

Pharmaceutical preparations for sublingual administration may be obtained by combining compositions of the invention with conventional pharmaceutical
30 additives and/or excipients used in the art for such preparations, and thereafter preferably directly compressed/compacted into unit dosage forms (e.g. tablets). (See, for example, *Pharmaceutical Dosage Forms: Tablets. Volume 1*, 2nd Edition, Lieberman *et al* (eds.), Marcel Dekker, New York and Basel (1989) p. 354-356 and the documents cited therein.) Suitable compacting equipment

includes standard tableting machines, such as the Kilian SP300, the Korsch EK0, the Korsch XP1, the Korsch XL100 or the Korsch PharmaPress 800.

Suitable final sublingual tablet weights are in the range of about 30 to about 400 mg, such as about 40 (e.g. about 50) to about 300 mg (e.g. about 250 mg, such as about 200 mg), for example about 50 (e.g. about 60) to 180 mg, more preferably between about 60 (e.g. about 70) and about 160 mg. Suitable final tablet diameters are in the range of about 3 to about 12 mm, for example about 4 to about 10 mm, and more preferably about 5 to about 9 mm. Suitable final tablet thicknesses are in the range of about 0.5 mm to about 4 mm, such as about 1.5 mm to about 3 mm. Various tablet shapes are possible (e.g. circular, triangular, square, diamond, polygon or oval). Suitable tablet hardnesses include crushing strengths in the range of about 10N to about 100N, for example about 15N to about 50N (depending on the size and/or weight of the tablet), according to US Pharmacopoeia method <1217>.

Irrespective of the foregoing, compositions of the invention comprising disintegrants (or other excipients that function by swelling) should be essentially free (e.g. less than about 20% by weight based on the total weight of the formulation) of water. It will be evident to the skilled person that "premature" hydration will dramatically decrease the performance of a tablet formulation in use and may result in premature dissolution of active ingredients.

Wherever the word "about" is employed herein in the context of dimensions (e.g. tablet sizes and weights, particle sizes etc.), surface coverage (e.g. of carrier particles by particles of active ingredients), amounts (e.g. relative amounts of individual constituents in a composition or a component of a composition and absolute doses (including ratios) of active ingredients), temperatures, pressures, times, pH values, concentrations, it will be appreciated that such variables are approximate and as such may vary by $\pm 10\%$, for example $\pm 5\%$ and preferably $\pm 2\%$ (e.g. $\pm 1\%$) from the numbers specified herein. Wherever the word "about" is employed herein in the context of pharmacokinetic properties ($C_{\max}$, $t_{\max}$, AUCs), etc., it will be appreciated that such variables are approximate and as such may vary by $\pm 15\%$, such as $\pm 10\%$.

35

Compositions of the invention may be administered by way of appropriate dosing means known to the skilled person. For example, a sublingual tablet may be placed under the tongue, and the active ingredients absorbed through the surrounding mucous membrane.

5

We have found that compositions of the invention surprisingly give rise to significantly improved bioavailability for buprenorphine when compared to prior art, commercially-available formulations. This means that formulations with lower single doses of buprenorphine may be administered by way of compositions of the invention, so reducing the "street value" of a single tablet when it comprises a composition of the invention, with more than one such tablet being required to give the same effect when illicitly administered parenterally (i.e. in "street" terms, the same "fix"). This means that compositions of the invention are less likely to be abused than prior art, commercially-available formulations (see Comer *et al*,
15 *Addiction*, **105**, 709–718 (2010)).

Additionally, we have found that compositions of the invention comprising naloxone also surprisingly give rise to significantly (and simultaneously with buprenorphine) improved bioavailability for naloxone when compared to prior art,
20 commercially-available formulations.

Compositions of the invention comprising naloxone thus surprisingly give rise to similar, almost parallel, degrees of improved bioavailability for both buprenorphine and naloxone, which means that the "optimal" ratio of buprenorphine to naloxone, which has been arrived at to reduce abuse potential
25 (see, for example, Mendelson and Jones, *Drug and Alcohol Dependence*, **70**, 829 (2003)), may be maintained, and doses of both active ingredients therefore lowered by an equivalent degree to preserve the same ratio.

30 According to a further aspect of the invention, there is provided a method of treating opioid dependency and/or addiction in a human,

- which method comprises sublingual administration to a human patient suffering from opioid dependency and/or addiction of
- at least one unit dose of a pharmaceutical composition (e.g. a tablet)
35 comprising buprenorphine or a pharmaceutically acceptable salt thereof,

in combination with naloxone or a pharmaceutically acceptable salt thereof, in about a 4:1 buprenorphine:naloxone dose ratio (calculated as free bases),

- wherein said unit dose composition comprises a dose of buprenorphine, which is about 75% of that of a random mixture compressed (RMC) tablet comprising buprenorphine, and
- which method achieves, after an initial dose in any given treatment program, a plasma-concentration time profile for buprenorphine (and/or naloxone) that is essentially equivalent to that/those exhibited by such RMC tablets.

"RMC tablets" include, but are not limited to, the commercially-available tablet product Suboxone® (NDA No. 20-733, approval date October 8th, 2002; buprenorphine strength 2 mg (Product No. 001; actual weight about 100 mg) and 8 mg (Product No. 002; actual weight about 400 mg)). The 8 mg tablets (at least) have a mean crushing strength (US Pharmacopeia method <1217>) of about 127 N. RMC tablet strengths are thus in the range of about 80 to about 180 N. RMC tablets are formed by compression of a random mixture, prepared by wet granulation of a standard mixture comprising buprenorphine hydrochloride, naloxone hydrochloride dihydrate, lactose monohydrate, mannitol, maize starch, povidone K30, citric acid (anhydrous granular), sodium citrate, natural lemon and lime flavour, acesulfame potassium and magnesium stearate.

By "a plasma-concentration time profile for buprenorphine and/or naloxone that is essentially equivalent to that/those exhibited by such RMC tablets", we include that, after an initial dose in any given treatment program, one or more of:

- (i) the maximum plasma concentration (C_{max}); and/or
- (ii) the time to maximum plasma concentration (t_{max}); and/or
- (iii) the total area under the plasma concentration-time curve from time zero to the time of the last measured plasma concentration (AUC_t); and/or
- (iv) the area under the plasma concentration-time curve from time zero to the last concentration extrapolated to infinity based on the elimination rate constant (AUC_{inf}),

as measured by standard pharmacokinetic monitoring means, e.g. as described in Example 2 hereinafter, for naloxone and/or, more preferably, for

buprenorphine, is between about 80% and about 125% of the corresponding values obtained for the aforementioned RMC tablets.

Thus, after an initial dose in any given treatment program, for tablets comprising a dose of buprenorphine that is about 75% of a RMC tablet comprising 8 mg of buprenorphine may present:

(i) a C_{max} of between about 3.0 ng/mL and about 5.6 (such as about 4.5) ng/mL; and/or

(ii) a t_{max} that is less than about 3 hours, preferably less than about 2 hours; and/or

(iii) an AUC_{inf} that is about 25 ng.h/mL to about 40 ng.h/mL, such as about 28 ng.h/mL to about 36 ng.h/mL, for buprenorphine; and/or

(a) a C_{max} of between about 150 pg/mL and about 300 (such as about 250) pg/mL; and/or

(b) a t_{max} that is less than about 1 hour, for naloxone.

According to a further aspect of the invention, there is provided a method of treating opioid dependency and/or addiction in a human,

- which method comprises sublingual administration to a human patient suffering from opioid dependency and/or addiction of
- at least one unit dose of a pharmaceutical composition (e.g. a tablet) comprising buprenorphine or a pharmaceutically acceptable salt thereof, in combination with naloxone or a pharmaceutically acceptable salt thereof, in about a 4:1 buprenorphine:naloxone dose ratio (calculated as free bases),
- wherein said unit dose composition comprises a dose of buprenorphine, which is about 75% of that of a RMC tablet as hereinbefore defined, and
- which method achieves after an initial dose in any given treatment program a mean relative bioavailability compared to such RMC tablets that is:

(A) about 1.2 to about 1.6 for buprenorphine; and/or

(B) about 1.2 to about 2.0 for naloxone.

According to a further aspect of the invention, there is provided a method of treating opioid dependency and/or addiction in a human, which method comprises sublingual administration to a human patient suffering from opioid dependency and/or addiction of at least one unit dose of a pharmaceutical composition (e.g. a tablet) comprising buprenorphine or a pharmaceutically acceptable salt thereof, in combination with naloxone or a pharmaceutically acceptable salt thereof, wherein said tablet comprises a dose of buprenorphine or salt thereof, which is about 6 mg or about 1.5 mg, and the buprenorphine:naloxone dose ratio is about 4:1 (calculated as the free base).

Compositions of the invention may also give rise to a lower norbuprenorphine:buprenorphine ratio in plasma when compared to prior art, commercially-available formulations. A lower norbuprenorphine to buprenorphine ratio is also seen after sublingual administration of an ethanol solution compared to a tablet formulation (see Harris *et al*, *Clin. Pharmacokinet.*, **43**, 329 (2004)) as dose is increased, suggesting that less buprenorphine is being swallowed. In addition, less norbuprenorphine is found in the plasma after parenteral administration compared to sublingual administration (Sigmon *et al*, *Addiction*, **101**, 420 (2005)), further supporting the notion that norbuprenorphine is formed from swallowed buprenorphine by first pass metabolism through the liver. Thus, the lower norbuprenorphine:buprenorphine ratio reported herein may be reflective of the fact that more buprenorphine is absorbed over the sublingual mucosa (and so less is swallowed) than with prior art, commercially available (e.g. RMC tablet) formulations. There may also be benefits from the reduction of the norbuprenorphine:buprenorphine ratio *per se*, such as reduced respiratory depression (see Megarbane *et al*, *Toxicology and Applied Pharmacology*, **212**, 256 (2006)).

According to a further aspect of the invention, there is further provided a method of treating opioid dependency and/or addiction in a human, which method comprises sublingual administration of a pharmaceutical composition comprising buprenorphine or a pharmaceutically acceptable salt thereof, in combination with naloxone or a pharmaceutically acceptable salt thereof, in about a 4:1 buprenorphine:naloxone dose ratio (calculated as the free base), wherein said composition comprises a dose of buprenorphine which is about 75% of that of a

88

RMC tablet as hereinbefore defined, to a human patient suffering from opioid dependency and/or addiction, wherein said formulation achieves after an initial dose in any given treatment program a ratio of norbuprenorphine/buprenorphine concentrations in plasma of less than about 0.8 based upon AUC₂₄.

5

Such methods may comprise administration of a composition of the invention as defined herein.

By "any given treatment program", we mean any course of treatment of a patient with a composition of the invention.

10

Without being limited by theory, it is understood that the compositions of the invention give rise to such surprisingly increased bioavailability when compared to prior art, commercially-available formulations, e.g. RMC tablets, such as Suboxone, because of a pH-timing effect, in which pH is lowered as hereinbefore described for a short period of time (e.g. between about 1 and about 3 minutes) after sublingual administration, resulting in improved and/or more rapid dissolution of microparticles of buprenorphine. Although such dissolution might be expected to be improved by decreasing pH, what is completely unexpected is that the degree of absorption across the sublingual mucosa does not appear to decrease. One would expect that lowering local pH would give rise to the presence of more buprenorphine in the ionized state at the site of absorption, which would in turn be expected to decrease the degree of absorption across the sublingual mucosa. The fact that the bioavailability is better per unit dose of buprenorphine for compositions of the invention than it is for prior art compositions is indeed remarkable.

15
20
25

According to a further aspect of the invention, there is provided a pharmaceutical composition comprising microparticles of buprenorphine or a pharmaceutically acceptable salt thereof, and particles of a weak acid or particles of weakly acidic buffer forming materials, characterized in that the composition exhibits, in an *in vitro* small-volume funnel dissolution method, for example as described in Example 5 hereinafter:

- a) a pH drop of about 0.5 to about 5 pH units;
- b) a maximum pH drop within about 1 minute of the start of the method; and

30
35

89

c) a return to the initial pH (± 0.5) within about 3 minutes.

According to a still further aspect of the invention, there is provided a pharmaceutical composition comprising microparticles of buprenorphine or a pharmaceutically acceptable salt thereof, and particles of a weak acid or particles of weakly acidic buffer forming materials, characterized in that the composition enables the provision (at the site of administration) of a pH of between about 4.0 and about 6.5 (e.g. less than about 6.25), and the maintenance of pH within this range for an appropriate length of time (e.g. about 30 seconds, such as about 1 minute) to about 3 minutes (e.g. about 2 minutes, such as about 1.5 minutes) to facilitate dissolution of, particularly, the buprenorphine microparticles, and/or absorption of buprenorphine across the sublingual mucosa thereafter.

Compositions of the invention comprising naloxone surprisingly give rise to similar, almost parallel, degrees of improved bioavailability for both buprenorphine and naloxone, which means that the "optimal" ratio of buprenorphine to naloxone, which has been arrived at to reduce abuse potential (see, for example, Mendelson and Jones, *Drug and Alcohol Dependence*, **70**, 829 (2003)), may be maintained, and doses of both active ingredients therefore lowered by an equivalent degree to preserve the same ratio.

The compositions of the invention are useful in the treatment of opioid dependency and/or addiction. Compositions of the invention may also be useful in the treatment of pain (including mild, moderate and severe pain).

25

According to three further aspects of the invention there are provided:

- (i) a method of treatment of opioid dependency and/or addiction;
- (ii) a method of treatment of pain; and
- (iii) a method of treatment of both pain and opioid dependency and/or addiction,

30

which methods comprise administration of a composition of the invention to a person suffering from, or susceptible to, the relevant conditions.

Compositions of the invention may also be administered in the induction phase (i.e. the start-up) of buprenorphine therapy, wherein buprenorphine is

35

administered once an opioid-addicted individual has abstained from using opioids for about 12–24 hours and is in the early stages of opioid withdrawal.

According to a further aspect of the invention there is provided a method of
5 treatment of opioid dependency and/or addiction, which method comprises administration of a composition of the invention to an individual that has abstained from using opioids for at least about 12 hours and/or is in the early stages of opioid withdrawal.

10 By "treatment" of pain we include the therapeutic treatment, as well as the symptomatic and palliative treatment of the condition. However, by "treatment" of opioid dependency and/or addiction, we further include the prophylaxis, or the diagnosis of the relevant condition in addition to therapeutic, symptomatic and palliative treatment. This is because, by employing buprenorphine in the
15 treatment of pain, compositions of the invention may prevent the development of opioid dependency and/or addiction.

The compositions of the invention enable the production of unit dosage forms that are easy and inexpensive to manufacture, and which enable the rapid release
20 and/or a rapid uptake of the active ingredients employed through the mucosa, such as the oral mucosa, thus enabling rapid relief of symptoms, such as those described hereinbefore.

The compositions of the invention also have the advantage that, if injected by an
25 opioid addict, they do not produce the euphoric effects that such an addict seeks and indeed induce opioid withdrawal symptoms.

Compositions of the invention may also have the advantage that they may be prepared using established pharmaceutical processing methods and employ
30 materials that are approved for use in foods or pharmaceuticals or of like regulatory status.

Compositions of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent
35 than, produce fewer side effects than, be more easily absorbed than, possess a

91
better patient acceptability than, have a better pharmacokinetic profile than, and/or have other useful pharmacological, physical, or chemical properties over, pharmaceutical compositions known in the prior art, whether for use in the treatment of opioid addiction or pain or otherwise.

5

The invention is illustrated by way of the following examples, with reference to the attached figures in which analyte concentration-time plasma profiles are presented in linear scale plots for buprenorphine (Figure 1), norbuprenorphine (Figure 2) and naloxone (Figure 3) following sublingual administration of tablets comprising a composition of the invention (diamonds) and the commercially-available comparator, Suboxone® (squares); Figure 4 shows an *in vivo* sublingual pH profile obtained for a placebo composition (analogous to one prepared in accordance with the invention); Figure 5 shows comparative *in vitro* pH profiles for composition of the invention *versus* Suboxone and other comparators in a small-volume funnel dissolution test; Figures 6 and 7 show release of buprenorphine and naloxone, respectively, from the compositions referred to in Figure 5; Figure 8 shows comparative *in vitro* pH profiles for compositions of the invention *versus* Suboxone and other comparators in a small-volume funnel dissolution test; and Figure 9 show release of buprenorphine from compositions referred to in Figure 8.

20

Example 1

Buprenorphine/Naloxone Sublingual Tablets I

25 Naloxone hydrochloride dihydrate (Macfarlan Smith, Edinburgh, UK) and buprenorphine hydrochloride (Macfarlan Smith, Edinburgh, UK) were micronised using an air jet mill (Pilotmill-1/Food and Pharma Systems, Italy). The volume based mean particle size (diameter) of the buprenorphine was 3.4 µm and of the naloxone was 4.6 µm.

30

9.15 g of the micronised naloxone hydrochloride dihydrate was mixed together with microcrystalline cellulose (47.50 g; Avicel™ PH102 (mean particle size 100 µm), FMC Biopolymer, Cork, Ireland) and croscarmellose sodium (18.00 g; AcDiSol™, FMC Biopolymer) in a tumble blender (Turbula, WAG, Switzerland) for 35 40 hours.

32.40 g of the micronised buprenorphine hydrochloride was mixed together with mannitol (314.20 g; Pearlitol™ 200SD, Roquette, Lestrem, France), sieved citric acid (15.00 g; fine granular 16/40 grade, DSM, Switzerland, Basel) and sieved (to
5 avoid agglomeration) sodium citrate (48.75 g) Emprove™ cryst., Merck, Darmstadt, Germany) in a tumble blender for 40 hours.

Menthol (5.00 g; Emprove™ cryst., Merck) was mortared until a fine powder was formed. This and also acesulfame potassium (5.00 g; Sunett Pharma D,
10 Nutrinova, Kelsterbach, Germany) and anhydrous colloidal silica (5.00 g; Aerosil™ 200 Pharma, Evonik Degussa, Hanau-Wolfgang, Germany) were added by sieving into the buprenorphine premix, together with the naloxone premix, and the whole mixed together in a tumble blender for 1 hour.

15 Sodium stearyl fumarate (10.00 g; Pruv™, JRS Pharma, Polanco, Spain) was then added by sieving into this mixture and mixing continued in the tumble blender for 5 minutes.

The final powder mixture was then compressed into tablets in a tablet machine
20 (Korsch XP1) equipped with 7 mm round, flat faced, radius-edged punches, to a tablet weight of 102 mg and a tablet crushing strength of 35 N.

Example 2

Clinical Trial

25

The tablets of Example 1 were sublingually administered in an open-label, 2-period crossover study with randomised treatment sequence.

The study comprised a screening visit conducted within 28 days prior to first
30 treatment, two treatment periods each of 4 days length (Day -1 to Day 3) and a washout period of at least 10 days between treatment periods. During the treatment periods, subjects were admitted to the clinical unit on the morning prior to first dosing (Day -1) and remained in the unit until the completion of Day 3 procedures. A follow-up visit was carried out 5 to 10 days after completion of the
35 second Investigational Medicinal Product (IMP) administration.

The IMPs were sublingual tablet prepared in accordance with Example 1 (6 mg buprenorphine/1.5 mg naloxone; hereafter "formulation of the invention") and, as the reference product, Suboxone sublingual tablet (8 mg buprenorphine/2 mg naloxone; Reckitt Benckiser Healthcare Ltd, Hull, UK). Treatment with formulation of the invention, or Suboxone (1 tablet) in alternate periods was open-label and was administered on Day 1 in each treatment period.

Naltrexone tablets (Nalorex[®], 50 mg, Bristol-Myers Squibb Pharmaceuticals Ltd; Uxbridge, UK) were administered orally (one 50 mg tablet), at -24 to -16 hours, -1 hour (± 5 minutes) and +24 hours (± 1 hour) in relation to administration of IMP, as a naltrexone block in the study (in order to alleviate opioid side effects during the study).

Eighteen healthy male volunteers aged between 18 and 50 years were enrolled. These received both treatments and were evaluated. The mean age was 29.8 years and ages ranged from 19 to 49 years. All subjects were male Caucasians. The mean weight was 78.16 kg and ranged from 63.0 to 93.5 kg. The mean body mass index of the subjects was 25.05 kg/m² and ranged from 20.7 to 28.9 kg/m².

All subjects (except one) reported current alcohol use ranging from 1 to 20 units per week. No subject was a current smoker. All subjects reported current caffeine use of 1 to 5 cups or cans per day. No subject had been treated with opioids within 1 year prior to screening.

No subject reported any pre-study medication (taken within 2 weeks prior to screening). One subject reported ongoing use of antihistamines for systemic use by oral tablet or capsule to treat seasonal allergic rhinitis.

Trial medication was administered in the clinic under the supervision of clinic personnel.

All subjects who were enrolled in the study and who received at least one dose of trial medication. All randomised subjects who received at least one treatment, had at least one evaluable plasma profile and had no major protocol deviations

that could have a substantial effect on the buprenorphine, norbuprenorphine or naloxone plasma concentration profile, such as:

- swallowing of study medication (applies to both formulation of the invention and Suboxone)
- 5 • vomiting within 4 hours after administration of either type of tablet
- having a pre-dose quantifiable concentration that is $> 5\%$ of a subject's $C_{\max}$

10 All randomised subjects who received at least one treatment and had disintegration or acceptability data present for at least one treatment.

Pharmacokinetic (PK) variables were based on plasma concentrations of buprenorphine, norbuprenorphine (a metabolite of buprenorphine) and naloxone and were calculated using standard, non-compartmental methods. The PK non-compartmental analysis was performed using WinNonlin™ Professional version 5.2. Data permitting, the following parameters were determined:

- t_{lag} lag time before the start of absorption
- $C_{\max}$ maximum plasma concentration
- $t_{\max}$ time to reach maximum plasma concentration
- 20 • AUC_{0-t} area under the plasma concentration-time curve from time zero to the time of the last quantifiable plasma concentration
- AUC_{0-48} area under the plasma concentration-time curve from time zero to 48 hours post-dose
- MR metabolic ratio

25

In addition, the relative bioavailability (F_{rel}) of formulation of the invention to Suboxone was derived based on dose-adjusted PK data.

30 Subjects were classified as evaluable or non-evaluable with respect to the PK evaluation by the pharmacokineticist after examining the subjects PK profiles and taking into account any deviations with respect to those listed above. The PK analyses based on the PK population included only those subjects with evaluable PK data.

Actual blood sampling times for buprenorphine, norbuprenorphine and naloxone were converted to a time from dosing (elapsed time). Elapsed times were listed by subject for each treatment, together with the individual buprenorphine, norbuprenorphine and naloxone concentrations. Elapsed times were used in the
5 PK analysis.

The buprenorphine, norbuprenorphine and naloxone concentrations were summarised by descriptive statistics of number of missing samples, number of samples less than the lower limit of quantification (<LOQ), n, arithmetic mean,
10 SD, CV(%), geometric mean, 95% confidence intervals (CI) for the arithmetic mean, median, minimum and maximum. All buprenorphine, norbuprenorphine and naloxone concentrations <LOQ were set to zero for the purpose of calculating descriptive statistics. If at any time-point 1/3 or more of subjects had values <LOQ, descriptive statistics were not calculated.

15

The PK parameters C_{max} , AUC_{0-t} and AUC_{0-48} of buprenorphine, norbuprenorphine and naloxone were compared between treatments using a mixed effects Analysis of Variance (ANOVA) procedure.

20 Arithmetic mean (+SEM) analyte concentration-time plasma profiles are presented in linear scale plots for each analyte in Figures 1 (buprenorphine), 2 (norbuprenorphine) and 3 (naloxone) with both treatments included on each plot. It can be seen from these figures that, for both buprenorphine and norbuprenorphine after administration of formulation of the invention (diamonds),
25 and Suboxone (squares), plasma concentrations of all three analytes increased to a maximum then declined in a biphasic manner.

In relation to other PK parameters:

- (i) on average, the lag time was slightly shorter after treatment with
30 formulation of the invention compared to Suboxone by 15% for buprenorphine, 29% for norbuprenorphine and 34% for naloxone;
- (ii) the range of times at which maximal concentrations were attained (t_{max}) was similar between treatments for all analytes. Median t_{max} values were less than or equal to 1 h for buprenorphine and naloxone
35 indicating rapid sublingual absorption following administration of both

formulation of the invention and Suboxone. For norbuprenorphine, $t_{\max}$ was generally similar to buprenorphine after both treatments indicating metabolism of buprenorphine to norbuprenorphine was rapid;

- 5 (iii) the mean metabolite ratios exceeded 0.5 indicating extensive metabolic conversion of buprenorphine to norbuprenorphine, with conversion being 31% lower following administration of formulation of the invention compared to Suboxone. This result is significant as it means that more buprenorphine is absorbed sublingually in the case
- 10 of formulation of the invention;
- (iv) the doses of both buprenorphine and naloxone were lower in the formulation of the invention, but mean systemic exposure, in terms of $C_{\max}$ and AUC, of buprenorphine and naloxone were higher when compared to Suboxone, and, as stated above, the values were lower
- 15 for norbuprenorphine; and
- (v) the mean relative bioavailabilities of formulation of the invention to Suboxone were 1.659 and 2.056 for buprenorphine and naloxone respectively, indicating higher dose-normalised systemic exposure following administration of formulation of the invention. For
- 20 norbuprenorphine the dose-normalised systemic exposure appeared to be similar between treatments with a mean relative bioavailability of 1.084. The buprenorphine result is surprising. The reported relative bioavailability of a sublingually-administered ethanol solution comprising buprenorphine (where conditions are theoretically optimised for rapid absorption over the sublingual mucosa) compared
- 25 to Suboxone was reported to be 1.5 (see Compton *et al*, *Drug and Alcohol Dependence*, **82**, 25 (2006)). The fact that the relative number reported in this study for a solid sublingual tablet was even higher than that reported for a solution is remarkable.

30

Disintegration time of the tablets was assessed by either a nurse or a physician by mouth inspections, and was also reported by the subjects, who were given thorough instructions of the dosing procedures prior to dosing on Day 1 in both treatment periods, including the procedures for observer and subject

assessments of disintegration. Subjects were to report any premature swallowing.

5 The sublingual space and the tablet were examined to determine the time to disintegration. The tablet residues were characterised as 'intact', 'fragments', 'paste like residue' or 'dissolved'. Inspections were carried out every 2 minutes and the findings recorded until the tablet was completely disintegrated. In addition, the subject was instructed to indicate when they thought the IMP was dissolved by raising their hand or to indicate whether they had swallowed the
10 tablet before it was dissolved. The time of dissolution or swallowing was recorded.

Median time to non-intact tablets was 2 minutes for the formulation of the invention and was 8 minutes for Suboxone.

15

Summary and Conclusions

The above-reported parameter ratios suggest that the formulation of the invention resulted in slightly higher plasma buprenorphine and naloxone concentrations
20 and slightly lower plasma norbuprenorphine concentrations than the comparator. The former result is despite the initial dose being lower which indicates that it may be possible to reduce dose still further. Tablets comprising formulations of the invention also disintegrated faster than the comparator.

Example 3

Buprenorphine/Naloxone Sublingual Tablets II

3.97 g of micronized naloxone hydrochloride dihydrate was mixed together with microcrystalline cellulose (20.00 g; Avicel™ PH102 (mean particle size 100 µm),
30 FMC Biopolymer) and croscarmellose sodium (7.20 g; AcDiSol™, FMC Biopolymer) in a tumble blender (Turbula, WAG, Switzerland) for 40 hours.

14.04 g of micronised buprenorphine hydrochloride was mixed together with mannitol (130.30 g; Pearlitol™ 200SD, Roquette, Lestrem, France), sieved citric
35 acid (6.00 g; fine granular 16/40 grade, DSM, Switzerland, Basel) and sieved (to

avoid agglomeration), sodium citrate (19.50 g) Emprove™ cryst., Merck, Darmstadt, Germany) and blended in a tumble blender for 42 hours.

5 Menthol (2.00 g; Emprove™ cryst., Merck KGaA, Darmstadt, Germany) was mortared until a fine powder was formed and was blended with silicon dioxide, colloidal (0.20 g; Aerosil™ 200 Pharma), (1:1 volume ratio).

10 Sucralose (6.00 g, Merck KGaA, Darmstadt, Germany) was added to the buprenorphine premix. The naloxone premix and the rest of the silicon dioxide colloidal (2.80 g) were added by co-sieving into the buprenorphine premix. The menthol-silicon dioxide blend was added by sieving to the buprenorphine premix and all ingredients were mixed for 1 hour.

15 Sodium stearyl fumarate (8.00 g; Pruv™, JRS Pharma, Polanco, Spain) was then added by sieving into this mixture and mixing continued in the tumble blender for 10 minutes.

20 The final powder mixture was then compressed into tablets in a tablet machine (Korsch EK0) equipped with 7 mm round, flat faced, radius-edged punches, to a tablet weight of 110 mg and a tablet crushing strength of 30-35 N.

Example 4

In Vivo Experiment

25 Placebo tablets prepared according to the procedure described in Example 1 above (excluding buprenorphine, but including naloxone) were first administered sublingually.

30 Sublingual saliva pH was measured *in vivo* using a Schott CG 842P pH Meter attached to a Schott Flatrode™-electrode (pH 0-14, 0-60°C). The Flatrode™ has a super-flat membrane for surface measurements and a robust plastic shaft with a ring diaphragm, which guarantees a quick response *via* enhanced contact between the sample and reference. The diameter of the flat surface of the electrode is 6.0 mm giving a measuring surface of 0.28 cm².

35

The Flatrode was positioned (at an open mouth angle of 45°) gently behind the lower teeth, just beside the tablet in the mouth. A very gentle pressure was applied in order to measure pH in saliva rather than venous blood pH (typically pH 7.4).

5

pH was measured at time intervals of 0, 30, 60 and 90 seconds (over 5 seconds until a stable value was observed). Care was taken to avoid accidental withdrawal of dissolved powder by the electrode. The mouth was shut between measurements with no active swallowing.

10

Triplicate runs were carried out to ensure a reliable pH-profile. Between runs, the mouth was washed thoroughly with water and pH measured prior to administration to obtain a new zero-value.

15

The results indicated that the pH decrease peaked at around 35-40 seconds. It can be seen from Figure 4 that the body rapidly compensates for the modified pH and also slightly overcompensates, and that the window of opportunity (i.e. the time range with a 0.5 pH unit decrease (at least) compared to resting pH) for increased solubility of buprenorphine is only about 80 seconds, starting after 10 seconds (n=4).

20

Example 5

Comparative *In Vitro* Small-Volume Funnel Dissolution Experiment I

25

In addition to the sublingual tablets described in Example 3 above, two other otherwise identical batches of sublingual tablets were prepared using the same methodology, except that, in one case, the buprenorphine hydrochloride was not micronized, and in the other, no citric acid and sodium citrate were included (instead a further 12.75 mg per tablet of mannitol was included).

30

Tablets from the three above-mentioned tablet batches, as well as Suboxone tablets (buprenorphine 8 mg/naloxone 2 mg; Reckitt Benckiser Healthcare Ltd, Hull, UK) were placed on top of a Porosity 1 20 mm diameter silica filter in a 55 mm (upper inner diameter) glass funnel.

35

100
Potassium phosphate buffer with a pH of 6.8 (USP/NF), which mimics saliva, was allowed to drip through a soft PVC plastic tube with an inner diameter of 3 mm onto the tablets at a rate, set by a peristaltic pump (Flocon 1003), of 2 mL per minute. The distance between the end of the plastic tube and the silica filter in the funnel was set at approximately 7.5 cm, in order, along with the dripping rate, to correspond to a force similar to the pressure of the underside of the tongue. The small amounts of water involved endeavour to mimic the low amounts of water available *in vivo* under the human tongue.

10 pH was measured over time using a Mettler Toledo InLab Expert Pro electrode (pH 0-14; 0-100°C) attached to standard Mettler Toledo 340 pH meter positioned at the outlet of the glass funnel.

To measure the release of active pharmaceutical ingredients over time from the tablets, a glass beaker equipped with a magnetic stirrer containing 490 mL of potassium phosphate buffer pH 6.8 (USP/NF) collected the drops from the funnel.

800 µL samples were withdrawn from the beaker using a calibrated micropipette at intervals of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 10.0, 15.0 and 20.0 minutes. These samples were emptied into 1 mL vials already containing 200 µL of diluted phosphoric acid. No additional buffer was added to the collection beaker to compensate. It started with a volume of 490 mL and ended with a volume of 520 mL (the difference between 40 mL added to the beaker over 20 minutes, and 10.4 mL removed in total (13 x 0.8 mL) is 29.6 mL (i.e. about 30 mL)). It was decided to start at 490 mL instead of 485 mL to be as close to 500 mL for as long a period as possible. The exact individual volumes were of course calculated for each sample.

Three tablets from each of the four tablet table batches in the trial were analysed as release test samples. Amounts of buprenorphine and naloxone were measured using HPLC (Agilent 1000; Diode array-detector, gradient pump, autosampler, column oven), with a gradient method with UV detection at 210 nm.

pH was plotted over time for the following four tablet batches and the results are shown in Figure 5 (tablets prepared according to Example 3 (squares); non-

micronised buprenorphine equivalents (crosses); equivalents without citric acid/sodium citrate (diamonds); and Suboxone (triangles)). The dashed line in Figure 5 is the superimposed *in vivo* profile from Figure 4.

- 5 The drug release profiles over the first 5 minutes for buprenorphine and naloxone are presented in Figures 6, and 7, respectively. Although Suboxone has a 23% higher drug loading than all of the other tablets, it produces a buprenorphine release after 20 minutes through the funnel of only 75% of that of the tablets according to the invention. The difference is most noticeable over the first 5 minutes.

Example 6

Buprenorphine/Naloxone Sublingual Tablets III

- 15 336.0 g of micronized naloxone hydrochloride dihydrate was mixed together with microcrystalline cellulose (2000.0 g; Avicel™ PH102 (mean particle size 100 µm), FMC Biopolymer, Wallington, Little Island, Co. Cork, Ireland) and croscarmellose sodium (720.0 g; AcDiSol™, FMC Biopolymer, Wallington, Little Island, Co. Cork, Ireland) in a 12 L double cone blender (Sewin, Zickert systems, Kungsbacka, Sweden) for 3 hours.

- Citric acid (600.0 g; fine granular 16/40 grade, DSM, Switzerland, Basel), sodium citrate (1950.0 g Emprove™ cryst., Merck, Darmstadt, Germany) and silicon dioxide, colloidal (480.0 g Aerosil™ 200 Pharma, Evonik Degussa GmbH, Rheinfelden, Germany) were deagglomerated together with Quadro comil apparatus (Quadro Engineering, Ontario, Canada) and premixed with two thirds of a pre-measured amount of mannitol (8737.3 g; Pearlitol™ 200SD, Roquette, Lestrem, France) in a 60 L double cone blender (Sewin, Zickert systems, Kungsbacka, Sweden) for 5 minutes.

- 30 1188.0 g of the micronised buprenorphine hydrochloride was added to the premix and the other third of the mannitol (4368.7 g) was added on top of the buprenorphine hydrochloride and all ingredients were mixed for 3 hours.

Menthol (200.0 g; Emprove™ cryst., Merck KGaA, Darmstadt, Germany) was milled with Quadro comill. Silicon dioxide, colloidal (20.0 g) and milled menthol (1:1 volume ratio) was processed with Quadro comill in order to deagglomerate the silicon dioxide (colloidal).

5

Sucralose (600.0 g, Merck KGaA, Darmstadt, Germany), the naloxone premix and the menthol-silicon dioxide blend were added to the buprenorphine premix and all ingredients were mixed for 1 hour.

10 Sodium stearyl fumarate (800.0 g; Pruv™, JRS Pharma, Polanco, Spain) was deagglomerated with Quadro comil and added to double cone blender and mixed for 10 minutes.

The final powder mixture was then compressed into tablets in a tablet machine
15 (Korsch XL100, Korsch AG, Berlin, Germany) equipped with 7 mm round, flat faced, radius-edged punches, to a tablet weight of 110 mg and a tablet crushing strength of 30-35 N.

Example 7

20 **Buprenorphine/Naloxone Sublingual Tablets IV**

200,000 100 mg buprenorphine/naloxone (4:1 dose ratio) tablets comprising a 1.4 mg dose of buprenorphine (calculated as the free base) were prepared using essentially the same procedure as described in Example 6.

25

Example 8

Buprenorphine/Naloxone Sublingual Tablets V

200,000 110 mg buprenorphine/naloxone (4:1 dose ratio) tablets comprising a 5.7
30 mg dose of buprenorphine (calculated as the free base) were prepared using essentially the same procedure as described in Example 6.

35

Example 9**Comparative *In Vitro* Small-Volume Funnel Dissolution Experiment II**

Using the *in vitro* small-volume funnel dissolution procedure described in
5 Example 5, pH profiles (measurement of pH over time) were obtained for:

- (a) buprenorphine/naloxone sublingual tablets prepared as described in Example 8;
- (b) buprenorphine/naloxone sublingual tablets prepared essentially as described in Example 8, except that the citric acid and sodium citrate were
10 included during the mixing step in which the two APIs are mixed together;
- (c) buprenorphine/naloxone sublingual tablets prepared essentially as described in Example 8, but without citric acid (i.e. sodium citrate only);
- (d) buprenorphine/naloxone sublingual tablets prepared essentially as described in Example 8, but without sodium citrate (i.e. citric acid only);
- 15 (e) buprenorphine/naloxone sublingual tablets prepared essentially as described in Example 8, except that tartaric acid (Sigma-Aldrich) was used instead of citric acid and sodium citrate; and
- (f) Suboxone® film (8 mg buprenorphine/2 mg naloxone; Reckitt Benckiser Healthcare Ltd, Hull, UK).

20

In the case of tablets (c), and (d), an equivalent amount of mannitol was employed instead of the citric acid, and the sodium citrate, respectively, that was excluded. In the case of tablets (e), 2 mg (per tablet) of tartaric acid and an extra 10.75 mg (per tablet) of mannitol were employed.

25

The results are shown in Figure 8 (tablets (a) - diamonds; tablets (b) - black triangles; tablets (c) - white triangles; tablets (d) - black squares; tablets (e) - white squares; Suboxone films (f) - circles). Also superimposed on Figure 8 are:

- (i) the *in vivo* profile from Figure 4 (dashed line); and
- 30 (ii) the *in vitro* pH profile previously obtained for Suboxone® tablets (solid line; originally presented in Figure 5).

The drug release/dissolution profiles over the first 5 minutes for buprenorphine are presented in Figure 9. It can be clearly seen from Figures 8 and 9 taken
35 together that drug dissolution correlates strongly with how much the pH is

lowered during first 1 minute to 2 minutes after the start of the experiment (corresponding to sublingual administration *in vivo*). It can also be seen that the largest pH drop, and the highest dissolution rate, were obtained when citric acid alone was used.

Claims

1. A pharmaceutical composition comprising microparticles of a pharmacologically-effective amount of buprenorphine, or a pharmaceutically-acceptable salt thereof, in associative admixture with particles comprising a weak acid, or particles comprising weakly-acidic buffer forming materials.
2. A composition as claimed in Claim 1, wherein the microparticles of buprenorphine have a weight based mean diameter of less than about 15 μm .
3. A composition as claimed in Claim 1 or Claim 2, wherein the weakly acidic material comprises citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, lactic acid, acetic acid, oxalic acid, maleic acid, ammonium chloride or a combination thereof.
4. A composition as claimed in Claim 1 or Claim 2, wherein the buffer forming materials comprise a combination of a weakly acidic material and a salt of a weakly acidic material.
5. A composition as claimed in Claim 4, wherein the weakly acidic material is as defined in Claim 3.
6. A composition as claimed in Claim 4 or Claim 5, wherein the salt is sodium citrate, potassium citrate, sodium tartrate or potassium tartrate.
7. A composition as claimed in any one of the preceding claims wherein the buffer system is citric acid/sodium citrate.
8. A composition as claimed in any one of the preceding claims which is presented as an interactive mixture comprising microparticles of buprenorphine or a pharmaceutically acceptable salt thereof presented upon the surfaces of carrier particles.
9. A composition as claimed in Claim 8, wherein the carrier particles are of a size that is between about 100 and about 800 μm .

10. A composition as claimed in Claim 8 or Claim 9, wherein the carrier particles are water-soluble.
- 5 11. A composition as claimed in any one of Claims 8 to 10, wherein the carrier particles comprise mannitol.
12. A composition as claimed in any one of Claims 8 to 11, wherein the particles of weak acid, or of weakly-acidic buffer forming materials, are presented and act
- 10 as carrier particles.
13. A pharmaceutical composition as claimed in any one of the preceding claims, which further comprises a disintegrant.
- 15 14. A composition as claimed in Claim 13, wherein the disintegrant is a superdisintegrant selected from croscarmellose sodium, sodium starch glycolate, crosslinked polyvinylpyrrolidone or a mixture thereof.
15. A pharmaceutical composition as claimed in any one of the preceding
- 20 claims, which further comprises a pharmacologically-effective amount of naloxone, or a pharmaceutically-acceptable salt thereof.
16. A pharmaceutical composition as claimed in Claim 15, wherein the composition comprises particles comprising naloxone or salt thereof and
- 25 disintegrant.
17. A composition as claimed in any one of the preceding claims which is in the form of a tablet suitable for sublingual administration.
- 30 18. A process for the preparation of a composition as defined in any one of Claims 8 to 17, which comprises dry mixing carrier particles with buprenorphine or salt thereof.

19. A process for the preparation of a composition as defined in any one of Claims 15 to 17, which comprises a process as claimed in Claim 18, followed by admixing with particles comprising naloxone or salt thereof and disintegrant.
- 5 20. A process for the preparation of a sublingual tablet as defined in Claim 17, which comprises directly compressing or compacting a composition as defined in any one of Claims 1 to 16.
- 10 21. A method of treatment of opioid dependency and/or addiction, and/or pain, which method comprises administration of a composition as defined in any one of Claims 1 to 17 to a person suffering from, or susceptible to, the relevant condition(s).
- 15 22. A composition as defined in any one of Claims 1 to 17 for use in a method of treatment of opioid dependency and/or addiction, and/or pain.
23. The use of a composition as defined in any one of Claims 1 to 17 for the manufacture of a medicament for a method of treatment of opioid dependency and/or addiction, and/or pain.

108

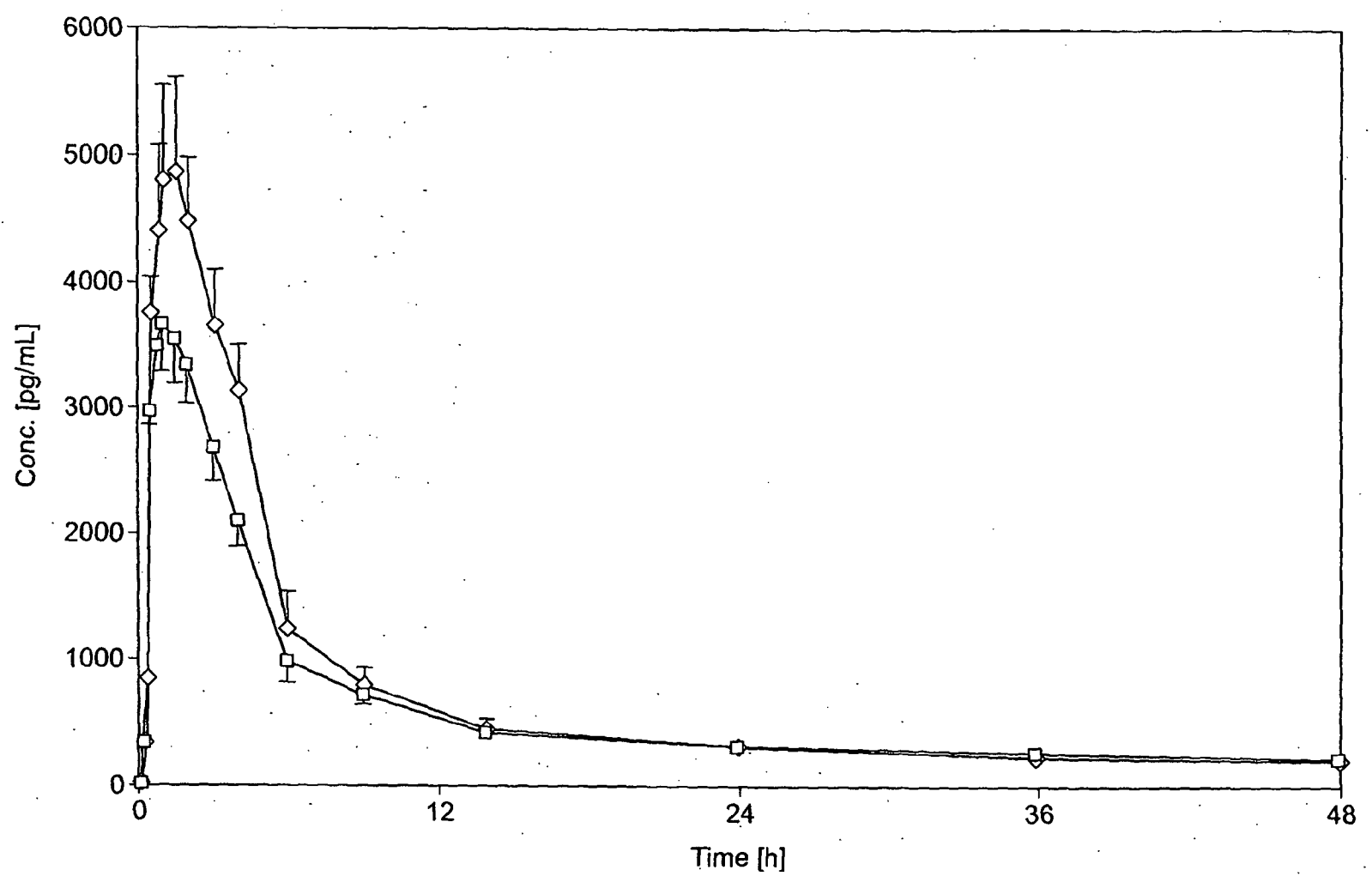


FIG. 1

108

109

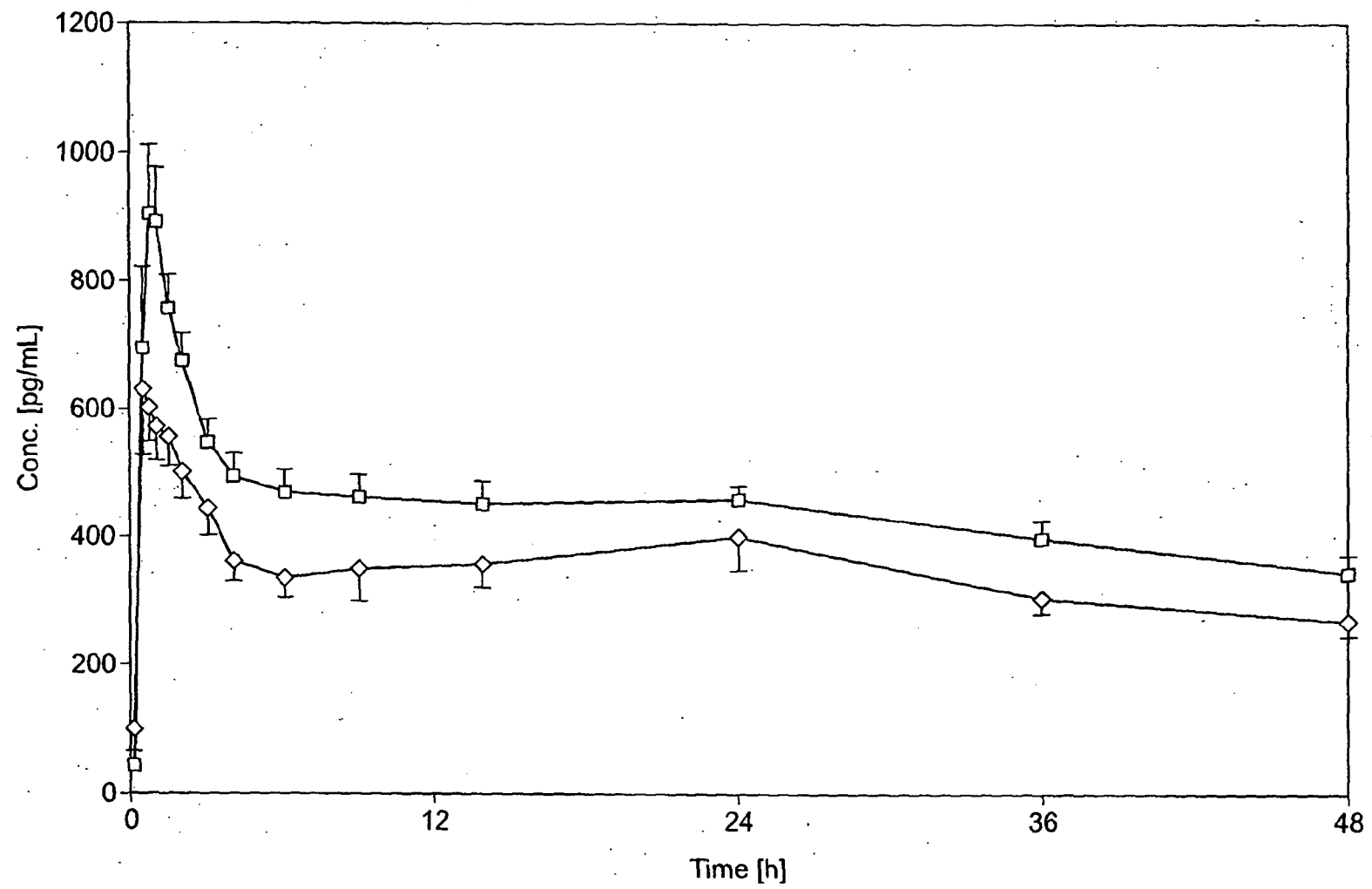


FIG. 2

109

110

WO 2013/041851

PCT/GB2012/052303

3 / 9

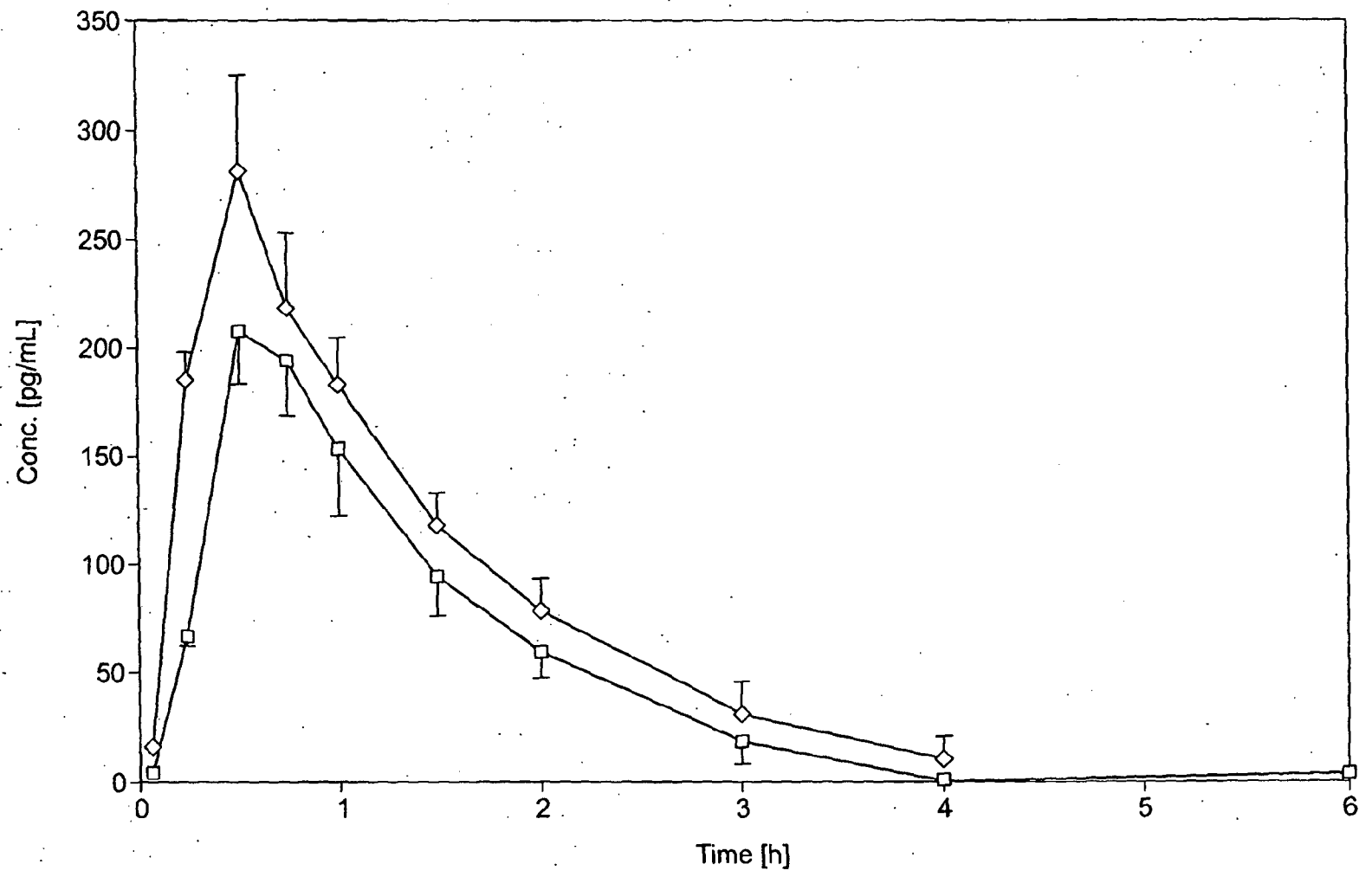


FIG. 3

110

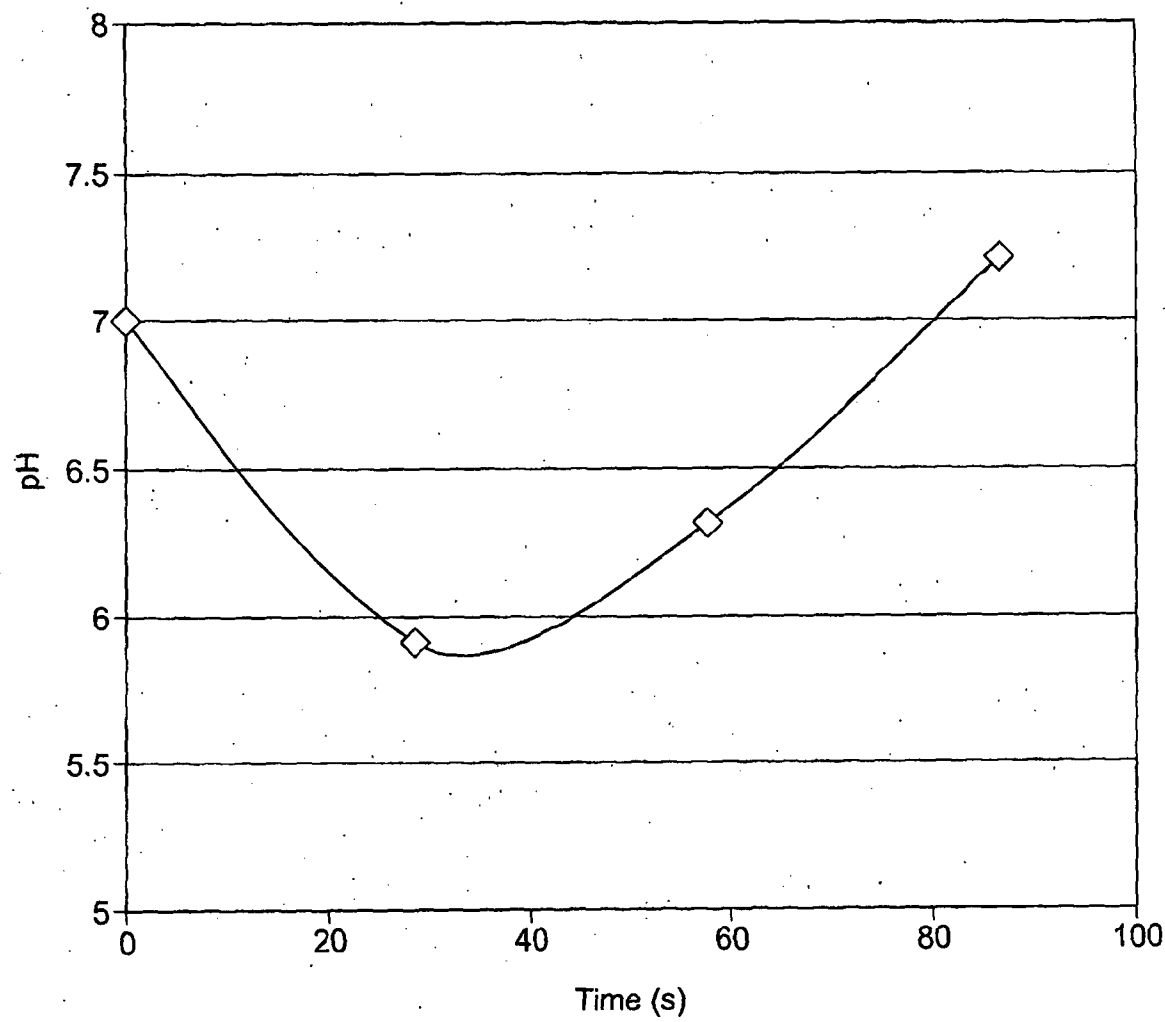


FIG. 4

112

WO 2013/041851

PCT/GB2012/052303

5/9

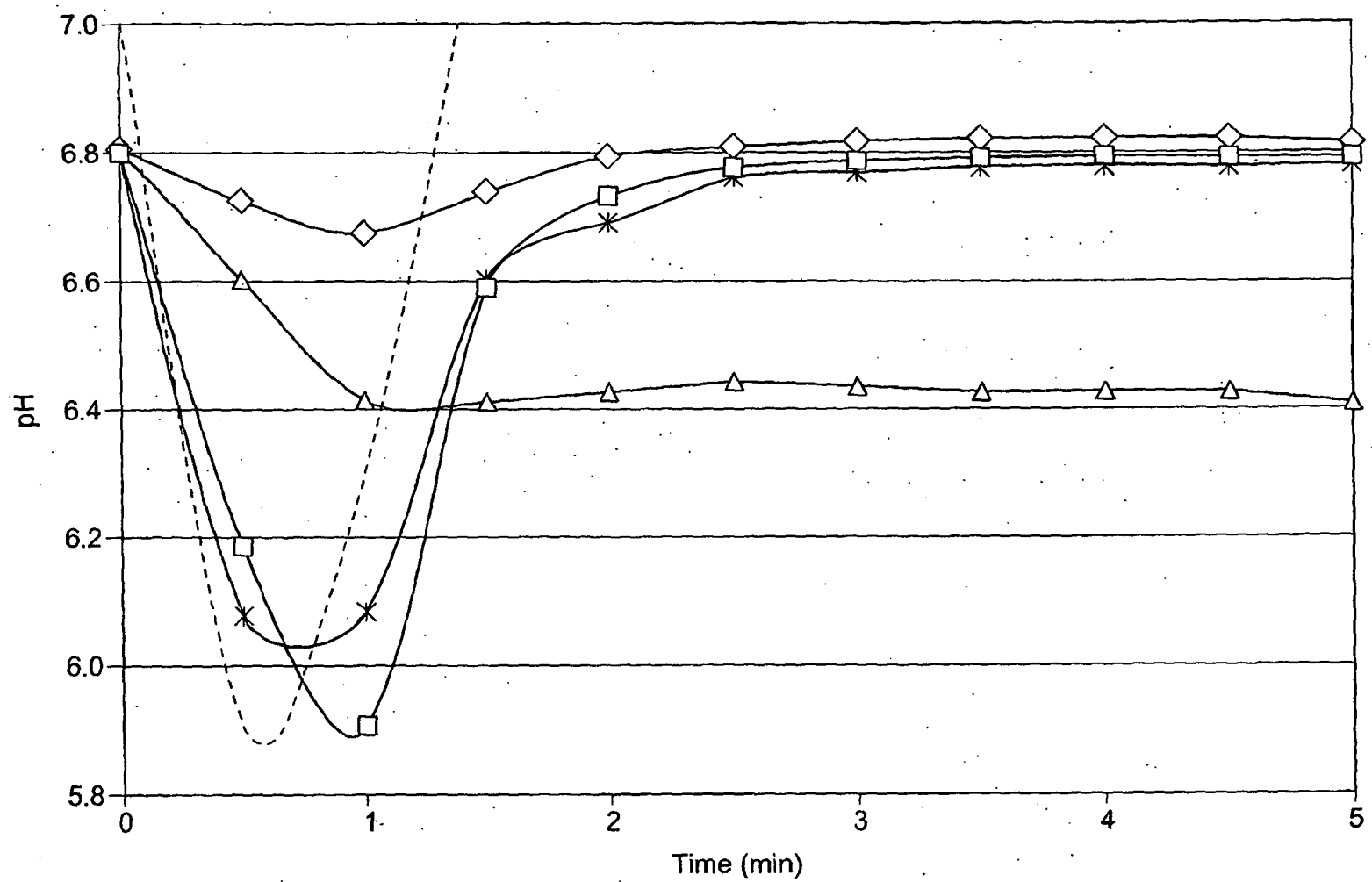


FIG. 5

SUBSTITUTE SHEET (RULE 26)

112

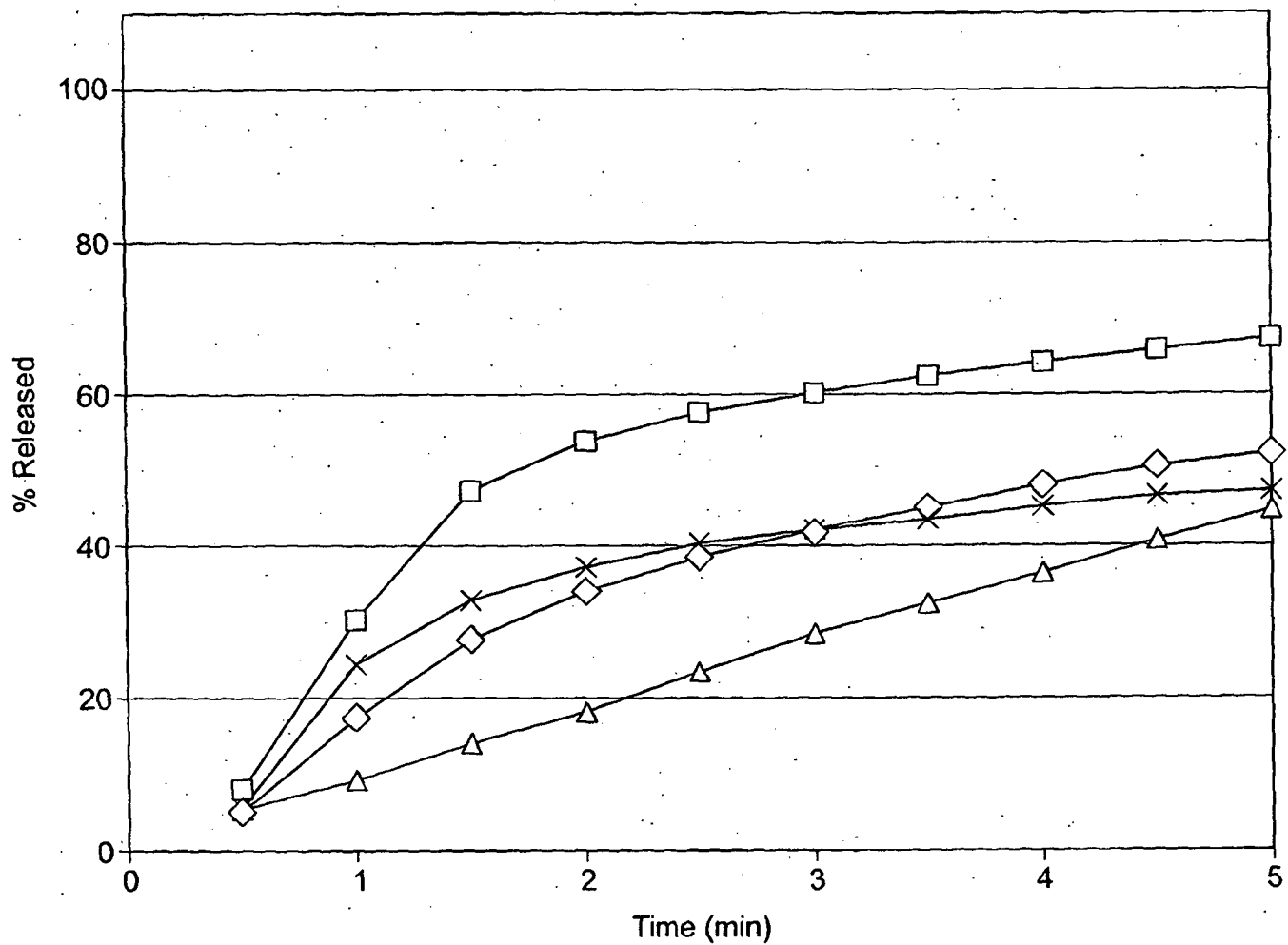


FIG. 6

114

WO 2013/041851

PCT/GB2012/052303

7 / 9

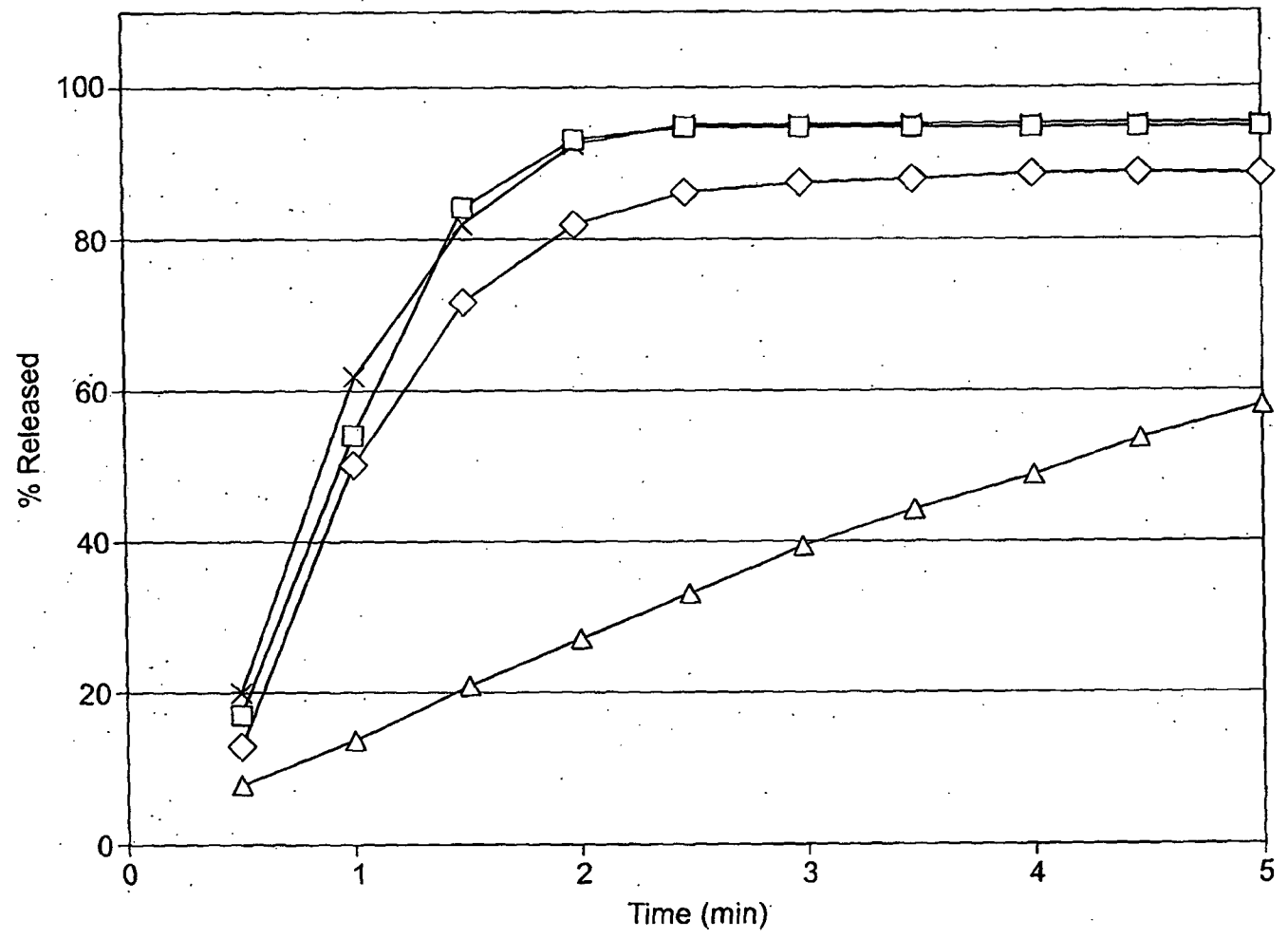


FIG. 7

114

115

WO 2013/041851

PCT/GB2012/052303

8/9

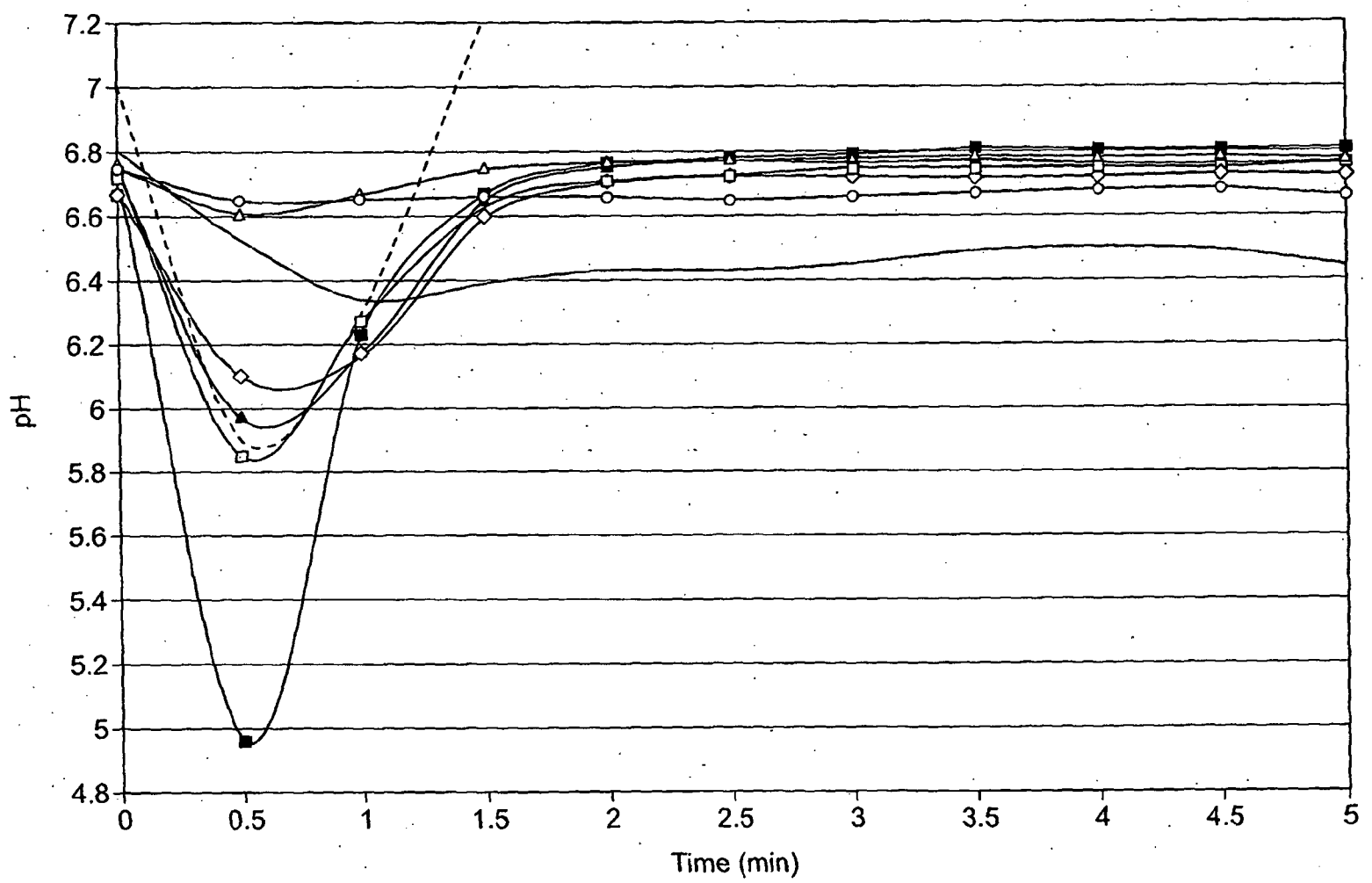


FIG. 8

SUBSTITUTE SHEET (RULE 26)

115

116

WO 2013/041851

PCT/GB2012/052303

9 / 9

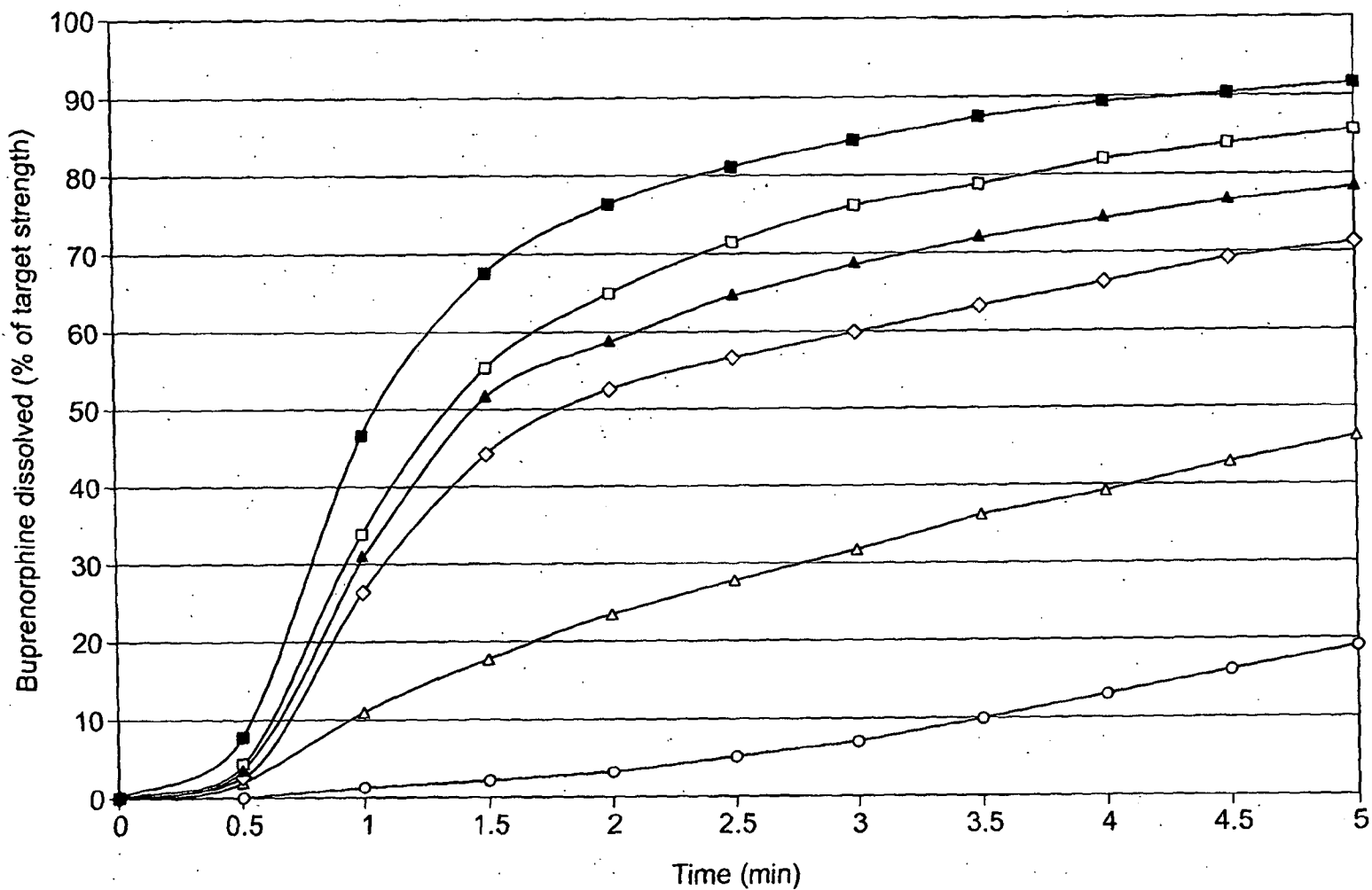


FIG. 9

116

117

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2012/052303

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/00 A61K31/485
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/117838 A1 (GALEPHAR M F [BE]; VANDERBIST FRANCIS [BE]; SERENO ANTONIO [BE]; BAUDI) 15 December 2005 (2005-12-15) example 3 claims 1-15 page 2, line 1 - page 7, line 15 example 1; table 2 -----	1-23
X	US 2010/233257 A1 (HERRY CATHERINE [FR] ET AL) 16 September 2010 (2010-09-16) paragraph [0043] - paragraph [0164] claims 1-41 -----	1-23
X	US 2004/229038 A1 (COOPER EUGENE R [US] ET AL) 18 November 2004 (2004-11-18) claims 1-62 paragraph [0084] - paragraph [0151] -----	1-23

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

28 November 2012

Date of mailing of the international search report

07/12/2012

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Schifferer, Hermann

118

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2012/052303

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005117838 A1	15-12-2005	AT 412404 T	15-11-2008
		EP 1750675 A1	14-02-2007
		WO 2005117838 A1	15-12-2005

US 2010233257 A1	16-09-2010	NONE	

US 2004229038 A1	18-11-2004	AT 431131 T	15-05-2009
		CA 2517679 A1	13-01-2005
		EP 1617816 A2	25-01-2006
		ES 2326085 T3	30-09-2009
		JP 4891774 B2	07-03-2012
		JP 2007505154 A	08-03-2007
		JP 2011042670 A	03-03-2011
		JP 2012012397 A	19-01-2012
		US 2004229038 A1	18-11-2004
		WO 2005002542 A2	13-01-2005

119



**DOCUMENT MADE AVAILABLE UNDER THE
PATENT COOPERATION TREATY (PCT)**

International application number:	PCT/GB2012/052303
International filing date:	18 September 2012 (18.09.2012)
Document type:	Certified copy of priority document
Document details:	Country/Office: US
	Number: 61/536,180
	Filing date: 19 September 2011 (19.09.2011)
Date of receipt at the International Bureau:	03 October 2012 (03.10.2012)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-bis)

PA 7371338

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME;

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

August 10, 2012

**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM
THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK
OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT
APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE UNDER 35 USC 111.**

APPLICATION NUMBER: 61/536,180

FILING DATE: September 19, 2011

**THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY
APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS
CONVENTION, IS US61/536,180**

By Authority of the

**Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office**



**N. WILLIAMS
Certifying Officer**

Electronic Acknowledgement Receipt	
EFS ID:	10976773
Application Number:	61536180
International Application Number:	
Confirmation Number:	4022
Title of Invention:	NEW PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Andreas Fischer
Customer Number:	23117
Filer:	Leonard Charles Mitchard/Linda Farmer
Filer Authorized By:	Leonard Charles Mitchard
Attorney Docket Number:	LCM-1090-275
Receipt Date:	19-SEP-2011
Filing Date:	
Time Stamp:	13:54:06
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$220
RAM confirmation Number	165
Deposit Account	141140
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

122

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Provisional Cover Sheet (SB16)	1090-275ProvisionalSB.pdf	2148900	no	3
			47c63982dacdd44600278541f53b8a7f860a7a2		
Warnings:					
Information:					
2	Specification	1090-275specification.pdf	228899	no	36
			4598b61a0392e52cd51be17b8cad0b9d50c6332		
Warnings:					
Information:					
3	Drawings-only black and white line drawings	1090-275Drawings.pdf	245627	no	5
			ff270fb5e3b05f7ca46f91f0a290310acd67a9		
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	29196	no	2
			7d1de88c57689db5a065ca5904038c487ab93322		
Warnings:					
Information:					
Total Files Size (in bytes):			2652622		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

123

Joc Code: TR.PROV
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)
Approved for use through 01/31/2014 OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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

Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

Inventor(s)

Inventor 1					Remove	
Given Name	Middle Name	Family Name	City	State	Country	
Andreas		Fischer	Uppsala		SE	

All Inventors Must Be Listed – Additional Inventor Information blocks may be generated within this form by selecting the Add button.

Add

Title of Invention	NEW PHARMACEUTICAL COMPOSITION
Attorney Docket Number (if applicable)	LCM-1090-275

Correspondence Address

Direct all correspondence to (select one):

☒ The address corresponding to Customer Number	☐ Firm or Individual Name
Customer Number	23117

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Doc Code: TR.PROV
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)
Approved for use through 01/31/2014 OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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

Entity Status

Applicant claims small entity status under 37 CFR 1.27

☐ Yes, applicant qualifies for small entity status under 37 CFR 1.27

☒ No

Warning

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

Signature

Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Leonard C. Mitchard/			Date (YYYY-MM-DD)	2011-09-19
First Name	Leonard	Last Name	Mitchard	Registration Number (If appropriate)	29009

This collection of information is required by 37 CFR 1.51. 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 1.11 and 1.14. This collection is estimated to take 8 hours 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. This form can only be used when in conjunction with EFS-Web. If this form is mailed to the USPTO, it may cause delays in handling the provisional application.

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.
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.

NEW PHARMACEUTICAL COMPOSITION

This invention relates to new pharmaceutical compositions comprising opioids that are useful in the treatment of opioid/opiate dependency and/or pain, which
5 compositions may be abuse-resistant, and may be administered transmucosally and in particular sublingually.

Opioids are widely used in medicine as analgesics. Indeed, it is presently
10 accepted that, in the palliation of more severe pain, no more effective therapeutic agents exist.

Opioid agonist analgesics are used to treat moderate to severe, chronic cancer pain, often in combination with non-steroidal anti-inflammatory drugs (NSAIDs), as well as acute pain (e.g. during recovery from surgery and breakthrough pain).
15 Further, their use is increasing in the management of chronic, non-malignant pain.

A perennial problem with potent opioid agonists however is one of abuse by drug addicts. Drug addiction is a worldwide problem of which opioid dependence,
20 notably of heroin, is a major component. The World Health Organisation (WHO) estimates that there are approximately 4.3 million opioid addicts globally, with approximately 0.7 million in Europe and 0.3 million in the US and Canada.

Opioid dependence is a major health problem and long-term heroin use is
25 connected to a substantially increased risk of premature death from drug overdoses, violence and suicide. Furthermore, sharing of needles among addicts contribute to the spreading of potentially fatal blood infections such as HIV, and hepatitis C. In addition, opioid dependence often leads to difficulties with social relations, inability to manage a normal job and increased criminality to finance
30 addiction, with severe implications for the opioid dependent person and his/her family.

Opioid addicts not only feed their addition by direct purchase of opioids "on the street", typically in the form of opioid-based powders (such as heroin), but may
35 also get hold of pharmaceutical formulations intended for the treatment of e.g.

pain. Such individuals then often apply innovative techniques in their abuse of such formulations, for example by extracting a large quantity of active ingredient from that formulation into solution, which is then injected intravenously. With most commercially-available pharmaceutical formulations, this can be done relatively easily, which renders them unsafe or "abusable". Thus, there is a general need for non-abusable pharmaceutical formulations comprising opioid agonists.

Opioid addicts are often treated by way of "substitution" therapy, in which mainly "street" opioids of unknown strength and purity are replaced by pharmaceutical-grade opioids with a longer duration of action, such as buprenorphine.

Further, a new cohort of opioid-dependent individuals has begun to emerge in the last decade, particularly in the US, namely so-called "white collar" addicts, who have become dependent upon prescription opioids, typically initiated for the treatment of pain. Substitution therapy is also required for this growing group of patients.

Opioid antagonists are used to reverse the pharmacological effects of opioids. Selective opioid antagonists, such as naloxone, may therefore be used to treat narcotic drug overdose or to diagnose suspected opioid addiction. Naloxone in particular has a poor bioavailability when administered transmucosally but is rendered fully bioavailable when administered by injection.

A simple mixture combination of the opioid partial agonist buprenorphine and naloxone in a 4:1 ratio for sublingual administration is available under the trademark Suboxone®. (This and other abuse-resistant opioid-containing formulations are reviewed by Fudula and Johnson in *Drug and Alcohol Dependence*, 83S, S40 (2006). See also US patent applications US 2003/0124061 and US 2003/0191147.)

Because of naloxone's poor transmucosal bioavailability, if Suboxone is taken sublingually, as directed, the small amount of naloxone that is absorbed should not interfere with the desired effects of buprenorphine.

On the other hand, if Suboxone is dissolved and injected by an addict with a view to achieving a "high", the increased availability of naloxone via the parenteral route should serve to antagonize the effects of buprenorphine, at the same time as precipitating unpleasant opioid withdrawal symptoms in an individual physically dependent on opioids.

Nonetheless, when administered parenterally, naloxone's functional blockade of buprenorphine's action is also only partial and is short-lived in its nature. In view of this, diversion and illicit use of Suboxone has frequently been reported, especially in hidden populations such as incarcerated and active drug abusers (see, for example, Alho *et al*, *Drug and Alcohol Dependence*, **88**, 75 (2007), Monte *et al*, *Journal of Addictive Diseases*, **28**, 226 (2009), Stimmel, *ibid.*, **26**, 1 (2007) and Smith *et al*, *ibid.*, **26**, 107, 2007). Indeed, a recent study of untreated intravenous abusers in Finland revealed that 68% reported abuse of Suboxone. Moreover, 66% of those that had abused the drug once admitted that they had abused it at least once subsequently, or even regularly thereafter (see Ahlo *et al*, *supra*).

Further, Suboxone has also been reported to have several other significant limitations. For example, the tablets are large and disintegrate slowly. The bioavailability of buprenorphine is also significantly lower than for a sublingual solution (see Compton *et al*, *Drug and Alcohol Dependence*, **82**, 25 (2006)). Moreover, the taste is not well tolerated by all patients and the tablet has an unpleasant gritty mouthfeel. A film-based product has recently been developed to counteract these problems, but the film formulation also does not dissolve particularly quickly. Furthermore, a maximum of only two films (with doses of 4 mg and 8 mg of buprenorphine) may be administered simultaneously. Sequential administration is thus required for (commonly administered) doses in excess of 12 mg or 24 mg of buprenorphine, respectively.

There is thus a presently unmet clinical need for an abuse-resistant product for use in opioid addiction substitution therapy, but which does not possess the afore-mentioned limitations. In particular, if it were possible to devise a formulation that was capable of significantly increasing the bioavailability of buprenorphine, it might be possible to reduce the amount of this active

pharmaceutical ingredient, giving rise to less opioid in the formulation and so reducing the amount available for injection if diverted by way of intravenous abuse.

5 International patent applications WO 00/16751, WO 2004/067004, WO 2006/103418 and WO 2008/068471 all disclose drug delivery systems for the treatment of e.g. acute pain by sublingual administration, applying an interactive mixture principle, in which the active ingredient in microparticulate form is adhered to the surfaces of larger carrier particles in the presence of a
10 bioadhesive and/or mucoadhesive promoting agent. WO 2008/068471 in particular discloses a formulation comprising particles of opioid agonist drug upon the surfaces of carrier particles comprising an opioid antagonist, such as naloxone.

15 Prior art documents, including international patent applications WO 03/005944, WO 02/067903, WO 2007/141328, WO 2010/132605, WO 01/30288 and US patent application US 2009/0263476 A1 employ pH modifying agents to promote dissolution and/or absorption of active ingredients.

20 We have now found that, by applying a specific formulation principle to a combination of specific active ingredients, buprenorphine and naloxone, we have provided a product with unexpected, significantly improved pharmaceutical and clinical properties.

25 According to a first aspect of the invention there is provided a pharmaceutical composition comprising microparticles of a pharmacologically-effective amount of buprenorphine, or a pharmaceutically-acceptable salt thereof, in associative admixture with particles comprising a weak acid, or particles comprising weakly-acidic buffer forming materials. Such compositions are referred to hereinafter as
30 "the compositions of the invention".

It is preferred that the pharmaceutical compositions comprising buprenorphine, or a pharmaceutically-acceptable salt thereof, are presented in admixture (e.g. in simple mixture) together with a disintegrant.

35

In this respect, there is further provided a pharmaceutical composition comprising:

- (i) a composition of the invention as hereinbefore defined ("Component (i)"); and
- 5 (ii) a disintegrant (hereinafter "Component (ii)").

Compositions comprising Components (i) and (ii) are also referred to together hereinafter as compositions of the invention.

10 It is further preferred that the pharmaceutical compositions comprising buprenorphine, or a pharmaceutically-acceptable salt thereof, are presented in admixture (e.g. in simple mixture) together with a disintegrant and naloxone.

In this respect, there is further provided a pharmaceutical composition comprising:

- 15 (a) a composition of the invention comprising Components (i) and/or (ii) as hereinbefore defined; and
- (b) particles of a pharmacologically-effective amount of naloxone, or a pharmaceutically-acceptable salt thereof (hereinafter "Component (iii)").

20 Compositions comprising Component (iii) formulated together with Components (i) and/or (ii) are also referred to together hereinafter as compositions of the invention.

25 Buprenorphine and pharmaceutically-acceptable salts thereof are presented in the compositions of the invention in the form of microparticles. Naloxone and pharmaceutically-acceptable salts thereof may also (e.g. preferably) be presented in compositions of the invention in the form of microparticles. Microparticles preferably possess a weight based mean diameter, number based mean diameter and/or a volume based mean diameter of between about 0.5 μm and
30 about 15 μm , such as about 1 μm and about 10 μm . As used herein, the term "weight based mean diameter" will be understood by the skilled person to include that the average particle size is characterised and defined from a particle size distribution by weight, i.e. a distribution where the existing fraction (relative amount) in each size class is defined as the weight fraction, as obtained by e.g.
35 sieving (e.g. wet sieving). As used herein, the term "number based mean

diameter" will be understood by the skilled person to include that the average particle size is characterised and defined from a particle size distribution by number, i.e. a distribution where the existing fraction (relative amount) in each size class is defined as the number fraction, as measured by e.g. microscopy. As used herein, the term "volume based mean diameter" will be understood by the skilled person to include that the average particle size is characterised and defined from a particle size distribution by volume, i.e. a distribution where the existing fraction (relative amount) in each size class is defined as the volume fraction, as measured by e.g. laser diffraction.

10 Microparticles of active ingredients may be prepared by standard micronisation techniques, such as grinding, jet milling, dry milling, wet milling, precipitation, etc. An air elutriation process may be utilised subsequently to prepare specific size fractions, if required.

15 Preferred salts of buprenorphine and naloxone include hydrochloride salts.

Buprenorphine and pharmaceutically-acceptable salts thereof are formulated together in associative admixture with particles of a weak acid, or with particles of weakly-acidic buffer forming materials, to provide compositions of the invention (or Component (i) of compositions of the invention).

25 Weakly acidic materials that may be mentioned include those that, when dissolved in water and/or saliva, enable the provision (at the site of administration of compositions of the invention) of a pH of between about 4.0 and about 6.5, and maintenance of pH within this range for an appropriate length of time (e.g. about 1 to about 3 minutes) to facilitate dissolution of, particularly, the buprenorphine microparticles. For the purpose of this invention, the term includes substances that are safe for use in mammals, and includes weak acids, weak acid derivatives and other chemicals that convert to weak acids *in vivo* (e.g. precursors that convert to acids *in vivo*, by for example being sequentially activated in accordance with properties of the local environment). Typical pKas of weak acids are in the range of between about -1.5 (e.g. about -1.74) and about 16 (e.g. about 15.74) (e.g. see Vollhardt, *Organic Chemistry* (1987). A preferred range is between about 1 and about 10. More preferably, the weakly

acidic material comprises a weak acid that is safe for human consumption, for example a food acid, such as citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, lactic acid, acetic acid, oxalic acid, maleic acid, ammonium chloride or a combination thereof. The skilled person will appreciate that, when weak acids are employed which are not solids (and therefore not particulate) at or around room temperature and atmospheric pressure, they may be adsorbed into a particulate carrier material (such as silica) in order to provide particles comprising the weakly acidic material.

Weakly-acidic buffer forming materials include materials that, when dissolved in water and/or saliva, provide a weakly acidic buffer system, enabling the provision (at the site of administration of compositions of the invention) of a pH of between about 4.0 and about 6.5, and maintenance of pH within this range for an appropriate length of time (e.g. about 1 to about 3 minutes) to facilitate dissolution of, particularly, the buprenorphone microparticles. Buffer forming materials thus include combinations of weak acid and salt of weak acid, such as combinations of the aforementioned acids with alkaline salts of those acids, including sodium citrate, potassium citrate, sodium tartrate, potassium tartrate and the like. Preferred buffer forming materials are citric acid and sodium citrate.

The skilled person will appreciate that, when materials are employed which are not solids (and therefore not particulate) at or around room temperature and atmospheric pressure, they may be adsorbed into a particulate carrier material (such as silica) in order to provide particles comprising the weakly-acidic buffer forming materials.

Suitable particles sizes of weakly acidic, or weakly-acidic buffer forming, materials are in the range about 1 μm and about 1000 μm (e.g. about 800 μm , such as about 750 μm), and preferably between about 40 (such as about 50 μm) and about 600 μm .

The disintegrant or "disintegrating agent" that may be employed as, or as part of, Component (ii) in compositions of the invention may be defined as any material that is capable of accelerating to a measurable degree the disintegration/dispersion of a composition of the invention. The disintegrant may thus provide for an *in vitro* disintegration time of about 30 seconds or less, as

measured according to e.g. the standard United States Pharmacopeia (USP) disintegration test method (see *FDA Guidance for Industry: Orally Disintegrating Tablets*; December 2008). This may be achieved, for example, by the material being capable of swelling, wicking and/or deformation when placed in contact
5 - with water and/or mucous (e.g. saliva), thus causing tablet formulations to disintegrate when so wetted.

Suitable disintegrants (as defined in, for example, Rowe *et al*, *Handbook of Pharmaceutical Excipients*, 6th ed. (2009)) include cellulose derivatives such as
10 hydroxypropyl cellulose (HPC), low substituted HPC, methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, microcrystalline cellulose, modified cellulose gum; starch derivatives such as moderately cross-linked starch, modified starch, hydroxypropyl starch and pregelatinized starch; and other disintegrants such as calcium alginate,
15 sodium alginate, alginic acid, chitosan, colloidal silicon dioxide, docusate sodium, guar gum, magnesium aluminium silicate, polacrilin potassium and polyvinylpyrrolidone. Combinations of two or more disintegrants may be used.

Preferred disintegrants include so-called "superdisintegrants" (as defined in, for
20 example, Mohanachandran *et al*, *International Journal of Pharmaceutical Sciences Review and Research*, 6, 105 (2011)), such as cross-linked polyvinylpyrrolidone, sodium starch glycolate and croscarmellose sodium. Combinations of two or more superdisintegrants may be used.

25 Disintegrants may also be combined with superdisintegrants in compositions of the invention.

Disintegrants and/or superdisintegrants are preferably employed in an (e.g. total) amount of between 0.5 and 15% by weight based upon the total weight of a
30 composition. A preferred range is from 1 to 8%, such as from about 2 to about 7% (e.g. about 5%, such as about 4%) by weight.

Compositions of the invention may be formulated together (along with any other materials that may be present) by standard simple mixing techniques or by way of
35 granulation.

Granules may be prepared by a process of dry granulation, wet granulation, melt granulation, thermoplastic pelletising, spray granulation or extrusion/spheronisation.

5

Wet granulation techniques are well known to those skilled in the art and include any technique involving the massing of a mix of dry primary powder particles using a granulating fluid, which fluid comprises a volatile, inert solvent, such as water, ethanol or isopropanol, either alone or in combination, and optionally in the presence of a binder or binding agent. The technique may involve forcing a wet mass through a sieve to produce wet granules which are then dried, preferably to a loss on drying of less than about 3% by weight.

10

Dry granulation techniques are also well known to those skilled in the art and include any technique in which primary powder particles are aggregated under high pressure, including slugging and roller compaction, for example as described hereinafter.

15

Melt granulation will be known by those skilled in the art to include any technique in which granules are obtained through the addition of a molten binder, or a solid binder which melts during the process. After granulation, the binder solidifies at room temperature. Thermoplastic pelletising will be known to be similar to melt granulation, but in which plastic properties of the binder are employed. In both processes, the agglomerates (granules) obtained comprise a matrix structure.

20

25

Spray granulation will be known by those skilled in the art to include any technique involving the drying of liquids (solutions, suspensions, melts) while simultaneously building up granulates in a fluid bed. The term thus includes processes in which foreign seeds (germs) are provided upon which granules are built up, as well as those in which inherent seeds (germs) form in the fluid bed due to abrasion and/or fracture, in addition to any spray coating granulation technique generally. The sprayed liquid coats the germs and assists further agglomeration of particles. It is then dried to form granules in the form of a matrix.

30

35

Extrusion/spheronisation will be well known to those skilled in the art to include any process involving the dry mixing of ingredients, wet massing along with a binder, extruding, spheronising the extrudate into spheroids of uniform size, and drying.

5

Microparticles of buprenorphine or salt thereof and particles of weakly acidic, weakly-acidic buffer forming, materials are presented in associative admixture with each other in compositions of the invention. By "associative admixture" we mean that whether or not Component (i) is subsequently formulated along with Components (ii) and (iii) as hereinbefore defined, some form of mixing step (simple mixing, granulation as described hereinbefore, or otherwise) takes place as between the buprenorphine/salt microparticles and particles of weakly acidic, weakly-acidic buffer forming, materials, rendering them in intimate contact with each other.

15

In this respect, Component (i) is preferably presented as, or as part of, a composition of the invention in the form of a interactive mixture comprising at least one population of carrier particles upon the surfaces of which are presented (e.g. adhered) microparticles of buprenorphine or a pharmaceutically acceptable salt thereof.

20

The term "interactive" mixture will be understood by those skilled in the art to include the term "ordered" mixture, and to denote a mixture in which particles do not appear as single units, as in random mixtures, but rather where smaller particles (e.g. microparticles of, for example, buprenorphine) are attached to (i.e. adhered to or associated with) the surfaces of larger carrier particles. Such mixtures are characterised by interactive forces (for example van der Waals forces, electrostatic or Coulomb forces, and/or hydrogen bonding) between carrier and surface-associated particles (see, for example, Staniforth, *Powder Technol.*, **45**, 75 (1985)). In final mixtures, and compositions comprising such mixtures, the interactive forces need to be strong enough to keep the adherent particles at the carrier surface.

25

30

When interactive mixtures are employed as the formulation principle by which the particulate Component (i) is presented in a composition of the invention, these

35

are made, preferably, with carrier particles that are of a size (weight and/or volume based average or mean diameter, *vide supra*) that is between about 30 μm and about 1000 μm (e.g. about 800 μm , such as about 750 μm), and preferably between about 40 (such as about 50 μm) and about 600 μm .

5

Carrier particles may comprise pharmaceutically-acceptable substances that are soluble in water, such as carbohydrates, e.g. sugars, such as lactose, and sugar alcohols, such as mannitol, sorbitol and xylitol; pharmaceutically-acceptable inorganic salts, such as sodium chloride. Water soluble carrier particles may also
 10 comprise the weakly acidic, and/or weakly acidic buffer forming materials, mentioned hereinbefore (such as citric acid and/or sodium citrate). Alternatively, carrier particles may comprise pharmaceutically-acceptable substances that are insoluble or sparingly soluble in water, such as dicalcium phosphate anhydrate, dicalcium phosphate dihydrate, tricalcium phosphate, calcium carbonate, and
 15 barium sulphate; starch and pre-gelatinised starch; bioadhesive and mucoadhesive materials, such as crosslinked polyvinylpyrrolidone and croscarmellose sodium; and other polymers, such as microcrystalline cellulose, cellulose and; or mixtures thereof.

20 By "soluble in water" we include that the material has a solubility in water that is greater than 33.3 mg/mL at atmospheric pressure (e.g. 1 bar) and room temperature (e.g. 21°C). On the other hand, the term "sparingly soluble or insoluble in water" includes materials that have a solubility in water that is less than 33.3 mg/mL under the same conditions. Preferred soluble carrier particle
 25 materials include sugar alcohols, such as sorbitol, xylitol and particularly mannitol. Preferred sparingly water-soluble or water-insoluble carrier particle materials include cellulose and starches, such as microcrystalline cellulose.

It is preferred that buprenorphine or pharmaceutically acceptable salt thereof is
 30 presented on the surfaces of water-soluble carrier particles.

In this respect, as stated above, weakly acidic materials, and/or weakly-acidic buffer forming materials, may also function as water-soluble carrier particle materials. Therefore, the associated admixture of such materials with
 35 buprenorphine/salt thereof may mean the former comprise carrier particles upon

which microparticles of the latter are presented. In such cases, it is preferred that such materials are presented at least as further water-soluble carrier particles, in addition to the presence of other water-soluble carrier particles, upon the surfaces of both of which are presented burprenorphine microparticles.

5

When carrier particles comprise such weakly acidic/buffer forming materials, composites of such materials with other water-soluble carrier particle materials (such as those described hereinbefore) may be provided. Such materials may be prepared by direct compression or granulation, for example. Alternatively, carrier particles may consist essentially of a weakly acidic material and/or one or more materials that, when dissolved in saliva, give rise to a weakly acidic buffer system. By "consisting essentially" of such materials, we mean that, excluding the possible presence of water (*vide infra*), the carrier particles comprise at least about 95%, such as at least about 98%, more preferably greater than about 99%, and particularly at least about 99.5% by weight (based on the total weight of the carrier particle) of such materials. These percentages exclude the presence of trace amounts of water (e.g. crystal water or water bound to external surfaces of materials), and/or any impurities that may be present in such materials, which impurities may arise following the production of such materials, either by a commercial or non-commercial third party supplier, or by a skilled person making a composition of the invention.

Alternatively (and/or in addition), in Component (i), particles of weakly acidic material, and/or of weakly-acidic buffer forming materials, may be presented, at least in part, upon the surfaces of, and/or between, carrier particles. In such cases, suitable particle sizes of such materials are as presented herein for active ingredients and/or disintegrants.

When employed in compositions of the invention, Components (ii) and (iii) are preferably formulated together, for example to form particles comprising naloxone or salt thereof and the disintegrant, prior to mixing with Component (i).

Furthermore, in Component (iii), particles of naloxone, or pharmaceutically-acceptable salts thereof, may also be presented upon the surfaces of carrier particles in compositions of the invention, but this is not essential. Such carrier

particles may be water-soluble (as hereinbefore defined), or may (preferably) be water-insoluble/sparingly soluble carrier particles.

5 Disintegrant and/or superdisintegrant materials, may also be presented, at least in part, as particles upon the surfaces of, and/or between, carrier particles, which may or may not also carry naloxone or salt thereof. If employed in particulate form, particles of disintegrants and/or superdisintegrants may be presented with a particle size (weight and/or volume based average or mean diameter, *vide supra*) of between about 0.1 and about 100 µm (e.g. about 1 and about 50 µm).

10 Alternatively, disintegrants and/or superdisintegrants may also be present as a constituent in composite excipients. Composite excipients may be defined as co-processed excipient mixtures. Examples of composite excipients comprising superdisintegrants are Parateck® ODT, Ludipress® and Prosolv® EASYtab.

15 Bio/mucoadhesive materials may also be presented in compositions of the invention. Such materials may be presented upon (e.g. adhered to) the surfaces of carrier particles when components of compositions of the invention are presented in the form of interactive mixtures.

20 Compositions of the invention may be employed in the treatment of opioid dependency and/or addiction as described hereinbefore, for example in substitution therapy programs. Opioid dependency and/or addiction may be defined in numerous ways (see, for example, www.who.int/substance_abuse/terminology/definition1), but may be characterized for example by physiological, behavioural, and cognitive phenomena wherein the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value, and/or characterised by a desire (often strong, and sometimes overpowering) to take
25 opioids and/or opiates (which may or may not have been medically prescribed). It is particularly preferred that compositions of the invention comprising naloxone are used in the treatment of opioid dependency and/or addiction.

35 Buprenorphine is a partial agonist at the µ-opioid receptor and an antagonist at the κ-opioid receptor. It has high binding affinity at both receptors and competes

with other agonists, such as methadone, heroin (diamorphine) and morphine, at the μ -opioid receptor. Opioid agonist effects of buprenorphine are less than the maximal effects of other, "full" opioid agonists, such as morphine, and are limited by a "ceiling" effect. The drug thus produces a lower degree of physical dependence than other opioid agonists, such as heroin, morphine or methadone and is therefore particularly useful in substitution therapy.

The term "pharmacologically effective amount" refers to an amount of an active ingredient, which is capable of conferring a desired therapeutic effect on a treated patient, whether administered alone or in combination with another active ingredient. Such an effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of, or feels, an effect).

Thus, appropriate pharmacologically effective amounts of buprenorphine (or salt thereof) include those that are capable of producing, and/or contributing to the production of, the desired therapeutic effect, namely decreased opioid and/or opiate craving and/or decreased illicit drug use, when administered transmucosally, whereas appropriate pharmacologically effective amounts of naloxone (or salt thereof) when employed must be sufficient so as not to compete with the above-mentioned pharmacological effect of the buprenorphine present in the composition of the invention upon transmucosal administration, but to antagonize the effect of the buprenorphine and precipitate withdrawal symptoms if an attempt is made by an opioid-addicted individual to inject a composition of the invention.

The amounts of active ingredients that may be employed in compositions of the invention may thus be determined by the skilled person, in relation to what will be most suitable for an individual patient. This is likely to vary with the route of administration, the type and severity of the condition that is to be treated, as well as the age, weight, sex, renal function, hepatic function and response of the particular patient to be treated.

The total amount of buprenorphine/salt thereof that may be employed in a composition of the invention may be in the range of about 0.1%, such as about 1%, to about 20%, such as about 10%, by weight based upon the total weight of

the composition. The amount of this active ingredient may also be expressed as the amount in a unit dosage form (e.g. a tablet). In such a case, the amount of buprenorphine/salt that may be present may be sufficient to provide a dose per unit dosage form that is in the range of between about 0.1 mg, such as about 1
5 mg and about 50, for example about 30, such as about 20 mg (e.g. about 15 mg, such as about 10 mg). Preferred ranges for the treatment of pain are about 0.1 mg to about 4 mg. Preferred ranges for substitution therapy are about 0.5 mg to about 50 mg, such as about 1 mg to about 10 mg.

10 When employed, the total amount of naloxone/salt thereof that may be employed in a composition of the invention may be in the range about 0.125%, such as about 0.25% to about 5%, such as about 2.5%, by weight based upon the total weight of the composition. The amount of this active ingredient may also be expressed as the amount in a unit dosage form (e.g. a tablet). In such a case,
15 the amount of naloxone/salt that may be present may be sufficient to provide a dose per unit dosage form that is in the range of between about 0.125 mg and about 12.5 mg, such as about 0.25 mg to about 2.5 mg.

Although, for compositions of the invention containing naloxone, it is preferred
20 that the dose ratio of buprenorphine:naloxone is maintained at about 4:1, the above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

25 Compositions of the invention, once prepared, are preferably directly compressed/compacted into unit dosage forms (e.g. tablets) for administration to mammalian (e.g. human) patients, for example as described hereinafter.

30 Compositions of the invention in the form of tablets for e.g. sublingual administration may also comprise a binder. A binder may be defined as a material that is capable of acting as a bond formation enhancer, facilitating the compression of the powder mass into coherent compacts. Suitable binders include cellulose gum and microcrystalline cellulose. If present, binder is preferably employed in an amount of between 0.5 and 20% by weight based

pd1

upon the total weight of the tablet formulation. A preferred range is from 1 to 15%, such as from about 2.0 to about 12% (e.g. about 10%) by weight.

5 Suitable further additives and/or excipients that may be employed in compositions of the invention, in particular those in the form of tablets for e.g. sublingual administration may comprise:

- (a) lubricants (such as magnesium stearate or, preferably, sodium stearyl fumarate);
- 10 (b) flavourings (e.g. lemon, peppermint powder or, preferably, menthol), sweeteners (e.g. neohesperidin, acesulfame K or, preferably, sucralose) and dyestuffs;
- (c) antioxidants, which may be naturally occurring or otherwise (e.g. butylated hydroxytoluene (BHT), vitamin C, vitamin E, β -carotene, uric acid, uniquon, superoxide dismutase (SOD), glutathione peroxidase or
- 15 peroxidase catalase); and/or
- (d) other ingredients, such as carrier agents, preservatives and gliding agents (e.g. colloidal silica).

20 Compositions of the invention may be prepared by standard techniques, and using standard equipment, known to the skilled person.

When presented in the form of interactive mixtures, particles of e.g. buprenorphine/salt may be dry mixed with relevant carrier particles over a period of time that is sufficiently long to enable appropriate amounts of respective active

25 ingredients to adhere to the surface of the carrier particles. This may also apply to other active ingredients and/or excipients defined hereinbefore.

The skilled person will appreciate that, in order to obtain a dry powder formulation in the form of an interactive mixture, larger carrier particles must be able to exert

30 enough force to break up agglomerates of smaller particles. This ability will primarily be determined by particle density, surface roughness, shape, flowability and, particularly, relative particle sizes.

Standard mixing equipment may be used in this regard. The mixing time period

35 is likely to vary according to the equipment used, and the skilled person will have

142
no difficulty in determining by routine experimentation a suitable mixing time for a given combination of active ingredient and carrier particle material(s).

Interactive mixtures may also be provided using techniques other than dry mixing,
5 which techniques will be well known to those skilled in the art.

Other ingredients may alternatively be incorporated by standard mixing or other formulation principles.

10 The compositions of the invention may be administered transmucosally, such as buccally, rectally, nasally or preferably sublingually by way of appropriate dosing means known to the skilled person. A sublingual tablet may be placed under the tongue, and the active ingredients absorbed through the surrounding mucous membranes.

15 In this respect, the compositions of the invention may be incorporated into various kinds of pharmaceutical preparations intended for transmucosal (e.g. sublingual) administration using standard techniques (see, for example, Lachman *et al*, "*The Theory and Practice of Industrial Pharmacy*", Lea & Febiger, 3rd edition (1986)
20 and "*Remington: The Science and Practice of Pharmacy*", Gennaro (ed.), Philadelphia College of Pharmacy & Sciences, 19th edition (1995)).

Pharmaceutical preparations for sublingual administration may be obtained by combining compositions of the invention with conventional pharmaceutical
25 additives and/or excipients used in the art for such preparations, and thereafter preferably directly compressed/compacted into unit dosage forms (e.g. tablets). (See, for example, *Pharmaceutical Dosage Forms: Tablets. Volume 1*, 2nd Edition, Lieberman *et al* (eds.), Marcel Dekker, New York and Basel (1989) p. 354-356 and the documents cited therein.) Suitable compacting equipment
30 includes standard tableting machines, such as the Kilian SP300, the Korsch EK0, the Korsch XP1, the Korsch XL100 or the Korsch PharmaPress 800.

Suitable final sublingual tablet weights are in the range of about 30 to about 400 mg, such as about 40 (e.g. about 50) to about 200 mg, for example about 50 (e.g.
35 about 60) to 180 mg, more preferably between about 60 (e.g. about 70) and

about 160 mg. Suitable final tablet diameters are in the range of about 3 to about 12 mm, for example about 4 to about 10 mm, and more preferably about 5 to about 9 mm. Suitable final tablet thicknesses are in the range of about 0.5 mm to about 4 mm, such as about 1.5 mm to about 3 mm. Various tablet weights are possible (e.g. circular, triangular, square, diamond, polygon or oval).

Irrespective of the foregoing, compositions of the invention comprising disintegrants (or other excipients that function by swelling) should be essentially free (e.g. less than about 20% by weight based on the total weight of the formulation) of water. It will be evident to the skilled person that "premature" hydration will dramatically decrease the performance of a tablet formulation in use and may result in premature dissolution of active ingredients.

Wherever the word "about" is employed herein in the context of dimensions (e.g. tablet sizes and weights, particle sizes etc.), surface coverage (e.g. of carrier particles by particles of active ingredients), amounts (e.g. relative amounts of individual constituents in a composition or a component of a composition and absolute doses (including ratios) of active ingredients), temperatures, pressures, times, pH values, concentrations, etc., it will be appreciated that such variables are approximate and as such may vary by $\pm 10\%$, for example $\pm 5\%$ and preferably $\pm 2\%$ (e.g. $\pm 1\%$) from the numbers specified herein.

Compositions of the invention may be administered by way of appropriate dosing means known to the skilled person. For example, a sublingual tablet may be placed under the tongue, and the active ingredients absorbed through the surrounding mucous membrane.

We have found that compositions of the invention surprisingly give rise to significantly improved bioavailability for buprenorphine when compared to prior art, commercially-available formulations. This means that formulations with lower single doses of buprenorphine may be administered by way of compositions of the invention, so reducing the "street value" of a single tablet when it comprises a composition of the invention, with more than one such tablet being required to give the same effect when illicitly administered parenterally (i.e. in "street" terms, the same "fix"). This means that compositions of the invention are less likely to

be abused than prior art, commercially-available formulations (see Comer *et al*, *Addiction*, **105**, 709–718 (2010)).

5 Additionally, we have found that compositions of the invention comprising naloxone also surprisingly give rise to significantly (and simultaneously with buprenorphine) improved bioavailability for naloxone when compared to prior art, commercially-available formulations.

10 Compositions of the invention comprising naloxone thus surprisingly give rise to similar, almost parallel, degrees of improved bioavailability for both buprenorphine and naloxone, which means that the "optimal" ratio of buprenorphine to naloxone, which has been arrived at to reduce abuse potential (see, for example, Mendelson and Jones, *Drug and Alcohol Dependence*, **70**, 829 (2003)), may be maintained, and doses of both active ingredients therefore
15 lowered by an equivalent amount.

Finally, compositions of the invention comprising naloxone give rise to a lower norbuprenorphine:buprenorphine ratio in plasma when compared to prior art, commercially-available formulations. A lower norbuprenorphine to buprenorphine
20 ratio is also seen after sublingual administration of an ethanol solution compared to a tablet formulation (see Harris *et al*, *Clin. Pharmacokinet.*, **43**, 329 (2004)) as dose is increased, suggesting that less buprenorphine is being swallowed. In addition, less norbuprenorphine is found in the plasma after parenteral administration compared to sublingual administration (Sigmon *et al*, *Addiction*,
25 **101**, 420 (2005)), further supporting the notion that norbuprenorphine is formed from swallowed buprenorphine by first pass metabolism through the liver. Thus, the lower norbuprenorphine:buprenorphine ratio reported herein may be reflective of the fact that more buprenorphine is absorbed over the sublingual mucosa (and less is swallowed) than with prior art, commercially available formulations. There
30 may also be benefits from the reduction of the norbuprenorphine:buprenorphine ratio *per se*, such as reduced respiratory depression (see Megarbane *et al*, *Toxicology and Applied Pharmacology*, **212**, 256 (2006)).

According to a further aspect of the invention, there is further provided a method
35 of treating opioid dependency and/or addiction in a human, which method

comprises sublingual administration of a pharmaceutical composition comprising buprenorphine or a pharmaceutically acceptable salt thereof, at a dose of 0.5 to 50 mg, in combination with naloxone or a pharmaceutically acceptable salt thereof, in about a 4:1 (buprenorphine:naloxone) dose ratio, to a human patient
 5 suffering from opioid dependency and/or addiction, wherein said formulation achieves after an initial dose in any given treatment program a ratio of norbuprenorphine/buprenorphine concentrations in plasma of less than about 1.0 based upon the total AUC (area under the plasma concentration-time curve from time zero to the time of the last quantifiable plasma concentration).

10 Such methods may comprise administration of a composition of the invention as defined herein.

By "any given treatment program", we mean any course of treatment of a patient
 15 with a composition of the invention.

The compositions of the invention are useful in the treatment of opioid dependency and/or addiction. Compositions of the invention may also be useful in the treatment of pain (including mild, moderate and severe pain).

20 According to three further aspects of the invention there are provided:
 (i) a method of treatment of opioid dependency and/or addiction;
 (ii) a method of treatment of pain; and
 (iii) a method of treatment of both pain and opioid dependency and/or addiction,
 25 which methods comprise administration of a composition of the invention to a person suffering from, or susceptible to, the relevant conditions.

By "treatment" of pain we include the therapeutic treatment, as well as the symptomatic and palliative treatment of the condition. However, by "treatment" of
 30 opioid dependency and/or addiction, we further include the prophylaxis, or the diagnosis of the relevant condition in addition to therapeutic, symptomatic and palliative treatment. This is because, by employing buprenorphine in the treatment of pain, compositions of the invention may prevent the development of opioid dependency and/or addiction.

35

The compositions of the invention enable the production of unit dosage forms that are easy and inexpensive to manufacture, and which enable the rapid release and/or a rapid uptake of the active ingredients employed through the mucosa, such as the oral mucosa, thus enabling rapid relief of symptoms, such as those described hereinbefore.

The compositions of the invention also have the advantage that, if injected by an opioid addict, they do not produce the euphoric effects that such an addict seeks and indeed induce opioid withdrawal symptoms.

Compositions of the invention may also have the advantage that they may be prepared using established pharmaceutical processing methods and employ materials that are approved for use in foods or pharmaceuticals or of like regulatory status.

Compositions of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, possess a better patient acceptability than, have a better pharmacokinetic profile than, and/or have other useful pharmacological, physical, or chemical properties over, pharmaceutical compositions known in the prior art, whether for use in the treatment of opioid addiction or pain or otherwise.

The invention is illustrated by way of the following examples, with reference to the attached figures in which analyte concentration-time plasma profiles are presented in linear scale plots for buprenorphine (Figure 1), norbuprenorphine (Figure 2) and naloxone (Figure 3) following sublingual administration of tablets comprising a composition of the invention (diamonds) and the commercially-available comparator, Suboxone® (squares); Figure 4 shows an *in vivo* sublingual pH profile obtained for a placebo composition (analogous to one prepared in accordance with the invention); Figure 5 shows comparative *in vitro* pH profiles for composition of the invention *versus* Suboxone and other comparators; and Figures 6 and 7 show release of buprenorphine and naloxone, respectively, from the compositions referred to in Figure 5.

Example 1

Buprenorphine/Naloxone Sublingual Tablets I

Naloxone hydrochloride dihydrate (Macfarlan Smith, Edinburgh, UK) and
5 buprenorphine hydrochloride (Macfarlan Smith, Edinburgh, UK) were micronised
using an air jet mill (Pilotmill-1/Food and Pharma Systems, Italy). The volume
based mean particle size (diameter) of the buprenorphine was 3.4 µm and of the
naloxone was 4.6 µm.

10 9.15 g of the micronised naloxone hydrochloride was mixed together with
microcrystalline cellulose (47.50 g; Avicel™ PH102 (mean particle size 100 µm),
FMC Biopolymer, Cork, Ireland) and croscarmellose sodium (18.00 g; AcDiSol™,
FMC Biopolymer) in a tumble blender (Turbula, WAG, Switzerland) for 40 hours.

15 32.40 g of the micronised buprenorphine hydrochloride was mixed together with
mannitol (314.20 g; Pearlitol™ 200SD, Roquette, Lestrem, France), sieved citric
acid (15.00 g; fine granular 16/40 grade, DSM, Switzerland, Basel) and sieved (to
avoid agglomeration) sodium citrate (48.75 g) Emprove™ cryst., Merck,
Darmstadt, Germany) in a tumble blender for 40 hours.

20 Menthol (5.00 g; Emprove™ cryst., Merck) was mortared until a fine powder was
formed. This and also acesulfame potassium (5.00 g; Sunett Pharma D,
Nutrinova, Kelsterbach, Germany) and anhydrous colloidal silica (5.00 g;
Aerosil™ 200 Pharma, Evonik Degussa, Hanau-Wolfgang, Germany) were added
25 by sieving into the buprenorphine premix, together with the naloxone premix, and
the whole mixed together in a tumble blender for 1 hour.

Sodium stearyl fumarate (10.00 g; Pruv™, JRS Pharma, Polanco, Spain) was
then added by sieving into this mixture and mixing continued in the tumble
30 blender for 5 minutes.

The final powder mixture was then compressed into tablets in a tablet machine
(Korsch XP1) equipped with 7 mm round, flat faced, radius-edged punches, to a
tablet weight of 102 mg and a tablet crushing strength of 35 N.

35

Example 2

Clinical Trial

5 The tablets of Example 1 were sublingually administered in an open-label, 2-period crossover study with randomised treatment sequence.

10 The study comprised a screening visit conducted within 28 days prior to first treatment, two treatment periods each of 4 days length (Day -1 to Day 3) and a washout period of at least 10 days between treatment periods. During the treatment periods, subjects were admitted to the clinical unit on the morning prior to first dosing (Day -1) and remained in the unit until the completion of Day 3 procedures. A follow-up visit was carried out 5 to 10 days after completion of the second Investigational Medicinal Product (IMP) administration.

15 The IMPs were sublingual tablet prepared in accordance with Example 1 (6 mg buprenorphine/1.5 mg naloxone; hereafter "formulation of the invention") and, as the reference product, Suboxone sublingual tablet (8 mg buprenorphine/2 mg naloxone; Reckitt Benckiser Healthcare Ltd, Hull, UK). Treatment with formulation of the invention, or Suboxone (1 tablet) in alternate periods was open-label and was administered on Day 1 in each treatment period.

25 Naltrexone tablets (Nalorex[®], 50 mg, Bristol-Myers Squibb Pharmaceuticals Ltd; Uxbridge, UK) were administered orally (one 50 mg tablet), at -24 to -16 hours, -1 hour (± 5 minutes) and +24 hours (± 1 hour) in relation to administration of IMP, as a naltrexone block in the study (in order to alleviate opioid side effects during the study).

30 Eighteen healthy male volunteers aged between 18 and 50 years were enrolled. These received both treatments and were evaluated. The mean age was 29.8 years and ages ranged from 19 to 49 years. All subjects were male Caucasians. The mean weight was 78.16 kg and ranged from 63.0 to 93.5 kg. The mean body mass index of the subjects was 25.05 kg/m² and ranged from 20.7 to 28.9 kg/m².

35 All subjects (except one) reported current alcohol use ranging from 1 to 20 units per week. No subject was a current smoker. All subjects reported current

149

caffeine use of 1 to 5 cups or cans per day. No subject had been treated with opioids within 1 year prior to screening.

5 No subject reported any pre-study medication (taken within 2 weeks prior to screening). One subject reported ongoing use of antihistamines for systemic use by oral tablet or capsule to treat seasonal allergic rhinitis.

Trial medication was administered in the clinic under the supervision of clinic personnel.

10

All subjects who were enrolled in the study and who received at least one dose of trial medication. All randomised subjects who received at least one treatment, had at least one evaluable plasma profile and had no major protocol deviations that could have a substantial effect on the buprenorphine, norbuprenorphine or naloxone plasma concentration profile, such as:

15

- swallowing of study medication (applies to both formulation of the invention and Suboxone)
- vomiting within 4 hours after administration of either type of tablet
- having a pre-dose quantifiable concentration that is > 5% of a subject's

20

C_{max}

All randomised subjects who received at least one treatment and had disintegration or acceptability data present for at least one treatment.

25

Pharmacokinetic (PK) variables were based on plasma concentrations of buprenorphine, norbuprenorphine (a metabolite of buprenorphine) and naloxone and were calculated using standard, non-compartmental methods. The PK non-compartmental analysis was performed using WinNonlin™ Professional version 5.2. Data permitting, the following parameters were determined:

30

- t_{lag} lag time before the start of absorption
- C_{max} maximum plasma concentration
- t_{max} time to reach maximum plasma concentration
- AUC_{0-t} area under the plasma concentration-time curve from time zero to the time of the last quantifiable plasma concentration

- AUC_{0-48} area under the plasma concentration-time curve from time zero to 48 hours post-dose
- MR metabolic ratio

5 In addition, the relative bioavailability (F_{rel}) of formulation of the invention to Suboxone was derived based on dose-adjusted PK data.

Subjects were classified as evaluable or non-evaluable with respect to the PK evaluation by the pharmacokineticist after examining the subjects PK profiles and
10 taking into account any deviations with respect to those listed above. The PK analyses based on the PK population included only those subjects with evaluable PK data.

Actual blood sampling times for buprenorphine, norbuprenorphine and naloxone
15 were converted to a time from dosing (elapsed time). Elapsed times were listed by subject for each treatment, together with the individual buprenorphine, norbuprenorphine and naloxone concentrations. Elapsed times were used in the PK analysis.

20 The buprenorphine, norbuprenorphine and naloxone concentrations were summarised by descriptive statistics of number of missing samples, number of samples less than the lower limit of quantification (<LOQ), n, arithmetic mean, SD, CV(%), geometric mean, 95% confidence intervals (CI) for the arithmetic mean, median, minimum and maximum. All buprenorphine, norbuprenorphine
25 and naloxone concentrations <LOQ were set to zero for the purpose of calculating descriptive statistics. If at any time-point 1/3 or more of subjects had values <LOQ, descriptive statistics were not calculated.

The PK parameters C_{max} , AUC_{0-t} and AUC_{0-48} of buprenorphine, norbuprenorphine
30 and naloxone were compared between treatments using a mixed effects Analysis of Variance (ANOVA) procedure.

Arithmetic mean (+SD) analyte concentration-time plasma profiles are presented in linear scale plots for each analyte in Figures 1 (buprenorphine), 2
35 (norbuprenorphine) and 3 (naloxone) with both treatments included on each plot.

It can be seen from these figures that, for both buprenorphine and norbuprenorphine after administration of formulation of the invention (diamonds), and Suboxone (squares), plasma concentrations of all three analytes increased to a maximum then declined in a biphasic manner.

5

In relation to other PK parameters:

- (i) on average, the lag time was slightly shorter after treatment with formulation of the invention compared to Suboxone by 15% for buprenorphine, 29% for norbuprenorphine and 34% for naloxone;
- 10 (ii) the range of times at which maximal concentrations were attained (t_{max}) was similar between treatments for all analytes. Median t_{max} values were less than or equal to 1 h for buprenorphine and naloxone indicating rapid sublingual absorption following administration of both formulation of the invention and Suboxone. For norbuprenorphine, 15 t_{max} was generally similar to buprenorphine after both treatments indicating metabolism of buprenorphine to norbuprenorphine was rapid;
- (iii) the mean metabolite ratios exceeded 0.5 indicating extensive metabolic conversion of buprenorphine to norbuprenorphine, with 20 conversion being 31% lower following administration of formulation of the invention compared to Suboxone. This result is significant as it means that more buprenorphine is absorbed sublingually in the case of formulation of the invention;
- (iv) the doses of both buprenorphine and naloxone were lower in the 25 formulation of the invention, but mean systemic exposure, in terms of C_{max} and AUC, of buprenorphine and naloxone were higher when compared to Suboxone, and, as stated above, the values were lower for norbuprenorphine; and
- (v) the mean relative bioavailabilities of formulation of the invention to 30 Suboxone were 1.659 and 2.056 for buprenorphine and naloxone respectively, indicating higher dose-normalised systemic exposure following administration of formulation of the invention. For norbuprenorphine the dose-normalised systemic exposure appeared to be similar between treatments with a mean relative bioavailability of 35 1.084. The buprenorphine result is significant. The reported relative

5 bioavailability of a sublingually-administered ethanol solution comprising buprenorphine (where conditions are theoretically optimised for rapid absorption over the sublingual mucosa) compared to Suboxone was reported to be 1.5 (see Compton *et al*, *Drug and Alcohol Dependence*, **82**, 25 (2006)). The fact that the relative number reported in this study for a solid sublingual tablet was even higher than that reported for a solution is remarkable.

10 Disintegration time of the tablets was assessed by either a nurse or a physician by mouth inspections, and was also reported by the subjects, who were given thorough instructions of the dosing procedures prior to dosing on Day 1 in both treatment periods, including the procedures for observer and subject assessments of disintegration. Subjects were to report any premature swallowing.

15 The sublingual space and the tablet were examined to determine the time to disintegration. The tablet residues were characterised as 'intact', 'fragments', 'paste like residue' or 'dissolved'. Inspections were carried out every 2 minutes and the findings recorded until the tablet was completely disintegrated. In addition, the subject was instructed to indicate when they thought the IMP was dissolved by raising their hand or to indicate whether they had swallowed the tablet before it was dissolved. The time of dissolution or swallowing was recorded.

25 Median time to non-intact tablets was 2 minutes for the formulation of the invention and was 8 minutes for Suboxone.

Summary and Conclusions

30 The above-reported parameter ratios suggest that the formulation of the invention resulted in slightly higher plasma buprenorphine and naloxone concentrations and slightly lower plasma norbuprenorphine concentrations than the comparator. The former result is despite the initial dose being lower which indicates that it may be possible to reduce dose still further. Tablets comprising formulations of the invention also disintegrated faster than the comparator.

Example 3

Buprenorphine/Naloxone Sublingual Tablets II

- 5 3.97 g of micronized naloxone hydrochloride was mixed together with microcrystalline cellulose (20.00 g; Avicel™ PH102 (mean particle size 100 µm), FMC Biopolymer) and croscarmellose sodium (7.20 g; AcDiSol™, FMC Biopolymer) in a tumble blender (Turbula, WAG, Switzerland) for 40 hours.
- 10 14.04 g of micronised buprenorphine hydrochloride was mixed together with mannitol (130.30 g; Pearlitol™ 200SD, Roquette, Lestrem, France), sieved citric acid (6.00 g; fine granular 16/40 grade, DSM, Switzerland, Basel) and sieved (to avoid agglomeration), sodium citrate (19.50 g) Emprove™ cryst., Merck, Darmstadt, Germany) and blended in a tumble blender for 42 hours.
- 15 Menthol (2.00 g; Emprove™ cryst., Merck KGaA, Darmstadt, Germany) was mortared until a fine powder was formed and was blended with silicon dioxide, colloidal (0.20 g; Aerosil™ 200 Pharma), (1:1 volume ratio).
- 20 Sucralose (6.00 g, Merck KGaA, Darmstadt, Germany) was added to the buprenorphine premix. The naloxone premix and the rest of the silicon dioxide colloidal (2.80 g) were added by co-sieving into the buprenorphine premix. The menthol-silicon dioxide blend was added by sieving to the buprenorphine premix and all ingredients were mixed for 1 hour.
- 25 Sodium stearyl fumarate (8.00 g; Pruv™, JRS Pharma, Polanco, Spain) was then added by sieving into this mixture and mixing continued in the tumble blender for 10 minutes.
- 30 The final powder mixture was then compressed into tablets in a tablet machine (Korsch EK0) equipped with 7 mm round, flat faced, radius-edged punches, to a tablet weight of 110 mg and a tablet crushing strength of 30-35 N.

35

Example 4

In Vivo Experiment

Placebo tablets prepared according to the procedure described in Example 1
5 above (excluding buprenorphine, but including naloxone) were first administered
sublingually.

Sublingual saliva pH was measured *in vivo* using a Schott CG 842P pH Meter
attached to a Schott Flatrode™-electrode (pH 0-14, 0-60°C). The Flatrode™ has
10 a super-flat membrane for surface measurements and a robust plastic shaft with
a ring diaphragm, which guarantees a quick response *via* enhanced contact
between the sample and reference. The diameter of the flat surface of the
electrode is 6.0 mm giving a measuring surface of 0.28 cm².

15 The Flatrode was positioned (at an open mouth angle of 45°) gently behind the
lower teeth, just beside the tablet in the mouth. A very gentle pressure was
applied in order to measure pH in saliva rather than venous blood pH (typically
pH 7.4).

20 pH was measured at time intervals of 0, 30, 60 and 90 seconds (over 5 seconds
until a stable value was observed). Care was taken to avoid accidental
withdrawal of dissolved powder by the electrode. The mouth was shut between
measurements with no active swallowing.

25 Triplicate runs were carried out to ensure a reliable pH-profile. Between runs, the
mouth was washed thoroughly with water and pH measured prior to
administration to obtain a new zero-value.

The results indicated that the pH decrease peaked at around 35-40 seconds. It
30 can be seen from Figure 4 that the body rapidly compensates for the modified pH
and also slightly overcompensates, and that the window of opportunity (i.e. the
time range with a 0.5 pH unit decrease compared to resting pH) for increased
solubility of buprenorphine is only about 80 seconds, starting after 10 seconds
(n=4).

35

155

Example 5

Comparative *In Vitro* Experiment

In addition to the sublingual tablets described in Example 3 above, two other
5 otherwise identical batches of sublingual tablets were prepared using the same
methodology, except that, in one case, the buprenorphine hydrochloride was not
micronized, and in the other, no citric acid and sodium citrate were included
(instead a further 12.75 mg per tablet of mannitol was included).

10 Tablets from the three above-mentioned tablet batches, as well as Suboxone
tablets (buprenorphine 8 mg/naloxone 2 mg; Reckitt Benckiser Healthcare Ltd,
Hull, UK) were placed on top of a Porosity 1 20 mm diameter silica filter in a 55
mm (upper inner diameter) glass funnel.

15 Potassium phosphate buffer with a pH of 6.8 (USP/NF), which mimics saliva, was
allowed to drip through a soft PVC plastic tube with an inner diameter of 3 mm
onto the tablets at a rate, set by a peristaltic pump (Flocon 1003), of 2 mL per
minute. The distance between the end of the plastic tube and the silica filter in
the funnel was set at approximately 7.5 cm, in order, along with the dripping rate,
20 to correspond to a force similar to the pressure of the underside of the tongue.
The small amounts of water involved endeavour to mimic the low amounts of
water available *in vivo* under the human tongue.

pH was measured over time using a Mettler Toledo InLab Expert Pro electrode
25 (pH 0-14; 0-100°C) attached to standard Mettler Toledo 340 pH meter positioned
at the outlet of the glass funnel.

To measure the release of active pharmaceutical ingredients over time from the
tablets, a glass beaker equipped with a magnetic stirrer containing 490 mL of
30 potassium phosphate buffer pH 6.8 (USP/NF) collected the drops from the funnel.

800 μ L samples were withdrawn from the beaker using a calibrated micropipette
at intervals of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 10.0, 15.0 and 20.0
minutes. These samples were emptied into 1 mL vials already containing 200 μ L
35 of diluted phosphoric acid. No additional buffer was added to the collection

beaker to compensate. It started with a volume of 490 mL and ended with a volume of 520 mL (the difference between 40 mL added to the beaker over 20 minutes, and 10.4 mL removed in total (13 x 0.8 mL) is 29.6 mL (i.e. about 30 mL)). It was decided to start at 490 mL instead of 485 mL to be as close to 500 mL for as long a period as possible. The exact individual volumes were of course calculated for each sample.

Three tablets from each of the four tablet table batches in the trial were analysed as release test samples. Amounts of buprenorphine and naloxone were measured using HPLC (Agilent 1000; Diode array-detector, gradient pump, autosampler, column oven), with a gradient method with UV detection at 210 nm.

pH was plotted over time for the following four tablet batches and the the results are shown in Figure 5 (tablets prepared according to Example 3 (squares); non-micronised buprenorphine equivalents (crosses); equivalents without citric acid/sodium citrate (diamonds); and Suboxone (triangles)). The dashed line in Figure 5 is the superimposed *in vivo* profile from Figure 4.

The drug release profiles over the first 5 minutes for buprenorphine and naloxone are presented in Figures 6, and 7, respectively. Although Suboxone has a 23% higher drug loading than all of the other tablets, it produces a buprenorphine release after 20 minutes through the funnel of only 75% of that of the tablets according to the invention. The difference is most noticeable over the first 5 minutes.

Example 6

Buprenorphine/Naloxone Sublingual Tablets III

336.0 g of micronized naloxone hydrochloride was mixed together with microcrystalline cellulose (2000.0 g; Avicel™ PH102 (mean particle size 100 µm), FMC Biopolymer, Wallington, Little Island, Co. Cork, Ireland) and croscarmellose sodium (720.0 g; AcDiSol™, FMC Biopolymer, Wallington, Little Island, Co. Cork, Ireland) in a 12 L double cone blender (Sewin, Zickert systems, Kungsbacka, Sweden) for 3 hours.

157

Citric acid (600.0 g; fine granular 16/40 grade, DSM, Switzerland, Basel), sodium citrate (1950.0 g Emprove™ cryst., Merck, Darmstadt, Germany) and silicon dioxide, colloidal (480.0 g Aerosil™ 200 Pharma, Evonik Degussa GmbH, Rheinfelden, Germany) were deagglomerated together with Quadro comil
5 apparatus (Quadro Engineering, Ontario, Canada) and premixed with two thirds of a pre-measured amount of mannitol (8737.3 g; Pearlitol™ 200SD, Roquette, Lestrem, France) in a 60 L double cone blender (Sewin, Zickert systems, Kungsbacka, Sweden) for 5 minutes.

10 1188.0 g of the micronised buprenorphine hydrochloride was added to the premix and the other third of the mannitol (4368.7 g) was added on top of the buprenorphine hydrochloride and all ingredients were mixed for 3 hours.

Menthol (200.0 g; Emprove™ cryst., Merck KGaA, Darmstadt, Germany) was
15 milled with Quadro comill. Silicon dioxide, colloidal (20.0 g) and milled menthol (1:1 volume ratio) was processed with Quadro comill in order to deagglomerate the silicon dioxide (colloidal).

Sucralose (600.0 g, Merck KGaA, Darmstadt, Germany), the naloxone premix
20 and the menthol-silicon dioxide blend were added to the buprenorphine premix and all ingredients were mixed for 1 hour.

Sodium stearyl fumarate (800.0 g; Pruv™, JRS Pharma, Polanco, Spain) was
25 deagglomerated with Quadro comil and added to double cone blender and mixed for 10 minutes.

The final powder mixture was then compressed into tablets in a tablet machine (Korsch XL100, Korsch AG, Berlin, Germany) equipped with 7 mm round, flat
30 faced, radius-edged punches, to a tablet weight of 110 mg and a tablet crushing strength of 30-35 N.

Claims

1. A pharmaceutical composition comprising microparticles of a pharmacologically-effective amount of buprenorphine, or a pharmaceutically-acceptable salt thereof, in associative admixture with particles comprising a weak acid, or particles comprising weakly-acidic buffer forming materials.
2. A composition as claimed in Claim 1, wherein the microparticles of buprenorphine have a weight based mean diameter of less than about 15 μm .
3. A composition as claimed in Claim 1 or Claim 2, wherein the weakly acidic material comprises citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, lactic acid, acetic acid, oxalic acid, maleic acid, ammonium chloride or a combination thereof.
4. A composition as claimed in Claim 1 or Claim 2, wherein the buffer forming materials comprise a combination of a weakly acidic material and a salt of a weakly acidic material.
5. A composition as claimed in Claim 4, wherein the weakly acidic material is as defined in Claim 3.
6. A composition as claimed in Claim 4 or Claim 5, wherein the salt is sodium citrate, potassium citrate, sodium tartrate or potassium tartrate.
7. A composition as claimed in any one of the preceding claims wherein the buffer system is citric acid/sodium citrate.
8. A composition as claimed in any one of the preceding claims which is presented as an interactive mixture comprising microparticles of buprenorphine or a pharmaceutically acceptable salt thereof presented upon the surfaces of carrier particles.
9. A composition as claimed in Claim 8, wherein the carrier particles are of a size that is between about 100 and about 800 μm .

10. A composition as claimed in Claim 8 or Claim 9, wherein the carrier particles are water-soluble.

5 11. A composition as claimed in any one of Claims 8 to 10, wherein the carrier particles comprise mannitol.

12. A composition as claimed in any one of Claims 8 to 11, wherein the particles of weak acid, or of weakly-acidic buffer forming materials, are presented and act
10 as carrier particles.

13. A pharmaceutical composition as claimed in any one of the preceding claims, which further comprises a disintegrant.

15 14. A composition as claimed in Claim 13, wherein the disintegrant is a superdisintegrant selected from croscarmellose sodium, sodium starch glycolate, crosslinked polyvinylpyrrolidone or a mixture thereof.

15. A pharmaceutical composition as claimed in any one of the preceding
20 claims, which further comprises a pharmacologically-effective amount of naloxone, or a pharmaceutically-acceptable salt thereof.

16. A pharmaceutical composition as claimed in Claim 15, wherein the
25 composition comprises particles comprising naloxone or salt thereof and disintegrant.

17. A composition as claimed in any one of the preceding claims which is in the form of a tablet suitable for sublingual administration.

30 18. A process for the preparation of a composition as defined in any one of Claims 8 to 17, which comprises dry mixing carrier particles with buprenorphine or salt thereof.

19. A process for the preparation of a composition as defined in any one of Claims 15 to 17, which comprises a process as claimed in Claim 18, followed by admixing with particles comprising naloxone or salt thereof and disintegrant.

5 20. A process for the preparation of a sublingual tablet as defined in Claim 17, which comprises directly compressing or compacting a composition as defined in any one of Claims 1 to 16.

10 21. A method of treating opioid dependency and/or addiction in a human, which method comprises sublingual administration of a pharmaceutical composition comprising buprenorphine or a pharmaceutically acceptable salt thereof, at a dose of 0.5 to 50 mg, in combination with naloxone or a pharmaceutically acceptable salt thereof, in about a 4:1 (buprenorphine:naloxone) dose ratio, to a human patient suffering from opioid dependency and/or addiction, wherein said
15 formulation achieves after an initial dose in any given treatment program a ratio of norbuprenorphine/buprenorphine concentrations in plasma of less than about 1.0 based upon the total AUC (area under the plasma concentration-time curve from time zero to the time of the last quantifiable plasma concentration).

20 22. A method as claimed in Claim 21 which comprises administration of a composition as defined in any one of Claims 1 to 17.

23. A method of treatment of opioid dependency and/or addiction, and/or pain, which method comprises administration of a composition as defined in any one of
25 Claims 1 to 17 to a person suffering from, or susceptible to, the relevant condition(s).

24. A composition as defined in any one of Claims 1 to 17 for use in a method of treatment of opioid dependency and/or addiction, and/or pain.

30

25. The use of a composition as defined in any one of Claims 1 to 17 for the manufacture of a medicament for a method of treatment of opioid dependency and/or addiction, and/or pain.

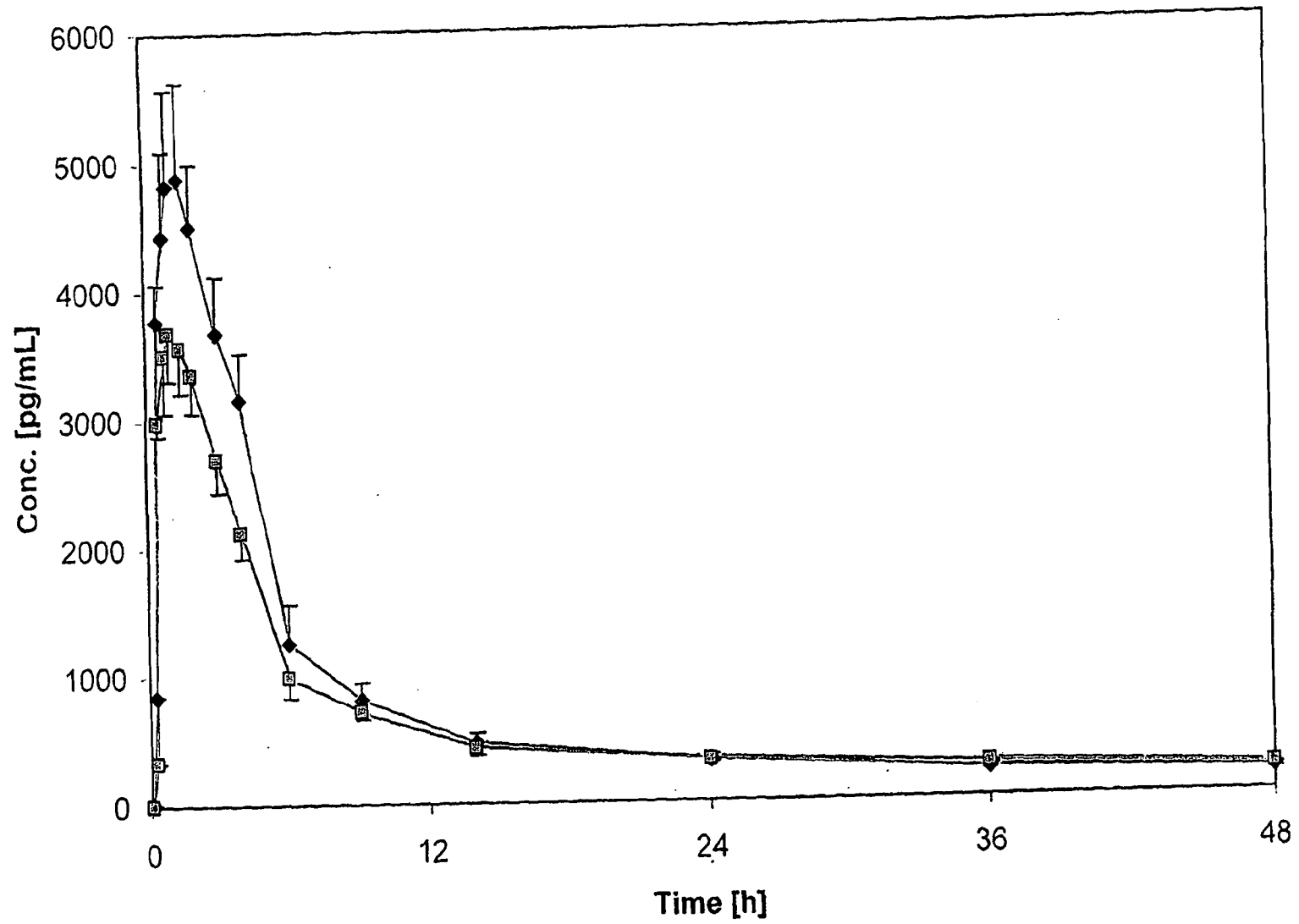
161
1

ABSTRACT

There is provided pharmaceutical compositions for the treatment of e.g. opioid dependency comprising microparticles of a pharmacologically-effective amount of buprenorphine, or a pharmaceutically-acceptable salt thereof, in associative admixture with particles comprising a weak acid, or particles comprising weakly-acidic buffer forming materials. The composition may further comprise a disintegrant and/or particles of a pharmacologically-effective amount of naloxone, or a pharmaceutically-acceptable salt thereof. The compositions are useful in the treatment of opioid dependency/addiction and/or pain.

162

FIGURE 1

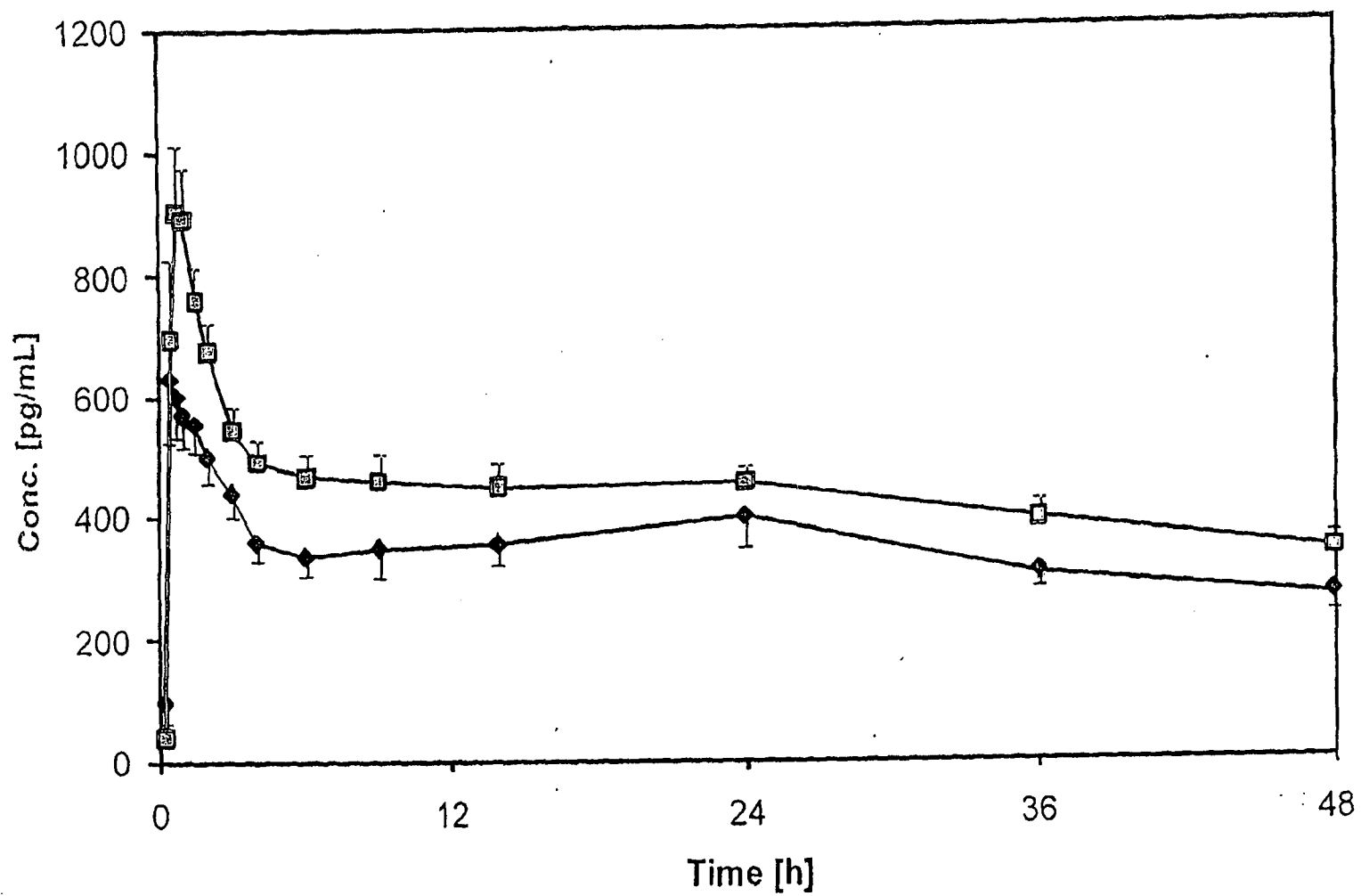


1/5

162

163

FIGURE 2

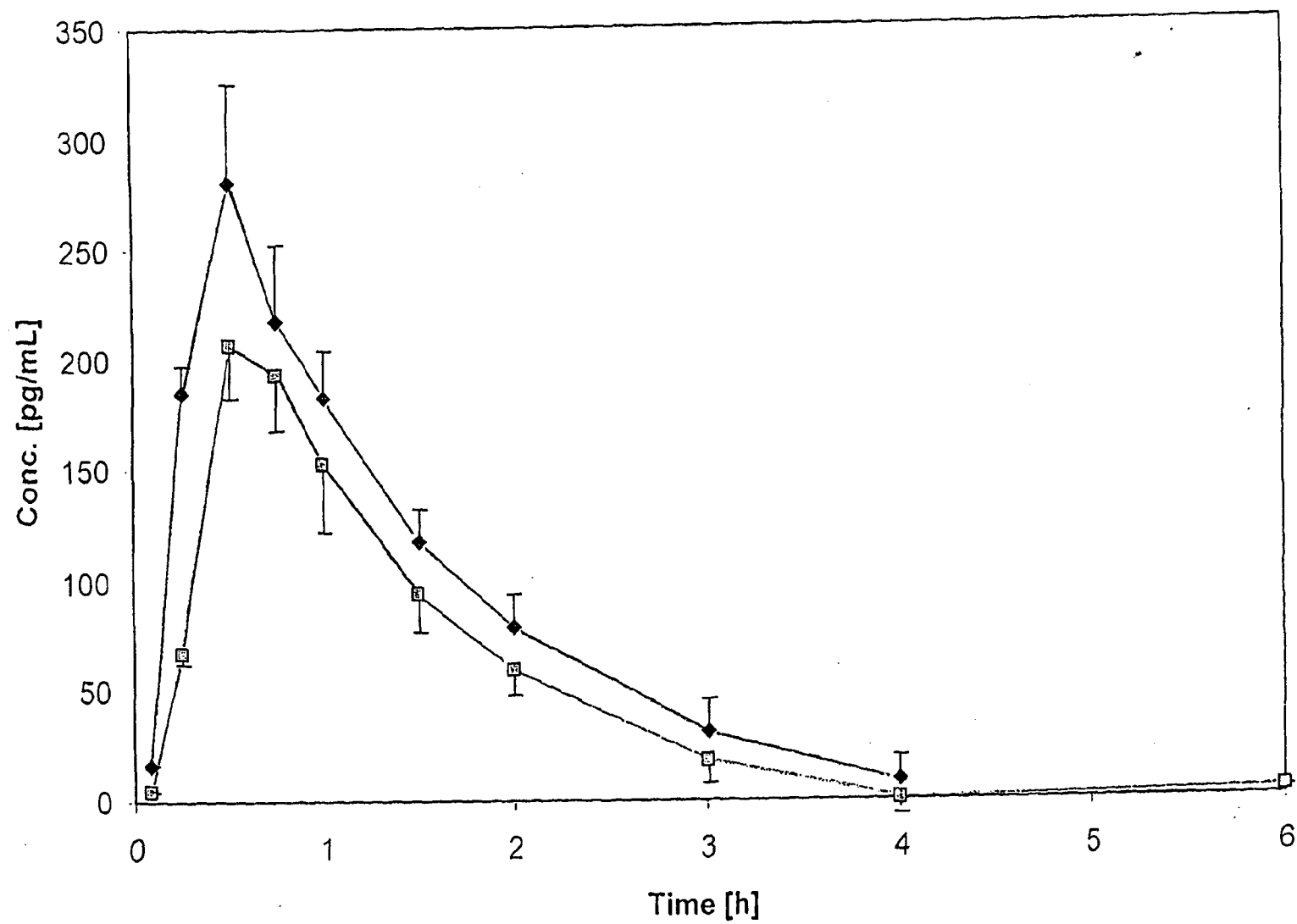


2/5

163

164

FIGURE 3



3/5

164

4/5

Figure 4

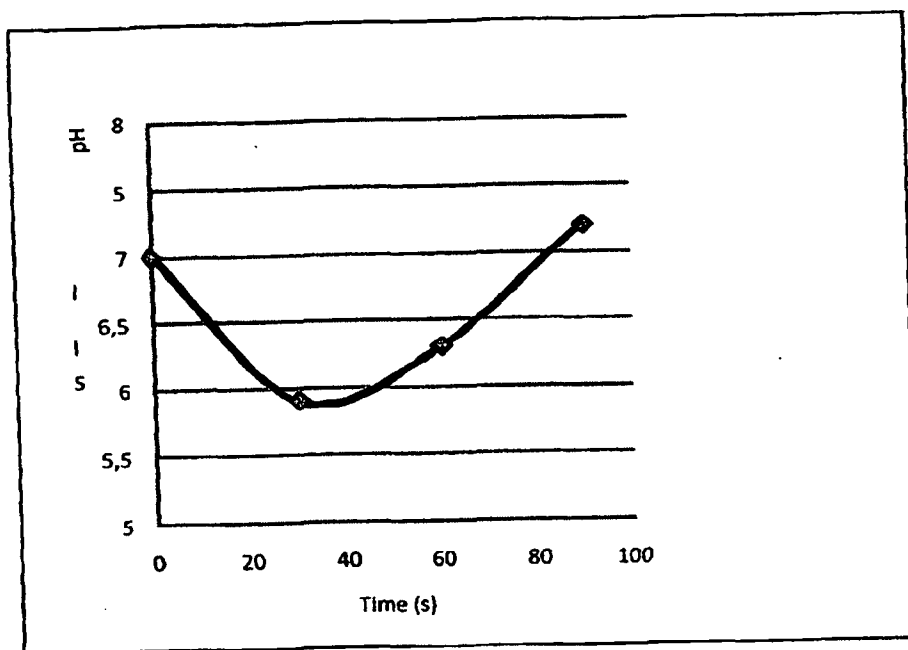
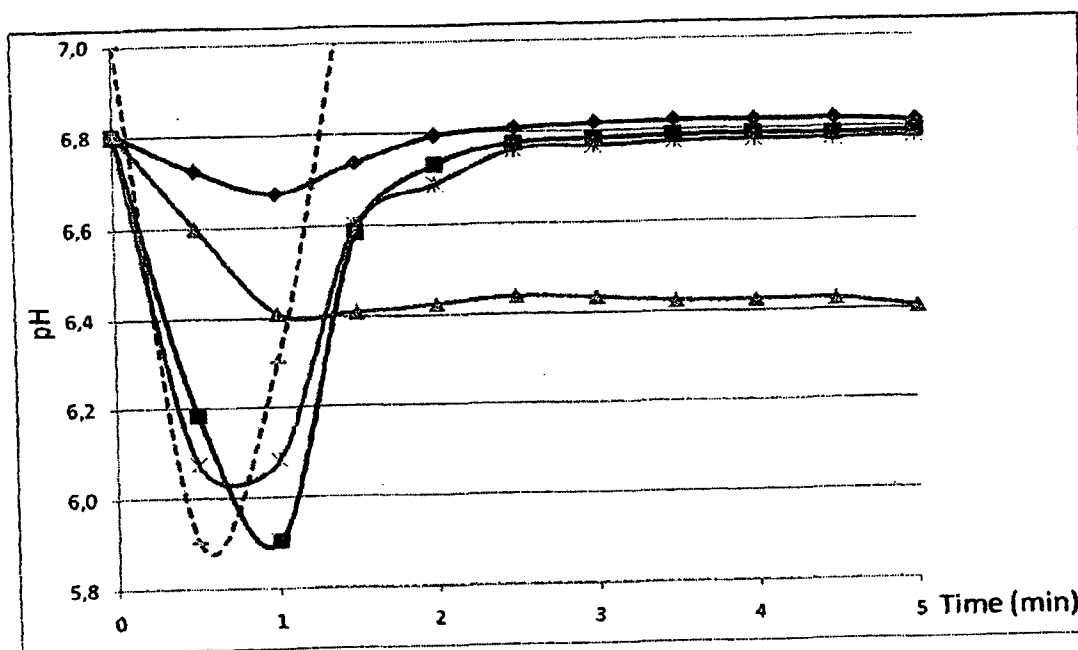


Figure 5



5/5

Figure 6

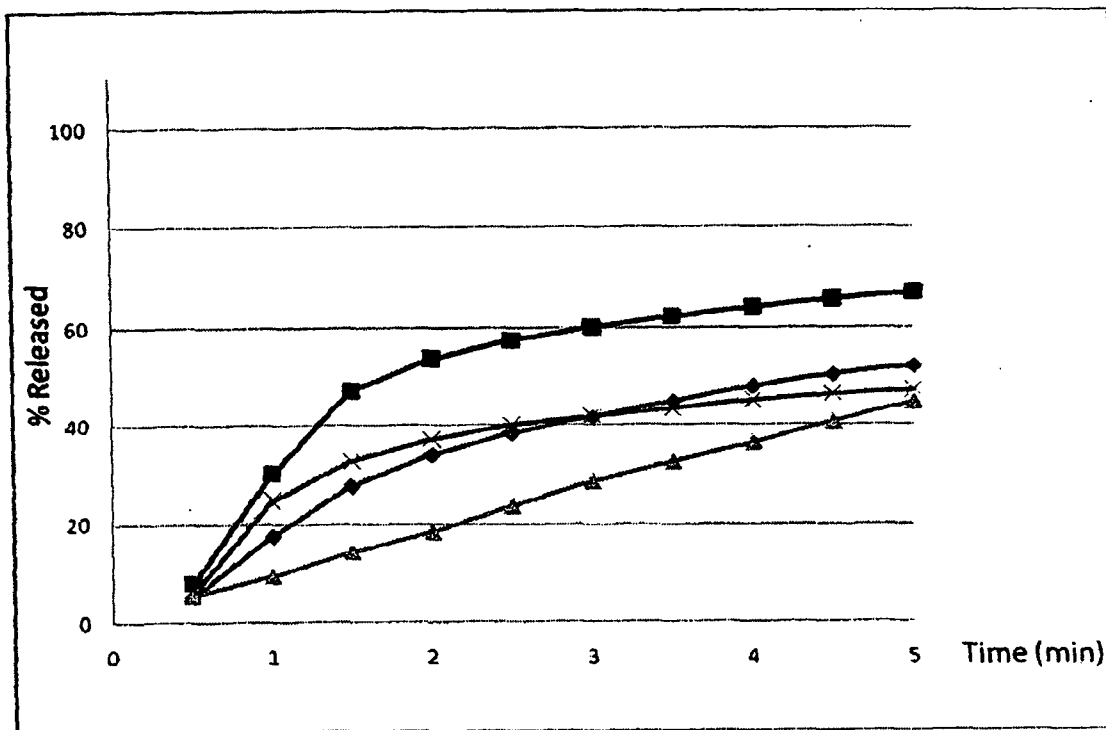
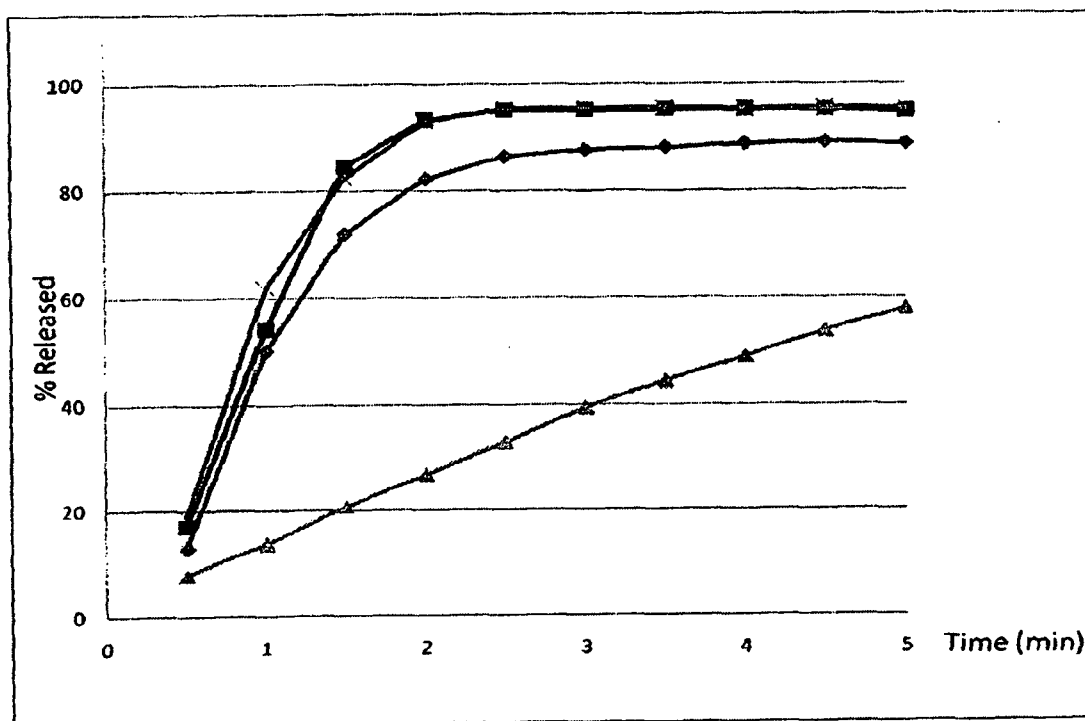


Figure 7



From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION,
OBTENTION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

MCNEENEY, Stephen Phillip
Park View House
58 The Ropewalk
Nottingham
Nottinghamshire NG1 5DD
ROYAUME-UNI

Date of mailing (day/month/year) 08 October 2012 (08.10.2012)	
Applicant's or agent's file reference ORECZ/P51901PC	IMPORTANT NOTIFICATION
International application No. PCT/GB2012/052303	International filing date (day/month/year) 18 September 2012 (18.09.2012)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 19 September 2011 (19.09.2011)
Applicant OREXO AB et al	

The applicant is hereby notified of the date of receipt (or of obtaining by the International Bureau) of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to the date of receipt, **the priority document concerned was submitted or transmitted to or obtained by the International Bureau in compliance with Rule 17.1(a), (b) or (b-bis)**. This Form replaces any previously issued notification concerning submission, transmittal or obtaining of priority documents.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
19 September 2011 (19.09.2011)	61/536,180	US	03 October 2012 (03.10.2012)

The letters "NR" denote a priority document which, on the date of mailing of this Form, had not yet been received or obtained by the International Bureau in compliance with Rule 17.1(a), (b) or (b-bis). Where the applicant has failed to either submit, request to prepare and transmit, or to request the International Bureau to obtain the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

An asterisk "*" next to a date of receipt, denotes a priority document submitted or transmitted to or obtained by the International Bureau but not in compliance with Rule 17.1(a), (b) or (b-bis) (the priority document was received after the time limit prescribed in Rule 17.1(a); the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b) or the request to the International Bureau to obtain the priority document was made after the applicable time limit under Rule 17.1(b-bis)). Even though the priority document was not furnished in compliance with Rule 17.1(a), (b) or (b-bis), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Birchen Mireille e-mail pt04.pct@wipo.int Telephone No. +41 22 338 74 04
Facsimile No. +41 22 338 89 95	

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

-/-

**Industria y Comercio**
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0022691

Bogotá D.C., Febrero 27 de 2014 - 14:32:34

RECIBIDO DE : POSSE HERRERA & RUIZ S.A.

NI 830.022.196

RE

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
RECIBO DE CA	999999999	17322	13/02/2014		1.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	529733525	27/02/2014	8.409.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	650524206	27/02/2014	3.390.000.00

*** Conceptos Pagados ***

CANT. RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCIÓN	515.000.00	515.000.00
			<u>\$515.000.00</u>

SON: **QUINIENTOSQUINCE MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

**No. 14-045641- -00000-0000**Fecha: 2014-03-04 14:29:05
Tra. 11 PATENTEIYII
Act. 411 PRESENTACIONDep. 2020 DIR.NUEVASCR
Eve: 379 FASENACIONALII
Folios: 169

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

, Febrero 27 de 2014 - 14:32:38

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -



Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0024301

Bogotá D.C., Marzo 04 de 2014 - 14:11:47

RECIBIDO DE : POSSE HERRERA & RUIZ S.A.

NI 830.022.196

RE

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
RECIBO DE CA	999999999	18336	17/02/2014		335.000.00
RECIBO DE CA	999999999	18337	17/02/2014		335.000.00

*** Conceptos Pagados ***

CANT. RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
13 50005-01-01 SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INIC	31.000.00	403.000.00
			<u>\$403.000.00</u>

SON: **CUATROCIENTOS TRES MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 14-045641- -00000-0000

Fecha: 2014-03-04 14:29:05
Tra. 11 PATENTE Y II
Act. 411 PRESENTACION

Dep. 2020 DIR. NUEVAS CR
Eve: 379 FASE NACIONAL II
Folios: 169

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: Info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

, Marzo 4 de 2014 - 14:11:49

170

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 14-045641- -00000-0000

Fecha: 2014-03-04 14:29:05 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 129

SOLICITUD (

1. INFORMACIÓN DEL SOLICITANTE

Solicitante(*): _____

Tipo de identificación(*): NIT ☐ Cédula ☐ CE ☐ Otro Cual? _____

Número: (*) _____

Dirección Correspondencia(*): _____ Teléfono _____

País(*): _____ Región / Dpto(*) _____ Ciudad(*) _____

Dirección de correo Electrónico: _____ Fax _____

Es importante que escriba correctamente los datos solicitados, para que su petición sea atendida oportuna y correctamente. Los campos marcados con asterisco (*) son de carácter obligatorio

Debe adjuntar a esta solicitud comprobante de pago correspondiente a la tasa de certificación vigente.

2. TIPO Y DESCRIPCIÓN CERTIFICACIÓN

2.1 Representación legal Cámara de Comercio:

Cámara de Comercio: _____

Nombre de la Sociedad: _____

2.2 Existencia y representación legal de la Cámara de Comercio

Cámara de Comercio: _____

2.3. Inscripción en el registro nacional de evaluadores

Nombre evaluador: _____

Documento de identificación: _____

2.4. Ejecutoria de Actos Administrativos

Acto administrativo No. _____ Expediente No. _____

2.5. Sanciones e investigaciones en curso en la SIC

Nombre (persona natural o jurídica): _____

Tipo de documento: NIT ☐ CC ☐ Número: _____