



Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 12-039899-00000-0000

Fecha: 2012-03-07 14:02:29

Tra. 11 PATENTE IYII

Act. 411 PRESENTACION

Dep. 2020 DIR. NUEVAS CR

Eve: 378 FASE NACIONAL I

Folios: 135

Act. 411 PRESENTACION

Folios: 134

DELEGATURA PROPIEDAD INDUSTRIAL

950

SOLICITUD DE PATENTE DE INVENCION
PCT

EXPEDIENTE No _____

TITULO COMPOSICIONES DE PELÍCULA
SUBLINGUALES Y BUCALES

CLASIFICACION INTERNACIONAL _____

SOLICITANTE RECKITT BENCKISER
HEALTHCARE (UK) LIMITED

DOMICILIO Reino Unido

APODERADO LUZ HELENA ADARVE GOMEZ

BOGOTA D.C. _____

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

①

SOLICITUD DE:

☒ X

Patente de Invención

☐

Patente de Modelo de Utilidad

☒ X

Capítulo I

☐

Capítulo II

②

SOLICITANTE
(71)

Nombre: **Reckitt Benckiser Healthcare (UK) Limited**

Dirección: 103-105 Bath Road Slough, Berkshire SL 1
3UH, Reino Unido

Nacionalidad o Domicilio: REINO UNIDO

Lugar de Constitución: REINO UNIDO

Teléfono: 3123600 Fax: 3122410

E-mail: general@cardenasycardenas.com

IDENTIFICACION

C.C. ☐

NIT ☐

C.E. ☐

Otro ☒ X

Cual _____

Número _____

③

REPRESENTANTE
O APODERADO

Nombre: **LUZ HELENA ADARVE GOMEZ**

Dirección: Carrera 7 No 71-52 Torre B Piso 9

Teléfono: 3123600 Fax: 3122410

E-Mail: general@cardenasycardenas.com

IDENTIFICACION

C.C. ☒ X

NIT ☐

C.E. ☐

Otro ☐

Número 41575435 BTA
Cual TP 14884

④

INVENTOR(ES)
(72)

Nombre: VER ANEXO

Dirección: VER ANEXO

Nacionalidad o Domicilio: VER ANEXO

⑤ PCT (86)

Solicitud Internacional No. PCT/US2010/044488 Fecha 05.08.2010

Publicación Internacional No. WO 2011/017483 A3 Fecha 10.02.2011

⑥

Título(54):

COMPOSICIONES DE PELÍCULA SUBLINGUALES Y BUCALES

⑦

Clasificación Internacional (51):

⑧

Prioridad

SI ☒ X NO ☐

(33)País de Origen

US

(32)Fecha

07.08.2009

(31)N° de Solicitud

12/537,571

⑨

Comprobante de Pago No.: 12-0020671

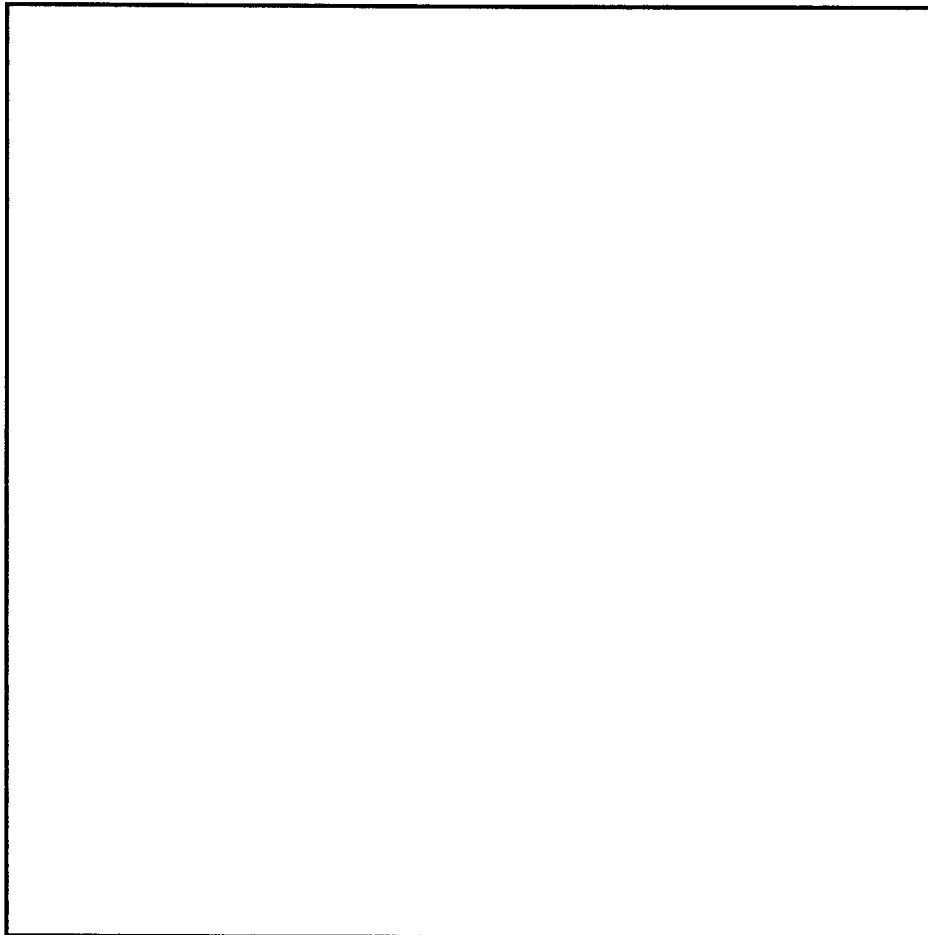
Fecha 28.02.2012

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Prioridad
<http://www.wipo.int/patentscope/search/en/detail.jsf.jsessionid=8F849988F4C991F3258A1628BF2ABA09.wapp2?docId=WO2011017483&recNum=1&tab=PCTDocuments&maxRec=&office=&prevFilter=&sortOption=&queryString=>

11 FIGURA CARACTERISTICA



12

Solicito la Concesión de la patente,

NOMBRE: LUZ HELENA ADARVE GOMEZ

FIRMA:

C.C. 41.575.435 BTA TP. 14.884
C.s.j.

④ INVENTOR(ES) (72)	Nombre: 1. Garry L. Myers 2. Samuel D. Hilbert 3. Bill J. Boone 4. Arlie B. Bogue 5. Pradeep Sanghvi 6. Madhusudan Hariharan Dirección: 1. 908 Colfax Avenue, Kingsport, TN 37660, Estados Unidos de América 2. 210 Mulberry Lane , Jonesboro, TN 37659, Estados Unidos de América 3. 900 Carroll Creek Road, Johnson City, TN 37601, Estados Unidos de América 4. 5306 N. Fox Hollow , New Castle, IN 46552, Estados Unidos de América 5. 7409 Bell Street, Schererville, IN 46375, Estados Unidos de América 6. 1746 Redwood Court, Munster, IN 46321, Estados Unidos de América Nacionalidad o Domicilio: 1. Estados Unidos de América 2. Estados Unidos de América 3. Estados Unidos de América 4. Estados Unidos de América 5. Estados Unidos de América 6. Estados Unidos de América
--	---



Industria y Comercio

SUPERINTENDENCIA

(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional :

(71)Solicitante(s) RECKITT BENCKISER HEALTHCARE (UK) LIMITED

(72) Inventor(es)

- 1. Garry L. Myers
- 2. Samuel D. Hilbert
- 3. Bill J. Boone
- 4. Arlie B. Bogue
- 5. Pradeep Sanghvi
- 6. Madhusudan Hariharan

(74) Apoderado: LUZ HELENA ADARVE GOMEZ

(30) Prioridad	(31) No. Prioridad	32) Fecha	(33) País
	12/537,571	07.08.2009	US

(85) Fecha inicio fase nacional: 07.03.2012

(86) Datos relativos a la presentación de la solicitud PCT

Fecha de presentación de la solicitud: 05.08.2010

No. de solicitud PCT/US2010/044488

(54) Titulo COMPOSICIONES DE PELÍCULA SUBLINGUALES Y BUCALES

17

(21) N° de solicitud:		(22) Fecha de solicitud:	
(51) Clasificación Internacional :			
(71) Solicitante(s) RECKITT BENCKISER HEALTHCARE (UK) LIMITED			
(72) Inventor(es) 1. Garry L. Myers 2. Samuel D. Hilbert 3. Bill J. Boone 4. Arlie B. Bogue 5. Pradeep Sanghvi 6. Madhusudan Hariharan			
(74) Apoderado: LUZ HELENA ADARVE GOMEZ			
(30) Prioridad	(31) No. Prioridad 12/537,571	32) Fecha 07.08.2009	(33) País US
(85) Fecha límite inicio fase nacional: 07.03.2012		(87) Publicación internacional:	
(86) Datos relativos a la presentación de la solíc. PCT Fecha de presentación de la solicitud: 05.08.2010 No. de solicitud PCT/US2010/044488		Fecha: 10.02.2011 No. Publicación WO 2011/017483 A3	

(54) Título: **COMPOSICIONES DE PELÍCULA SUBLINGUALES Y BUCALES**

(57) Resumen:

La presente invención se refiere a productos y métodos para el tratamiento de la dependencia de narcóticos en un usuario. La invención se refiere más particularmente a formas de dosificación autosoportadas que proporcionan un agente activo para tratar la dependencia de narcóticos a la vez que se proporciona una adhesión bucal suficiente de la forma de dosificación.

5

(21) N° de solicitud:		(51) Int Cl:	
22) Fecha de solicitud:		(71) Solicitante(s) RECKITT BENCKISER HEALTHCARE (UK) LIMITED	
(30) Prioridad	(31) No. Prioridad 12/537,571	(32) Fecha 07.08.2009	(33) País US
		(72) Inventor(es) 1. Garry L. Myers 2. Samuel D. Hilbert 3. Bill J. Boone 4. Arlie B. Bogue 5. Pradeep Sanghvi 6. Madhusudan Hariharan	
		(74) Apoderado: LUZ HELENA ADARVE GOMEZ	
(85)	Fecha limite inicio fase nacional: 07.03.2012		(87) Publicación internacional
(86)	Datos relativos a la presentación de la solicitud PCT		Fecha 10.02.2011
	Fecha de presentación de la solicitud: 05.08.2010		N° publicación: WO 2011/017483 A3
	No. de solicitud PCT/US2010/044488		
(54) Título: COMPOSICIONES DE PELÍCULA SUBLINGUALES Y BUCALES			

Resumen:

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John Venn & Sons

Scrivener Notaries
Translators

William B Kennan LL.B. • Jessica M Reeve M.A.

Associates: Agnes Corless • Jonathan P Coutts M.A., M.L.

Consultants: Keith F C Baker LL.B., F.I.L. • Bridget M Ellison B.A.

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United Kingdom

Telephone: 020 7395 4300

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011855

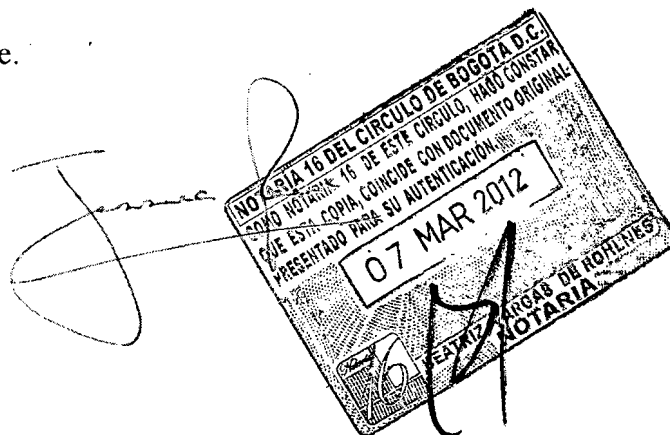
I, JESSICA MARGARET REEVE, a duly admitted Notary Public,
having jurisdiction throughout England and Wales and practising in London,
England, hereby certify:

1. THAT the Power of Attorney annexed hereto was signed for and
on behalf of **RECKITT BENCKISER HEALTHCARE (UK) LIMITED** by
PAUL JAMES WILSON, Secretary of the said Company;

2. THAT the said Company is duly incorporated and existing under
English Law, having its Registered Office at 103-105 Bath Road, Slough,
Berkshire SL1 3UH, England;

3. AND THAT the said Power of Attorney, being so signed, is duly
executed on behalf of and binding on the said Company.

IN WITNESS whereof I have issued this Certificate under my
signature and Seal of Office at London, aforesaid, the twenty-sixth day of
November Two thousand and one.



4x

APOSTILLE

(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by **J M Reeve**
a été signé par
3. Acting in the capacity of **Notary Public**
agissant en qualité de
4. Bears the seal/stamp of **The Said Notary Public**
est revêtu du sceau/timbre de

Certified/Attesté

5. at London/Londres

6. the/le **27 November 2001**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No

G961778

9. Stamp:
timbre:

10. Signature: **J. M. A. Mason**



2002/187

mbia

POWER OF ATTORNEY

the city of _____, in the state _____, on the _____ day of the month of _____, two thousand and _____ (200_), before me, _____, Notary Public, appeared _____ of age, and domiciled at _____ and stated:

FIRST: That he/she acts in his/her capacity of COMPANY SECRETARY of RECKITT BENCKISER HEALTHCARE (UK) LIMITED a company under the laws of ENGLAND and domiciled at 103-105 BATH ROAD SLOUGH BERKSHIRE UNITED KINGDOM, as evidenced in by the laws, documents which I have examined.

SECOND: That in such capacity he/she grants hereby special, ample and sufficient Power of Attorney to **DARIO CÁRDENAS NAVAS**, and/or **EDUARDO CÁRDENAS CABALLERO**, and/or **BERNADO P. CÁRDENAS MARTINEZ** and/or **LUZ HELENA ADARVE GÓMEZ** and/or **JUANITA ACOSTA GÓMEZ ANA** and/or **MARÍA RUIZ RUEDA** registered lawyers of the firm **CÁRDENAS & CÁRDENAS LAWYERS INTELLECTUAL PROPERTY LTD.**, domiciled at Carrera 7 No. 71-52, Torre B, Piso 9 Santafé de Bogotá, D.C. Colombia, to carry before the corresponding Colombian national offices and authorities the proceedings to obtain patent, industrial models and designs and trademark registrations, as well as proceedings of renewals, assignments, change of name or domicile of the owner, waivers and licenses of the same for which purpose they are empowered to take before said authorities all necessary actions for the indicated purposes; to file applications, statements, claims, withdrawals, formulate descriptions, amendments, oppositions, appeals and cancellation actions; pay all taxes and installments and make any other payments determined by law; to receive every document and values issuing the respective discharge; to fulfill any other requirements and take, in general, every measure that they shall deem opportune for the defense and protection of the trademarks of the company in the event of infringements, oppositions, proceedings for cancellation or annulment, imposition of fines, passing the antecedents to the courts; they are empowered to appear as plaintiff or defendant before the competent judges, being entitled to transact, submit to arbitration, waive, receive, resign, appeal and all other legal powers which may be necessary, and it is hereby declared ever since now valid and good whatever such attorneys do for its benefit, granting them also power to substitute this proxy and if necessary to revoke such substitutions.

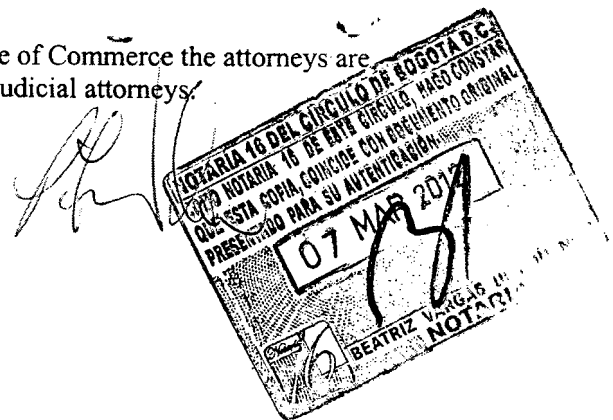
THIRD: That for purposes of articles 597 and 543 of the Colombian code of Commerce the attorneys are empowered to receive service of notice and designate judicial and extrajudicial attorneys.

SIGNED AT
ON
BY

SLOUGH ENGLAND
5 NOVEMBER 2001
P J WILSON

NOTARY PUBLIC

(APOSTILLE IS NECESSARY)



ADUCCION OFICIAL NO. 2002/187

traducción Oficial No. 2002/187 de un documento escrito en inglés el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Hilda Aguilera de Piedrahita, traductora oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y autorizada por el Ministerio de Justicia y del Derecho por Resolución No. 323 de 1980.

PODER

Colombia

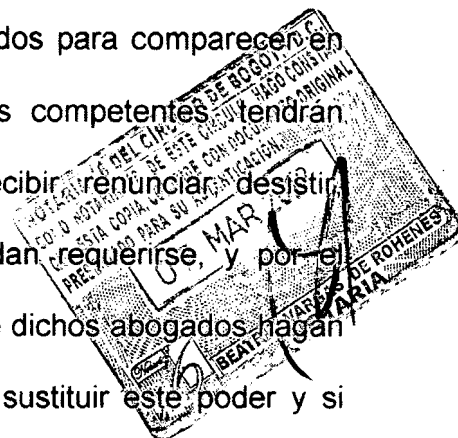
En la ciudad de _____, en el estado de _____ el día _____ del mes _____ del dos mil _____ (200_), ante mí, _____ Notario Público, compareció _____ mayor de edad, y con domicilio en _____ y manifestó:

PRIMERO: Que el obra en su calidad de Secretario de la Compañía de RECKITT BENCKISER HEALTHCARE (UK) LIMITED, una compañía bajo las leyes de Inglaterra y con domicilio en Berkshire, Reino Unido, como se evidencia en los Estatutos, documentos que he examinado.

SEGUNDO: que en tal calidad el otorga por el presente poder especial amplio y suficiente a **DARÍO CÁRDENAS-NAVAS y/o EDUARDO CÁRDENAS CABALLERO, y/o BERNARDO P. CARDENAS MARTINEZ y/o LUZ HELENA ADARVE GOMEZ y/o JUANITA ACOSTA GÓMEZ y/o ANA MARÍA RUIZ RUEDA**, abogados registrados de la firma **CÁRDENAS & CÁRDENAS ABOGADOS PROPIEDAD INTELECTUAL LTDA.**, domiciliada en la Carrera 7

TRADUCCIÓN OFICIAL No. 2002/187
HILDA AGUILERA DE PIEDRAHITA
INTERPRETE OFICIAL
RES No. 323 DEL MIN. DE JUSTICIA

No. 71-52, Torre B, Piso 9, Bogotá D.C., Colombia, para llevar a cabo ante las correspondientes Oficinas Nacionales Colombianas y autoridades los trámites para obtener patentes, modelos industriales y diseños y registros de marcas, así como trámites para renovaciones, traspasos, cambios de nombre o domicilio del propietario, renunciaciones y licencias de los mismos para cuyo fin están facultados para realizar ante dichas autoridades todas las acciones necesarias para los fines indicados; para presentar solicitudes, declaraciones, reivindicaciones, desistimientos, formular descripciones, modificaciones, oposiciones, y apelaciones y acciones de cancelación; pagar todos los impuestos y derechos y hacer cualesquiera otros pagos que la ley determine; recibir todos los documentos y valores con expedición del respectivo descargo; cumplir cualesquiera otros requisitos y tomar en general todas las medidas que juzguen oportunas para la defensa y protección de las marcas de la compañía en el evento de infracciones, oposiciones, procesos de cancelación o anulación, imposición de multas, presentar antecedentes ante las cortes; quedan facultados para comparecer en calidad de demandante o demandado ante los jueces competentes, tendrán derecho de transar, someterse a arbitraje, renunciar, recibir, renunciar, desistir, apelar y todas las demás facultades legales que puedan requerirse, y por el presente declara desde ahora válido y satisfactorio lo que dichos abogados hagan en nuestro beneficio, otorgándoles también poder para sustituir este poder y si fuere necesario para revocar tales sustituciones.



TRADUCCION OFICIAL No. 2002/187
NILDA AGUIRRE DE PIEDRAALTA
INTERPRETE OFICIAL
RES No. 323 DEL MIN. DE JUSTICIA

TERCERO: que para fines de los artículos 597 y 543 del Código Colombiano de Comercio, los abogados están facultados para recibir notificaciones y para designar apoderados judiciales y extrajudiciales.

FIRMADO EN: Slough, Inglaterra

EL: 5 de Noviembre de 2001.

POR: J WILSON

(Firmado: Ilegible)

NOTARIO PUBLICO

(Se requiere Apostilla)

John Venn & Sons

Notarios Escribanos, Traductores

William B. Kennair LLB * Jessica M. Reeve M.A.

Asociados: Agnes Corless*Jonathan P. Coutts M.A. MIL

Consultores: Keith F.C. Baker LL.B, FIL*Bridget M. Ellison B.A.

95 Aldwych Londres WC2B 4JF

Reino Unido

Teléfono: 020 73954300

Fax: 020 7395 4310

e-mail: notary@johnvenn.co.uk

<http://www.johnvenn.co.uk>

Yo, JESSICA MARGARET REEVE, un Notario Público debidamente admitido, teniendo jurisdicción por toda Inglaterra y Gales y ejerciendo en Londres, Inglaterra, por el presente certifico:

EXEMPTION OFFICIAL No: 2002/187
APOSTILLA
REINO UNIDO

1. QUE el Poder que se adjunta a la presente fue suscrito por y en nombre de **RECKITT BENCKISER HEALTHCARE (UK) LIMITED** , por **PAUL JAMES WILSON**, Secretario de la dicha Compañía;
2. QUE la dicha Compañía está debidamente constituida y existe bajo la Ley Inglesa, teniendo su oficina registrada en 103-105 Bath Road, Slough, Berkshire SL1 3UH, Inglaterra.
3. Y QUE el dicho Poder, así firmado, está debidamente suscrito en nombre de y obligando a dicha Compañía.

EN TESTIMONIO de lo cual he expedido este Certificado bajo mi firma y Sello de la oficina en Londres, el veintiséis de Noviembre de Dos mil uno.

(Firmado: Ilegible)

(Sello en Relieve)

(Sello de Oblea)



APOSTILLA

(Convención de la Haya de Octubre 5 de 1961)

1. País: Reino Unido de la Gran Bretaña e Irlanda del Norte

RECEIVED... 2002/187
...
...
...
16

Este documento público

2. Ha sido firmado por JM Reeve
3. Actuando en calidad de Notario Público
4. Lleva el sello/estampilla de dicho Notario Público

CERTIFICADO

5. En Londres
6. Hoy 27 de Noviembre, 2001
7. Por El Secretario de Estado Principal de Su Majestad para Relaciones Exteriores y de la Mancomunidad
8. Número G961778
9. Sello (Sello Redondo en Relieve) (Sello Pre-impreso)
10. Firma (Firmado)
JMA Mason
Por el Secretario de Estado

ES TRADUCCIÓN FIEL Y COMPLETA de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito.

Bogotá, Octubre 15 de 2002.

[Firma]
TRADUCCION OFICIAL NO. 2002/187
MILDA AGUILERA DE PINOCHET
INTERPRETE OFICIAL
C.R.S. No. 323 DEL MIN. DE JUSTICIA

MINISTERIO DE
RELACIONES EXTERIORES

257946

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2007 OCT 16 P 12:10

JEFE DE LEGALIZACIONES
BOGOTÁ D.C.



REGISTRO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -

Industria y Comercio

SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0020671

Bogotá D.C., Febrero 28 de 2012 - 13:11:42

RECIBIDO DE : CARDENAS & CARDENAS ABOGADOS PI LTDA

NI 830.083.491

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	186848314	28/02/2012	5.380.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCIÓN	590.000.00	590.000.00
				\$590.000.00
			=====	

SON: QUINIENTOS NOVENTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 12-039899- -00000-0000

Fecha: 2012-03-07 14:02:29 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 135

Act. 411 PRESENTACION Folios: 134

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

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

Febrero 28 de 2012 - 13:11:51

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Excedente

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO NIT : 800.176.089-2 - / -					
 Industria y Comercio SUPERINTENDENCIA	RECIBO DE CAJA			No. 12 - 0023371	
				Bogotá D.C., Marzo 06 de 2012 - 11:06:05	
RECIBIDO DE : CARDENAS & CARDENAS ABOGADOS PI LTDA				NI 830.083.491	
*** Soporte del Pago ***					
TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	467325865	06/03/2012	11.986.000.00
*** Conceptos Pagados ***					
CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO	
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				\$630.000.00	
=====					
SON: **SEISCIENTOS TREINTA MIL PESOS MONEDA CORRIENTE**					
Responsable: _____			SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO		
Recibo de Caja Aplicado al Expediente No. _____					
			No. 12-039899- -00000-0000		
			Fecha: 2012-03-07 14:02:29 Dep. 2020 DIR.NUEVASCR		
			Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI		
			Act. 411 PRESENTACION Folios: 135		
			Act. 411 PRESENTACION Folios: 134		
					
Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia					
Web: www.sic.gov.co e-mai: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240					
Marzo 6 de 2012 - 11:06:08					

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COMPOSICIONES DE PELÍCULA SUBLINGUALES Y BUCALES

CAMPO DE LA INVENCION

La presente invención se refiere a composiciones, a métodos de fabricación, a productos y a métodos de uso referentes a películas que contienen agentes activos terapéuticos. La invención se refiere más particularmente a formas de dosificación de película autosoportada que proporcionan una dosificación terapéuticamente eficaz, que coincide esencialmente con la de comprimidos comercializados actualmente que contienen el mismo agente activo. Tales composiciones son particularmente útiles para tratar la dependencia de narcóticos a la vez que se proporciona una adhesión bucal suficiente de la forma de dosificación.

ANTECEDENTES DE LA TECNOLOGÍA RELACIONADA

La administración oral de dos agentes activos terapéuticos en una única forma de dosificación puede ser compleja si la intención es hacer que se absorba un agente activo en el organismo y que el otro agente activo permanezca sustancialmente sin absorber. Por ejemplo, un agente activo puede ser relativamente soluble en la boca a un pH, y el otro agente activo puede ser relativamente insoluble al mismo pH. Además, la cinética de absorción de cada agente terapéutico puede ser sustancialmente diferente debido a una absorción distinta de la especie cargada y no cargada. Estos factores representan algunos de los retos en la coadministración apropiada de agentes terapéuticos.

La coadministración de agentes terapéuticos tiene muchas aplicaciones. Entre tales áreas de tratamiento se incluyen el tratamiento de individuos que padecen dependencia de narcóticos. Tales individuos tienen una tendencia a padecer una grave dependencia física respecto al narcótico, lo que da como resultado síndromes de abstinencia potencialmente peligrosos cuando no se administra el narcótico al individuo. Con el fin de ayudar a individuos adictos a narcóticos, se sabe cómo proporcionar un nivel reducido de un fármaco, que proporciona un efecto de satisfacer la necesidad del organismo del narcótico, pero no proporcionar el "colocón" que se proporciona mediante el uso indebido del narcótico. El fármaco proporcionado puede ser un agonista o un agonista parcial, que proporciona una sensación reducida y puede ayudar a reducir la dependencia del fármaco.

Sin embargo, aunque estos fármacos proporcionan sólo un bajo nivel de efecto eufórico, pueden ser objeto de abuso por parte de los individuos por vía parenteral. En tales casos, es deseable proporcionar una combinación del fármaco con un segundo fármaco, que puede disminuir la probabilidad de desviación y abuso del primer fármaco. Por ejemplo, se sabe cómo proporcionar una dosificación de un antagonista en combinación con el agonista o agonista parcial. El antagonista del narcótico se une a un receptor en el cerebro para bloquear el receptor, reduciendo así el efecto del agonista.

Se ha comercializado una combinación de fármacos de este tipo con el nombre comercial Suboxone® como comprimido ingerible por vía oral. Sin embargo, tales combinaciones en forma de comprimido tienen potencial para el abuso. En algunos casos, el paciente al que se le ha proporcionado el fármaco puede guardar el comprimido en su boca sin tragar el comprimido, luego más tarde extrae el agonista del comprimido e inyecta el fármaco en el cuerpo de un individuo. Aunque pueden usarse determinados antagonistas (tales como antagonistas altamente solubles en agua) para ayudar a reducir la capacidad para separar el agonista, existe todavía potencial para el abuso. Se desea proporcionar una dosificación que no pueda retirarse fácilmente de la boca una vez que se ha administrado.

Existe actualmente la necesidad de una forma de dosificación de película que pueda disolverse por vía oral que proporcione los niveles de absorción deseados del agonista y el antagonista, a la vez que proporcione un efecto adhesivo en la boca, haciendo que sea difícil retirarla una vez situada en la boca, haciendo de ese modo que sea difícil el abuso del agonista.

SUMARIO DE LA INVENCION

En una realización de la presente invención, se proporciona una composición de dosificación de película que incluye: una matriz portadora polimérica; una cantidad terapéuticamente eficaz de buprenorfina o una sal farmacéuticamente aceptable de la misma; una cantidad terapéuticamente eficaz de naloxona o una sal farmacéuticamente aceptable de la misma; y un tampón en una cantidad para proporcionar un pH de la composición de un valor suficiente para optimizar la absorción de la buprenorfina.

En otra realización de la presente invención, se proporciona una composición de dosificación de película que incluye: una matriz portadora polimérica; una cantidad terapéuticamente eficaz de buprenorfina o una sal farmacéuticamente aceptable de la misma; una cantidad terapéuticamente eficaz de naloxona o una sal farmacéuticamente aceptable de la misma; y un tampón en una cantidad suficiente para inhibir la absorción de la naloxona cuando se administra por vía oral.

Todavía en otras realizaciones, puede proporcionarse una composición de dosificación de película que incluye: una matriz portadora polimérica; una cantidad terapéuticamente eficaz de buprenorfina o una sal farmacéuticamente aceptable de la misma; una cantidad terapéuticamente eficaz de naloxona o una sal farmacéuticamente aceptable de la misma; y un sistema de tamponamiento; en la que el sistema de tamponamiento incluye una capacidad tamponante suficiente para mantener la ionización de la naloxona durante el tiempo en el que la composición está en la cavidad oral de un usuario.

En otra realización de la invención, se proporciona un método de tratamiento de la dependencia de narcóticos de un usuario, que incluye las etapas de: proporcionar una composición que incluye: una matriz portadora polimérica; una cantidad terapéuticamente eficaz de buprenorfina o una sal farmacéuticamente aceptable de la misma; una cantidad terapéuticamente eficaz de naloxona o una sal farmacéuticamente aceptable de la misma; y un tampón en una cantidad para proporcionar un pH de la composición de un valor suficiente para optimizar la absorción de la buprenorfina; y administrar la composición a la cavidad oral de un usuario.

Todavía en otra realización de la invención, se proporciona un procedimiento de formación de una composición de dosificación de película que incluye las etapas de: colar una composición formadora de película, incluyendo la composición formadora de película: una matriz portadora polimérica; una cantidad terapéuticamente eficaz de buprenorfina o una sal farmacéuticamente aceptable de la misma; una cantidad terapéuticamente eficaz de naloxona o una sal farmacéuticamente aceptable de la misma; y un tampón en una cantidad para proporcionar un pH de la composición de un valor suficiente para

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optimizar la absorción de la buprenorfina y secar la composición formadora de película para formar una composición de dosificación de película autoportada.

En otra realización, se proporciona una composición de dosificación de película que incluye una cantidad terapéuticamente suficiente de buprenorfina o una sal farmacéuticamente aceptable de la misma y una cantidad terapéuticamente suficiente de naloxona o una sal farmacéuticamente aceptable de la misma, teniendo la composición de dosificación de película un perfil de liberación bioequivalente en comparación con un comprimido Suboxone® que contiene aproximadamente 2 veces la cantidad de buprenorfina o una sal farmacéuticamente aceptable de la misma.

Todavía otras realizaciones de la presente invención proporcionan una formulación de película de disolución por vía oral que incluye buprenorfina y naloxona, proporcionando la formulación un perfil plasmático *in vivo* que tiene una C_{max} de entre aproximadamente 0,624 ng/ml y aproximadamente 5,638 ng/ml para buprenorfina y un perfil plasmático *in vivo* que tiene una C_{max} de entre aproximadamente 41,04 pg/ml y aproximadamente 323,75 pg/ml para naloxona.

DESCRIPCIÓN DETALLADA DE LAS REALIZACIONES PREFERIDAS

Definiciones

Tal como se usa en el presente documento, el término C_{max} se refiere a la concentración plasmática máxima media tras la administración de la composición a un sujeto humano. También tal como se usa en el presente documento, el término AUC se refiere al valor de área media bajo la curva de concentración plasmática-tiempo tras la administración de las composiciones formadas en el presente documento. Tal como se expondrá en más detalle a continuación, la expresión "optimizar la absorción" no se refiere a alcanzar la máxima absorción de la composición, y se refiere más bien a alcanzar el nivel de absorción óptimo a un pH de aproximadamente 2 a aproximadamente 4. La absorción "óptima" puede ser, por ejemplo, un nivel que proporciona una absorción bioequivalente a la administración del comprimido disponible actualmente Suboxone®. Una C_{max} "óptima" de buprenorfina es de aproximadamente 0,67 a aproximadamente 5,36 mg/ml a dosificaciones de desde 2-16 mg de buprenorfina a un pH

dado. De manera similar, una AUC "óptima" de buprenorfina puede ser de aproximadamente 7,43 a aproximadamente 59,46 h*ng/ml a dosificaciones de desde 2-16 mg de buprenorfina a un pH dado. Tal como se describirá en más detalle a continuación, se ha descubierto sorprendentemente que la absorción de un agonista particular, buprenorfina, puede proporcionar una absorción óptima a un pH de aproximadamente 2-4 así como de aproximadamente 5,5-6,5. Por tanto, puede "optimizarse" la absorción de buprenorfina proporcionando un pH de aproximadamente 2-4 o de aproximadamente 5,5-6,5.

"Maximizar la absorción" se refiere a los valores de absorción *in vivo* máximos logrados a un pH de aproximadamente 4 a aproximadamente 9.

La expresión "pH local" se refiere al pH de la región de la matriz portadora que rodea inmediatamente al agente activo a medida que se hidrata y/o disuelve la matriz, por ejemplo, en la boca del usuario.

Por "inhibir" la absorción de un agente activo, quiere decirse lograr un estado de ionización del agente activo tan completo como sea posible, de manera que se absorba de manera medible de poco a nada del agente activo. Por ejemplo, a un pH de 3-3,5, la Cmax de un agente activo tal como naloxona para la dosificación de 0,5 mg a 4,0 mg oscila entre 32,5 y 260 pg/ml, y una AUC de naloxona para la dosificación de 0,5 mg a 4,0 mg oscila entre 90,55 y 724,4 h*pg/ml. Se entiende que a un pH inferior a 3,0, se esperaría una ionización adicional y por tanto daría como resultado una menor absorción.

El término "bioequivalente" significa obtener del 80% al 125% de los valores de Cmax y AUC para un agente activo dado en un producto diferente. Por ejemplo, suponiendo que los valores de Cmax y AUC de buprenorfina para un comprimido disponible comercialmente Suboxone® (que contiene 2 mg de buprenorfina y 0,5 mg de naloxona) son de 0,780 ng/ml y 6,789 h*ng/ml, respectivamente, un producto bioequivalente tendría una Cmax de buprenorfina en el intervalo de 0,624-0,975 ng/ml, y un valor de AUC de buprenorfina de 5,431-8,486 h*ng/ml.

Se entenderá que el término "película" incluye láminas y películas delgadas, en cualquier forma, incluyendo forma rectangular, cuadrada o cualquier otra deseada. Las películas descritas en el presente documento pueden ser de cualquier

grosor y tamaño de manera que pueda colocarse en la cavidad oral del usuario. Por ejemplo, las películas pueden tener un grosor relativamente delgado de desde aproximadamente 0,1 hasta aproximadamente 10 mils, o pueden tener un grosor algo más grueso de desde aproximadamente 10 hasta aproximadamente 30 mils. Para algunas películas, el grosor puede ser incluso mayor, es decir, superior a aproximadamente 30 mils. Las películas pueden ser de una sola capa o pueden ser de múltiples capas, incluyendo películas laminadas.

Las películas de disolución oral se dividen generalmente en tres clases principales: de disolución rápida, de disolución moderada y de disolución lenta. Las películas de disolución rápida se disuelven generalmente en de aproximadamente 1 segundo a aproximadamente 30 segundos en la boca. Las películas de disolución moderada se disuelven generalmente en de aproximadamente 1 a aproximadamente 30 minutos en la boca, y las películas de disolución lenta se disuelven generalmente en más de 30 minutos en la boca. Las películas de disolución rápida pueden consistir en polímeros hidrófilos de bajo peso molecular (es decir, polímeros que tienen un peso molecular de entre aproximadamente 1.000 y 9.000, o polímeros que tienen un peso molecular de hasta 200.000). En cambio, las películas de disolución lenta tienen generalmente polímeros de alto peso molecular (es decir, que tienen un peso molecular de millones).

Las películas de disolución moderada tienden a encontrarse entre las películas de disolución rápida y lenta. Las películas de disolución moderada se disuelven bastante rápidamente, pero también tienen un buen nivel de mucoadhesión. Las películas de disolución moderada también son flexibles, rápidamente humectables y normalmente no son irritantes para el usuario. Para la presente invención, es preferible usar películas que se encuentren entre las categorías de disolución rápida y de disolución moderada. Tales películas de disolución moderada proporcionan una velocidad de disolución suficientemente rápida, de la manera más deseable de entre aproximadamente 1 minuto y aproximadamente 20 minutos, a la vez que proporcionan un nivel de mucoadhesión aceptable de manera que la película no puede retirarse fácilmente una vez que se coloca en la cavidad oral del usuario.

Las películas de la invención descritas en el presente documento pueden incluir uno o más agonistas o agonistas parciales usados para el tratamiento de la drogadicción. Tal como se usa en el presente documento, el término "agonista" se refiere a una sustancia química que puede proporcionar una actividad o respuesta fisiológica en el organismo del usuario. Las películas descritas en el presente documento pueden incluir además uno o más antagonistas. Tal como se usa en el presente documento, el término "antagonista" se refiere a cualquier sustancia química que actúa dentro del organismo del usuario para reducir la actividad fisiológica de otra sustancia química. En algunas realizaciones, un antagonista usado en el presente documento puede actuar para reducir y/o bloquear la actividad fisiológica del agonista. Los agentes activos pueden ser solubles en agua, o pueden ser insolubles en agua. Tal como se usa en el presente documento, la expresión "solubles en agua" se refiere a sustancias que pueden disolverse al menos parcialmente en un disolvente, que incluye pero no se limita a agua. La expresión "soluble en agua" no significa necesariamente que la sustancia pueda disolverse al 100% en el disolvente. La expresión "insolubles en agua" se refiere a sustancias que no pueden disolverse en un disolvente, que incluye pero no se limita a agua. Los disolventes pueden incluir agua, o alternativamente pueden incluir otros disolventes polares por sí mismos o en combinación con agua.

Películas de la invención

La presente invención se refiere a métodos de tratamiento de la dependencia de narcóticos en un individuo. De manera más deseable, la invención se refiere al tratamiento de la dependencia de opioides en un individuo, mientras que se usa una formulación y administración que dificultan el uso indebido del narcótico. Actualmente, el tratamiento de la dependencia de opioides se ve ayudado por la administración de Suboxone®, que es un comprimido que puede disolverse por vía oral. Este comprimido proporciona una combinación de buprenorfina (un agonista opioide) y naloxona (un antagonista opioide). Por tanto, la presente invención proporciona un método de tratamiento de la dependencia de narcóticos proporcionando una dosificación de película que puede disolverse por vía oral, que

proporciona un efecto bioequivalente a Suboxone®. La dosificación de película proporciona preferiblemente adhesión bucal mientras que está en la boca del usuario, haciendo que sea difícil retirarla tras su colocación.

La composición de dosificación de película incluye preferiblemente una matriz portadora polimérica. Puede usarse cualquier matriz portadora polimérica deseada, siempre que pueda disolverse por vía oral. De manera deseable, la dosificación debe tener suficiente bioadhesión para no retirarse fácilmente y debe formar una estructura similar a un gel cuando se administra. Las películas que pueden consumirse por vía oral son preferiblemente de disolución moderada en la cavidad oral y particularmente adecuadas para la administración de agentes activos, aunque las composiciones de liberación rápida y sostenida también se encuentran entre las diversas realizaciones contempladas.

Las películas usadas en los productos farmacéuticos pueden producirse mediante una combinación de al menos un polímero y un disolvente, que incluye opcionalmente otras cargas conocidas en la técnica. El disolvente puede ser agua, un disolvente orgánico polar que incluye, pero no se limita a, etanol, isopropanol, acetona o cualquier combinación de los mismos. En algunas realizaciones, el disolvente puede ser un disolvente orgánico apolar, tal como cloruro de metileno. La película puede prepararse utilizando un método de deposición o colada seleccionado y un procedimiento de secado controlado. Por ejemplo, la película puede prepararse a través de procedimientos de secado controlados, que incluyen la aplicación de calor y/o energía de radiación a la matriz de película húmeda para formar una estructura viscoelástica, controlando de ese modo la uniformidad del contenido de la película. Tales procedimientos se describen en más detalle en la solicitud estadounidense legalmente cedida n.º 10/074.272, presentada el 14 de febrero de 2002, y publicada como publicación de patente estadounidense n.º 2003/0107149 A1, cuyo contenido se incorpora al presente documento como referencia en su totalidad. Alternativamente, las películas pueden extruirse tal como se describe en la solicitud estadounidense legalmente cedida n.º 10/856.176, presentada el 28 de mayo de 2004, y publicada como publicación de patente

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estadounidense n.º 2005/0037055 A1, cuyo contenido se incorpora al presente documento como referencia en su totalidad.

El polímero incluido en las películas puede ser soluble en agua, hinchable con agua, insoluble en agua, o una combinación de uno o más polímeros o bien solubles en agua, hinchables con agua o bien insolubles en agua. El polímero puede incluir celulosa o un derivado de celulosa. Los ejemplos específicos de polímeros solubles en agua útiles incluyen, pero no se limitan a, poli(óxido de etileno), pululano, hidroxipropilmetilcelulosa, hidroxietilcelulosa, hidroxipropilcelulosa, polivinilpirrolidona, carboximetilcelulosa, poli(alcohol vinílico), alginato de sodio, polietilenglicol, goma xantana, goma tragacanto, goma guar, goma de acacia, goma arábiga, poli(ácido acrílico), copolímero de metacrilato de metilo, copolímeros de carboxivinilo, almidón, gelatina y combinaciones de los mismos. Los ejemplos específicos de polímeros insolubles en agua útiles incluyen, pero no se limitan a, etilcelulosa, hidroxipropiletilcelulosa, acetato-ftalato de celulosa, ftalato de hidroxipropilmetilcelulosa y combinaciones de los mismos. Para dosificaciones superiores, puede ser deseable incorporar un polímero que proporciona un alto nivel de viscosidad en comparación con dosificaciones inferiores.

Tal como se usa en el presente documento, la expresión "polímero soluble en agua" y variantes de la misma se refieren a un polímero que es al menos parcialmente soluble en agua, y de manera deseable completa o predominantemente soluble en agua, o absorbe agua. Se hace referencia a menudo a los polímeros que absorben agua como polímeros que pueden hincharse con agua. Los materiales útiles con la presente invención pueden ser solubles en agua o hinchables con agua a temperatura ambiente y otras temperaturas, tales como temperaturas que superan la temperatura ambiente. Además, los materiales pueden ser solubles en agua o hinchables con agua a presiones inferiores a la presión atmosférica. De manera deseable, los polímeros solubles en agua son solubles en agua o hinchables con agua, teniendo una captación de agua de al menos el 20 por ciento en peso. También son útiles polímeros hinchables con agua que tienen una captación de agua del 25 por ciento en peso o más. En algunas realizaciones, las películas formadas a partir de tales polímeros solubles en agua pueden ser lo suficientemente

solubles en agua como para poder disolverse tras el contacto con líquidos corporales.

Otros polímeros útiles para su incorporación en las películas incluyen polímeros, copolímeros, polímeros de bloque biodegradables y combinaciones de los mismos. Se entiende que el término "biodegradable" pretende incluir materiales que se degradan químicamente, en oposición a materiales que se separan físicamente (es decir, materiales bioerosionables). Entre los polímeros o clases de polímeros útiles conocidos que cumplen con los criterios anteriores están: poli(ácido glicólico) (PGA), poli(ácido láctico) (PLA), polidioxanos, polioxalatos, poli(α -ésteres), polianhídridos, poliacetatos, policaprolactonas, poli(ortoésteres), poliaminoácidos, poliaminocarbonatos, poliuretanos, policarbonatos, poliamidas, poli(cianoacrilatos de alquilo), y mezclas y copolímeros de los mismos. Los polímeros útiles adicionales incluyen estereopolímeros de ácido L- y D-láctico, copolímeros de ácido bis(p-carboxifenoxi)propanoico y ácido sebácico, copolímeros de ácido sebácico, copolímeros de caprolactona, copolímeros de poli(ácido láctico)/poli(ácido glicólico)/polietilenglicol, copolímeros de poliuretano y (poli(ácido láctico), copolímeros de poliuretano y poli(ácido láctico), copolímeros de α -amino ácidos, copolímeros de α -aminoácidos y ácido caproico, copolímeros de α -glutamato de bencilo y polietilenglicol, copolímeros de succinato y poli(glicoles), polifosfazeno, polihidroxialcanoatos y mezclas de los mismos. Se contemplan sistemas binarios y ternarios.

Otros polímeros útiles específicos incluyen los comercializados con las marcas comerciales Medisorb y Biodel. Los materiales Medisorb se comercializan por la Dupont Company de Wilmington, Delaware y se identifican genéricamente como un "copolímero de lactida/glicolida" que contiene "2-hidroxi-polímero de ácido propanoico, con hidroxipolímero con ácido hidroxiacético". Cuatro de tales polímeros incluyen lactida/glicolida 100L, que se cree que es lactida al 100% que tiene un punto de fusión dentro del intervalo de 338°-347°F (170°-175°C); lactida/glicolida 100L, que se cree que es glicolida al 100% que tiene un punto de fusión dentro del intervalo de 437°-455°F (225°-235°C); lactida/glicolida 85/15, que se cree que es el 85% de lactida y el 15% de glicolida con un punto de fusión dentro del intervalo de 338°-347°F (170°-175°

C); y lactida/glicolida 50/50, que se cree que es un copolímero del 50% de lactida y el 50% de glicolida con un punto de fusión dentro del intervalo de 338°-347°F (170°-175°C). Los materiales Bidel representan una familia de diversos polianhídridos que difieren químicamente.

Aunque puede usarse una variedad de diferentes polímeros, se desea seleccionar polímeros que proporcionen propiedades mucoadhesivas a la película, así como una velocidad de disolución y/o disgregación deseada. En particular, el periodo de tiempo durante el que se desea mantener la película en contacto con el tejido de la mucosa depende del tipo de agente activo contenido en la composición. Algunos agentes activos pueden requerir sólo unos pocos minutos para su administración a través del tejido de la mucosa, mientras que otros agentes activos pueden requerir hasta varias horas o incluso más. Por consiguiente, en algunas realizaciones, pueden usarse uno o más polímeros solubles en agua, tal como se describió anteriormente, para formar la película. En otras realizaciones, sin embargo, puede ser deseable usar combinaciones de polímeros solubles en agua y polímeros que son hinchables con agua, insolubles en agua y/o biodegradables, tal como se proporcionó anteriormente. La inclusión de uno o más polímeros que son hinchables con agua, insolubles en agua y/o biodegradables puede proporcionar películas con velocidades de disolución o disgregación más lentas que las películas formadas a partir de polímeros solubles en agua solos. Como tal, la película puede adherirse al tejido de la mucosa durante periodos o un tiempo más prolongado, tal como de hasta varias horas, lo que puede ser deseable para la administración de determinados componentes activos.

De manera deseable, la dosificación de película individual tiene un pequeño tamaño, que es de entre aproximadamente 0,5-1 pulgada por aproximadamente 0,5-1 pulgada. Lo más preferiblemente, la dosificación de película es de aproximadamente 0,75 pulgadas x 0,5 pulgadas. La dosificación de película debe tener una buena adhesión cuando se coloca en la cavidad bucal o en la región sublingual del usuario. Además, la dosificación de película debe dispersarse y disolverse a una velocidad moderada, de la manera más deseable dispersarse en el plazo de aproximadamente 1 minuto y disolverse en el plazo de aproximadamente 3 minutos. En algunas realizaciones, la

dosificación de película puede ser capaz de dispersarse y disolverse a una velocidad de entre aproximadamente 1 y aproximadamente 1,5 minutos.

5 Por ejemplo, en algunas realizaciones, las películas pueden incluir poli(óxido de etileno) solo o en combinación con un segundo componente de polímero. El segundo polímero puede ser otro polímero soluble en agua, un polímero hinchable con agua, un polímero insoluble en agua, un polímero biodegradable o cualquier combinación de los mismos. Los polímeros solubles en agua adecuados incluyen, sin limitación, cualquiera de los proporcionados anteriormente. En algunas realizaciones, el polímero soluble en agua puede incluir polímeros celulósicos hidrófilos, tales como hidroxipropilcelulosa y/o hidroxipropilmetilcelulosa. Según algunas realizaciones, el poli(óxido de etileno) puede oscilar entre aproximadamente el 20% y el 100% en peso en el componente de polímero, más específicamente entre aproximadamente el 30% y aproximadamente el 70% en peso, e incluso más específicamente entre aproximadamente el 40% y aproximadamente el 60% en peso. En algunas realizaciones, también pueden incluirse uno o más polímeros hinchables con agua, insolubles en agua y/o biodegradables en la película a base de poli(óxido de etileno). Puede emplearse cualquiera de los polímeros hinchables con agua, insolubles en agua o biodegradables proporcionados anteriormente. Puede emplearse el segundo componente de polímero en cantidades de aproximadamente el 0% a aproximadamente el 80% en peso en el componente de polímero, más específicamente de aproximadamente el 30% a aproximadamente el 70% en peso, e incluso más específicamente de aproximadamente el 40% a aproximadamente el 60% en peso.

El peso molecular del poli(óxido de etileno) también puede variarse. En algunas realizaciones, puede desearse un poli(óxido de etileno) de alto peso molecular, tal como aproximadamente 4 millones, para aumentar la mucoadhesividad de la película. En algunas otras realizaciones, el peso molecular puede oscilar entre aproximadamente 100.000 y 900.000, más específicamente entre aproximadamente 100.000 y 600.000, e incluso más específicamente entre aproximadamente 100.000 y 300.000. En algunas realizaciones, puede ser deseable combinar poli(óxido de etileno) de alto peso molecular (de 600.000 a 900.000) con

poli(óxido de etileno) de bajo peso molecular (de 100.000 a 300.000) en el componente de polímero.

También puede añadirse una variedad de componentes y cargas opcionales a las películas. Estos pueden incluir, sin limitación: surfactantes; plastificantes; polialcoholes; agentes antiespumantes, tales como compuestos que contienen silicona, que promueven un superficie más lisa de la película liberando oxígeno desde la película; geles termoendurecibles tales como pectina, carragenanos y gelatina, que ayudan a mantener la dispersión de componentes; compuestos de inclusión, tales como ciclodextrinas y moléculas de tipo jaula; agentes de coloración; y aromas. En algunas realizaciones, puede incluirse más de un componente activo en la película.

Pueden incluirse aditivos en las películas. Los ejemplos de clases de aditivos incluyen excipientes, lubricantes, agentes tamponantes, estabilizantes, agentes de expansión, pigmentos, agentes de coloración, cargas, agentes de relleno, agentes edulcorantes, agentes aromatizantes, fragancias, modificadores de la liberación, adyuvantes, plastificantes, aceleradores del flujo, agentes de desmoldeo, polioles, agentes de granulación, diluyentes, aglutinantes, tampones, absorbentes, deslizantes, adhesivos, antiadherentes, acidulantes, suavizantes, resinas, emolientes, disolventes, surfactantes, emulsionantes, elastómeros y mezclas de los mismos. Estos aditivos pueden añadirse con el/los principio(s) activo(s).

Los aditivos útiles incluyen, por ejemplo, gelatina, proteínas vegetales tales como proteína del girasol, proteínas de la soja, proteínas de la semilla de algodón, proteínas del cacahuete, proteínas de la pepita de uva, proteínas del lactosuero, aislados de proteínas del lactosuero, proteínas de la sangre, proteínas del huevo, proteínas acriladas, polisacáricos solubles en agua tales como alginatos, carragenanos, goma guar, agar-agar, goma xantana, goma gelán, goma arábiga y gomas relacionadas (goma ghatti, goma karaya, goma tragancanto), pectina, derivados de celulosa solubles en agua: alquilcelulosas, hidroxialquilcelulosas e hidroxialquilalquilcelulosas, tales como metilcelulosa, hidroximetilcelulosa, hidroxietilcelulosa, hidroxipropilcelulosa, hidroxietilmetilcelulosa, hidroxipropilmetilcelulosa, hidroxibutilmetilcelulosa, ésteres

de celulosa y ésteres de hidroxialquilcelulosa tales como acetato-ftalato de celulosa (CAP), hidroxipropilmetilcelulosa (HPMC); carboxialquilcelulosas, carboxialquilalquilcelulosas, ésteres de carboxialquilcelulosa tales como carboximetilcelulosa y sus sales de metales alcalinos; polímeros sintéticos solubles en agua tales como poli(ácidos acrílicos) y poli(ésteres de ácido acrílico), poli(ácidos metacrílicos) y poli(ésteres de ácido metacrílico), poli(acetatos de vinilo), poli(alcoholes vinílicos), poli(acetato-ftalatos de vinilo) (PVAP), polivinilpirrolidona (PVP), copolímero de PVY/acetato de vinilo, y poli(ácidos crotónicos); también son adecuados gelatina ftalada, succinato de gelatina, gelatina reticulada, goma laca, derivados químicos de almidón solubles en agua, acrilatos y metacrilatos modificados de manera catiónica que presentan, por ejemplo, un grupo amino terciario o cuaternario, tal como el grupo dietilaminoetilo, que puede cuaternizarse si se desea; y otros polímeros similares.

Tales extensores pueden añadirse opcionalmente en cualquier cantidad deseada, de manera deseable dentro del intervalo de hasta aproximadamente el 80%, de manera deseable de aproximadamente el 3% al 50% y de manera más deseable dentro del intervalo del 3% al 20% basado en el peso de todos los componentes de la película.

Aditivos adicionales pueden ser agentes de flujo y opacificantes, tales como los óxidos de magnesio, aluminio, silicio, titanio, etc. de manera deseable en un intervalo de concentración de aproximadamente el 0,02% a aproximadamente el 3% en peso y de manera deseable de aproximadamente el 0,02% a aproximadamente el 1% basado en el peso de todos los componentes de la película.

Ejemplos adicionales de aditivos son plastificantes que incluyen poli(óxidos de alquileo), tales como polietilenglicoles, polipropilenglicoles, polietilenglicoles, plastificantes orgánicos con bajos pesos moleculares, tales como glicerol, monoacetato, diacetato o triacetato de glicerol, triacetina, polisorbato, alcohol cetílico, propilenglicol, sorbitol, dietilsulfosuccinato de sodio, citrato de trietilo, citrato de tributilo y similares, añadidos en concentraciones que oscilan entre aproximadamente el 0,5% y aproximadamente el 30%, y de manera deseable que oscilan

entre aproximadamente el 0,5% y aproximadamente el 20% basado en el peso del polímero.

Puede haber además compuestos añadidos para mejorar las propiedades de textura del material de almidón tales como grasas animales o vegetales, de manera deseable en su forma hidrogenada, especialmente las que son sólidas a temperatura ambiente. Estas grasas tienen de manera deseable un punto de fusión de 50°C o superior. Se prefieren triglicéridos con ácidos grasos C₁₂, C₁₄, C₁₆, C₁₈, C₂₀ y C₂₂. Estas grasas pueden añadirse solas sin añadir extensores ni plastificantes y pueden añadirse ventajosamente solas o junto con mono y/o diglicéridos o fosfátidos, especialmente lecitina. Los mono y diglicéridos se derivan de manera deseable de los tipos de grasas descritos anteriormente, es decir, con ácidos grasos C₁₂, C₁₄, C₁₆, C₁₈, C₂₀ y C₂₂.

Las cantidades totales usadas de las grasas, mono, diglicéridos y/o lecitinas son de hasta aproximadamente el 5% y preferiblemente dentro del intervalo de aproximadamente el 0,5% a aproximadamente el 2% en peso de la composición de película total.

Además, puede ser útil añadir dióxido de silicio, silicato de calcio o dióxido de titanio en una concentración de aproximadamente el 0,02% a aproximadamente el 1% en peso de la composición total. Estos compuestos actúan como agentes de flujo y opacificantes.

La lecitina es un agente tensioactivo para su uso en las películas descritas en el presente documento. Puede incluirse lecitina en la materia prima en una cantidad de desde aproximadamente el 0,25% hasta aproximadamente el 2,00% en peso. Otros agentes tensioactivos, es decir surfactantes, incluyen, pero no se limitan a, alcohol cetílico, laurilsulfato de sodio, los SpanTM y TweenTM que están disponibles comercialmente de ICI Americas, Inc. Los aceites etoxilados, incluyendo aceites de ricino etoxilados, tales como Cremophor® EL que está disponible comercialmente de BASF, también son útiles. CarbowaxTM es aún otro modificador que es muy útil en la presente invención. Pueden usarse los TweenTM o combinaciones de agentes tensioactivos para lograr el equilibrio hidrófilo-lipófilo ("HLB", *hydrophilic-lipophilic balance*) deseado. La presente invención, sin embargo, no requiere el uso de un surfactante, y

las películas o composiciones formadoras de película de la presente invención pueden estar esencialmente libres de un surfactante a la vez que proporcionan todavía las características de uniformidad deseables de la presente invención.

Otros componentes incluyen aglutinantes que contribuyen a la facilidad de formación y calidad general de las películas. Los ejemplos no limitativos de aglutinantes incluyen almidones, almidones pregelatinizados, gelatina, polivinilpirrolidona, metilcelulosa, carboximetilcelulosa sódica, etilcelulosa, poliacrilamidas, poliviniloxoazolidona y poli(alcoholes vinílicos).

Posibles aditivos adicionales incluyen agentes de potenciación de la solubilidad, tales como sustancias que forman compuestos de inclusión con componentes activos. Tales agentes pueden ser útiles en la mejora de las propiedades de agentes activos muy insolubles y/o inestables. En general, estas sustancias son moléculas de forma toroidal con cavidades internas hidrófobas y partes exteriores hidrófilas. Los agentes activos insolubles y/o inestables pueden encajarse dentro de la cavidad hidrófoba, produciendo de ese modo un complejo de inclusión, que es soluble en agua. Por consiguiente, la formación del complejo de inclusión permite que agentes activos muy insolubles y/o inestables se disuelvan en agua. Un ejemplo particularmente deseable de tales agentes son las ciclodextrinas, que son hidratos de carbono cíclicos derivados del almidón. Otras sustancias similares, sin embargo, se consideran muy dentro del alcance de la presente invención.

Los agentes de coloración adecuados incluyen colores para alimentos, fármacos y cosméticos (FD&C), colores para fármacos y cosméticos (D&C) o colores para cosméticos y fármacos externos (Ext. D&C). Estos colores son colorantes, sus correspondientes lacas y determinados colorantes naturales y derivados. Las lacas son colorantes absorbidos sobre hidróxido de aluminio.

Otros ejemplos de agentes de coloración incluyen colorantes azoicos conocidos, pigmentos orgánicos o inorgánicos, o agentes de coloración de origen natural. Se prefieren los pigmentos inorgánicos, tales como los óxidos de hierro o titanio, añadiéndose estos óxidos en concentraciones que oscilan entre aproximadamente el 0,001 y aproximadamente el 10%, y

preferiblemente entre aproximadamente el 0,5 y aproximadamente el 3%, basado en el peso de todos los componentes.

Los aromas pueden elegirse de líquidos aromatizantes naturales y sintéticos. Una lista ilustrativa de tales agentes incluye aceites volátiles, aceites de aromas sintéticos, compuestos aromáticos aromatizantes, aceites, líquidos, oleorresinas o extractos derivados de plantas, hojas, flores, frutos, tallos y combinaciones de los mismos. Una lista representativa no limitativa de ejemplos incluye aceites de menta, cacao y aceites de cítricos tales como limón, naranja, uva, lima y pomelo y esencias de frutas que incluyen aromas de manzana, pera, melocotón, uva, fresa, frambuesa, cereza, ciruela, piña, albaricoque u otras frutas.

Otros aromatizantes útiles incluyen aldehídos y ésteres tales como benzaldehído (cereza, almendra), citral, es decir, alfacitral (limón, lima), neral, es decir, beta-citral (limón, lima), decanal (naranja, limón), aldehído C-8 (cítricos), aldehído C-9 (cítricos), aldehído C-12 (cítricos), tolilaldehído (cereza, almendra), 2,6-dimetiloctanol (fruta verde) y 2-dodecenal (cítricos, mandarina), combinaciones de los mismos y similares.

Los edulcorantes pueden elegirse de la siguiente lista no limitativa: glucosa (jarabe de maíz), dextrosa, azúcar invertido, fructosa y combinaciones de los mismos; sacarina y sus diversas sales tales como la sal de sodio; edulcorantes de dipéptido tales como aspartamo; compuestos de dihidrochalcona, glicirrizina; *Stevia rebaudiana* (esteviósido); cloroderivados de sacarosa tales como sucralosa; alcoholes de azúcar tales como sorbitol, manitol, xilitol y similares. También se contemplan hidrolizados de almidón hidrogenados y el edulcorante sintético 2,2-dióxido de 3,6-dihidro-6-metil-1-1-1,2,3-oxatiazin-4-ona, particularmente la sal de potasio (acesulfamo K), y las sales de sodio y calcio de los mismos, y edulcorantes naturales intensos, tales como Lo Han Kuo. También pueden usarse otros edulcorantes.

También pueden usarse componentes antiespumantes y/o desespumantes con las películas. Estos componentes ayudan en la eliminación de aire, tal como aire atrapado, de las composiciones formadoras de película. Tal aire atrapado puede conducir a películas no uniformes. La simeticona es un agente antiespumante y/o desespumante particularmente útil. La presente

invención, sin embargo, no está limitada de ese modo y pueden usarse de forma adecuada otros agentes antiespumantes y/o desespumantes.

Como asunto relacionado, pueden emplearse simeticona y agentes relacionados para fines de densificación. Más específicamente, tales agentes pueden facilitar la eliminación de huecos, aire, humedad y componentes no deseados similares, proporcionando de ese modo películas más densas, y por tanto más uniformes. Los agentes o componentes que realizan esta función pueden denominarse agentes de densificación o densificantes. Tal como se describió anteriormente, el aire atrapado o los componentes no deseados pueden conducir a películas no uniformes.

La simeticona se usa generalmente en el campo médico como tratamiento para los gases o cólicos en bebés. La simeticona es una mezcla de polímeros de siloxano lineales completamente metilados que contienen unidades de repetición de polidimetilsiloxano que se estabiliza con unidades de bloqueo de extremos de trimetilsiloxilo, y dióxido de silicio. Habitualmente contiene el 90,5-99% de polimetilsiloxano y el 4-7% de dióxido de silicio. La mezcla es un fluido viscoso, gris y translúcido que es insoluble en agua.

Cuando se dispersa en agua, la simeticona se extenderá a través de la superficie, formando una película delgada de baja tensión superficial. De esta manera, la simeticona reduce la tensión superficial del aire en burbujas ubicado en la disolución, tal como burbujas de espuma, provocando su colapso. La función de la simeticona imita la doble acción del aceite y alcohol en agua. Por ejemplo, en una disolución oleosa cualquier burbuja de aire atrapada ascenderá hasta la superficie y se disipará más rápida y fácilmente, debido a que un líquido oleoso tiene una menor densidad en comparación con una disolución acuosa. Por otra parte, se sabe que una mezcla de alcohol/agua disminuye la densidad del agua así como disminuye la tensión superficial del agua. Así, cualquier burbuja de aire atrapada en el interior de esta disolución de mezcla también se disipará fácilmente. La disolución de simeticona proporciona estas dos ventajas. Disminuye la energía superficial de cualquier burbuja de aire que quede atrapada en el interior de la disolución acuosa, así como disminuye la tensión superficial de la

disolución acuosa. Como resultado de esta funcionalidad única, la simeticona tiene una excelente propiedad antiespumante que puede usarse para procesos fisiológicos (contra los gases en el estómago) así como cualquier proceso externo que requiera la eliminación de burbujas de aire de un producto.

Con el fin de impedir la formación de burbujas de aire en las películas, puede realizarse la etapa de mezclado a vacío. Sin embargo, tan pronto como se completa la etapa de mezclado, y la disolución de película se devuelve a las condiciones atmosféricas normales, volverá a introducirse aire o a entrar en contacto con la mezcla. En muchos casos, quedarán atrapadas de nuevo burbujas de aire diminutas en el interior de esta disolución viscosa polimérica. La incorporación de simeticona en la composición formadora de película o bien reduce sustancialmente o bien elimina la formación de burbujas de aire.

La simeticona puede añadirse a la mezcla formadora de película como agente antiespumante en una cantidad de desde aproximadamente el 0,01 por ciento en peso hasta aproximadamente el 5,0 por ciento en peso, de manera más deseable desde aproximadamente el 0,05 por ciento en peso hasta aproximadamente el 2,5 por ciento en peso, y de la manera más deseable desde aproximadamente el 0,1 por ciento en peso hasta aproximadamente el 1,0 por ciento en peso.

También puede incluirse cualquier otro componente opcional descrito en la patente estadounidense legalmente cedida n.º 7.425.292 y la solicitud estadounidense n.º 10/856.176, a las que se hizo referencia anteriormente, en las películas descritas en el presente documento.

Cuando la forma de dosificación incluye al menos un antagonista, puede desearse controlar la liberación del antagonista, de modo que se retarde o se impida por completo la liberación del antagonista desde la dosificación cuando se toma por vía oral. De manera deseable, la forma de dosificación es una composición de película autosoportada, que se coloca en la cavidad oral del usuario. En una forma de dosificación que va a colocarse en la cavidad oral, se desea que el agonista se absorba por vía bucal, de modo que se proporcione una rápida integración del agonista en el organismo del usuario. Al mismo tiempo, puede desearse impedir o reducir la absorción de cualquier antagonista por vía bucal, permitiendo de ese modo que

se trague el antagonista y se destruya en el estómago. La reducción de la absorción de un antagonista puede lograrse mediante medios físicos, tal como encapsulando el antagonista en un material que bloquea la absorción. Se desea, sin embargo, reducir la absorción del antagonista por medios químicos, tales como controlando el pH local de la dosificación.

Se ha encontrado que controlando el pH local de la forma de dosificación, puede controlarse la liberación y/o absorción de los agentes activos en la misma. Por ejemplo, en una dosificación que incluye una cantidad de un agonista, puede controlarse el pH local hasta un nivel que maximiza su liberación y/o absorción en la cavidad oral del usuario. En dosificaciones que incorporan una cantidad de un agonista y una cantidad de un antagonista, puede controlarse el pH local hasta un nivel que maximiza la liberación y/o absorción del agonista, a la vez que se minimiza simultáneamente la liberación y/o absorción del antagonista.

La forma de dosificación incluye preferiblemente una combinación de un agonista parcial y un antagonista, mientras que la dosificación tiene un pH controlado. En una realización, el agonista parcial pueden incluir buprenorfina o una sal farmacéuticamente aceptable de la misma, mientras que el antagonista incluye naloxona o una sal terapéuticamente aceptable de la misma. Debe entenderse que la presente invención no se limita al uso de buprenorfina y naloxona, y pueden incorporarse cualquier agonista (o agonista parcial) y cualquier antagonista en la presente invención para su uso en el tratamiento de la drogadicción. El agonista y el antagonista opcional deben seleccionarse de los agonistas y antagonistas que son útiles en el tratamiento de la dependencia de narcóticos particular que esté tratándose.

Tal como se trató anteriormente, el pH local de la dosificación se controla preferiblemente para proporcionar la liberación y/o absorción deseada del agonista y el antagonista. Se sabe que la buprenorfina tiene un pKa de aproximadamente 8,42, mientras que la naloxona tiene un pKa de aproximadamente 7,94. Según la teoría de reparto del pH, se esperaría que la saliva (que tiene un pH de aproximadamente 6,5) maximizase la absorción de ambos agentes activos. Sin embargo, se ha descubierto sorprendentemente por parte de los solicitantes que

tamponando la dosificación hasta un nivel de pH particular, pueden lograrse los niveles de absorción óptimos del agonista y el antagonista. De manera deseable, el pH local de una composición que incluye un agonista y un antagonista es de entre aproximadamente 2 y aproximadamente 4, y de la manera más deseable es de desde 3 hasta 4. A este nivel de pH local, se logra la absorción óptima del agonista y el antagonista. Tal como se describirá en más detalle en los ejemplos a continuación, el control del pH local de las composiciones de película de la presente invención proporciona un sistema en el que la liberación y/o absorción deseada de los componentes es bioequivalente a la de un comprimido Suboxone® similar.

En una realización, la forma de dosificación es una película autosoportada. En esta realización, la dosificación de película incluye una matriz portadora de polímero, una cantidad terapéuticamente eficaz de buprenorfina, un agonista. El tampón puede proporcionar preferiblemente un pH local de la composición dentro de un intervalo que proporciona el nivel de absorción deseado de la buprenorfina. La dosificación resultante es una composición de película que permite una liberación rápida y eficaz de buprenorfina en la cavidad oral del usuario. Al mismo tiempo, la composición de película tiene preferiblemente un perfil de adhesión suficiente, de manera que la película no pueda retirarse fácilmente de la cavidad oral del usuario una vez que se ha colocado en la cavidad. La liberación completa de la buprenorfina tiene lugar preferiblemente en un plazo inferior a aproximadamente treinta minutos, y preferiblemente permanece en la cavidad oral durante al menos 1 minuto.

Tal como se explicó anteriormente, aunque proporcionar un nivel farmacéuticamente aceptable de un agonista es útil en el tratamiento de aquellas personas con adicción a narcóticos, puede ser deseable proporcionar la buprenorfina en combinación con naloxona (un antagonista) de modo que se reduzca el efecto del agonista y por tanto ayudar a reducir la dependencia del narcótico. Por tanto, puede ser deseable combinar el agonista opioide (o agonista parcial) en la composición de película con un antagonista opioide o una sal farmacéuticamente aceptable del mismo. Los agentes activos pueden dispersarse por la totalidad de la dosificación por separado o pueden combinarse entre sí y dispersarse en la dosificación. De la manera más deseable, el

antagonista incluye naloxona, pero puede seleccionarse cualquier antagonista básico adecuado, según se desee. El antagonista puede ser opcionalmente soluble en agua, de modo que se vuelva difícil la separación del antagonista y el agonista, reduciendo de ese modo el potencial para el abuso del agonista.

Como con una película que incluye un agonista, la película que incluye un agonista y un antagonista es de pH controlado a través de la inclusión de un tampón. En tales películas de combinación, se ha descubierto que el pH local de la composición de película debe estar preferiblemente en el intervalo de aproximadamente 2 a aproximadamente 4, y más preferiblemente de aproximadamente 3 a aproximadamente 4 de modo que se proporcione un producto bioequivalente al comprimido disponible comercialmente Suboxone®. Lo más preferiblemente, el pH local de la composición de película es de aproximadamente 3,5. A este nivel de pH local, se optimiza la absorción de la buprenorfina mientras que se inhibe la absorción de la naloxona.

La película puede contener cualquier nivel deseado de polímero formador de película autosoportada, de manera que se proporcione una composición de película autosoportada. En una realización, la composición de película contiene un polímero formador de película en una cantidad de al menos el 25% en peso de la composición. El polímero formador de película puede estar presente alternativamente en una cantidad de al menos el 50% en peso de la composición. Tal como se explicó anteriormente, puede usarse cualquier polímero formador de película que confiera la mucoadhesión y velocidad de disolución de película deseadas, según se desee.

Puede incluirse en la dosificación cualquier nivel deseado de agonista y antagonista opcional, de modo que se proporcione el efecto deseado. En una realización particular, la composición de película incluye de aproximadamente 2 mg a aproximadamente 16 mg de agonista por dosificación. De manera más deseable, la composición de película incluye de aproximadamente 4 mg a aproximadamente 12 mg de agonista por dosificación. Si se desea, la composición de película puede incluir de aproximadamente 0,5 mg a aproximadamente 5 mg de antagonista por dosificación. De manera más deseable, la composición de película incluye de aproximadamente 1 mg a aproximadamente 3 mg de antagonista por dosificación. Si se incorpora un antagonista en la película, la

composición de película puede incluir el antagonista en una razón de aproximadamente 6:1 - 2:1 de agonista con respecto a antagonista. De la manera más deseable, la composición de película contiene aproximadamente 4:1 de agonista con respecto a antagonista por dosificación. Por ejemplo, en una realización, la dosificación incluye un agonista en una cantidad de aproximadamente 12 mg, e incluye un antagonista en una cantidad de aproximadamente 3 mg.

Las composiciones de película contienen además de manera deseable un tampón de modo que se controle el pH local de la composición de película. Puede incorporarse cualquier nivel deseado de tampón en la composición de película de modo que se proporcione el nivel de pH local deseado. El tampón se proporciona preferiblemente en una cantidad suficiente para controlar la liberación desde la película y/o la absorción en el organismo del agonista y el antagonista opcional. En una realización deseada, la composición de película incluye tampón en una razón de tampón con respecto a agonista en una cantidad de desde aproximadamente 2:1 hasta aproximadamente 1:5 (tampón:agonista). El tampón puede proporcionarse alternativamente en una razón 1:1 de tampón con respecto a agonista. Tal como se estableció anteriormente, la composición de película tiene preferiblemente un pH local de aproximadamente 2 a aproximadamente 4, y lo más preferiblemente tiene un pH local de aproximadamente 3,5. Puede usarse cualquier sistema tamponante, según se desee. En algunas realizaciones, el tampón puede incluir citrato de sodio, ácido cítrico y combinaciones de los mismos.

En esta realización, la composición de película resultante incluye una matriz de polímero, un agonista y un antagonista opcional, mientras que la composición de película tiene un pH local controlado hasta el nivel deseado. El tampón está presente preferiblemente en una cantidad para proporcionar una absorción del agonista terapéuticamente adecuada, mientras que simultáneamente limita la absorción del antagonista. El control del pH local permite la liberación y/o absorción deseada de los componentes y, por tanto, proporciona una dosificación más útil y eficaz.

La composición de dosificación de película puede incluir una matriz portadora de polímero, una cantidad terapéuticamente

eficaz de agonista, una cantidad terapéuticamente eficaz de antagonista y un sistema de tamponamiento. El sistema de tamponamiento puede incluir un tampón además de un disolvente. El sistema de tamponamiento incluye de manera deseable un nivel suficiente de tampón de modo que se proporcione un nivel de pH local deseado de la composición de dosificación de película.

Además de un nivel de pH local deseado, el tampón tiene preferiblemente una capacidad tamponante suficiente para mantener la ionización del antagonista opcional durante el tiempo en el que la composición está en la cavidad oral de un usuario. El mantenimiento de la ionización del antagonista sirve para limitar la absorción del antagonista, y por tanto proporcionar el control deseado del antagonista. Aunque la ionización del antagonista sea limitada, la ionización del agonista puede no estar limitada de ese modo. Como tal, la forma de dosificación resultante proporciona la absorción del agonista al usuario, mientras que se reduce y/o impide de manera suficiente la absorción del antagonista. Manteniendo el antagonista ionizado y el pH local al pH óptimo, el antagonista tiene una absorción limitada, si alguna, pero todavía está presente en el caso de que se hiciera un abuso del producto o se tomara a través de una vía de administración diferente. Sin embargo, cuando se toma según se administra, el antagonista tiene de poco a ningún efecto en el bloqueo del agonista.

La composición de dosificación de película que incluye un agonista puede configurarse para proporcionar un perfil plasmático *in vivo* que tiene una concentración plasmática máxima media (C_{max}) en un intervalo deseado. Se ha descubierto por parte de los solicitantes que el control de la C_{max} de la composición de película permite que se controle la absorción del agente activo (tal como un agonista) en el usuario. La composición de película resultante es más eficaz y adecuada para su administración a un usuario.

Tal como se explicó, la composición de dosificación de película proporciona un resultado bioequivalente a un producto disponible comercialmente, Suboxone®. Tal como se explicará más en los ejemplos a continuación, el Suboxone® disponible comercialmente proporciona diferentes niveles de absorción dependiendo de la cantidad de buprenorfina y naloxona administrada. La presente invención proporciona de manera

deseable un producto de película que proporciona una liberación bioequivalente a la del producto Suboxone®. Como con el producto Suboxone®, la buprenorfina puede estar presente en una cantidad de desde aproximadamente 2 mg hasta aproximadamente 16 mg por dosificación, o, si se desea de aproximadamente 4 mg a aproximadamente 12 mg por dosificación. Adicionalmente, la naloxona puede estar presente en cualquier cantidad deseada, preferiblemente a aproximadamente el 25% del nivel de buprenorfina. Por ejemplo, un producto de película de la invención puede tener 2 mg de buprenorfina y 0,5 mg de naloxona, 4 mg de buprenorfina y 1 mg de naloxona, 8 mg de buprenorfina y 2 mg de naloxona, 12 mg de buprenorfina y 3 mg de naloxona, 16 mg de buprenorfina y 4 mg de naloxona, o cantidades similares cualesquiera.

Se ha descubierto además que, controlando el valor medio del área bajo la curva (AUC) de la composición de película, puede proporcionarse una forma de dosificación más eficaz. Tal como se describe en más detalle en los ejemplos a continuación, la composición de película de la invención proporciona preferiblemente un valor de AUC de modo que se proporciona un resultado bioequivalente al proporcionado por el comprimido disponible comercialmente Suboxone®. En una realización, la composición de película puede incluir un valor medio de AUCinf de aproximadamente 6,8 h.ng/ml o superior. Alternativamente, la composición de película puede incluir un valor medio de AUCinf de desde aproximadamente 6,8 h.ng/ml hasta aproximadamente 66 h.ng/ml.

Tal como se explicó anteriormente, las composiciones de película pueden incluir naloxona, un antagonista. Cuando la composición de película incluye una combinación de agonista y antagonista, la composición de película puede configurarse para proporcionar una Cmax y/o AUCinf particular para el antagonista. Por ejemplo, cuando se incorporan un agonista de buprenorfina y un antagonista de naloxona en la composición de película, la naloxona puede configurarse para proporcionar una Cmax inferior a aproximadamente 400 pg/ml, inferior a aproximadamente 318 pg/ml, inferior a aproximadamente 235 pg/ml, inferior a aproximadamente 92 pg/ml o inferior a aproximadamente 64 pg/ml. En tales películas, la naloxona puede proporcionar un valor medio de AUCinf inferior a aproximadamente 1030 h.ng/ml.

En formulaciones que incluyen un agonista en combinación con un antagonista, la composición de película puede prepararse para proporcionar un valor de C_{max} y/o AUC_{inf} deseado para cada uno del agonista y el antagonista. En una realización, la composición de película proporciona un perfil plasmático *in vivo* que tiene una C_{max} inferior a aproximadamente 6,4 ng/ml para el agonista y un perfil plasmático *in vivo* que tiene una C_{max} inferior a aproximadamente 400 pg/ml para el antagonista. En tales realizaciones, la formulación puede proporcionar un valor de AUC_{inf} superior a aproximadamente 6,8 h.ng/ml para el agonista. Si se desea, la formulación puede proporcionar un valor de AUC_{inf} inferior a aproximadamente 1030 h. pg/ml para el antagonista. Tales composiciones pueden incluir el agonista y el antagonista en cualquier deseado cantidad, y en una realización preferida, la composición incluye de aproximadamente 2 mg a aproximadamente 16 mg del agonista por dosificación y de aproximadamente 0,5 mg a aproximadamente 4 mg del antagonista por dosificación.

La presente invención proporciona un método de tratamiento de la dependencia de narcóticos en un paciente. En una realización, el paciente tiene dependencia de narcóticos opioides, pero el paciente puede tener una dependencia de narcóticos no opioides. De manera deseable, el paciente se trata proporcionando una dosificación al paciente, que proporciona una liberación eficaz de agentes activos pero que proporciona simultáneamente una adhesión adecuada de modo que la dosificación no puede retirarse fácilmente. En un método de tratamiento, se proporciona una composición de película que puede disolverse por vía oral a un paciente.

Dependiendo del narcótico particular del que el paciente experimenta dependencia, la composición de película puede incluir uno o más componentes activos particulares. En una realización, la composición de película incluye una matriz portadora de polímero y una cantidad terapéuticamente eficaz de un agonista. De manera deseable el agonista es un agonista parcial. Para la dependencia de opioides, el agonista puede ser un agonista opioide, tal como buprenorfina o una sal farmacéuticamente aceptable de la misma. La composición de película incluye preferiblemente un tampón en una cantidad suficiente para controlar el pH local de la composición de

película. Puede usarse cualquier sistema tamponante, incluyendo citrato de sodio, ácido cítrico y combinaciones de los mismos. En composiciones que incluyen únicamente un agonista, el pH local de la composición de película es de manera deseable de aproximadamente 5 a aproximadamente 6,5, y de la manera más deseable el pH local es de aproximadamente 5,5. A este nivel, la absorción del agonista es la más eficaz. Para tratar la dependencia, la composición de película se administra al paciente, de la manera más deseable en la cavidad oral del paciente.

Si se desea, la composición puede incluir una cantidad terapéuticamente eficaz de un antagonista, para impedir el abuso del agonista. Una "cantidad terapéuticamente eficaz" de un antagonista pretende referirse a una cantidad del antagonista que puede ser útil para eludir el abuso del agonista por parte de un usuario. El antagonista puede ser cualquier antagonista deseado, y en una realización incluye naloxona o una sal farmacéuticamente aceptable de la misma. La composición de película se administra preferiblemente a un paciente a través de la cavidad oral del paciente, pero puede administrarse en cualquier medio deseado. Entonces se permite que la composición de película que puede disolverse por vía oral se disuelva en la cavidad oral del paciente durante un tiempo suficiente de modo que se libere(n) el/los agente(s) activo(s) en la misma. En algunas realizaciones, la composición de película puede permanecer en la cavidad oral durante al menos 30 segundos, y en algunas realizaciones puede permanecer en la cavidad oral durante al menos 1 minuto. Después de colocarse la composición de película en la cavidad oral del paciente, la película se adhiere preferiblemente lo suficiente de modo que se vuelve difícil su retirada. Tras haberse administrado la composición de película al paciente, el/los agente(s) activo(s) se libera(n) de manera suficiente desde la composición y se permite que tengan efecto sobre el paciente.

Las composiciones de película de la presente invención pueden formarse mediante cualquier procedimiento deseado. Se exponen procedimientos adecuados en las patentes estadounidenses n.ºs 7.425.292 y 7.357.891, cuyo contenido completo se incorpora como referencia al presente documento. En una realización, la composición de dosificación de película se forma preparando en

primer lugar una composición húmeda, incluyendo la composición húmeda una matriz portadora polimérica, una cantidad terapéuticamente eficaz de un agonista y un tampón en una cantidad suficiente para controlar el pH local de la composición hasta un nivel deseado. La composición húmeda se cuele entonces para dar una película y luego se seca de manera suficiente para formar una composición de película autosoportada. La composición húmeda puede colarse para dar dosificaciones individuales, o puede colarse para dar una lámina, cortándose entonces la lámina en dosificaciones individuales. El agonista puede ser un agonista parcial. Si se desea, la composición húmeda puede incluir una cantidad terapéuticamente eficaz de un antagonista.

El agonista y el antagonista opcional se seleccionan preferiblemente para tratar una dependencia de narcóticos particular. Para la dependencia de opioides, por ejemplo, el agonista puede incluir buprenorfina o una sal farmacéuticamente aceptable de la misma, mientras que el antagonista puede incluir naloxona o una sal farmacéuticamente aceptable de la misma. El pH local de la composición de película se mantiene de manera deseable a de aproximadamente 2 a aproximadamente 4.

EJEMPLOS

Ejemplo 1 - Composición de películas de buprenorfina/naloxona a diversas concentraciones

Se prepararon tiras de película que incluían una combinación de buprenorfina y naloxona. Se prepararon composición de película de cuatro concentraciones diferentes, incluyendo una razón de buprenorfina con respecto a naloxona de 16/4, 12/3, 8/2 y 2/0,5. Se resumen las composiciones en la tabla 1 a continuación.

Tabla 1 - Diversas composiciones de dosificaciones de película

Componentes	Películas de buprenorfina/naloxona Fórmula unitaria (mg por tira de película)			
Razones de buprenorfina/naloxona	16/4	12/3	8/2	2/0,5
Componentes activos				
Buprenorfina HCl	17,28	12,96	8,64	2,16

Naloxona HCl dihidratada	4,88	3,66	2,44	0,61
Componentes inactivos				
Poli(óxido de etileno), NF (PM 200.000)	27,09	20,32	13,55	--
Poli(óxido de etileno), NF (PM 100.000)	12,04	9,03	6,02	19,06
Poli(óxido de etileno), NF (PM 900.000)	4,82	3,62	2,41	2,05
Maltitol, NF	12,04	9,03	6,02	5,87
Aroma	6,0	4,5	3,0	2,4
Ácido cítrico, USP	5,92	4,44	2,96	2,96
HPMC	4,22	3,16	2,11	2,34
Ace-K	3,0	2,25	1,5	1,2
Citrato de sodio, anhidro	2,68	2,01	1,34	1,34
Colorante	0,03	0,02	0,01	0,1
Total (mg)	100	75	50	40

Ejemplo 2 - Estudios de absorción para productos Suboxone®

Se prepararon diversos productos de comprimido y película y se sometieron a prueba para determinar los datos de absorción, incluyendo los niveles de absorción de AUC y Cmax. Los productos sometidos a prueba incluyeron comprimidos Suboxone® preparados con o bien 2 mg o bien 16 mg de buprenorfina así como o bien 0,5 mg o bien 4,0 mg de naloxona. Para comprimidos de 16 mg de buprenorfina, se combinaron entre sí dos comprimidos de 8 mg de buprenorfina para proporcionar el nivel de componentes de un comprimido de 16 mg de buprenorfina. En los casos en los que se evaluó un comprimido de 12 mg de buprenorfina, se obtuvo esta dosificación combinando un comprimido de 8 mg de buprenorfina y dos comprimidos de 2 mg de buprenorfina. Se sometieron a prueba estos productos para determinar los niveles de absorción, con las cantidades enumeradas en la tabla 2 a continuación.

Tabla 2 - Datos de absorción para productos Suboxone®

Muestra	Cmax	AUC
Comprimido Suboxone® de buprenorfina (2 mg)	0,780 ng/ml	6,789 h*ng/ml
Comprimido Suboxone® de naloxona (0,5 mg)	51,30 pg/ml	128,60 h*pg/ml

Comprimido Suboxone® de buprenorfina (16 mg)	4,51 ng/ml	44,99 h*ng/ml
Comprimido Suboxone® de naloxona (4 mg)	259,00 pg/ml	649,60 h*pg/ml

Usando los datos de la tabla 2, se exponen los datos de absorción para los comprimidos Suboxone® para otros niveles de buprenorfina y naloxona en la tabla 2A a continuación.

Tabla 2A - Datos de absorción extrapolados para productos
Suboxone®

Muestra	Cmax	AUC
Comprimido Suboxone® de buprenorfina (4 mg)	1,35 ng/ml	12,25 h*ng/ml
Comprimido Suboxone® de naloxona (1 mg)	80,97 pg/ml	203 h*pg/ml
Comprimido Suboxone® de buprenorfina (8 mg)	2,29 ng/ml	23,17 h*ng/ml
Comprimido Suboxone® de naloxona (2 mg)	140,31 pg/ml	351,8 h*pg/ml
Comprimido Suboxone® de buprenorfina (12 mg)	3,23 ng/ml	34,08 h*ng/ml
Comprimido Suboxone® de naloxona (3 mg)	199,7 pg/ml	500,6 h*pg/ml

Ejemplo 3 - Evaluación de la bioequivalencia de comprimidos
Suboxone®

Usando los datos generados para comprimidos Suboxone® en la tabla 2 anterior, se generan intervalos de bioequivalencia aceptables para proporcionar un nivel de tratamiento equivalente al del comprimido Suboxone®. Tal como se entiende actualmente, un producto proporciona un efecto bioequivalente si proporciona niveles de absorción de entre aproximadamente el 80% y aproximadamente el 125% del comprimido Suboxone®. Se considera que la absorción en este intervalo es bioequivalente.

Tabla 3 - Intervalos de bioequivalencia aceptables para
comprimidos Suboxone® (del 80 al 125%)

Descripción de la muestra	Cmax	AUC
2 mg de buprenorfina	De 0,624 a 0,975 ng/ml	De 5,431 a 8,486 h*ng/ml
0,5 mg de naloxona	De 41,04 a 64,13 pg/ml	De 102,88 a 160,75 h*pg/ml

16 mg de buprenorfina	De 3,608 a 5,638 ng/ml	De 35,992 a 56,238 h*ng/ml
4 mg de naloxona	De 207,20 a 323,75 pg/ml	De 519,68 a 812,00 h*pg/ml

Por tanto, para considerarse bioequivalente al comprimido Suboxone®, la Cmax de buprenorfina es de entre aproximadamente 0,624 y 5,638, y la AUC de buprenorfina es de entre aproximadamente 5,431 y aproximadamente 56,238. De manera similar, para considerarse bioequivalente al comprimido Suboxone®, la Cmax de naloxona es de entre aproximadamente 41,04 y aproximadamente 323,75, y la AUC de naloxona es de entre aproximadamente 102,88 y aproximadamente 812,00.

Ejemplo 4 - Estudios de absorción para productos de película a pH 3,5

Se prepararon diversos productos de película y se sometieron a prueba para determinar los datos de absorción, incluyendo los niveles de absorción de AUC y Cmax. Los productos sometidos a prueba incluyeron tiras de película de la invención, teniendo las tiras de película o bien 2 mg o bien 16 mg de buprenorfina así como o bien 0,5 mg o bien 4,0 mg de naloxona. Se sometieron a prueba estos productos para determinar los niveles de absorción, con las cantidades enumeradas en la tabla 4 a continuación.

Tabla 4 - Datos de absorción para productos de película de la invención a pH 3,5

Muestra	Cmax	AUC
Película sublingual de buprenorfina (2 mg)	0,947 ng/ml	7,82 h*ng/ml
Película sublingual de naloxona (0,5 mg)	51,10 pg/ml	128,60 h*pg/ml
Película sublingual de buprenorfina (16 mg)	5,47 ng/ml	55,30 h*ng/ml
Película sublingual de naloxona (4 mg)	324,00 pg/ml	873,60 h*pg/ml

Tal como puede observarse, en este experimento, los valores para la absorbancia de buprenorfina estaban directamente en el intervalo de bioequivalencia evaluado anteriormente. Se

determinó, por tanto, que las películas de la invención habían proporcionado una absorción de buprenorfina bioequivalente a un pH local de 3,5 a la del comprimido disponible comercialmente Suboxone®. Los valores para la absorción de naloxona eran muy próximos al intervalo de bioequivalencia de Suboxone®. La absorción de naloxona ligeramente superior no se debió al pH local sino más bien a la cantidad de tampón (capacidad tamponante tal como se trata en la solicitud). Esto se confirma por el hecho de que la dosis inferior de 2/0,5 mg está en el intervalo para la naloxona y esto se debe a la mayor capacidad tamponante para la dosis de 2/0,5 tal como se señala en el gráfico de capacidad tamponante.

Ejemplo 5 - Preparación de películas para el estudio *in vivo*

Se prepararon dosificaciones de película para su uso en un estudio *in vivo* para determinar la biodisponibilidad de comprimidos de buprenorfina/naloxona y formulaciones de película. Específicamente, se sometieron a prueba las películas para determinar si la película proporciona un efecto bioequivalente al de una formulación de comprimido.

Se prepararon tres formulaciones de película que incluían 8 mg de buprenorfina y 2 mg de naloxona, tamponándose cada una a un pH diferente. La primera película no incluía ningún tampón, proporcionando un pH local de aproximadamente 6,5. La segunda se tamponó a un nivel de pH local de aproximadamente 3-3,5. La tercera se tamponó a un nivel de pH local de aproximadamente 5-5,5. Se exponen las formulaciones en la tabla 5 a continuación.

Tabla 5 - Formulaciones de películas de prueba a diversos niveles de pH

Componente	Formulación de prueba 1		Formulación de prueba 2		Formulación de prueba 3	
	8 mg/2 mg pH = 6,5		8 mg/2 mg pH = 3-3,5		8 mg/2 mg pH = 5-5,5	
	%p/p	Mg/ película	%p/p	Mg/ película	%p/p	Mg/ película
Buprenor- fina HCl	21,61	8,64	17,28	8,64	17,28	8,64
Naloxona HCl	6,10	2,44	4,88	2,44	4,88	2,44

dihidratada						
Polímero	5,05	2,02	4,82	2,41	4,82	2,41
Polímero	28,48	11,39	27,09	13,55	27,09	13,55
Polímero	12,65	5,06	12,04	6,02	12,04	6,02
Polímero	4,43	1,77	4,22	2,11	4,22	2,11
Edulco- rante	12,65	5,06	12,04	6,02	12,04	6,02
Edulco- rante	3	1,2	3	1,5	3	1,5
Aroma	6	2,4	6	3	6	3
Ácido cítrico	0	0	5,92	2,96	2,51	1,26
Citrato de sodio	0	0	2,68	1,34	6,08	3,04
Amarillo F&C n.º6	0,025	0,01	0,03	0,02	0,03	0,02
Total	100	40	100	50	100	50

Ejemplo 6 - Análisis de la absorción *in vivo* de la película que tenía un pH de 6,5

Se analizó la composición de dosificación de película de la película que tenía un pH local de 6,5. Específicamente, se analizó *in vivo* la formulación de prueba 1, tal como se preparó en el ejemplo 5, para determinar la absorción de buprenorfina y de naloxona. Se comparó la película comparativa con la absorción de buprenorfina y de naloxona proporcionada por un comprimido de una dosis (Suboxone®). Se comparó la película de prueba para determinar si proporcionaba un efecto bioequivalente al del producto de comprimido.

Los resultados para la formulación de prueba 1, que tenía un pH local de aproximadamente 6,5, en comparación con el comprimido de una dosis, se exponen en las tablas 6 y 7 a continuación.

Tabla 6 - Datos de absorción *in vivo* de buprenorfina para la formulación de prueba 1

Parámetro	Suboxone® sublingual				Formulación de prueba 1 (pH = 6,5)			
	n	Media	D.E.	%CV	n	Media	D.E.	%CV
T _{max} (h)	15	1,60	0,47	29,41	15	1,5	0,62	41,23
C _{max} (ng/ml)	15	2,27	0,562	24,77	15	2,60	0,872	33,53

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AUC _{última} (h*ng/ml)	15	27,08	10,40	38,41	15	31,00	12,93	41,72
AUC _{inf} (h*ng/ml)	15	29,58	11,15	37,68	15	33,37	13,88	41,61
T _{1/2} (h)	15	44,76	20,86	46,60	15	40,73	14,93	36,66

Tabla 7 - Datos de absorción *in vivo* de naloxona para la formulación de prueba 1

	Suboxone® sublingual				Formulación de prueba 1 (pH = 6,5)			
Parámetro	n	Media	D.E.	%CV	n	Media	D.E.	%CV
T _{max} (h)	15	0,90	0,23	25,32	15	0,68	0,18	25,75
C _{max} (ng/ml)	15	94,6	39,1	41,33	15	410	122	29,75
AUC _{última} (h*ng/ml)	15	297,1	120,7	40,62	15	914,8	158,1	17,29
AUC _{inf} (h*ng/ml)	15	306,1	122,6	40,06	15	924,2	158,8	17,18
T _{1/2} (h)	15	6,62	2,60	39,26	15	6,86	2,08	30,27

Tal como puede observarse, los datos *in vivo* indican que la buprenorfina se absorbe muy bien desde la formulación de película a un pH local de 6,5, y coincidía estrechamente con la absorción observada en el comprimido de una dosis Suboxone®. Sin embargo, la absorción también se maximizó para la naloxona, lo que era indeseable. Se determinó que una película que tenía una combinación de buprenorfina y naloxona y un pH local de 6,5 no proporcionaba un efecto bioequivalente al del comprimido Suboxone® tanto para buprenorfina como naloxona.

Ejemplo 7 - Análisis de la absorción *in vivo* de la película que tenía un pH de 5-5,5

Habiendo determinado la absorción de buprenorfina y naloxona en la película que tenía un pH local de 6,5, se analizó una composición de dosificación de película de la película que tenía un pH local de 5-5,5. Específicamente, se analizó *in vivo* la formulación de prueba 3, tal como se preparó en el ejemplo 5, para determinar la absorción de buprenorfina y de naloxona. Se compararon las películas comparativas con la absorción de buprenorfina y de naloxona proporcionada por el comprimido de una dosis Suboxone®. Se comparó la película de prueba para

determinar si proporcionaba un efecto bioequivalente al del comprimido Suboxone®.

Los resultados para la formulación de prueba 3, que tenía un pH local de aproximadamente 5-5,5, en comparación con el comprimido Suboxone®, se exponen en las tablas 8 y 9 a continuación.

Tabla 8 - Datos de absorción *in vivo* de buprenorfina para la formulación de prueba 3

Parámetro	Suboxone® sublingual				Formulación de prueba 3 (pH = 5-5,5)			
	n	Media	D.E.	%CV	n	Media	D.E.	%CV
T _{max} (h)	15	1,60	0,47	29,41	14	1,50	0,43	28,50
C _{max} (ng/ml)	15	2,27	0,562	24,77	14	3,47	1,57	45,40
AUC _{última} (h*ng/ml)	15	27,08	10,40	38,41	14	33,25	16,01	48,16
AUC _{inf} (h*ng/ml)	15	29,58	11,15	37,68	13	38,34	15,38	40,13
T _{1/2} (h)	15	44,76	20,86	46,60	13	41,71	17,70	42,42

Tabla 9 - Datos de absorción *in vivo* de naloxona para la formulación de prueba 3

Parámetro	Suboxone® sublingual				Formulación de prueba 3 (pH = 5-5,5)			
	n	Media	D.E.	%CV	n	Media	D.E.	%CV
T _{max} (h)	15	0,90	0,23	25,32	14	0,98	0,62	63,51
C _{max} (ng/ml)	15	94,6	39,1	41,33	14	173	84,5	48,79
AUC _{última} (h*ng/ml)	15	297,1	120,7	40,62	14	455,2	195,5	42,94
AUC _{inf} (h*ng/ml)	15	306,1	122,6	40,06	13	474,4	203,1	42,81
T _{1/2} (h)	15	6,62	2,60	39,26	13	9,45	6,90	73,00

Tal como puede observarse, los datos *in vivo* indicaron que la absorción de buprenorfina aumentó a medida que disminuyó el nivel de pH local. Parecía que disminuyendo el pH local desde 6,5 hasta 5,5, se desplazaba la absorción de buprenorfina hasta un nivel más alejado de el del comprimido de una dosis. Además, los valores de naloxona no proporcionaron un resultado bioequivalente al del comprimido de una dosis. Por tanto, se determinó que la película que tenía un pH local de 5,5 no

proporcionaba un resultado bioequivalente al del comprimido Suboxone® tanto para buprenorfina como naloxona.

Se observó que reduciendo el pH local de la película hasta un nivel de 5,5, se proporcionaría un aumento del nivel de absorción de buprenorfina. Por tanto, puede ser deseable tamponar una composición de película que incorpora la propia buprenorfina a un nivel de aproximadamente 5,5 para proporcionar un aumento de la absorción.

Ejemplo 8 - Análisis de la absorción *in vivo* de la película que tenía un pH de 3-3,5

Habiendo determinado la absorción de buprenorfina y naloxona en películas que tenían un pH local de 6,5 y 5,5, se analizó una composición de dosificación de película de la película que tenía un pH local de aproximadamente 3-3,5. Se supuso que la absorción de buprenorfina continuaría aumentando tal como se había demostrado a un pH local de 5,5. Por tanto, se supuso que a un pH local de 3,5, la película no sería bioequivalente al comprimido.

Específicamente, se analizó *in vivo* la formulación de prueba 2, tal como se preparó en el ejemplo 5, para determinar la absorción de buprenorfina y de naloxona. Se compararon las películas comparativas con la absorción de buprenorfina y de naloxona proporcionada por el comprimido de una dosis Suboxone®. Se comparó la película de prueba para determinar si proporcionaba un efecto bioequivalente al del producto de comprimido.

Los resultados para la formulación de prueba 2, que tenía un pH local de aproximadamente 3-3,5, en comparación con el comprimido Suboxone®, se exponen en las tablas 10 y 11 a continuación.

Tabla 10 - Datos de absorción *in vivo* de buprenorfina para la formulación de prueba 2

Parámetro	Suboxone® sublingual				Formulación de prueba 2 (pH = 3-3,5)			
	n	Media	D.E.	%CV	n	Media	D.E.	%CV
T _{max} (h)	15	1,60	0,47	29,41	14	1,68	0,58	34,68
C _{max} (ng/ml)	15	2,27	0,562	24,77	14	2,68	0,910	33,99
AUC _{última}	15	27,08	10,40	38,41	14	29,73	12,05	40,54

(h*ng/ml)								
AUC _{inf} (h*ng/ml)	15	29,58	11,15	37,68	14	31,45	12,98	41,26
T _{1/2} (h)	15	44,76	20,86	46,60	14	30,03	13,95	46,46

Tabla 11 - Datos de absorción *in vivo* de naloxona para la formulación de prueba 2

	Suboxone® sublingual				Formulación de prueba 2 (pH = 3-3,5)			
Parámetro	n	Media	D.E.	%CV	n	Media	D.E.	%CV
T _{max} (h)	15	0,90	0,23	25,32	14	0,84	0,19	22,19
C _{max} (ng/ml)	15	94,6	39,1	41,33	14	130	72,9	56,04
AUC _{última} (h*ng/ml)	15	297,1	120,7	40,62	14	362,2	155,9	43,03
AUC _{inf} (h*ng/ml)	15	306,1	122,6	40,06	12	350,4	142,3	40,61
T _{1/2} (h)	15	6,62	2,60	39,26	12	8,07	4,75	58,84

Tal como puede observarse, los datos *in vivo* indicaron que la absorción de buprenorfina era sustancialmente bioequivalente a la del comprimido de una dosis cuando se disminuyó el pH local de la composición de película hasta aproximadamente 3-3,5. Este resultado era sorprendente ya que no parecía seguir la teoría de reparto del pH. Además, a un pH local de aproximadamente 3-3,5, se observó que la absorción de naloxona era sustancialmente bioequivalente a la del comprimido de una dosis.

Por tanto, se determinó que el producto de película que incluía buprenorfina y naloxona a un pH local de 3-3,5 era sustancialmente bioequivalente al comprimido de una dosis Suboxone®.

Ejemplo 9 - Valores normalizados para naloxona en películas y comprimidos

Se prepararon diversas composiciones de película que incluían buprenorfina y naloxona en dosificaciones de 8/2 mg y 2/0,5 mg, y que tenían diferentes valores de pH local de desde 6,5 hasta 3,5, y se analizaron. Se normalizaron los datos y se compararon con el comprimido de una dosis. Los resultados se exponen en la tabla 12 a continuación.

Tabla 12 - Valores normalizados para película de naloxona en comparación con comprimido

pH	Dosis (mg) buprenorfina /naloxona	AUC (normalizada)	Cmax	Mg de ácido cítrico	Razón de ácido cítrico (mg)/naloxona (mg)
6,5	8/2	3,02	4,33	1,34	0,67
5,5	8/2	1,55	1,83	1,34	0,67
3,5	8/2	1,14	1,37	1,34	0,67
3,5	2/0,5	0,98	0,90	1,34	2,68
5,5	2/0,5	1,41	1,41	1,34	2,68

Los datos indican que no sólo es de importancia significativa el pH local, sino que la cantidad de tampón presente en la fórmula también es importante. La mejora de la dosis de 8/2 con respecto a la dosis de 2/0,5 (a un pH local de 3,5) demuestra esta importancia. La dosis de 8/2 tiene una razón de tampón/naloxona de 0,67, y esta dosis proporcionó resultados bioequivalentes aceptables limítrofes. En cambio, la dosis de 2/0,5 tiene una razón de tampón/naloxona de 2,68, y proporciona un valor de absorción más bioequivalente que la dosis de 8/2.

De hecho, los datos muestran que la dosis de 2/0,5 a un pH local de 3,5 tenía una absorción bucal incluso menor que el comprimido de una dosis, tal como se observa a partir de los valores normalizados para la AUC y Cmax. Esto demuestra que se produce una absorción de la naloxona incluso menor para la formulación de película a un pH local de 3,5 que para la formulación de comprimido. Dado el objetivo de reducir la absorción de naloxona, parece que el producto de película tamponado a un pH local de 3,5 con una razón de tampón/naloxona de 2,68 proporciona resultados incluso mejores que la formulación de comprimido Suboxone®.

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REIVINDICACIONES

1. Composición de dosificación de película que comprende:
 - a. una matriz portadora polimérica;
 - b. una cantidad terapéuticamente eficaz de buprenorfina o una sal farmacéuticamente aceptable de la misma;
 - c. una cantidad terapéuticamente eficaz de naloxona o una sal farmacéuticamente aceptable de la misma; y
 - d. un tampón en una cantidad para proporcionar un pH local de dicha composición de un valor suficiente para optimizar la absorción de dicha buprenorfina.
2. Composición según la reivindicación 1, en la que dicho pH local es de aproximadamente 2 a aproximadamente 4.
3. Composición según la reivindicación 2, en la que el pH local de dicha composición es de desde aproximadamente 3 hasta aproximadamente 4.
4. Composición según la reivindicación 1, en la que dicha composición de dosificación de película proporciona una absorción de buprenorfina bioequivalente a la de un comprimido que tiene una cantidad equivalente de buprenorfina o una sal farmacéuticamente aceptable de la misma.
5. Composición según la reivindicación 1, en la que dicha matriz portadora polimérica comprende al menos un polímero en una cantidad de al menos el 25% en peso de dicha composición.
6. Composición según la reivindicación 1, en la que dicho tampón está presente en una cantidad de desde aproximadamente 2:1 hasta aproximadamente 1:5 en peso de tampón con respecto a buprenorfina.
7. Composición según la reivindicación 1, en la que dicha matriz portadora polimérica comprende al menos un polímero formador de película autosoportada.
8. Composición de dosificación de película según la reivindicación 1, en la que dicha buprenorfina está presente en una cantidad de desde aproximadamente 2 mg hasta aproximadamente 16 mg por dosificación.
9. Composición de dosificación de película según la reivindicación 1, en la que dicho tampón comprende citrato de sodio, ácido cítrico y combinaciones de los mismos.

10. Composición de dosificación de película según la reivindicación 1, en la que dicho tampón comprende ácido acético, acetato de sodio y combinaciones de los mismos.
11. Composición de dosificación de película que comprende:
- a. una matriz portadora polimérica;
 - b. una cantidad terapéuticamente eficaz de buprenorfina o una sal farmacéuticamente aceptable de la misma;
 - c. una cantidad terapéuticamente eficaz de naloxona o una sal farmacéuticamente aceptable de la misma; y
 - d. un tampón en una cantidad suficiente para inhibir la absorción de dicha naloxona cuando se administra por vía oral.
12. Composición según la reivindicación 11, en la que dicha composición tiene un pH local de aproximadamente 2 a aproximadamente 4.
13. Composición según la reivindicación 11, en la que dicho tampón está presente en una cantidad suficiente para proporcionar una absorción de buprenorfina terapéuticamente adecuada.
14. Composición según la reivindicación 13, en la que una absorción de buprenorfina terapéuticamente adecuada comprende un nivel bioequivalente de absorción de buprenorfina como comprimido que tiene una cantidad equivalente de buprenorfina o una sal farmacéuticamente aceptable de la misma.
15. Composición de dosificación de película que comprende:
- a. una matriz portadora polimérica;
 - b. una cantidad terapéuticamente eficaz de buprenorfina o una sal farmacéuticamente aceptable de la misma;
 - c. una cantidad terapéuticamente eficaz de naloxona o una sal farmacéuticamente aceptable de la misma; y
 - d. un sistema de tamponamiento;
- en la que dicho sistema de tamponamiento comprende una capacidad tamponante suficiente para mantener la ionización de la naloxona durante el tiempo en el que dicha composición está en la cavidad oral de un usuario.
16. Composición según la reivindicación 15, en la que dicha composición tiene un pH local de aproximadamente 2 a aproximadamente 4.

17. Método de tratamiento de la dependencia de narcóticos de un usuario, que comprende las etapas de:
- a. proporcionar una composición que comprende:
 - i. una matriz portadora polimérica;
 - ii. una cantidad terapéuticamente eficaz de buprenorfina o una sal farmacéuticamente aceptable de la misma;
 - iii. una cantidad terapéuticamente eficaz de naloxona o una sal farmacéuticamente aceptable de la misma; y
 - iv. un tampón en una cantidad para proporcionar un pH local de dicha composición de un valor suficiente para optimizar la absorción de dicha buprenorfina;
 - y
 - b. administrar dicha composición a la cavidad oral de un usuario.
18. Composición según la reivindicación 17, en la que dicho método proporciona una absorción de buprenorfina bioequivalente a la de un comprimido que tiene una cantidad equivalente de buprenorfina o una sal farmacéuticamente aceptable de la misma.
19. Método según la reivindicación 17, en el que dicha composición tiene un pH local de aproximadamente 2 a aproximadamente 4.
20. Método según la reivindicación 17, en el que dicha composición de dosificación de película se administra al usuario a través de administración bucal, administración sublingual y combinaciones de las mismas.
21. Método según la reivindicación 17, en el que dicha composición de dosificación de película permanece en la cavidad oral del usuario durante un periodo de al menos 1 minuto.
22. Método según la reivindicación 17, en el que dicha composición de dosificación de película permanece en la cavidad oral del usuario durante un periodo de entre aproximadamente 1 y 1,5 minutos.
23. Método según la reivindicación 17, en el que dicha composición de dosificación de película permanece en la cavidad oral del usuario durante un periodo de hasta 3 minutos.

24. Procedimiento de formación de una composición de dosificación de película que comprende las etapas de:
- a. colar una composición formadora de película, comprendiendo dicha composición formadora de película:
 - i. una matriz portadora polimérica;
 - ii. una cantidad terapéuticamente eficaz de buprenorfina o una sal farmacéuticamente aceptable de la misma;
 - iii. una cantidad terapéuticamente eficaz de naloxona o una sal farmacéuticamente aceptable de la misma; y
 - iv. un tampón en una cantidad para proporcionar un pH local de dicha composición de un valor suficiente para optimizar la absorción de dicha buprenorfina;
 - y
 - b. secar dicha composición formadora de película para formar una composición de dosificación de película autosoportada.
25. Procedimiento según la reivindicación 24, en el que dicha composición tiene un pH local de aproximadamente 2 a aproximadamente 4.
26. Composición de dosificación de película que comprende una cantidad terapéuticamente suficiente de buprenorfina o una sal farmacéuticamente aceptable de la misma y una cantidad terapéuticamente suficiente de naloxona o una sal farmacéuticamente aceptable de la misma, teniendo dicha composición de dosificación de película un perfil de liberación bioequivalente como comprimido que contiene aproximadamente 2 veces la cantidad de buprenorfina o una sal farmacéuticamente aceptable de la misma.
27. Formulación de película de disolución por vía oral que comprende buprenorfina y naloxona, proporcionando dicha formulación un perfil plasmático *in vivo* que tiene una C_{max} de entre aproximadamente 0,624 ng/ml y aproximadamente 5,638 ng/ml para buprenorfina y un perfil plasmático *in vivo* que tiene una C_{max} de entre aproximadamente 41,04 pg/ml y aproximadamente 323,75 pg/ml para naloxona.
28. Formulación según la reivindicación 27, proporcionando dicha formulación una AUC media de entre aproximadamente 5,431 h.ng/ml y aproximadamente 56,238 h.ng/ml para buprenorfina.

29. Formulación según la reivindicación 27, proporcionando dicha formulación una AUC media de entre aproximadamente 102,88 h.pg/ml y aproximadamente 812,00 h.pg/ml para naloxona.
- 5 30. Formulación según la reivindicación 27, comprendiendo dicha formulación de aproximadamente 2 a aproximadamente 16 mg de buprenorfina o una sal de la misma.
- 10 31. Formulación según la reivindicación 27, comprendiendo dicha formulación de aproximadamente 0,5 a aproximadamente 4 mg de naloxona o una sal de la misma.

RESUMEN

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La presente invención se refiere a productos y métodos para el tratamiento de la dependencia de narcóticos en un usuario. La invención se refiere más particularmente a formas de dosificación autosoportadas que proporcionan un agente activo para tratar la dependencia de narcóticos a la vez que se proporciona una adhesión bucal suficiente de la forma de dosificación.

SUBLINGUAL AND BUCCAL FILM COMPOSITIONS

FIELD OF THE INVENTION

[0001] The present invention relates to compositions, methods of manufacture, products and methods of use relating to films containing therapeutic actives. The invention more particularly relates to self-supporting film dosage forms which provide a therapeutically effective dosage, essentially matching that of currently-marketed tablets containing the same active. Such compositions are particularly useful for treating narcotic dependence while providing sufficient buccal adhesion of the dosage form.

BACKGROUND OF THE RELATED TECHNOLOGY

[0002] Oral administration of two therapeutic actives in a single dosage form can be complex if the intention is to have one active absorbed into the body and the other active remain substantially unabsorbed. For example, one active may be relatively soluble in the mouth at one pH, and the other active may be relatively insoluble at the same pH. Moreover, the absorption kinetics of each therapeutic agent may be substantially different due to differing absorption of the charged and uncharged species. These factors represent some of the challenges in appropriately co-administering therapeutic agents.

[0003] Co-administration of therapeutic agents has many applications. Among such areas of treatment include treating individuals who suffer from narcotic dependence. Such individuals have a tendency to suffer from serious physical dependence on the narcotic, resulting in potentially dangerous withdrawal effects when the narcotic is not administered to the individual. In order to help individuals addicted to narcotics, it is known to provide a reduced level of a drug, which provides an effect of satisfying the body's urge for the narcotic, but does not provide the "high" that is provided by the misuse of the narcotic. The drug provided may be an agonist or a partial agonist, which provides a reduced sensation and may help lower dependence on the drug. However, even though these drugs provide only a low level of euphoric effect, they are capable of being abused by the individuals parenterally. In such cases, it is desirable to provide a combination of the drug with a second drug, which may decrease the likelihood of diversion and abuse of the first drug. For example, it is known to provide a dosage of an antagonist in combination with the agonist or partial agonist. The narcotic antagonist binds to a receptor in the brain to block the receptor, thus reducing the effect of the agonist.

[0004] One such combination of drugs has been marketed under the trade name Suboxone® as an orally ingestible tablet. However, such combinations in tablet form have the potential for abuse. In some instances, the patient who has been provided the drug may store the tablet in his mouth without swallowing the tablet, then later extract the agonist from the tablet and inject the drug into an individual's body. Although certain antagonists (such as highly water-soluble antagonists) may be used to help reduce the

ability to separate the agonist, the potential for abuse still exists. It is desired to provide a dosage that cannot be easily removed from the mouth once it has been administered.

[0005] There is currently a need for an orally dissolvable film dosage form that provides the desired absorption levels of the agonist and antagonist, while providing an adhesive effect in the mouth, rendering it difficult to remove once placed in the mouth, thereby making abuse of the agonist difficult.

SUMMARY OF THE INVENTION

[0006] In one embodiment of the present invention, there is provided a film dosage composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof; a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffer in an amount to provide a pH of the composition of a value sufficient to optimize absorption of the buprenorphine.

[0007] In another embodiment of the present invention, there is provided a film dosage composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof; a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffer in an amount sufficient to inhibit the absorption of the naloxone when administered orally.

[0008] In still other embodiments, there may be provided a film dosage composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof; a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffering system; where the buffering system includes a buffer capacity sufficient to maintain the ionization of naloxone during the time which the composition is in the oral cavity of a user.

[0009] In another embodiment of the invention, there is provided a method of treating narcotic dependence of a user, including the steps of: providing a composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof; a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffer in an amount to provide a pH of the composition of a value sufficient to optimize absorption of the buprenorphine; and administering the composition to the oral cavity of a user.

[0010] In still another embodiment of the invention, there is provided a process of forming a film dosage composition including the steps of: casting a film-forming composition, the film-forming composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof; a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffer in an amount to provide a pH of the composition of a value

sufficient to optimize absorption of the buprenorphine and drying the film-forming composition to form a self-supporting film dosage composition.

[0011] In another embodiment, there is provided a film dosage composition including a therapeutically sufficient amount of buprenorphine or a pharmaceutically acceptable salt thereof and a therapeutically sufficient amount of naloxone or a pharmaceutically acceptable salt thereof, the film dosage composition having a bioequivalent release profile as compared to a Suboxone® tablet containing about 2 times the amount of buprenorphine or a pharmaceutically acceptable salt thereof.

[0012] Still other embodiments of the present invention provide an orally dissolving film formulation including buprenorphine and naloxone, where the formulation provides an in-vivo plasma profile having a C_{max} of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in-vivo plasma profile having a C_{max} of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Definitions

[0013] As used herein, the term C_{max} refers to the mean maximum plasma concentration after administration of the composition to a human subject. As also used herein, the term AUC refers to the mean area under the plasma concentration-time curve value after administration of the compositions formed herein. As will be set forth in more detail below, the term “optimizing the absorption” does not refer to reaching the maximum absorption of the composition, and rather refers to reaching the optimum level of absorption at a pH of about 2 to about 4. The “optimum” absorption may be, for example, a level that provides a bioequivalent absorption as administration of the currently available Suboxone® tablet. An “optimum” C_{max} of buprenorphine is about 0.67 to about 5.36 mg/ml at dosages of from 2-16 mg buprenorphine at a given pH. Similarly, an “optimum” AUC of buprenorphine may be about 7.43 to about 59.46 hr*ng/ml at dosages of from 2-16 mg buprenorphine at a given pH. As will be described in more detail below, it has been surprisingly discovered that the absorption of one particular agonist, buprenorphine, can provide an optimum absorption at a pH of about 2-4 as well as about 5.5-6.5. Thus, one may “optimize” the absorption of buprenorphine by providing a pH of about 2-4 or about 5.5-6.5.

[0014] “Maximizing the absorption” refers to the maximum in vivo absorption values achieved at a pH of about 4 to about 9.

[0015] The term “local pH” refers to the pH of the region of the carrier matrix immediately surrounding the active agent as the matrix hydrates and/or dissolves, for example, in the mouth of the user.

[0016] By “inhibiting” the absorption of an active, it is meant achieving as complete an ionization state of the active as possible, such that little to none of the active is measurably absorbable. For example, at a pH of 3-3.5, the C_{max} of an active such as naloxone for dosage of 0.5 mg to 4.0 mg ranges from 32.5 to 260 pg/ml, and an AUC of naloxone for dosage of 0.5 mg to 4.0 mg ranges from 90.55 to 724.4 hr*pg/ml. It is understood that at a pH lower than 3.0, further ionization would be expected and thus result in lower absorption.

[0017] The term “bioequivalent” means obtaining 80% to 125% of the C_{max} and AUC values for a given active in a different product. For example, assuming C_{max} and AUC values of buprenorphine for a commercially-available Suboxone® tablet (containing 2 mg buprenorphine and 0.5 mg naloxone) are 0.780 ng/ml and 6.789 hr*ng/ml, respectively, a bioequivalent product would have a C_{max} of buprenorphine in the range of 0.624-0.975 ng/ml, and an AUC value of buprenorphine of 5.431-8.486 hr*ng/ml.

[0018] It will be understood that the term “film” includes thin films and sheets, in any shape, including rectangular, square, or other desired shape. The films described herein

may be any desired thickness and size such that it may be placed into the oral cavity of the user. For example, the films may have a relatively thin thickness of from about 0.1 to about 10 mils, or they may have a somewhat thicker thickness of from about 10 to about 30 mils. For some films, the thickness may be even larger, i.e., greater than about 30 mils. Films may be in a single layer or they may be multi-layered, including laminated films.

[0019] Oral dissolving films generally fall into three main classes: fast dissolving, moderate dissolving and slow dissolving. Fast dissolving films generally dissolve in about 1 second to about 30 seconds in the mouth. Moderate dissolving films generally dissolve in about 1 to about 30 minutes in the mouth, and slow dissolving films generally dissolve in more than 30 minutes in the mouth. Fast dissolving films may consist of low molecular weight hydrophilic polymers (i.e., polymers having a molecular weight between about 1,000 to 9,000, or polymers having a molecular weight up to 200,000). In contrast, slow dissolving films generally have high molecular weight polymers (i.e., having a molecular weight in the millions).

[0020] Moderate dissolving films tend to fall in between the fast and slow dissolving films. Moderate dissolving films dissolve rather quickly, but also have a good level of mucoadhesion. Moderate dissolving films are also flexible, quickly wettable, and are typically non-irritating to the user. For the instant invention, it is preferable to use films that fall between the categories of fast dissolving and moderate dissolving. Such moderate dissolving films provide a quick enough dissolution rate, most desirably between about 1 minute and about 20 minutes, while providing an acceptable mucoadhesion level such that the film is not easily removable once it is placed in the oral cavity of the user.

[0021] Inventive films described herein may include one or more agonists or partial agonists used for the treatment of drug addiction. As used herein, the term “agonist” refers to a chemical substance that is capable of providing a physiological response or activity in the body of the user. The films described herein may further include one or more antagonists. As used herein, the term “antagonist” refers to any chemical substance that acts within the body of the user to reduce the physiological activity of another chemical substance. In some embodiments, an antagonist used herein may act to reduce and/or block the physiological activity of the agonist. The actives may be water-soluble, or they may be water-insoluble. As used herein, the term “water-soluble” refers to substances that are at least partially dissolvable in a solvent, including but not limited to water. The term “water-soluble” does not necessarily mean that the substance is 100% dissolvable in the solvent. The term “water-insoluble” refers to substances that are not dissolvable in a solvent, including but not limited to water. Solvents may include water,

or alternatively may include other polar solvents by themselves or in combination with water.

Inventive Films

[0022] The present invention relates to methods of treating narcotic dependence in an individual. More desirably, the invention relates to the treatment of opioid dependence in an individual, while using a formulation and delivery that hinders misuse of the narcotic. Currently, treatment of opioid dependence is aided by administration of Suboxone®, which is an orally dissolvable tablet. This tablet which provides a combination of buprenorphine (an opioid agonist) and naloxone (an opioid antagonist). Therefore, the present invention provides a method of treating narcotic dependence by providing an orally dissolvable film dosage, which provides a bioequivalent effect to Suboxone®. The film dosage preferably provides buccal adhesion while it is in the user's mouth, rendering it difficult to remove after placement.

[0023] The film dosage composition preferably includes a polymeric carrier matrix. Any desired polymeric carrier matrix may be used, provided that it is orally dissolvable. Desirably, the dosage should have enough bioadhesion to not be easily removed and it should form a gel like structure when administered. The orally consumable films are preferably moderate-dissolving in the oral cavity and particularly suitable for delivery of actives, although both fast and sustained release compositions are also among the various embodiments contemplated.

[0024] The films used in the pharmaceutical products may be produced by a combination of at least one polymer and a solvent, optionally including other fillers known in the art. The solvent may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, or any combination thereof. In some embodiments, the solvent may be a non-polar organic solvent, such as methylene chloride. The film may be prepared by utilizing a selected casting or deposition method and a controlled drying process. For example, the film may be prepared through controlled drying processes, which include application of heat and/or radiation energy to the wet film matrix to form a visco-elastic structure, thereby controlling the uniformity of content of the film. Such processes are described in more detail in commonly assigned U.S. Application No. 10/074,272, filed on February 14, 2002, and published as U.S. Patent Publication No. 2003/0107149 A1, the contents of which are incorporated herein by reference in their entirety. Alternatively, the films may be extruded as described in commonly assigned U.S. Application No. 10/856,176, filed on May 28, 2004, and published as U.S. Patent Publication No. 2005/0037055 A1, the contents of which are incorporated herein by reference in their entirety.

[0025] The polymer included in the films may be water-soluble, water-swellaable, water-insoluble, or a combination of one or more either water-soluble, water-swellaable or

water-insoluble polymers. The polymer may include cellulose or a cellulose derivative. Specific examples of useful water-soluble polymers include, but are not limited to, polyethylene oxide, pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof. Specific examples of useful water-insoluble polymers include, but are not limited to, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate and combinations thereof. For higher dosages, it may be desirable to incorporate a polymer that provides a high level of viscosity as compared to lower dosages.

[0026] As used herein the phrase “water-soluble polymer” and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water-swellaable polymers. The materials useful with the present invention may be water-soluble or water-swellaable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water-soluble or water-swellaable at pressures less than atmospheric pressure. Desirably, the water-soluble polymers are water-soluble or water-swellaable having at least 20 percent by weight water uptake. Water-swellaable polymers having a 25 or greater percent by weight water uptake are also useful. In some embodiments, films formed from such water-soluble polymers may be sufficiently water-soluble to be dissolvable upon contact with bodily fluids.

[0027] Other polymers useful for incorporation into the films include biodegradable polymers, copolymers, block polymers and combinations thereof. It is understood that the term “biodegradable” is intended to include materials that chemically degrade, as opposed to materials that physically break apart (i.e., bioerodable materials). Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA), poly(lactic acid) (PLA), polydioxanes, polyoxalates, poly(α -esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy) propane acid and sebacic acid, sebacic acid copolymers, copolymers of caprolactone, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, copolymers of polyurethane and (poly(lactic acid)), copolymers of polyurethane and poly(lactic acid), copolymers of α -amino acids, copolymers of α -amino acids and caproic acid, copolymers of α -benzyl glutamate and polyethylene glycol, copolymers of succinate and

poly(glycols), polyphosphazene, polyhydroxy-alkanoates and mixtures thereof. Binary and ternary systems are contemplated.

[0028] Other specific polymers useful include those marketed under the Medisorb and Bidel trademarks. The Medisorb materials are marketed by the Dupont Company of Wilmington, Delaware and are generically identified as a "lactide/glycolide co-polymer" containing "propanoic acid, 2-hydroxy-polymer with hydroxy-polymer with hydroxyacetic acid." Four such polymers include lactide/glycolide 100L, believed to be 100% lactide having a melting point within the range of 338°-347°F (170°-175°C); lactide/glycolide 100L, believed to be 100% glycolide having a melting point within the range of 437°-455°F (225°-235°C); lactide/glycolide 85/15, believed to be 85% lactide and 15% glycolide with a melting point within the range of 338°-347°F (170°-175° C); and lactide/glycolide 50/50, believed to be a copolymer of 50% lactide and 50% glycolide with a melting point within the range of 338°-347°F (170°-175°C).

[0029] The Bidel materials represent a family of various polyanhydrides which differ chemically.

[0030] Although a variety of different polymers may be used, it is desired to select polymers that provide mucoadhesive properties to the film, as well as a desired dissolution and/or disintegration rate. In particular, the time period for which it is desired to maintain the film in contact with the mucosal tissue depends on the type of active contained in the composition. Some actives may only require a few minutes for delivery through the mucosal tissue, whereas other actives may require up to several hours or even longer. Accordingly, in some embodiments, one or more water-soluble polymers, as described above, may be used to form the film. In other embodiments, however, it may be desirable to use combinations of water-soluble polymers and polymers that are water-swellaable, water-insoluble and/or biodegradable, as provided above. The inclusion of one or more polymers that are water-swellaable, water-insoluble and/or biodegradable may provide films with slower dissolution or disintegration rates than films formed from water-soluble polymers alone. As such, the film may adhere to the mucosal tissue for longer periods or time, such as up to several hours, which may be desirable for delivery of certain active components.

[0031] Desirably, the individual film dosage has a small size, which is between about 0.5-1 inch by about 0.5-1 inch. Most preferably, the film dosage is about 0.75 inches x 0.5 inches. The film dosage should have good adhesion when placed in the buccal cavity or in the sublingual region of the user. Further, the film dosage should disperse and dissolve at a moderate rate, most desirably dispersing within about 1 minute and dissolving within about 3 minutes. In some embodiments the film dosage may be capable of dispersing and dissolving at a rate of between about 1 to about 1.5 minutes.

[0032] For instance, in some embodiments, the films may include polyethylene oxide alone or in combination with a second polymer component. The second polymer may be another water-soluble polymer, a water-swellaable polymer, a water-insoluble polymer, a biodegradable polymer or any combination thereof. Suitable water-soluble polymers include, without limitation, any of those provided above. In some embodiments, the water-soluble polymer may include hydrophilic cellulosic polymers, such as hydroxypropyl cellulose and/or hydroxypropylmethyl cellulose. In accordance with some embodiments, polyethylene oxide may range from about 20% to 100% by weight in the polymer component, more specifically about 30% to about 70% by weight, and even more specifically about 40% to about 60% by weight. In some embodiments, one or more water-swellaable, water-insoluble and/or biodegradable polymers also may be included in the polyethylene oxide-based film. Any of the water-swellaable, water-insoluble or biodegradable polymers provided above may be employed. The second polymer component may be employed in amounts of about 0% to about 80% by weight in the polymer component, more specifically about 30% to about 70% by weight, and even more specifically about 40% to about 60% by weight.

[0033] The molecular weight of the polyethylene oxide also may be varied. In some embodiments, high molecular weight polyethylene oxide, such as about 4 million, may be desired to increase mucoadhesivity of the film. In some other embodiments, the molecular weight may range from about 100,000 to 900,000, more specifically from about 100,000 to 600,000, and even more specifically from about 100,000 to 300,000. In some embodiments, it may be desirable to combine high molecular weight (600,000 to 900,000) with low molecular weight (100,000 to 300,000) polyethylene oxide in the polymer component.

[0034] A variety of optional components and fillers also may be added to the films. These may include, without limitation: surfactants; plasticizers; polyalcohols; anti-foaming agents, such as silicone-containing compounds, which promote a smoother film surface by releasing oxygen from the film; thermo-setting gels such as pectin, carageenan, and gelatin, which help in maintaining the dispersion of components; inclusion compounds, such as cyclodextrins and caged molecules; coloring agents; and flavors. In some embodiments, more than one active components may be included in the film.

[0035] Additives may be included in the films. Examples of classes of additives include excipients, lubricants, buffering agents, stabilizers, blowing agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants, adhesives, anti-adherents, acidulants, softeners, resins, demulcents, solvents, surfactants, emulsifiers,

elastomers and mixtures thereof. These additives may be added with the active ingredient(s).

[0036] Useful additives include, for example, gelatin, vegetable proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, grape seed proteins, whey proteins, whey protein isolates, blood proteins, egg proteins, acrylated proteins, water-soluble polysaccharides such as alginates, carrageenans, guar gum, agar-agar, xanthan gum, gellan gum, gum arabic and related gums (gum ghatti, gum karaya, gum tragacanth), pectin, water-soluble derivatives of cellulose: alkylcelluloses hydroxyalkylcelluloses and hydroxyalkylalkylcelluloses, such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose esters and hydroxyalkylcellulose esters such as cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose (HPMC); carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters such as carboxymethylcellulose and their alkali metal salts; water-soluble synthetic polymers such as polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinylacetates, polyvinylalcohols, polyvinylacetatephthalates (PVAP), polyvinylpyrrolidone (PVP), PVY/vinyl acetate copolymer, and polycrotonic acids; also suitable are phthalated gelatin, gelatin succinate, crosslinked gelatin, shellac, water-soluble chemical derivatives of starch, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized if desired; and other similar polymers.

[0037] Such extenders may optionally be added in any desired amount desirably within the range of up to about 80%, desirably about 3% to 50% and more desirably within the range of 3% to 20% based on the weight of all film components.

[0038] Further additives may flow agents and opacifiers, such as the oxides of magnesium aluminum, silicon, titanium, etc. desirably in a concentration range of about 0.02% to about 3% by weight and desirably about 0.02% to about 1% based on the weight of all film components.

[0039] Further examples of additives are plasticizers which include polyalkylene oxides, such as polyethylene glycols, polypropylene glycols, polyethylene-propylene glycols, organic plasticizers with low molecular weights, such as glycerol, glycerol monoacetate, diacetate or triacetate, triacetin, polysorbate, cetyl alcohol, propylene glycol, sorbitol, sodium diethylsulfosuccinate, triethyl citrate, tributyl citrate, and the like, added in concentrations ranging from about 0.5% to about 30%, and desirably ranging from about 0.5% to about 20% based on the weight of the polymer.

[0040] There may further be added compounds to improve the texture properties of the starch material such as animal or vegetable fats, desirably in their hydrogenated form, especially those which are solid at room temperature. These fats desirably have a melting point of 50°C or higher. Preferred are tri-glycerides with C₁₂-, C₁₄-, C₁₆-, C₁₈-, C₂₀- and C₂₂- fatty acids. These fats can be added alone without adding extenders or plasticizers and can be advantageously added alone or together with mono- and/or di-glycerides or phosphatides, especially lecithin. The mono- and di-glycerides are desirably derived from the types of fats described above, i.e. with C₁₂-, C₁₄-, C₁₆-, C₁₈-, C₂₀- and C₂₂- fatty acids.

[0041] The total amounts used of the fats, mono-, di-glycerides and/or lecithins are up to about 5% and preferably within the range of about 0.5% to about 2% by weight of the total film composition.

[0042] It further may be useful to add silicon dioxide, calcium silicate, or titanium dioxide in a concentration of about 0.02% to about 1% by weight of the total composition. These compounds act as flow agents and opacifiers.

[0043] Lecithin is one surface active agent for use in the films described herein. Lecithin may be included in the feedstock in an amount of from about 0.25% to about 2.00% by weight. Other surface active agents, i.e. surfactants, include, but are not limited to, cetyl alcohol, sodium lauryl sulfate, the Spans™ and Tweens™ which are commercially available from ICI Americas, Inc. Ethoxylated oils, including ethoxylated castor oils, such as Cremophor® EL which is commercially available from BASF, are also useful. Carbowax™ is yet another modifier which is very useful in the present invention. Tweens™ or combinations of surface active agents may be used to achieve the desired hydrophilic-lipophilic balance ("HLB"). The present invention, however, does not require the use of a surfactant and films or film-forming compositions of the present invention may be essentially free of a surfactant while still providing the desirable uniformity features of the present invention.

[0044] Other ingredients include binders which contribute to the ease of formation and general quality of the films. Non-limiting examples of binders include starches, pregelatinize starches, gelatin, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinylloxazolidone, and polyvinylalcohols.

[0045] Further potential additives include solubility enhancing agents, such as substances that form inclusion compounds with active components. Such agents may be useful in improving the properties of very insoluble and/or unstable actives. In general, these substances are doughnut-shaped molecules with hydrophobic internal cavities and hydrophilic exteriors. Insoluble and/or instable actives may fit within the hydrophobic cavity, thereby producing an inclusion complex, which is soluble in water. Accordingly,

the formation of the inclusion complex permits very insoluble and/or instable actives to be dissolved in water. A particularly desirable example of such agents are cyclodextrins, which are cyclic carbohydrates derived from starch. Other similar substances, however, are considered well within the scope of the present invention.

[0046] Suitable coloring agents include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors are dyes, their corresponding lakes, and certain natural and derived colorants. Lakes are dyes absorbed on aluminum hydroxide.

[0047] Other examples of coloring agents include known azo dyes, organic or inorganic pigments, or coloring agents of natural origin. Inorganic pigments are preferred, such as the oxides of iron or titanium, these oxides, being added in concentrations ranging from about 0.001 to about 10%, and preferably about 0.5 to about 3%, based on the weight of all the components.

[0048] Flavors may be chosen from natural and synthetic flavoring liquids. An illustrative list of such agents includes volatile oils, synthetic flavor oils, flavoring aromatics, oils, liquids, oleoresins or extracts derived from plants, leaves, flowers, fruits, stems and combinations thereof. A non-limiting representative list of examples includes mint oils, cocoa, and citrus oils such as lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot or other fruit flavors.

[0049] Other useful flavorings include aldehydes and esters such as benzaldehyde (cherry, almond), citral i.e., aliphatic citral (lemon, lime), neral, i.e., beta-citral (lemon, lime), decanal (orange, lemon), aldehyde C-8 (citrus fruits), aldehyde C-9 (citrus fruits), aldehyde C-12 (citrus fruits), tolyl aldehyde (cherry, almond), 2,6-dimethyloctanol (green fruit), and 2-dodecenal (citrus, mandarin), combinations thereof and the like.

[0050] The sweeteners may be chosen from the following non-limiting list: glucose (corn syrup), dextrose, invert sugar, fructose, and combinations thereof; saccharin and its various salts such as the sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; Stevia Rebaudiana (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol, mannitol, xylitol, and the like. Also contemplated are hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methyl-1,1,1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and calcium salts thereof, and natural intensive sweeteners, such as Lo Han Kuo. Other sweeteners may also be used.

[0051] Anti-foaming and/or de-foaming components may also be used with the films. These components aid in the removal of air, such as entrapped air, from the film-forming compositions. Such entrapped air may lead to non-uniform films. Dimethicone is one particularly useful anti-foaming and/or de-foaming agent. The present invention,

however, is not so limited and other anti-foam and/or de-foaming agents may suitable be used.

[0052] As a related matter, simethicone and related agents may be employed for densification purposes. More specifically, such agents may facilitate the removal of voids, air, moisture, and similar undesired components, thereby providing denser, and thus more uniform films. Agents or components which perform this function can be referred to as densification or densifying agents. As described above, entrapped air or undesired components may lead to non-uniform films.

[0053] Simethicone is generally used in the medical field as a treatment for gas or colic in babies. Simethicone is a mixture of fully methylated linear siloxane polymers containing repeating units of polydimethylsiloxane which is stabilized with trimethylsiloxy end-blocking unites, and silicon dioxide. It usually contains 90.5-99% polymethylsiloxane and 4-7% silicon dioxide. The mixture is a gray, translucent, viscous fluid which is insoluble in water.

[0054] When dispersed in water, simethicone will spread across the surface, forming a thin film of low surface tension. In this way, simethicone reduces the surface tension of bubbles air located in the solution, such as foam bubbles, causing their collapse. The function of simethicone mimics the dual action of oil and alcohol in water. For example, in an oily solution any trapped air bubbles will ascend to the surface and dissipate more quickly and easily, because an oily liquid has a lighter density compared to a water solution. On the other hand, an alcohol/water mixture is known to lower water density as well as lower the water's surface tension. So, any air bubbles trapped inside this mixture solution will also be easily dissipated. Simethicone solution provides both of these advantages. It lowers the surface energy of any air bubbles that trapped inside the aqueous solution, as well as lowering the surface tension of the aqueous solution. As the result of this unique functionality, simethicone has an excellent anti-foaming property that can be used for physiological processes (anti-gas in stomach) as well as any for external processes that require the removal of air bubbles from a product.

[0055] In order to prevent the formation of air bubbles in the films, the mixing step can be performed under vacuum. However, as soon as the mixing step is completed, and the film solution is returned to the normal atmosphere condition, air will be re-introduced into or contacted with the mixture. In many cases, tiny air bubbles will be again trapped inside this polymeric viscous solution. The incorporation of simethicone into the film-forming composition either substantially reduces or eliminates the formation of air bubbles.

[0056] Simethicone may be added to the film-forming mixture as an anti-foaming agent in an amount from about 0.01 weight percent to about 5.0 weight percent, more desirably

from about 0.05 weight percent to about 2.5 weight percent, and most desirably from about 0.1 weight percent to about 1.0 weight percent.

[0057] Any other optional components described in commonly assigned U.S. Patent No. 7,425,292 and U.S. Application No. 10/856,176, referred to above, also may be included in the films described herein.

[0058] When the dosage form includes at least one antagonist, it may be desired to control the release of the antagonist, so as to delay or wholly prevent the release of the antagonist from the dosage when taken orally. Desirably, the dosage form is a self-supporting film composition, which is placed into the oral cavity of the user. In a dosage form that is to be placed in the oral cavity, it is desired to absorb the agonist buccally, so as to provide rapid integration of the agonist into the body of the user. At the same time, it may be desired to prevent or reduce absorption of any antagonist buccally, thereby allowing the antagonist to be swallowed and destroyed in the stomach. Reducing the absorption of an antagonist may be achieved via physical means, such as by encapsulating the antagonist in a material that blocks absorption. It is desired, however, to reduce the absorption of the antagonist by chemical means, such as by controlling the local pH of the dosage.

[0059] It has been found that by controlling the local pH of the dosage form, the release and/or absorption of the actives therein may be controlled. For example, in a dosage that includes an amount of an agonist, the local pH may be controlled to a level that maximizes its release and/or absorption into the oral cavity of the user. In dosages incorporating an amount of an agonist and an amount of an antagonist, the local pH may be controlled to a level that maximizes the release and/or absorption of the agonist while simultaneously minimizing the release and/or absorption of the antagonist.

[0060] The dosage form preferably includes a combination of a partial agonist and an antagonist, while the dosage has a controlled pH. In one embodiment, the partial agonist may include buprenorphine or a pharmaceutically acceptable salt thereof, while the antagonist includes naloxone or a therapeutically acceptable salt thereof. It should be understood that the present invention is not limited to the use of buprenorphine and naloxone, and any agonist (or partial agonist) and any antagonist may be incorporated into the present invention for use in treatment of drug addiction. The agonist and optional antagonist should be selected from those agonists and antagonists that are useful in treating the particular narcotic dependence being treated.

[0061] As discussed above, the local pH of the dosage is preferably controlled to provide the desired release and/or absorption of the agonist and antagonist. Buprenorphine is known to have a pKa of about 8.42, while naloxone has a pKa of about 7.94. According to pH partition theory, one would expect that saliva (which has a pH of about 6.5) would maximize the absorption of both actives. However, it has been surprisingly discovered

by the Applicants that by buffering the dosage to a particular pH level, the optimum levels of absorption of the agonist and antagonist may be achieved. Desirably, the local pH of a composition including an agonist and an antagonist is between about 2 to about 4, and most desirably is from 3 to 4. At this local pH level, the optimum absorption of the agonist and the antagonist is achieved. As will be described in more detail in the Examples below, controlling the local pH of the film compositions of the present invention provides a system in which the desired release and/or absorption of the components is bioequivalent to that of a similar Suboxone® tablet.

[0062] In one embodiment, the dosage form is a self-supporting film. In this embodiment, the film dosage includes a polymer carrier matrix, a therapeutically effective amount of buprenorphine, an agonist. The buffer is preferably capable of providing a local pH of the composition within a range that provides the desired level of absorption of the buprenorphine. The resulting dosage is a film composition that allows for a rapid and effective release of buprenorphine into the oral cavity of the user. At the same time, the film composition preferably has a sufficient adhesion profile, such that the film cannot easily be removed from the oral cavity of the user once it has been placed into the cavity. Full release of the buprenorphine preferably takes place within less than about thirty minutes, and preferably remains in the oral cavity for at least 1 minute.

[0063] As explained above, while providing a pharmaceutically acceptable level of an agonist is helpful in treating those with narcotic addiction, it may be desirable to provide the buprenorphine in combination with naloxone (an antagonist) so as to reduce the effect of the agonist and therefore aid in reducing dependency of the narcotic. Therefore, it may be desirable to combine the opioid agonist (or partial agonist) in the film composition with an opioid antagonist or a pharmaceutically acceptable salt thereof. The actives may be dispersed throughout the dosage separately or they may be combined together and dispersed into the dosage. Most desirably the antagonist includes naloxone, but any suitable basic antagonist may be selected as desired. The antagonist may optionally be water-soluble, so as to render separation of the antagonist and agonist difficult, thereby lessening the potential for abuse of the agonist.

[0064] As with a film including an agonist, the film including an agonist and an antagonist is desirably pH-controlled through the inclusion of a buffer. In such combination films, it has been discovered that the local pH of the film composition should preferably be in the range of about 2 to about 4, and more preferably about 3 to about 4 so as to provide a bioequivalent product as the commercially-available Suboxone® tablet. Most preferably the local pH of the film composition is about 3.5. At this local pH level, absorption of the buprenorphine is optimized while the absorption of the naloxone is inhibited.

[0065] The film may contain any desired level of self-supporting film forming polymer, such that a self-supporting film composition is provided. In one embodiment, the film composition contains a film forming polymer in an amount of at least 25% by weight of the composition. The film forming polymer may alternatively be present in an amount of at least 50% by weight of the composition. As explained above, any film forming polymers that impart the desired mucoadhesion and rate of film dissolution may be used as desired.

[0066] Any desired level of agonist and optional antagonist may be included in the dosage, so as to provide the desired effect. In one particular embodiment, the film composition includes about 2 mg to about 16 mg of agonist per dosage. More desirably, the film composition includes about 4 mg to about 12 mg of agonist per dosage. If desired, the film composition may include about 0.5 mg to about 5 mg of antagonist per dosage. More desirably, the film composition includes about 1 mg to about 3 mg of antagonist per dosage. If an antagonist is incorporated into the film, the film composition may include the antagonist in a ratio of about 6:1 – 2:1 agonist to antagonist. Most desirably, the film composition contains about 4:1 agonist to antagonist per dosage. For example, in one embodiment, the dosage includes an agonist in an amount of about 12 mg, and includes an antagonist in an amount of about 3 mg.

[0067] The film compositions further desirably contains a buffer so as to control the local pH of the film composition. Any desired level of buffer may be incorporated into the film composition so as to provide the desired local pH level. The buffer is preferably provided in an amount sufficient to control the release from the film and/or the absorption into the body of the agonist and the optional antagonist. In a desired embodiment, the film composition includes buffer in a ratio of buffer to agonist in an amount of from about 2:1 to about 1:5 (buffer:agonist). The buffer may alternatively be provided in a 1:1 ratio of buffer to agonist. As stated above, the film composition preferably has a local pH of about 2 to about 4, and most preferably has a local pH of about 3.5. Any buffer system may be used as desired. In some embodiments, the buffer may include sodium citrate, citric acid, and combinations thereof.

[0068] In this embodiment, the resulting film composition includes a polymer matrix, an agonist, and an optional antagonist, while the film composition has a controlled local pH to the level desired. The buffer is preferably present in an amount to provide a therapeutically adequate absorption of the agonist, while simultaneously limiting the absorption of the antagonist. Controlling of the local pH allows for the desired release and/or absorption of the components, and thus provides a more useful and effective dosage.

[0069] The film dosage composition may include a polymer carrier matrix, a therapeutically effective amount of agonist, a therapeutically effective amount of

antagonist, and a buffering system. The buffering system may include a buffer in addition to a solvent. The buffering system desirably includes a sufficient level of buffer so as to provide a desired local pH level of the film dosage composition.

[0070] In addition to a desired local pH level, the buffer preferably has a buffer capacity sufficient to maintain the ionization of the optional antagonist during the time that the composition is in the oral cavity of a user. Maintaining the ionization of the antagonist serves to limit the absorption of the antagonist, and thus provide the desired control of the antagonist. While the ionization of the antagonist is limited, the ionization of the agonist may not be so limited. As such, the resulting dosage form provides absorption of the agonist to the user, while sufficiently reducing and/or preventing absorption of the antagonist. By keeping the antagonist ionized and the local pH at the optimum pH, the antagonist has limited if any absorption, but is still present should the product be abused or taken via a different route of administration. However, when taken as administered, the antagonist has little to no effect in blocking the agonist.

[0071] The film dosage composition including an agonist may be configured to provide an in vivo plasma profile having a mean maximum plasma concentration (C_{max}) in a desired range. It has been discovered by the Applicants that controlling the C_{max} of the film composition allows one to control the absorption of the active (such as an agonist) into the user. The resulting film composition is more effective and suitable for delivery to a user.

[0072] As explained, the film dosage composition provides a bioequivalent result to a commercially available Suboxone® product. As will be explained more in the Examples below, commercially available Suboxone® provides different absorption levels depending on the amount of buprenorphine and naloxone administered. The present invention desirably provides a film product providing bioequivalent release as that of the Suboxone® product. As with the Suboxone® product, the buprenorphine may be present in an amount of from about 2 mg to about 16 mg per dosage, or, if desired about 4 mg to about 12 mg per dosage. Additionally, the naloxone may be present in any desired amount, preferably at about 25% the level of buprenorphine. For example, an inventive film product may have 2 mg buprenorphine and 0.5 mg naloxone, 4 mg buprenorphine and 1 mg naloxone, 8 mg buprenorphine and 2 mg naloxone, 12 mg buprenorphine and 3 mg naloxone, 16 mg buprenorphine and 4 mg naloxone, or any similar amounts.

[0073] It has further been discovered that, by controlling the mean area under the curve (AUC) value of the film composition, a more effective dosage form may be provided. As is described in more detail in the Examples below, the inventive film composition preferably provides an AUC value so as to provide a bioequivalent result as that provided by the commercially available Suboxone® tablet. In one embodiment, the film composition may include a mean AUC_{inf} value of about 6.8 hr.ng/ml or greater.

Alternatively, the film composition may include a mean AUCinf value of from about 6.8 hr.ng/ml to about 66 hr.ng/ml.

[0074] As explained above, the film compositions may include naloxone, an antagonist. When the film composition includes a combination of agonist and antagonist, the film composition may be configured to provide a particular Cmax and/or AUCinf for the antagonist. For example, when a buprenorphine agonist and a naloxone antagonist are incorporated into the film composition, the naloxone may be configured to provide a Cmax of less than about 400 pg/ml, less than about 318 pg/ml, less than about 235 pg/ml, less than about 92 pg/ml or less than about 64 pg/ml. In such films, the naloxone may provide a mean AUCinf value of less than about 1030 hr.ng/ml.

[0075] In formulations which include an agonist in combination with an antagonist, the film composition may be prepared to provide a desired Cmax and/or AUCinf value for each of the agonist and antagonist. In one embodiment, the film composition provides an in vivo plasma profile having a Cmax of less than about 6.4 ng/ml for the agonist and an in vivo plasma profile having a Cmax of less than about 400 pg/ml for the antagonist. In such embodiments, the formulation may provide an AUCinf value of more than about 6.8 hr.ng/ml for the agonist. If desired, the formulation may provide an AUCinf value of less than about 1030 hr.pg/ml for the antagonist. Such compositions may include the agonist and the antagonist in any desired amount, and in a preferred embodiment, the composition includes about 2 mg to about 16 mg of the agonist per dosage and about 0.5 mg to about 4 mg of the antagonist per dosage.

[0076] The present invention provides a method of treating narcotic dependence in a patient. In one embodiment, the patient is dependent on opioid narcotics, but the patient may have a dependence on non-opioid narcotics. Desirably, the patient is treated by providing a dosage to the patient, which provides an effective release of actives but simultaneously provides a suitable adhesion so that the dosage cannot be easily removed. In one method of treatment, an orally dissolvable film composition is provided to a patient.

[0077] Depending on the particular narcotic that the patient experiences dependence upon, the film composition may include one or more particular active components. In one embodiment, the film composition includes a polymer carrier matrix and a therapeutically effective amount of an agonist. Desirably the agonist is a partial agonist. For opioid dependency, the agonist may be an opioid agonist, such as buprenorphine or a pharmaceutically acceptable salt thereof. The film composition preferably includes a buffer in an amount sufficient to control the local pH of the film composition. Any buffer system may be used, including sodium citrate, citric acid, and combinations thereof. In compositions solely including an agonist, the local pH of the film composition is desirably about 5 to about 6.5, and most desirably the local pH is about 5.5. At this level,

the absorption of the agonist is most effective. To treat the dependency, the film composition is administered to the patient, most desirably into the oral cavity of the patient.

[0078] If desired, the composition may include a therapeutically effective amount of an antagonist, to prevent abuse of the agonist. A “therapeutically effective amount” of an antagonist is intended to refer to an amount of the antagonist that may be useful in diverting abuse of the agonist by a user. The antagonist may be any desired antagonist, and in one embodiment includes naloxone or a pharmaceutically acceptable salt thereof. The film composition is preferably administered to a patient through the oral cavity of the patient, but may be administered in any desired means. The orally dissolvable film composition is then allowed to dissolve in the oral cavity of the patient for a sufficient time so as to release the active(s) therein. In some embodiments, the film composition may remain in the oral cavity for at least 30 seconds, and in some embodiments may remain in the oral cavity for at least 1 minute. After the film composition is placed into the oral cavity of the patient, the film preferably becomes sufficiently adhered so as to render its removal difficult. After the film composition has been administered to the patient, the active(s) are sufficiently released from the composition and allowed to take effect on the patient.

[0079] The film compositions of the present invention may be formed via any desired process. Suitable processes are set forth in U.S. Patent Nos. 7,425,292 and 7,357,891, the entire contents of which are incorporated by reference herein. In one embodiment, the film dosage composition is formed by first preparing a wet composition, the wet composition including a polymeric carrier matrix, a therapeutically effective amount of an agonist, and a buffer in an amount sufficient to control the local pH of the composition to a desired level. The wet composition is cast into a film and then sufficiently dried to form a self-supporting film composition. The wet composition may be cast into individual dosages, or it may be cast into a sheet, where the sheet is then cut into individual dosages. The agonist may be a partial agonist. If desired, the wet composition may include a therapeutically effective amount of an antagonist.

[0080] The agonist and the optional antagonist are preferably selected to treat a particular narcotic dependency. For opioid dependency, for example, the agonist may include buprenorphine or a pharmaceutically acceptable salt thereof, while the antagonist may include naloxone or a pharmaceutically acceptable salt thereof. The local pH of the film composition is desirably maintained at about 2 to about 4.

EXAMPLES

Example 1 – Composition of Buprenorphine/Naloxone Films at Various Strengths

[0081] Film strips including a combination of buprenorphine and naloxone were prepared. Four different strength film compositions were prepared, which include a ratio

of buprenorphine to naloxone of 16/4, 12/3, 8/2, and 2/0.5. The compositions are summarized in Table 1 below.

Table 1 – Various Compositions of Film Dosages

Components	Buprenorphine/Naloxone Films			
	Unit Formula (mg per film strip)			
Buprenorphine/Naloxone Ratios	16/4	12/3	8/2	2/0.5
Active Components				
Buprenorphine HCl	17.28	12.96	8.64	2.16
Naloxone HCl Dihydrate	4.88	3.66	2.44	0.61
Inactive Components				
Polyethylene Oxide, NF (MW 200,000)	27.09	20.32	13.55	--
Polyethylene Oxide, NF (MW 100,000)	12.04	9.03	6.02	19.06
Polyethylene Oxide, NF (MW 900,000)	4.82	3.62	2.41	2.05
Maltitol, NF	12.04	9.03	6.02	5.87
Flavor	6.0	4.5	3.0	2.4
Citric Acid, USP	5.92	4.44	2.96	2.96
HPMC	4.22	3.16	2.11	2.34
Ace-K	3.0	2.25	1.5	1.2
Sodium Citrate, anhydrous	2.68	2.01	1.34	1.34
Colorant	0.03	0.02	0.01	0.01
Total (mg)	100	75	50	40

Example 2 – Absorption studies for Suboxone® products

[0082] Various film and tablet products were prepared and tested for absorption data, including Cmax and AUC absorption levels. The products tested included Suboxone® tablets made with either 2 mg or 16 mg buprenorphine as well as either 0.5 mg or 4.0 mg naloxone. For 16 mg buprenorphine tablets, two 8 mg buprenorphine tablets were combined together to provide the level of components of a 16 mg buprenorphine tablet. In instances where a 12 mg buprenorphine tablet was evaluated, this dosage was obtained by combining one 8 mg buprenorphine tablet and two 2 mg buprenorphine tablets. These products were tested for absorption levels, with the amounts listed in Table 2 below.

Table 2 - Absorption Data for Suboxone® products

Sample	C max	AUC
Buprenorphine (2 mg) Suboxone® Tablet	0.780 ng/ml	6.789 hr*ng/ml

Naloxone (0.5 mg) Suboxone® Tablet	51.30 pg/ml	128.60 hr*pg/ml
Buprenorphine (16 mg) Suboxone® Tablet	4.51 ng/ml	44.99 hr*ng/ml
Naloxone (4 mg) Suboxone® Tablet	259.00 pg/ml	649.60 hr*pg/ml

[0083] Using the data from Table 2, absorption data for the Suboxone® tablets for other levels of buprenorphine and naloxone are set forth in Table 2A below.

Table 2A – Extrapolated Absorption Data for Suboxone® products

Sample	C max	AUC
Buprenorphine (4 mg) Suboxone® Tablet	1.35 ng/ml	12.25 hr*ng/ml
Naloxone (1 mg) Suboxone® Tablet	80.97 pg/ml	203 hr*pg/ml
Buprenorphine (8 mg) Suboxone® Tablet	2.29 ng/ml	23.17 hr*ng/ml
Naloxone (2 mg) Suboxone® Tablet	140.31 pg/ml	351.8 hr*pg/ml
Buprenorphine (12 mg) Suboxone® Tablet	3.23 ng/ml	34.08 hr*ng/ml
Naloxone (3 mg) Suboxone® Tablet	199.7 pg/ml	500.6 hr*pg/ml

Example 3 – Evaluation of Bioequivalence of Suboxone® Tablets

[0084] Using the data generated for Suboxone® tablets in Table 2 above, acceptable bioequivalence ranges are generated to provide an equivalent treatment level as the Suboxone® tablet. As currently understood, a product provides a bioequivalent effect if it provides absorption levels between about 80% to about 125% of the Suboxone® tablet. Absorption in this range is considered to be bioequivalent.

Table 3 - Acceptable Bioequivalence Ranges for Suboxone® Tablets (80 to 125%)

Description of Sample	C max	AUC
Buprenorphine 2 mg	0.624 to 0.975 ng/ml	5.431 to 8.486 hr*ng/ml
Naloxone 0.5 mg	41.04 to 64.13 pg/ml	102.88 to 160.75 hr*pg/ml
Buprenorphine 16 mg	3.608 to 5.638 ng/ml	35.992 to 56.238 hr*ng/ml
Naloxone 4 mg	207.20 to 323.75 pg/ml	519.68 to 812.00 hr*pg/ml

[0085] Thus, to be considered bioequivalent to the Suboxone® tablet, the Cmax of buprenorphine is between about 0.624 and 5.638, and the AUC of buprenorphine is between about 5.431 to about 56.238. Similarly, to be considered bioequivalent to the Suboxone® tablet, the Cmax of naloxone is between about 41.04 to about 323.75, and the AUC of naloxone is between about 102.88 to about 812.00.

Example 4 – Absorption studies for film products at pH 3.5

[0086] Various film products were prepared and tested for absorption data, including Cmax and AUC absorption levels. The products tested included inventive film strips, the film strips having either 2 mg or 16 mg buprenorphine as well as either 0.5 mg or 4.0 mg

naloxone. These products were tested for absorption levels, with the amounts listed in Table 4 below.

Table 4 - Absorption Data for inventive film products at pH 3.5

Sample	C max	AUC
Buprenorphine (2 mg) Sublingual Film	0.947 ng/ml	7.82 hr*ng/ml
Naloxone (0.5 mg) Sublingual Film	51.10 pg/ml	128.60 hr*pg/ml
Buprenorphine (16 mg) Sublingual Film	5.47 ng/ml	55.30 hr*ng/ml
Naloxone (4 mg) Sublingual Film	324.00 pg/ml	873.60 hr*pg/ml

[0087] As can be seen, in this experiment, the values for buprenorphine absorbance were squarely in the bioequivalence range evaluated above. The inventive films were therefore determined to have provided a bioequivalent absorption of buprenorphine at a local pH of 3.5 as the commercially available Suboxone® tablet. The values for absorption of naloxone were very close to the bioequivalent range of Suboxone®. The slightly higher absorption of Naloxone was not due to the local pH but rather to the amount of buffer (buffer capacity as discussed in the application). This is confirmed by the fact that the lower 2/0.5 mg dose is in range for the Naloxone and this is due to the higher buffer capacity for the 2/0.5 dose as pointed out in the buffer capacity chart.

Example 5 – Preparation of Films For In Vivo Study

[0088] Film dosages were prepared for use in an *in vivo* study to determine the bioavailability of buprenorphine/naloxone tablets and film formulations. Specifically, the films were tested to determine whether the film provides a bioequivalent effect to that of a tablet formulation.

[0089] Three film formulations including 8 mg buprenorphine and 2 mg naloxone were prepared, each being buffered to a different pH. The first film did not include any buffer, providing a local pH of about 6.5. The second was buffered to a local pH level of about 3-3.5. The third was buffered to a local pH value of about 5-5.5. The formulations are set forth in Table 5 below.

Table 5 – Formulations of Test Films at Various pH Levels

Component	Test formulation 1 8 mg/2 mg pH = 6.5		Test formulation 2 8 mg/2 mg pH = 3-3.5		Test formulation 3 8 mg/2 mg pH = 5-5.5	
	%w/w	Mg/film	%w/w	Mg/film	%w/w	Mg/film
Buprenorphine HCl	21.61	8.64	17.28	8.64	17.28	8.64
Naloxone HCl Dihydrate	6.10	2.44	4.88	2.44	4.88	2.44
Polymer	5.05	2.02	4.82	2.41	4.82	2.41

Polymer	28.48	11.39	27.09	13.55	27.09	13.55
Polymer	12.65	5.06	12.04	6.02	12.04	6.02
Polymer	4.43	1.77	4.22	2.11	4.22	2.11
Sweetener	12.65	5.06	12.04	6.02	12.04	6.02
Sweetener	3	1.2	3	1.5	3	1.5
Flavor	6	2.4	6	3	6	3
Citric acid	0	0	5.92	2.96	2.51	1.26
Sodium citrate	0	0	2.68	1.34	6.08	3.04
FD&C yellow #6	0.025	0.01	0.03	0.02	0.03	0.02
Total	100	40	100	50	100	50

Example 6 – Analysis of *In Vivo* Absorption of Film Having a pH of 6.5

[0090] The film dosage composition of film having a local pH of 6.5 was analyzed. Specifically, Test Formulation 1, as prepared in Example 5 was analyzed in vivo to determine the absorption of buprenorphine and of naloxone. The comparative film was compared to the absorption of buprenorphine and of naloxone provided by a one dose tablet (Suboxone®). The test film was compared to determine whether it provided a bioequivalent effect as the tablet product.

[0091] The results for Test Formulation 1, which had a local pH of about 6.5, as compared to the one dose tablet, are set forth in Tables 6 and 7 below.

Table 6 – Buprenorphine In Vivo Absorption Data for Test Formulation 1

	Suboxone® sublingual				Test Formulation 1 (pH = 6.5)			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	15	1.60	0.47	29.41	15	1.50	0.62	41.23
C _{max} (ng/mL)	15	2.27	0.562	24.77	15	2.60	0.872	33.53
AUC _{last} (hr*ng/mL)	15	27.08	10.40	38.41	15	31.00	12.93	41.72
AUC _{inf} (hr*ng/mL)	15	29.58	11.15	37.68	15	33.37	13.88	41.61
T _{1/2} (hr)	15	44.76	20.86	46.60	15	40.73	14.93	36.66

Table 7 – Naloxone In Vivo Absorption Data for Test Formulation 1

	Suboxone® sublingual				Test Formulation 1 (pH = 6.5)			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	15	0.90	0.23	25.32	15	0.68	0.18	25.75
C _{max} (pg/mL)	15	94.6	39.1	41.33	15	410	122	29.75
AUC _{last} (hr*pg/mL)	15	297.1	120.7	40.62	15	914.8	158.1	17.29
AUC _{inf} (hr*pg/mL)	15	306.1	122.6	40.06	15	924.2	158.8	17.18
T _{1/2} (hr)	15	6.62	2.60	39.26	15	6.86	2.08	30.27

[0092] As can be seen, the in vivo data indicates that buprenorphine is absorbed very well from the film formulation at a local pH of 6.5, and matched closely the absorption seen in the Suboxone® one dose tablet. However, the absorption was also maximized for

the naloxone, which was undesirable. It was determined that a film having a combination of buprenorphine and naloxone and a local pH of 6.5 did not provide a bioequivalent effect as the Suboxone® tablet for both buprenorphine and naloxone.

Example 7 – Analysis of In Vivo Absorption of Film Having a pH of 5-5.5

[0093] Having determined the absorption of buprenorphine and naloxone in film having a local pH of 6.5, a film dosage composition of film having a local pH of 5-5.5 was analyzed. Specifically, Test Formulation 3, as prepared in Example 5 was analyzed in vivo to determine the absorption of buprenorphine and of naloxone. The comparative films were compared to the absorption of buprenorphine and of naloxone provided by the Suboxone® one dose tablet. The test film was compared to determine whether it provided a bioequivalent effect as the Suboxone® tablet.

[0094] The results for Test Formulation 3, which had a local pH of about 5-5.5, as compared to the Suboxone® tablet, are set forth in Tables 8 and 9 below.

Table 8 – Buprenorphine In Vivo Absorption Data for Test Formulation 3

	Suboxone® sublingual				Test Formulation 3 (pH = 5-5.5)			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	15	1.60	0.47	29.41	14	1.50	0.43	28.50
C _{max} (ng/mL)	15	2.27	0.562	24.77	14	3.47	1.57	45.40
AUC _{last} (hr*ng/mL)	15	27.08	10.40	38.41	14	33.25	16.01	48.16
AUC _{inf} (hr*ng/mL)	15	29.58	11.15	37.68	13	38.34	15.38	40.13
T _{1/2} (hr)	15	44.76	20.86	46.60	13	41.71	17.70	42.42

Table 9 – Naloxone In Vivo Absorption Data for Test Formulation 3

	Suboxone® sublingual				Test Formulation 3 (pH = 5-5.5)			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	15	0.90	0.23	25.32	14	0.98	0.62	63.51
C _{max} (pg/mL)	15	94.6	39.1	41.33	14	173	84.5	48.79
AUC _{last} (hr*pg/mL)	15	297.1	120.7	40.62	14	455.2	195.5	42.94
AUC _{inf} (hr*pg/mL)	15	306.1	122.6	40.06	13	474.4	203.1	42.81
T _{1/2} (hr)	15	6.62	2.60	39.26	13	9.45	6.90	73.00

[0095] As can be seen, the in vivo data indicated that the absorption of buprenorphine increased as the local pH level decreased. It appeared that by decreasing the local pH from 6.5 to 5.5, the absorption of buprenorphine was being moved to a level further away from that of the one dose tablet. In addition, the naloxone values did not provide a bioequivalent result as the one dose tablet. Thus, it was determined that the film having a

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local pH of 5.5 did not provide a bioequivalent result as that of the Suboxone® tablet for both buprenorphine and naloxone.

[0096] It was noted that by reducing the local pH of the film to a level of 5.5, there would be provided an increased level of absorption of buprenorphine. Thus, it may be desirable to buffer a film composition incorporating buprenorphine itself to a level of about 5.5 to provide an increased absorption.

Example 8 – Analysis of In Vivo Absorption of Film Having a pH of 3-3.5

[0097] Having determined the absorption of buprenorphine and naloxone in films having a local pH of 6.5 and 5.5, a film dosage composition of film having a local pH of about 3-3.5 was analyzed. It was assumed that the absorption of buprenorphine would continue to be increased as it had demonstrated at a local pH of 5.5. Thus, it was assumed that at a local pH of 3.5, the film would not be bioequivalent to that of the tablet.

[0098] Specifically, Test Formulation 2, as prepared in Example 5, was analyzed in vivo to determine the absorption of buprenorphine and of naloxone. The comparative films were compared to the absorption of buprenorphine and of naloxone provided by the Suboxone® one dose tablet. The test film was compared to determine whether it provided a bioequivalent effect as the tablet product.

[0099] The results for Test Formulation 2, which had a local pH of about 3-3.5, as compared to the Suboxone® tablet, are set forth in Tables 10 and 11 below.

Table 10 – Buprenorphine In Vivo Absorption Data for Test Formulation 2

	Suboxone® sublingual				Test Formulation 2 (pH = 3-3.5)			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	15	1.60	0.47	29.41	14	1.68	0.58	34.68
C _{max} (ng/mL)	15	2.27	0.562	24.77	14	2.68	0.910	33.99
AUC _{last} (hr*ng/mL)	15	27.08	10.40	38.41	14	29.73	12.05	40.54
AUC _{inf} (hr*ng/mL)	15	29.58	11.15	37.68	14	31.45	12.98	41.26
T _{1/2} (hr)	15	44.76	20.86	46.60	14	30.03	13.95	46.46

Table 11 – Naloxone In Vivo Absorption Data for Test Formulation 2

	Suboxone® sublingual				Test Formulation 2 (pH = 3-3.5)			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	15	0.90	0.23	25.32	14	0.84	0.19	22.19
C _{max} (pg/mL)	15	94.6	39.1	41.33	14	130	72.9	56.04
AUC _{last} (hr*pg/mL)	15	297.1	120.7	40.62	14	362.2	155.9	43.03
AUC _{inf} (hr*pg/mL)	15	306.1	122.6	40.06	12	350.4	142.3	40.61
T _{1/2} (hr)	15	6.62	2.60	39.26	12	8.07	4.75	58.84

[00100] As can be seen, the in vivo data indicated that the absorption of buprenorphine was substantially bioequivalent to that of the one dose tablet when the film composition local pH was lowered to about 3-3.5. This result was surprising as it did not appear to follow the pH partition theory. Further, at a local pH of about 3-3.5, it was seen that the absorption of naloxone was substantially bioequivalent to that of the one dose tablet.

[00101] Thus, it was determined that the film product including buprenorphine and naloxone at a local pH of 3-3.5 was substantially bioequivalent to that of the Suboxone® one dose tablet.

Example 9 – Normalized Values for Naloxone in Films and Tablets

[00102] Various film compositions including buprenorphine and naloxone in 8/2 mg and 2/0.5 mg dosages, and having different local pH values from 6.5 to 3.5, were prepared and analyzed. The data was normalized and compared to the one dose tablet. The results are set forth in Table 12 below.

Table 12 – Normalized Values for Naloxone Film Compared to Tablet

pH	Dose (mg) Buprenorphine/ Naloxone	AUC (Normalized)	Cmax	Mg Citric Acid	Ratio Citric Acid (mg)/Naloxone (mg)
6.5	8/2	3.02	4.33	1.34	0.67
5.5	8/2	1.55	1.83	1.34	0.67
3.5	8/2	1.14	1.37	1.34	0.67
3.5	2/0.5	0.98	0.90	1.34	2.68
5.5	2/0.5	1.41	1.41	1.34	2.68

[00103] The data indicates that not only is the local pH of significant importance, but the amount of buffer present in the formula is also important. The improvement from the 8/2 dose to the 2/0.5 dose (at a local pH of 3.5) demonstrates this importance. The 8/2 dose has a ratio of buffer/naloxone of 0.67, and this dose provided borderline acceptable bioequivalent results. In contrast, the 2/0.5 dose has a ratio of buffer/naloxone of 2.68, and provides a more bioequivalent absorption value than the 8/2 dose.

[00104] In fact, the data shows that the 2/0.5 dose at a local pH of 3.5 had an even lower buccal absorption than the one dose tablet, as seen from the normalized values for the AUC and Cmax. This demonstrates that even less absorption of the naloxone occurs for the film formulation at a local pH of 3.5 than the tablet formulation. Given the goal of reducing the absorption of naloxone, it appears that the film product buffered at a local pH of 3.5 with a buffer ratio of buffer/Naloxone of 2.68 provides even better results than the Suboxone® tablet formulation.

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What is claimed is:

1. A film dosage composition comprising:
 - a. A polymeric carrier matrix;
 - b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
 - c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
 - d. A buffer in an amount to provide a local pH of said composition of a value sufficient to optimize absorption of said buprenorphine.
2. The composition of claim 1, wherein said local pH is about 2 to about 4.
3. The composition of claim 2, wherein the local pH of said composition is from about 3 to about 4.
4. The composition of claim 1, wherein said film dosage composition provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
5. The composition of claim 1, wherein said polymeric carrier matrix comprises at least one polymer in an amount of at least 25% by weight of said composition.
6. The composition of claim 1, wherein said buffer is present in an amount of from about 2:1 to about 1:5 by weight of buffer to buprenorphine.
7. The composition of claim 1, wherein said polymeric carrier matrix comprises at least one self-supporting film forming polymer.
8. The film dosage composition of claim 1, wherein said buprenorphine is present in an amount of from about 2 mg to about 16 mg per dosage.
9. The film dosage composition of claim 1, wherein said buffer comprises sodium citrate, citric acid, and combinations thereof.
10. The film dosage composition of claim 1, wherein said buffer comprises acetic acid, sodium acetate, and combinations thereof.
11. A film dosage composition comprising:
 - a. A polymeric carrier matrix;
 - b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
 - c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
 - d. A buffer in an amount sufficient to inhibit the absorption of said naloxone when administered orally.
12. The composition of claim 11, wherein said composition has a local pH of about 2 to about 4.

13. The composition of claim 11, wherein said buffer is present in an amount sufficient to provide a therapeutically adequate absorption of buprenorphine.
14. The composition of claim 13, wherein a therapeutically adequate absorption of buprenorphine comprises a bioequivalent level of absorption of buprenorphine as a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
15. A film dosage composition comprising:
 - a. A polymeric carrier matrix;
 - b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
 - c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
 - d. A buffering system;wherein said buffering system comprises a buffer capacity sufficient to maintain the ionization of naloxone during the time which said composition is in the oral cavity of a user.
16. The composition of claim 15, wherein said composition has a local pH of about 2 to about 4.
17. A method of treating narcotic dependence of a user, comprising the steps of:
 - a. providing a composition comprising:
 - i. A polymeric carrier matrix;
 - ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
 - iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
 - iv. A buffer in an amount to provide a local pH of said composition of a value sufficient to optimize absorption of said buprenorphine; and
 - b. administering said composition to the oral cavity of a user.
18. The composition of claim 17, wherein said method provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
19. The method of claim 17, wherein said composition has a local pH of about 2 to about 4.
20. The method of claim 17, wherein said film dosage composition is administered to the user through buccal administration, sublingual administration, and combinations thereof.

21. The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of at least 1 minute.
22. The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of between about 1 and 1.5 minutes.
23. The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of up to 3 minutes.
24. A process of forming a film dosage composition comprising the steps of:
 - a. casting a film-forming composition, said film-forming composition comprising:
 - i. A polymeric carrier matrix;
 - ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
 - iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
 - iv. A buffer in an amount to provide a local pH of said composition of a value sufficient to optimize absorption of said buprenorphine; and
 - b. drying said film-forming composition to form a self-supporting film dosage composition.
25. The process of claim 24, wherein said composition has a local pH of about 2 to about 4.
26. A film dosage composition comprising a therapeutically sufficient amount of buprenorphine or a pharmaceutically acceptable salt thereof and a therapeutically sufficient amount of naloxone or a pharmaceutically acceptable salt thereof, said film dosage composition having a bioequivalent release profile as a tablet containing about 2 times the amount of buprenorphine or a pharmaceutically acceptable salt thereof.
27. An orally dissolving film formulation comprising buprenorphine and naloxone, wherein said formulation provides an in vivo plasma profile having a C_{max} of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in vivo plasma profile having a C_{max} of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone.
28. The formulation of claim 27, wherein said formulation provides a mean AUC of between about 5.431 hr.ng/ml to about 56.238 hr.ng/ml for buprenorphine.
29. The formulation of claim 27, wherein said formulation provides a mean AUC of between about 102.88 hr.pg/ml to about 812.00 hr.pg/ml for naloxone.
30. The formulation of claim 27, wherein said formulation comprises about 2 to about 16 mg of buprenorphine or a salt thereof.

31. The formulation of claim 27, wherein said formulation comprises about 0.5 to about 4 mg of naloxone or a salt thereof.

ABSTRACT

The present invention relates to products and methods for treatment of narcotic dependence in a user. The invention more particularly relates to self-supporting dosage forms which provide an active agent for treating narcotic dependence while providing sufficient buccal adhesion of the dosage form.

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(54) Title: SUBLINGUAL AND BUCCAL FILM COMPOSITIONS

(57) Abstract: The present invention relates to products and methods for treatment of narcotic dependence in a user. The invention more particularly relates to self-supporting dosage forms which provide an active agent for treating narcotic dependence while providing sufficient buccal adhesion of the dosage form.

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SUBLINGUAL AND BUCCAL FILM COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to compositions, methods of manufacture,
5 products and methods of use relating to films containing therapeutic actives. The
invention more particularly relates to self-supporting film dosage forms which
provide a therapeutically effective dosage, essentially matching that of currently-
marketed tablets containing the same active. Such compositions are particularly
useful for treating narcotic dependence while providing sufficient buccal adhesion of
10 the dosage form.

BACKGROUND OF THE RELATED TECHNOLOGY

Oral administration of two therapeutic actives in a single dosage form can be
complex if the intention is to have one active absorbed into the body and the other
active remain substantially unabsorbed. For example, one active may be relatively
15 soluble in the mouth at one pH, and the other active may be relatively insoluble at the
same pH. Moreover, the absorption kinetics of each therapeutic agent may be
substantially different due to differing absorption of the charged and uncharged
species. These factors represent some of the challenges in appropriately co-
administering therapeutic agents.

20 Co-administration of therapeutic agents has many applications. Among such
areas of treatment include treating individuals who suffer from narcotic dependence.
Such individuals have a tendency to suffer from serious physical dependence on the
narcotic, resulting in potentially dangerous withdrawal effects when the narcotic is not
administered to the individual. In order to help individuals addicted to narcotics, it is
25 known to provide a reduced level of a drug, which provides an effect of satisfying the
body's urge for the narcotic, but does not provide the "high" that is provided by the
misuse of the narcotic. The drug provided may be an agonist or a partial agonist,
which provides a reduced sensation and may help lower dependence on the drug.
However, even though these drugs provide only a low level of euphoric effect, they
30 are capable of being abused by the individuals parenterally. In such cases, it is
desirable to provide a combination of the drug with a second drug, which may
decrease the likelihood of diversion and abuse of the first drug. For example, it is
known to provide a dosage of an antagonist in combination with the agonist or partial

agonist. The narcotic antagonist binds to a receptor in the brain to block the receptor, thus reducing the effect of the agonist.

One such combination of drugs has been marketed under the trade name Suboxone® as an orally ingestible tablet. However, such combinations in tablet form
5 have the potential for abuse. In some instances, the patient who has been provided the drug may store the tablet in his mouth without swallowing the tablet, then later extract the agonist from the tablet and inject the drug into an individual's body. Although certain antagonists (such as highly water-soluble antagonists) may be used to help reduce the ability to separate the agonist, the potential for abuse still exists. It is
10 desired to provide a dosage that cannot be easily removed from the mouth once it has been administered.

There is currently a need for an orally dissolvable film dosage form that provides the desired absorption levels of the agonist and antagonist, while providing an adhesive effect in the mouth, rendering it difficult to remove once placed in the
15 mouth, thereby making abuse of the agonist difficult.

SUMMARY OF THE INVENTION

In one embodiment of the present invention, there is provided a film dosage composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof; a therapeutically
20 effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffer in an amount to provide a pH of the composition of a value sufficient to optimize absorption of the buprenorphine.

In another embodiment of the present invention, there is provided a film dosage composition including: a polymeric carrier matrix; a therapeutically effective
25 amount of buprenorphine or a pharmaceutically acceptable salt thereof; a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffer in an amount sufficient to inhibit the absorption of the naloxone when administered orally.

In still other embodiments, there may be provided a film dosage composition
30 including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof; a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffering system; where the buffering system includes a buffer capacity sufficient to

maintain the ionization of naloxone during the time which the composition is in the oral cavity of a user.

In another embodiment of the invention, there is provided a method of treating narcotic dependence of a user, including the steps of: providing a composition
5 including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof; a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffer in an amount to provide a pH of the composition of a value sufficient to optimize absorption of the buprenorphine; and administering the composition to the
10 oral cavity of a user.

In still another embodiment of the invention, there is provided a process of forming a film dosage composition including the steps of: casting a film-forming composition, the film-forming composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable
15 salt thereof; a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffer in an amount to provide a pH of the composition of a value sufficient to optimize absorption of the buprenorphine and drying the film-forming composition to form a self-supporting film dosage composition.

In another embodiment, there is provided a film dosage composition including
20 a therapeutically sufficient amount of buprenorphine or a pharmaceutically acceptable salt thereof and a therapeutically sufficient amount of naloxone or a pharmaceutically acceptable salt thereof, the film dosage composition having a bioequivalent release profile as compared to a Suboxone® tablet containing about 2 times the amount of buprenorphine or a pharmaceutically acceptable salt thereof.

25 Still other embodiments of the present invention provide an orally dissolving film formulation including buprenorphine and naloxone, where the formulation provides an in-vivo plasma profile having a C_{max} of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in-vivo plasma profile having a C_{max} of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Definitions

As used herein, the term C_{max} refers to the mean maximum plasma concentration after administration of the composition to a human subject. As also
5 used herein, the term AUC refers to the mean area under the plasma concentration-time curve value after administration of the compositions formed herein. As will be set forth in more detail below, the term “optimizing the absorption” does not refer to reaching the maximum absorption of the composition, and rather refers to reaching the optimum level of absorption at a pH of about 2 to about 4. The “optimum”
10 absorption may be, for example, a level that provides a bioequivalent absorption as administration of the currently available Suboxone® tablet. An “optimum” C_{max} of buprenorphine is about 0.67 to about 5.36 mg/ml at dosages of from 2-16 mg buprenorphine at a given pH. Similarly, an “optimum” AUC of buprenorphine may be about 7.43 to about 59.46 hr*ng/ml at dosages of from 2-16 mg buprenorphine at a
15 given pH. As will be described in more detail below, it has been surprisingly discovered that the absorption of one particular agonist, buprenorphine, can provide an optimum absorption at a pH of about 2-4 as well as about 5.5-6.5. Thus, one may “optimize” the absorption of buprenorphine by providing a pH of about 2-4 or about 5.5-6.5.

20 “Maximizing the absorption” refers to the maximum in vivo absorption values achieved at a pH of about 4 to about 9.

The term “local pH” refers to the pH of the region of the carrier matrix immediately surrounding the active agent as the matrix hydrates and/or dissolves, for example, in the mouth of the user.

25 By “inhibiting” the absorption of an active, it is meant achieving as complete an ionization state of the active as possible, such that little to none of the active is measurably absorbable. For example, at a pH of 3-3.5, the C_{max} of an active such as naloxone for dosage of 0.5 mg to 4.0 mg ranges from 32.5 to 260 pg/ml, and an AUC of naloxone for dosage of 0.5 mg to 4.0 mg ranges from 90.55 to 724.4 hr*pg/ml. It
30 is understood that at a pH lower than 3.0, further ionization would be expected and thus result in lower absorption.

The term “bioequivalent” means obtaining 80% to 125% of the C_{max} and AUC values for a given active in a different product. For example, assuming C_{max} and AUC values of buprenorphine for a commercially-available Suboxone® tablet

(containing 2 mg buprenorphine and 0.5 mg naloxone) are 0.780 ng/ml and 6.789 hr*ng/ml, respectively, a bioequivalent product would have a C_{max} of buprenorphine in the range of 0.624-0.975 ng/ml, and an AUC value of buprenorphine of 5.431-8.486 hr*ng/ml.

5 It will be understood that the term “film” includes thin films and sheets, in any shape, including rectangular, square, or other desired shape. The films described herein may be any desired thickness and size such that it may be placed into the oral cavity of the user. For example, the films may have a relatively thin thickness of from about 0.1 to about 10 mils, or they may have a somewhat thicker thickness of from
10 about 10 to about 30 mils. For some films, the thickness may be even larger, i.e., greater than about 30 mils. Films may be in a single layer or they may be multi-layered, including laminated films.

 Oral dissolving films generally fall into three main classes: fast dissolving, moderate dissolving and slow dissolving. Fast dissolving films generally dissolve in
15 about 1 second to about 30 seconds in the mouth. Moderate dissolving films generally dissolve in about 1 to about 30 minutes in the mouth, and slow dissolving films generally dissolve in more than 30 minutes in the mouth. Fast dissolving films may consist of low molecular weight hydrophilic polymers (i.e., polymers having a molecular weight between about 1,000 to 9,000, or polymers having a molecular
20 weight up to 200,000). In contrast, slow dissolving films generally have high molecular weight polymers (i.e., having a molecular weight in the millions).

 Moderate dissolving films tend to fall in between the fast and slow dissolving films. Moderate dissolving films dissolve rather quickly, but also have a good level of mucoadhesion. Moderate dissolving films are also flexible, quickly wettable, and
25 are typically non-irritating to the user. For the instant invention, it is preferable to use films that fall between the categories of fast dissolving and moderate dissolving. Such moderate dissolving films provide a quick enough dissolution rate, most desirably between about 1 minute and about 20 minutes, while providing an acceptable mucoadhesion level such that the film is not easily removable once it is
30 placed in the oral cavity of the user.

 Inventive films described herein may include one or more agonists or partial agonists used for the treatment of drug addiction. As used herein, the term “agonist” refers to a chemical substance that is capable of providing a physiological response or activity in the body of the user. The films described herein may further include one or

more antagonists. As used herein, the term "antagonist" refers to any chemical substance that acts within the body of the user to reduce the physiological activity of another chemical substance. In some embodiments, an antagonist used herein may act to reduce and/or block the physiological activity of the agonist. The actives may be
5 water-soluble, or they may be water-insoluble. As used herein, the term "water-soluble" refers to substances that are at least partially dissolvable in a solvent, including but not limited to water. The term "water-soluble" does not necessarily mean that the substance is 100% dissolvable in the solvent. The term "water-insoluble" refers to substances that are not dissolvable in a solvent, including but not
10 limited to water. Solvents may include water, or alternatively may include other polar solvents by themselves or in combination with water.

Inventive Films

The present invention relates to methods of treating narcotic dependence in an individual. More desirably, the invention relates to the treatment of opioid
15 dependence in an individual, while using a formulation and delivery that hinders misuse of the narcotic. Currently, treatment of opioid dependence is aided by administration of Suboxone®, which is an orally dissolvable tablet. This tablet which provides a combination of buprenorphine (an opioid agonist) and naloxone (an opioid antagonist). Therefore, the present invention provides a method of treating narcotic
20 dependence by providing an orally dissolvable film dosage, which provides a bioequivalent effect to Suboxone®. The film dosage preferably provides buccal adhesion while it is in the user's mouth, rendering it difficult to remove after placement.

The film dosage composition preferably includes a polymeric carrier matrix.
25 Any desired polymeric carrier matrix may be used, provided that it is orally dissolvable. Desirably, the dosage should have enough bioadhesion to not be easily removed and it should form a gel like structure when administered. The orally consumable films are preferably moderate-dissolving in the oral cavity and particularly suitable for delivery of actives, although both fast and sustained release
30 compositions are also among the various embodiments contemplated.

The films used in the pharmaceutical products may be produced by a combination of at least one polymer and a solvent, optionally including other fillers known in the art. The solvent may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, or any combination thereof. In some

embodiments, the solvent may be a non-polar organic solvent, such as methylene chloride. The film may be prepared by utilizing a selected casting or deposition method and a controlled drying process. For example, the film may be prepared through controlled drying processes, which include application of heat and/or
5 radiation energy to the wet film matrix to form a visco-elastic structure, thereby controlling the uniformity of content of the film. Such processes are described in more detail in commonly assigned U.S. Application No. 10/074,272, filed on February 14, 2002, and published as U.S. Patent Publication No. 2003/0107149 A1, the contents of which are incorporated herein by reference in their entirety.
10 Alternatively, the films may be extruded as described in commonly assigned U.S. Application No. 10/856,176, filed on May 28, 2004, and published as U.S. Patent Publication No. 2005/0037055 A1, the contents of which are incorporated herein by reference in their entirety.

The polymer included in the films may be water-soluble, water-swella-
15 ble, water-insoluble, or a combination of one or more either water-soluble, water-swella-
ble or water-insoluble polymers. The polymer may include cellulose or a cellulose derivative. Specific examples of useful water-soluble polymers include, but are not limited to, polyethylene oxide, pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone,
20 carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof. Specific examples of useful water-insoluble polymers include, but are not limited to, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate
25 phthalate, hydroxypropyl methyl cellulose phthalate and combinations thereof. For higher dosages, it may be desirable to incorporate a polymer that provides a high level of viscosity as compared to lower dosages.

As used herein the phrase "water-soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or
30 predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water-swella-
ble polymers. The materials useful with the present invention may be water-soluble or water-swella-
ble at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water-soluble or water-swella-
ble at pressures less than atmospheric

pressure. Desirably, the water-soluble polymers are water-soluble or water-swella-
ble having at least 20 percent by weight water uptake. Water-swella-
ble polymers having
a 25 or greater percent by weight water uptake are also useful. In some embodiments,
films formed from such water-soluble polymers may be sufficiently water-soluble to
5 be dissolvable upon contact with bodily fluids.

Other polymers useful for incorporation into the films include biodegradable
polymers, copolymers, block polymers and combinations thereof. It is understood
that the term "biodegradable" is intended to include materials that chemically
degrade, as opposed to materials that physically break apart (i.e., bioerodable
10 materials). Among the known useful polymers or polymer classes which meet the
above criteria are: poly(glycolic acid) (PGA), poly(lactic acid) (PLA), polydioxanes,
polyoxalates, poly(α -esters), polyanhydrides, polyacetates, polycaprolactones,
poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes,
polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers
15 thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid,
copolymers of bis(p-carboxyphenoxy) propane acid and sebacic acid, sebacic acid
copolymers, copolymers of caprolactone, poly(lactic acid)/poly(glycolic
acid)/polyethyleneglycol copolymers, copolymers of polyurethane and (poly(lactic
acid), copolymers of polyurethane and poly(lactic acid), copolymers of α -amino acids,
20 copolymers of α -amino acids and caproic acid, copolymers of α -benzyl glutamate and
polyethylene glycol, copolymers of succinate and poly(glycols), polyphosphazene,
polyhydroxy-alkanoates and mixtures thereof. Binary and ternary systems are
contemplated.

Other specific polymers useful include those marketed under the Medisorb and
25 Bidel trademarks. The Medisorb materials are marketed by the Dupont Company of
Wilmington, Delaware and are generically identified as a "lactide/glycolide co-
polymer" containing "propanoic acid, 2-hydroxy-polymer with hydroxy-polymer with
hydroxyacetic acid." Four such polymers include lactide/glycolide 100L, believed to
be 100% lactide having a melting point within the range of 338°-347°F (170°-175°C);
30 lactide/glycolide 100L, believed to be 100% glycolide having a melting point within
the range of 437°-455°F (225°-235°C); lactide/glycolide 85/15, believed to be 85%
lactide and 15% glycolide with a melting point within the range of 338°-347°F (170°-
175° C); and lactide/glycolide 50/50, believed to be a copolymer of 50% lactide and
50% glycolide with a melting point within the range of 338°-347°F (170°-175°C).

The Bidel materials represent a family of various polyanhydrides which differ chemically.

Although a variety of different polymers may be used, it is desired to select polymers that provide mucoadhesive properties to the film, as well as a desired
5 dissolution and/or disintegration rate. In particular, the time period for which it is desired to maintain the film in contact with the mucosal tissue depends on the type of active contained in the composition. Some actives may only require a few minutes for delivery through the mucosal tissue, whereas other actives may require up to several hours or even longer. Accordingly, in some embodiments, one or more water-
10 soluble polymers, as described above, may be used to form the film. In other embodiments, however, it may be desirable to use combinations of water-soluble polymers and polymers that are water-swellaable, water-insoluble and/or biodegradable, as provided above. The inclusion of one or more polymers that are water-swellaable, water-insoluble and/or biodegradable may provide films with slower
15 dissolution or disintegration rates than films formed from water-soluble polymers alone. As such, the film may adhere to the mucosal tissue for longer periods or time, such as up to several hours, which may be desirable for delivery of certain active components.

Desirably, the individual film dosage has a small size, which is between about
20 0.5-1 inch by about 0.5-1 inch. Most preferably, the film dosage is about 0.75 inches x 0.5 inches. The film dosage should have good adhesion when placed in the buccal cavity or in the sublingual region of the user. Further, the film dosage should disperse and dissolve at a moderate rate, most desirably dispersing within about 1 minute and dissolving within about 3 minutes. In some embodiments the film dosage may be
25 capable of dispersing and dissolving at a rate of between about 1 to about 1.5 minutes.

For instance, in some embodiments, the films may include polyethylene oxide alone or in combination with a second polymer component. The second polymer may be another water-soluble polymer, a water-swellaable polymer, a water-insoluble polymer, a biodegradable polymer or any combination thereof. Suitable water-soluble
30 polymers include, without limitation, any of those provided above. In some embodiments, the water-soluble polymer may include hydrophilic cellulosic polymers, such as hydroxypropyl cellulose and/or hydroxypropylmethyl cellulose. In accordance with some embodiments, polyethylene oxide may range from about 20% to 100% by weight in the polymer component, more specifically about 30% to about

70% by weight, and even more specifically about 40% to about 60% by weight. In some embodiments, one or more water-swella-
ble, water-insoluble and/or biodegradable polymers also may be included in the polyethylene oxide-based film. Any of the water-swella-
ble, water-insoluble or biodegradable polymers provided
5 above may be employed. The second polymer component may be employed in amounts of about 0% to about 80% by weight in the polymer component, more specifically about 30% to about 70% by weight, and even more specifically about 40% to about 60% by weight.

The molecular weight of the polyethylene oxide also may be varied. In some
10 embodiments, high molecular weight polyethylene oxide, such as about 4 million, may be desired to increase mucoadhesivity of the film. In some other embodiments, the molecular weight may range from about 100,000 to 900,000, more specifically from about 100,000 to 600,000, and even more specifically from about 100,000 to 300,000. In some embodiments, it may be desirable to combine high molecular
15 weight (600,000 to 900,000) with low molecular weight (100,000 to 300,000) polyethylene oxide in the polymer component.

A variety of optional components and fillers also may be added to the films. These may include, without limitation: surfactants; plasticizers; polyalcohols; anti-foaming agents, such as silicone-containing compounds, which promote a smoother
20 film surface by releasing oxygen from the film; thermo-setting gels such as pectin, carageenan, and gelatin, which help in maintaining the dispersion of components; inclusion compounds, such as cyclodextrins and caged molecules; coloring agents; and flavors. In some embodiments, more than one active components may be included in the film.

25 Additives may be included in the films. Examples of classes of additives include excipients, lubricants, buffering agents, stabilizers, blowing agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants,
30 adhesives, anti-adherents, acidulants, softeners, resins, demulcents, solvents, surfactants, emulsifiers, elastomers and mixtures thereof. These additives may be added with the active ingredient(s).

Useful additives include, for example, gelatin, vegetable proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, grape seed

proteins, whey proteins, whey protein isolates, blood proteins, egg proteins, acrylated proteins, water-soluble polysaccharides such as alginates, carrageenans, guar gum, agar-agar, xanthan gum, gellan gum, gum arabic and related gums (gum ghatti, gum karaya, gum tragacanth), pectin, water-soluble derivatives of cellulose:

- 5 alkylcelluloses hydroxyalkylcelluloses and hydroxyalkylalkylcelluloses, such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose esters and hydroxyalkylcellulose esters such as cellulose acetate phthalate (CAP),
- 10 hydroxypropylmethylcellulose (HPMC); carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters such as carboxymethylcellulose and their alkali metal salts; water-soluble synthetic polymers such as polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinylacetates, polyvinylalcohols,
- 15 polyvinylacetatephthalates (PVAP), polyvinylpyrrolidone (PVP), PVY/vinyl acetate copolymer, and polycrotonic acids; also suitable are phthalated gelatin, gelatin succinate, crosslinked gelatin, shellac, water-soluble chemical derivatives of starch, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be
- 20 quaternized if desired; and other similar polymers.

Such extenders may optionally be added in any desired amount desirably within the range of up to about 80%, desirably about 3% to 50% and more desirably within the range of 3% to 20% based on the weight of all film components.

- Further additives may flow agents and opacifiers, such as the oxides of
- 25 magnesium aluminum, silicon, titanium, etc. desirably in a concentration range of about 0.02% to about 3% by weight and desirably about 0.02% to about 1% based on the weight of all film components.

- [0001] Further examples of additives are plasticizers which include polyalkylene oxides, such as polyethylene glycols, polypropylene glycols, polyethylene-propylene
- 30 glycols, organic plasticizers with low molecular weights, such as glycerol, glycerol monoacetate, diacetate or triacetate, triacetin, polysorbate, cetyl alcohol, propylene glycol, sorbitol, sodium diethylsulfosuccinate, triethyl citrate, tributyl citrate, and the like, added in concentrations ranging from about 0.5% to about 30%, and desirably ranging from about 0.5% to about 20% based on the weight of the polymer.

There may further be added compounds to improve the texture properties of the starch material such as animal or vegetable fats, desirably in their hydrogenated form, especially those which are solid at room temperature. These fats desirably have a melting point of 50°C or higher. Preferred are tri-glycerides with C₁₂-, C₁₄-, C₁₆-,
5 C₁₈-, C₂₀- and C₂₂- fatty acids. These fats can be added alone without adding extenders or plasticizers and can be advantageously added alone or together with mono- and/or di-glycerides or phosphatides, especially lecithin. The mono- and di-glycerides are desirably derived from the types of fats described above, i.e. with C₁₂-, C₁₄-, C₁₆-, C₁₈-, C₂₀- and C₂₂- fatty acids.

10 The total amounts used of the fats, mono-, di-glycerides and/or lecithins are up to about 5% and preferably within the range of about 0.5% to about 2% by weight of the total film composition.

It further may be useful to add silicon dioxide, calcium silicate, or titanium dioxide in a concentration of about 0.02% to about 1% by weight of the total
15 composition. These compounds act as flow agents and opacifiers.

Lecithin is one surface active agent for use in the films described herein. Lecithin may be included in the feedstock in an amount of from about 0.25% to about 2.00% by weight. Other surface active agents, i.e. surfactants, include, but are not limited to, cetyl alcohol, sodium lauryl sulfate, the Spans™ and Tweens™ which are
20 commercially available from ICI Americas, Inc. Ethoxylated oils, including ethoxylated castor oils, such as Cremophor® EL which is commercially available from BASF, are also useful. Carbowax™ is yet another modifier which is very useful in the present invention. Tweens™ or combinations of surface active agents may be used to achieve the desired hydrophilic-lipophilic balance ("HLB"). The present
25 invention, however, does not require the use of a surfactant and films or film-forming compositions of the present invention may be essentially free of a surfactant while still providing the desirable uniformity features of the present invention.

Other ingredients include binders which contribute to the ease of formation and general quality of the films. Non-limiting examples of binders include starches, pregelatinize starches, gelatin, polyvinylpyrrolidone, methylcellulose, sodium
30 carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinylloxazolidone, and polyvinylalcohols.

Further potential additives include solubility enhancing agents, such as substances that form inclusion compounds with active components. Such agents may

be useful in improving the properties of very insoluble and/or unstable actives. In general, these substances are doughnut-shaped molecules with hydrophobic internal cavities and hydrophilic exteriors. Insoluble and/or instable actives may fit within the hydrophobic cavity, thereby producing an inclusion complex, which is soluble in water. Accordingly, the formation of the inclusion complex permits very insoluble and/or instable actives to be dissolved in water. A particularly desirable example of such agents are cyclodextrins, which are cyclic carbohydrates derived from starch. Other similar substances, however, are considered well within the scope of the present invention.

Suitable coloring agents include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors are dyes, their corresponding lakes, and certain natural and derived colorants. Lakes are dyes absorbed on aluminum hydroxide.

Other examples of coloring agents include known azo dyes, organic or inorganic pigments, or coloring agents of natural origin. Inorganic pigments are preferred, such as the oxides of iron or titanium, these oxides, being added in concentrations ranging from about 0.001 to about 10%, and preferably about 0.5 to about 3%, based on the weight of all the components.

Flavors may be chosen from natural and synthetic flavoring liquids. An illustrative list of such agents includes volatile oils, synthetic flavor oils, flavoring aromatics, oils, liquids, oleoresins or extracts derived from plants, leaves, flowers, fruits, stems and combinations thereof. A non-limiting representative list of examples includes mint oils, cocoa, and citrus oils such as lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot or other fruit flavors.

Other useful flavorings include aldehydes and esters such as benzaldehyde (cherry, almond), citral i.e., alphacitral (lemon, lime), neral, i.e., beta-citral (lemon, lime), decanal (orange, lemon), aldehyde C-8 (citrus fruits), aldehyde C-9 (citrus fruits), aldehyde C-12 (citrus fruits), tolyl aldehyde (cherry, almond), 2,6-dimethyloctanol (green fruit), and 2-dodecenal (citrus, mandarin), combinations thereof and the like.

The sweeteners may be chosen from the following non-limiting list: glucose (corn syrup), dextrose, invert sugar, fructose, and combinations thereof; saccharin and its various salts such as the sodium salt; dipeptide sweeteners such as aspartame;

5 dihydrochalcone compounds, glycyrrhizin; Stevia Rebaudiana (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol, mannitol, xylitol, and the like. Also contemplated are hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methyl-1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and calcium salts thereof, and natural intensive sweeteners, such as Lo Han Kuo. Other sweeteners may also be used.

10 Anti-foaming and/or de-foaming components may also be used with the films. These components aid in the removal of air, such as entrapped air, from the film-forming compositions. Such entrapped air may lead to non-uniform films. Simethicone is one particularly useful anti-foaming and/or de-foaming agent. The present invention, however, is not so limited and other anti-foam and/or de-foaming agents may suitably be used.

15 As a related matter, simethicone and related agents may be employed for densification purposes. More specifically, such agents may facilitate the removal of voids, air, moisture, and similar undesired components, thereby providing denser, and thus more uniform films. Agents or components which perform this function can be referred to as densification or densifying agents. As described above, entrapped air or undesired components may lead to non-uniform films.

20 Simethicone is generally used in the medical field as a treatment for gas or colic in babies. Simethicone is a mixture of fully methylated linear siloxane polymers containing repeating units of polydimethylsiloxane which is stabilized with trimethylsiloxy end-blocking units, and silicon dioxide. It usually contains 90.5-99% polymethylsiloxane and 4-7% silicon dioxide. The mixture is a gray, translucent, viscous fluid which is insoluble in water.

30 When dispersed in water, simethicone will spread across the surface, forming a thin film of low surface tension. In this way, simethicone reduces the surface tension of bubbles of air located in the solution, such as foam bubbles, causing their collapse. The function of simethicone mimics the dual action of oil and alcohol in water. For example, in an oily solution any trapped air bubbles will ascend to the surface and dissipate more quickly and easily, because an oily liquid has a lighter density compared to a water solution. On the other hand, an alcohol/water mixture is known to lower water density as well as lower the water's surface tension. So, any air bubbles trapped inside this mixture solution will also be easily dissipated.

Simethicone solution provides both of these advantages. It lowers the surface energy of any air bubbles that trapped inside the aqueous solution, as well as lowering the surface tension of the aqueous solution. As the result of this unique functionality, simethicone has an excellent anti-foaming property that can be used for physiological processes (anti-gas in stomach) as well as any for external processes that require the removal of air bubbles from a product.

In order to prevent the formation of air bubbles in the films, the mixing step can be performed under vacuum. However, as soon as the mixing step is completed, and the film solution is returned to the normal atmosphere condition, air will be re-introduced into or contacted with the mixture. In many cases, tiny air bubbles will be again trapped inside this polymeric viscous solution. The incorporation of simethicone into the film-forming composition either substantially reduces or eliminates the formation of air bubbles.

Simethicone may be added to the film-forming mixture as an anti-foaming agent in an amount from about 0.01 weight percent to about 5.0 weight percent, more desirably from about 0.05 weight percent to about 2.5 weight percent, and most desirably from about 0.1 weight percent to about 1.0 weight percent.

Any other optional components described in commonly assigned U.S. Patent No. 7,425,292 and U.S. Application No. 10/856,176, referred to above, also may be included in the films described herein.

When the dosage form includes at least one antagonist, it may be desired to control the release of the antagonist, so as to delay or wholly prevent the release of the antagonist from the dosage when taken orally. Desirably, the dosage form is a self-supporting film composition, which is placed into the oral cavity of the user. In a dosage form that is to be placed in the oral cavity, it is desired to absorb the agonist buccally, so as to provide rapid integration of the agonist into the body of the user. At the same time, it may be desired to prevent or reduce absorption of any antagonist buccally, thereby allowing the antagonist to be swallowed and destroyed in the stomach. Reducing the absorption of an antagonist may be achieved via physical means, such as by encapsulating the antagonist in a material that blocks absorption. It is desired, however, to reduce the absorption of the antagonist by chemical means, such as by controlling the local pH of the dosage.

It has been found that by controlling the local pH of the dosage form, the release and/or absorption of the actives therein may be controlled. For example, in a

dosage that includes an amount of an agonist, the local pH may be controlled to a level that maximizes its release and/or absorption into the oral cavity of the user. In dosages incorporating an amount of an agonist and an amount of an antagonist, the local pH may be controlled to a level that maximizes the release and/or absorption of the agonist while simultaneously minimizing the release and/or absorption of the antagonist.

The dosage form preferably includes a combination of a partial agonist and an antagonist, while the dosage has a controlled pH. In one embodiment, the partial agonist may include buprenorphine or a pharmaceutically acceptable salt thereof, while the antagonist includes naloxone or a therapeutically acceptable salt thereof. It should be understood that the present invention is not limited to the use of buprenorphine and naloxone, and any agonist (or partial agonist) and any antagonist may be incorporated into the present invention for use in treatment of drug addiction. The agonist and optional antagonist should be selected from those agonists and antagonists that are useful in treating the particular narcotic dependence being treated.

As discussed above, the local pH of the dosage is preferably controlled to provide the desired release and/or absorption of the agonist and antagonist. Buprenorphine is known to have a pKa of about 8.42, while naloxone has a pKa of about 7.94. According to pH partition theory, one would expect that saliva (which has a pH of about 6.5) would maximize the absorption of both actives. However, it has been surprisingly discovered by the Applicants that by buffering the dosage to a particular pH level, the optimum levels of absorption of the agonist and antagonist may be achieved. Desirably, the local pH of a composition including an agonist and an antagonist is between about 2 to about 4, and most desirably is from 3 to 4. At this local pH level, the optimum absorption of the agonist and the antagonist is achieved. As will be described in more detail in the Examples below, controlling the local pH of the film compositions of the present invention provides a system in which the desired release and/or absorption of the components is bioequivalent to that of a similar Suboxone® tablet.

In one embodiment, the dosage form is a self-supporting film. In this embodiment, the film dosage includes a polymer carrier matrix, a therapeutically effective amount of buprenorphine, an agonist. The buffer is preferably capable of providing a local pH of the composition within a range that provides the desired level of absorption of the buprenorphine. The resulting dosage is a film composition that

allows for a rapid and effective release of buprenorphine into the oral cavity of the user. At the same time, the film composition preferably has a sufficient adhesion profile, such that the film cannot easily be removed from the oral cavity of the user once it has been placed into the cavity. Full release of the buprenorphine preferably
5 takes place within less than about thirty minutes, and preferably remains in the oral cavity for at least 1 minute.

As explained above, while providing a pharmaceutically acceptable level of an agonist is helpful in treating those with narcotic addiction, it may be desirable to provide the buprenorphine in combination with naloxone (an antagonist) so as to
10 reduce the effect of the agonist and therefore aid in reducing dependency of the narcotic. Therefore, it may be desirable to combine the opioid agonist (or partial agonist) in the film composition with an opioid antagonist or a pharmaceutically acceptable salt thereof. The actives may be dispersed throughout the dosage separately or they may be combined together and dispersed into the dosage. Most
15 desirably the antagonist includes naloxone, but any suitable basic antagonist may be selected as desired. The antagonist may optionally be water-soluble, so as to render separation of the antagonist and agonist difficult, thereby lessening the potential for abuse of the agonist.

As with a film including an agonist, the film including an agonist and an
20 antagonist is desirably pH-controlled through the inclusion of a buffer. In such combination films, it has been discovered that the local pH of the film composition should preferably be in the range of about 2 to about 4, and more preferably about 3 to about 4 so as to provide a bioequivalent product as the commercially-available Suboxone® tablet. Most preferably the local pH of the film composition is about 3.5.
25 At this local pH level, absorption of the buprenorphine is optimized while the absorption of the naloxone is inhibited.

The film may contain any desired level of self-supporting film forming polymer, such that a self-supporting film composition is provided. In one embodiment, the film composition contains a film forming polymer in an amount of at
30 least 25% by weight of the composition. The film forming polymer may alternatively be present in an amount of at least 50% by weight of the composition. As explained above, any film forming polymers that impart the desired mucoadhesion and rate of film dissolution may be used as desired.

Any desired level of agonist and optional antagonist may be included in the dosage, so as to provide the desired effect. In one particular embodiment, the film composition includes about 2 mg to about 16 mg of agonist per dosage. More desirably, the film composition includes about 4 mg to about 12 mg of agonist per dosage. If desired, the film composition may include about 0.5 mg to about 5 mg of antagonist per dosage. More desirably, the film composition includes about 1 mg to about 3 mg of antagonist per dosage. If an antagonist is incorporated into the film, the film composition may include the antagonist in a ratio of about 6:1 – 2:1 agonist to antagonist. Most desirably, the film composition contains about 4:1 agonist to antagonist per dosage. For example, in one embodiment, the dosage includes an agonist in an amount of about 12 mg, and includes an antagonist in an amount of about 3 mg.

The film compositions further desirably contains a buffer so as to control the local pH of the film composition. Any desired level of buffer may be incorporated into the film composition so as to provide the desired local pH level. The buffer is preferably provided in an amount sufficient to control the release from the film and/or the absorption into the body of the agonist and the optional antagonist. In a desired embodiment, the film composition includes buffer in a ratio of buffer to agonist in an amount of from about 2:1 to about 1:5 (buffer:agonist). The buffer may alternatively be provided in a 1:1 ratio of buffer to agonist. As stated above, the film composition preferably has a local pH of about 2 to about 4, and most preferably has a local pH of about 3.5. Any buffer system may be used as desired. In some embodiments, the buffer may include sodium citrate, citric acid, and combinations thereof.

In this embodiment, the resulting film composition includes a polymer matrix, an agonist, and an optional antagonist, while the film composition has a controlled local pH to the level desired. The buffer is preferably present in an amount to provide a therapeutically adequate absorption of the agonist, while simultaneously limiting the absorption of the antagonist. Controlling of the local pH allows for the desired release and/or absorption of the components, and thus provides a more useful and effective dosage.

The film dosage composition may include a polymer carrier matrix, a therapeutically effective amount of agonist, a therapeutically effective amount of antagonist, and a buffering system. The buffering system may include a buffer in

addition to a solvent. The buffering system desirably includes a sufficient level of buffer so as to provide a desired local pH level of the film dosage composition.

In addition to a desired local pH level, the buffer preferably has a buffer capacity sufficient to maintain the ionization of the optional antagonist during the time that the composition is in the oral cavity of a user. Maintaining the ionization of the antagonist serves to limit the absorption of the antagonist, and thus provide the desired control of the antagonist. While the ionization of the antagonist is limited, the ionization of the agonist may not be so limited. As such, the resulting dosage form provides absorption of the agonist to the user, while sufficiently reducing and/or preventing absorption of the antagonist. By keeping the antagonist ionized and the local pH at the optimum pH, the antagonist has limited if any absorption, but is still present should the product be abused or taken via a different route of administration. However, when taken as administered, the antagonist has little to no effect in blocking the agonist.

The film dosage composition including an agonist may be configured to provide an in vivo plasma profile having a mean maximum plasma concentration (Cmax) in a desired range. It has been discovered by the Applicants that controlling the Cmax of the film composition allows one to control the absorption of the active (such as an agonist) into the user. The resulting film composition is more effective and suitable for delivery to a user.

As explained, the film dosage composition provides a bioequivalent result to a commercially available Suboxone® product. As will be explained more in the Examples below, commercially available Suboxone® provides different absorption levels depending on the amount of buprenorphine and naloxone administered. The present invention desirably provides a film product providing bioequivalent release as that of the Suboxone® product. As with the Suboxone® product, the buprenorphine may be present in an amount of from about 2 mg to about 16 mg per dosage, or, if desired about 4 mg to about 12 mg per dosage. Additionally, the naloxone may be present in any desired amount, preferably at about 25% the level of buprenorphine. For example, an inventive film product may have 2 mg buprenorphine and 0.5 mg naloxone, 4 mg buprenorphine and 1 mg naloxone, 8 mg buprenorphine and 2 mg naloxone, 12 mg buprenorphine and 3 mg naloxone, 16 mg buprenorphine and 4 mg naloxone, or any similar amounts.

It has further been discovered that, by controlling the mean area under the curve (AUC) value of the film composition, a more effective dosage form may be provided. As is described in more detail in the Examples below, the inventive film composition preferably provides an AUC value so as to provide a bioequivalent result
5 as that provided by the commercially available Suboxone® tablet. In one embodiment, the film composition may include a mean AUC_{inf} value of about 6.8 hr.ng/ml or greater. Alternatively, the film composition may include a mean AUC_{inf} value of from about 6.8 hr.ng/ml to about 66 hr.ng/ml.

As explained above, the film compositions may include naloxone, an
10 antagonist. When the film composition includes a combination of agonist and antagonist, the film composition may be configured to provide a particular C_{max} and/or AUC_{inf} for the antagonist. For example, when a buprenorphine agonist and a naloxone antagonist are incorporated into the film composition, the naloxone may be configured to provide a C_{max} of less than about 400 pg/ml, less than about 318
15 pg/ml, less than about 235 pg/ml, less than about 92 pg/ml or less than about 64 pg/ml. In such films, the naloxone may provide a mean AUC_{inf} value of less than about 1030 hr.ng/ml.

In formulations which include an agonist in combination with an antagonist, the film composition may be prepared to provide a desired C_{max} and/or AUC_{inf}
20 value for each of the agonist and antagonist. In one embodiment, the film composition provides an in vivo plasma profile having a C_{max} of less than about 6.4 ng/ml for the agonist and an in vivo plasma profile having a C_{max} of less than about 400 pg/ml for the antagonist. In such embodiments, the formulation may provide an AUC_{inf} value of more than about 6.8 hr.ng/ml for the agonist. If desired, the
25 formulation may provide an AUC_{inf} value of less than about 1030 hr.pg/ml for the antagonist. Such compositions may include the agonist and the antagonist in any desired amount, and in a preferred embodiment, the composition includes about 2 mg to about 16 mg of the agonist per dosage and about 0.5 mg to about 4 mg of the antagonist per dosage.

30 The present invention provides a method of treating narcotic dependence in a patient. In one embodiment, the patient is dependent on opioid narcotics, but the patient may have a dependence on non-opioid narcotics. Desirably, the patient is treated by providing a dosage to the patient, which provides an effective release of actives but simultaneously provides a suitable adhesion so that the dosage cannot be

easily removed. In one method of treatment, an orally dissolvable film composition is provided to a patient.

Depending on the particular narcotic that the patient experiences dependence upon, the film composition may include one or more particular active components. In one embodiment, the film composition includes a polymer carrier matrix and a therapeutically effective amount of an agonist. Desirably the agonist is a partial agonist. For opioid dependency, the agonist may be an opioid agonist, such as buprenorphine or a pharmaceutically acceptable salt thereof. The film composition preferably includes a buffer in an amount sufficient to control the local pH of the film composition. Any buffer system may be used, including sodium citrate, citric acid, and combinations thereof. In compositions solely including an agonist, the local pH of the film composition is desirably about 5 to about 6.5, and most desirably the local pH is about 5.5. At this level, the absorption of the agonist is most effective. To treat the dependency, the film composition is administered to the patient, most desirably into the oral cavity of the patient.

If desired, the composition may include a therapeutically effective amount of an antagonist, to prevent abuse of the agonist. A "therapeutically effective amount" of an antagonist is intended to refer to an amount of the antagonist that may be useful in diverting abuse of the agonist by a user. The antagonist may be any desired antagonist, and in one embodiment includes naloxone or a pharmaceutically acceptable salt thereof. The film composition is preferably administered to a patient through the oral cavity of the patient, but may be administered in any desired means. The orally dissolvable film composition is then allowed to dissolve in the oral cavity of the patient for a sufficient time so as to release the active(s) therein. In some embodiments, the film composition may remain in the oral cavity for at least 30 seconds, and in some embodiments may remain in the oral cavity for at least 1 minute. After the film composition is placed into the oral cavity of the patient, the film preferably becomes sufficiently adhered so as to render its removal difficult. After the film composition has been administered to the patient, the active(s) are sufficiently released from the composition and allowed to take effect on the patient.

The film compositions of the present invention may be formed via any desired process. Suitable processes are set forth in U.S. Patent Nos. 7,425,292 and 7,357,891, the entire contents of which are incorporated by reference herein. In one embodiment, the film dosage composition is formed by first preparing a wet

composition, the wet composition including a polymeric carrier matrix, a therapeutically effective amount of an agonist, and a buffer in an amount sufficient to control the local pH of the composition to a desired level. The wet composition is cast into a film and then sufficiently dried to form a self-supporting film composition.

5 The wet composition may be cast into individual dosages, or it may be cast into a sheet, where the sheet is then cut into individual dosages. The agonist may be a partial agonist. If desired, the wet composition may include a therapeutically effective amount of an antagonist.

10 The agonist and the optional antagonist are preferably selected to treat a particular narcotic dependency. For opioid dependency, for example, the agonist may include buprenorphine or a pharmaceutically acceptable salt thereof, while the antagonist may include naloxone or a pharmaceutically acceptable salt thereof. The local pH of the film composition is desirably maintained at about 2 to about 4.

EXAMPLES

15 Example 1 – Composition of Buprenorphine/Naloxone Films at Various Strengths

Film strips including a combination of buprenorphine and naloxone were prepared. Four different strength film compositions were prepared, which include a ratio of buprenorphine to naloxone of 16/4, 12/3, 8/2, and 2/0.5. The compositions are summarized in Table 1 below.

20 Table 1 – Various Compositions of Film Dosages

Components	Buprenorphine/Naloxone Films			
	Unit Formula (mg per film strip)			
Buprenorphine/Naloxone Ratios	16/4	12/3	8/2	2/0.5
Active Components				
Buprenorphine HCl	17.28	12.96	8.64	2.16
Naloxone HCl Dihydrate	4.88	3.66	2.44	0.61
Inactive Components				
Polyethylene Oxide, NF (MW 200,000)	27.09	20.32	13.55	--
Polyethylene Oxide, NF (MW 100,000)	12.04	9.03	6.02	19.06
Polyethylene Oxide, NF (MW 900,000)	4.82	3.62	2.41	2.05

Maltitol, NF	12.04	9.03	6.02	5.87
Flavor	6.0	4.5	3.0	2.4
Citric Acid, USP	5.92	4.44	2.96	2.96
HPMC	4.22	3.16	2.11	2.34
Ace-K	3.0	2.25	1.5	1.2
Sodium Citrate, anhydrous	2.68	2.01	1.34	1.34
Colorant	0.03	0.02	0.01	0.01
Total (mg)	100	75	50	40

Example 2 – Absorption studies for Suboxone® products

Various film and tablet products were prepared and tested for absorption data, including Cmax and AUC absorption levels. The products tested included Suboxone® tablets made with either 2 mg or 16 mg buprenorphine as well as either 0.5 mg or 4.0 mg naloxone. For 16 mg buprenorphine tablets, two 8 mg buprenorphine tablets were combined together to provide the level of components of a 16 mg buprenorphine tablet. In instances where a 12 mg buprenorphine tablet was evaluated, this dosage was obtained by combining one 8 mg buprenorphine tablet and two 2 mg buprenorphine tablets. These products were tested for absorption levels, with the amounts listed in Table 2 below.

Table 2 - Absorption Data for Suboxone® products

Sample	C max	AUC
Buprenorphine (2 mg) Suboxone® Tablet	0.780 ng/ml	6.789 hr*ng/ml
Naloxone (0.5 mg) Suboxone® Tablet	51.30 pg/ml	128.60 hr*pg/ml
Buprenorphine (16 mg) Suboxone® Tablet	4.51 ng/ml	44.99 hr*ng/ml
Naloxone (4 mg) Suboxone® Tablet	259.00 pg/ml	649.60 hr*pg/ml

Using the data from Table 2, absorption data for the Suboxone® tablets for other levels of buprenorphine and naloxone are set forth in Table 2A below.

Table 2A – Extrapolated Absorption Data for Suboxone® products

Sample	C max	AUC
Buprenorphine (4 mg) Suboxone® Tablet	1.35 ng/ml	12.25 hr*ng/ml
Naloxone (1 mg) Suboxone® Tablet	80.97 pg/ml	203 hr*pg/ml

Buprenorphine (8 mg) Suboxone® Tablet	2.29 ng/ml	23.17 hr*ng/ml
Naloxone (2 mg) Suboxone® Tablet	140.31 pg/ml	351.8 hr*pg/ml
Buprenorphine (12 mg) Suboxone® Tablet	3.23 ng/ml	34.08 hr*ng/ml
Naloxone (3 mg) Suboxone® Tablet	199.7 pg/ml	500.6 hr*pg/ml

Example 3 – Evaluation of Bioequivalence of Suboxone® Tablets

Using the data generated for Suboxone® tablets in Table 2 above, acceptable bioequivalence ranges are generated to provide an equivalent treatment level as the Suboxone® tablet. As currently understood, a product provides a bioequivalent effect if it provides absorption levels between about 80% to about 125% of the Suboxone® tablet. Absorption in this range is considered to be bioequivalent.

Table 3 - Acceptable Bioequivalence Ranges for Suboxone® Tablets (80 to 125%)

Description of Sample	C max	AUC
Buprenorphine 2 mg	0.624 to 0.975 ng/ml	5.431 to 8.486 hr*ng/ml
Naloxone 0.5 mg	41.04 to 64.13 pg/ml	102.88 to 160.75 hr*pg/ml
Buprenorphine 16 mg	3.608 to 5.638 ng/ml	35.992 to 56.238 hr*ng/ml
Naloxone 4 mg	207.20 to 323.75 pg/ml	519.68 to 812.00 hr*pg/ml

Thus, to be considered bioequivalent to the Suboxone® tablet, the Cmax of buprenorphine is between about 0.624 and 5.638, and the AUC of buprenorphine is between about 5.431 to about 56.238. Similarly, to be considered bioequivalent to the Suboxone® tablet, the Cmax of naloxone is between about 41.04 to about 323.75, and the AUC of naloxone is between about 102.88 to about 812.00.

Example 4 – Absorption studies for film products at pH 3.5

Various film products were prepared and tested for absorption data, including Cmax and AUC absorption levels. The products tested included inventive film strips, the film strips having either 2 mg or 16 mg buprenorphine as well as either 0.5 mg or 4.0 mg naloxone. These products were tested for absorption levels, with the amounts listed in Table 4 below.

Table 4 - Absorption Data for inventive film products at pH 3.5

Sample	C max	AUC
Buprenorphine (2 mg) Sublingual Film	0.947 ng/ml	7.82 hr*ng/ml

Naloxone (0.5 mg) Sublingual Film	51.10 pg/ml	128.60 hr*pg/ml
Buprenorphine (16 mg) Sublingual Film	5.47 ng/ml	55.30 hr*ng/ml
Naloxone (4 mg) Sublingual Film	324.00 pg/ml	873.60 hr*pg/ml

As can be seen, in this experiment, the values for buprenorphine absorbance were squarely in the bioequivalence range evaluated above. The inventive films were therefore determined to have provided a bioequivalent absorption of buprenorphine at a local pH of 3.5 as the commercially available Suboxone® tablet. The values for absorption of naloxone were very close to the bioequivalent range of Suboxone®. The slightly higher absorption of Naloxone was not due to the local pH but rather to the amount of buffer (buffer capacity as discussed in the application). This is confirmed by the fact that the lower 2/0.5 mg dose is in range for the Naloxone and this is due to the higher buffer capacity for the 2/0.5 dose as pointed out in the buffer capacity chart.

Example 5 – Preparation of Films For In Vivo Study

Film dosages were prepared for use in an *in vivo* study to determine the bioavailability of buprenorphine/naloxone tablets and film formulations. Specifically, the films were tested to determine whether the film provides a bioequivalent effect to that of a tablet formulation.

Three film formulations including 8 mg buprenorphine and 2 mg naloxone were prepared, each being buffered to a different pH. The first film did not include any buffer, providing a local pH of about 6.5. The second was buffered to a local pH level of about 3-3.5. The third was buffered to a local pH value of about 5-5.5. The formulations are set forth in Table 5 below.

Table 5 – Formulations of Test Films at Various pH Levels

Component	Test formulation 1 8 mg/2 mg pH = 6.5		Test formulation 2 8 mg/2 mg pH = 3-3.5		Test formulation 3 8 mg/2 mg pH = 5-5.5	
	%w/w	Mg/film	%w/w	Mg/film	%w/w	Mg/film
Buprenorphine HCl	21.61	8.64	17.28	8.64	17.28	8.64
Naloxone HCl Dihydrate	6.10	2.44	4.88	2.44	4.88	2.44
Polymer	5.05	2.02	4.82	2.41	4.82	2.41

Polymer	28.48	11.39	27.09	13.55	27.09	13.55
Polymer	12.65	5.06	12.04	6.02	12.04	6.02
Polymer	4.43	1.77	4.22	2.11	4.22	2.11
Sweetener	12.65	5.06	12.04	6.02	12.04	6.02
Sweetener	3	1.2	3	1.5	3	1.5
Flavor	6	2.4	6	3	6	3
Citric acid	0	0	5.92	2.96	2.51	1.26
Sodium citrate	0	0	2.68	1.34	6.08	3.04
FD&C yellow #6	0.025	0.01	0.03	0.02	0.03	0.02
Total	100	40	100	50	100	50

Example 6 – Analysis of *In Vivo* Absorption of Film Having a pH of 6.5

The film dosage composition of film having a local pH of 6.5 was analyzed. Specifically, Test Formulation 1, as prepared in Example 5 was analyzed in vivo to determine the absorption of buprenorphine and of naloxone. The comparative film was compared to the absorption of buprenorphine and of naloxone provided by a one dose tablet (Suboxone®). The test film was compared to determine whether it provided a bioequivalent effect as the tablet product.

The results for Test Formulation 1, which had a local pH of about 6.5, as compared to the one dose tablet, are set forth in Tables 6 and 7 below.

Table 6 – Buprenorphine In Vivo Absorption Data for Test Formulation 1

	Suboxone® sublingual				Test Formulation 1 (pH = 6.5)			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	15	1.60	0.47	29.41	15	1.50	0.62	41.23
C _{max} (ng/mL)	15	2.27	0.562	24.77	15	2.60	0.872	33.53
AUC _{last} (hr*ng/mL)	15	27.08	10.40	38.41	15	31.00	12.93	41.72
AUC _{inf} (hr*ng/mL)	15	29.58	11.15	37.68	15	33.37	13.88	41.61
T _{1/2} (hr)	15	44.76	20.86	46.60	15	40.73	14.93	36.66

Table 7 – Naloxone In Vivo Absorption Data for Test Formulation 1

	Suboxone® sublingual				Test Formulation 1 (pH = 6.5)			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	15	0.90	0.23	25.32	15	0.68	0.18	25.75
C _{max} (pg/mL)	15	94.6	39.1	41.33	15	410	122	29.75
AUC _{last} (hr*pg/mL)	15	297.1	120.7	40.62	15	914.8	158.1	17.29
AUC _{inf} (hr*pg/mL)	15	306.1	122.6	40.06	15	924.2	158.8	17.18

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T_{1/2} (hr)	15	6.62	2.60	39.26	15	6.86	2.08	30.27
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As can be seen, the in vivo data indicates that buprenorphine is absorbed very well from the film formulation at a local pH of 6.5, and matched closely the absorption seen in the Suboxone® one dose tablet. However, the absorption was also maximized for the naloxone, which was undesirable. It was determined that a film having a combination of buprenorphine and naloxone and a local pH of 6.5 did not provide a bioequivalent effect as the Suboxone® tablet for both buprenorphine and naloxone.

Example 7 – Analysis of In Vivo Absorption of Film Having a pH of 5-5.5

Having determined the absorption of buprenorphine and naloxone in film having a local pH of 6.5, a film dosage composition of film having a local pH of 5-5.5 was analyzed. Specifically, Test Formulation 3, as prepared in Example 5 was analyzed in vivo to determine the absorption of buprenorphine and of naloxone. The comparative films were compared to the absorption of buprenorphine and of naloxone provided by the Suboxone® one dose tablet. The test film was compared to determine whether it provided a bioequivalent effect as the Suboxone® tablet.

The results for Test Formulation 3, which had a local pH of about 5-5.5, as compared to the Suboxone® tablet, are set forth in Tables 8 and 9 below.

Table 8 – Buprenorphine In Vivo Absorption Data for Test Formulation 3

	Suboxone® sublingual				Test Formulation 3 (pH = 5-5.5)			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	15	1.60	0.47	29.41	14	1.50	0.43	28.50
C_{max} (ng/mL)	15	2.27	0.562	24.77	14	3.47	1.57	45.40
AUC_{last} (hr*ng/mL)	15	27.08	10.40	38.41	14	33.25	16.01	48.16
AUC_{inf} (hr*ng/mL)	15	29.58	11.15	37.68	13	38.34	15.38	40.13
T_{1/2} (hr)	15	44.76	20.86	46.60	13	41.71	17.70	42.42

Table 9 – Naloxone In Vivo Absorption Data for Test Formulation 3

	Suboxone® sublingual				Test Formulation 3 (pH = 5-5.5)			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	15	0.90	0.23	25.32	14	0.98	0.62	63.51
C_{max}	15	94.6	39.1	41.33	14	173	84.5	48.79

Anexo

(pg/mL)								
AUC _{last} (hr*pg/mL)	15	297.1	120.7	40.62	14	455.2	195.5	42.94
AUC _{inf} (hr*pg/mL)	15	306.1	122.6	40.06	13	474.4	203.1	42.81
T _{1/2} (hr)	15	6.62	2.60	39.26	13	9.45	6.90	73.00

As can be seen, the in vivo data indicated that the absorption of buprenorphine increased as the local pH level decreased. It appeared that by decreasing the local pH from 6.5 to 5.5, the absorption of buprenorphine was being moved to a level further away from that of the one dose tablet. In addition, the naloxone values did not provide a bioequivalent result as the one dose tablet. Thus, it was determined that the film having a local pH of 5.5 did not provide a bioequivalent result as that of the Suboxone® tablet for both buprenorphine and naloxone.

It was noted that by reducing the local pH of the film to a level of 5.5, there would be provided an increased level of absorption of buprenorphine. Thus, it may be desirable to buffer a film composition incorporating buprenorphine itself to a level of about 5.5 to provide an increased absorption.

Example 8 – Analysis of In Vivo Absorption of Film Having a pH of 3-3.5

Having determined the absorption of buprenorphine and naloxone in films having a local pH of 6.5 and 5.5, a film dosage composition of film having a local pH of about 3-3.5 was analyzed. It was assumed that the absorption of buprenorphine would continue to be increased as it had demonstrated at a local pH of 5.5. Thus, it was assumed that at a local pH of 3.5, the film would not be bioequivalent to that of the tablet.

Specifically, Test Formulation 2, as prepared in Example 5, was analyzed in vivo to determine the absorption of buprenorphine and of naloxone. The comparative films were compared to the absorption of buprenorphine and of naloxone provided by the Suboxone® one dose tablet. The test film was compared to determine whether it provided a bioequivalent effect as the tablet product.

The results for Test Formulation 2, which had a local pH of about 3-3.5, as compared to the Suboxone® tablet, are set forth in Tables 10 and 11 below.

Table 10 – Buprenorphine In Vivo Absorption Data for Test Formulation 2

	Suboxone® sublingual	Test Formulation 2
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					(pH = 3-3.5)			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	15	1.60	0.47	29.41	14	1.68	0.58	34.68
C _{max} (ng/mL)	15	2.27	0.562	24.77	14	2.68	0.910	33.99
AUC _{last} (hr*ng/mL)	15	27.08	10.40	38.41	14	29.73	12.05	40.54
AUC _{inf} (hr*ng/mL)	15	29.58	11.15	37.68	14	31.45	12.98	41.26
T _{1/2} (hr)	15	44.76	20.86	46.60	14	30.03	13.95	46.46

Table 11 – Naloxone In Vivo Absorption Data for Test Formulation 2

	Suboxone® sublingual				Test Formulation 2 (pH = 3-3.5)			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	15	0.90	0.23	25.32	14	0.84	0.19	22.19
C _{max} (pg/mL)	15	94.6	39.1	41.33	14	130	72.9	56.04
AUC _{last} (hr*pg/mL)	15	297.1	120.7	40.62	14	362.2	155.9	43.03
AUC _{inf} (hr*pg/mL)	15	306.1	122.6	40.06	12	350.4	142.3	40.61
T _{1/2} (hr)	15	6.62	2.60	39.26	12	8.07	4.75	58.84

5 As can be seen, the in vivo data indicated that the absorption of buprenorphine was substantially bioequivalent to that of the one dose tablet when the film composition local pH was lowered to about 3-3.5. This result was surprising as it did not appear to follow the pH partition theory. Further, at a local pH of about 3-3.5, it was seen that the absorption of naloxone was substantially bioequivalent to that of the one dose tablet.

10 Thus, it was determined that the film product including buprenorphine and naloxone at a local pH of 3-3.5 was substantially bioequivalent to that of the Suboxone® one dose tablet.

15 Example 9 – Normalized Values for Naloxone in Films and Tablets

 Various film compositions including buprenorphine and naloxone in 8/2 mg and 2/0.5 mg dosages, and having different local pH values from 6.5 to 3.5, were prepared and analyzed. The data was normalized and compared to the one dose tablet. The results are set forth in Table 12 below.

20 Table 12 – Normalized Values for Naloxone Film Compared to Tablet

pH	Dose (mg)	AUC (Normalized)	Cmax	Mg Citric	Ratio Citric Acid
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	Buprenorphine/ Naloxone			Acid	(mg)/Naloxone (mg)
6.5	8/2	3.02	4.33	1.34	0.67
5.5	8/2	1.55	1.83	1.34	0.67
3.5	8/2	1.14	1.37	1.34	0.67
3.5	2/0.5	0.98	0.90	1.34	2.68
5.5	2/0.5	1.41	1.41	1.34	2.68

The data indicates that not only is the local pH of significant importance, but the amount of buffer present in the formula is also important. The improvement from the 8/2 dose to the 2/0.5 dose (at a local pH of 3.5) demonstrates this importance. The
5 8/2 dose has a ratio of buffer/naloxone of 0.67, and this dose provided borderline acceptable bioequivalent results. In contrast, the 2/0.5 dose has a ratio of buffer/naloxone of 2.68, and provides a more bioequivalent absorption value than the 8/2 dose.

In fact, the data shows that the 2/0.5 dose at a local pH of 3.5 had an even
10 lower buccal absorption than the one dose tablet, as seen from the normalized values for the AUC and Cmax. This demonstrates that even less absorption of the naloxone occurs for the film formulation at a local pH of 3.5 than the tablet formulation. Given the goal of reducing the absorption of naloxone, it appears that the film product buffered at a local pH of 3.5 with a buffer ratio of buffer/Naloxone of 2.68 provides
15 even better results than the Suboxone® tablet formulation.

What is claimed is:

1. A film dosage composition comprising:
 - a. A polymeric carrier matrix;
 - b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
 - c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
 - d. A buffer in an amount to provide a local pH of said composition of a value sufficient to optimize absorption of said buprenorphine.
2. The composition of claim 1, wherein said local pH is about 2 to about 4.
3. The composition of claim 2, wherein the local pH of said composition is from about 3 to about 4.
4. The composition of claim 1, wherein said film dosage composition provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
5. The composition of claim 1, wherein said polymeric carrier matrix comprises at least one polymer in an amount of at least 25% by weight of said composition.
6. The composition of claim 1, wherein said buffer is present in an amount of from about 2:1 to about 1:5 by weight of buffer to buprenorphine.
7. The composition of claim 1, wherein said polymeric carrier matrix comprises at least one self-supporting film forming polymer.
8. The film dosage composition of claim 1, wherein said buprenorphine is present in an amount of from about 2 mg to about 16 mg per dosage.
9. The film dosage composition of claim 1, wherein said buffer comprises sodium citrate, citric acid, and combinations thereof.
10. The film dosage composition of claim 1, wherein said buffer comprises acetic acid, sodium acetate, and combinations thereof.
11. A film dosage composition comprising:
 - a. A polymeric carrier matrix;
 - b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;

- c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
 - d. A buffer in an amount sufficient to inhibit the absorption of said naloxone when administered orally.
- 5 12. The composition of claim 11, wherein said composition has a local pH of about 2 to about 4.
- 13. The composition of claim 11, wherein said buffer is present in an amount sufficient to provide a therapeutically adequate absorption of buprenorphine.
- 10 14. The composition of claim 13, wherein a therapeutically adequate absorption of buprenorphine comprises a bioequivalent level of absorption of buprenorphine as a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
- 15 15. A film dosage composition comprising:
 - a. A polymeric carrier matrix;
 - b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
 - c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
 - d. A buffering system;
- 20 wherein said buffering system comprises a buffer capacity sufficient to maintain the ionization of naloxone during the time which said composition is in the oral cavity of a user.
- 16. The composition of claim 15, wherein said composition has a local pH of about 2 to about 4.
- 25 17. A method of treating narcotic dependence of a user, comprising the steps of:
 - a. providing a composition comprising:
 - i. A polymeric carrier matrix;
 - ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
 - 30 iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
 - iv. A buffer in an amount to provide a local pH of said composition of a value sufficient to optimize absorption of said buprenorphine; and

- b. administering said composition to the oral cavity of a user.
18. The composition of claim 17, wherein said method provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
- 5 19. The method of claim 17, wherein said composition has a local pH of about 2 to about 4.
20. The method of claim 17, wherein said film dosage composition is administered to the user through buccal administration, sublingual administration, and combinations thereof.
- 10 21. The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of at least 1 minute.
22. The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of between about 1 and 1.5 minutes.
23. The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of up to 3 minutes.
- 15 24. A process of forming a film dosage composition comprising the steps of:
- a. casting a film-forming composition, said film-forming composition comprising:
- i. A polymeric carrier matrix;
- 20 ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
- iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
- iv. A buffer in an amount to provide a local pH of said composition of a value sufficient to optimize absorption of said buprenorphine; and
- 25 b. drying said film-forming composition to form a self-supporting film dosage composition.
25. The process of claim 24, wherein said composition has a local pH of about 2 to about 4.
- 30 26. A film dosage composition comprising a therapeutically sufficient amount of buprenorphine or a pharmaceutically acceptable salt thereof and a therapeutically sufficient amount of naloxone or a pharmaceutically acceptable salt thereof, said film dosage composition having a bioequivalent release

profile as a tablet containing about 2 times the amount of buprenorphine or a pharmaceutically acceptable salt thereof.

27. An orally dissolving film formulation comprising buprenorphine and naloxone, wherein said formulation provides an in vivo plasma profile having a Cmax of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in vivo plasma profile having a Cmax of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone.
28. The formulation of claim 27, wherein said formulation provides a mean AUC of between about 5.431 hr.ng/ml to about 56.238 hr.ng/ml for buprenorphine.
29. The formulation of claim 27, wherein said formulation provides a mean AUC of between about 102.88 hr.pg/ml to about 812.00 hr.pg/ml for naloxone.
30. The formulation of claim 27, wherein said formulation comprises about 2 to about 16 mg of buprenorphine or a salt thereof.
31. The formulation of claim 27, wherein said formulation comprises about 0.5 to about 4 mg of naloxone or a salt thereof.

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- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(88) Date of publication of the international search report:

3 June 2011

(54) Title: SUBLINGUAL AND BUCCAL FILM COMPOSITIONS

(57) Abstract: The present invention relates to products and methods for treatment of narcotic dependence in a user. The invention more particularly relates to self-supporting dosage forms which provide an active agent for treating narcotic dependence while providing sufficient buccal adhesion of the dosage form.



WO 2011/017483 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/044488

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/00 A61K31/485		
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 practical, search terms used) EPO-Internal, WPI Data, EMBASE, BIOSIS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"SUBOXONE Sublingualtabletten" In: Verlag Rote Liste Service GmbH: "ROTE LISTE 2008" 2008, Verlag Rote Liste Service GmbH , Frankfurt/Main , XP002624986page 39018, the whole document -----	1-31
X	EP 1 897 543 A1 (EURO CELTIQUE SA [LU]) 12 March 2008 (2008-03-12) paragraphs [0016] - [0024], [0 31], [0039] - [0043], [0047] - [0053], [0056], [0057], [0060], [0061], [0079], [0082], [0093], [0100]; claims 1-10 ----- -/--	1-31
☒ 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 document 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 25 February 2011		Date of mailing of the international search report 11/04/2011
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 Toulacis, C

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/044488

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 447 016 A (RECKITT BENCKISER HEALTHCARE [GB]) 3 September 2008 (2008-09-03) the whole document -----	1-31
A	US 2005/192309 A1 (PALERMO PHILIP J [US] ET AL) 1 September 2005 (2005-09-01) the whole document -----	1-31
A	WO 03/030883 A1 (KOSMOS PHARMA [US]; FUISZ RICHARD C [US]; YANG ROBERT K [US]; MYERS GA) 17 April 2003 (2003-04-17) the whole document -----	1-31

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2010/044488

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1897543	A1	12-03-2008	AU 2007291245 A1	06-03-2008
			CA 2661759 A1	06-03-2008
			DE 202006018608 U1	10-05-2007
			EP 2059243 A1	20-05-2009
			WO 2008025791 A1	06-03-2008
			JP 2010501628 T	21-01-2010
			US 2010087470 A1	08-04-2010

GB 2447016	A	03-09-2008	AR 065579 A1	17-06-2009
			AU 2008220574 A1	04-09-2008
			CA 2678582 A1	04-09-2008
			CL 6062008 A1	03-10-2008
			CN 101626766 A	13-01-2010
			EP 2129380 A1	09-12-2009
			WO 2008104738 A1	04-09-2008
			JP 2010520186 T	10-06-2010
			KR 20090117891 A	13-11-2009
			PE 01682009 A1	19-03-2009
			US 2011046172 A1	24-02-2011
			ZA 200905664 A	27-10-2010

US 2005192309	A1	01-09-2005	NONE	

WO 03030883	A1	17-04-2003	CA 2473970 A1	17-04-2003
			EP 1458367 A1	22-09-2004
			JP 2005536443 T	02-12-2005

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

SCOLA, Daniel A. Jr., et al
Hoffmann & Baron, LLP
6900 Jericho Turnpike
Syosset, NY 11791
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 08 February 2012 (08.02.2012)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 1199-82 PCT	
International application No. PCT/US2010/044488	International filing date (day/month/year) 05 August 2010 (05.08.2010)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address SCOLA, Daniel A. Jr., et al Hoffmann & Baron, LLP 6900 Jericho Turnpike Syosset, NY 11791 United States of America	State of Nationality	State of Residence
	Telephone No. 973-331-1700	
	Facsimile No. 973-331-1717	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address SCOLA, Daniel A. Jr., et al Hoffmann & Baron, LLP 6900 Jericho Turnpike Syosset, NY 11791 United States of America	State of Nationality	State of Residence
	Telephone No. 516 822 3550	
	Facsimile No. 516 822 3582	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:
Telephone numbers have changed.

4. A copy of this notification has been sent to:

☒ the receiving Office	☐ the International Preliminary Examining Authority
☐ the International Searching Authority	☒ the designated Offices concerned
☐ the Authority(ies) specified for supplementary search	☐ the elected Offices concerned
	☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Malek David e-mail pt03.pct@wipo.int Telephone No. +41 22 338 74 03
---	---

Facsimile No. +41 22 338 70 80

PCT/US2010/044488

PCT

(PCT Rule 92*bis*.1 and
Administrative Instructions, Section 422)

SCOLA, Daniel A. Jr., et al
Hoffmann & Baron, LLP
6900 Jericho Turnpike
Syosset, NY 11791
ETATS-UNIS D'AMERIQUE

Date of mailing (<i>day/month/year</i>) 08 February 2012 (08.02.2012)	
Applicant's or agent's file reference 1199-82 PCT	IMPORTANT NOTIFICATION
International application No. PCT/US2010/044488	International filing date (<i>day/month/year</i>) 05 August 2010 (05.08.2010)

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address RECKITT BENCKISER HEALTHCARE (UK) LIMITED Dansom Lane Hull HU8 7DS United Kingdom	State of Nationality	State of Residence
	GB	GB
	Telephone No.	
	Facsimile No.	
E-mail address		

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address RECKITT BENCKISER HEALTHCARE (UK) LIMITED 103-105 Bath Road Slough SL1 3UH United Kingdom	State of Nationality	State of Residence
	GB	GB
	Telephone No.	
	Facsimile No.	
E-mail address ☐ Notifications by e-mail authorized		

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search

☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Malek David
Facsimile No. +41 22 338 70 80	e-mail pt03.pct@wipo.int Telephone No. +41 22 338 74 03

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 1199-82 PCT	FOR FURTHER ACTION		See item 4 below
International application No. PCT/US2010/044488	International filing date (day/month/year) 05 August 2010 (05.08.2010)	Priority date (day/month/year) 07 August 2009 (07.08.2009)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant RECKITT BENCKISER HEALTHCARE (UK) LIMITED			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

	Date of issuance of this report 07 February 2012 (07.02.2012)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Nora Lindner
Facsimile No. +41 22 338 82 70	e-mail: pt03.pct@wipo.int

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No. PCT/US2010/044488	International filing date (day/month/year) 05.08.2010	Priority date (day/month/year) 07.08.2009
--	--	--

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/00 A61K31/485

Applicant
Reckitt Benckiser Healthcare (UK) Limited

1. This opinion contains indications relating to the following items:
- ☒ Box No. I Basis of the opinion
 - ☐ Box No. II Priority
 - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - ☐ Box No. IV Lack of unity of invention
 - ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
 - ☐ Box No. VI Certain documents cited
 - ☐ Box No. VII Certain defects in the international application
 - ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Toulacis, C
Telephone No. +49 89 2399-8638



Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:
- a. (means)
- ☐ on paper
 - ☐ in electronic form
- b. (time)
- ☐ in the international application as filed
 - ☐ together with the international application in electronic form
 - ☐ subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement		
Novelty (N)	Yes: Claims	<u>1-31</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-31</u>
Industrial applicability (IA)	Yes: Claims	<u>1-31</u>
	No: Claims	

2. Citations and explanations
- see separate sheet

V

Reference is made to the following documents:

D1= Verlag Rrote Liste Service GmbH: "SUBOXONE Sublingualtabletten" In: Verlag Rote Liste Service GmbH: "ROTE LISTE 2008", 2008, Verlag Rote Liste Service GmbH, Frankfurt/Main, XP002624986, page 39018,

D2 = EP 1 897 543 A1 (EURO CELTIQUE SA [LU]) 12 March 2008 (2008-03-12)

D3 = WO 03/030883 A1 (KOSMOS PHARMA [US]; FUISZ RICHARD C [US]; YANG ROBERT K [US]; MYERS GA) 17 April 2003 (2003-04-17)

Claims 1-31

(N)

The subject-matter of claims 1-31 is novel over document D1 and D2 either due to the defined dosage form being a **film** or to the presence of a **buffer**.

In context with novelty it is pointed out that the expressions:

i) "... in an amount to provide a local pH of said composition of a value sufficient to optimize absorption of said buprenorphine" (claims 1, 17, 24)

ii) "... in an amount sufficient to inhibit the absorption of said naloxone when administered orally" (claim 11)

iii) "... a buffer capacity sufficient to maintain the ionization of naloxone during the time which said composition is in the oral cavity of a user"

iv) "... having a bioequivalent release profile as a tablet containing about 2 times the amount of buprenorphine or a pharmaceutically acceptable salt thereof." (claim 26),

do not imply any delimiting technical feature to the claimed subject-matter, since they characterise the invention by indication of the result to be achieved and are considered to be unclear (Art. 6 PCT).

Characterisation of the invention or one of its features by indication of the result to be achieved is not permissible unless the invention can only be defined in such terms and if the result is one which can be directly and positively verified by tests or procedures adequately specified in the description and involving nothing more than trial and error (cf. Guidelines for Examination, chapter III, 4.7 PCT).

These prerequisite conditions are, however, not fulfilled in the present case.

In the present case it is possible to define the subject-matter in more concrete terms; i.e. a defined pH.

(IS)

The object of the present application is to provide an orally dissolvable film that provides the desired absorption levels of the agonist and antagonist, while providing an adhesive effect in the mouth, rendering it difficult to remove once placed in the mouth, thereby making abuse of the agonist difficult (description of the present application page 2, lines 12-15).

Said object has been achieved by using a polymer carrier matrix and forming an orally dissolvable film comprising the active ingredients of the sublingual tablet, marketed under the trade name Suboxone®.

The Applicant provided comparative data showing that the absorption and the in vivo absorption data of the presently claimed sublingual film compositions and the sublingual tablet, marketed under the trade name Suboxone®, are bioequivalent (see Tables 1-12).

Said results however, are considered to be expected by the person skilled in the art being aware of documents D1 and D2.

The sublingual tablets disclosed in document D1 comprise already the pair agonist/antagonist (Buprenorphine-HCl/Naloxon-HCL) in the presently claimed amounts and the buffer citric acid / sodium citrate as presently claimed, providing already the desired results with regard to absorption and in vivo absorption of the active agents.

Thus, the only problem which has been solved is the transformation of the sublingual tablet Suboxone® into a sublingual film by using a polymeric carrier matrix.

Besides the fact that said transformation is considered to lie within the merits of the person skilled in the art without the exercise of inventive skill, document D2 does clearly teach said transformation (see D2; particularly paragraphs 60, 82, 93, 100).

According to the description only a certain pH combined with a certain buffer/Naloxone ratio, provided results which can be regarded as surprising.

Said features however, are not reflected in the present claims (see description; page 30, lines 12-15).

(IA) The industrial applicability is beyond any doubt.



No. 12-039899- -00000-0000

Fecha: 2012-03-07 14:02:29

Dep. 2020 DIR.NUEVASCR

Tra. 11 PATENTEIYII

Eve: 378 FASENACIONALI

Act. 411 PRESENTACION

Folios: 135

Industria y Comercio
SUPERINTENDENCIAPATENTE DE INVENCION ☐

MODELO L

Act. 411 PRESENTACION Folios: 134

☐	Indicación que se solicita una patente.
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Descripción de la invención
☐	Dibujos de ser estos pertinentes
☐	Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)
Completa ☐	Incompleta ☐

PATENTE DE INVENCION PCT ☒MODELO DE UTILIDAD PCT ☐

Art.33 Decisión 486/00, Circular Única

☒	Indicación que se solicita una PCT
☒	Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
☒	Dibujos de ser estos pertinentes
☒	Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)
Completa ☒	Incompleta ☐

DISEÑO INDUSTRIAL ☐

(Art. 119 Decisión 486/00)

☐	Indicación que se solicita Diseño industrial
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
☐	Comprobante de pago de las tasas establecidas
Completa ☐	Incompleta ☐

ESQUEMA DE TRAZADO ☐

(Art. 92 Decisión 486/00)

☐	Indicación que se solicita un esquema de trazado
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Representación gráfica de un esquema de trazado
☐	Comprobante de pago de las tasas establecidas
Completa ☐	Incompleta ☐