PETITORIO

AS: 88.337

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA Y COMERCIO
Radicacion : 02052756 02333369 Folios: 134n
Fecha (DMA): 2002-06-19 16:54:07
Tracite : 211 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

02 052756 0

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)

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5 PCT (86)

Solicitud Internacional No. ~~PCT/CA 01/00951~~ PCT/CA01/00951 Fecha ~~21-06-2001~~ 21-06-2001 ✓
Publicación Internacional No. WO 01/19901 A2 Fecha 22-03-2001 X
WO 03/000263 03-01-2003 ✓

6 Título (54): FORMULACIÓN DE ACCIÓN RAPIDA

7 Clasificación Internacional (51) A61K 9/00, 33/12

8 Prioridad SI ☒ NO ☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
~~CA~~ US	~~01-06-21~~ 01-06-21	~~2.350.195~~ 2.350.195 ✓

9 Comprobante de pago No. 02 31475 y 02 34 713 **Fecha** 19-06-2002

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

2020-F06 (01-11-15)

10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $378.000
- [x] Comprobante de pago por reivindicación de prioridad. $106.000
- [ ] Documento que acredite 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
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar 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.
- [ ] Otros

11 **FIGURA CARACTERÍSTICA:**

12 Solicitud con cesión de derechos

NOMBRE: RAMIRO CASTRO DUQUE C.

FIRMA:

C.C. 17.022 de Bogotá T.P. 1003 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

3

SUPERINDUSTRIA Y COMERCIO
Radicacion : 02052756 02300000 Folios: 134
Fecha (AMD): 2002-06-19 15:54:07
Tramite : 911 PCT-PATENT 379 FASE INCI 411 PRESENTE
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 02 - 34.713
FECHA : MAYO 28 DE 2002

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	2003081	28/05/2002	2.945.000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	30005-01-01 SOLICITUDES	02 INVOCACION DE UNA PRIORIDAD EN NU	106.000.00
		TOTAL : $	106.000.00

SON: CIENTO SEIS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

Carrera 13 No. 27-00 Pisos 5, 7 y 10
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SUPERINDUSTRIA Y COMERCIO
Radicacion : C2852756 03220290
Fecha (GMD): 2002-05-19 16:54:07 Folios: 13
Tramite : 011 PCT-PATENT 379 PASE MACI 411 PRESENTE
Dependencia: 2200 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 02 - 31.475
FECHA : MAYO 14 DE 2002

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	2738745	14/05/2002	14.890.000.00

C O N C E P T O

CANT.	REMTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	7 TRAMITES DE SOL. DE DISENOS INDUS	378.000.00
		TOTAL : $	378.000.00

SON: TRESCIENTOS SETENTA Y OCHO MIL PESOS

RESPONSABLE :

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Título de la invención

FORMULACION DE ACCION RAPIDA

Fundamentos de la invención

Campo de la Invención

La presente invención se refiere a una formulación de acción rápida, preferentemente en la forma de una tableta recubierta entéricamente, para un medicamento que comprende un dúo sinérgico de ingredientes activos, a saber, succinato de doxilamina y piridoxina HCl, al que se hará referencia de aquí en más como "SD-P". El SD-P es útil en el tratamiento de náusea y vómito, especialmente, pero sin limitarse a, durante el embarazo, a las que se hará referencia de aquí en más como "NVE". De este modo, la presente invención está relacionada con todas las indicaciones terapéuticas conocidas y futuras del SD-P.

Técnica anterior

Son conocidas formulaciones farmacéuticas de SD-P. La formulación usual, obtenible comercialmente en Canadá bajo el nombre de Diclectin (Ducheanay Inc.) comprende los siguientes ingredientes activos: piridoxina HCl y succinato de doxilamina. Comprende adicionalmente los siguientes excipientes: lactosa, celulosa microcristalina, trisilicato de magnesio, dióxido de silicio y estearato de magnesio.

El Diclectin es la droga más estudiada en el mundo en lo concerniente a la

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seguridad durante el embarazo. Debido a su excelente perfil de seguridad, el Diclectin es la droga a elegir para el tratamiento de NVE. La formulación corriente está recubierta con azúcar y adolece de inconvenientes, uno de los cuales es su demora en el comienzo de la acción. De tal manera, la formulación usual puede tomar, una vez ingerida, más de 4 horas antes de que los dos ingredientes activos (piridoxina HCl y succinato de doxilamina) logren la disolución casi completa en el intestino delgado, donde es absorbida. Este retraso es a menudo considerado excesivo en el caso de pacientes, tales como mujeres que sufren de NVE, que requieren un alivio urgente de los síntomas.

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Otra desventaja de la formulación corriente está relacionada con la aceptación del paciente. Las mujeres que sufren de NVE se quejan a menudo de hipersensibilidad olfativa, que significa que diversos olores y sabores pueden desencadenar la náusea o el vómito. El olor y el sabor del azúcar de la formulación usual recubierta con azúcar, así como también el uso de solventes orgánicos y ftalatos en la preparación de los recubrimientos entéricos utilizados habitualmente, incomodan a muchas mujeres embarazadas hasta el punto en que se inhibe esencialmente la toma de la droga.

El tamaño de las tabletas usualmente disponibles es también problemático. Un tamaño más pequeño mejoraría la aceptación del paciente debido a que las mujeres de sufren de NVE tienen a menudo problemas al tragar. Además, una tableta más

pequeña parece menos dañina y los pacientes tendrán la impresión de que está ingiriendo una cantidad menor de droga. Esto aumentará significativamente a su vez la aceptación del paciente.

Por último, la formulación corriente contiene lactosa. Esto es objetable en el caso de aquellos pacientes que sufren de intolerancia a la lactosa.

Es deseable de tal modo proporcionar a pacientes que adolecen de náusea y vómito una formulación de acción rápida mejorada que supere los inconvenientes de la técnica anterior.

Sin embargo, debido a que el SD-P se administra por vía oral como una tableta recubierta entérica, la formulación oral novedosa debe transitar intacta a través del estómago y liberar rápidamente ambos ingredientes activos una vez que la forma de dosificación alcance su destino pretendido, a saber, el intestino.

El principal desafío a vencer por la presente invención era lograr una forma de dosificación capaz de superar los inconvenientes de la técnica anterior, a la vez que suministrar el dúo sinérgico de ingredientes activos para una acción rápida. Fue también importante proporcionar una formulación que presentara curvas de disolución similares para ambos ingredientes activos de modo de evitar la disolución de un ingrediente activo en detrimento del otro. Esto resultó de importancia en vista del efecto terapéutico sinérgico del dúo de ingredientes activos.

Resumen de la Invención

En términos generales, la invención proporciona una nueva formulación

acuosa de recubrimiento entérico que comprende SD-P, presentando la formulación un perfil de disolución indicativo de un comienzo de acción rápido.

La invención también procura proporcionar una composición farmacéutica que tenga perfiles de disolución específicos *in vitro* que indiqueñ un comienzo de acción rápido de los ingredientes activos. La composición farmacéutica es adecuada para fabricación simple y reproducible.

Otros alcances de aplicabilidad serán deducibles de la descripción detallada que se brinda a continuación. Deberá entenderse, sin embargo, que esta descripción detallada, si bien indica realizaciones preferidas de la invención, se brinda solamente con fines ilustrativos, debido a que diversos cambios y modificaciones dentro del espíritu y marco de la invención serán evidentes para aquéllos con conocimientos en la materia.

Descripción de los dibujos

La Figura 1 muestra dos ejemplos de perfiles de disolución de acuerdo con la formulación de acción rápida de la presente invención en comparación con un perfil de disolución de la formulación de la técnica anterior. El primer perfil de disolución (Ejemplo 1) corresponde a una formulación de acción rápida de la cual aproximadamente el 100 % de ambos ingredientes activos es liberado dentro de los 45 minutos. El segundo perfil de disolución (Ejemplo 2) corresponde a una formulación de acción rápida de la cual aproximadamente el 95 % de ambos ingredientes activos es liberado dentro de los 120 minutos. El último perfil de

disolución de tipo comparativo (técnica anterior) corresponde a la formulación corrientemente disponible de la cual aproximadamente el 100 % de la piridoxina HCl y aproximadamente el 90 % del succinato de doxilamina son liberados dentro de los 240 minutos.

La Figura 2 es un diagrama de flujo esquemático del proceso de fabricación preferido de una formulación preferida de acuerdo con la presente invención.

Descripción detallada de la invención

Otros propósitos y aspectos concurrentes de la presente invención serán fácilmente apreciados, a medida que la misma se vuelva más comprensible con referencia a la siguiente descripción detallada de una realización preferida descripta con fines ilustrativos.

En un sentido amplio, la invención proporciona una formulación de acción rápida que comprende piridoxina HCl y succinato de doxilamina.

La formulación de la presente invención puede emplearse en los campos de la medicina humana y veterinaria en todos los casos en que los síntomas de náusea y / o vómito requieran intervención médica. Debido a que la formulación de la presente invención está prevista para propósitos médicos, la formulación y sus componentes deberán ser por lo tanto farmacéuticamente aceptables. La formulación preferida se encuentra en la forma de una forma de dosificación oral tal como una tableta, píldora o glóbulos encapsulados o solución. La forma de formulación más preferida es una tableta.

La tableta de la presente invención es preferentemente capaz de transitar intacta a través del estómago. Para poner a prueba este aspecto, la tableta de la presente invención se ensayó para determinar si resistía la desintegración en jugo gástrico simulado "JGS" durante un período mínimo de 1 hora.

De acuerdo con la presente invención, la formulación deberá satisfacer los siguientes perfiles de disolución al medirlos en 1000 ml de tampón de fosfato a pH 6,8 y 37° C en un aparato de disolución tipo 2 a 100 rpm; medido preferentemente mediante cromatografía líquida de alto rendimiento:

a) por lo menos aproximadamente el 40 % de las cantidades totales de tanto la piridoxina HCl como el succinato de doxilamina se disuelven después de 30 minutos de medición;

b) por lo menos aproximadamente el 70 % de las cantidades totales de tanto la piridoxina HCl como el succinato de doxilamina se disuelven después de 60 minutos de medición;

c) por lo menos aproximadamente el 80 % de las cantidades totales de tanto la piridoxina HCl como el succinato de doxilamina se disuelven después de 90 minutos de medición;

d) por lo menos aproximadamente el 90 % de las cantidades totales de tanto la piridoxina HCl como el succinato de doxilamina se disuelven después de 120 minutos de medición;

En la presente invención, cualquier referencia al perfil de disolución deberá ser interpretada como haciendo referencia a los resultados de un ensayo de disolución

en el cual la cantidad de piridoxina HCl y de succinato de doxilamina liberadas es medida en 1000 ml de tampón de fosfato a pH 6,8 y 37° C utilizando un aparato de disolución USP (United States Pharmacopoeia) tipo 2 a 100 rpm; medido preferentemente mediante cromatografía líquida de alto rendimiento.

Tal como se lo emplea aquí y en las reivindicaciones, se entiende que un "recubrimiento entérico" significa un recubrimiento que comprende una o más capas generalmente resistentes a la desintegración en jugo gástrico humano, pero que se desintegrará en los fluidos intestinales humanos, así como también recubrimientos que se desintegran muy lentamente en jugo gástrico humano, pero más rápidamente en los fluidos intestinales humanos. En un sentido amplio, "recubrimiento entérico" puede abarcar, por ejemplo, cualquier revestimiento de sellado aplicado sobre el núcleo comprimido de una tableta antes del recubrimiento entérico en sí mismo, así como también cualquier revestimiento estético de terminación aplicado sobre el recubrimiento entérico en sí mismo.

En una de las realizaciones más preferidas, la formulación de la presente invención contiene un núcleo revestido con un recubrimiento entérico acuoso. El núcleo comprende los ingredientes activos piridoxina HCl y succinato de doxilamina conjuntamente con excipientes no activos tales como un relleno o ligante, un agente desintegrante, un lubricante, un acondicionador de flujo silícico y un agente de estabilización.

Ejemplos de rellenos o ligantes incluyen goma arábiga, ácido algínico, fosfato (dibásico) de calcio, carboximetilcelulosa, carboximetilcelulosa sódica,

hidroxietilcelulosa, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, dextrina, dextratos, sacarosa, tilosa, almidón pregelatinizado, sulfato de calcio, amilosa, glicina, bentonita, maltosa, sorbitol, etilcelulosa, fosfato ácido disódico, fosfato disódico, pirosulfito disódico, alcohol polivinílico, gelatina, glucosa, goma de guar, glucosa líquida, azúcar compresible, silicato de magnesio y aluminio, maltodextrina, óxido de polietileno, polimetacrilatos, povidona, alginato de sodio, tragacanto, celulosa microcristalina, almidón y ceína. Uno de los rellenos o ligantes más preferidos consiste en celulosa microcristalina.

Ejemplos de agentes desintegrantes incluyen ácido algínico, carboximetilcelulosa, carboximetilcelulosa sódica, hidroxipropilcelulosa (de baja substitución), celulosa microcristalina, celulosa en polvo, dióxido de silicio coloidal, croscarmelosa sódica, crospovidona, metilcelulosa, polacrilina potásica, povidona, alginato de sodio, glicolato de almidón sódico, almidón, disulfito disódico, edatamil disódico, edetato disódico, etilendiaminotetraacetato de sodio (EDTA), polivinilpirrolidinas reticuladas, almidón pregelatinizado, carboximetil almidón, carboximetil almidón sódico, celulosa microcristalina. Uno de los agentes desintegrantes más preferidos consiste en croscarmelosa sódica.

Ejemplos de lubricantes incluyen estearato de calcio, aceite de canola, palmitoestearato de glicerilo, aceite vegetal hidrogenado (tipo 1), óxido de magnesio, estearato de magnesio, aceite mineral, poloxámero, polietilen glicol, lauril sulfato de sodio, fumarato estearato de sodio, ácido esteárico, talco y estearato de zinc, behapato de glicerilo, lauril sulfato de magnesio, ácido bórico, benzoato de sodio,

acetato de sodio, benzoato de sodio / acetato de sodio (en combinación), leucina DL. Uno de los agentes lubricantes más preferidos consiste en estearato de magnesio.

Ejemplos de acondicionadores de flujo silícicos incluyen dióxido de silicio, silicato de aluminio y magnesio y goma de guar. Uno de los acondicionadores de flujo silícicos más preferidos consiste en dióxido de silicio.

Ejemplos de agentes estabilizadores incluyen goma arábiga, albúmina, alcohol polivinílico, ácido algínico, bentonita, fosfato dicálcico, carboximetilcelulosa, hidroxipropilcelulosa, dióxido de silicio coloidal, ciclodextrinas, monoestearato de glicerilo, hidroxipropil metilcelulosa, trisilicato de magnesio, silicato de magnesio y aluminio, propilen glicol, alginato de propilen glicol, alginato de sodio, cera carnauba, goma de xantano, almidón, estearato(s), ácido esteárico, monoglicérido esteárico y alcohol estearílico. Uno de los agentes estabilizadores más preferidos consiste en trisilicato de magnesio.

En una realización preferida, el núcleo de la formulación de Diclectin de acción rápida novedosa contendrá aproximadamente alrededor de 4 a 10 %, más preferentemente alrededor de 7 % en peso de piridoxina HCl; alrededor de 4 a 10 %, más preferentemente alrededor de 7 % en peso de succinato de doxilamina; alrededor de 40 a 80 %, más preferentemente alrededor de 62 % en peso de celulosa microcristalina; alrededor de 10 a 30 %, más preferentemente alrededor de 18 % en peso de trisilicato de magnesio; alrededor de 0,5 a 5 %, más preferentemente alrededor de 1 % en peso de dióxido de silicio; 0,5 a 5 %, más preferentemente alrededor de 3 % en peso de croscarmelosa sódica y alrededor de

0,5 a 5 %, más preferentemente alrededor de 3 % en peso de estearato de magnesio.

Ejemplo 1

El siguiente es un ejemplo de una formulación de núcleo de Diclectin de acción rápida de 145 mg:

Tabla 1: Ingredientes de núcleo

Ingredientes	Peso mg/tab.	Peso %/tab.	Tamaño del lote 100 kg
Succinato de doxilamina	10,0	6,9	6,897
Piridoxina HCl	10,0	6,9	6,897
Trisilicato de magnesio	26,4	18,2	18,207
Celulosa microcristalina PH 102	90,0	62,1	62,069
Croscarmelosa sódica tipo A	3,6	2,5	2,483
Estearato de magnesio	4,0	2,8	2,759
Dióxido de silicio NF	1,0	0,7	0,690
Total:	145,0	100	100

El núcleo puede ser recubierto entéricamente entonces con un revestimiento entérico acuoso que permitirá que la formulación transite a través del estómago relativamente intacta, posibilitando a la vez la rápida disolución en el intestino.

La formulación de recubrimiento puede ser como se indica a continuación:

Tabla 2: Formulación de recubrimiento

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Ingredientes	Peso mg/tab.	Peso %	Tamaño del lote 100 kg
Revestimiento de sellado			
Opadry® Clear YS-1-7472	4,82	3,33	3,327
Agua purificada USP			
Total:	4,82	3,33	3,33
Revestimiento entérico			
Solución de recubrimiento entérica Estacryl® 30D *	39,58	27,29	27,294
Talco USP malla 200	2,85	1,97	1,968
Polietilen glicol 400 USP	1,20	0,83	0,826
Antiespuma 1520	0,12	0,08	0,081
Agua purificada USP			
Total:	16,04	30,17	30,17
Revestimiento de terminación			
Opadry® White YS-1-7003	1,61	1,11	1,108
Agua purificada USP			
Total:	1,61	1,11	1,11

* La solución de recubrimiento entérica Estacryl® 30D contiene 30 % de sólidos. Por consiguiente, el recubrimiento entérico total real asciende a 11,07 %.

Peso total de la tableta recubierta 167,47 mg.

El propósito del revestimiento de sellado es proporcionar una superficie suave para el revestimiento entérico, evitando de ese modo montículos, huecos o fisuras en los que se aplicarían cantidades desiguales de revestimiento entérico.

Datos de disolución

La formulación de acción rápida del ejemplo anterior ha exhibido los perfiles de disolución *in vitro* que se muestran en la Tabla 3 a continuación, al medirlos en 1000 ml de tampón de fosfato a pH 6,8 y 37° C en un aparato de disolución tipo 2 a 100 rpm. Los valores numéricos se expresan como porcentajes de ingrediente activo disuelto en relación a la cantidades iniciales.

Tabla 3: Perfiles de disolución

Piridoxina HCl	corrida 1	corrida 2	corrida 3	corrida 4	corrida 5	corrida 6	Promedio
5 minutos	20	2	0	77	79	79	43
10 minutos	91	90	90	91	94	95	92
15 minutos	96	96	94	94	95	96	95
30 minutos	95	98	96	95	98	96	96
45 minutos	97	96	97	94	99	98	97
Succinato de doxilamina	**corrida 1**	**corrida 2**	**corrida 3**	**corrida 4**	**corrida 5**	**corrida 6**	**Promedio**
5 minutos	17	2	0	70	75	76	40
10 minutos	90	87	89	89	97	96	91
15 minutos	96	97	96	92	98	97	96
30 minutos	97	98	96	94	99	97	97
45 minutos	98	96	98	92	100	99	97

Los valores de disolución extremadamente bajos obtenidos después de 5 minutos para las corridas 1 a 3, pueden ser explicados por la no desintegración de la formulación de núcleo en el intervalo de 5 minutos.

Ejemplo de método de fabricación

La formulación de la presente invención se preparó utilizando los ingredientes mostrados en la Tabla 1 anterior. El succinato de doxilamina y el dióxido de silicio NF

son pre-mezclados en un molino V de 0,057 m^3 (2 pies cúbicos). La pre-mezcla resultante es luego molida por medio de un molino Quadro Co, modelo 196S, equipado con un tamiz de malla 40.

La piridoxina HCl es también molida por medio de un molino Quadro Co, modelo 196S, equipado con un tamiz de malla 40. La piridoxima HCl molida es luego combinada con la pre-mezcla de doxilamina / dióxido de silicio NF, mezclando la mezcla resultante de la combinación

La celulosa microcristalina es molida a través de un tamiz de malla 40 y dividida en dos porciones aproximadamente iguales. Una porción es combinada subsecuentemente en un depósito de galera ("Gallay") 650L con la pre-mezcla previamente formada que contiene ambos ingredientes activos, adicionándose a continuación la segunda porción. El material cargado es luego mezclado, agregándose seguidamente el trisilicato de magnesio y la croscarmelosa sódica. La mixtura formada en último término es mezclada. La adición de estearato de magnesio seguida de un mezclado adicional completa la preparación de la formulación de núcleo.

La mezcla final es llevada a la forma de tabletas por compresión y se le aplica subsecuentemente el recubrimiento de sellado, el recubrimiento entérico utilizando recubrimiento entéricos acuosos adecuados disponibles comercialmente y el recubrimiento de terminación con fines estéticos. El proceso de fabricación en conjunto es descripto en la Figura 2.

Todas las etapas de revestimiento utilizando los ingredientes de la Tabla 2, a

saber, el recubrimiento de sellado sobre el núcleo, el recubrimiento entérico y el opadry white (recubrimiento de color) se llevan a cabo ventajosamente en una batea de revestimiento Vector Hi (marca registrada) equipada con una bomba peristáltica.

Ejemplo 2

El siguiente es otro ejemplo de una formulación de núcleo de Diclectin de acción rápida de 146 mg. La formulación fue fabricada siguiendo los mismos métodos de fabricación descriptos anteriormente en el ejemplo 1. Este Ejemplo demuestra que la característica de rápida acción de la formulación de la presente invención se obtiene con un grupo diferente de excipientes.

Tabla 4: Ingredientes de núcleo

Ingredientes	Peso mg/tab.	Peso %/tab.
Succinato de doxilamina	10,5	7,2
Piridoxina HCl	10,5	7,2
Trisilicato de magnesio	30,0	20,6
Celulosa microcristalina PH 102	65,0	44,5
Fosfato de calcio (dibásico)	25,0	17,1
Estearato de magnesio	4,0	2,7
Dióxido de silicio coloidal	1,0	0,7
Total:	146,0	100

La formulación de recubrimiento puede ser la siguiente:

Tabla 5: Formulación de recubrimiento

Ingredientes	Peso mg/tab.
Opadry® White YS-1-7003	4,38
Emulsión antiespuma AF	0,07
Sureteric YAE-6-18107	16,06
Antiespuma 1520	0,12
Agua purificada USP	
Opadry® Clear YS-1-7472	0,73

Peso total de la tableta recubierta: 167,24 mg.

La formulación de acción rápida del Ejemplo anterior ha exhibido perfiles de disolución *in vitro* que se muestran en la Tabla 6 a continuación, al medirlos en 1000 ml de tampón de fosfato a pH 6,8 y 37° C en un aparato de disolución tipo 2 a 100 rpm. Los valores numéricos se expresan como porcentajes de ingrediente activo disuelto.

Tabla 6: Perfiles de disolución

Piridoxina HCl	corrida 1	corrida 2	corrida 3	corrida 4	corrida 5	corrida 6	Promedio
15 minutos	17	13	25	31	17	22	21
30 minutos	31	28	60	63	36	43	43
45 minutos	51	45	78	80	55	60	61

60 minutos	69	64	86	89	67	72	75
75 minutos	79	76	94	94	77	81	83
90 minutos	84	84	97	97	83	87	89
105 minutos	88	89	98	99	87	90	92
120 minutos	91	93	98	98	89	92	93

Tabla 6: continuación

Succinato de doxilamina	corrida 1	corrida 2	corrida 3	corrida 4	corrida 5	corrida 6	Promedio
15 minutos	16	14	22	31	47	61	32
30 minutos	31	27	64	63	38	40	44
45 minutos	47	44	75	79	58	61	61
60 minutos	71	61	90	85	68	74	75
75 minutos	76	71	96	89	81	82	82
90 minutos	85	80	101	88	83	81	86
105 minutos	92	86	103	96	93	92	93
120 minutos	93	88	101	96	96	95	95

Se infiere de estos resultados que la formulaciones novedosas demuestran una acción rápida como muestra su perfil de disolución. La piridoxina HCl presenta un perfil de disolución medio de más de 90 % dentro de los 120 minutos del comienzo de las mediciones. De manera similar, el succinato de doxilamina muestra un perfil de disolución medio de más de 90 % dentro de los 120 minutos del comienzo de las mediciones.

Ejemplo 3 (Ejemplo comparativo empleando formulaciones de la técnica

anterior)

El siguiente es un ejemplo de formulación de Diclectin de la técnica anterior. Se brinda un ejemplo de una tableta de 146,2 mg. Este Ejemplo demuestra una comienzo de disolución llamativamente más lento en comparación con la presente invención.

Tabla 7: Ingredientes de núcleo

Ingredientes	Peso mg/tab.	Peso %/tab.
Piridoxina HCl	11,0	7,5
Succinato de doxilamina	10,2	7,0
Lactosa NF	25,0	17,1
Celulosa microcristalina NF	65,0	44,4
Trisilicato de magnesio	30,0	20,6
Dióxdo de silicio	1,0	0,7
Estearato de magnesio	4,0	2,7
Total:	146,2	100

La formulación de recubrimiento puede ser la siguiente

Tabla 8: Formulación de recubrimiento

Ingredientes
Solución de recubrimiento No. 714
Polvo de recubrimiento No. 303

Solución de C.A.P. al 10 %
Solución de C.A.P. al 5 %
Solución de gelatina No. 105
Polvo para empolvadura No. 755
Jarabe suavizante blanco
Jarabe de azúcar No. 111
Opalux AS-7000-B blanco
Solución de cera No. 723

La formulación corriente del Ejemplo anterior ha exhibido perfiles de disolución *in vitro* que se muestran en la Tabla 9 a continuación, al medirlos en 1000 ml de tampón de fosfato a pH 6,8 y 37° C en un aparato de disolución tipo 2 a 100 rpm. Los valores numéricos se expresan como porcentajes de ingrediente activo disuelto.

Tabla 9: Perfiles de disolución

Piridoxina HCl	corrida 1	corrida 2	corrida 3	corrida 4	corrida 5	corrida 6	Promedio
15 minutos	9	11	18	11	16	12	13
30 minutos	22	23	32	25	28	23	25
45 minutos	37	34	45	39	42	34	38
60 minutos	50	44	56	49	51	44	49
90 minutos	69	63	73	69	67	63	67
120 minutos	83	76	84	82	80	76	80
150 minutos	94	86	91	91	86	86	89
180 minutos	99	94	98	96	93	92	95
240 minutos	93	93	100	100	99	101	98
Succinato de doxilamina	**corrida 1**	**corrida 2**	**corrida 3**	**corrida 4**	**corrida 5**	**corrida 6**	**Promedio**
15 minutos	12	15	17	8	18	16	14
30 minutos	17	21	31	18	27	30	24

23

45 minutos	24	32	45	25	38	38	34
60 minutos	34	41	56	36	46	49	44
90 minutos	52	55	69	55	62	66	60
120 minutos	69	65	75	68	71	75	71
150 minutos	80	74	80	78	79	82	79
180 minutos	82	78	86	82	80	84	82
240 minutos	95	89	89	82	80	87	87

Se deduce de estos resultados que la formulación de la técnica anterior exhibe un patrón de disolución notablemente más lento si se lo compara con las formulaciones novedosas. Ciertamente, después de 90 minutos se disuelven solamente en promedio el 60 % de la doxilamina y el 67 % de la piridoxina. Un perfil de disolución *in vivo* más lento es indicativo de un comienzo de acción demorado. Las formulaciones novedosas, según se describe en los Ejemplos 1 y 2, muestran perfiles de disolución de comienzo marcadamente más rápido que se traducen en un rápido inicio de acción. Las nuevas formulaciones superan la mayoría de, sino todos, los inconvenientes asociados con la técnica anterior.

Los términos y descripciones utilizados en la presente son realizaciones preferidas expuestas solamente con fines ilustrativos, y no están concebidos como limitaciones sobre las muchas variaciones que aquéllos con experiencia en la materia podrán reconocer como que son posibles en la práctica de la presente invención. Es la intención que todas las variantes, tanto conocidas en el presente como desconocidas, que no tengan un efecto directo sobre la forma en que trabaja la invención, sean cubiertas por las siguientes reivindicaciones.

Reivindicaciones

Habiendo así especialmente descripto y determinado la naturaleza de la presente invención y la forma como la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo:

1. Una formulación de acción rápida de piridoxina HCl y succinato de doxilamina recubierta entéricamente que comprende un agente desintegrante tal que se satisfagan los siguientes perfiles de disolución al medirlos en 1000 ml de tampón de fosfato a pH 6,8 y 37° C.en un aparato de disolución tipo 2 a 100 rpm:

a) por lo menos aproximadamente el 40 % de las cantidades totales de tanto la piridoxina HCl como el succinato de doxilamina se disuelven después de 30 minutos de medición;

b) por lo menos aproximadamente el 70 % de las cantidades totales de tanto la piridoxina HCl como el succinato de doxilamina se disuelven después de 60 minutos de medición;

c) por lo menos aproximadamente el 80 % de las cantidades totales de tanto la piridoxina HCl como el succinato de doxilamina se disuelven después de 90

minutos de medición;

d) por lo menos aproximadamente el 90 % de las cantidades totales de tanto la piridoxina HCl como el succinato de doxilamina se disuelven después de 120 minutos de medición.

2. Una formulación de acción rápida de piridoxina HCl y succinato de doxilamina recubierta entéricamente de acuerdo con la reivindicación 1 en la que se satisfacen también las siguientes características de disolución al medirlas en 1000 ml de tampón de fosfato a pH 6,8 y 37° C en un aparato de disolución tipo 2 a 100 rpm:

a) por lo menos aproximadamente el 20 % de las cantidades totales de tanto la piridoxina HCl como el succinato de doxilamina se disuelven después de 15 minutos de medición;

b) por lo menos aproximadamente el 60 % de las cantidades totales de tanto la piridoxina HCl como el succinato de doxilamina se disuelven después de 45 minutos de medición;

c) por lo menos aproximadamente el 80 % de las cantidades totales de tanto la piridoxina HCl como el succinato de doxilamina se disuelven después de 75 minutos de medición.

3. La formulación de acción rápida de acuerdo con las reivindicaciones 1 ó 2, en la cual aproximadamente el 40 % de las cantidades totales de tanto la piridoxina HCl como el succinato de doxilamina se disuelven dentro de los 5 minutos de medición al medirlas en 1000 ml de tampón de fosfato a pH 6,8 y 37° C en un aparato

de disolución tipo 2 a 100 rpm.

4. La formulación de acción rápida de acuerdo con las reivindicaciones 1 ó 2, en la cual dicha formulación contiene un núcleo recubierto con por lo menos un recubrimiento entérico, comprendiendo dicho núcleo piridoxina HCl, succinato de doxilamina y los siguientes excipientes no activos: un relleno o ligante, un agente desintegrante, un lubricante, un acondicionador de flujo silícico y un agente estabilizador.

5. La formulación de acción rápida de acuerdo con la reivindicación 4, en la cual dicho relleno o ligante consiste en celulosa microcristalina.

6. La formulación de acción rápida de acuerdo con la reivindicación 4, en la cual dicho agente desintegrante consiste en croscarmelosa sódica.

7. La formulación de acción rápida de acuerdo con la reivindicación 4, en la cual dicho lubricante consiste en estearato de magnesio.

8. La formulación de acción rápida de acuerdo con la reivindicación 4, en la cual dicho acondicionador de flujo silícico consiste en dióxido de silicio.

9. La formulación de acción rápida de acuerdo con la reivindicación 4, en la cual dicho agente estabilizador consiste en trisilicato de magnesio.

10. La formulación de acción rápida de acuerdo con la reivindicación 1 ó 2, en la cual dicho núcleo comprende:

a) aproximadamente 4-10 % en peso de piridoxina HCl;

b) aproximadamente 4-10 % en peso de succinato de doxilamina;

c) aproximadamente 40-80 % en peso de celulosa microcristalina;

d) aproximadamente 10-30 % en peso de trisilicato de magnesio;

e) aproximadamente 0,5-5 % en peso de dióxido de silicio;

f) aproximadamente 0,5-5 % en peso de croscarmelosa sódica; y

g) aproximadamente 0,5-5 % en peso de estearato de magnesio.

11. La formulación de acción rápida de acuerdo con la reivindicación 10, en la cual dicho núcleo comprende:

a) aproximadamente 7 % en peso de piridoxina HCl;

b) aproximadamente 7 % en peso de succinato de doxilamina;

c) aproximadamente 62 % en peso de celulosa microcristalina;

d) aproximadamente 18 % en peso de trisilicato de magnesio;

e) aproximadamente 0,7 % en peso de dióxido de silicio;

f) aproximadamente 2,5 % en peso de croscarmelosa sódica; y

g) aproximadamente 2,8 % en peso de estearato de magnesio.

12. La formulación de acción rápida de acuerdo con la reivindicación 4, en la cual dicho por lo menos un recubrimiento entérico es de base acuosa.

13. La formulación de acción rápida de acuerdo con la reivindicación 12, en la cual dicho recubrimiento entérico consiste en un revestimiento de sellado aplicado al

núcleo, un revestimiento entérico en sí mismo aplicado sobre el revestimiento de sellado y un revestimiento de terminación estético aplicado sobre el revestimiento entérico en sí mismo.

14. El uso de la formulación de acción rápida de acuerdo con las reivindicaciones 1 ó 2 para aliviar los síntomas de náusea y vómito en un mamífero.

15. El uso de la formulación de acción rápida de acuerdo con las reivindicaciones 1 ó 2 para aliviar los síntomas de náusea y vómito durante el embarazo humano.

16. Un medicamento para atenuar los síntomas asociados con náusea y vómito que consiste esencialmente en la formulación de la reivindicación 4.

17. Un proceso para preparar la formulación de acción rápida de la reivindicación 4, comprendiendo dicho proceso las etapas de:

- mezclar dicho succinato de doxilamina y dicho acondicionador de flujo silícico para obtener una pre-mezcla;
- mezclar dicha pre-mezcla con dicha piridoxina HCl para obtener una mezcla de ingrediente activo;
- mezclar dicha mezcla de ingrediente activo con dichos excipientes no activos restantes, a saber: un relleno o ligante, un agente desintegrante, un lubricante, y un agente estabilizador para obtener una mezcla final; y
- darle a dicha mezcla final la forma de tabletas y recubrirla.

18. Un proceso de acuerdo con la reivindicación 17 en la cual dicha etapa final de conformación de las tabletas y recubrimiento comprende la compresión de dicha mezcla final para darle una forma de tableta, el revestimiento de sellado de dicha forma de tableta, seguido por el revestimiento entérico, seguido por un revestimiento de color.

p. DUCHESNAY INC.

Resumen

Se proporciona en la presente una formulación novedosa de acción rápida de piridoxina HCl y succinato de doxilamina recubierta entéricamente que comprende un

agente desintegrante tal que se satisfagan los siguientes perfiles de disolución al medirlos en 1000 ml de tampón de fosfato a pH 6,8 y 37° C en un aparato de disolución tipo 2 a 100 rpm:

a) por lo menos aproximadamente el 40 % del total de la piridoxina HCl y del succinato de doxilamina se disuelven después de 30 minutos de medición;

b) por lo menos aproximadamente el 70 % del total de la piridoxina HCl y del succinato de doxilamina se disuelven después de 60 minutos de medición;

c) por lo menos aproximadamente el 80 % del total de la piridoxina HCl y del succinato de doxilamina se disuelven después de 90 minutos de medición;

d) por lo menos aproximadamente el 90 % del total de la piridoxina HCl y del succinato de doxilamina se disuelven después de 120 minutos de medición.

Preferentemente la formulación contendrá un núcleo recubierto con por lo menos un revestimiento entérico, comprendiendo el núcleo piridoxina HCl, succinato de doxilamina y los siguientes excipientes no activos: un relleno o ligante, un agente desintegrante, un lubricante, un acondicionador de flujo silícico y un agente estabilizador.

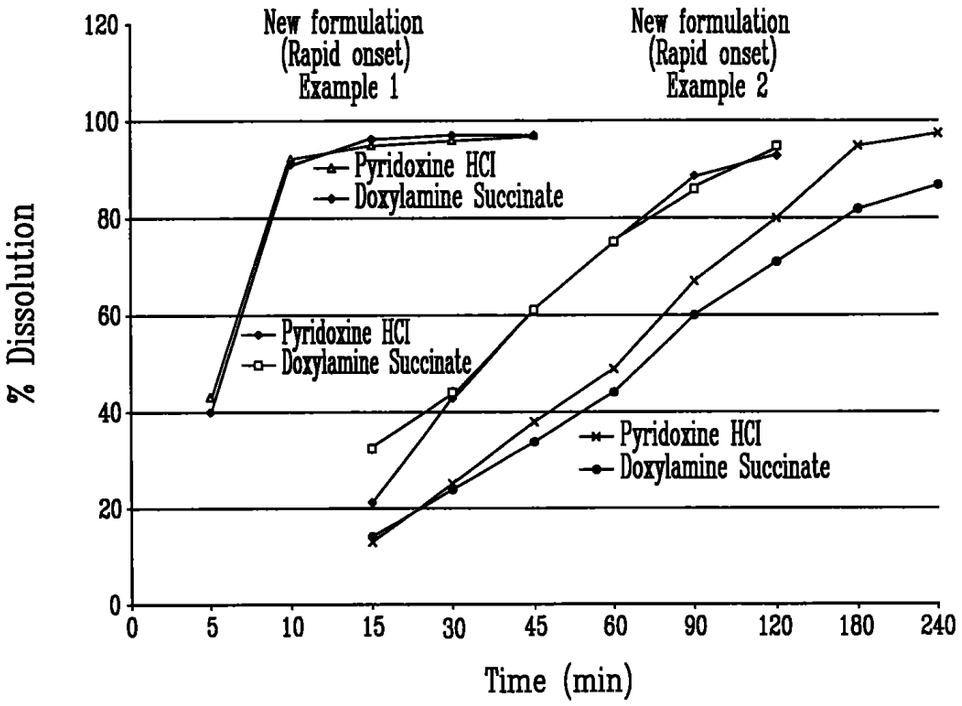
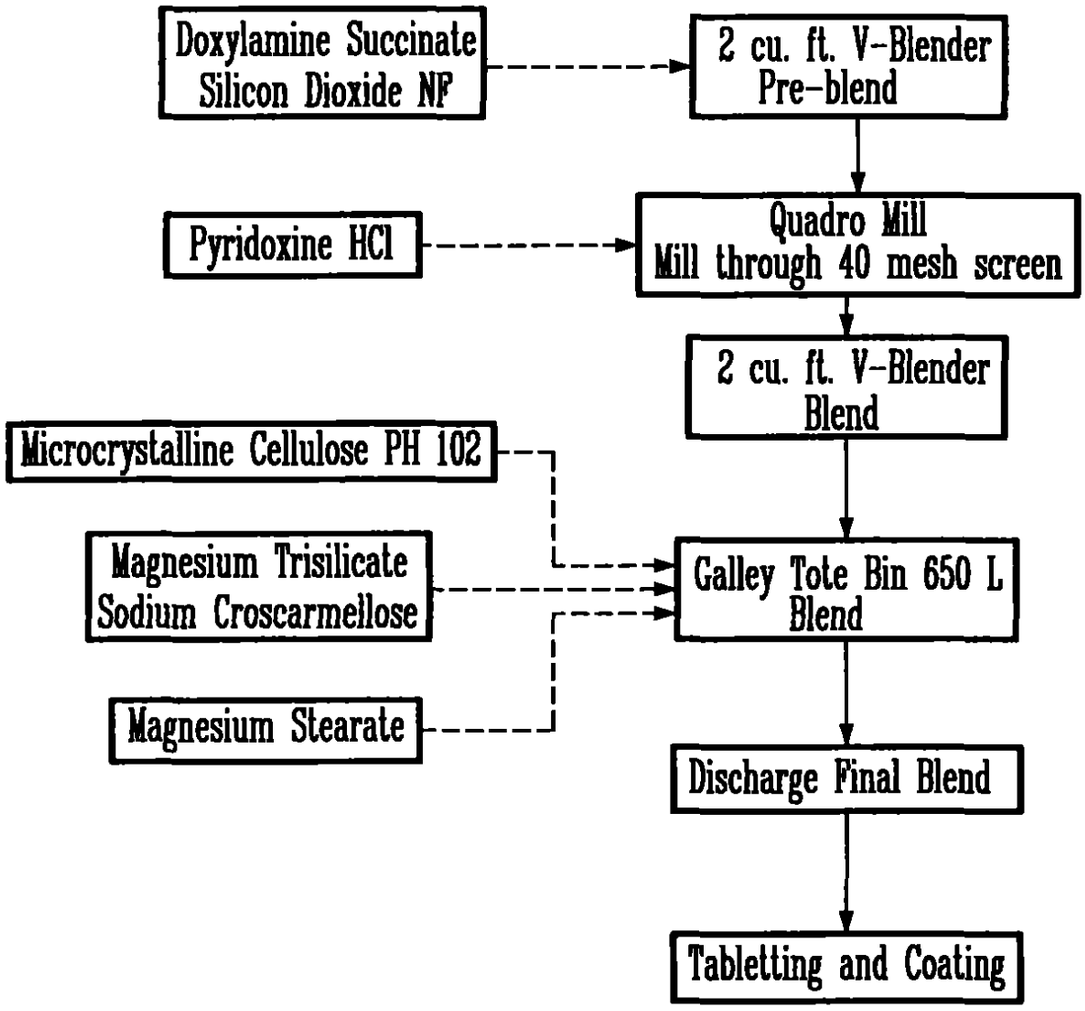


Fig. 1 *(Prior Art)*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Silicon Dioxide NF
2 cu. ft. V-Blender
Pre-blend
Pyridoxine HCl
Quadro Mill
Mill through 40 mesh screen
2 cu. ft. V-Blender
Blend
Microcrystalline Cellulose PH 102
Magnesium Trisilicate
Sodium Croscarmellose
Galley Tote Bin 650 L
Blend
Magnesium Stearate
Discharge Final Blend
Tabletting and Coating

Fig. 2

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

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International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

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RAPID ONSET FORMULATION

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State *(that is, country)* of residence: CA

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The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

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☒ **TM** Turkmenistan .....
☒ **TR** Turkey .....
☒ **TT** Trinidad and Tobago .....
.....
☒ **TZ** United Republic of Tanzania
☒ **UA** Ukraine .....
☒ **UG** Uganda .....
☒ **US** United States of America .....
.....
☒ **UZ** Uzbekistan .....
☒ **VN** Viet Nam .....
☒ **YU** Yugoslavia .....
☒ **ZA** South Africa .....
☒ **ZW** Zimbabwe .....

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ ....EC. ECUADOR..... ☐ ..... ☐ .....
☐ ..... ☐ ..... ☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1)				
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* *Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii))*: . . . .

. . . . . .

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / EPO . . . . . .

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*:		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☒ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. VIII (ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (ii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

in relation to this international application,

DUCHESNAY INC. is entitled to apply for and be granted a patent by virtue of the following:

an assignment from

GERVAIS, Eric, 2526, des Oiseaux, Laval, Quebec, H7L 4W9, CANADA

to DUCHESNAY INC., dated 20 June 2001.

This designation is made for the purpose of all designations, except the designation of the United States of America.

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (ii)".

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) the following number of sheets in paper form:

request (including declaration sheets)	:	5
description (excluding sequence listing part)	:	19
claims	:	4
abstract	:	1
drawings	:	2
Sub-total number of sheets	:	0
sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)*	:	
Total number of sheets	:	31

(b) sequence listing part of description filed in computer readable form

(i) ☐ only (under Section 801(a)(i))

(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(ii), in right column)*: .....

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:

		Number of items
1. ☒ fee calculation sheet	:	1
2. ☒ original separate power of attorney	:	1
3. ☐ original general power of attorney	:	
4. ☐ copy of general power of attorney; reference number, if any:	:	
5. ☐ statement explaining lack of signature	:	
6. ☐ priority document(s) identified in Box No. VI as item(s):	:	
7. ☐ translation of international application into *(language)*:	:	
8. ☐ separate indications concerning deposited microorganism or other biological material	:	
9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))		
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	:	
10. ☒ other *(specify)*: Assignment of Invention	:	1

Figure of the drawings which should accompany the abstract: 1

Language of filing of the international application: ENGLISH

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

GOUDREAU GAGE DUBUC

JEAN H. DUBUC

For receiving Office use only

1. Date of actual receipt of the purported international application:

2. Drawings:
☐ received:
☐ not received:

3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:

4. Date of timely receipt of the required corrections under PCT Article 11(2):

5. International Searching Authority (if two or more are competent): ISA /

6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International Application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: AML/11621.23

Applicant: DUCHESNAY INC., ET AL

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . 200 T

2. SEARCH FEE . . . . . 1320 S

International search to be carried out by EPO

(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

Where item (b) of Box No. IX applies, enter Sub-total number of sheets
Where item (b) of Box No. IX does not apply, enter Total number of sheets } 31

b1 first 30 sheets 562 b1

b2 1 (number of sheets in excess of 30) x 13 (fee per sheet) = 13 b2

b3 additional component (only if sequence listing part of description is filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)):

400 x _____ (fee per sheet) = _____ b3

Add amounts entered at b1, b2 and b3 and enter total at B . . . . 575 B

Designation Fees

The international application contains ALL designations.

6 (number of designation fees payable *(maximum 6)*) x 121 (amount of designation fee) = 726 D

Add amounts entered at B and D and enter total at I . . . . . 1301 I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . P

5. TOTAL FEES PAYABLE . . . . . 2821 TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☒ authorization to charge deposit account (see below) ☐ postal money order ☐ cash ☐ coupons

☐ cheque ☐ bank draft ☐ revenue stamps ☐ other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all receiving Offices)

Receiving Office: RO/ CA

Deposit Account No.: 600000102

Date: 21 June 2001

Name: GOUDREAU GAGE DUBUC

Signature:

☒ Authorization to charge the total fees indicated above.

☒ *(This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

☐ Authorization to charge the fee for priority document.

See Notes to the fee calculation sheet

PATENT COOPERATION TRE..Y

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
GOUDREAU GAGE DUBUC
The Stock Exchange Tower
Attn. Dubuc J.
800 Place Victoria, Suite 3400
P.O.Box 242
Montréal, Quebec H4Z 1E9
CANADA

Applicant's or agent's file reference AML/11621.23	Date of mailing *(day/month/year)* 21/02/2002
International application No. PCT/CA 01/00951	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant DUCHESNAY INC.	International filing date *(day/month/year)* 21/06/2001

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

RECU
RECEIVED

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

26 FEV 2002
GOUDREAU GAGE DUBUC
3400 TOUR DE LA BOURSE
C.P. 242, PLACE VICTORIA
MONTREAL, QUEBEC H4Z 1E9

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for International preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Petronella Vaassen-Elsackers

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

FORMXXII: <XSISA220NOTFNP4 1 >

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. References to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

BNSDOCID: <XXISA220NOENP4 1 >

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
AML/11621.23		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 01/00951	21/06/2001	
Applicant		
DUCHESNAY INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] Certain claims were found unsearchable (See Box I).

3. [ ] Unity of invention is lacking (see Box II).

4. With regard to the title,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] None of the figures.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 01/00951

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4402 A61K31/4415 A61K9/28 A61P1/08

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)
IPC 7 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)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	CA 2 350 195 A (DUCHESNAY INC.,CA) 11 August 2001 (2001-08-11) the whole document	1-16
A	WO 01 19901 A (SMITHKLINE BEECHAM) 22 March 2001 (2001-03-22) claims 24,26,27,29,38,39 page 6, line 24 page 11, line 19 - line 36	1-16
A	CA 2 139 896 A (DUCHESNAY INC.,CA) 11 July 1996 (1996-07-11) the whole document	1-16

-/--

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in 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	Date of mailing of the international search report
14 February 2002	21/02/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 01/00951

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 085 641 A (INVESTIGATIONS SCIENTIFIQUES PHARMACEUTIQUES,FR) 31 December 1971 (1971-12-31) claims example 3	1-16
A	US 4 642 231 A (D. PETERS ET AL.) 10 February 1987 (1987-02-10) claims column 4, line 19 - line 32	1-16
A	WO 93 13758 A (PFIZER INC.,U.S.A.) 22 July 1993 (1993-07-22) claims	1-16

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 01/00951

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
CA 2350195	A		NONE		
WO 0119901	A	22-03-2001	AU	7581800 A	17-04-2001
			WO	0119901 A2	22-03-2001
CA 2139896	A	11-07-1996	CA	2139896 A1	11-07-1996
FR 2085641	A	31-12-1971	FR	2085641 A5	31-12-1971
US 4642231	A	10-02-1987	US	4581232 A	08-04-1986
			AT	44130 T	15-07-1989
			AU	563740 B2	23-07-1987
			AU	2068983 A	24-01-1985
			CA	1207232 A1	08-07-1986
			DE	3380090 D1	27-07-1989
			DK	553283 A ,B,	21-01-1985
			EP	0132472 A1	13-02-1985
			ES	526990 D0	01-06-1986
			ES	8607723 A1	16-11-1986
			FI	840615 A ,B,	21-01-1985
			IE	56510 B1	28-08-1991
			JP	1776857 C	28-07-1993
			JP	4065811 B	21-10-1992
			JP	60112722 A	19-06-1985
			NZ	206101 A	13-09-1985
			US	4632822 A	30-12-1986
			US	4632823 A	30-12-1986
			US	4632821 A	30-12-1986
			US	4643898 A	17-02-1987
			US	4647459 A	03-03-1987
			US	4643892 A	17-02-1987
			US	4647450 A	03-03-1987
			US	4650663 A	17-03-1987
			US	4647449 A	03-03-1987
			US	4649041 A	10-03-1987
			ZA	8308080 A	27-06-1984
WO 9313758	A	22-07-1993	AT	147261 T	15-01-1997
			CA	2117351 A1	22-07-1993
			DE	69216642 D1	20-02-1997
			DE	69216642 T2	07-05-1997
			DK	620728 T3	07-07-1997
			EP	0620728 A1	26-10-1994
			ES	2096103 T3	01-03-1997
			FI	943327 A	12-07-1994
			GR	3022458 T3	30-04-1997
			JP	2640570 B2	13-08-1997
			JP	7503237 T	06-04-1995
			PT	101175 A ,B	31-03-1994
			WO	9313758 A1	22-07-1993
			US	5853758 A	29-12-1998

Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2350195 A1 2001/08/11

(21) 2 350 195

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(22) Date de dépôt/Filing Date: 2001/06/21

(41) Mise à la disp. pub./Open to Public Insp.: 2001/08/11

(51) Cl.Int.^{7}/Int.Cl.^{7} A61K 31/4415, A61K 31/4402, A61P 1/08

(71) Demandeur/Applicant:
DUCHESNAY INC., CA

(72) Inventeur/Inventor:
GERVAIS, ERIC, CA

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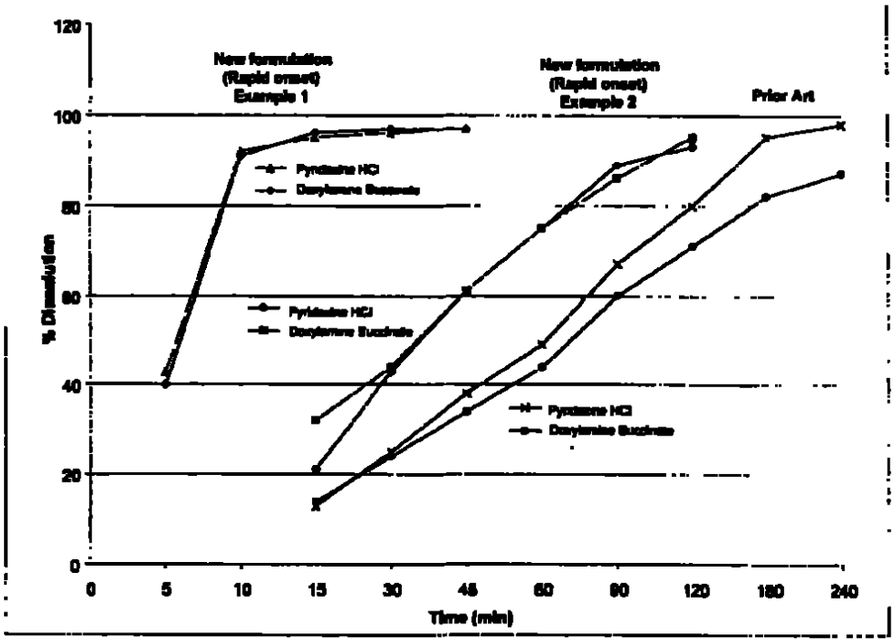
(54) Titre : PREPARATION A DELAI D'ACTION RAPIDE
(54) Title: RAPID ONSET FORMULATION



(57) Abrégé/Abstract:
Provided herein is a novel enterically-coated pyridoxine HCl and doxylamine succinate rapid onset formulation comprising a disintegrating agent such that the following dissolution profiles are satisfied when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm: (a) at least about 40% of the total pyridoxine HCl and doxylamine succinate is dissolved after 30 minutes of measurement; (b) at least about 70% of the total pyridoxine HCl and doxylamine succinate is dissolved after 60 minutes of measurement; (c) at least about 80% of the total pyridoxine HCl and doxylamine succinate is dissolved after 90 minutes of measurement; (d) at about 90% of the total pyridoxine HCl and doxylamine succinate is dissolved after 120 minutes of measurement. Preferably the formulation will contain a core coated with at least one enteric coating, the core comprising pyridoxine HCl, doxylamine succinate and the following non-active excipients: a filler or binder, a disintegrating agent, a lubricant, a silica flow conditioner and a stabilizing agent.

ABSTRACT

Provided herein is a novel enterically-coated pyridoxine HCl and doxylamine succinate rapid onset formulation comprising a disintegrating agent such that the following dissolution profiles are satisfied when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm:

(a) at least about 40% of the total pyridoxine HCl and doxylamine succinate is dissolved after 30 minutes of measurement;

(b) at least about 70% of the total pyridoxine HCl and doxylamine succinate is dissolved after 60 minutes of measurement;

(c) at least about 80% of the total pyridoxine HCl and doxylamine succinate is dissolved after 90 minutes of measurement;

(d) at about 90% of the total pyridoxine HCl and doxylamine succinate is dissolved after 120 minutes of measurement.

Preferably the formulation will contain a core coated with at least one enteric coating, the core comprising pyridoxine HCl, doxylamine succinate and the following non-active excipients: a filler or binder, a disintegrating agent, a lubricant, a silica flow conditioner and a stabilizing agent.

TITLE OF THE INVENTION

RAPID ONSET FORMULATION

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to a rapid onset formulation, preferably in form of an enterically coated tablet, for a medicament comprising a synergistic duo of active ingredients namely, doxylamine succinate and pyridoxine HCl, hereinafter referred to as "DS-P". DS-P is useful in the treatment of nausea and vomiting, especially, but not limited to, during pregnancy, hereinafter referred to as "NVP". Thus the present invention is concerned with all known and future therapeutic indications of DS-P.

THE PRIOR ART

Pharmaceutical formulations of DS-P are known. The current formulation, commercially available in Canada under the name Diclectin (Duchesnay Inc.) comprises the following active ingredients: pyridoxine HCl and Doxylamine succinate. It additionally comprises the following excipients: lactose, microcrystalline cellulose, magnesium trisilicate, silicon dioxide and magnesium stearate.

Diclectin is the world's most studied drug in regard to its safety during pregnancy. Because of its excellent safety profile, Diclectin is the drug of choice for the treatment of NVP. The current formulation is sugar coated and suffers from drawbacks, one of which being its delayed onset of action. However, the current formulation once ingested, can take more than 4 hours before the two active ingredients (pyridoxine HCl and doxylamine succinate) reach nearly full dissolution in the small intestines, where it is absorbed. This delay is often considered too long for patients, such as women suffering from NVP, who require urgent relief of symptoms.

Another drawback of the current formulation is related to patient compliance. Women suffering from NVP often complain of hyper olfaction, which means that various odors and tastes can trigger nausea or vomiting problems. The smell and taste of sugar on the current sugar coated formulation as well as the use of organic solvents and phthalates in

the preparation of the currently used enteric coating, bothers many pregnant women to the point where the intake of the drug is essentially inhibited.

The size of the currently available tablet is also problematic. A smaller size tablet would improve patient compliance since women suffering from NVP often have problems swallowing. Furthermore, a smaller tablet looks less harmful than a bigger one and patients will have the impression that they are taking a lesser amount of drug. This will in turn significantly increase patient compliance.

Finally, the current formulation contains lactose. This is objectionable for those patients suffering from lactose intolerance.

Thus, it is desirable to provide patients suffering from nausea and vomiting an improved rapid onset formulation overcoming the drawbacks of the prior art.

However, since DS-P is orally delivered as an enteric coated tablet, the novel oral formulation must transit through the stomach unscathed and rapidly release both active ingredients once the dosage form reaches its intended destination, namely the intestines.

The main challenge surmounted by the present invention was to arrive at a dosage form capable of overcoming the drawbacks of the prior art while simultaneously delivering the synergistic duo of active ingredients for rapid onset. It was also important to provide a formulation exhibiting similar dissolution curves for both active ingredients so as to avoid the dissolution of one active ingredient to the detriment of the other. This was important in view of the synergistic therapeutic effect of the duo of active ingredients.

SUMMARY OF THE INVENTION

In general terms, the invention provides a new aqueous enteric-coated formulation comprising DS-P, the formulation exhibiting a dissolution profile indicative of a rapid onset.

The invention also seeks to provide a pharmaceutical composition having *specific in-vitro* dissolution profiles indicative of rapid onset of the active ingredients. The pharmaceutical composition being suitable for simple and reproducible manufacture.

Further scope of applicability will become apparent from the detailed description given hereinafter. It should be understood however, that this detailed description, while indicating preferred embodiments of the invention, is given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art.

DESCRIPTION OF THE DRAWINGS

Figure 1 depicts two examples of dissolution profiles in accordance to the rapid onset formulation of the present invention in comparison to a dissolution profile of the prior art formulation. The first dissolution profile (example 1) corresponds to a rapid onset formulation from which nearly 100% of both active ingredients is released within 45 minutes. The second dissolution profile (example 2) corresponds to a rapid onset formulation from which approximately 95% of both active ingredients is released within 120 minutes. The last and comparative dissolution profile (prior art) corresponds to the currently available formulation from which approximately 100% of the pyridoxine HCl and approximately 90% of the doxylamine succinate is released within 240 minutes.

Figure 2 is a schematic flowchart of the preferred manufacturing process of a preferred formulation in accordance with the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Other objects and attendant features of the present invention will become readily appreciated, as the same becomes better understood by reference to the following detailed description of a preferred embodiment described for the purpose of illustration.

In a broad sense, the invention provides a rapid onset formulation comprising pyridoxine HCl and doxylamine succinate.

The formulation of the present invention may be used in the human and veterinary fields of medicine whenever symptoms of nausea and/or vomiting require medical intervention. Since the formulation of the present invention is intended for medicinal purposes, then the formulation and its components should be pharmaceutically acceptable. The preferred formulation is in the form of an oral dosage form such as a tablet, pill or encapsulated beads or solution. The most preferred formulation is a tablet.

The tablet of the present invention is preferably capable of transiting through the stomach unscathed. To test this feature, the tablet of the present invention was tested to resist disintegration in simulated gastric fluid "SGF" for a minimum period of 1 hour.

In accordance with the present invention, the formulation will satisfy the following dissolution profiles when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm; preferably measured by high performance liquid chromatography:

(a) at least about 40% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 30 minutes of measurement;

(b) at least about 70% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 60 minutes of measurement;

(c) at least about 80% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 90 minutes of measurement;

(d) at least about 90% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 120 minutes of measurement;

In the present invention, any reference to dissolution profile should be construed as referring to the results of a dissolution test in which the amount of pyridoxine HCl and of doxylamine succinate released is measured in 1000 ml phosphate buffer at pH 6.8 and 37°C using a USP (United States Pharmacopoeia) type 2 dissolution apparatus at 100 rpm; preferably measured by high performance liquid chromatography.

As used herein and in the claims, an "enteric coating" is understood to mean a coating comprising one or more layers generally resistant to disintegration in human gastric fluids, but which will disintegrate in human intestinal fluids, as well as coatings which

disintegrate very slowly in human gastric fluids, but more rapidly in human intestinal fluids. In a broad sense, "enteric coating" can encompass for example any seal coat placed on the compressed core of a tablet prior to the enteric coating *per se* as well as any finishing aesthetic coat placed on the enteric coating *per se*.

In a most preferred embodiment, the formulation of the present invention contains a core coated with an aqueous enteric coating. The core comprises the active ingredients pyridoxine HCl and doxylamine succinate along with non-active excipients such as a filler or binder, a disintegrating agent, a lubricant, a silica flow conditioner and a stabilizing agent.

Examples of fillers or binders include acacia, alginic acid, calcium phosphate (dibasic), carboxymethylcellulose, carboxymethylcellulose sodium, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, dextrin, dextrates, sucrose, tylose, pregelatinized starch, calcium sulfate, amylose, glycine, bentonite, maltose, sorbitol, ethylcellulose, disodium hydrogen phosphate, disodium phosphate, disodium pyrosulfite, polyvinyl alcohol, gelatin, glucose, guar gum, liquid glucose, compressible sugar, magnesium aluminum silicate, maltodextrin, polyethylene oxide, polymethacrylates, povidone, sodium alginate, tragacanth microcrystalline cellulose, starch, and zein. A most preferred filler or binder consists of microcrystalline cellulose.

Examples of disintegrating agents include alginic acid, carboxymethylcellulose, carboxymethylcellulose sodium, hydroxypropylcellulose (low substituted), microcrystalline cellulose, powdered cellulose, colloidal silicon dioxide, sodium croscarmellose, crospovidone, methylcellulose, polacrilin potassium, povidone, sodium alginate, sodium starch glycolate, starch, disodium disulfite, disodium edathamil, disodium edetate, disodiumethylenediaminetetraacetate (EDTA) crosslinked polyvinylpyrollidines, pregelatinized starch, carboxymethyl starch, sodium carboxymethyl starch, microcrystalline cellulose. A most preferred disintegrating agent consists of sodium crosscarmelose.

Examples of lubricants include calcium stearate, canola oil, glyceryl palmitostearate, hydrogenated vegetable oil (type I), magnesium oxide, magnesium stearate, mineral oil,

poloxamer, polyethylene glycol, sodium lauryl sulfate, sodium stearate fumarate, stearic acid, talc and, zinc stearate, glyceryl behapate, magnesium lauryl sulfate, boric acid, sodium benzoate, sodium acetate, sodium benzoate/sodium acetate (in combination), DL leucine. A most preferred lubricant consists of magnesium stearate.

Examples of silica flow conditioners include colloidal silicon dioxide, magnesium aluminum silicate and guar gum. A most preferred silica flow conditioner consists of silicon dioxide.

Examples of stabilizing agents include acacia, albumin, polyvinyl alcohol, alginic acid, bentonite, dicalcium phosphate, carboxymethylcellulose, hydroxypropylcellulose, colloidal silicon dioxide, cyclodextrins, glyceryl monostearate, hydroxypropyl methylcellulose, magnesium trisilicate, magnesium aluminum silicate, propylene glycol, propylene glycol alginate, sodium alginate, carnauba wax, xanthan gum, starch, stearate(s), stearic acid, stearic monoglyceride and stearyl alcohol. A most preferred stabilizing agent consists of magnesium trisilicate.

In a preferred embodiment, the core of the new rapid onset Diclectin formulation will contain approximately about 4 to 10%, most preferably about 7% by weight of pyridoxine HCl; about 4 to10%, most preferably about 7% by weight of doxylamine succinate; about 40 to 80%, most preferably about 62% by weight of microcrystalline cellulose; about 10 to 30%, most preferably about 18% by weight of magnesium trisilicate; about 0.5 to 5%, most preferably about 1% by weight of silicon dioxide; 0.5 to 5% most preferably about 3% by weight of sodium croscarmellose and about 0.5 to 5%, most preferably about 3% by weight of magnesium stearate.

Example 1

The following is an example of a 145 mg Diclectin rapid onset core formulation:

Table 1: Core Ingredients:

Ingredients	Weight Mg/Tab	% Weight % w/w	Batch size 100 kg
Doxylamine Succinate	10.0	6.9	6.897
Pyridoxine HCl	10.0	6.9	6.897
Magnesium trisilicate	26.4	18.2	18.207
Microcrystalline Cellulose PH 102	90.0	62.1	62.069
Sodium Croscarmellose Type A	3.6	2.5	2.483
Magnesium Stearate	4.0	2.8	2.759
Silicon Dioxide NF	1.0	0.7	0.690
Total:	145.0	100%	100%

The core can then be enterically coated with an aqueous enteric coating which will allow the formulation to transit through the stomach relatively unscathed while allowing rapid dissolution in the intestines.

The coating formulation can be as follows:

Table 2: Coating Formulation

Ingredients	Weight Mg/Tab	% Weight % w/w	Batch size 100 kg
Seal Coating			
Opadry™ Clear YS-1-7472	4.82	3.33	3.327
Purified Water USP			
Total:	4.82	3.33	3.33
Enteric Coating			
Estacryl™ 30D Enteric Coating Solution*	39.58	27.29	27.294

Ingredient	Weight %	Weight (mg)	Batch size (100 kg)
Talc USP 200 Mesh	2.85	1.97	1.968
Polyethylene Glycol 400 USP	1.20	0.83	0.826
Antifoam 1520	0.12	0.08	0.081
Purified Water USP			
Total:	16.04	30.17	30.17
[illegible]			
Opadry™ White YS-1-7003	1.61	1.11	1.108
Purified Water USP			
Total:	1.61	1.11	1.11

*Estacryl 30D Enteric Coating Solution contains 30% of solids. Therefore, the total actual enteric coating amounts to 11.07%.

Total coated tablet weight 167.47 mg.

The purpose of the seal coat is to provide a smooth surface for the enteric coating, thereby avoiding mounds, pits or crevasses wherein uneven amounts of enteric coating would be applied.

Dissolution Data

The rapid onset formulation of the previous example has exhibited in-vitro dissolution profiles as shown in Table 3 below, when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm. The numerical values are expressed as percentages of dissolved active ingredient in relation to starting quantities.

Table 3: Dissolution profiles

Pyridoxine HCl	Run 1	Run 2	Run 3	[illegible]	Run 5	Run 6	Avg
5 minutes	20	2	0	77	79	79	43
10 minutes	91	90	90	91	94	95	92
15 minutes	98	96	94	94	95	96	95
30 minutes	95	98	96	95	98	96	96
45 minutes	97	96	97	94	99	98	97

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Doxylamine Succinate	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Avg.
5 minutes	17	2	0	70	75	76	40
10 minutes	90	87	89	89	97	96	91
15 minutes	98	97	96	92	98	97	96
30 minutes	97	98	96	94	99	97	97
45 minutes	98	96	98	92	100	99	97

The extremely low dissolution values obtained after 5 minutes for runs 1 to 3, can be explained by the non-disintegration of the core formulation at the 5 minute interval.

Example of method of manufacture

The formulation of the present invention was prepared using the ingredients shown in Table 1, above. Doxylamine succinate and silicon dioxide NF are pre-blended in a 2 cu. Ft. V-Blender. The resulting pre-blend is then milled through a Quadro Co Mill, Model 196S, equipped with a 40 mesh screen.

Pyridoxine HCl is also milled through a Quadro Co Mill, Model 196S, equipped with a 40 mesh screen. The milled pyridoxine HCl is then combined with the doxylamine / silicon dioxide NF pre-blend and the combined mixture blended.

Microcrystalline Cellulose is milled through a 40 mesh screen and split into two approximately equal portions. One portion is subsequently combined in a 650L Gallay Bin with the previously formed pre-blend containing both the active ingredients, followed by the addition of the second portion. The loaded material is then blended followed by the addition of magnesium trisilicate and sodium croscarmellose. The newly formed mixture is blended. The addition of magnesium stearate followed by an additional blending completes the preparation of the core formulation.

The final blend is compressed in tablet form and is subsequently seal coated, enteric coated using a suitable commercially available aqueous enteric coating and top coated for aesthetics. The overall manufacturing process is depicted in Figure 2.

All coating steps using the ingredients of Table 2, namely, the seal coat on the core, the enteric coating and the opadry white (color coat) are advantageously performed in a Vector Hi (trade-mark) coater pan equipped with a peristaltic pump.

Example 2

The following is another example of a 146 mg Diclectin rapid onset core formulation. The formulation was manufactured along the same manufacturing methods as described above in example 1. This example demonstrates that the rapid onset feature of the formulation of the present invention was obtained with a different group of excipients.

Table 4: Core Ingredients:

Ingredient	Weight (mg/tab)	Weight (%/tab)
Doxylamine Succinate	10.5	7.2
Pyridoxine HCl	10.5	7.2
Magnesium trisilicate	30.0	20.6
Microcrystalline Cellulose PH 102	65.0	44.5
Calcium Phosphate (Dibasic)	25.0	17.1
Magnesium Stearate	4.0	2.7
Colloidal Silicon Dioxide	1.0	0.7
Total	146.0	100

The coating formulation can be as follows:

Table 5: Coating Formulation

Ingredients	Weight (mg)
Opadry™ White YS-1-7003	4.38
Antifoam AF Emulsion	0.07
Sureteric YAE-6-18107	16.06
Purified Water USP	
Opadry™ Clear YS-1-7472	0.73

Total coated tablet weight 167.24 mg.

The rapid onset formulation of the previous example has exhibited in-vitro dissolution profiles as shown in Table 6 below, when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm. The numerical values are expressed as percentages of dissolved active ingredient.

Table 6: Dissolution profiles:

15 minutes	17	13	25	31	17	22	21
30 minutes	31	28	60	63	36	43	43
45 minutes	51	45	78	80	55	60	61
60 minutes	69	64	88	89	67	72	75
75 minutes	79	76	94	94	77	81	83
90 minutes	84	84	97	97	83	87	89
105 minutes	88	89	98	99	87	90	92
120 minutes	91	93	98	98	89	92	93
15 minutes	16	14	22	31	47	61	32
30 minutes	31	27	64	63	38	40	44
45 minutes	47	44	75	79	58	61	61
60 minutes	71	61	90	85	68	74	75
75 minutes	76	71	96	89	81	82	82
90 minutes	85	80	101	88	83	81	86
105 minutes	92	86	103	95	93	92	93
120 minutes	93	88	101	96	96	95	95

It follows from these results that the novel formulation demonstrates a rapid onset as shown by its dissolution profile. Pyridoxine HCl presents an average dissolution profile of over 90% within 120 minutes of starting the measurements. Similarly, Doxylamine succinate displays an average dissolution profile of over 90% within 120 minutes of starting the measurements.

Example 3 (Comparative example using prior art formulation)

The following is an example of the prior art Diclectin formulation. An example for a 146.2 mg tablet is provided. This example demonstrates a strikingly slower onset of dissolution in comparison to the present invention.

Table 7: Core Ingredients:

Ingredients	Weight (mg)	Weight (%)
Pyridoxine HCl	11.0	7.5
Doxylamine Succinate	10.2	7.0
Lactose NF	25.0	17.1
Microcrystalline Cellulose NF	65.0	44.4
Magnesium Trisilicate	30.0	20.6
Silicon Dioxide	1.0	0.7
Magnesium Stearate	4.0	2.7
Total:	146.2	100

The coating formulation is as follows:

Table 8: Coating Formulation

Ingredients
Coating Solution No. 714
Coating Powder No. 303
C.A.P. solution 10%
C.A.P. solution 5%
Gelatin Solution No. 105
Dusting Powder No. 755
White Smoothing Syrup
Sugar Syrup No. 111
Opalux AS-7000-B white
Wax Solution No. 723

The current formulation of the previous example has exhibited in-vitro dissolution profiles as shown in Table 9 below, when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm. The numerical values are expressed as percentages of dissolved active ingredient.

Table 9: Dissolution profiles:

15 minutes	9	11	18	11	16	12	13
30 minutes	22	23	32	25	28	23	25
45 minutes	37	34	45	39	42	34	38
60 minutes	50	44	56	49	51	44	49
90 minutes	69	63	73	69	67	63	67
120 minutes	83	76	84	82	80	76	80
150 minutes	94	86	91	91	86	86	89
180 minutes	99	94	98	96	93	92	95
240 minutes	93	93	100	100	99	101	98
15 minutes	12	15	17	8	18	16	14
30 minutes	17	21	31	18	27	30	24
45 minutes	24	32	45	25	38	38	34
60 minutes	34	41	56	36	46	49	44
90 minutes	52	55	69	55	62	66	60
120 minutes	69	65	75	68	71	75	71
150 minutes	80	74	80	78	79	82	79
180 minutes	82	78	86	82	80	84	82
240 minutes	95	89	89	82	80	87	87

It follows from these results that the prior art formulation, exhibits a noticeably slower dissolution pattern when compared with the novel formulations. Indeed, after 90 minutes averages of only 60% doxylamine and 67% pyridoxine HCl are dissolved. A slower in-vivo dissolution profile is indicative of a delayed onset of action. The novel formulations,

as depicted by examples 1 and 2, show markedly faster onset dissolution profiles resulting in a rapid onset of action. The new formulations overcome most, if not all of the drawbacks associated with the prior art.

The terms and descriptions used herein are preferred embodiments set forth by way of illustration only, and are not intended as limitations on the many variations which those of skill in the art will recognize to be possible in practicing the present invention. It is the intention that all variants whether presently known or unknown, that do not have a direct effect upon the way the invention works, are to be covered by the following claims.

CLAIMS

1. An enterically-coated pyridoxine HCl and doxylamine succinate rapid onset formulation comprising a disintegrating agent such that the following dissolution profiles are satisfied when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm:

(a) at least about 40% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 30 minutes of measurement;

(b) at least about 70% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 60 minutes of measurement;

(c) at least about 80% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 90 minutes of measurement;

(d) at least about 90% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 120 minutes of measurement.

2. An enterically-coated pyridoxine HCl and doxylamine succinate rapid onset formulation as in claim 1, wherein the following dissolution characteristics are also satisfied when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm:

(a) at least about 20% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 15 minutes of measurement;

(b) at least about 60% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 45 minutes of measurement;

(c) at least about 80% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 75 minutes of measurement.

3. The rapid onset formulation of claims 1 or 2, wherein at least about 40% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved within 5 minutes when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm.

4. The rapid onset formulation of claims 1 or 2, wherein said formulation contains a core coated with at least one enteric coating, said core comprising pyridoxine HCl, doxylamine succinate and the following non-active excipients: a filler or binder, a disintegrating agent, a lubricant, a silica flow conditioner and a stabilizing agent.

5. The rapid onset formulation of claim 4, wherein said filler or binder consists of microcrystalline cellulose.

6. The rapid onset formulation of claim 4, wherein said disintegrating agent consists of sodium crosscarmellose.

7. The rapid onset formulation of claim 4, wherein said lubricant consists of magnesium stearate.

8. The rapid onset formulation of claim 4, wherein said silica flow conditioner consists of silicon dioxide.

9. The rapid onset formulation of claim 4, wherein said stabilizing agent consists of magnesium trisilicate.

10. The rapid onset formulation of claims 1 or 2, wherein said core comprises:

(a) about 4-10% by weight of pyridoxine HCl;

(b) about 4-10% by weight of doxylamine succinate;

(c) about 40-80% by weight of microcrystalline cellulose;

(d) about 10-30% by weight of magnesium trisilicate;

(e) about 0.5-5% by weight of silicon dioxide;

(f) about 0.5-5% by weight of sodium croscarmellose; and

(g) about 0.5-5% by weight of magnesium stearate.

11. The rapid onset formulation of claim 10, wherein said core comprises:

(a) about 7% by weight of pyridoxine HCl;

(b) about 7% by weight of doxylamine succinate;

(c) about 62% by weight of microcrystalline cellulose;

(d) about 18% by weight of magnesium trisilicate;

(e) about 1% by weight of silicon dioxide;

(f) about 3% by weight of sodium croscarmellose; and

(g) about 3% by weight of magnesium stearate.

12. The rapid onset formulation of claim 4, wherein said enteric coating(s) is (are) aqueous based.

13. The rapid onset formulation of claim 12, wherein said enteric coating consists of a seal coat applied to the core, an enteric coating *per se* applied on the seal coat and an aesthetic top coat applied on the enteric coating *per se*.

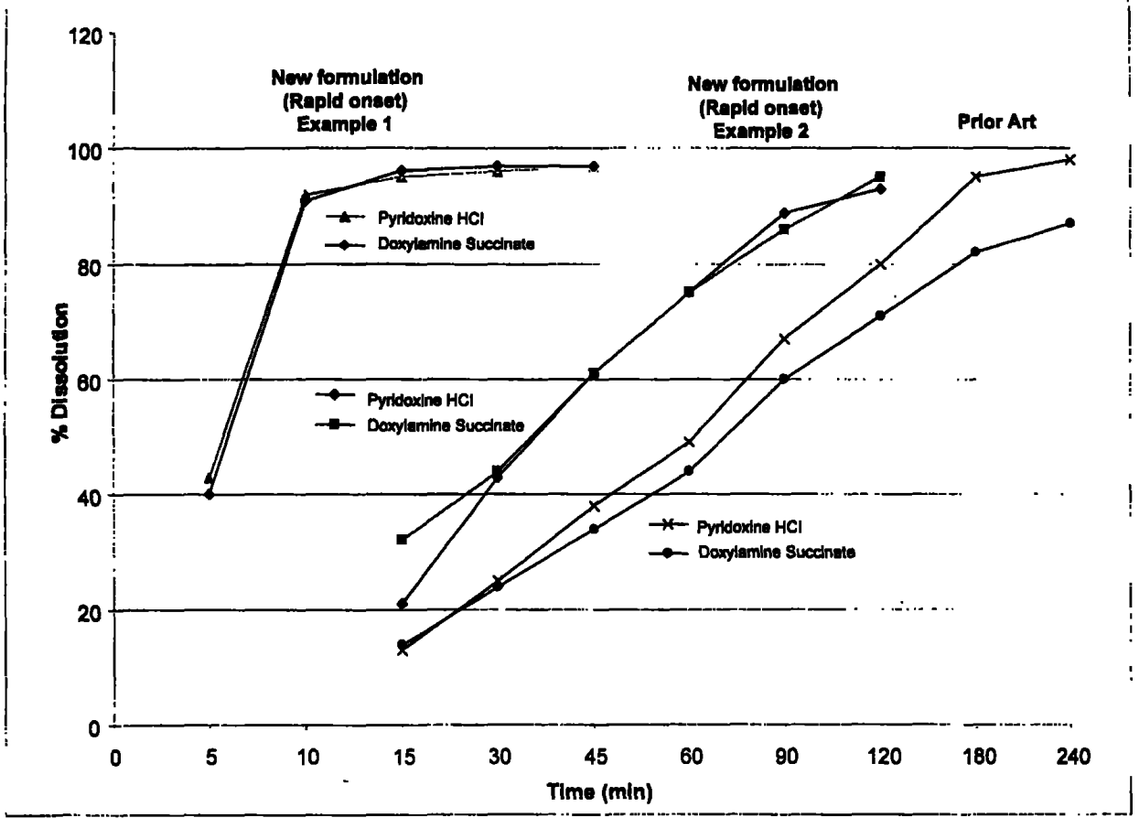
14. A method of treating nausea and vomiting comprising administering a therapeutically effective amount of the rapid onset formulation of claims 1 or 2 to a patient in need thereof.

15. A method of treating nausea and vomiting during pregnancy comprising administering a therapeutically effective amount of the rapid onset formulation of claims 1 or 2.

16. A medicament for attenuating the symptoms associated with nausea and vomiting consisting essentially of the formulation of claim 4.

CA 02350195 2001-06-21

FIGURE 1



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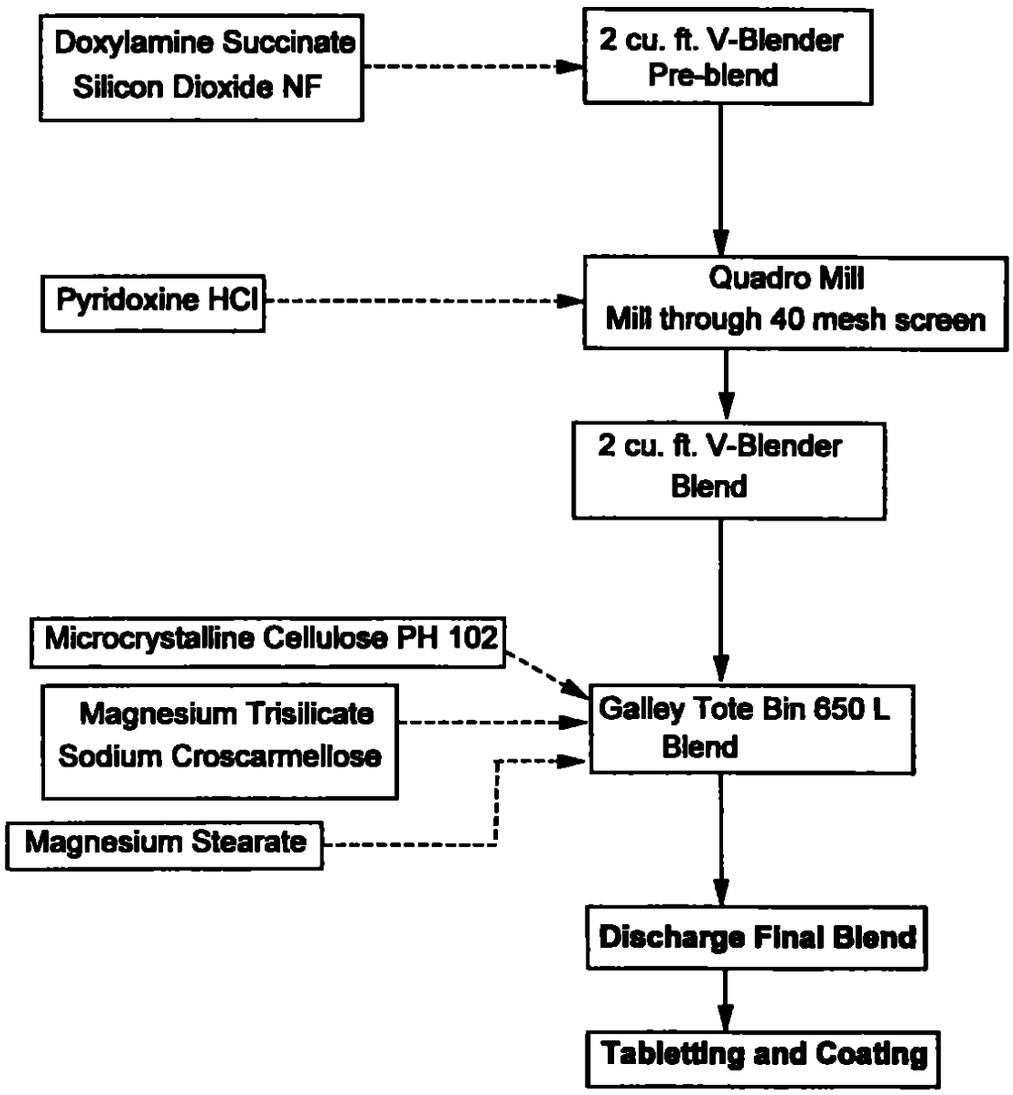

FIGURE 2

ENSDOCID: <CA 2350195A1 I >

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 March 2001 (22.03.2001)

PCT

(10) International Publication Number
WO 01/19901 A2

(51) International Patent Classification[7]: C08J

(21) International Application Number: PCT/US00/25279

(22) International Filing Date:
14 September 2000 (14.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/153,850 14 September 1999 (14.09.1999) US

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(81) Designated States *(national)*: AE, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CZ, DZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/19901 A2

(54) Title: PROCESS FOR MAKING AQUEOUS COATED BEADLETS

(57) Abstract: The present invention is directed to application of novel process conditions for aqueous coating techniques of water soluble active agents, and its application to production of sustained release beadlets of said agents. The improvement lies in the determination and use of the glass transition point for the water swellable polymer used to produce the sustained release effect, and control of the moisture content of the air by dew point.

PROCESS FOR MAKING AQUEOUS COATED BEADLETS

BACKGROUND OF THE INVENTION

Traditional Spansule technology developed in the 1950's and still used today, utilizes a sugar pellet which is first coated with a drug/s substance followed by application of a dissolution "retarding" substance such as wax. These waxes provide the prolonged and slow release of the drug substance from the pellet. Hence, the pellet exhibits a controlled release profile over time.

The active material/drug and "retarding" wax are dissolved separately in a volatile organic solvent and applied or "layered" onto the sugar pellet in a multiple step process. In many instances, the drug/solvent and wax/solvent liquids are applied in an alternating fashion once the previous layer is dry. Drying occurs rapidly since the solvents used in the process are highly volatile and "flash" evaporated from the pellet. The process is typically carried out in rotating coating pans.

There are numerous process and safety concerns with use of this technology as summarized below.

Purchase of organic solvents for manufacturing/processing has been banned in developed countries (Montreal Agreement of 1987) due to their depleting effects on the Ozone layer.

Organic solvents are toxic, flammable and are a potential health hazard to workers.

Waxes used to retard the dissolution are naturally occurring, hence a large variation in their retarding properties upon use can occur.

The rotating pans used to process the pellets allow for operator intervention. Therefore the dissolution character of the pellet can vary from process operator to process operator. Thus, this process is deemed " difficult or un-validatable" by current Good Manufacturing Process (cGMP) practices required by regulatory agencies.

Due to the highly variable nature of these wax "retarded" pellets, numerous populations of pellets are blended together to achieve the desired final drug dissolution profile. It is not uncommon to combine 8 to 12 populations of pellets to achieve the desired dissolution effects.

Dosing of the pellets into the gelatin capsule is achieved by a single-head capsule filler that fills the capsule (by a predetermined weight) in one massive fill. Since there can be as many as 12 different lots of pellets, the relative standard variation for any one pellet could be high. These variations could potentially change the rate of release of the drug from capsule to capsule.

Capsule products may contain multiple drugs on individual beadlets and hence are more complex to (pharmacokinetically) model.

The "retarding" waxes used to control the drug release from the pellets are susceptible to rapid and adverse degradation in the gastrointestinal tract in the presence of low pH and bile salts. This situation is exaggerated with the ingestion of food. Hence, the drug release characteristics and in-vivo effect can be drastically altered(figure 1).

Drug release from the pellet is caused by erosion of the pellet as it moves through the gastrointestinal tract (GI). The erosion release mechanism is dated. Generally in-vivo performance of this technology is more difficult to mathematically predict and control versus newer release mechanisms such as diffusion which is used for the current invention.

Therefore, it has become necessary to utilize newer technology, which will retain the beadlets of a traditional capsule or spansule product(s), yet use an environmentally friendly, water based polymer technology, instead of organic solvents and wax. The present invention is directed towards this end.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 demonstrates traditional wax-coated spansule technology with ingestion of food.

Figure 2 demonstrates the new aqueous coating process with ingestion of food, 75/8 formulation of PPA/CPM.

Figure 3 demonstrates In-Vitro Dissolution Results of the effect of Surelease® on the dissolution of 50% w/w drug loaded phenylpropanolamine (PPA) from beadlets having varying rates of sustained release coatings, 3 to 18%, applied in accordance with Examples 1 to 3 herein.

Figure 4 demonstrates In-Vitro Dissolution Results of the effect of Surelease® on the dissolution of 10% w/w chlorpheneramine maleate (CPM) from beadlets having varying rates of sustained release coatings, 4 to 18%, applied in accordance with Examples 4 to 6 herein.

Figure 5 demonstrates In-Vitro Dissolution of Sustained Release PPA (50mg) from 50/4 formulation beadlets having a 9% Surelease coating, in 0.1N HCl media.

Figure 6 demonstrates In-Vitro Dissolution of Sustained Release CPM (4mg) from 50/4 formulation beadlets having a 6.5% Surelease coating.

Figure 7 demonstrates the effect of pH of the dissolution media, containing a phosphate buffer, on Sustained Release PPA (50mg) from 50/4 formulation beadlets having a 9% Surelease coating.

Figure 8 demonstrates the effect of pH of the dissolution media, containing a phosphate buffer, on Sustained Release CPM release (4mg) from 50/4 formulation beadlets having a 6.5% Surelease coating.

Figure 9 demonstrates CPM *in vivo* blood profiles following a single dose of the 50/4 formulation containing both IR/SR PPA and IR/SR CPM (1:1:1:1), or where indicated for PPA as .3:7 (IR:SR) in fed and fasted individuals.

Figure 10 demonstrates PPA *In Vivo* blood profiles following a single dose of the 50/4 formulation containing both IR/SR PPA and IR/SR CPM (1:1:1:1) or where indicated for PPA as .3:7 (IR:SR) in fed and fasted individuals.

Figure 11 CPM *In Vivo* Blood Levels, Single Dose 75/8 Formulation (IR:SR CPM is 1:1, 4mg IR CPM:4mg CPM SR). The IR Comparitor product is Chlortrimeton® 4mg tablets, dosed at time 0, and 6 hours.

Figure 12 demonstrate PPA *In Vivo* Blood Levels following a Single Dose of the 75/8 Formulation (1:2 ratio IR:SR PPA, 25mg IR:50mg SR). IR Comparitor Product is a 25mg solution of PPA, given at time 0, 4, and 8 hours.

Figure 13 demonstrates the new aqueous coating process with ingestion of food for the 75/8mg PPA/SR formulation.

Figure 14 demonstrates the PSE dissolution Profiles of Formulations with Different levels of Surelease Coatings.

Figure 15 demonstrates the Effect of Media on Dissolution Rates of 10% PSE formulation and Sudafed 12 Hour Formulation.

Figure 16 demonstrates the *in vivo* release rates of three PSE formulations, 6% SR, 10% SR and 14% SR, as well as the SR Comparitor, Sudafed 12 Hour caplets and IR Comparitor, Sudafed Immediate Release 30 mg tablets (6mg dosed at 6 hours apart), using medium values.

Figure 17 demonstrates particle size distribution curve of dextromethorphan HBr powder.

Figure 18 demonstrates particle size distribution curve of micronized dextromethorphan HBr that is 90% less than 5 microns.

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Figure 19 demonstrate in vitro dissolution profile of Dextromethorphan HBr (DXM) pellets containing varying amounts of a sustainted release coating, 0%, a 5% and a 7%, applied in accordance with Examples 10 and 11 herein.

Figure 20 demonstrates the *in-vivo* release rates of IR DXM (listed as DLSC), 5% and 7% SR DXM pellets along with the IR Comparitor, Robitussin Dry Cough syrup. This figure provides for concentration (Cp = Concentration of plasma) of Dextromethorphan in the plasma.

Figure 21 demonstrates the *in-vivo* release rates of IR DXM (listed as DLSC), 5% and 7% SR DXM pellets along with the IR Comparitor, Robitussin Dry Cough syrup. This figure provides for concentration of Free Dextromethorphan in the plasma.

Figure 22 demonstrates the *in-vivo* release rates of IR DXM (listed as DLSC), 5% and 7% SR DXM pellets along with the IR Comparitor, Robitussin Dry Cough syrup. This figure provides for concentration of Total Dextromethorphan in the plasma.

SUMMARY OF THE INVENTION

The present invention is directed towards sustained release beadlets of chlorpheneramine maleate, phenylpropanolamine, pseudoephedrine and dextromethorphan having specific AUC values, C_{max}, and T_{max} values as described in the figures.

More specifically, the present invention is directed towards a product comprising a sustained release (SR) phase of PPA beadlets coated with about 9 to about 24% (weight gain) of a pseudolatex water swellable polymer dispersion.

Another embodiment is the SR product of PPA which further comprises an immediate release phase of PPA beadlets.

The immediate release phase of PPA beadlets are coated with about 0.5 to about 8% (weight gain) of a pseudolatex water swellable polymer dispersion.

Another embodiment of the present invention is a product comprising a sustained release (SR) phase of CPM beadlets coated with about 5 to about 18% (weight gain)of a pseudolatex water swellable polymer dispersion.

Another embodiment is an SR product of CPM beadlets which further comprises an immediate release phase of CPM beadlets.

The immediate release phase of CPM beadlets are coated with about 0.5 to less than 5% (weight gain) of a pseudolatex water swellable polymer dispersion.

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Another aspect of the present invention is a combination product which contains a ratio of immediate release beadlets to sustained release beadlets of both chlorpheneramine maleate and phenylpropanolamine.

Another aspect of the present invention is directed towards a product comprising a sustained release (SR) phase of PSE beadlets coated with about 3 to about 20 % (weight gain) of a pseudolatex water swellable polymer dispersion.

Another embodiment is an SR product of PSE beadlets which further comprises an immediate release phase of PSE beadlets.

Another aspect of the present invention is a combination product which contains a ratio of immediate release beadlets to sustained release beadlets of both chlorpheneramine maleate and pseudoephedrine.

Another aspect of the present invention is a combination product which contains a ratio of immediate release beadlets to sustained release beadlets of chlorpheneramine maleate, pseudoephedrine, and phenylpropanolamine.

Another aspect of the present invention is directed towards a product comprising a sustained release (SR) phase of Dextromethorphan HBr (DXM) beadlets coated with about 0.5 to about 15% (weight gain) of a pseudolatex water swellable polymer dispersion.

Another aspect of the present invention is the SR product of DXM beadlets which further comprises an immediate release phase of Dextromethorphan (DXM) beadlets.

Another aspect of the present invention is the ratio of IR beadlets to SR beadlets of Dextromethorphan.

Another apsect of the present invention is immediate release phase beadlets of Dextromethorphan HBr, which beadlets may be contained in a hard or soft gelatin capsule or as a unit dose sachet.

Another aspect of the present invention is a combination product which contains a ratio of immediate release beadlets to sustained release beadlets of DXM in with chlorpheneramine maleate, pseudoephedrine, and/or phenylpropanolamine in varying ratios of each other.

Another aspect of the present invention relates to the use of micronized dextromethophan HBr for making IR and SR beadlets.

Yet another aspect of the present invention relates to novel process conditions for aqueous coating techniques which is:

An aqueous coating process for the manufacture of sustained release beadlets of a water soluble active agent coated with a water swellable polymer as the sustained releasing agent which process comprises

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a) applying to a drug loaded sphere a seal coat of a protective polymer;

b) applying to the sphere of step a) a coating of an aqueous water swellable polymeric dispersion; wherein the aqueous water swellable polymeric dispersion of step b) is a pseudolatex ethyl cellulose dispersion having a glass transition point of about 38 to 41 °C; and which process for applying said dispersion utilizes atmospheric conditions exhibiting a dew point of < 9 +/- 3 °C.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed towards utilization of a new dissolution "retarding" polymer, for commercial scale production, which may be employed to provide a slow and steady release of a drug substance from pellets over an extended time period, such as a 12 hour period. For simplicity of description, and for the manufacturing and pharmacokinetic modeling necessary to achieve the desired end product, the active ingredients are preferably loaded onto separate pellets.

The term "active ingredients" as used herein, is meant to include any pharmaceutically acceptable agent having medicinal properties, such as the over-the-counter medications phenylpropanolamine hydrochloride (PPA), pseudoephedrine hydrochloride (PSE), and other amines, chlorpheniramine maleate (CPM), and other antihistamines, diphenhydramine, dextromethorphan (DXM) and its salts, loratadine (Claritin®), descarboethoxyloratadine (DCL), fexofenadine (Allegra®), and cetirizine hydrochloride (Zyrtec®), guaifenesin, acetaminophen, aspirin, ascorbic acid, cimetidine, clemastine and its salts, codeine phosphate, dextroamphetamine and its salts, dexbromopheniramine and its salts, dimenhydrinate, docusate sodium, doxylamine succinate, ephedrine salts, non-steriodal inflammatory agents, such as ibuprofen and its salts, ketoprofen and its salts, naproxen, sodium naproxen, other salts, meclizine and it salts, nicotine and it salts, nizatidine, phenylephrine and its salts, pyrilamine and its salts, salicylamide, triprolidine and its salts, etc.

Water solubility of the active agent is defined by the United States Pharmacoepia. Therefore, active agents which meet the criteria of very soluble, freely soluble, soluble and sparingly soluble as defined therein are encompassed this invention.

For purposes herein the term "beadlets" and "pellets" are used interchangeably.

It is recognized that the more water soluble the active ingredient is the better the In-vitro/InVivo Correlation (IV/IVC) will be. IV/IVC is a form of pharmacokinetic modeling described further below which was conducted on pellets

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produced with the process described herein. It has subsequently been determined that use of this process provides for a highly predictable outcome.

The present invention is a novel use of advanced technology as applied to over-the-counter medications, although prescription medicaments may also be used. Primarily, this new technology includes the use of 1) a Wurster Fluid Bed processor or equivalent, to ensure a more precise application of the active to each pellet, 2) drug delivery by a diffusion mechanism which uses a specialized polymer to control the medicine release with greater reproducibility, 3) separate immediate release (IR)/sustained release (SR) beads for each medicine to allow for an immediate and sustained release of drug; and 4) a multi-head capsule filler to ensure that the proper mixture of medicines with the correct ratios of IR to SR pellets is achieved in each capsule.

This technology has not previously been used within the OTC arena, and in particular for large scale medicaments, such as cold preparations. In many instances, this technology is used whereby the final product does not produce drug delivery by a diffusion mechanism but instead by an erosion process, or a combination thereof. The parameters described herein enable the skilled artisan to produce a product in which the diffusion process is directly related to the thickness of the coating polymer. No additional talc, etc. is necessary to correct for the tackiness or other properties of the polymers used in the coating process.

There are several critical elements in the production process for the OTC medicaments that mirror the production processes used for several prescription drugs such as:

1) Encapsulating pellets in a two piece hard gelatin capsule;

2) Use of pellets coated with a special water swellable polymer (such as ethylcellulose or its equivalent) to control the medicament release mechanism, allowing for sustained release of the drug substance; and

3) Use of a Wurster Fluid bed processor or equivalent to apply the special polymer coating.

While Applicants are not privy to the manufacturing details of other products, a review of publicly available information suggests that many prescription products may use these critical technological elements including, Kadian (analgesic) manufactured by Faulding, Micro-K Extendcaps (Potassium replacement) manufactured by A.H. Robins, Dilatrate-SR (cardiac, vasodilator) manufactured by Schwarz Pharma, Theo-24 (a bronchodilator) manufactured by UCB Pharma. All of these products feature pellets encapsulated in a two piece hard gelatin capsule. Based on ingredient statements, it appears that water swellable polymers are used.

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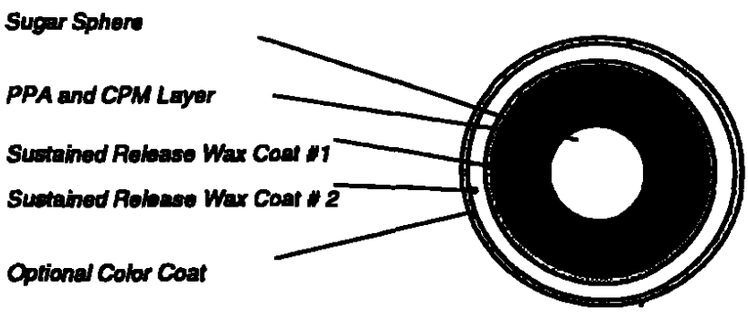
In turn, the application of this type of polymer typically requires a Wurster fluid bed processor or a unit of similar design. It is therefore highly likely that all three critical parameters are used in these three products.

This type of technology does not appear to have been used for any OTC medicines, based on a review of all products contained within the 1998 Physicians Desk Reference For Non-Prescription Drugs, for instance. An essential element of this technology is the use of sustained release pellets delivered within a two piece hard gelatin capsule. Within the 1998 PDR For Non Rx Drugs, there are 5 OTC, non-herbal capsule products that use a two piece hard gelatin capsule. They are: Basaljel (Wyeth-Ayerst); Benadryl Allergy (Warner-Lambert); Contac Capsules (SmithKline Beecham); Sleepinal (Thompson); and Teldrin (Hogil Pharmaceutical).

Of these products, Basaljel, Benadryl Allergy and Sleepinal are immediate release products and are conventional powder filled capsules. These products do not contain sustained release (SR) pellets, and therefore do fit within the use of this process for SR technology.

This leaves Contac Capsules and Teldrin as the only sustained release OTC medicine products in two piece hard gelatin capsules. The technology used for the "old" Contac Capsule employed organic solvents and waxes to achieve its sustained release effect. Teldrin, a sustained release pellet, uses traditional spansule technology, i.e. a pharmaceutical glaze, commonly known as Lacquer, to retard the drug release and provide the sustained release mechanism. Both wax and Lacquer layering is traditionally carried out in rotating pans using organic solvents. Thus, no OTC medicine product applies all the critical elements of the present invention.

A beadlet using the old wax technology process is shown below:



Thus, the present invention is directed towards production of a new formulation which is quite different from previous OTC formulations, such as Contac Capsules, due to major differences in the type of beads used (different IR/SR beads for each active ingredient), differences in coating techniques (the new

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capsules use the patented Wurster coating process and water swellable polymer versus the pan-sprayed wax/organic solvent coating of the previous capsule), and improved batch-to batch variability.

As noted above, the prior art capsules are/were manufactured using a wax/organic solvent coating technique which does not provide consistent release profiles between similar lots of pellets. This is due to the fact that wax is a natural product and subject to a high degree of variability between lots. The present process overcomes this difficulties by utilizing a water swellable polymer, preferably ethylcellulose. Use of an ethylcellulose polymer dispersion provides for a highly reproducible product, with low lot to lot variation.

A suitable aqueous ethyl cellulose latex dispersion for use herein is Surelease®, Colorcon, PA. Alternative ethyl cellulose dispersions are available from other suppliers.

The mechanism of release for the old Contac capsule was based upon the erosion of the wax matrix in the gastrointestinal (GI) tract. This type of release mechanism is difficult to mathematically model. The new formulation's release mechanism is based on diffusion and follows standard Fickian Diffusion. This allows for easy mathematical modeling of the release of the medicine in-vivo. As evidence of the greater control diffusion release has over erosion, in-vitro tests of the new formulation provide for reliable measurements of percent release at more regular intervals. This would not have been feasible with the older erosion mechanism as the release was not as reliable at every time point.

The pellet layering/coating process of present invention is carried out in fluid bed coater. The fluid bed suspends the pellets in a continuous stream of air that passes the beads through alternating stages of coating (layering) and drying. The process consists of spraying a predetermined amount of drug onto a sugar pellet followed by a protective polymer coat, which is termed the "seal coat". Alternatively, a spherionized pellet of the drug/active agent may be used instead of a sugar sphere loaded with drug. The spherionized pellet is also coated with a protective polymer. Later, the seal coated beads are coated with an aqueous polymeric dispersion (also termed as sustained release or functional coat) which regulates the drug release from the beads. Preferably, an aqueous ethyl cellulose latex dispersion is used as the functional, or sustained release, polymeric coat. Finally, a color coat is applied to achieve pharmaceutical elegance and consumer appeal. At this stage, beads are generally termed "sustained release" beads (SR beads). Although, for purposes herein SR beads need not include the "top coat" or "colour" coat to be referred to as SR beads.

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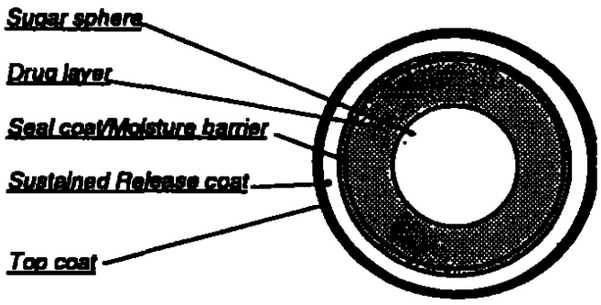
Depending upon the solubility of the active ingredient, a small amount of the functional coating may be added for purposes of stability and to insure that the "immediate release" of the agent corresponds to the generally accepted idea that IR release occurs within about a 45 minute time period and that the product consistently releases at this rate. Therefore,the term immediate release as used herein may also include a slightly delayed response so that the drug is fully released w/in the generally accepted parameters of an immediate release dosage form. For instance, PPA is highly soluble and hence the IR beadlets require a small amount of functional coating to produce a bioequivalent product to the art recognized IR tablets on the market. CPM performs similarly. However, in contrast both PSE and the DXM IR pellets do not require functional coating in the IR phase.

The type of sphere onto which the active ingredient is loaded is well with the skilled artisan's choice. Generally, the spheres are sugar spheres, such as sucrose, however microcrystalline cellulose, such as Avicel®, is also a suitable alternative. If the osmotic nature of the sphere is increased, there will be an increase in the diffusion rate of the active moiety as well. All of which parameters need to be taken into account with the thickness of the functional sustained release coating.

The protective polymer coating used as a "seal coat" is well recognized by the skilled artisan who would readily determine a suitable barrier coating agent. Preferred barrier coats for use herein with the pseudolatex ethyl cellulose dispersion coating is one which contains polyvinyl alcohol, such as Opadry AMB®, or hydroxypropylmethylcellullose (HPMC), hydroxypropylcellulose (HPC), acrylic polymers such as Carbopol, or an enteric coating which is water dispersible/soluble and pH sensitive, such as several of the Eudragit® coatings.

An SR bead is shown below.



To provide initial and rapid (immediate) availability of the drug, some drug layered and seal coated beads are coated with a substantially reduced functional (sustained release) coat and then color coated. These beads are termed "immediate

release" (IR) beads. For purposes herein IR beads need not include the "top coat" or "colour" coat to be referred to as IR beads. As necessary, one may use a predetermined composition of IR and SR beads to achieve the desired pharmacological effect. To do so, the predetermined amounts of each bead are filled into a two piece hard gelatin capsule using suitable, well and well known high speed, multi-head capsule filling machines. A soft gelatin capsule may also be used. The ratio of IR to SR beads in a mixture may be varied in order to obtain the desired blood levels and comply with appropriate regulatory requirements of any particular country.

Benefits of the instant process include use of water as a solvent/carrier, which is safe to humans and environmentally friendly. The process also uses ethylcellulose, not waxes (as used in the prior art) to provide the sustained release effects. Ethylcellulose modulates drug release in a highly consistent and predictable manner under various gastrointestinal/ biological and simulated conditions. This illustrates that drug release for the new technology is virtually the same across multiple conditions, unlike traditional wax coated pellets. Other benefits include no toxic emissions or aging time of the product, improved economic manufacturing conditions.

For purposes herein Opadry® AMB Pink, is a product produced by Colorcon, West Point, PA, having a composition of Polyvinyl alcohol, partially hydrolyzed (USP, JPS); Talc, Alumina Hydrate, titanium dioxide, carmine, lecithin, and xanthan gum.

For purposes herein Opadry® Pink, is a product produced by Colorcon, West Point, PA, having a composition of HPMC 2910/hypromellose 3cp, HPMC 2910/hypromellose 6cp, titanium dioxide, macrogol/PEG 400, and carmine.

For purposes herein Opadry® yellow, is a product produced by Colorcon, West Point, PA, having a composition of HPMC 2910/hypromellose 3cp, HPMC 2910/hypromellose 6cp, titanium dioxide, macrogol/PEG 400, iron oxide yellow, and polysorbate 80.

For purposes herein Surelease® clear, is an aqueous pseudolatex of ethylcellulose, produced by Colorcon, West Point, PA, having a composition of purified water, ethylcellulose, ammonium hydroxide, medium chain triglycerides, and oleic acid.

For purposes herein, AquaCoat® is a product produced by FMC Corporation, Philadelphia, PA. Both Aquacoat and Surelease are pseudolatex ethylcellulose dispersions.

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For purposes herein, Sugar spheres, NF are spherical particles used as a substrate onto which the drug or active agent is loaded. Sugar spheres, NF contain mostly sugar (62.5-91.5%), with the remainder consisting of starch. For purposes herein, Methocel E5, Premium (hydroxypropylmethyl cellulose, USP/NF) is a Dow chemical grade product for a hydroxypropyl substitution specification of 7-12% and a methoxyl substitution specification of 28-30%. These substitution specifications meet the requirements for hydroxypropyl-methylcellulose USP substitution #2910 (1). Where appropriate, Methocel E5, Premium, is used in the pellet formulations of the present invention with drug solution, to help the drug adhere to the sugar sphere surface and, used to "seal" the Drug Loaded Sugar Core (DLSC) pellets, after the drug has been applied.

It is recognized that the skilled artisan may chose to use other pharmacologically inactive spherical seed cores for use herein, and it is contemplated that all such spheres are within the context of this invention. One suitable alternative is a sphere composed primarily of microcrystalline cellulose.

For purposes of illustration of the process, a capsule containing 4 populations of pellets has been prepared and is described in the Examples below. Each pellet fraction is dosed separately and filling is accomplished by a high speed multi-head capsule filler, such as an MG2 Futura. Using the active ingredients, phenylpropanolamine hydrochloride (PPA) and chlorpheniramine maleate (CPM) the pellets are given the designations: CPM IR for chlorpheniramine immediate release; CPM SR for chlorpheniramine sustained release; PPA IR and PPA SR for phenylpropanolamine immediate and sustained release respectively. Similarly, pellets of IR PSE, SR PSE, IR DXM and SR DXM represent immediate release pseudoephedrine, sustained release pseudoephedrine, immediate release dextromethorphan and sustained release dextromethorphan respectively.

The fact that the process used herein is highly reproducible allows it to meet all global regulatory standards in terms of process validation and cGMP's. The process utilizes a one-polymer system to modulate drug release. This system has distinct advantages over the wax "retarded" systems developed in the 1950's as this process provides for only one drug per pellet, which makes designing in-vivo release profile for combination products more predictable and controllable than the previous two drugs per pellet.

Many different formulation prototypes were developed using different drug loading, seal coating and functional coating membranes. These formulations were analyzed for their drug content (assay), dissolution profiles, and stability at ambient and accelerated conditions.

Release from the beads coated with ethylcellulose polymer follows standard Fickian Diffusion and is highly predictable and is based on the following equation:

$$M_t/M_{inf}=kt^n$$

Where M_t/M_{inf} is the fraction of drug released at time t, k is the proportionality constant; n is the exponent characteristic of the mode of transport. In most of the cases, release from the spheres is proportional to the square root of time, i.e. n = 0.5.

During experiments it was observed that the thickness of functional coat (Surelease®, 25% w/w ethyl cellulose) controls the rate of drug release. To systematically investigate this issue, beads were coated with different amounts of Surelease® and studied for their drug release at ambient and accelerated conditions. In this exercise, the quantitative formula was kept constant for both PPA and CPM (as shown in Table 1 below), and only the Surelease® level was changed to study the effect of varying polymer levels.

For purposes herein "functional coat" and "sustained release coat" are unsed interchangeably.

It is recognized that the thickness of the seal coat, the thickness of the sustained release coat and the permeability of the sustained release coat will play a role in the diffusion profile of the active agent in the beadlet. Consequently, it is the process parameters as defined herein which allow the skilled artisan to achieve reproducibility of the product and stability of the product.

PPA Beads:

Drug Loading (PPA):	50% weight gain
Seal Coat (Opadry AMB white):	5% weight gain
Functional Coat (Surelease®):	3 to 24% w/w
Color Coat (Opadry AMB Pink):	2% weight gain

CPM Beads:

Drug Loading (CPM):	10% weight gain
Seal Coat (HPMC E-5):	2% weight gain
Functional Coat (Surelease®):	2 to 18% weight gain
Color Coat (Opadry Yellow):	2% weight gain

PSE Beads:

Drug Loading (PSE):	60% weight gain
Seal Coat (HPMC E-5):	2% weight gain

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Functional Coat (Surelease®):	6 to 14% weight gain
Color Coat (Opadry Pink):	2% weight gain

DXM Beads:

Drug Loading (PSE):	50% weight gain
Seal Coat (HPMC E-5):	2% weight gain
Functional Coat (Surelease®):	6 to 10% weight gain
Color Coat (Opadry Pink):	2% weight gain

Shown in Table 1 below are actual examples of % functional coat used in preparation of beadlets pursuant to the procedures shown in the working examples:

Table 1. The percent of Surelease® used to coat seal coated beads

	Surelease® Levels (weight gain)					
PPA	3 %	6%	9%	14%	18%	24%
CPM	2%	5%	6.5%	12%	16%	18%

Mean dissolution values for both PPA and CPM are shown in Figures 3 and 4, respectively. For both PPA and CPM, a systematic increase in polymer content (Surelease®) decreases the release rate of the drug. This is also applicable to PSE, and the DXM pellets of the present invention and is likely to be consistent for all the active agents listed herein.. It is obvious from the plot that if the polymer level in the formulation is known, in-vitro dissolution can be estimated with reasonable accuracy.

Based on these experiments it was determined that beads coated with 3 to 24%, preferably 9 to 18% of Surelease® for PPA and 2 to 18%, preferably 6 to 16% of Surelease® for CPM (more preferably 6.5 to 9%) show satisfactory stability up to six months under accelerated conditions.

These formulations were subjected to stability evaluation at room temperature and at accelerated conditions (40° C/75%RH). At room temperature, all beads showed good stability and release profiles compared to their initial release.

Alternative formulations were developed to evaluate the *in-vivo* release performance of the beads. Formulations containing beads with 9% Surelease® for PPA and 6.5% Surelease® for CPM were selected with the PPA beadlets containing 50 mg of PPA and the CPM beadlets containing 4 mg of CPM. It is recognized that the amount of active ingredient may vary, such as beadlets containing 75mg PPA

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and 8 mg CPM. It is also recognized that the amount of functional coat of Surelease may also vary. However, two preferred formulations are shown below:
Formula (1): PPA SR: 50% PPA loaded on a sphere/ 5% Opadry (seal coat) / 9% Surelease® (functional coat)/ 2% Opadry (top coat)
CPM SR: 10% CPM loaded on a sphere / 2% HPMC (seal coat) / 6.5% Surelease®(functional coat)/ 2% Opadry Yellow

Formula (2): PPA SR: 50% PPA loaded on a sphere/ 5% Opadry (seal coat) / 12% Surelease® (functional coat)/ 2% Opadry (top coat)
CPM SR: 10% CPM loaded on a sphere / 2% HPMC (seal coat) / 8% Surelease®(functional coat)/ 2% Opadry Yellow

Another aspect of the invention is a preferred formulation of IR beads (alone) or in combination for and IR phase of an admixture.
PPA IR: 50% PPA loaded on a sphere/ 5% Opadry (seal coat) / 4% Surelease® (functional coat)/ 2% Opadry (top coat)
CPM IR: 10% CPM loaded on a sphere / 2% HPMC (seal coat) / 3% Surelease®(functional coat)/ 2% Opadry Yellow

Another aspect of the invention is a combination of 3 or more SR beadlets in the extentended or sustained release phase/portion of the admixture, such as the following preferred formulation:
PPA SR: 50% PPA loaded on a sphere/ 5% Opadry (seal coat) / 18% Surelease® (functional coat)/ 2% Opadry (top coat)
PPA SR: 50% PPA loaded on a sphere/ 5% Opadry (seal coat) / 11 or 12% Surelease® (functional coat)/ 2% Opadry (top coat)
CPM SR: 10% CPM loaded on a sphere / 2% HPMC (seal coat) / 8% Surelease®(functional coat)/ 2% Opadry Yellow

Suitably, the range of PPA in an IR:SR formulation is from 1:1 to about 1:6. One embodiment is a ratio of 0.3 :0.7. The range of CPM in an IR:SR formulation is about 1:3, preferably about 1:1. Given the particular type of drug a ratio of IR:SR will generally be from about 1:6.

Also contemplated herein are pediatric dosage forms with pellets produced in accordance with the teachings herein. A suitable dosage amount for pediatric use for IR to SR for PPA is 6.25 to 12.5 mg IR PPA : 37.5 to 44 SR PPA; and a suitable

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dosage amount for CPM is IR to SR for CPM is 0.5 to 3.5 mg IR CPM : 2 to 4mg SR CPM. Dextromethorphan is about 2.5 mg IR L 2.5mg SR.

The PPA SR and CPM SR beads above were each encapsulated into a hard gelatin capsule. In order to evaluate the performance of this extended release technology, no immediate release beads were added to the capsules. The capsules were analyzed for drug content and in-vitro dissolution profile. The in-vitro dissolution profiles are shown in Figures 5 and 6.

Dissolution studies of the above noted formulation were conducted in tenth normal hydrochloric acid (0.1N HCl) and in phosphate buffer of pH 7.4. Identical profiles obtained at both conditions suggest that the release is independent of the pH of the dissolution media (Figures 7 and 8).

Immediate release beads (IR) beads of both PPA and CPM have been produced as shown in the working Examples (dissolution data for the IR pellets is shown in Figures 3 and 4).

Therefore, another aspect of the present invention is the immediate release and coated (IR) form of the active ingredients, such as CPM, PPA, PSE and DXM as produced by the process herein, as well as the sustained releases forms of CPM, PPA, PSE and DXM produced by the process herein.

The IR pellets require a seal coat as these drug loaded and sealed pellets will pick up moisture, have decreased stability, and are deliquescent, i.e. they pick up moisture and dissolve in their own liquid. The moisture they pick up comes from the environment. The gelatin capsule (hard or soft) contain 12-18% moisture and the active agents pick up moisture from the gelatin capsule. Consequently, the capsule becomes brittle over time, deforms, pinholes form in the capsule shell, the active agent has decreased stability due to these changes, and the dissolution profile of the finished product is altered. Therefore, it is important to coat the drug loaded pellets with a layer of a suitable water swellable polymeric dispersion (seal coat). This aspect will be discussed in greater detail below.

Another aspect of the present invention is the blending of the IR and SR beads of both PPA and CPM in a dosage form, as well as the blending of IR and SR beads of PSE and CPM. Suitably, the dosage form is a gelatin capsule, preferably a hard gelatin capsule. Each capsule may contain IR PPA and SR PPA, or IR CPM and SR CPM in any variation of ratio or coating thickness. Alternatively all 4 populations may be blended together: IR PPA, SR PPA, IR CPM and SR CPM in any suitable ratio, and/or coating thickness. While this is essentially a biphasic system for each active moiety, it is recognized that multi-phasic systems can be prepared which have not only immediate release of an active component if desired,

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but release of the active moiety over a number of time points. In a similar manner each capsule may contain IR PSE and SR PSE, or IR CPM and SR CPM in any variation of ratio or coating thickness. Alternatively all 4 populations may be blended together: IR PSE, SR PSE, IR CPM and SR CPM in any suitable ratio, and/or coating thickness. In yet another emodiment, each capsule may contain IR DXM and SR DXM with IR PSE and SR PSE, IR CPM and SR CPM, or IR PPA and SR PPA in any suitable ratio, and/or coating thickness.

For purposes herein a preferred ratio for a 12 hour time release with a two component IR/SR beadlet for each active moiety is:

IR PPA : SR PPA 1:5, preferably 1:2 . or a 0.3:.7 ratio

IR CPM : SR CPM 1:4, preferably 1:1.

In-vitro/InVivo Correlation (IV/IVC) form of pharmacokinetic modeling, has been conducted on these pellets and has determined that use of this process provides for a highly predictable outcome.

The purpose of In vitro/In vivo correlation is to model in vivo response as a function of the in vitro data and use as a predictive tool in development

In vivo response = f (In vitro data)

The *in vivo* response is dependent upon the concentration of the drug in plasma, whereas *in vitro* data is determined using a USP dissolution test for the particular drug in question.

To establish the in vitro-in vivo correlation, in vivo blood concentration data upon the dosing of the drug is converted into cumulative fraction absorbed (Fa) using the Wagner-Nelson method for studying absorption pharmacokinetics. In vitro dissolution studies were carried out at varying pH conditions. When in vivo fraction absorbed is compared with the in vitro dissolution, for instance in 0.1% SLS in water and 0.1N HCl, an acceptable correction level may be observed. For the examples herein of CPM and PPA, and acceptable correlation was had.

Results of these biostudies provide a good correlation between in vitro drug release and in vivo drug absorption. Thus, the established IV/IVC may then be used to determine the desired in vitro profile that would match the observed in vivo absorption profile of a predetermined drug. To match the profile of that drug, *in vivo*, it is required that the dose for the active agents be a combination of immediate release and sustained release components. The IV/IVC is also used to generate an array of in vitro profiles using a predetermined type of IR and SR beads (in terms of polymer coating) and different amounts of coating on the beadlets as well as the ratio of IR and SR components.

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Using this system it was found that comparing the new process technology of the examples herein to the old wax coated product of Contac that biologically, overall equivalency was not achieved.

Biologically, the formulations of PPA SR and CPM SR have AUC's, Cmax and Tmax, which are the same as (or similar to) the immediate release. In other words, a 75 mg dose of PPA is biologically equivalent to three 25mg immediate release PPA doses taken every 4 hours.

The U.S. bioequivalence criteria is that the 90% confidence interval for the ratio of the means of the AUC_{0-12} and C_{max} should lie completely within the range 0.80-1.25 for log transformed data. Canada has the same criterion as the U.S. for AUC_{0-12} but Canadian guidelines require only that the ratio of means for C_{max} lie within the range 0.80-1.25 (not the confidence interval of the ratio of the means).

Therefore, it is contemplated that the scope of the invention includes the full breadth of bioequivelence of the data presented in all the figures herein and not be solely limited to acutal ratio of the means.

As demonstrated herein in the accompanying figures:

Figure 1 is a demonstration of traditional wax coated spansule technology with stimulated food effects, with Contac 12 hour. The simulated stomach dissolution assay is performed in USP 1 apparatus and in 0.1N HCl media. The simulated food effect assay is the same as above but includes anionic surfactant to simulate emulsifying aspects of gastric juices. The simulated food effects illustrate high variability in the release of the active agents under fed conditions.

Figure 2 is a demonstration of aqueous coated spansules of the present invention. The active agent is PPA 75/8 formulation. The simulated stomach assay is shown by the 0.1N HCl line, the simulated intestine assay performed in a USP 1 apparatus, with phosphate buffer of pH 7.4 is shown as pH 7.4 line. The simulated food effect is shown as the SLS 0.1% line. The SGF line is simulated gastric fluid, USP, and the Simulated Intestinal USP assay is shown as the SIF line. This graph illustrates minimal variability under food effects, in stomach and in intestinal fluids.

In Figure 11, the Contac 12-Hour Fasted formula is a 1:1 ratio of IR:SR of CPM, or 4 mg IR:4mg SR. The Comparitor product was Chlortrimeton 4mg tablets, given at time 0 and 6 hours. The figure provides AUC, C_{max} and t_{max} parameters:

For the parameter $AUC_{0-\infty}$ the comparison 75/8 formulation vs the IR Comparitor is bioequivalent (CI: 0.99 – 1.08).

For the parameter AUC_{0-t} the comparison 75/8 vs Comparitor is bioequivalent (CI: 0.98 – 1.08).

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For the parameter C_{max} the comparison 75/8 vs Comparitor is bioequivalent (CI: 0.93 – 1.04).

For Contac 12-Hour® Sustained Release Capsules, the comparison 75/8 vs 75/8, (fed vs fasted), the parameters, $AUC_{0-\infty}$, AUC_{0-t} and C_{max} are bioequivalent.

In Figure 12, the Contac 12-Hour Fasted is a 1:1 ratio of IR:SR of CPM, or 4 mg IR:4mg SR. The Comparitor product was a 25 mg PPA solution, given at time 0 4, and 8 hours. The figure provides AUC, C_{max} and t_{max} parameters:

For the parameter $AUC_{0-\infty}$ the comparison 75/8 vs Comp is bioequivalent (CI: 0.98 – 1.06).

For the parameter AUC_{0-t} the comparison 75/8 vs Comp is bioequivalent (CI: 0.95 – 1.03).

For the parameter C_{max} the comparison 75/8 vs Comp is bioequivalent (CI: 0.85 – 0.94).

For Contac 12-Hour® Sustained Release Capsules, the comparison 75/8 vs 75/8, (fed vs fasted), the parameters, $AUC_{0-\infty}$, AUC_{0-t} and C_{max} are bioequivalent.

While not shown herein, in a multidosing study using the 75/8 formulation of PPA (1:2 or 25mg IR PPA: 50 mg SR PPA), and CPM (1:1, 4mg IR:4mg SR), and as a Comparitor product, 4mg Chlortrimeton tablets, 1 tablet every 6 hours, and for the IR PPA, 25mg tablets of Propagest®, given every 4 hours, for six days.

For the parameter Area Under the Curve (AUC) the present 75/8 formulation of PPA has been found bioequivalent as compared to immediate release (log transformed 90% CI 1.00 – 1.04).

For the parameter C_{max} the present formulation of PPA is bioequivalent compared to immediate release (log transformed 90% CI 1.01 – 1.08).

For the parameter C_{min} the present formulation of PPA is significantly smaller compared to immediate release (log transformed 95% CI 0.79-0.87).

For the parameter AUC the present formulation of CPM is bioequivalent compared to immediate release (log transformed 90% CI 0.94 – 1.00).

For the parameter C_{max} the present formulation of CPM is bioequivalent compared to immediate release (log transformed 90% CI 0.96 – 1.03).

For the parameter C_{min} the present formulation of CPM is significantly smaller compared to immediate release (log transformed 95% CI 0.87-0.98).

Figure 13 is a demonstration of aqueous coated spansules of the present invention. The active agent is CPM 75/8 formulation. The simulated stomach assay is shown by the 0.1N HCl line, the simulated intestine assay performed in a USP 1 apparatus, with phosphate buffer of pH 7.4 is shown as pH 7.4 line. The simulated food effect is shown as the SLS 0.1% line. The SGF line is simulated gastric fluid,

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USP, and the Simulated Intestinal USP assay is shown as the SIF line. This graph illustrates minimal variability under food effects, in stomach and in intestinal fluids.

As noted above, the present invention is also directed to a pseudoephedrine HCl (PSE) immediate and sustained release capsule formulations developed by the process conditions and parameters as shown and described herein.

The *in-vitro* drug release profile of the new PSE pellet formulation is not affected by changes in the dissolution media pH, the presence of an anionic surfactant in the media or by the ionic strength of the media.

Similar to the manufacture of CPM and PPA, the manufacture of the PSE pellets are carried-out by first loading the PSE onto a sphere, preferably a sugar sphere, by spraying an aqueous solution of the drug with a binder. The drug-loaded pellets were then "sealed" by spraying on a layer of hydroxypropylmethylcellulose (HPMC) to which a functional coat (if desired for SR) is applied. Finally, a water-soluble topcoat is applied as an aqueous suspension to provide protection and color to both the IR and SR pellets.

As with CPM and PPA, critical processing parameters were found to include pellet bed temperatures while pellet spraying, solution/suspension spray rates and, inlet air dew point temperatures during ethylcellulose.

In a pharmacokinetic comparison, the results showed that three formulations, a "fast" formula, a "moderate" or "target" formula, and a "slow" releasing formula were bioequivalent to the Comparitor products, a Sudafed 12 Hour 120 mg caplet and to Sudafed immediate release tablets, with respect to $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max}.

The moderate releasing capsule formulation (a 10% SR coat) overall for subjects averaged plasma drug levels vs. time profile was the most similar to the Sudafed 12 Hour caplet averaged plasma vs. time profile

Again, similar to CPM and PPA, an in vitro-in vivo correlation (IV/IVC) was established for the three pseudoephedrine HCl formulations (fast, target and, slow releasing) using the Wagner-Nelson method.

(+)-Pseudoephedrine HCl (d-pseudoephedrine HCl);(1S, 2S)-2-Methylamino-1-phenyl-1-propanol hydrochloride (CAS no. [345-78-8]), has a molecular formula of $C_{10}H_{15}NO{\cdot}HCl$ and a molecular weight of 201.69. Ephedrine and pseudoephedrine are diesteromers, the former having the erythro and the latter the threo configuration.

Pseudoephedrine HCl is a fine, white to off-white, practically odorless, crystalline or powder material. It melts between 182° and 186° C and is very freely

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soluble in water, freely soluble in ethanol and, soluble in chloroform. It has an optical rotation $[\alpha]D^{20}$ + 62° and a pKa of 9.22 (1,2,3).

Pseudoephedrine HCl can be found in many "over-the counter" as well as prescription cold, flu and hay fever preparations. The elimination half life of d-pseudoephedrine HCl is 5-8 hours and a number of immediate release formulations on the market are commercially available with a dosing recommendation of 60 mg every six hours. Commercial sustained release preparations of pseudoephedrine HCl typically have a recommended dosing regimen of 120 mg of pseudoephedrine HCl every 12 hours.

Therefore, a preferred formulation of this invention is a formulation designed to release 120 mg of (+)-pseudoephedrine hydrochloride from, preferably, a hard gelatin capsule, and preferably over a 12 hour time course.

An improvement seen with the new pseudoephedrine hydrochloride 120 mg formulation versus currently available formulations is the use of a single population of pellets. Eliminating multiple pellet populations greatly reduces processing time and serves to simplify the drug product manufacture. Using a single population of SR pellets also increases batch to batch drug release profile consistency due to the use of a single lot of pellets.

As discussed previously, the in-vitro drug dissolution profiles of the formulations of this invention, using baskets (USP apparatus II) can be modulated using different levels of Surelease. Increasing the level of Surelease® gives slower drug release rates. The drug release rate can also be modulated by changing the drug load, however, this approach is not preferred because drug release rate is far less sensitive to changes in the level of drug loading than to changes in the level of the Surelease barrier coat.

Suitably, the drug loading onto the sugar spheres for PSE may range from 6% to 90% weight gain. Preferably, 40 to 75% and more preferably 50 to 70, and most preferably 55 to 66%.

Seal coating for PSE can vary somewhat from about 0% to about 20 %. Preferably, the seal coat is less than 10%, more preferably less than 5%, and most preferably about 2%.

Functional coating of the pseudolatex water swellable polymer dispersion for PSE may range from about 3 to 20%, preferably 6 to 14 % and more preferably about 10 to 12 % w/w.

Figure 14 demonstrate the in-vitro dissolution profiles of different Pseudoephedrine HCl 120 mg SR pellet capsule formulations coated with 6%, 8%, 10%, 11% and 14% Surelease® levels. Also shown on the plot is the dissolution of

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the Comparitor product. Sudafed 12 Hour Caplets. which were purchased at a local pharmacy.

The dissolution profile data shows that increasing the Surelease® level results in decreasing drug release rates. The dissolution profile for the 8% SR formulation is between the 6% and 10% profiles. Likewise, the profile for the 10% formulation lies between the profiles for the 8% and the 11% formulations. Finally, the 11% formula lies between the 10% and 14% formulations. The Sudafed® 12 Hour profile most closely matches that of the 10% SR.

Changing the dissolution media on the release rate of, for instance, a 12% Surelease pellet formulation of PSE and for Sudafed 12 Hour (which also delivers 120mg of PSE) demonstrated that dissolution of PSE from either formulation was not affected by changes in pH or buffer content. See Figure 15, for effect of media on the dissolution rates.

Consequently, PSE pellets are suitably produced herein with a % functional coat of Surelease for a SR bead of 6% to 14% SR. The 6% SR is considered a "fast" releasing formulation, whereas the 14% are considered a "slow" releasing formulation. A "moderate" releasing formulation would be considered a 10 to 12% SR formulation. The in-vitro release rate of the 10% SR formula released drug approximately 25% slower and 25% faster than the 6% and 14% SR formulations, respectively.

It is recognized that combinations of sustained release to immediate release pellets of PSE may be used herein. Suitable weight ratio of immediate release PSE to sustained release PSE is at its broadest useage, 0.1 : 1 to 1: 0.1, with approximately 8:1 to about 1:1 being prefered. In terms of mg dosage amounts this would result in a weight ratio dose of 15mg immediate to 105 mg SR, to a 60mg IR : 60mg SR dose.

Figure 16 will demonstrate the *in vivo* release rates of the fast (6% SR), moderate (10% SR) and slow releasing (14% SR) formulations of the present invention. Additionally this figure will demonstrate the Sudafed 12 Hour caplets and the Sudafed Immediate Release 2 x 30 mg tablets (60mg dosed at 6 hours apart).

The linear plot of plasma concentration vs. time shows that of the three PSE 120 mg formulations, the fast releasing (6% SR coat) formulation gave the greatest C_{max}, followed by the 10% SR coat formulation, followed by the slow 14% SR coat formulation with the lowest C_{max}. The 10% SR coat formulation profile closely matched that of the Sudafed 12 Hour Caplet.

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This figure also demonstrates that each of the three test formulations (fast, target and slow releasing) were bioequivalent to Sudafed 12 Hour Caplets with respect to $AUC_{(0-t)}$, $AUC_{(0\text{-infinity})}$, and C_{max}.

Each of the three SR test formulations (slow, target and fast releasing), were bioequivalent to immediate release Sudafed with respect to $AUC_{(0-t)}$, $AUC_{(0\text{-inf})}$, and C_{max}.

The t_{max} was significantly ($p<0.05$) shorter for the "fast" formulation compared with Sudafed® 12 Hour Caplets. There was no significant difference between the "slow" and the "moderate" formulations.

The t_{max} for each of the three test formulations was significantly ($p<0.0001$) delayed compared with the first dose of immediate release Sudafed®.

In Figure 16, the Comparitor products are Sudafed® 12-Hour 120mg SR caplet and a Sudafed ® immediate release (IR) tablet 2x 30mg. The three SR PSE formula are fast, target and slow as defined herein. The figure provides AUC, C_{max} and t_{max} parameters:

For the parameter AUC_{0-t} (ng.h/ml) the comparison slow PSE formulation vs the SR Comparitor is bioequivalent (CI: 0.91 – 1.01), with mean of 0.95

For the parameter AUC_{0-t} the comparison target PSE formulation vs the SR Comparitor is bioequivalent (CI: 0.92 – 1.02), with mean of 0.97.

For the parameter AUC_{0-t} the comparison fast PSE formulation vs the SR Comparitor is bioequivalent (CI: 0.95 – 1.05), with mean of 1.0.

For the parameter AUC_{0-t} (ng.h/ml) the comparison slow PSE formulation vs the IR Comparitor is bioequivalent (CI: 0.93 – 1.03), with mean of 0.98.

For the parameter AUC_{0-t} the comparison target PSE formulation vs the IR Comparitor is bioequivalent (CI: 0.95 – 1.05), with mean of 0.99.

For the parameter AUC_{0-t} the comparison fast PSE formulation vs the IR Comparitor is bioequivalent (CI: 0.98 – 1.08), with mean of 1.03.

For the parameter $AUC_{0-\infty}$ (ng.h/ml) the comparison slow PSE formulation vs the SR Comparitor is bioequivalent (CI: 0.93 – 1.03), with mean of 0.98.

For the parameter $AUC_{0-\infty}$ the comparison target PSE formulation vs the SR Comparitor is bioequivalent (CI: 0.92 – 1.03), with mean of 0.98.

For the parameter $AUC_{0-\infty}$ the comparison fast PSE formulation vs the SR Comparitor is bioequivalent (CI: 0.95 – 1.06), with mean of 1.00.

For the parameter $AUC_{0-\infty}$ (ng.h/ml) the comparison slow PSE formulation vs the IR Comparitor is bioequivalent (CI: 0.96 – 1.07), with mean of 1.02.

For the parameter $AUC_{0-\infty}$ the comparison target PSE formulation vs the IR Comparitor is bioequivalent (CI: 0.96 – 1.06), with mean of 1.01.

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For the parameter $AUC_{0-\infty}$ the comparison fast PSE formulation vs the IR Comparitor is bioequivalent (CI: 0.98 – 1.08), with mean of 1.03.

For the parameter C_{max} (ng./ml) the comparison slow PSE formulation vs the SR Comparitor is bioequivalent (CI: 0.843 – .93), with mean of 0.88.

For the parameter C_{max} the comparison target PSE formulation vs the SR Comparitor is bioequivalent (CI: 0.97 – 1.08), with mean of 1.02.

For the parameter C_{max} the comparison fast PSE formulation vs the SR Comparitor is bioequivalent (CI: 1.11 – 1.23), with mean of 1.17

For the parameter C_{max} (ng/ml) the comparison slow PSE formulation vs the IR Comparitor is bioequivalent (CI: 0.82 –.91), with mean of 0.87.

For the parameter C_{max} the comparison target PSE formulation vs the IR Comparitor is bioequivalent (CI: 0.95 – 1.05), with mean of 1.0.

For the parameter C_{max} the comparison fast PSE formulation vs the IR Comparitor is bioequivalent (CI: 1.09 – 1.21), with mean of 1.15.

The establishment of an *in vitro-in vivo* correlation for PSE was similar to that of CPM and PPA, and in this instance was done by estimating the time course of the fraction of dose absorbed and comparing the transformed data to an *in vitro* time course of dissolution of the fraction of dose release of the same = formulation. The Wagner-Nelson method, described previously, was used to estimate the fraction of dose absorbed time course *in vivo*. Averaged subject plasma vs. time data were used for each Clock formulation at each of the nineteen time points and the Wagner-Nelson method was used to estimate fraction of dose absorbed (FA).

PSE exhibits a first order elimination rate constant and along with the blood plasma concentrations and time intervals, were used in the Wagner-Nelson method calculated estimates of the time course of fraction of dose absorbed. Overall subject averages of plasma blood levels vs. time were used to estimate the fraction of dose absorbed when using the Wagner-Nelson calculation.

In order to obtain the best *in vitro-in vivo* correlation, the PSE 120 mg SR formulations were subjected to different *in vitro* dissolution conditions. It was found that *in-vitro* dissolution vs. time profiles of the PSE SR formulations were not significantly affected by the following: changing dissolution media pH, changes in ionic strength, using simulated gastric fluid, changing basket speeds or, by the addition of sodium dodecyl sulfate in the media. The final *in vitro* condition selected, to achieve the IV/IVC, was 900 ml of 0.1 N HCl as the dissolution media, using USP Apparatus I (baskets) at 100 RPM. These data provided that basis for linear correlation coefficients for each of the three formulations.

Another aspect of the present invention relates to the manufacture of beadlets of Dextromethorphan HBr (DXM) produced by the processes disclosed herein, and to the pellets themselves. The beadlets may be immediate release or sustained release.

As previously noted various admixtures of (DXM) are contemplated with other suitable cough/cold preparations such as the CPM, PPA, and PSE beadlets produced herein (in varying strengths, and amounts).

The solubility of Dextromethorphan HBr in water was found to be 2g/l (%w/v). The solids concentration of the drug layering solutions in the CPM, PPA, and PSE products herein were found to be about ~20%w/v. To use a solution for drug layering the Dextromethorphan would require a much more dilute solution that than the other products. The process would take far too long to be commercially feasible. Attempts were made to improve the solubility of the Dextromethorphan HBr by heating the drug layering suspension up to 60°C, adjusting the pH of the solution between 2 and 8 and adding suitable solubilizing agents (Tween 80 and Sodium Lauryl Sulfate). None of these changes to the drug layering preparation improved the solubility of the drug to a degree as to make spraying from a solution feasible.

Because of the solubility issue, drug layering proceeded via a suspension coating process. While a number of different process conditions may be utilized a preferred method is to add the drug and suspended it using a lightning type mixer and apply it directly to the sugar spheres. Initially, the Dextromethorphan HBr was added in the form of a powder. The particle size distribution of this powder can be seen in Figure 17. The process was conducted on the GPCG-1 with a Wurster insert. This process gave poor yields (70% Max). The poor yields were attributed to the relatively large particle size of the drug in comparison to the starting sphere. The drug-layered spheres produced were very rough with large drug particles sticking out from the surface of the pellet. The drug was then micronized using a jet mill to obtain a pulverized drug powder that had a particle size distribution as shown in Figure 18. Figure 18 will demonstrate that greater than 90% of the particles are smaller than 5 microns. The micronized drug was then added to the drug suspension and was sprayed with constant mixing. The process was performed on the GPCG 5 with a 9" Wurster HS insert. This process improved yields into the upper 90%'s. The process with the micronized drug also gave much smoother pellets than the powder process.

Therefore, another aspect of the present invention is the use of micronized DXM for production of a beadlet produced using an aqueous coated processes as

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claimed herein. Suitable. the DXM particles are less than 50 microns. preferably less than 25, more preferably less than 10, and most preferably less than 5 microns in size. This invention also provides for the micronized DXM particles themselves having a particle size between about 0.1-50 microns.

Process parameters typically are to keep the pellet to suspension particulate to a ratio of 20:1.

30-35 mesh sugar spheres were utilized for the DXM beadlets with a drug load chosen to be ~50%. However, a drug load could range from 5 to about 90%, preferably 30 to 70, and more preferably 40 to 60%. To adhere the drug to the sugar sphere, hydroxypropylmethyl cellulose (HPMC) was chosen as a suitable binder. A range of drug to binder ratios may be used for this step in the drug layering suspension. They range from 10:0.8, 10:1.0, 10:1.2, 10:1.5, 10:1.8 to 10:2.1. A ratio of 10:1.2 provides for the smoothest, hardest pellets and good yields while minimizing the use of HPMC. All the other ratios with higher levels of HPMC also produce high quality pellets.

For purposes herein (for any active agent), alternative binders may be used, such as but not limited to PVP, HPC, CMC, gum acacia, xanthan, corn syrup, sorbitol, maltitol, or polyvinyl alcohol.

The amount of DXM solids in the drug layering suspension may then be optimized, from about 1 to about 40% being suitable. Preferably, from about 10 to about 30, more preferably about 15 to 25%, with 19 % (w/w) as most prefered. Suspensions with greater solids contents (as much as 30%) on became quite viscous and difficult to spray and do not decrease the batch processing time.

Another aspect of the present invention is directed towards a product comprising a sustained release (SR) phase of Dextromethorphan (DXM) beadlets coated with about 0.5 to about 15% (weight gain) of a pseudolatex water swellable polymer dispersion. Preferably, from 3 to 10%, more preferably 4 to 7% and most preferably about 5% weight gain of polymer dispersion.

Another aspect of the present invention is DXM pellets intended for use as an immediate release phase. Dextromethorphan is commonly used in amounts for immediate release of about 5 to 30mg/dose and in a sustained release about of about 10 to 60mg/dose. Suitably, the sustained release is over a 12 hour period, although less (8 hours) or more (16 hours) may also be obtained using the process conditions herein. Therefore, another aspect of the present invention is micronized DXM/per dosage form containing from about 5 to 60mg/dose, be for IR or SR use.

Another aspect of the present invention is the ratio of IR beadlets to SR beadlets of Dextromethorphan. Suitable ratios of IR:SR pellets of DXM are 90:10 to 10:90, 70:30 to 30:70, 60:40 to 40:60, and 50:50 (or 1:1).

Combinations of DXM beadlets with other cough/cold products is also recognized as another aspect of the present invention. Suitable combinations are use with decongestants such as PSE or PPA, and also in combination with an antihistamine such CPM, BPM, or the non-sedating antihistamines. Suitable combinations are PPA (50 to 75mg) /CPM (4 to 12mg) /DXM (15 to 30mg) in dosages of 50mg/4mg/15mg; or a 50mg/4mg/30mg dosage form. For a larger sustained release formulation, a 75mg/8mg/60mg dosage would be suitable. For PSE combinations suitable dosage amounts are PSE (60 to 120mg)/DXM (15 to 30mg)/CPM (4 to 12mg).

It is also contemplated to combine DXM with an NSAID, such as the OTC or Rx available ibuprofen, ketoprofen or naproxen sodium. Also suitable for use are the newer COX-1 or COX-2 active agents, such as Vioxx, or Celebrex. Suitable amounts of ibuprofen are 200 to 1200mg ibuprofen (12 hour) with 15 to 30mg DXM.

It is also recognized that various pediatric dosage forms of the above active agents may be formulated herein, such as a 2.5 mg IR DXM with 2.5 mg SR DXM dosage.

The level of a HPMC seal coat for DXM is preferably between 1 and 3%, most preferably about 2%.

Similar to the other products herein, for the drug layered and sealed pellets of DXM ethylcellulose is the preferred polymer to control the release rate. The target release is bioequivalant to a single active, 15 mg Dextromethorphan HBr immediate release cough syrup dosed at 6 hour intervals. The level of ethylcellulose was evaluated at 0, 5, 7, and 9% and the release profiles were determined in vitro. The three formulations with 0, 5 and 7% SR were chosen as formulations to be dosed in a PK study to obtain blood level data. The in-vitro dissolution profiles can be seen in Figure 19.

Another aspect of the present invention is the AUC, C*max*, and t_{max} of the IR and 5% and 7% SR pellets of DXM as demonstrated in Figures 20 to 22 for dextromethorphan, free dextromethorphan and total dextromethorphanThe Comparitor product is the IR liquid, Robitussin Dry Cough Syrup. 10mg of Robitussin cough syup is dosed at 0 hours and 6hours, and each 10ml contains 15mg dextromethorphan HBr.

The Mean C_{max} Ratio and 90% Confidence Intervals for the formulations demonstrated in Figure 20 are shown below in Table 1.

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Table 1

Variable	Mean Ratio	Lower 90% CI	Upper 90% CI
IR DXM v Robitussin	1.5188	0.5941	3.8826
5% SR DXM v Robitussin	0.5449	0.2113	1.4047
7% SR DXM v Robitussin	0.1103	0.0429	0.2831

The Mean AUC_{0-t} Ratio and 90% Confidence for the formulations demonstrated in Figure 20 are shown below in Table 2.

Table 2:

Variable	Mean Ratio	Lower 90% CI	Upper 90% CI
IR DXM v Robitussin	0.9728	0.3717	2.5460
5% SR DXM v Robitussin	0.3826	0.1449	1.0100
7% SR DXM v Robitussin	0.0385	0.0146	0.1011

The Mean C_{max} Ratio and 90% Confidence Intervals for the formulations demonstrated in Figure 21 for Free Dextromethorphan are shown below in Table 3.

Table 3

Variable	Mean Ratio	Lower 90% CI	Upper 90% CI
IR DXM v Robitussin	1.5689	1.2399	1.9851
5% SR DXM v Robitussin	0.6711	0.5292	0.8509
7% SR DXM v Robitussin	0.2470	0.1940	0.3145

The Mean AUC_{0-t} Ratio and 90% Confidence Intervals for the formulations demonstrated in Figure 21 for Free Dextromethorphan are shown below in Table 4.

Table 4

Variable	Mean Ratio	Lower 90% CI	Upper 90% CI
IR DXM v Robitussin	1.0266	0.7199	1.4640
5% SR DXM v Robitussin	0.6891	0.4817	0.9859
7% SR DXM v Robitussin	0.1570	0.1090	0.2260

The Mean C_{max} Ratio and 90% Confidence Intervals for the formulations demonstrated in Figure 22 for total dextomethorphan are shown below in Table 5.

Table 5

Variable	Mean Ratio	Lower 90% CI	Upper 90% CI
IR DXM v Robitussin	1.7549	1.4842	2.0760
5% SR DXM v Robitussin	0.7484	0.6320	0.8862
7% SR DXM v Robitussin	0.2840	0.2400	0.3361

The Mean AUC_{0-t} Ratio and 90% Confidence Intervals for the formulations demonstrated in Figure 22 for total dextomethorphan are shown below in Table 6.

Table 6

Variable	Mean Ratio	Lower 90% CI	Upper 90% CI
IR DXM v Robitussin	1.0572	0.9371	1.1926
5% SR DXM v Robitussin	0.8942	0.7918	1.0099
7% SR DXM v Robitussin	0.5260	0.4660	0.5937

The Median T_{max} Difference and 95% Confidence Intervals for the formulations demonstrated in Figure 22 for total dextomethorphan are shown below in Table 7.

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Table 7

Variable	Median	Lower 95% CI	Upper 95% CI	p value
IR DXM v Robitussin	5.500	3.983	5.999	0.0018
5% SR DXM v Robitussin	2.517	0.984	3.000	0.0172
7% SR DXM v Robitussin	1.500	-0.016	2.501	0.0599

A positive value for median difference indicates that the test product has a faster T_{max} than the reference product.

Similar to the other products herein, a top coat is applied to the beadlets containing a coating of Surelease® in the final product. The ethylcellulose coating needs to be "cured" after it is applied to the pellets. This curing ensures that the coat has polymerized completely and is uniform. In order to cure the product the temperature must be raised to about 60°C and held there for about 1 hour. At this temperature, the ethylcellulose (in Surelease®) is above its' glass transition temperature (t_g) and is in a rubbery state and rather "sticky". The product cannot be cured with Surelease on the outside of the pellet because all the pellets would stick together while in this rubber state. A top coat provides an outer layer that allows the product to be cured while maintaining discrete, fluidized particles in the coating unit.

Therefore, another aspect of this invention is the need, and length of time for curing of final products having the desired characteristics. The dissolution profile is stablized and provides for a uniform membrane or completely coalesed film surrounding the beadlet/pellet. It has now been found that for ethylcellulose that a suitable time period is about 60 minutes, at a temperature about or above 60°C.

While a number of top coats well known in the art can be used, a suitable top coat for the DXM beadlets was considered to be a hydroxypropylmethylcellulose based product, such as Colorcon Opadry ® Pink.

Levels for Top Coat and Drug Weight were determined and the top coat level is taken from the other pellets (CPM, PPA ,PSE). The Drug Weight represents a 1:1 ratio of drug to sugar sphere. The remaining % is the binder and seal coat.

Ethylcellulose is the functional barrier coat (sustained release coat) common to all the formulations herein More specifically, an aqueous pseudo-latex of ethylcellulose is preferred (trade name Surelease E-7-19010), as this product provided the best ease of processing and drug release reproducibility. In such a

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system, changing the level of ethylcellulose coat will most easily modulate drug release. Changing the pellet drug load, to a lesser extent, can also modulate the rate of drug release from such coated pellet drug delivery systems. The levels of water-soluble coats, such as hydroxypropylmethylcellulose (HPMC) seal coat and the Opadry® color topcoat do not substantially affect the rate of drug release and cannot be used as a drug release rate modulator in this system.

One aspect of the present invention is the optimization of parameters involved in aqueous coating techniques for use on water soluble active agents. It is an unexpected finding that this technology can be applied to active agents which would readily dissolve during the manufacturing process. It has now been found that by use of tightly held procedures as described herein that products, containing a water soluble dispersion for either sustained release or immediate release may be produced.

Development of a manufacturing procedure to produce IR and SR beads or pellets that are physically, chemically and therapeutically equivalent to currently marketed pharmaceutical standards is one use of the process described herein. The ability to develop a new manufacturing procedure for production of IR and SR beads of new marketed products is another aspect of this invention.

One drawback to global manufacturing procedures has been the use of ingredients, and processing conditions used to manufacture the pellets or beads which do not meet each countries standards and local market regulations. It appears that use of the preferred polymer coating herein, ethylcellulose, and the process conditions described are suitable for world wide manufacturing.

The process herein uses fluid bed coating equipment based upon the Wurster design, also called a Wurster column. This process is considered the best suited to coating of beads or beadlets. It is the industry standard and widely accepted in many companies around the globe. Wurster columns provide more efficient drying that other coating units which results in higher spray rates, faster processing (shorter processing time) and high quality finished products.

It consists of two columns, one inside the other. The air-flow pattern is such that most of the air flows through the inside column. This facilitates the beadlets movement in an upward direction inside the smaller column and in a downward direction in the space between the columns. The spraying nozzle is located at the bottom in the middle of the smaller column so that the beadlets are coated when they travel up and dry outside the smaller column in the space between the two columns. The geometric proportions of the inner and outer columns are such that a continuously moving column of beads or tablets passes through the spray path with

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every tablet/bead capturing some of the coating, and at the same time, ensuring that little or no solution reaches the wall of the inner column.

Smaller model are usually equipped with either 6- or 12-inch diameter outer chambers (having capacities in the range of 1-2 kg and 10-15 kg, respectively), production models are usually based on an 18-inch chamber diameter. Any attempt to increase the diameter while retaining only a single spraygun usually results in some beads passing through the spray gun without receiving any coating. Consequently, larger models use multiples of the 18-inch concept; for example, the 32-inch model has 3 inner coating partitions and sprayguns, while the 46 inch model has seven, all based on the 18-inch geometry, allowing for capacities up to 400kg.

The actives and excipients can be delivered to the spraying zone as solutions, suspensions, emulsions or melts. The most acceptable processing solvent for processes and coatings is water. The cost is minimal, and there are no environmental considerations.

It is important to have the liquid in atomized state prior to contact between the liquid particle and the beadlets (substrate). Large droplet size can cause agglomeration and reduce the yield.

The liquid delivery system consists of pumps and spraying nozzles. The liquids are atomized when they leave the nozzles by compressed air running into the nozzle simultaneously with the liquid. The higher the atomization air pressure the smaller is the atomized droplet. Peristaltic pumps are the most widely accepted for liquid delivery systems because of their accuracy and conformity to GMP requirements.

The major principal of the technology is uniform liquid delivery and controlled evacuation of the moisture from the product/beadlet during processing. An equilibrium must be maintained through the entire coating process to prevent agglomeration (when evaporation is inadequate) or spray drying (when evaporation is too fast).

The following are "industry accepted" critical process parameters for Fluid Bed Technology and Wurster coating processes.

- Product Temperature
- Spray Rate
- Inlet Air Flow (Velocity)
- Inlet Air Temperature
- Atomization Air Pressure
- Atomization Air Flow
- Inlet Air Humidity; and

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- Bead Surface

The most important processing parameters are Product Temperature and Spray Rate. All other parameters can be derived from these parameters. Product Temperature is important for maintaining a drying environment, surface characteristics (the surface porosity and uniformity/sphericity depends on the rate of crystallization and film forming properties and maintaining the product above/below the glass transition point of the polymers used in the coating process.

Spray Rate is an important factor for achieving the correct processing environment, i.e. rate of evaporation. This parameter can also influence surface characteristics (the surface porosity and uniformity/spherosity depends on the rate of crystallization and film forming properties of the material being applied). When Spray Rate is balanced with the desired product temperature, the product can be maintained at the selected "Steady-State" conditions.

Inlet Airflow and Inlet Air Temperature are also important factors, however they are derivatives of Product Temperature and Spray Rate. The Inlet Airflow and Inlet air temperature provide energy to the coating process by means of "conditioned" fluidization air. This conditioned air provides the correct thermodynamic equilibrium so that the product is not under/over-wet during processing.

The present invention has determined optimal ranges of product temperature, spray rates for different liquids, air flows and inlet air temperatures to provide necessary product temperature ranges at different spray rates, atomization air pressures to accommodate different spray rates of liquids used for coatings, and the significance of inlet and exhaust air humidity for coating processing for a select group of actives and coating polymers. Use of this information will enable the skilled artisan to readily apply this data to other water soluble actives with ease and to work with other water soluble polymers for coating said active ingredients.

It has been determined that optimal sustained release coating agents should not require the addition of significant amounts of suspending agents, such as talc which are dispersed in the coating liquids. For instance, Eudragit™ coatings require talc to reduce tackiness of the polymer during the coating process. Rigorous mixing with a homogenizer during the liquid preparation is necessary. The presence of talc presents the potential for nozzle clogging. Talc also creates more dust in the fluid bed during the coating process that affects the appearance of the bead surface.

Suitably, the sustained release coating agents is one which is useful world wide, is compatible with water as a solvent, is environmentally friendly, easy to use, and provides a stable product. Preferably, the coating is ethyl cellulose. The preferred

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delivery of ethyl cellulose is a pseudolatex ethyl cellulose dispersion, as ethyl cellulose is insoluble in water. Such dispersions are produced by multiple manufactures, FMC and Colorcon. The FMC product uses dibutyl sebecate as a plasticizer where as the Colorcon product uses a medium chain triglyceride, coconut oil. While the Colorcon product is preferred, it is a suitable alternative to utilize a different manufacturer's ethylcellulose dispersion with modifications, such as addition of vegetable oils, lecthicins, or citrate salts.

During evaluation of the coating process, it was determined that a seal or barrier coat between the drug layer and the sustained release coating is essential to provide a consistent release profile from the beads. Preferably the seal coat is from about 1 to 12 % weight gain, depending upon the ability of the drug to migrate. In the case of CPM and PPA herein a 1 to 7 %, more preferably about a 2 –5 % weight gain is utilized, respectively. Weight gain as used herein means the amount of solids added to a pellet at that particular coating stage.

The amount of sustained release coating and color coating applied to the beadlets can be problematic. Higher concentrations of the latex dispersion requires careful monitoring and control of product temperature and solution spray rate during transition from sustained releaser to the color coating to ensure that the beadlets do not agglomerate and stall in the fluidized bed.

A minimum of 3.7 bar steam is required to maintain adequate in-let air temperature in a Glatt fluidized bed processing machine. Control of in-let air temperature and bed temperature is critical during application of the ethylcellulose coating. A high in-let air temperature (>70° C) will cause the bottom plate of the Glatt to over heat. The sustained release coated beadlets will stick and agglomerate on the hot bottom plate and stall the bed.

The spray rate for the sustained release should also be conservative, starting with 450gms/min and increasing to about 850 gms/min. The relatively slow spray rate is to allow for a lower in-let air temperature and formation of fine droplets to produce a smooth film on the beads.

The transition temperature from SR coating to color coating of the in-let air must be brought up slowly to achieve drying of the color solution but not too hot as to cause agglomeration of the SR coated beads. The initial stages of color coating is especially sensitive. The in-let air temperature should not exceed about 65 °C and application of the color coating should begin as soon as the bed temperature reaches about 45°C. After 30 minutes into the color coating, an increase in the spray rate to 750gm/min may be made with adjustment of the in-let air temperature such that the bed temperature is maintained at about 40 to about 50°C.

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An important feature of this process is the use of the glass transition temperature of the water swellable polymer. Above this high temperature, the film will become tacky, and beadlet agglomerates will form. This will result in loss of beadlets due to screening/sizing and require a higher amount of polymer to be applied. The product appearance and drug content will vary, and produce unsatisfactory product.

It has now been found that the glass transition temperature of Surelease® is about 38°C to about 41°C, (closer to 39 – 41°C) dependent somewhat upon the amount of dilution with water. Therefore, it is relatively safe to conduct the process at 43 ± 4 °C at the beginning and then reduce the Product temperature to a steady state target of about 37 (± 4) °C. Depending upon suitable changes in the equipment, scale of commercial reaction process and amount of functional coating agent, the skilled artisan may find that the temperature range can be expanded to 38°C to about 41° +/- 2° C. Product temperature is the actual temperature of the beadlet in the Wurster column. The relatively higher initial Product temperature is to prevent water soluble drug penetration into the SR coating layer. If the coating process has a reduced spray rate the product temperature may increase above 45 °C. This is above the glass transition temperature of Surelease ®.

The process of the present invention requires coating the drug loaded, and sealed pellet with the aqueous water swellable polymeric dispersion. Initially the coating of the polymeric dispersion is at a product temperature above the glass transition point of the polymeric dispersion. The temperature of the product is then lowered to below the glass transition point of the polymeric dispersion and maintained at a steady state temperature after a sufficient amount of the water swellable polymeric dispersion has been applied. Although the skilled artisan would readily recognize when a sufficient amount of polymer has been applied, about a 30 minute spraying time, after about a 1/2 % of weight gain of polymer has been applied is deemed a "sufficient amount". The purpose of a "sufficient amount" is to create a protective layer of functional coat to prevent water getting into the seal coat.

It is recognized that in-let air temperature and in-let air flow are determined from the two parameters, spray rate and product temperature. They are also determined by the size of the equipment and the type of means by which the air is heated. For instance, in a small Wurster unit (15/12") the in let air temperature may range form about 64 to about 109 °C. For a 60/18" from about 55 to about 89; and in a 120/32" from about 70 to about 100 °C. Similarly in-let air flow may vary from 600, to 1150-3000 and from 2400-3300 respectively. The calculation and control of

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these parameters is well within the skilled artisan's means knowing the spray rate and product temperature. Air flow is important to maintain for two reasons: it provides sufficient fluidization and enough energy to evacuate the moisture without resorting to high Inlet Air Temperature in the chamber.

The product temperature is controlled by the inlet air flow and temperature, it is preferably maintained within +/- 4°C of the target temperature, more preferably +/- 1.5°C of the target temperature during the steady state process.

The product temperature during the initial application stage of the water swellable polymer application, (about 30 minutes) should be maintained above the glass transition point temperature. During the rest of the application, the temperature may be maintained at below the glass transition point.

The product temperature during the initial stage of top coating is preferably maintained below the glass transition point. The temperature may be increased above the glass transition point about 30 minutes into the top coat application.

Another important parameter of this process is dew point. A lower dew point will produce drier air. This will reduce drug mobility through the functional coat, such as the ethylcellulose layer. It will also reduce the tackiness, which develops in the ethyl cellulose dispersion application. If the dew point is to high moisture will be entrapped in the pellet as layers of the SR coating are applied. During the curing process molecules of water, i.e. moisture, will remain entrapped in the beadlet and produce a product which will not meet specifications. For purposes herein, dew point is preferably maintained at about 8 +/- 3°C to about 11 +/- 3 °C (or 9 +/- 5°C) with 9 +/- 3°C preferred for conditioned/filtered/chilled/air. More preferably, the dew point is sharply maintained with a small variation of about +/- 1 °, if possible.

The dew point may be varied depending upon the stage in the manufacturing process, for instance Drug layering as opposed to functional coating. It may also very within the broader parameters by the active agent. Drug layering (for all actives) requires tighter controls on dew point, hence the 9 +/- 5°C noted above. However, for functional coating the dew point may be broaded to 5°C to 20°C. In particular for CPM, 5°C to 20°C is suitable, with 14 +/- 6 better, and 15 +/- 3 °C more preferable. PSE produces a better product at the 9 +/-6, with 9+/- 3 being preferable. As long as the thermodynamic equilibrium is present, and the drying is sufficient, there is no large effect of the DEW point variable.

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

The following examples will demonstrate the production of drug loaded pellets with two different active ingredients, chlorpheramine maleate and phenylpropanolamine. The drug load pellets are then utilized to make either immediate release beads (IR) or sustained released beads (SR). The 4 populations of beads are then filled into capsules at a predetermined ratio.

EXAMPLE 1

GENERAL PROCESS - PPA Drug Load Pellets

In this example phenylpropanolamine HCl, as the active ingredient, is loaded onto 30-35 mesh Sugar spheres. layered in GPCG fluidized bed unit. seal coated and screened through #20 and #30 mesh screens.

RAW MATERIAL DATA

Ingredient	%, w/w	Quantity per Batch (Kg)
Purified Water 1	------	1.32
HPMC E5 USP/EP	1.35	0.014
Phenylpropanolamine Hydrochloride	47.62	0.48
Non Pareil Seeds 30-35# USP/NF	46.27	0.46
Opadry White	4.76	0.048
TOTAL	100.00	1.00

This example will produce 50 mg of Phenylpropanolamine Hydrochloride per capsule.

MANUFACTURING FORMULAS

HPMC, 10 % Solution

Ingredient	%, w/w	Quantity per Batch (Kg)
Purified Water	90.00	0.12
Methocel, NF	10.00	0.01
TOTAL	100.00	0.13

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Phenylpropanolamine HCL Solution

Ingredient	%, w/w	Quantity per Batch (Kg)
Purified Water	55.06	0.76
Phenylpropanolamine HCL, USP Powder	35.00	0.49
Methocel, NF 10% Solution	9.94	0.14
TOTAL	100.00	1.39

Opadry Dispersion

Ingredient	%, w/w	Quantity per Batch (Kg)
Purified Water	90.00	0.43
Opadry White	10.00	0.05
TOTAL	100.00	0.48

Phenylpropanolamine HCl and Opadry, 10% Dispersion (Seal Coat) Layering

Ingredient	%, w/w	Quantity per Batch (kg)
Non Pareil Seeds 30-35# USP/NF	19.89	0.46
Phenylpropanolamine Hydrochloride, 35% Solution*	59.65	1.39
Opadry White, 10% Dispersion	20.47	0.48
TOTAL**	100.00	2.33

* Water evaporates during the processing.
Total solids content is about 36%. (Solids total consists of Phenylpropanolamine HCl and HPMC E5 USP/EP)

PROCESSING.

HPMC E5, 10% SOLUTION

Pursuant to directions of the manufacture of the particular brand of HPMC, heat .062 kg of Purified Water to 70 ± 10 °C. Add HPMC E5 USP/EP, and mix for 15 minutes (until visually dissolved). Add .062074 kg of cold Purified Water, and mix for 15 minutes (until visually dissolved). Allow the solution to cool and de-aerate if

desired. The HPMC E5 USP/EP 10% Solution will be used for the manufacturing of the Phenylpropanolamine HCl (PPA).

PHENYLPROPANOLAMINE HCl 35% SOLUTION

1. Weigh out Purified Water into stainless steel container with a Lightnin' Mixer.
2. Heat the water to 65 ± 5 °C.
3. Turn on the mixer. Adjust the air pressure to form a vortex.
4. Charge the Phenylpropanolamine HCl (PPA) into the vortex.
5. When all the Phenylpropanolamine HCl (PPA) is charged allow the solution to mix for 15 (± 5) minutes.
6. Add HPMC E5 USP/EP 10% solution to the Phenylpropanolamine HCl (PPA) solution.
7. Continue mixing.

OPRADRY WHITE DISPERSION

Prepare according to manufacturer's directions.

Weigh out Purified Water into stainless steel container with a Lightnin' mixer. Add Opadry White. Mix for 65 (± 5) minutes. Continue mixing until ready to use and through the spraying.

FLUIDIZED BED PROCESSING

PHENYLPROPANOLAMINE HCl and SEAL COAT LAYERING

1. Adjust the inlet air temperature as necessary to control the product temperature.
2. Machine Configuration: GPCG
3. Weigh Non Pareil Seeds #25-30 mesh into a suitable stainless steel container and charge into fluidized bed processor.

Set up the process parameters and conduct the processing as per following recipe:

Process Parameters:	Min.	Setup	Max	Unit
Temp. Inlet Air	55.0		75.0	°C
Temp. Product	35.0		55.0	°C
Spray Rate	1.0		10.0*	g/min
Prod. Filter Shaking Active		Off		s
Prod. Filter Shaking Pause		Off		s
Prod. Filter Shaking Mode		GPCG		
Temp. Exhaust Air	30.0		55.0	°C

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Time				min

Begin fluidization process. Begin spraying the drug solution. PPA 35% solution until complete using the above noted process parameters.

Connect liquid pumping system to the seal coat solution (Opradry White dispersion solution) and continue spraying until complete.

Screen the batch through the sifter fitted with 20 and 30 mesh screens.

EXAMPLE 2

GENERAL PROCESS (PPA SR Beads)

This example is directed a process for making phenylpropanolamine HCl sustained release beads (PPA SR) having a 12 % coating of Surelease.

The Phenylpropanolamine HCL is layered on to the sugar spheres , seal coated, and sifted as described above in Example 1. The Drug Loaded pellets are charged into a GPCG fluidized bed unit. Sustained Release coat and Top coat as described herein are put on the pellets. The product is cured. and the finished product is screened through #20 and #30 mesh screens.

RAW MATERIAL DATA

Ingredient	%, w/w	Quantity per Batch (Kg)
PPA Drug layered Pellets of Example 1	86.24	0.86
Surelease®	11.76	0.47
Opadry AMB	2.00	0.02
TOTAL	100.0000	1.35

This will produce 50 mg of Phenylpropanolamine Hydrochloride per capsule

MANUFACTURING FORMULAS

Surelease, 15 % Dispersion

Ingredient	%, w/w	Quantity per Batch (Kg)
Surelease (Colorcon)	60.00	0.47
Purified Water	40.00	0.31
TOTAL	100.00	0.78

OPADRY AMB, 10%
DISPERSION

Ingredient	%, w/w	Quantity per Batch (Kg)
Opadry AMB	10.000	0.001
Purified Water	90.00	0.179
TOTAL	100.00	0.199

PROCESSING

SURELEASE, 15 % SOLIDS DISPERSION

1. Charge Surelease in container equipped with Lightnin' Mixer.
2. Turn on the mixer in the Surelease container. Adjust the compressed air for adequate mixing.
3. Charge the Purified Water into the Surelease container.
4. Mix for 20 ± 5 minutes.

OPADRY 10% DISPERSION

Mix in accordance with the Manufactures directions.
Weigh out Purified Water into stainless steel container equipped with a Lightnin' Mixer. Add Opadry Pink. Mix for 65 (± 5) minutes. Reduce the air pressure to the dispersion to de-aerate. Continue mixing until ready to use and through the spraying.

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FLUIDIZED BED PROCESSING

Surelease, 15% Solids (Sustained Release Dispersion) and Opadry, 10% Dispersion Layering

1. Machine Configuration: GPCG
2. Weigh PPA Seal coated Pellets of Example 1 and charge into the fluidized bed.
3. Set up the process parameters and conduct the manufacturing as per following recipe:

Process Parameters:	Min.	Setup	Max	Unit
Temp. Inlet Air	55.0		75.0	°C
Temp. Product	35.0		55.0	°C
Spray Rate	1.0		10.0	g/min
Prod. Filter Shaking Active		Off		s
Prod. Filter Shaking Pause		Off		s
Prod. Filter Shaking Mode		GPCG		
Temp. Exhaust Air	30.0		55.0	°C
Time				min

Begin fluidization process. Begin spraying the Surelease 15% solids dispersion until complete using the above noted process parameters. During the initial spraying of the SR coating, the initial product temperature is higher than the glass transition point to get rapid drying. Once sufficient coating of the polymer is applied, the product temperature is decreased to below the glass transition point to avoid agglomeration. The Inlet Air flow is adjusted as necessary.

Connect liquid pumping system to the top coat solution (Opradry Pink dispersion) and continue spraying until complete. The product temperature is maintained below the glass transition point at steady state, adjusting the inlet air flow rate as necessary.

The pellets are cured, and the batch is screened through # 20 and # 30 mesh screens.

EXAMPLE 3

GENERAL PROCESS – PPA IR BEADS

The following example utilizes the drug layered PPA beads of Example 1.

The process for manufacture of the IR pellets is identical to that of the SR pellets as exemplified in Example 2 above, except for the quantity of Surelease applied. In this instance the IR beadlets have a 4% coating of Surelease applied.

The amounts of Surelease applied is:

RAW MATERIAL DATA

Ingredient	%, w/w	Quantity per Batch (Kg)
PPA Drug layered Pellets	94.00	0.94
Surelease®	4.00	0.16
Opadry AMB	2.00	0.02
TOTAL	100.0000	1.12

EXAMPLE 4

GENERAL PROCESS (CPM Drug Loaded and Seal Coated Beads)

Similar to that for PPA described above in Example 1, CPM is loaded onto sugar spheres and used in the IR and SR preparation of Beadlets described in the Examples below.

30-35 mesh Sugar spheres are layered with Chlorpheniramine Maleate in a GPCG fluidized bed unit, seal coated and screened through #20 and #30 mesh screens.

RAW MATERIAL DATA

Ingredient	%, w/w	Quantity per Batch (Kg)
Purified Water		0.68
Non Pareil Seeds #25-30 mesh	87.92	0.88
HPMC E-5 Premium, NF*	2.28	0.02
Chlorpheniramine Maleate*	9.80	0.099
TOTAL	100.00	1.00

This process produces 4 mg of Chlorpheniramine Maleate per capsule.

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MANUFACTURING FORMULAS

HPMC, 10 % Solution

Ingredient	%, w/w	Theoretical Batch (Kg)
Purified Water	90.00	0.21
HPMC E-5 Premium, NF	10.00	0.023
TOTAL	100.00	0.23

CHLORPHENIRAMINE MALEATE SOLUTION

Ingredient	%, w/w	Quantity per Batch (Kg)
Purified Water	78.70	0.47
Chlorpheniramine Maleate	16.59	0.10
HPMC E-5 Premium, 10% Solution	4.71	0.03
	100.00	0.60

PROCESSING

HPMC E5, 10% SOLUTION

The solution is produced in accordance with manufacturer directions and similar to that in the above examples.

1. harge .58625 kg of Purified Water into a stainless steel container equipped with a Lightnin' Mixer. Turn the mixer on. Adjust the air pressure to 3.5-4.5 bars (50-65 lb/in^2) to form a vortex. Heat up the Purified Water to 65 ± 5 °C.
2. Weigh out 0.111875 kg of Purified Water from step 1 into stainless steel container equipped with a Lightnin' Mixer.
3. Cool the rest of the hot water in the stainless steel container to 40 ± 5 °C. Continue mixing. This portion of the Purified Water will be used for the manufacturing of the Chlorpheniramine Maleate Solution.
4. Turn the mixer in the stainless steel container on. Adjust the compressed air pressure to 60-75 lb/in^2 (4-5 bars) to create vortex.
5. Add HPMC E5 into the vortex in the stainless steel container.
6. Mix for 15 minutes (until visually dissolved).
7. Add 0.09375 kg of Purified Water.
8. Mix for 15 minutes (until visually dissolved).

9. Turn OFF the mixer and allow the solution to cool and de-aerate. The HPMC E5 USP/EP 10% Solution will be used for the manufacturing of the Chlorpheniramine Maleate solution and for Seal Coat Solution. The solution can be used for the manufacturing of the Chlorpheniramine Maleate solution prior to completion of de-aeration and cooling.

CHLORPHENIRAMINE MALEATE SOLUTION

1. Charge the Chlorpheniramine Maleate into stainless steel container from step 3, HPMC E5, 10% Solution.
2. When all the Chlorpheniramine Maleate is charged allow the solution to mix for 15 (± 5) minutes.
3. Add 0.0284375 kg of HPMC E5 10% solution to the Chlorpheniramine Maleate solution..
4. Mix for 5-10 minutes.

FLUIDIZED BED PROCESSING

CHLORPHENIRAMINE MALEATE and SEAL COAT LAYERING

1. Machine Configuration: GPCG
2. Weigh Non Pareil Seeds #25-30 mesh into a suitable stainless steel container.
3. Set up the process parameters and conduct the processing as per following recipe:

Process Parameters:	Min.	Setup	Max	Unit
Temp. Inlet Air	55.0		75.0	°C
Temp. Product	35.0		55.0	°C
Spray Rate	1.0		10.0	g/min
Prod. Filter Shaking Active		Off		s
Prod. Filter Shaking Pause		Off		s
Prod. Filter Shaking Mode		GPCG		
Temp. Exhaust Air	30.0		55.0	°C
Time				min

Begin fluidization process. Begin spraying the drug solution, CPM SOLUTION until complete using the above noted process parameters.

Connect liquid pumping system to the seal coat solution (HPMC 10% Solution) and continue spraying until complete.

Screen the batch through the sifter fitted with 20 and 30 mesh screens.

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EXAMPLE 5

GENERAL PROCESS (CPM SR Beads)

Similar to the IR process below, the Chlorpheniramine Maleate layered, seal coated and sifted Pellets of Example 4 are charged in GPCG fluidized bed unit. Sustained Release coat and Top coat are put on the Pellets. The amount of sustained release coating is 8% Surelease. The product is cured, and the finished product is screened through #20 and #30 mesh.

RAW MATERIAL DATA

Ingredient	%, w/w	Quantity per Batch (Kg)
Purified Water		0.39
CPM drug loaded, seal coated Pellets of Example 6	90.16	0.90
Surelease	7.84	0.31
Opadry Yellow	1.99	0.02
	100.00	1.23

Process produces 4 mg of Chlorpheniramine Maleate per capsule.

Surelease, 15 % Dispersion

Ingredient	%, w/w	Theoretical Quantity per Batch (Kg)
Surelease	60.00	0.31
Purified Water	40.00	0.21
TOTAL	100.00	0.52

Opadry Yellow, 10% Dispersion

Ingredient	%, w/w	Quantity per Batch (kg)
Opadry Yellow	10.00	0.02
Purified Water	90.00	0.18
TOTAL	100.00	0.20

PROCESSING

SURELEASE, 15 % SOLIDS DISPERSION

1. Charge Surelease in container equipped with Lightnin' Mixer.
2. Turn on the mixer in the Surelease container. Adjust the compressed air pressure to 30-45 lb/in^2 (2-3 bars) for adequate mixing.
3. Charge the Purified Water into the Surelease container.
4. Mix for 20 ± 5 minutes.

OPADRY YELLOW, 10% DISPERSION

1. Weigh out Purified Water into stainless steel container equipped with a Lightnin' Mixer.
2. Turn on the mixer, adjust the air pressure to 3.5-4.5 bars to form a vortex.
3. Add Opadry Yellow into the vortex. Avoid splashing and excess foaming. Mix for 35 (± 5) minutes..
4. Reduce the mixer air pressure to 2.5-3.5 bars and allow the dispersion to de-aerate.
5. Continue mixing until ready to use and through the spraying.

FLUIDIZED BED PROCESSING

SURELEASE 15% SOLIDS DISPERSION (SUSTAINED RELEASE DISPERSION) AND OPADRY YELLOW 10% DISPERSION (TOP COAT) LAYERING

1. Machine Configuration: GPCG
2. Weigh CPM Seal coated Pellets into a suitable stainless steel container.
3. Set up the process parameters and conduct the manufacturing as per following recipe:

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Process Parameters:	Min.	Setup	Max	Unit
Temp. Inlet Air	55.0		75.0	°C
Temp. Product	35.0		55.0	°C
Spray Rate	1.0		10.0	g/min
Prod. Filter Shaking Active		Off		s
Prod. Filter Shaking Pause		Off		s
Prod. Filter Shaking Mode		GPCG		
Temp. Exhaust Air	30.0		55.0	°C
Time				min

Begin fluidization process. Begin spraying the Surelease 15% solids dispersion until complete using the above noted process parameters. During the initial spraying of the SR coating, the initial product temperature is higher than the glass transition point to get rapid drying. Once sufficient coating of the polymer is applied, the product temperature is decreased to below the glass transition point to avoid agglomeration. The Inlet Air flow is adjusted as necessary.

Connect liquid pumping system to the top coat solution (Opradry Yellow dispersion) and continue spraying until complete. The product temperature is maintained below the glass transition point at steady state, adjusting the inlet air flow rate as necessary.

The pellets are cured, and the batch is screened through # 20 and # 30 mesh screens.

EXAMPLE 6

GENERAL PROCESS – CPM IR BEADS

Using the Chlorpheniramine Maleate layered, seal coated and sifted pellets of Example 4 above, they are charged into a GPCG fluidized bed unit. Sustained Release coat and Top coat are put on the Pellets. The product is cured, and the finished product is screened through #20 and #30 mesh screens.

The process for the IR pellets is identical to that of the SR pellets except for the quantity of Surelease applied, which in the IR pellet is 3% Surelease.

RAW MATERIAL DATA

Ingredient	%, w/w	Quantity per Batch (Kg)
Purified Water		0.26
CPM drug loaded, seal coated Pellets of Example 4	95.067	0.95
Surelease	2.95	0.12
Opadry Yellow	1.99	0.02
Total	100.00	1.08

Process produces 4 mg of Chlorpheniramine Maleate per capsule.

Shown below in Table II, is a summary of the processing parameters for the beadlets of the above Examples.

Table II Summary of the Processing Parameters

Processing Parameters	General range of processing Conditions °C	
PPA pellets	Product Temperature °C	Spray Rates, grams/minute per nozzle
Drug Loading	43.9 – 54.7	100 - 500
Seal Coating	45.9 – 58.7	100 - 250
Surelease Coating	32.0 – 46.5	100 - 375
Top Coating	35.5 – 53.0	100 - 250
CPM Pellets		
Drug Loading	39.0 - 52.4	100 - 400
Seal Coating	35.4 – 47.5	100 - 200
Surelease Coating	33.0 – 46.0	100 - 285
Top Coating	36.6 - 45.0	150 – 250

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EXAMPLE 7

To the populations of beadlets produced in the above examples, blends of PPA IR, PPA SR, CPM IR, and CPM SR are filled into hard gelatin capsules in ratios of: 1:2: 1:1 for the 75/8 form

EXAMPLE 8

Populations of beadlets of PSE SR release are produced as shown below. The pellets are manufactured in two stages. The first stage consists of making the drug-loaded/seal-coated (DLSC) pellets, whose formula is shown below.

Formula for DLSC Pellets

Ingredient	%, w/w	mg per Dose
Pseudoephedrine HCl, USP Powder	59.057	120.000
Non-Pareil 35/40 Mesh Sugar Spheres	37.354	75.901
HPMC E5 Premium, NF (from drug loading)	1.588	3.227
HPMC E5 Premium, NF (from seal-coating)	2.000	4.064
TOTALS	100.00	203.192

In a second stage, the SR pellet manufacture, the DLSC pellets are coated with Surelease and then are top coated with Opadry. A "typical formula" of Surelease coated SR pellets is shown below.

Finished pellet formula for a "10%" SR coat level.

10% Surelease* PSE HCl Finished Pellet Formula

Ingredient	%, w/w	Mg per Dose (120 mg Pseudoephedrine)
Pseudoephedrine HCl, USP Powder	52.080	120.000
Non-Pareil 35/40 Mesh Sugar Spheres	32.941	75.901
HPMC E5 Premium, NF	3.164	7.290
Surelease (25% Solids)	9.799**	22.578**
Opadry	2.016	4.645
TOTALS	100.000	230.414

* % (w/w) at the Surelease-coated beadlet stage.

** Based on dried solids weight.

The pellet formulas at various stages of manufacture of the 10% SR pellets are shown below. The first step in the manufacture of the sustained release pellets is to layer the pseudoephedrine HCl by spraying the drug solution onto the sugar spheres. Hydroxypropylmethylcellulose (HPMC) serves as a binder for the drug (Step 1). The next step involves applying an HPMC "seal" coat to the drug-loaded pellets (Step 2). In the next step (Step 3) the barrier coat, Surelease®, is applied. After the Surelease layer has been applied, a "top-coat"/color-coat layer is applied (Step 4).

Step 1: Drug-Layering Step

Ingredient	% (w/w)	mg/120 mg PSE
Sugar Spheres (35/40 Mesh)	38.12	75.90
Pseudoephedrine HCl, USP Powder	60.26	120.00
HPMC E5, Premium, NF	1.620	3.23
Totals:	*100.00*	*199.13*

Step 2: Drug-Loaded/Seal Coated (DLSC) Pellets

Ingredient	% (w/w)	mg/ 120 mg PSE
Drug-Layered Pellets (from step 1)	*98.00*	*199.13*
HPMC E5, Premium, NF	*2.00*	*4.07*
	100.00	*203.20*

Step 3: Functional Coat

Ingredients	% (w/w)	mg/ 120 mg PSE
DLSC Pellets	*90.00*	*203.20*
Surelease	*10.00*	*22.58*
	100.00	*225.78*

Step 4: Top Coat Application

Ingredients	% (w/w)	mg/ 120 mg PSE
Barrier-Coated Pellets	*97.98*	*225.78*
Opadry	*2.02*	*4.65*
	100.00	*230.43*

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The level of HPMC binder can be varied, with a preferred level in the 1-2% w/w range. The grade of HPMC used (E5), at the 2% level, does not significantly affect drug release through the barrier coat, as it is fairly water-soluble.

Preferably, the functional coat suspension (Surelease ®) is applied as a 15% (w/w) Surelease® solids suspension (pseudolatex) in water (Step #3). The "top coat" is applied in Step 4, at the 2.02% (w/w) level and is applied as a 10% (w/w) solids suspension of Opadry in water.

The pellets are then subjected to a "cure" period, of approximately sixty-minutes at a temperature of about 60° C.

In an alternative embodiment of the present example, the functional coat may be applied as a aqueous dispersion having a % (w/w) solids suspension of about 1 to about 60%. Generally, for purposes of commercial manufacture the solids dispersion is diluted to about 25 to 30 w/w. It is more suitably diluted to about 15% w/w for ease of spraying but the diluent may be other than water, such as any soap, surfactant, alchohol, edible oils etc. which will solubilize in the dispersion.

Batches of DLSC pellets were coated with a 25% w/w solids dispersion instead of the 15% w/w dispersion of Step 3 above.

The composition of the solutions/suspensions, mentioned above (drug solution, barrier coat suspension and, top coat suspension), are shown below:

1. Drug Solution

Ingredient	% (w/w)	
Pseudoephedrine HCl USP Powder	37.20	
Hydroxypropylmethylcellulose E5, USP	1.00	
Purified Water, USP	61.80	
	Total:	*100.00*

2. HPMC Solution

Ingredient	% (w/w)	
Hydroxypropylmethylcellulose	10.00	
Purified Water, USP	90.00	
	Total:	*100.00*

3. Surelease Suspension

Ingredient	% (w/w)	
Surelease (25% solid dispersion)	60.00	
Purified Water, USP	40.00	
	Total:	*100.00*

4. Top Coat Suspension

Ingredient	% (w/w)	
Opadry	10.00	
Purified Water, USP	90.00	
	Total:	*100.00*

EXAMPLE 9

Using the same process conditions of Example 8 above, sustained release pellets of PSE were made with a 6, 9, 11, 12 and 14 % w/w coating level of a functional coat of Surelease.

EXAMPLE 10

Using process conditions similar to those of Examples 1 to 8 above, immediate release beadlets were produced using Dextromethorphan HBr as the active agent with the following characteristics.

The formulation for producing a beadlet layered with DXM is shown below.

INGREDIENT	% w/w	mg/dose ^
DRUG LAYERED BEADLETS		
Dextromethorphan HBr	47.170	30.000
Sugar Spheres NF	47.170	30.000
Hydroxypropylmethylcellulose, 5 cps	5.660	3.600
Water, Purified, USP.	-----	137.400
	100.000	63.600

Notes: "^" Dose denotes 30 mg of Dextromethorphan HBr per capsule

Using the drug layered beadlets of Step A above, immediate release beadlets of DXM are produced coated with an HPC seal coat in accordance with the following formulation.

DXM IMMEDIATE RELEASE BEADLETS		
DRUG LAYERED BEADLETS	98.000	63.600
Hydroxypropylmethylcellulose, 5 cps	2.000	1.298
Water, Purified, USP .	-----	11.682
	100.000	64.898

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Notes: "*" Denotes water evaporated during processing

Using similar Drug Layering Processing Parameters to the CPM, PSE, and PPA examples above, a GPCG-15, 12" Wurster column is used to apply both the Drug Layer and the Seal Coat.

While unit specific for manufacturing conditons, it is suitable to apply the DXM suspension at a spray rate of 100 to 400 grams per minute/per nozzle; the product temperature is kept within a temperature range of about 43 +/- 3 ° C. Because the drug is sprayed as a suspension the temperature may be increased up to 50 °C. The lower end of the temperature range is down to about 32 °C depending upon unit size. Therefore the range is from about 32 to about 50 °C.

EXAMPLE 11

After the drug loaded sealed coated beadlets of Example 9 are prepared, the pellets are now coated with the release rate agent, with set up and process parameters for two formulas, the 5 and 7% SR formulations are shown below.

For a 5% sustained release formulation:

5% SR Formulation

INGREDIENT	% w/w	mg/dose ^
SURELEASE COAT		
Dextromethorphan DLSC Pellets from the example above	95.00	64.898
Surelease (25% solids Dispersion)	5.00	3.416
Water, Purified, USP.	—	9.108
total	100.00	68.314
DXM IMMEDIATE RELEASE BEADLET		
Surelease Coated Pellets	98.00	68.314
Opadry White	2.00	1.394
Water, Purified, USP .	—	
total	100.00	69.708

Notes: "^" Dose denotes 30 mg of Dextromethorphan HBr per capsule

For a 7% SR Formulation

INGREDIENT		% w/w	mg/dose ^
SURELEASE COAT			
Dextromethorphan DLSC Pellets		93.00	64.898
Surelease (25% solids Dispersion)		7.00	4.885
Water, Purified, USP.		-----	13.027
	total	100.00	69.783
DXM IMMEDIATE RELEASE BEADLET			
Surelease Coated Pellets		98.00	69.783
Opadry White		2.00	1.424
Water, Purified, USP .		----	
	total	100.00	71.207

Notes: "^" Dose denotes 30 mg of Dextromethorphan HBr per capsule

Using process conditions similar to those above in Examples 1 to 9, the functional coat and top coat films were applied, and cured.

EXAMPLE 12

Similar to Example 11 above, sustained release pellets with a 9% w/w functional coat layer were also made.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

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What is Claimed Is:

1. A product comprising a sustained release (SR) phase of PPA beadlets coated with about 9 to about 24% (weight gain) of a pseudolatex water swellable polymer dispersion.
2. A product according to Claim 2 wherein the PPA beadlets are coated with about 9% to 18% (weight gain) of the pseudolatex water swellable polymer dispersion.
3. A product according to Claim 1 wherein the PPA beadlets are coated with about 12% (weight gain) of the pseudolatex water swellable polymer dispersion.
4. A product according to any of Claims 1 to 4 wherein the amount of PPA in a beadlet is about 20 to 80 % w/w drug load.
5. A product according to any one of Claims 1 to 5 further comprising an immediate release phase of PPA beadlets.
6. A product according to Claim 5 wherein the PPA beadlets are coated with about 0.5 to about 8% (weight gain) of a pseudolatex water swellable polymer dispersion.
7. A product according to Claim 5 wherein the PPA beadlets are coated with about 4% (weight gain) of a pseudolatex water swellable polymer dispersion.
8. A product according to claim 5 wherein the weight ratio of sustained release PPA to immediate release PPA is 2:1, and is 50mg SR PPA: 25 mg IR PPA.
9. A product according to claim 5 wherein the weight ratio of sustained release PPA to immediate release PPA is 1:1, and is 25mg SR PPA: 25 mg IR PPA.
10. A product according to Claim 1 having an AUC, C_{max}, and t_{max}, according to Figure 10, or 12.
11. A product comprising a sustained release (SR) phase of CPM beadlets coated with about 5 to about 18% (weight gain) of a pseudolatex water swellable polymer dispersion.
12. A product according to Claim 11 wherein the CPM beadlets are coated with about 6.5 to about 9% (weight gain) of the pseudolatex water swellable polymer dispersion.
13. A product according to claim 12 wherein the CPM beadlets are coated with about 8% (weight gain) of the pseudolatex water swellable polymer dispersion.
14. A product according to any one of Claims 11 to 14 wherein the amount of CPM in a beadlet is about 2 to 60% w/w drug load.

15. A product according to any one of Claims 11 to 15 further comprising an immediate release phase of CPM beadlets.

16. A product according to Claim 15 wherein the CPM beadlets are coated with about 0.5 to less than 5% (weight gain) of the pseudolatex water swellable polymer dispersion.

17. A product according to claim 16 wherein the CPM beadlets are coated with about 3% (weight gain) of the pseudolatex water swellable polymer dispersion.

18. A product according to claim 15 wherein the weight ratio of sustained release CPM to immediate release CPM is 1:1, and is 2 mg IR CPM : 2mg SR CPM.

19. A product according to claim 15 wherein the weight ratio of sustained release CPM to immediate release CPM is 1:1, and is 4 mg IR CPM:4mg SR CPM.

20. A product according to Claim 15 having an AUC, C_{max}, and t_{max}, according to Figure 9, or 11.

21. A product comprising PPM beadlets as defined in any of Claims 1 to 10 admixed with CPM beadlets as defined in any one of Claims 11 to 20.

22. A product according to any one of Claims 1 to 21 wherein the water swellable polymer in the pseudolatex dispersion is ethyl cellulose.

23. A product according to Claim 22 wherein the pseudolatex ethyl cellulose dispersion is Surelease®.

24. An aqueous coating process for the manufacture of sustained release beadlets of a water soluble active agent coated with a water swellable polymer as the sustained releasing agent which process comprises

a) applying a seal coat of a protective polymer to a drug loaded sphere;

b) applying a coating of an aqueous water swellable polymeric dispersion to the sphere of step a); wherein the aqueous water swellable polymeric dispersion of step b) is a pseudolatex ethyl cellulose dispersion having a glass transition point of about 38 to 41 °C; and which process for applying said dispersion utilizes atmospheric conditions exhibiting a dew point of 9 +/- 5 °C.

25. The process according to Claim 24 wherein the dew point is 9 +/- 3 °C.

26. The process according to Claim 24 or 25 wherein the drug loaded sphere is a sugar sphere or microcrystalline cellulose sphere coated with a water soluble active agent.

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27. The process according to Claim 24 or 25 wherein the drug loaded sphere is a spherionized pellet comprised of the water soluble active agent.

28. The process according to any one of Claims 24 to 27 wherein the active agent is chlorpheneramine maleate, phenylpropanolamine, pseudoephedrine, or dextromethorphan.

29. The process according to any one of Claims 24 to 28 wherein the pseudolatex ethyl cellulose dispersion is Surelease®.

30. The process according to any one of Claims 24 to 29 wherein the amount of ethyl cellulose dispersion applied to a beadlet of chlorpheneramine maleate is from about 2 to 18 %.

31. The process according to any one of Claims 24 to 29 wherein the amount of ethyl cellulose dispersion applied to a beadlet of phenylpropanolamine is from about 3 to 24 %.

32. The process according to any one of Claims 24 to 29, and 30 wherein the amount of chlorpheneramine maleate in a beadlet is about 8 to 12 % w/w drug load.

33. The process according to Claims 24 to 29, and 31 wherein the amount of phenylpropanolamine in a beadlet is about 40 to 60 w/w% drug load.

34. The process according to any one of Claims 24 to 30 wherein the sphere of part b) containing chlorpheneramine maleate as the active agent is coated with the aqueous water swellable polymeric dispersion initially at a product temperature above the glass transition point of the polymeric dispersion.

35. The process according to Claim 34 wherein the temperature of the product is lowered to below the glass transition point of the polymeric dispersion and maintained at a steady state temperature after a sufficient amount of the water swellable polymeric dispersion has been applied.

36. The process according to any one of Claims 24 to 29, or 31 wherein the beadlet of drug sphere of part b) containing phenylpropanolamine as the active agent is coated with the aqueous water swellable polymeric dispersion initially at a product temperature above the glass transition point of the polymeric dispersion.

37. The process according to Claim 36 wherein the temperature of the product is lowered to below the glass transition point of the polymeric dispersion and maintained at a steady state temperature after a sufficient amount of the water swellable polymeric dispersion has been applied.

38. The process according to any one of Claims 24 to 36 wherein the seal coat is hydroxypropylmethylcellulose.

39. The process according to any one of Claims 24 to 36 wherein the seal coat is polyvinyl alcohol.

40. The process according to Claim 38 or 39 wherein the seal coat applied is from about 1 to 7 % weight gain.

41. A product comprising a sustained release (SR) phase of PSE beadlets coated with about 3 to about 20 % (weight gain) of a pseudolatex water swellable polymer dispersion.

42. A product according to Claim 41 wherein the PSE beadlets are coated with about 6 to about 14 % (weight gain) of a pseudolatex water swellable polymer dispersion.

43. A product according to Claim 41 wherein the PSE beadlets are coated with about 10 to 12 % (weight gain) of the pseudolatex water swellable polymer dispersion.

44. A product according to any one of Claims 41 to 43 comprising a drug content of PSE between 6 to 90 % w/w in the sustained release phase.

45. A product according to Claim 44 comprising 40 to 70 % w/w of PSE.

46. A product according to any one of Claim 41 to 45 further comprising an immediate release phase of PSE beadlets.

47. A product according to Claim 46 wherein the weight ratio of immediate release PSE to sustained release PSE is 0.1:1 to 1:0.1.

48. A product according to Claim 46 wherein the weight ratio of immediate release PSE to sustained release PSE is 1:8 to 1:1 and is 15 mg of IR PSE:105mg SR PSE.

49. A product according to Claim 46 wherein the weight ratio of immediate release PSE to sustained release PSE is 1:1 and is 60 mg of IR PSE:60 mg SR PSE.

50. A product according to Claim 41 having an AUC, C_{max}, and t_{max}, according to Figure 16.

51. A product according to any one of Claims 41 to 49 wherein the water swellable polymer in the pseudolatex dispersion is ethyl cellulose.

52. A product according to Claim 51 wherein the pseudolatex ethyl cellulose dispersion is Surelease®.

53. A product according to any one of Claims 41 to 49 admixed with CPM beadlets as defined in any one of claims 11 to 20.

54. The process according to any one of Claims 24 to 29 wherein the amount of ethyl cellulose dispersion applied to a beadlet of pseudoephedrine is from about 3 to 20 %.

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55. The process according to any one of Claims 24 to 29 wherein the amount of pseudoephedrine in a beadlet is about 6 to 90 % w/w drug load.

56. The process according to any one of Claims 24 to 29 wherein the sphere of part b) containing pseudoephedrine as the active agent is coated with the aqueous water swellable polymeric dispersion initially at a product temperature above the glass transition point of the polymeric dispersion.

57. The process according to Claim 56 wherein the temperature of the product is lowered to below the glass transition point of the polymeric dispersion and maintained at a steady state temperature after a sufficient amount of the water swellable polymeric dispersion has been applied.

58. The process according to any one of Claims 24 to 29, or 54 to 57, wherein the seal coat is hydroxypropylmethylcellulose.

59. The process according to any one of Claims 24 to 29, or 54 to 57, wherein the seal coat is polyvinyl alcohol.

60. The process according to Claim 58 or 59 wherein the seal coat applied is from about 1 to 7 % weight gain.

61. The product produced by the process according to any one of Claims 24 to 40, or 54 to 60.

62. A product comprising a sustained release (SR) phase of dextromethorphan beadlets coated with about 0.5 to about 15% (weight gain) of a pseudolatex water swellable polymer dispersion.

63. A product according to Claim 62 wherein the dextromethorphan beadlets are coated with about 3 to about 10 % (weight gain) of a pseudolatex water swellable polymer dispersion.

64. A product according to Claim 62 wherein the dextromethorphan beadlets are coated with about 4 to 7 % (weight gain) of the pseudolatex water swellable polymer dispersion.

65. A product according to any of Claims 62 to 64 comprising a drug content of DXM between 30 to 70 % w/w of dextromethorphan in the sustained release phase.

66. A product according to Claim 65 comprising a drug content of DXM between 40 to 60 % w/w of dextromethorphan in the sustained release phase.

67. A product according to any one of claims 62 to 66 comprising an immediate release phase of DXM.

68. An IR, or SR product according to Claim 67 having an AUC, C_{max}, and t_{max}, according to Figure 20.

69. An IR or SR product according to Claim 67 having an AUC. C_{max}, and t_{max}, according to Figure 21.

70. An IR or SR product according to Claim 67 having an AUC. C_{max}, and t_{max}, according to Figure 22.

71. A product according to Claim 67 wherein the weight ratio of immediate release DXM to sustained release DXM is 0:100 to 100:0.

72. A product according to Claim 67 wherein the weight ratio of immediate release DXM to sustained release DXM is 1:1.

73. A product according to Claim 72 which contains 30 mg of IR DXM: 30 mg SR DXM: or 2.5mg IR and 2.5mg SR DXM.

74. A product according to any one of Claims 62 to 73 admixed with PPM beadlets as defined in any of Claims 1 to 10.

75. A product according to any one of Claims 62 to 73 admixed with PSE beadlets as defined in any of Claims 41 to 49.

76. The product according to Claim 74 or 75 which further comprises an admixture with CPM beadlets as defined in any one of Claims 11 to 20.

77. The product according to Claim 70 admixed with 200 to 1200mg ibuprofen.

78. A product according to any one of Claims 62 to 67, or 71 to 73 wherein the water swellable polymer in the pseudolatex dispersion is ethyl cellulose.

79. A product according to Claim 78 wherein the pseudolatex ethyl cellulose dispersion is Surelease®.

80. A product acccording to any one of claims 62 to 79 wherein the DXM is micronized.

81. The product according to Claim 80 wherein the micronized Dextromethorphan HBr has a particle size of 25 microns or less.

82. The product according to Claim 81 wherein the micronized DXM HBr has a particle size of 10 microns or less.

83. The product according to Claim 81 or 82 wherein at least 90% of the particles are 5 microns or less.

84. A product comprising a immediate release (IR) phase of dextromethorphan as a pellet filled capsule.

85. The product according to Claim 84 wherein the dextormethorphan is micronized has a particle size of 25 microns or less.

86. The product according to Claim 85 wherein the micronized DXM HBr has a particle size of 10 microns or less.

87. The product according to Claim 86 wherein at least 90% of the particles are 5 microns or less.

EMSDOCID: <WO__0119901A2_I_>

88. Micronized Dextromethorphan HBr having a particle size of less than 50 microns.

89. The micronized DXM according to Claim 88 having a particle size of less than 25 microns.

90. The micronized DXM according to Claim 89 having a particle size of less than 10 microns.

91. The micronized DXM according to any one of Claims 88 to 90 wherein at least 90% of the particles are 5 microns or less.

92. The micronized DXM particles of Claim 88 produced by air-jet milling, grinding or impact milling.

93. The process according to Claim 27 wherein the amount of dextromethorphan in a beadlet is about 30 to 70 w/w drug load.

94. The process according to Claim 93 wherein the amount of ethyl cellulose dispersion applied to a beadlet of dextromethorphan is from about 0.5 to 15%.

95. The process according to any one of Claims 24 to 29 wherein the sphere of part a) containing dextromethorphan as the active agent is coated with the aqueous water swellable polymeric dispersion initially at a product temperature above the glass transition point of the polymeric dispersion.

96. The process according to Claim 95 wherein the temperature of the product is lowered to below the glass transition point of the polymeric dispersion and maintained at a steady state temperature after a sufficient amount of the water swellable polymeric dispersion has been applied.

97. The process according to any one of Claims 24 to 29, 62 to 67, 71 to 73, 80 to 88, or 89 wherein the seal coat is hydroxypropylmethylcellulose.

98. The process according to any one of Claims 24 to 29, 62 to 67, 71 to 73, 80 to 88, or 89 wherein the seal coat is polyvinyl alcohol.

99. The process according to Claim 97 or 98 wherein the seal coat applied is from about 1 to 7 % weight gain.

100. The process according to any one of Claim 24 to 29, 62 to 67, 71 to 73, or 80 to 99 wherein the sustained release coated beadlet is cured for about 1 hour at a temperature of about 60° C.

101. A product produced by the process according to any one of claims 94 to 100.

102. The product according to any one of Claims 1 to 10 wherein the weight ratio of IR to SR for PPA is 6.25 to 12.5 mg IR PPA : 37.5 to 44 SR PPA.

103. The product according to any one of Claim 11 to 20 wherein the weight ratio of IR to SR for CPM is 0.5 to 3.5 mg IR CPM : 2 to 4mg SR CPM.

FIGURE 1 Traditional Wax Coated Spansule Technology

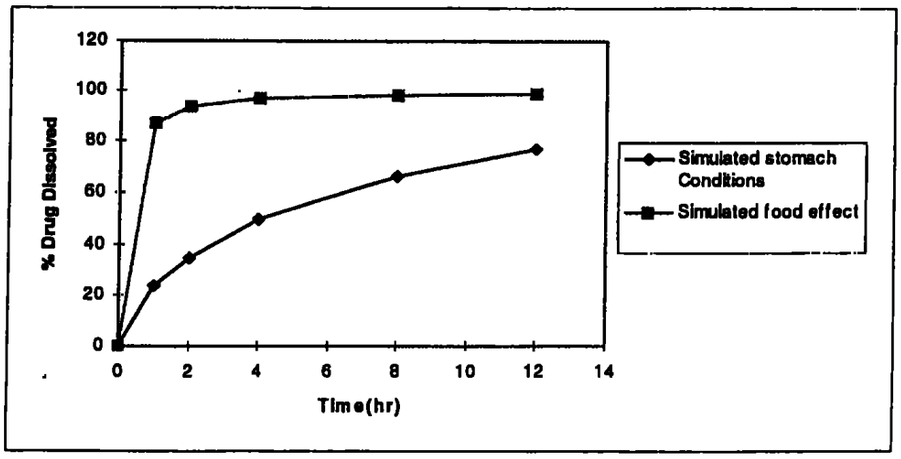

Figure 2 NEW AQUEOUS COATING SPANSULE TECHNOLOGY (for PPA)

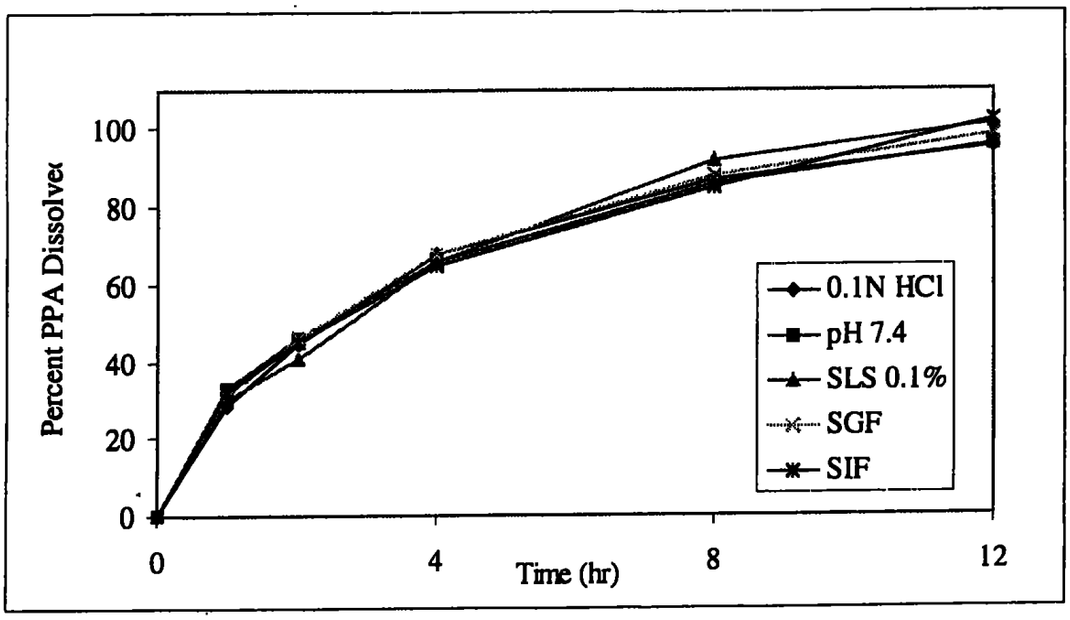

Figure 3. Effect of Surelease Levels on the dissolution of PPA from the beads

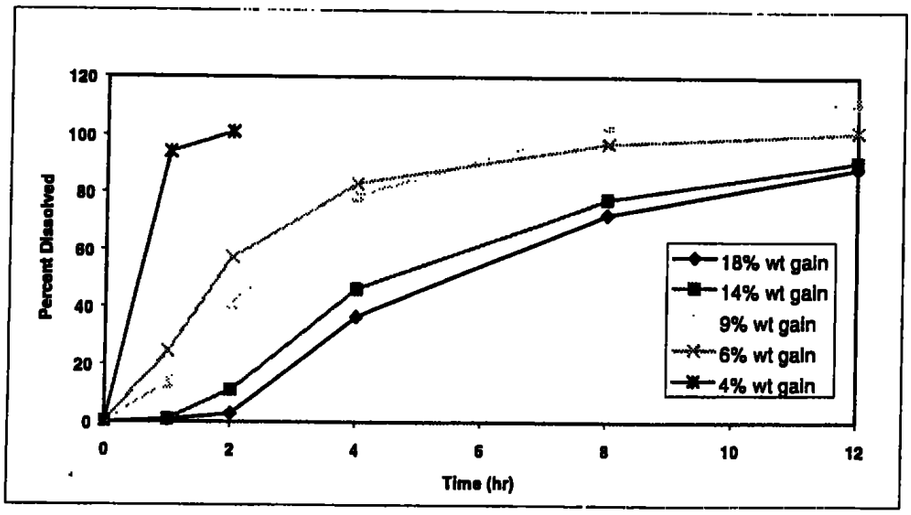

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Figure 4 Effect of Surelease Levels on the dissolution of CPM from the beads

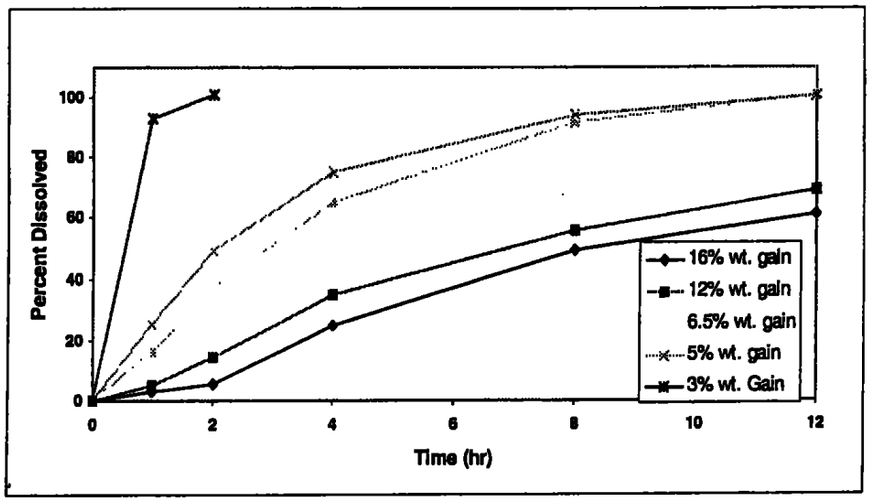


Figure 5. In-vitro dissolution of PPA from 50/4 formulation

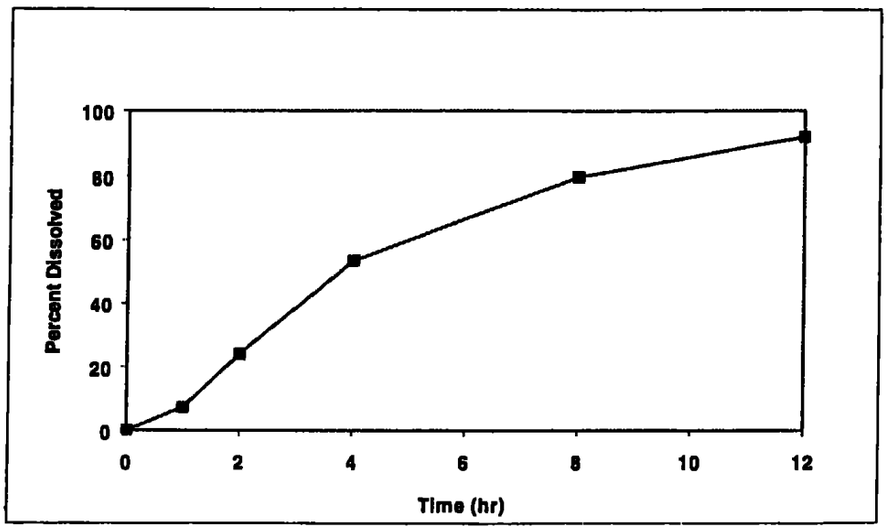


Figure 6. In-vitro dissolution of CPM from 50/4 formulation

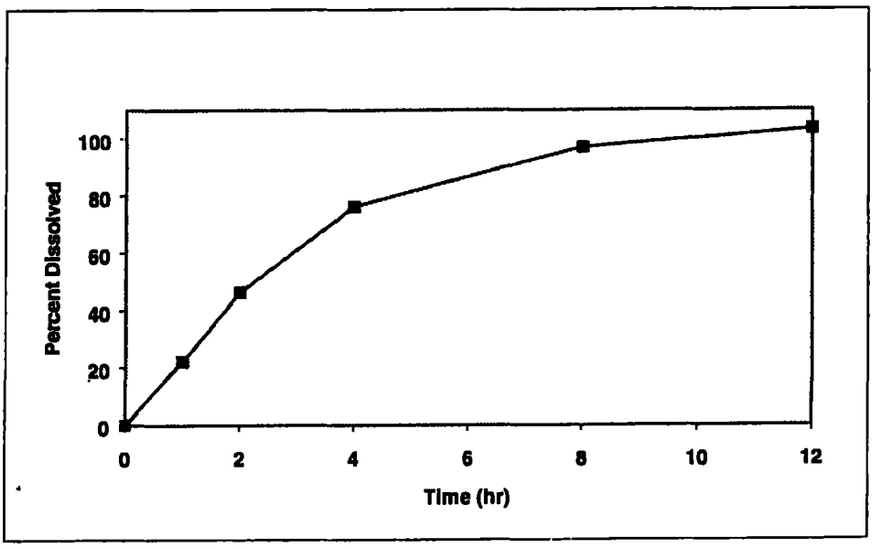


Figure 7 Effect of pH of the Dissolution Media on PPA Release from 50/4 Formulation

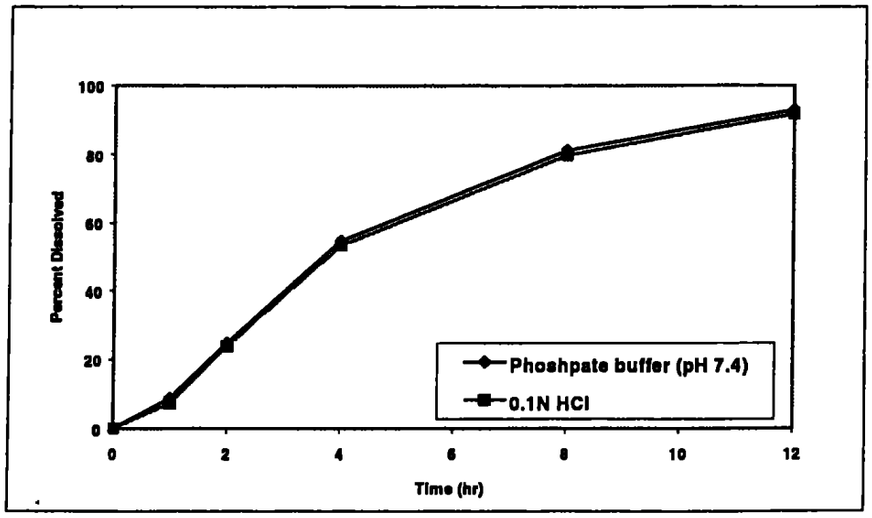


Figure 8. Effect of pH of dissolution media on CPM release from 50/4 Formulation

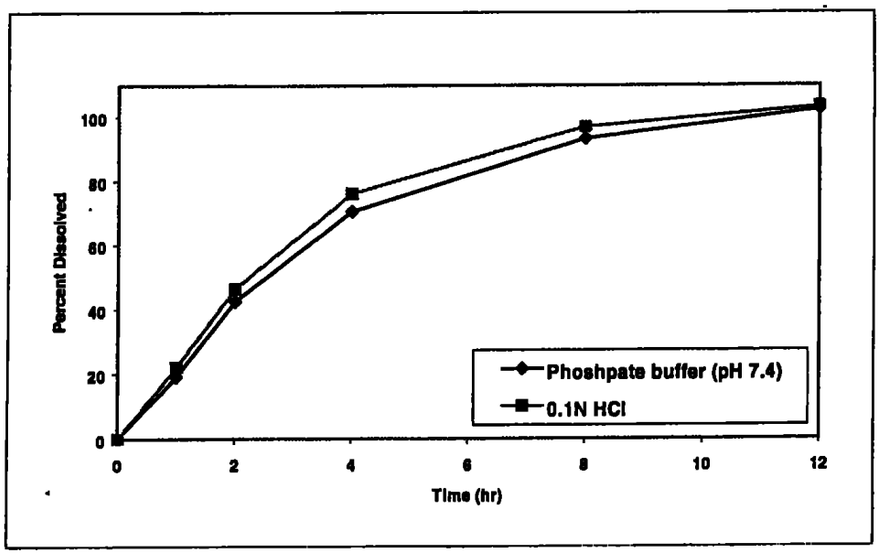


Figure 9 CPM BLOOD PROFILES, SINGLE DOSE

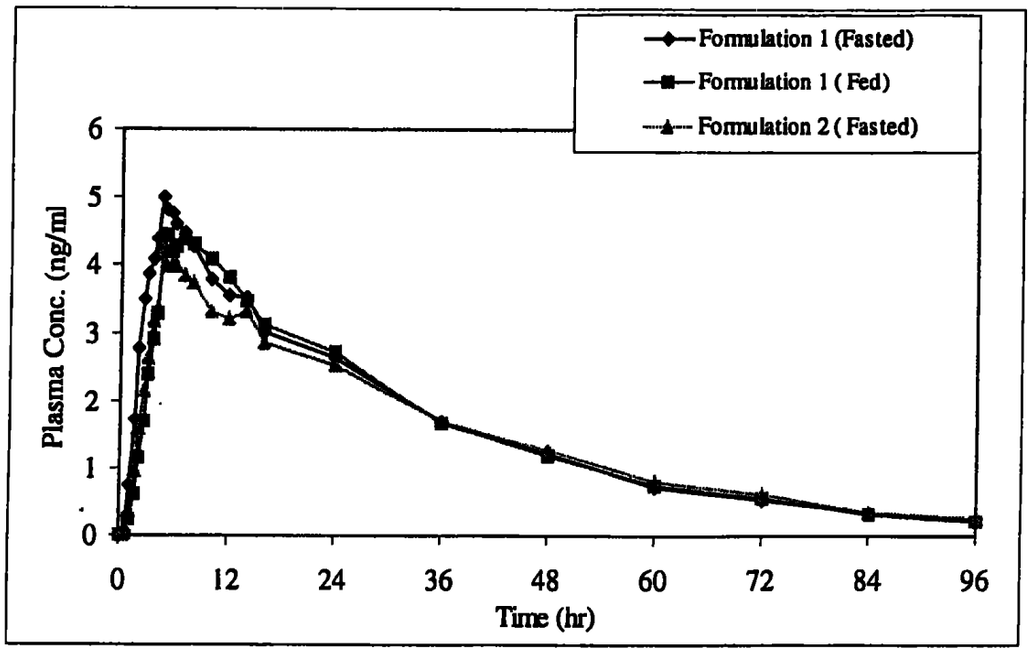


FIGURE 10 PPA BLOOD PROFILES, SINGLE DOSE

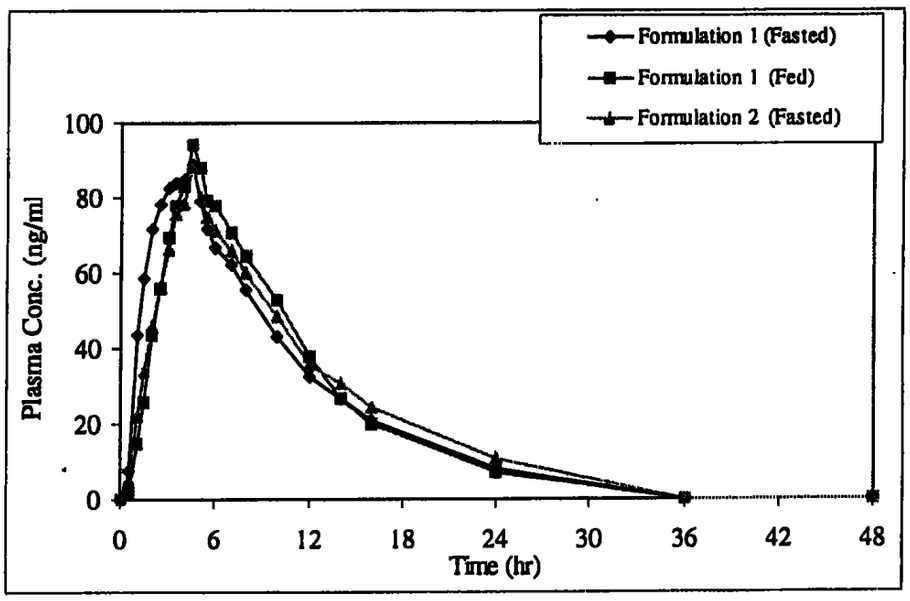


FIGURE 11 CPM In Vivo Blood Levels, Single Dose 75/8 Formulation

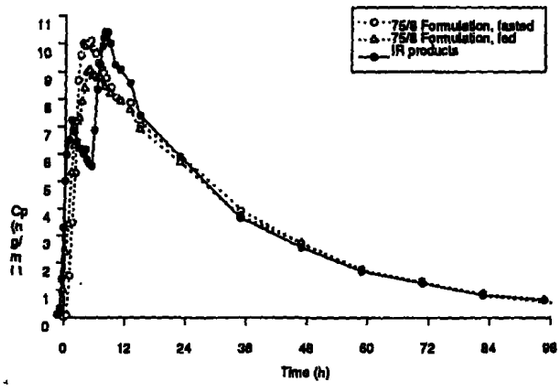
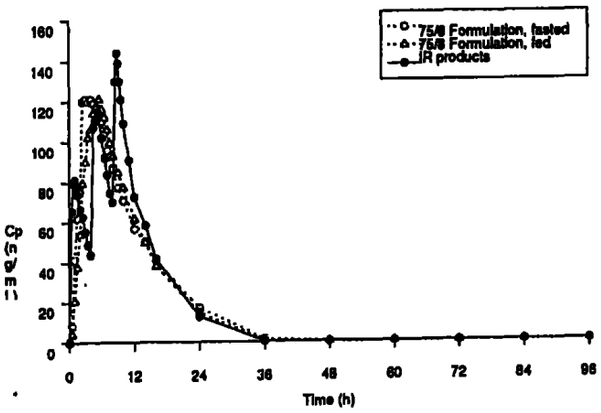


FIGURE 12 PPA In Vivo Blood Levels, Single Dose 75/8 Formulation



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PCT/US00/25279

Figure 13 NEW AQUEOUS COATING SPANSULE TECHNOLOGY (for CPM)

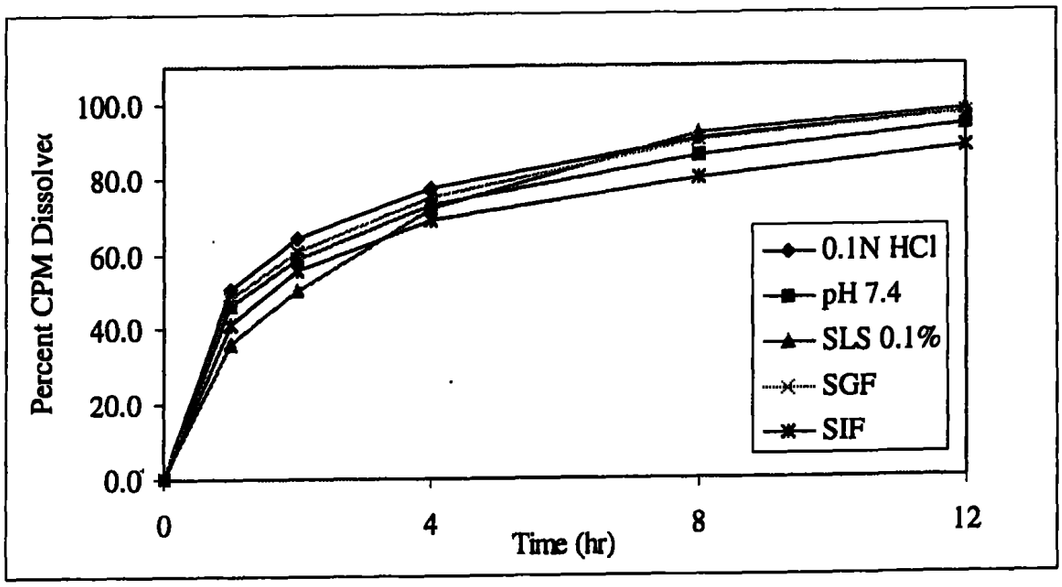

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Figure 14 Effect of changes in Surelease levels on pseudoephedrine HCl release rates

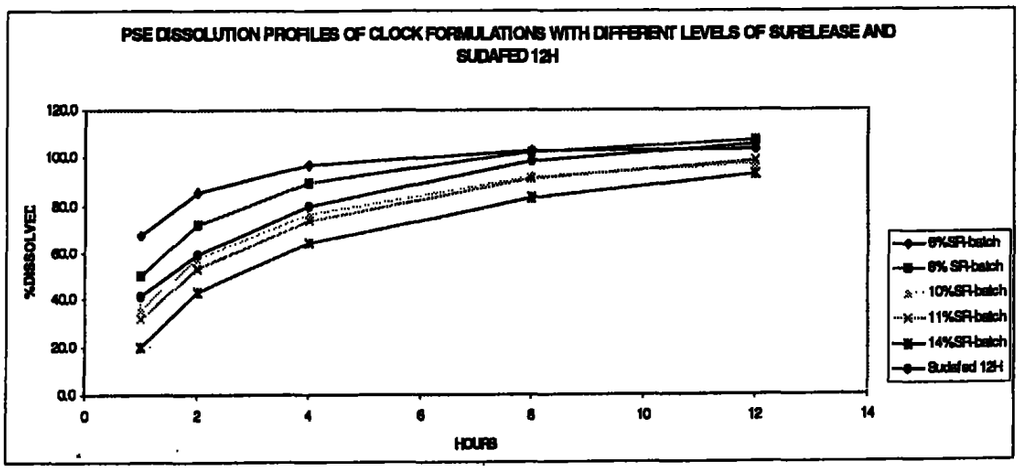

Figure 15 Effect of Media on Dissolution Rates of a Clock Formulation and Sudafed 12 Hour

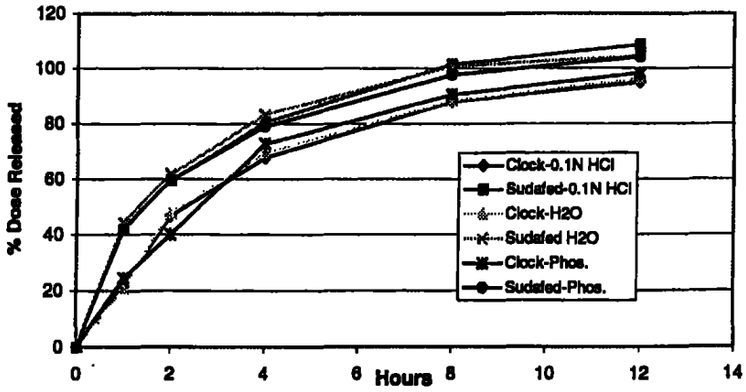

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Figure 16 Mean Plasma Levels of PSE Concentration as a Linear Plot

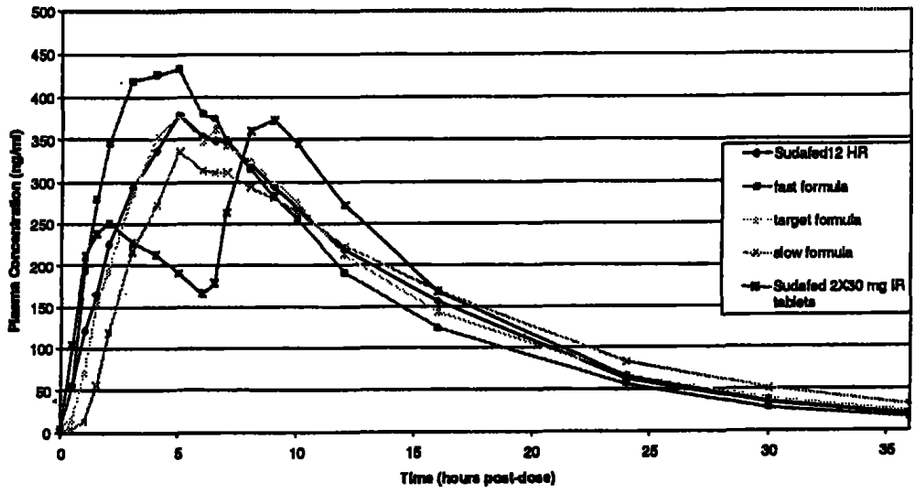

Figure 17 Particle Size distribution of Dextromethorphan HBr Powder

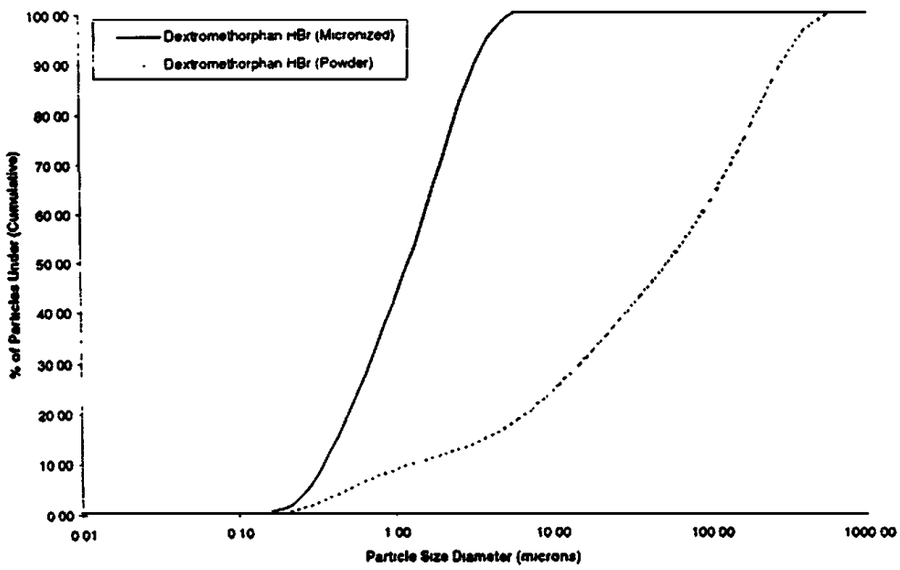

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Figure 18 Particle Size distribution of Micronized Dextromethorphan HBr

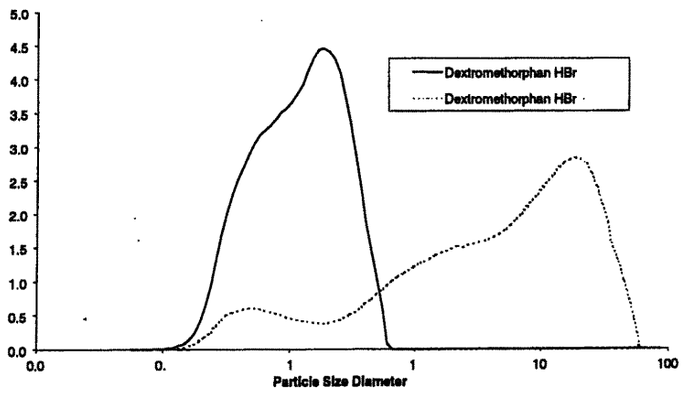

Figure 19 In-Vitro Dissolution Profile of Dextromethorphan Beadlets

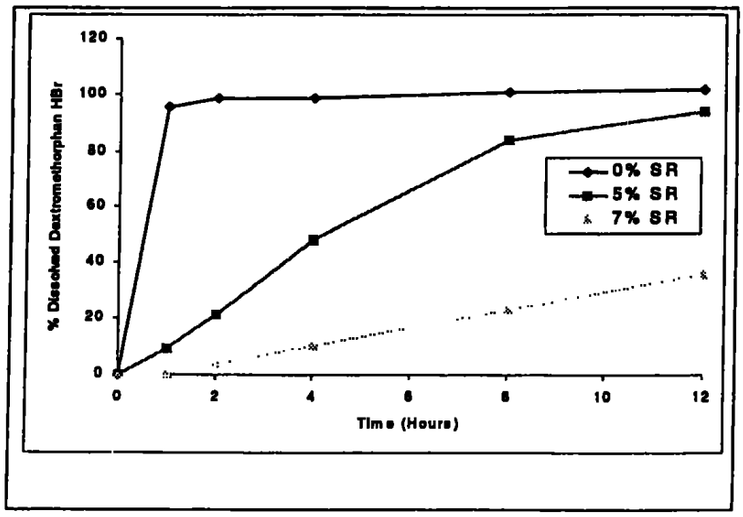

Figure 20 In Vivo Blood Levels of Dextromethorphan

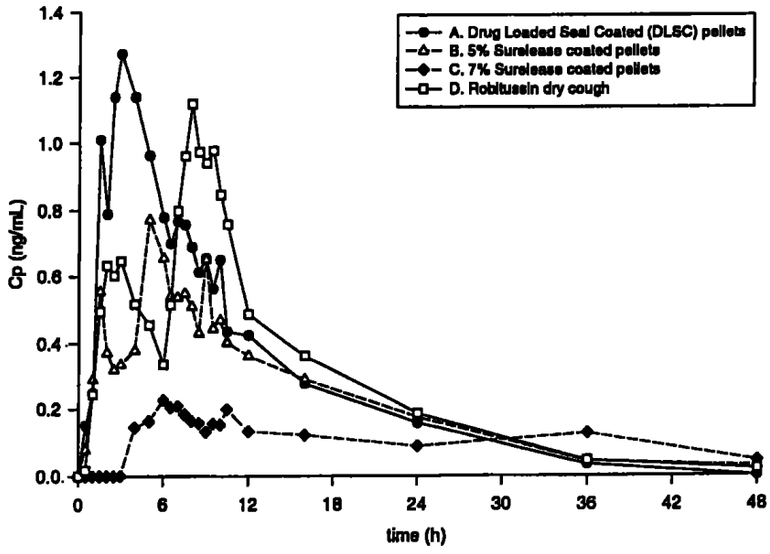

Figure 21 In Vivo Blood Levels of Free Dextromethorphan

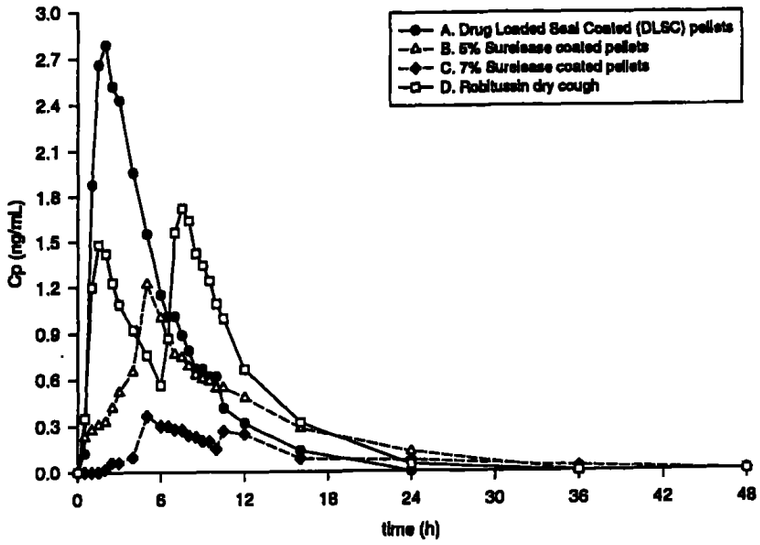

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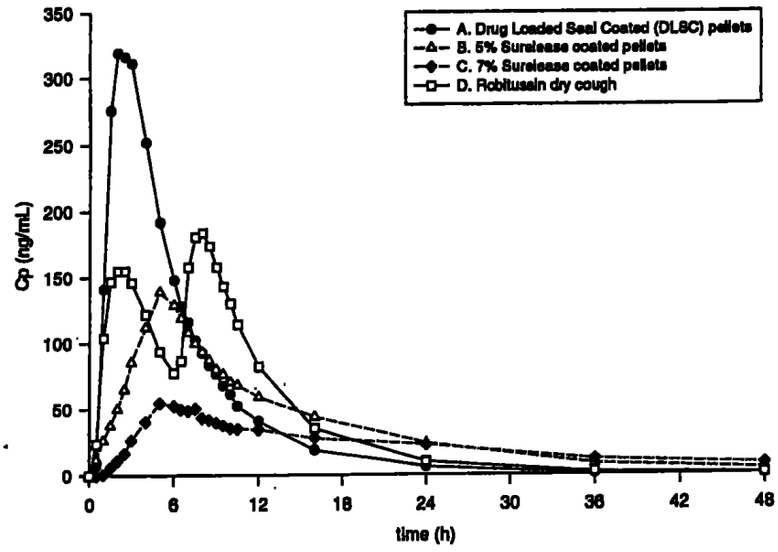
Figure 22 In Vivo Blood Levels of Total Dextromethorphan



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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 March 2001 (22.03.2001)

PCT

(10) International Publication Number
WO 01/19901 A3

(51) International Patent Classification[7]: A61K 9/14, 9/16, 9/20, 9/22, 9/26

(21) International Application Number: PCT/US00/25279

(22) International Filing Date:
14 September 2000 (14.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/153,850 14 September 1999 (14.09.1999) US

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).

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(74) Agents: DINNER, Dara, L. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(81) Designated States *(national)*: AE, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CZ, DZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
27 September 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/19901 A3

(54) Title: PROCESS FOR MAKING AQUEOUS COATED BEADLETS

(57) Abstract: The present invention is directed to application of novel process conditions for aqueous coating techniques of water soluble active agents, and its application to production of sustained release beadlets of said agents. The improvement lies in the determination and use of the glass transition point for the water swellable polymer used to produce the sustained release effect, and control of the moisture content of the air by dew point.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/25979

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 9/14, 9/16, 9/20, 9/22, 9/26.
US CL. :424/464, 465, 468, 469, 470, 489, 490, 497.
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)

U.S. : 424/464, 465, 468, 469, 470, 489, 490, 497.

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

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

west

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,780,055 A (HABIB et al.) 14 July 1998; see column 15, lines 31-63, column 26, lines 20-62, column 27, lines 57-67, column 31, lines 20-54, column 32, lines 10-54, column 67, lines 1-35.	1-4
Y	US 5,500,227 A (OSHLACK et al.) 19 March 1996; see column 2, lines 55 through column 3, lines 1-12, column 5, lines 65 through column 6, lines 1-40, column 8, lines 53-63, column 14, lines 7-39.	1-4

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

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search 20 FEBRUARY 2001	Date of mailing of the international search report 23 MAR 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SUSAN T FRAN Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*

ENSDOCID: <WO___0116601A3_I_>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/25879

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-4

Remark on Protest
☒ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/25279

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-4, drawn to product comprising phenylpropanolamine coated with pseudolatex polymer.
Group II, claim(s) 11-13, drawn to beadlets of chlorpheneramine coated with pseudolatex polymer.
Group III, claim(s) 24-27, drawn to aqueous coating process.
Group IV, claim(s) 41-44, drawn to pseudoephedrin beadlets coating with pseudolatex polymer.
Group V, claim(s) 62-65, drawn to dextromethorphan beadlets coating with pseudolatex polymer.
Group VI, claim(s) 84-92, drawn to dextromethorphan in capsule form.

The inventions listed as Groups I-VI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

They do not share the same essential features that define the "special technical feature" necessary to specify a contribution over the prior art. The technical feature common to all the groups is coated beadlets which is known in the art and, therefore, cannot be said to be the special technical feature which makes a contribution over the prior art. All other substituents differ from each other, in example, dextromethorphan in capsule form and phenylpropanolamine in coated beadlets, each of which are known in the prior art. Thus, these claims lack the corresponding special technical feature(s) necessary to link them together to fulfill the Unity of Invention requirement.

Applicant is advised that the reply to this requirement to be completed must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

EN3DOCID: <WO___0116601A2_I_>

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CANADIAN INTELLECTUAL PROPERTY OFFICE

Ottawa Hull K1A 0C9

(21) (A1) 2,139,896
(22) 1995/01/10
(43) 1996/07/11

(51) Int.Cl.[6] A61K 31/44

(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Use of Antinauseant Agent for Terminally Ill Humans

(72) McDonah, Don B. - U.S.A. ;

(71) Duchesnay Inc. - Canada ;

(57) 7 Claims

Notice: This application is as filed and may therefore contain an incomplete specification.

ABSTRACT OF THE DISCLOSURE

Disclosed herein is the use of a mixture of Doxylamine succinate and Pyridoxine HCl (Vitamin B6) in approximately equal weight ratios together with a pharmaceutically acceptable carrier to prevent and suppress the symptoms of nausea and vomiting among terminally ill individuals.

ENSDOCID: <CA__2139896A1_I_>

FIELD OF THE INVENTION

The present invention relates to the field of antinauseant agents and their use. More specifically, the present invention relates to the noval use f an antinauseant agent, namely a mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight ratios, directed to terminally ill humans.

BACKGROUND OF THE INVENTION

Nausea is probably the second most frequently encountered symptom in the management of people approaching death. It is second only to pain. Nausea is a poorly understood condition which may be subjectively described as the unpleasant feeling of the need to vomit and is often accompanied by other symptoms such as dizziness, vertigo, chills and sweating. It has a wide range of effects ranging from being a mild nuisance to a severely debilitating problem.

It is generally agreed that the vomiting control zone in the human body in situated in the brain stem. This vomiting centre has a direct effect n the gut. The vomiting centre is understood to be affected by various sources such as:

(i) local receptors in the gut during digestion, local irritation by medications or alcohol;

(ii) the vestibular apparatus as stimulated by motion, sight, smell and taste;

(iii) the cerebral cortex as stimulated by stress or other psychological factors such as anxiety disorders;
(iv) increased intra-cranial pressure associated with brain tumours;
(v) the chemoreceptor trigger zone (CTZ), situated in the medulla of the brain stem and having direct link to the vomiting centre.

For terminally ill patients, pain control often requires the use of various pain killers such as narcotics which will stimulate the CTZ. Chemotherapy agents are also generally known to stimulate the CTZ. This will often trigger nausea because of its effect f the vomiting centre. Accordingly, both the drug therapy and the disease afflicting the terminally ill patient contribute to the debilitating symptoms of nausea.

A number of classes of antinauseant agents are known to work with varying degrees of success for terminally ill humans. One important drawback with most known antinauseant agents are their unwanted side effects. Another drawback is that many patients will fail to respond to traditional antinauseant agents used in palliative care.

One class of known antinauseant are the phenothiazines. These act mainly as dopamine antagonists, in other words by blocking the dopamine receptors in the CTZ. However, they also have sedating properties, may cause confusion and have other extra-pyramidal side effects such as low blood pressure,

negative cardiac effects, mobility decrease effects. Consequently, this medication should not be used for severely depressed patients, those with liver disease, renal insufficiency, important cardiovascular dis rders or Parkinson's disease. The two most commonly used phenothiazines are Prochlorperazine (sold as Stemetil™) and Haloperidol (sold for example as Haldol™, Novo-Peridol™).

Another class of antinauseant medication are the upper gastro-intestinal motility agents. One such agent is Metoclopramide HCl (sold as Maxeran™) which acts both on the gut and centrally by crossing the blood brain barrier to block dopamine receptors in the CTZ. It is particularly indicated for patients undergoing chemotherapy. Among their side effects profile is inducing confusion, especially among elder patients. Two other gastro-intestinal motility agents are Domperid ne maleate (sold as Motilium™) and Cisapride (sold as Prepulsid™). However, these latter two agents do not cross the blood brain barrier to block dopamine receptors in the CTZ. Their side effects profile includes confusion.

Another class of antinauseant agent is Nabilone (sold as Cesamet™) which is a marijuana derivative. Its mechanism of action is not quite understood. Although it may be quite effective for some patients, it is accompanied by side effects which may be distressing t

the patient, such as drowsiness, vertigo and psychotropic effects.

Dexamethazone (sold as Decadron™ or Dexasone™) is another class of agent used on occasion to treat the symptoms of nausea and vomiting. It works quite well f r patients having increased intercranial pressure resulting from for example brain tumours. It is believed to help in chemotherapy induced nausea and vomiting by what appears to be a decrease in cerebral edema which may occur around both the CTZ and the vomiting centre.

Antihistamines are commonly used in nausea and vomiting but are generally less effective than phenothiazines. The most common antihistamine nausea medication is Gravol™. They are known to work well in nausea and vomiting related to vestibular stimulation and may, in some instances, have a sedating effect.

Benzodiazepines are another class of agents sometimes used as antinauseants. They are felt to work at the cerebral cortex level by decreasing anxiety and other psychological disorders.

Consequently, there remains a need for an improved antinauseant agent showing minimal or no side effects and effective in a palliative care setting where the symptoms associated with nausea and vomiting are particularly debilitating. The need is exacerbated where the traditional antinauseant agents bear a number of unwanted side effects or are merely effective for some sources of nausea and vomiting. The need is also

exacerbated when the patient is not responsive or only partially responsive to traditional palliative care antinauseant agent.

Another class of antinauseant agent, not previously used in palliative care but rather for treating the symptoms of morning sickness among pregnant women and, in some extreme cases hyperemesis gravidarum, consists of a mixture of Doxylamine succinat and Pyridoxine HCl in approximately equal weight. This antinauseant agent is currently available under the trademark Diclectin™. So far, the use of Diclectin™ has been restricted to the treatment of the specific forms of nausea and vomiting among pregnant women such as hyperemesis gravidarum and morning sickness. Pri r to the present invention, it was not known nor predictable that a mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight could be effectively used in a palliative care setting to treat the nausea and vomiting associated with chemotherapy, pain-killing pharmacological therapy, various terminal diseases and conditions. Indeed, the physiological and therapeutical causes of nausea and vomiting encountered in a palliative care setting are completely different from the causes of nausea and vomiting among pregnant women which are generally thought to be related to hormonal changes during pregnancy.

Accordingly, it is an object f the present invention to divulge a novel use f r a mixture f

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Doxylamine succinate and Pyridoxine HCl in approximately equal weight, namely for the treatment of the symptoms of nausea and vomiting among terminally ill humans.

Other objects and further scope of applicability of the present invention will become apparent from the detailed description given hereinafter. It should be understood, however, that this detailed description, while indicating preferred embodiments of the invention, is given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art.

SUMMARY OF THE INVENTION

The invention provides the use of a therapeutically effective amount of a mixture f Doxylamine succinate and Pyridoxine HCl in approximately equal weight for preventing and suppressing the symptoms of nausea and vomiting in terminally ill humans.

In a preferred embodiment, the use of a mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight is directed to patients undergoing chemotherapy.

In other embodiments, the use of a mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight is directed to patients suffering from cancer or from Acquired Immunity Deficiency Syndrome (A.I.D.S.).

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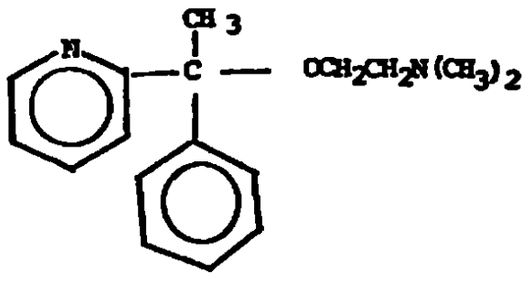
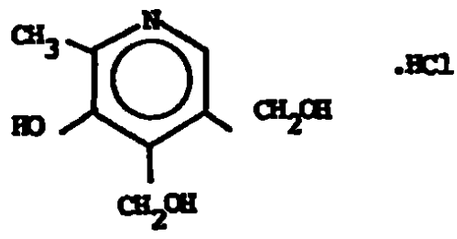
Other features and advantages of the invention will become apparent to those of ordinary skill in the art upon review of the following detailed descripti n and claims.

DETAILED DESCRIPTION

Diclectin™ consists of a mixture of two pharmaceutical substances in approximately equal proportions together with a pharmaceutically acceptable carrier. The two pharmaceutical substances are Doxylamine succinate, an antihistamine, and Pyridoxine HCl, which is Vitamin B6. The shorthand chemical formulas of the substances are illustrated below:



Doxylamine succinate



Pyridoxine HCl

The precise mechanism of how Diclectin™ is effective f r treating the symptoms of morning sickness and hyperemesis gravidarum remains unknown. It is generally agreed that there is a synergistic effect between the two active ingredients found in Diclectin™. Diclectin™ is known to be prescribed in delayed release tablet form; each tablet

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containing 10mg of each of Doxylamine succinate and Pyridoxine HCl, for pregnant women suffering from the symptoms of morning sickness or hyperemesis gravidarum during the first few weeks of pregnancy. The dosage is usually 1-4 tablets daily.

Diclectin™ is not known as a general antinauseant agent. However, it was surprisingly found that Diclectin™ can be used for effectively controlling the symptoms of nausea and vomiting experienced by terminally ill patients without the debilitating side-effects encountered with other antinauseant agents, such side effects as trembling, low blood pressure, mobility decrease, rigidity, negative cardiac effects, confusion, vertigo, etc. It was also surprisingly found that when patients poorly responded to other antinauseant agents traditionally used for patients suffering from a terminal illness, those patients often did respond to Diclectin™. It was also surprisingly found that following examples given for illustrative purposes demonstrate the novel use of Diclectin™ among terminally ill patients suffering from excessive nausea and vomiting.

EXPERIMENTAL

The following examples are given solely for illustrative purposes and to demonstrate the novel use f Diclectin™ among terminally ill patients suffering from excessive nausea and vomiting.

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Example 1

A female patient, 50 years of age, had an advanced form of colon carcinoma. At the time f diagnosis, the carcinoma was disseminated through her pelvis and abdomen. She suffered from pain but also from extreme and debilitating nausea and vomiting. Her nausea and vomiting had forced her to remain hospitalized for extanded periods of time although the rate of progression of her disease would have allowed to perform some normal activities for a few months. She was poorly responsive to traditional antinauseants such as gastro-intestinal motility agents, for example, Maxeran™ or Motilium™ or phenothiazines. Diclectin™ was then administered to her in an effort to control her nausea and vomiting. She took 40mg in tablet form at night and 20mg also in tablet form in the morning. She showed a dramatic improvement and was, a short while later, able to go home and resume some normal activities by taking Diclectin™ f r approximately four months. She was even able to enjoy her sailboat a few times during that summer. It is noted that at one point during her Diclectin™ therapy, feeling better, she attempted to discontinue the use of Diclectin™ only to find a resurgence of her nausea and vomiting. She resumed taking Diclectin™ and was soon cleared again of her nausea and vomiting problem.

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Example 2

A male patient, 74 years of age, diagnosed with carcinoma of the prostate and metastatic disease to his bones. Not only did he experience pain but he had a severe problem of nausea. He would be nauseated upon waking up to about noon and would then feel somewhat better as the day went on. It was not determined why the patient was nauseated. He was poorly responsive to traditional antinauseants. Diclectin™ was administered to him in small doses of 20mg. In the space of approximately 4 days, he showed a dramatic improvement. He was not able to leave the hospital because of the advanced state of his disease but during the two weeks prior to his death, he was able to take fluids and did not experience that terrible feeling of nausea which had afflicted him prior to taking Diclectin™.

Example 3

A female patient, diagnosed with breast cancer. She frequently was plagued by bouts with nausea and vomiting. She was initially treated with a phenothiazines (Stemetil™) to which she responded poorly because of the adverse side extra-pyramidal reacti ns including tremor, rigidity, etc. which made her appear to be developing Parkinson's disease. The phenothiazine therapy was discontinued and replaced by Diclectin™.

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Shortly thereafter, in the space of approximately one week, the patient's nausea was controlled and the extra-pyramidal effects of the previous medication were gone.

Although the invention has been described above with respect with one specific form, it will be evident to a person skilled in the art that it may be modified and refined in various ways. It is therefore wished to have it understood that the present invention should not be limited in scope, except by the terms of the following claims.

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The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. The use of a therapeutically effective amount of a mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight ratios f r preventing and suppressing the symptoms of nausea and vomiting in terminally ill humans.

2. The use of claim 1 wherein said therapeutically effective amount of a mixture f Doxylamine succinate and Pyridoxine HCl in approximately equal weight ratios is administered orally together with a pharmaceutically acceptable carrier.

3. The use of claim 1 wherein said therapeutically effective amount of a mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight ratios is administered as a rectal suppository.

4. The use of claim 1 wherein said therapeutically effective amount of a mixture f Doxylamine succinate and Pyridoxine HCl in approximately equal weight ratios is administered intravenously.

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5. The use of any of the preceding claims wherein said terminally ill humans suffer from cancer.

6. The use of any of claims 1 to 4 wherein said terminally ill humans suffer from acquired immunity deficiency syndrome (A.I.D.S.).

7. The use of any of claims 1 to 4 wherein said mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight ratios is administered 1 to 4 times daily, each daily dose consisting of 20-240mg.

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(19) RÉPUBLIQUE FRANÇAISE

INSTITUT NATIONAL
DE LA PROPRIÉTÉ INDUSTRIELLE

PARIS

(11) N° de publication : **2.085.641**
(A n'utiliser que pour le classement et les commandes de reproduction.)

(21) N° d'enregistrement national : **70.14333**
(A utiliser pour les paiements d'annuités, les demandes de copies officielles et toutes autres correspondances avec l'I.N.P.I.)

(13) DEMANDE DE BREVET D'INVENTION

1re PUBLICATION

(22) Date de dépôt..... 20 avril 1970, à 10 h 30 mn.
(41) Date de la mise à la disposition du public de la demande..... B.O.P.I. — «Listes» n. 52 du 31-12-1971.

(51) Classification internationale (Int. Cl.).. A 61 k 27/00.

(71) Déposant : INVESTIGATIONS SCIENTIFIQUES PHARMACEUTIQUES, résidant en France.

Titulaire : *Idem* (71)

(74) Mandataire : Jean Pierre Dóst.

(54) Nouveau médicament à action antiinflammatoire.

(72) Invention de :

(33) (32) (31) Priorité conventionnelle :

Vente des fascicules à l'IMPRIMERIE NATIONALE, 27, rue de la Convention - PARIS (15e)

BNSDOCID: <FR___2085641A1_I_>

La présente invention a pour objet, à titre de médicament nouveau des compositions pharmaceutiques renfermant une association de succinate de Doxylamine et de Noramidopyrine methane sulfonate de sodium.

La Noramidopyrine est connue pour ses propriétés analgésiques, antipyrétiques et antiinflammatoires, tandis que le succinate de doxylamine est utilisé pour ses propriétés antihistaminiques.

L'intérêt de la présente invention réside dans la potentialisation des effets de la Noramidopyrine par la Doxylamine, en particulier de l'activité antiinflammatoire.

Les nouvelles compositions pharmaceutiques conformes à l'invention sont des compositions administrables par voie orale et voie rectale.

Les travaux pharmacologiques ont porté, notamment, sur l'activité antiinflammatoire, étudiée au moyen de plusieurs tests. La technique de l'oedème à la carragenine décrite par Winter, a montré que la différence d'action entre la Noramidopyrine et l'association est significative ; le principe de cette technique est le suivant : on administre à plusieurs séries de rats, pendant trois jours consécutifs, la drogue et le troisième jour, une heure après l'ingestion, les animaux reçoivent, par voie intradermique, une injection d'une suspension à 2 % de carragenine ; on note l'augmentation de volume de la patte traitée par rapport à son volume initial. On calcule le pourcentage aux différentes heures de lecture (1 h - 3 h - 4 h - 6 h après l'injection) : la différence entre les animaux témoins, ceux traités par la Noramidopyrine seule et ceux traités par l'association est très significative.

Une autre technique pour la mise en évidence de cette potentialisation a été employée : celle des granulomes par pellets de coton. Elle consiste à traiter par voie orale les animaux comme précédemment, pendant 5 jours : le premier jour, 4 pellets de coton stérile de poids identique, sont mis en place sur la peau du dos, distants les uns des autres d'au moins 3 cm. Le troisième jour, les animaux sont sacrifiés, autopsiés, les granulomes sont disséqués et pesés :

- par rapport aux témoins, les deux lots traités se distinguent de manière évidente et l'association Noramidopyrine-Doxylamine donne des résultats supérieurs d'au moins 30 % à ceux de la Noramidopyrine seule.

La potentialisation de l'action antiinflammatoire de la nouvelle composition est donc bien mise en évidence.

D'autres tests ont porté également sur l'activité analgésique :

- étude des contorsions après injection intra peritonéale de phenylbenzoquinone selon la technique de KOSLER ;
- étude des contorsions après injection d'acide acétique ;

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- test de la plaque chauffante.

Pour tous ces tests on constate également une augmentation du pouvoir antalgique.

L'activité antipyrétique a été, d'autre part, testée selon la technique de Bianchi qui consiste à pratiquer une injection sous-cutanée d'une suspension à 20 % de levure de bière Codex, micronisée.

Les températures rectales sont relevées avant et 16 heures après l'injection, les produits sont alors administrés par voie orale et les températures relevées 45 minutes, 2 h - 3 h - 5 h - et 8 h après.

L'activité antipyrétique de l'association par rapport à la Noramidopyrine s'est revélée là aussi supérieure.

Ces tests d'activité sont donc probants et montrent bien la potentialisation existant dans l'association considérée et donc l'intérêt thérapeutique d'un tel produit.

Il était donc intéressant de mettre à profit ces excellents résultats en clinique humaine : ils ont d'ailleurs été confirmés.

Nous pouvons ainsi relever de cette expérimentation, à titre d'exemple, les résultats obtenus.

Ils sont particulièrement remarquables (85 % des cas) dans les algies et avulsions dentaires. Administrées dès la veille de l'intervention, ces compositions pharmaceutiques, permettent, d'une façon générale, une anesthésie plus rapide ; d'autre part, elles diminuent l'anxiété et la nervosité précédant habituellement ces interventions.

Elles permettent ensuite une sédation rapide de la douleur et un effet antiinflammatoire très utile pour une meilleure résorption de l'oedème consécutif à l'avulsion.

Dans les algomenorrhées les résultats sont excellents dans 65 % des cas.

On retrouve l'intérêt d'une telle association en rhumatologie (lombalgies, sciatiques, etc...) où 75 % de bons résultats ont été observés.

Les états fébriles sont susceptibles d'être améliorés par cette médication qui constitue un excellent traitement symptomatique.

En cancérologie, dans 50 % des cas, on obtient de bons résultats particulièrement intéressants car ce médicament permet de réduire les traitements des opiacés et dérivés similaires (posologie et durée).

On a pu enfin enregistrer quelques résultats positifs dans le traitement du zona, la composition agissant particulièrement sur la douleur, apportant d'autre part un effet légèrement tranquillisant.

Il est à noter que ces compositions sont peu toxiques et n'ont

pas entraîné l'apparition d'effets secondaires : brûlures gastriques, diarrhées, réactions allergiques, etc.

Le médicament peut être administré par voie orale ou rectale, sous forme de comprimés, gélules, dragées, sirop, suppositoires, les produits étant associés aux véhicules et excipients appropriés.

On peut également, bien entendu, l'associer à d'autres substances pharmaceutiques actives telles que, par exemple, vitamines (groupe B) et Vitamine C, tranquillisants, barbituriques, antispasmodiques.

Exemple 1

Comprimés

Noramidopyrine	0.500 g
Doxylamine -succinate-	0,0125 g
Excipient QSP	1 comprimé

Exemple 2

Comprimés

Noramidopyrine	0.500 g
Doxylamine (succinate)	0.0125 g
Caféine	0.050 g
Excipient QSP	1 comprimé

Exemple 3

Comprimés dragéifiés

Noramidopyrine	0.500 g
Doxylamine (succinate)	0.0125 g
Vitamine B 1	0.250 g
Vitamine B 12	1 000 mcg
Excipient QSP	1 comprimé dragéifié

Exemple 4

Suppositoires

Noramidopyrine	0.500 g
Doxylamine (succinate)	0.0125 g
Caféine	0.050 g
Excipient QSP	1 suppositoire

Exemple 5

Sirop

Noramidopyrine	0.500 g
Doxylamine (succinate)	0.0125 g
Paracetamol	0.50 g
Excipient QSP	100 ml

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REVENDICATIONS

1. A titre de médicament nouveau, utile notamment comme antiinflammatoire analgésique et antipyrétique, des compositions renfermant notamment comme principes actifs de la Noramidopyrine methane sulfonate de sodium et du succinate de Doxylamine à doses therapeutiquement actives mais dont les effets analgésiques et antiinflammatoires notamment, sont la résultante d'une nette potentialisation.
2. Des compositions pharmaceutiques selon la revendication 1 présentées sous forme de comprimés, dragées, gélules, sirop ou suppositoires.
3. Les compositions pharmaceutiques selon les revendications 1 et 2 dans lesquelles d'autres principes actifs peuvent être éventuellement associés : vitamines, tranquillisants, barbituriques et antispasmodiques.

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United States Patent [19]

Peters et al.

[11] **Patent Number: 4,642,231**

[45] **Date of Patent: Feb. 10, 1987**

[54] **MAGNESIUM TRISILICATE SUITABLE FOR PREPARATION OF MEDICAMENT ADSORBATES OF ANTIHISTAMINES**

[75] Inventors: **David Peters, Long Valley; John Denick, Jr., Newton; Anil K. Talwar, Long Valley, all of N.J.**

[73] Assignee: **Warner-Lambert Company, Morris Plains, N.J.**

[21] Appl. No.: **811,053**

[22] Filed: **Dec. 19, 1985**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 516,002, Jul. 20, 1983, Pat. No. 4,581,232.

[51] Int. Cl.[4] A61K 9/18; A61K 33/12

[52] U.S. Cl. 424/15; 424/155; 514/770; 514/849; 514/948

[58] Field of Search 424/15, 155; 514/770, 514/948, 849

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Primary Examiner—Shep K. Rose
Attorney, Agent, or Firm—Charles A. Gaglia, Jr.; Gary M. Nath

[57] **ABSTRACT**

A medicament adsorbate containing a magnesium trisilicate having a surface area of at least 400 m^2/g and having a flake-like structure with multiple interstitial spaces, and having adsorbed therein from about 1% to about 20% by weight of the adsorbate of a medicament drug, wherein the medicament drug is an antihistamine.

7 Claims, 4 Drawing Figures

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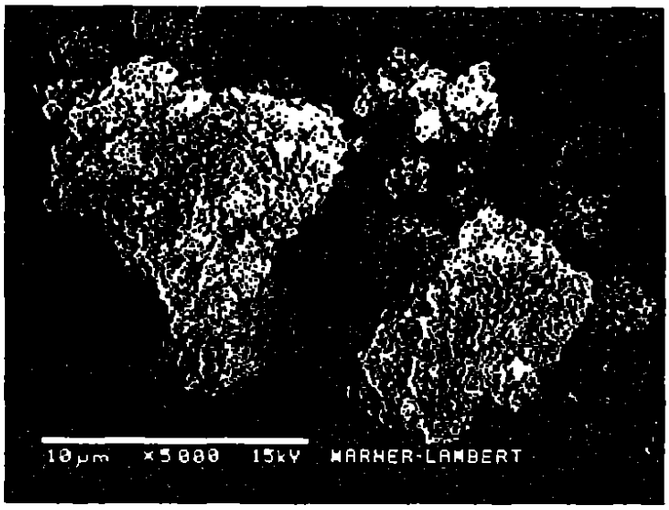

FIG. 1

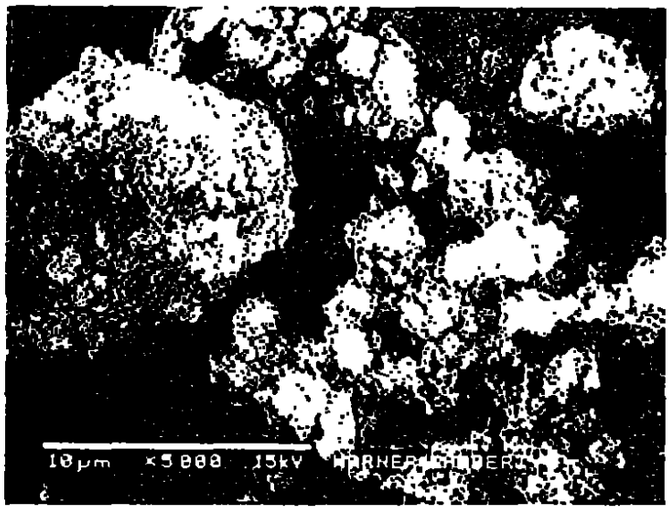

FIG. 2

FIG.3

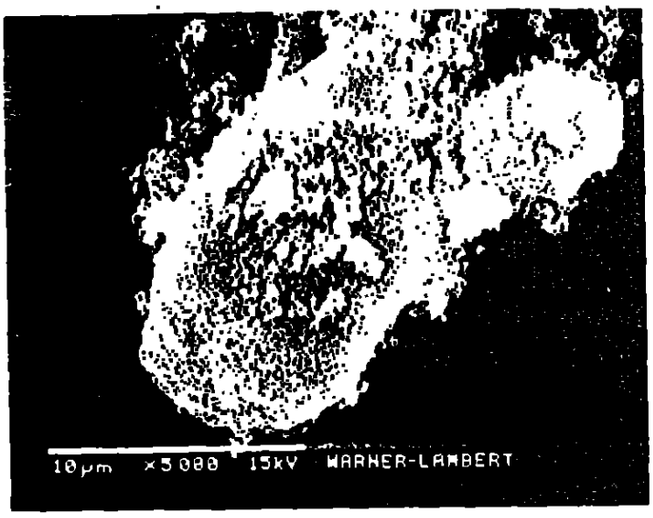

FIG.4

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MAGNESIUM TRISILICATE SUITABLE FOR PREPARATION OF MEDICAMENT ADSORBATES OF ANTIHISTAMINES

This is a continuation in part of copending U.S. application Ser. No. 516,002 filed July 20, 1983, now U.S. Pat. No. 4,581,232.

This invention relates to a medicament adsorbate composition containing magnesium trisilicate and in particular to a medicament adsorbate which employs a magnesium trisilicate having a surface area of at least 400 m^2/g with a surface structure having multiple interstitial-flaked spaces.

The use of magnesium trisilicates in the preparation of medicament adsorbates has been taught in the literature as a method to render bitter drug principles tasteless in liquid, tablet and chewable dosage forms which become readily bioavailable when the adsorbate reaches the low pH acid media of the stomach.

U.S. Pat. No. 3,085,942 to Magid discloses the formation of an antitussive composition using dextromethorphan and its acid addition salts adsorbed, in part, on magnesium trisilicate. Magid notes that particle size of the magnesium trisilicate is not critical in preparing the adsorbates and that average particle sizes of about 0.1 to about 150 microns are usable. Magid also notes that when the ingredients are intimately mixed, the bitter taste associated with dextromethorphan is reduced or eliminated. The adsorbate may be mixed with other ingredients to form compressed tablets, candy lozenges, chewing gum tablets and the like.

Most of these products when placed in the mouth and chewed, however, cause release of the medicament drug from the adsorbate resulting in the sensation of off-taste medicine to the user. Efforts therefore have been diverted to the development of products that either reduce the amount of medicament or mask the after-taste, such as by minimizing stimulation of the taste buds. These methods have involved various techniques such as microencapsulation as a method of coating particles or liquid droplets with edible polymeric materials; adsorption onto substrates capable of keeping the drugs adsorbed while in the mouth but releasing them eventually in the stomach or gastrointestional tract; spray congealing and spray coating involving taste masking of materials with fatty acids or monoglycerides and diglycerides of edible fatty acids; formation of different salts or derivatives by modification of the chemical composition of the drug substance itself.

It would, therefore, be desirable to develop a medicament adsorbate that would enable such products to be made without the bitter after-taste characteristics, that result from incorporating effective amounts of bitter medicaments, and that can be made and used easily without elaborate processing procedures.

Applicants have unexpectedly discovered that use of a particular magnesium trisilicate, rather than conventional magnesium trisilicates broadly, such as described by Magid, results in the formation of an adsorbate having adsorbency potentials greater than commercially available grades of magnesium silicates and achieves optimum medicament taste-masking characteristics while providing rapid bioavailability.

In particular, applicants have found that an adsorbate exhibiting unexpected results is only achieved with a magnesium trisilicate having a critical surface area of at least 400 mhu 2/g when the particles of the magnesium trisilicate exhibit a flake-like structure having multiple interstitial spaces.

This particular magnesium trisilicate has been found to be suitable for preparation of tasteless medicament adsorbates.

While the invention is not to be limited to theoretical considerations, it is believed that the surface area of the magnesium trisilicate coupled with the flaked-like surface results in an unusual ability to adsorb the medicament drug within the channels, convolutions or interstitial spaces of the adsorbate. Once adsorbed within the magnesium trisilicate, the drug is not available for organoleptic taste prior to passage into the digestive tract and subsequent desorption by the gastric juice. This pronounced adsorption effect is not found in normal commercially available magnesium trisilicate and appears to be unrelated to particle size.

Accordingly, the applicants have unexpectedly discovered a medicament adsorbate which comprises magnesium trisilicate having a surface area of at least 400 mhhu 2/g which has a flake-like structure having multiple interstitial space, containing from about 1% to about 20% by weight of the adsorbate of a medicament drug.

Applicants have also unexpectedly discovered a process for preparing the medicament adsorbate which process involves dissolving the medicament drug in a solvent, admixing magnesium trisilicate having a surface area of at least 400 m^2/g which has a flake-like structure with multiple interstitial spaces therewith to prepare a mass having a homogenous consistency to enable the medicament drug to migrate within the magnesium trisilicate interstitial spaces and recovering the medicament adsorbate product.

The medicament adsorbate of the invention may further include a pharmaceutically acceptable carrier and be in the form of a lozenge, tablet, toffee, nougat, chewy candy, and chewing gum.

Referring to the drawings:

FIG. 1 represents a photomicrograph of magnesium trisilicate of this invention magnified 5000X.

FIG. 2 represents a photomicrograph of a dextromethorphan HBr adsorbate of this invention magnified 5000X.

FIG. 3 represents a photomicrograph of a normal magnesium trisilicate magnified 5000X.

FIG. 4 represents a photomicrograph of a normal dextromethorphan HBr adsorbate magnified 5000X.

The magnesium trisilicate of the invention is a fine, white odorless powder free from grittiness having a surface area of at least 400 m^2/g, and preferably at least 400 m^2/g to about 1000 m^2/g and most preferably from about 440 to about 600 m^2/g which has a flake-like structure with multiple interstitial spaces. It has been unexpectedly found that magnesium trisilicates having these characteristics when used as an adsorbent aid in masking the bitter after-taste associated with various drug compounds.

The instant magnesium trisilicate is distinct from normally available magnesium trisilicates. The term magnesium trisilicate does not have a precise description but approximates the formula $2MgO_3SiO_2.xH_2O$. The physical texture and absorptive properties of magnesium silicates have been heretofore varied depending predominately upon their mode of preparation. These materials, however, generally possess a water content of 17 to 34%, a minimum of 20% magnesium oxide, a minimum of 45% silicon dioxide, and a ratio of MgO to SiO_2 of about 2.10 to about 2.30.

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The normal magnesium trisilicate has a surface area of less than 400 m^2/g and preferably less than 250m^2/g. These materials likewise are globular semi-spherical structures which are non-flake in appearance and are void of interstitial spaces. Such materials when used as an adsorbent have heretofore failed to effectively mask the bitter taste associated with adsorbed medication while maintaining satisfactory levels of drug activity. It is believed that such conventional materials have heretofore only been able to partially adsorb the medicament as described in U.S. Pat. No. 3,085,942 to Magid on the surface of the magnesium trisilicate. Since the surface of these materials is relatively smooth, efficient adsorption has not been possible and additional after-taste masking ingredients have been employed.

The method of making the magnesium trisilicates used in this invention is not critical and is not considered a part of this invention. Magnesium trisilicates of this invention are believed to occur naturally or may be prepared by standard techniques well known to the ordinary skilled artisan which would not involve undue experimentation. Such techniques generally use normal reactants, such as sodium silicate and magnesium sulfate which are reacted under heat, the magnesium trisilicate is precipitated and recovered. See for example U.S. Pat. No. 3,272,594.

The medicament drugs used herein may be selected from a wide variety of drugs and their acid addition salts. Both organic and inorganic salts may be used provided the drug maintains its medicament value and is soluble in the solvent. Exemplary acid salts include hydrochloride, hydrobromide, orthophosphate, benzoate, maleate, tartrate, succinate, citrate, salicylate, sulfate, and acetate.

The weight percent of the drug or its acid addition salt thereof, based on the weight of the adsorbate is preferably from about 1% to about 20%, and most preferably about 5% to about 15%, which amounts will vary depending upon the therapeutic dosage permitted.

Suitable categories of drugs that may be employed in the instant absorbate may vary widely and generally represent any stable adsorbate drug combination. Illustrative categories and specific examples include:

(a) Antitussives, such as dextromethorphan, dextromethorphan hydrobromide, noscapine, carbetapentane citrate, and chlophedianol hydrochloride;

(b) Antihistamines, such as chlorpheniramine maleate, phenindamine tartrate, pyrilamine maleate, doxylamine succinate, phenyltoloxamine citrate, diphenhydramine hydrochloride, promethazine and triprolidine;

(c) Decongestants, such as phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride, ephedrine; and

(d) Various Alkaloids, such as codeine phosphate, codeine sulfate and morphine.

These materials may be used alone or in combination on the adsorbate within the ranges specified above.

A particularly effective medicament adsorbate has been prepared using diphenydramine hydrochloride.

The medicament adsorbate of the invention can be prepared by conventional granulation and or slurry techniques. Both processes involve the initial step of dissolving the medicament drug in a suitable inert solvent and then mixing with the magnesium trisilicate. Solvent concentrations may vary widely but are generally from about 15% to about 60% by weight of the total composition. When mixing is performed with low amounts of solvent, for example 15% to about 35% by weight of the total composition, the resulting granulated product is removed and dried to a predetermined moisture content between 5% and 20% by weight of the final composition. When higher solvent concentrations are employed a slurry is formed containing the drug and magnesium trisilicate. Solvent concentrations may range from about 30% to 60% by weight of the total composition for optimum results. The solvent is then removed and the adsorbate recovered and used as a paste or dried to a free flowing powder.

Any solvent may be used in the inventive process to prepare the adsorbate providing it is capable of dissolving the medicament drug. Representative solvents include water; polyhalogenated lower hydrocarbons such as chloroform, methylene chloride; lower alcohols, such as methanol, ethanol, propanol and butanol; and aromatic solvents such as benzene, with water being the preferred solvent.

The medicament adsorbate once prepared may be stored for future use or formulated with conventional additives, that is pharmaceutically acceptable carriers, to prepare medicated compositions which offer a variety of textures to suit particular applications. Such compositions may be in the form of a lozenge, tablet, toffee, nougat, chewy candy, chewing gum, and so forth. The pharmaceutically acceptable carriers may be selected from a wide range of materials. Without being limited thereto, such materials include diluents, binders and adhesives, lubricants, disintegrants, colorants, flavorings, sweeteners and miscellaneous materials such as buffers and adsorbents in order to prepare a particular medicated composition. The preparation of confectionery and chewing gum products is historically well known and has changed very little over the years.

Lozenges are flavored medicated dosage forms intended to be sucked and held in the mouth. They may be in the form of various shapes, the most common being flat, circular, octagonal and biconvex forms. The lozenge bases are generally in two forms, hard, boiled candy lozenges and compressed tablet lozenges.

The hard boiled candy lozenges are prepared from a mixture of sugar and other carbohydrates that are kept in an amorphous or glassy condition. This form can be considered a solid syrup of sugars generally having from 0.5 to 1.5% moisture. Such materials normally contain up to 92% corn syrup, up to 55% sugar and from 0.1% to 5.0% water. The syrup component generally is prepared from corn syrups high in fructose, but may include other materials. Further ingredients such as flavorings, sweeteners, acidulents, colorants and so forth may also be added. In contrast, compressed tablet lozenges contain particular materials and are formed into structures under pressure. They generally contain sugars in amounts up to 95% and typical tablet excipients such as binders and lubricants as well as flavors, colorants and so forth.

The lozenges may be made of soft confectionary materials such as those contained in nougat. These materials contain two primary components, namely a high boiling syrup such as corn syrup or the like, and a relatively light textured frappe, generally prepared from gelatin, egg albumen, milk proteins such as casein, and vegetable proteins such as soy protein, and the like. The frappe is generally relatively light, and may, for example, range in density from about 0.5 to about 0.7g/cc.

By comparison, the high boiling syrup, or "bob syrup", is relatively viscous and possesses a higher density, and frequently contains a substantial amount of

sugar. Conventionally, the final nougat composition is prepared by the addition of the "bob syrup" to the frappe under agitation, to form the basic nougat mixture. Further ingredients such as flavorings, oils, additional sugar and the like may be added thereafter also under agitation. A general discussion of the composition and preparation of nougat confections may be found in B. W. Minifie, *Chocolate, Cocoa and Confectionery*: Science and Technology, 2nd edition, AVI Publishnig Co., Inc., Westport, Conn., (1980), at Pages 424–425.

Pharmaceutical tablets of this invention may also be in the form of chewable forms. This form is particularly advantageous because of convenience and patient acceptance and rapid onset of bioactivity. To achieve acceptable stability and quality as well as good taste and mouth feel several considerations are important, namely amount of active substance per tablet, flavor, compressibility and organoleptic properties of the drug.

The preparation of chewable medicated candy is prepared by procedures similar to those used to make soft confectionary. This procedure generally involves the formation of a boiled sugar-corn syrup blend to which is added a frappe mixture. The boiled sugar-corn syrup blend may be prepared from sugar and corn syrup blended in parts by weight ratio of 90 to 10:10 to 90. This blend is heated to temperatures above 250° F. to remove water and to form a molten mass. The frappe is generally prepared from gelatin, egg albumen, milk proteins such as casein, and vegetable proteins such as soy protein, and the like which are added to a gelatin solution and rapidly mixed at ambient temperature to form an aerated sponge like mass. The frappe is then added to the molten candy base and mixed until homogenous at temperatures between 150° F. and 250° F. The medicament adsorbate can then be added as the temperature of the mix is lowered to around 150° F. to 200° F. whereupon additional ingredients are added such as flavors, and colorants. The formulation is further cooled and formed to pieces of desired dimensions.

A general discussion of the lozenge and chewable tablet forms of confectionery may be found in H. A. Lieberman and L. Lachman, *Pharmaceutical Dosage Forms: Tablets* Volume 1, Marcel Dekker, Inc., New York, N.Y. at pages 289 to 466.

With regard to the chewing gum formulation in particular, the amount of gum base employed will vary greatly depending on various factors such as the type of base used, consistency desired and other components used to make the final product. In general, amounts of about 5% to about 45% by weight of the final chewing gum composition are acceptable for use in chewing gum compositions with preferred amounts of about 15% to about 25% by weight. The gum base may be any water-insoluble gum base well known in the art. Illustrative examples of suitable polymers in gum bases include both natural and synthetic elastomers and rubbers. For example, those polymers which are suitable in gum bases, include, without limitation, substances of vegetable origin such as chicle, jelutong, gutta percha and crown gum. Synthetic elastomers such as butadiene-styrene copolymers, isobutylene-isoprene copolymers, polyethylene, polyisobutylene and polyvinylacetate and mixtures thereof, are particularly useful.

The gum base composition may contain elastomer solvents to aid in softening the rubber component. Such elastomer solvents may comprise methyl, glycerol or pentaerythritol esters of rosins or modified rosins, such as hydrogenated, dimerized or polymerized rosins or mixtures thereof. Examples of elastomer solvents suitable for use herein include the pentaerythritol ester of partially hydrogenated wood rosin, pentaerythritol ester of wood rosin, glycerol ester of wood rosin, glycerol ester of partially dimerized rosin, glycerol ester of polymerized rosin, glycerol ester of tall oil rosin, glycerol ester of wood rosin and partially hydrogenated wood rosin and partially hydrogenated methyl ester of rosin, such as polymers of α-pinene or, β-pinene; terpene resins including polyterpene and mixtures thereof. The solvent may be employed in an amount ranging from about 10% to about 75% and preferable about 45% to about 70% by weight to the gum base.

A variety of traditional ingredients such as plasticizers or softeners such as lanolin, stearic acid, sodium stearate, potassium stearate, glyceryl triacetate, glycerine and the like for example, natural waxes, petroleum waxes, such as polyurethene waxes, paraffin waxes and microcrystalline waxes may also be incorporated into the gum base to obtain a variety of desirble textures and consistency properties. These individual additional materials are generally employed in amounts of up to about 30% by weight and preferably in amounts of from about 3% to about 20% by weight of the final gum base composition.

The chewing gum composition may additionally include the conventional additives of flavoring agents, coloring agents such as titanium dioxide; emulsifiers such as lecithin and glyceryl monostearate; and additional fillers such as aluminum hydroxide, alumina, aluminum silicates, calcium carbonate, and talc and combinations thereof. These fillers may also be used in the gum base in various amounts. Preferably the amount of fillers when used will vary from about 4% to about 30% by weight of the final chewing gum.

In the instance where auxiliary sweeteners are utilized, the present invention contemplates the inclusion of those sweeteners well known in the art, including both natural and artificial sweeteners. Thus, additional sweeteners may be chosen from the following non-limiting list:

A. Water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, sugar, maltose, partially hydrolyzed starch, or corn syrup solids and sugar alcohols such as sorbitol, xylitol, mannitol and mixtures thereof.

B. Water-soluble artificial sweeteners such as the soluble saccharin salts, i.e., sodium, or calcium saccharin salts, cyclamate salts, acesulfam-K and the like, and the free acid form of saccharin.

C. Dipeptide based sweeteners such as L-aspartylphenylalanine methyl ester and materials described in U.S. Pat. No. 3,492,131 and the like.

In general, the amount of sweetener will vary with the desired amount of sweeteners selected for a particular chewing gum. This amount will normally be 0.001% to about 90% by weight when using an easily extractable sweetener. The water-soluble sweeteners described in category A above, are preferably used in amounts of about 25% to about 75% by weight, and most preferably from about 50% to about 65% by weight of the final chewing gum composition. In contrast, the artificial sweeteners described in categories B and C are used in amounts of about 0.005% to about 5.0% and most preferably about 0.05 to about 2.5% by weight of the final chewing gum composition. These amounts are ordinar-

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ily necessary to achieve a desired level of sweetness independent from the flavor level achieved from flavor oils. While water may be added independently with dry sweeteners, it will generally be added as part of a corn syrup or corn syrup mixture.

Suitable flavorings include both natural and artificial flavors, and mints such as peppermint, menthol, artificial vanilla, cinnamon, various fruit flavors, both individual and mixed, and the like are contemplated. The flavorings are generally utilized in amounts that will vary depending upon the individual flavor, and may, for example, range in amounts of about 0.5% to about 3% by weight of the final composition weight.

The colorants useful in the present invention, include the pigments such as titanium dioxide, that may be incorporated in amounts of up to about 1% by weight, and preferably up to about 0.6% by weight. Also, the colorants may include other dies suitable for food, drug and cosmetic applications, and known as F.D. & C. dyes and the like. The materials acceptable for the foregoing spectrum of use are preferably water-soluble. Illustrative examples include indigoid die, known as F.D. & C. Blue No. 2, which is the disodium salt of 5,5'-indigotindisulfonic acid. Similarly, the dye known as F.D. & C. Green No. 1, comprises a triphenylmethane dye and is the monosodium salt of 4-[4-Nethyl-p-sulfobenzylamino)diphenylmethylene]-[1-(N-ethyl-N-p-sulfoniumbenzyl)- 2,5-cyclohexadienimine]. A full recitation of all F.D. & C. and D. & C. and their corresponding chemical structures may be found in the Kirk-Othmer Encyclopedia of Chemical Technology, in volume 5, at Pages 857–884, which text is accordingly incorporated herein by reference.

Suitable oils and fats that are useable would include partially hydrogenated vegetable or animal fats, such as coconut oil, palm kernel oil, beef tallow, lard, and the like. These ingredients are generally utilized in amounts with respect to the comestible product of up to about 7.0% by weight, and preferably up to about 3.5% by weight of the final product.

It is generally accepted that as the required amount of active substance per structure gets smaller and/or less bad tasting, the task at arriving at an acceptable formulation becomes easier due to the greater number of formulations available. Alternately, extremely bad-tasting and/or high-dose drugs are difficult to formulate into medicament/chewable tablets. The medicament adsorbates of this invention overcome these difficulties.

The quantity of adsorbate used may vary widely depending upon the particular medicament drug dosage. Amounts of medicament of about 1.0 to about 400 mg per medicated dosage are useable dependant upon the particular medicament. Naturally amounts of medicament adsorbate used will be higher depending on the therapeutic dosage required and amount of medicament adsorbed on the substrate. Illustrative examples are described below.

The usual dosage of diphenhydramine hydrochloride is between 10 and 50 mg per tablet. Incorporation of the adsorbate into, for example, a candy base is not difficult because of its melting point and solvent solubility. It is compatible with most flavors and is stable over a wide pH range. The diphenhydramine hydrochloride when added as the medicament adsorbate avoids its bitter taste and flavoring difficulty.

The usual dosage of phenidamine tartrate is about 10 to 50 mg per tablet. The formulation is not difficult to flavor because of the absence of medicament after-taste. The usual dosage of pyrilamine maleate is 25 to 50 mg per tablet. The usual dosage range of chlorophenirамine maleate is 2 to 4 mg and lends itself easily to incorporation into a candy base. Naturally, the exact amount used will vary with the particular application and drug.

The medicament adsorbate is generally present with the pharmaceutically acceptable carrier in an amount of from about 1% to about 60% by weight of the final composition. The exact amount will be dependent upon the particular medicament and dosage required.

The present invention is further illustrated by the following examples. All parts and percentages in the examples and throughout the specification and claims are by weight unless otherwise indicated.

EXAMPLE 1

(Inventive Runs 1 and 2)

This Example demonstrates a method for preparing a dextromethorphan hydrobromide adsorbate.

To 30 grams water is mixed 6 grams dextromethorphan hydrobromide, at a water temperature around 90° C., until the drug was in solution. The solution was added to 60 grams magnesium trisilicate having a mean specific surface area of 506.1 m2/g and mixed until a homogenous dispersion resulted, approximately 30 minutes. The mix was then oven dried at 70° C. until a moisture content of below 15% was obtained. The product was then milled to prepare a white free-flowing powder containing 10% by weight dextromethorphan hydrobromide.

An organoleptic evaluation test was performed on the product to determine the presence or absence of bitterness. The instant product did not exhibit any bitterness or off taste when tested by a human panel of experts.

The specific mean surface area of the materials were measured using the Quantasorb Sorption System (Quantachrome Corporation, N.Y.)

The results are set forth in Table I.

FIG. 1 represents a photomicrograph of magnesium trisilicate of this invention magnified 5000X. The Figure depicted shows a flake-like structure having extensive interstitial spaces. The flake-like character is evident throughout the entire structure and does not merely appear on the surface. No agglomeration or other spherical particles are noted.

FIG. 2 represents a photomicrograph of the dextromethorphan HBr adsorbate prepared in this inventive example magnified 5000X. The Figure depicts a flake-like structure having extensive interstitial spaces. The flake-like character is evident throughout the structure and does not merely appear on the surface. No agglomerates or other spherical particles are noted.

EXAMPLE 2

(Comparative Runs A and B)

This Example demonstrates a dextromethorphan hydrobromide adsorbate believed to be prepared by the process of Example 1 of U.S. Pat. No. 3,085,942 to Hoffman-La Roche Inc. These materials are at least 10 years old. The process used broadly involved forming a mixture of dextromethorphan hydrobromide and magnesium trisilicate having an average particle size of 5-microns by dissolving the dextromethorphan hydrobromide in distilled water (80° C.), and then pouring the resulting solution onto the magnesium trisilicate. The resulting mixture is then thoroughly mixed by stirring

to form a slurry. The solvent is then removed by spray-drying. A white free-flowing powder is obtained.

An organoleptic evaluation test was performed on the adsorbate product to determine the presence or absence of bitterness. The product demonstrated acceptable characteristics in that it reduced the bitterness of the drug.

The mean specific surface area was measured as in Example 1, Run 1 with results set forth in Table I.

FIG. 3 represents a photomicrograph of the old magnesium trisilicate magnified 5000X. The Figure depicts an agglomerated product, with some interstitial spaces but absence of flake-like character throughout its structure.

FIG. 4 represents a photomicrograph of the old dextromethorphan HBr adsorbate magnified 5000X. The Figure depicts a smooth surfaced particle lacking interstitial spaces and flaked structure.

TABLE I

Run	Material	Mean Specific Surface Area (M^2/g)	Structure
Inventive 1	Magnesium trisilicate	506.1	Flaked (FIG. 1)
Comparative A	Old magnesium trisilicate	415.1	Agglomerated (FIG. 3)
Inventive 2	Dextromethorphan HBr-10% adsorbate	209.8	Flaked (FIG. 2)
Comparative B	Old dextromethorphan HBr-10% adsorbate	66.35	Smooth (FIG. 4)

EXAMPLE 3

Inventive Runs 3, 4, 5 and 6

Comparative Runs C, D, E and F

This Example compares the properties derived from various dextromethorphan HB adsorbates prepared by the process of Example 1 using different magnesium trisilicates from different commercial sources. The results are set forth in Table II.

TABLE II

	Magnesium Trisilicate		
Run	Adsorbate Taste	Mean Specific Surface Area (m^2/g)	Structure
Inventive 3	Good	441.8	Flaked
Inventive 4	Good	460.4	Flaked
Inventive 5	Good	564.2	Flaked
Inventive 6	Good	—	Flaked
Comparative C	Bitter	181.8	Smooth Surface
Comparative D	Bitter	240.8	Smooth Surface
Comparative E	Bitter	—	—
Comparative F	Bitter	—	—

Example 4

This example demonstrates a method for preparing a cold/sinus/asthma tablet formulation using an adsorbing prepared with chlorophenbramine maleate and pseudoephendrine HCl.

The following ingredients are mixed in the order indicated:

No.	Ingredients	Mg/Tablet
1.	Chlorpheniramine maleate-10% adsorbate (4.0 mg drug/tablet)	40.0
2.	Pseudoephedrine HCl 10% adsorbate (60.0 mg drug/tablet)	600.0
3.	Microcrystalline cellulose	37.3
4.	Lactose	113.0
5.	Modified cellulose gum	2.2
6.	Fumed silica	1.1
7.	Stearic acid	1.3
8.	Magnesium stearate	1.1
		796.0

Procedure

Screen #2, #7 and #8 through a 40 mesh sieve. Blend #1, #2, and #3 in V blender for 3 minutes. Add #4, #5 and #6 to step #2 and blend for 17 minutes. Add #7 to step #3 and blend for 3 minutes. Add #8 to step #4 and blend for 5 minutes to a hardness of 5.3 mg using 5/16" standard concave punches.

Example 5

This example demonstrates a method for preparing a antihistamine tablet formulation using an adsorgate prepated from pyrilamine maleate. The following ingredients are mixed in the order indicated.

No.	Ingredients	Mg/tablet
1.	Pyrilamine maleate - adsorbate (25 mg drug/tablet)	250.0
2.	Microcrystalline cellulose	34.0
3.	Lactose	136.8
4.	Modified cellulose gum	2.0
5.	Fumed Silica	0.7
6.	Stearic acid	0.5
7.	Magnesium stearate	1.0
		425.0

Procedure

Screen #1, #6 and #7 through 40 mesh sieve. Blend #1 and #3 for 3 minutes in V blender. Add #2, #4 and #5 to step #2 and blend for 17 minutes. Add #6 to step #3 and blend for 3 minutes. Add #7 to step #4 and blend for 5 minutes. Tablet using 5/16" standard concave punchdes to a hardness of 5.5 kg.

EXAMPLE 6

(Inventive Run 7)

This example demonstrates a method for preparing a pyrilamine maleate adsorbate.

To 700 grams water is mixed 100 grams pyrilamine, maleate at a water temperature around 90° C., until the drug was in solution. The solution was added to 1,000 grams magnesium trisilicate having a mean specific surface area of at least 400 m^2/g and mixed until a homogeneous dispersion resulted, approximately 30 minutes. The mix was then oven dried at 85° C. until a moisture content of below 15% was obtained. The product was then milled to prepare a white free-flowing powder containing 10% by weight pyrilamine maleate.

An organoleptic evaluation test was performed on the product to determine the presence or absence of bitterness. The instant product did not exhibit objectional bitterness or off taste when tested by a human panel of experts.

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EXAMPLE 7

(Inventive Run 8)

This example demonstrates a method for preparing a diphenhydramine hydrochloride adsorbate.

To 873 grams water is mixed 99.4 grams diphenhydramine hydrochloride, at a water temperature around 90° C., until the drug was in solution. The solution was added to 1,000 grams magnesium trisilicate having a mean specific surface area of at least 400 m^2/g and mixed until a homogeneous dispersion resulted, approximately 30 minutes. The mix was then oven dried at 75° C. until a moisture content of below 15% was obtained. The product was then milled to prepare a white free-flowing powder containing 9.94% by weight diphenhydramine hydrochloride.

An organoleptic evaluation test was performed on the product to determine the presence or absence of bitterness. The instant product did not exhibit objectional bitterness or off taste when tested by a human panel of experts.

EXAMPLE 8

(Inventive Run 9)

This example demonstrates a method for preparing a phenyltoloxamine citrate adsorbate.

To 700 grams water is mixed 100 grams phenyltoloxamine citrate, at a water temperature around 90° C., until the drug was in solution. The solution was added to 1,000 grams magnesium trisilicate having a mean specific surface area of at least 400 m^2/g and mixed until a homogeneous dispersion resulted, approximately 30 minutes. The mix was then oven dried at 85° C. until a moisture content of below 15% was obtained. The product was then milled to prepare a white free-flowing powder containing 10% by weight phenyltoloxamine citrate.

An organoleptic evaluation test was performed on the product to determine the presence or absence of bitterness. The instant product did not exhibit objectional bitterness or off taste when tested by a human panel of experts.

EXAMPLE 9

(Inventive Run 10)

This example demonstrates a method for preparing a phenindamine tartrate adsorbate.

To 700 grams water is mixed 100 grams phenindamine tartrate, at a water temperature around 90° C., until the drug was in solution. The solution was added to 1,000 grams magnesium trisilicate having a mean specific surface area of at least 400 m^2/g and mixed until a homogeneous dispersion resulted, approximately 30 minutes. The mix was then oven dried at 85° C. until a moisture content of below 15% was obtained. The product was then milled to prepare a white free-flowing powder containing 10% by weight phenindamine tartrate.

An organoleptic evaluation test was performed on the product to determine the presence or absence of bitterness. The instant product did not exhibit objectional bitterness or off taste when tested by a human panel of experts.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

What is claimed is:

1. A medicament adsorbate which comprises magnesium trisilicate having a surface area of at least 400 m^2/g and having a flake-like structure with multiple interstitial spaces, and containing adsorbed therein from about 1% to about 20% by weight of the adsorbate of a medicament drug wherein the medicament drug is selected from the group of antihistamine materials consisting of chlorpheniramine maleate, phenindamine tartrate, pyrilamine maleate, doxylamine succinate, phenyltoloxamine citrate, diphenhydramine hydrochloride, promethazine, triprolidine, and mixtures thereof.

2. The adsorbate of claim 1 wherein the medicament drug is present in the amount of about 5% to about 15% by weight of the adsorbate.

3. The adsorbate of claim 1 wherein the medicament trisilicate has a surface area of about 440 m^2/g to about 600 m^2/g.

4. A process for preparing a medicament adsorbate which comprises dissolving a medicament drug selected from the group of antihistamine materials consisting of chlorpheniramine maleate, phenindamine tartrate, pyrilamine maleate, doxylamine succinate, phenyltoloxamine citrate, diphenhydramine hydrochloride, promethazine, triprolidine, and mixtures thereof in solvent, admixing magnesium trisilicate having a surface area of at least 400 m^2/g and having a flake-like structure with multiple interstitial spaces therewith to prepare a mass having a homogenous consistency to enable migration of the medicament drug within the interstitial spaces of the magnesium trisilicate and recovering the medicament adsorbate product.

5. The process of claim 4 which comprises employing about 15% to about 35% by weight solvent to prepare a granulated admixture containing the medicament drug and magnesium trisilicate adsorbate which is dried to a final moisture content of about 5% to about 20% weight.

6. The process of claim 4 which comprises employing about 30% to about 60% solvent by weight of the total composition to prepare a slurry and thereafter removing the solvent from the slurry to form a paste.

7. The process of claim 6 wherein the paste is dried and recovered as a free flowing powder.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,642,231

DATED : Feb. 10, 1987

INVENTOR(S) : David Peters, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 12, line 29, delete "medicament" and insert therefor --magnesium--.

Signed and Sealed this

Thirteenth Day of October, 1987

Attest:

Attesting Officer

DONALD J. QUIGG

Commissioner of Patents and Trademarks

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(51) International Patent Classification 5 : A61K 9/20 — A1

(11) International Publication Number: WO 93/13758

(43) International Publication Date: 22 July 1993 (22.07.93)

(21) International Application Number: PCT/US92/07497

(22) International Filing Date: 10 September 1992 (10.09.92)

(30) Priority data:
819,553 13 January 1992 (13.01.92) US

(60) Parent Application or Grant
(63) Related by Continuation
US 819,553 (CON)
Filed on 13 January 1992 (13.01.92)

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(81) Designated States: CA, FI, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).

Published
With international search report.

(54) Title: PREPARATION OF TABLETS OF INCREASED STRENGTH

(57) Abstract

Tablets of increased strength are manufactured by combining and compressing a meltable binder, excipients and a pharmaceutically active agent into a tablet, melting the binder in the tablet, and then solidifying the binder.

EN9DOCID: <WO___9313758A1_I_>

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PREPARATION OF TABLETS OF INCREASED STRENGTH

This invention relates to a method for the preparation of a tablet of increased strength, and to tablets when made by said method. The method is particularly useful in the manufacture of tablets, that contain pharmaceutically active agents which are difficult to compress; that are soft and chewable; and that are fast-disintegrating and porous.

Pharmaceuticals are often administered orally in the form of a tablet. The tablet is usually manufactured by combining tablet ingredients and compressing the combined ingredients in a mold. Due to the compression, tablets of mechanical stability are formed capable of withstanding disintegration during handling including removal from the mold, packing and transport. Mechanical stability depends on many factors, one of which is the compressibility of the pharmaceutically active agent in the tablet, particularly when large amounts of the agent are contained in a single tablet, and another one of which is the porosity of the tablet.

The porosity of a tablet relates to ease of tablet disintegration not only during handling but also during administration whether orally or rectally, and whether disintegration takes place in the mouth, or in the stomach. An increase in the disintegration rate in the mouth facilitates administration to patients in general, and to the very young, the elderly, and non-human animals, in particular. Administration is also facilitated by use of soft chewable tablets. Since such tablets are soft, having a hardness of less than about 6 kp, tablet friability is often a problem.

Tablets of increased porosity and disintegration rates are disclosed in United States Patent Nos. 3,885,026, 4,134,943 and 4,305,502. These patents suggest various ways of dealing with the problems associated with the handling of such highly porous tablets. U.S. Patent No. 4,305,502 suggests reducing the amount of handling of the tablets by forming them in situ in a substrate having depressions for deposition of tablets. However, removal of tablets from these depressions is more difficult than simple removal from a bottle or tube.

U.S. Patent Nos. 3,885,026 and 4,134,943 suggest increasing tablet strength of porous tablets by first compressing the tablet and then volatilizing a readily-volatilizable solid adjuvant incorporated in the tablet to attain desired porosity. The maximum

porosity obtained according to U.S. Patent No. 3,885,026 is 50% and preferably 10 to 30%.

The invention provides a method for the preparation of a tablet of increased strength by including the steps of (a) combining and compressing a meltable binder, at least one excipient, and a pharmaceutically active agent into a tablet, (b) melting said binder in said tablet, and (c) solidifying said binder.

Figure 1 shows surface views of a tablet of the invention and a comparison tablet under a scanning electron microscope at 100X magnification.

Figure 2 shows a friability comparison between Tablet F according to the invention and comparison Tablet E.

In the context of the invention, a tablet of increased strength refers to a tablet having a higher tablet strength than one made by blending the same tablet ingredients followed by compressing in a conventional tablet compressor.

The tablet ingredients of use in the present invention include a meltable binder, at least one excipient, and a pharmaceutically active agent.

The meltable binder increases the strength of the final tablet when processed according to the method of the invention. The binder has a melting point generally ranging from about 20°C to about 100°C, preferably from about 40°C to about 70°C. The melting point of the binder is usually at least about 20°C since the mixing of the ingredients is usually carried out at about 20°C and the binder is solid at the mixing temperature. Of course, if mixing is carried out at lower temperatures, a lower melting binder may be used which is solid at that temperature.

The melting point of the binder is usually not higher than about 100°C since the melting of the binder should be at a temperature at which the activity of the pharmaceutically active agent is not adversely affected. For instance, the melting of the binder should be at a temperature lower than the decomposition temperature of the pharmaceutically active agent as well as any one of the excipients present.

The amount of the meltable binder in the tablet ranges from about 5% to about 40% by weight, preferably from about 8% to about 25% by weight, based on the weight of the tablet. The specific amount depends on several factors, e.g., on use of

excessive amounts of the meltable binder the tablet may deform during melting whereas on use of insufficient amounts the desired increase in strength may not be attained.

The meltable binders of the invention may be nonwatersoluble or water soluble. Suitable nonwatersoluble meltable binders include natural fats such as cocoa butter, monoglycerides such as 1-monolaurin (m.p. 63°C), 2-monolaurin (m.p. 51°C), 1-monopalmitin (m.p. 77°C), and 2-monopalmitin (m.p. 68.5°C), diglycerides such as 1,2-dipalmitin (m.p. 63.5°C), 1,3-dipalmitin (m.p. 74°C), 1,2-distearin (m.p. 71°C), 1,3-distearin (m.p. 80°C) and 1,3-dioleostearin (m.p. 49°C), triglycerides such as tripalmitin (m.p. 56°C) and trimyristin (m.p. 46.5°C), ethoxylated fatty esters such as polyethylene (12) distearate and polyoxyethylene (20) sorbitan tristearate, and natural waxes such as carnauba wax (m.p. 83-86°C), beeswax (m.p. 62°C), and paraffins (m.p. 52-74°C). Suitable water soluble meltable binders of use in the invention include polyethylene glycols (PEG) having molecular weights ranging from about 1,500 to about 20,000 such as PEG 3350 (m.p. 58°C) and PEG 8000 (m.p. 62°C), sucrose esters such as sucrose monostearate (m.p. 49-56°C), and sucrose monopalmitate (m.p. 40-48°C), ethoxylated fatty acids such as polyoxyethylene (40) stearate (m.p. 47°C) (Myrj-52S), and ethoxylated alcohols such as polyoxyethylene (23) lauryl ester (m.p. 38-40°C). Specific meltable water-soluble binders are PEG 3350 and polyoxyethylene (40) stearate. The meltable water-soluble binders of use in the invention are of particular use in the preparation of tablets having increased disintegration rates in the mouth, e.g., rapid disintegration rates of less than ten seconds, for instance 1 to 5 seconds.

The meltable binder may be combined with the excipient or excipients and the pharmaceutically active agent in any sequence. The binder may be combined in dry form or in a suitable solvent such as alcohol, isopropanol or water. The dissolved binder on addition to the remaining tablet ingredients forms a wet granulation. If desired, the pharmaceutically active agent is added after drying of the wet granulation. Usually, the combined tablet ingredients are milled and mixed with a tabletting lubricant before the dry granules are compressed into tablets.

The excipients of use in the invention are generally known in the art, e.g., as described in Remington's Pharmaceutical Sciences, 18th Edition (1990), particularly pages 1633 to 1638. They impart necessary processing and compression characteristics either to the tablet formulation before tabletting, or to the finished tablet.

Examples of excipients are diluents, binders, lubricants, flavors, and sweetening agents. Specific diluents of use in the invention are water soluble diluents such as mannitol, xylitol, sucrose, lactose, and sodium chloride. Suitable binders of use in the invention, in addition to the meltable binder of use in the invention, impart cohesive properties and include starch, gelatin, microcrystalline cellulose and sugars such as sucrose, glucose, dextrose, and lactose. As is clear from the above, the same excipient may be used for different purposes within the same tablet formulation.

In one embodiment of the invention, a disintegrating agent is present to increase the disintegration rate of the tablet after oral intake. Examples of disintegrating agents are cellulose such as carboxymethylcellulose, starches, clay, algins, gums and crosslinked polymers, such as crosslinked polyvinylpyrrolidone (PVP-XL).

In another embodiment of the invention, a volatilizable component is present in the tablet formation to manufacture porous tablets. After combination and compression of the tablet ingredients, the volatilizable component is removed from the tablets by heating at atmospheric or reduced pressure to form porous tablets. Suitable volatilizable components include sublimable materials such as menthol, camphor, urea, and vanillin, and materials that decompose at or below the melting point of the binder such as ammonium bicarbonate. The amount of volatilizable material ranges from about 1% to about 95% by weight, based on the weight of the combined tablet ingredients. For instance, when using ammonium bicarbonate, the amount is usually from about 60% to about 90% by weight, and when using menthol, the amount ranges from about 30% to about 55% by weight. Preferably, the volatilizable material is removed during melting step (b) according to the invention when the compressed tablets are heated above the melting point of the meltable binder for a period of time sufficient to melt the meltable binder and to remove the volatilizable material. When using menthol, removal thereof is by heating to about 40°C under vacuum.

The terms "porosity" and "% porous" of a tablet as used herein refer to the void spaces created by the removal of the volatilizable component of the tablet. Since removal of the volatilizable component does not affect the inner or outer dimensions of the tablet, the porosity as defined above is the percentage by weight of the volatilizable component in the original tablet formation.

In general, the melting step (b) to melt the binder in the tablet is for a period of time sufficient to melt the meltable binder. The binder solidifies after the tablets are

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cooled to ambient temperature. The melting and solidifying of the meltable binder in the tablet strengthens the bonding among the tablet particles by filling of the minor cracks in the tablet matrix, as shown in the scanning electron micrographs of Figure 1.

The tablets prepared by the method of the invention may be coated with a thin layer of a coating material to improve the surface integrity of the tablet. Suitable coating materials include disaccharides such as sucrose, polysaccharides such as maltodextrins and pectin, and cellulose derivatives such as hydroxypropylmethylcellulose and hydroxypropylcellulose.

The pharmaceutically active agent of use in the invention may be any compound that is pharmaceutically active on oral intake or on rectal administration. Examples of such agents include antifungal agents such as fluconazole, pain relievers such as acetaminophen and acetylsalicylic acid, antihistamines such as diphenhydramine, doxylamine succinate and meclizine, decongestants such as pseudoephedrine hydrochloride, antibiotics such as azithromycin and erythromycin, penicillins such as sultamicillin tosylate and amoxicillin trihydrate, enzyme inhibitors such as sulbactam sodium, antihypertensives such as nifedipine, doxazosin mesylate and amlodipine besylate, antidiabetics such as glipizide, bronchodilators such as pirbuterol hydrochloride and theophylline, anti-inflammatory agents such as piroxicam and tenidap, anti-depressants such as sertraline hydrochloride, antacids such as calcium carbonate and magnesium oxide, and non-sedative antihistamines such as cetirizine. It is understood that the pharmaceutically active agents of use in the invention include nutritional and dietary supplements, for example, vitamins.

The following examples illustrate the invention. The strength of the tablets was measured with a tablet hardness tester, particularly the Schleuniger Hardness Tester, and a friability tester, particularly the Vanderkamp Friabilator. The hardness of the tablet is the force in kp (kilopond) required to break a tablet. The higher the kp value, the stronger the tablet is. Friability is the percentage of the tablet weight loss after a certain number of revolutions in the Vanderkamp Friabilator. The lower the percentage is, the stronger the tablet. As used in the Examples, the term "failed" refers to tablets which break during friability testing.

EXAMPLE 1

54.5% Porous Tablets

Tablet A: The following ingredients were blended and compressed into tablets of 0.5 inch diameter and 0.130 inch thickness. These tablets were then heated at 72°C under vacuum for 18 hours. This temperature is above the melting point of PEG 3350, 58°C. A 54.5% porous structure was formed after the ammonium bicarbonate was removed by thermal decomposition.

	INGREDIENTS OF TABLET A	MG/TABLET
1	Ammonium bicarbonate (pore former)	(300.00) later removed
2	Mannitol	168.00
3	Banana flavor	8.00
4	Aspartame	4.00
5	PEG 3350	20.00
6	PVP-XL	40.00
7	Sodium stearyl fumarate	10.00
	TOTAL	250.00

Tablet B: Tablets of 0.5 inch diameter and 0.125 inch thickness were made based on the following formulation which contained no PEG 3350. The tablet size, weight, and the relative amounts (weight to weight ratios) of the non-volatilizable components (ingredients 2 to 6) remained the same as in Tablet A in order to make a fair comparison between the two tablets. The porosity of the comparative tablet was therefore maintained at 54.5%.

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	INGREDIENTS OF TABLET B	MG/TABLET
1	Ammonium bicarbonate (pore former)	(300.00) later removed
2	Mannitol	183.27
3	Banana flavor	8.73
4	Aspartame	4.36
6	PVP-XL	43.64
7	Sodium stearyl fumarate	10.00
	TOTAL	250.00

The physical characterization of these two tablets is shown in Table 1.

TABLE 1

	Diameter (inch)	Thickness (inch)	Hardness (kp)	Friability (%) 100 revolutions
Tablet A	0.5	0.130	4.0	0.8
Tablet B	0.5	0.125	2.4	6.8

The tablet strength of Tablet A is much better than that of Tablet B because of the presence of melted and solidified PEG 3350.

EXAMPLE 2

38% Porous Tablets

Tablet C: The following ingredients were blended and compressed into tablets of 0.5 inch diameter and 0.114 inch thickness. These tablets were then heated at 42°C under vacuum. A 38% porous structure was formed after the menthol was removed by sublimation.

Tablet D: These tablets were made by further heating Tablet C at 72°C under vacuum for one hour.

	INGREDIENTS OF TABLETS C AND D	MG/TABLET
1	Menthol (pore former)	(150) later removed
2	Mannitol	150
3	Banana flavor	8
4	Aspartame	4
5	PEG 3350	60
6	PVP-XL	15
7	Sodium stearyl fumarate	8
	TOTAL	(395) 245

The physical characterization of these two tablets is shown in Table 2.

TABLE 2

	Diameter (inch)	Thickness (inch)	Hardness (kp)	Friability (%) 100 revolutions
Tablet C	0.5	0.114	below scale	Failed
Tablet D	0.5	0.114	2.7	0.4

The improvement in both hardness and friability was dramatic with the tablets (Tablet D) that were heated above the melting point of PEG 3350 (58°C). The amount of void space in Tablet D was not compromised by further heating and melting of PEG 3350. This is demonstrated by the microscopic views of both tablets in Figure 1. In comparing the photographs of the two tablets, it is evident that the melted PEG 3350 had filled and connected the hairline cracks of the type visible in Tablet C.

EXAMPLE 3

54.5% Porous Tablets

Tablet E: The following ingredients were blended and compressed into tablets of 0.5 inch diameter and 0.168 inch thickness. These tablets were then heated at 40°C under vacuum for 18 hours. A 54.5% porous structure was formed after the menthol was removed by sublimation.

Tablet F: These tablets were made by further heating Tablet E at 70°C under vacuum for 16 hours.

	INGREDIENTS OF TABLETS E AND F	MG/TABLET
1	Menthol (pore former)	(300) later removed
2	Mannitol	168
3	Banana flavor	8
4	Aspartame	4
5	PEG 3350	30
6	PVP-XL	30
7	Sodium stearyl fumarate	10
	TOTAL	(550) 250

The physical characterization of these two tablets is shown in Table 3.

TABLE 3

	Diameter (inch)	Thickness (inch)	Hardness (kp)	Friability (%) 25 revolutions
Tablet E	0.5	0.168	below scale	failed
Tablet F	0.5	0.168	below scale	8.5

The difference in friability of both tablets due to the melting and solidifying of PEG 3350 is demonstrated in Figure 2, which is a plot of the tablet weight loss as a function of the number of revolutions in the Vanderkamp friabilator.

EXAMPLE 4

75% Porous Tablets

Tablet G: The following ingredients 1, 2, 3, 5, 6, and 7 were blended and then wet-granulated with a solution of PEG 3350 (ingredient 4) in ethanol. The dry granulates were milled and blended with sodium stearyl fumarate (ingredient 8). The final blend was compressed into tablets of 0.625 inch diameter. These tablets were then heated at 70°C under vacuum. A 75% porous structure was formed after the ammonium bicarbonate was removed during the heating by thermal decomposition.

	INGREDIENTS OF TABLET G	MG/TABLET
1	Ammonium bicarbonate (pore former)	(600) later removed
2	Mannitol	90
3	Avicel PH101 (microcrystalline cellulose)	35
4	PEG 3350	20
5	PVP XL	10
6	Aspartame	15
7	Banana flavor	15
8	Sodium stearyl fumarate	15
	TOTAL	(880) 200

The friability of the tablets after 10 revolutions in the Vanderkamp friabilator was 4%.

EXAMPLE 5

Tablets Not Containing Volatilizable Component

Tablet H: The following ingredients were blended and compressed into tablets of 0.625 inch diameter and 0.2 inch thickness.

Tablet I: These tablets were made by heating tablet H at 70°C for 3 hours. These tablets remained non-porous in the absence of a volatilizable component.

	INGREDIENTS OF TABLETS H AND I	MG/TABLET
1	Lactose	733.33
2	PEG 3350	129.4
3	Sodium stearyl fumarate	17.27
	TOTAL	880

The physical characterization of these two tablets is shown in Table 4.

TABLE 4

	Diameter (inch)	Thickness (inch)	Hardness (kP)	Friability (%) 100 revolutions
Tablet H	5/8	0.2	3.5	failed after 20 rev.
Tablet I	5/8	0.2	3.5	0.5

The friability of Tablet I was improved because of the melting and then solidifying of PEG 3350.

EXAMPLE 6

36% Porous Tablets

Tablet J: The following ingredients were blended and compressed into tablets of 0.5 inch diameter and 0.125 inch thickness. These tablets were then heated at 40°C under vacuum for 18 hours. A 36% porous structure was formed after the menthol was removed by sublimation.

Tablet K: These tablets were made by further heating Tablet J at 70°C under vacuum for 4 hours.

INGREDIENTS OF TABLETS J AND K		MG/TABLET
1	Menthol (pore former)	(150) later removed
2	Mannitol	150
3	PVP-XL	15
4	Myrj-52S	60
5	Piroxicam	20
6	Banana flavor	8
7	Aspartame	4
8	Sodium stearyl fumarate	8
	TOTAL	(415) 265

The physical characterization of these two tablets is shown in Table 5.

TABLE 5

	Diameter (inch)	Thickness (inch)	Hardness (kp)	Friability (%) 80 revolutions
Tablet J	0.5	0.125	below scale	Failed after 20 rev.
Table K	0.5	0.125	2 kp	0.0

Both hardness and friability of Tablet K were improved because of the melting and solidifying of Myrj-52S.

EXAMPLE 7

75% Porous Tablets

Tablet L: The following ingredients 1, 2, 3, 4, 8 and 9 were blended and then wet-granulated with a solution of ingredients 5 and 6 in isopropanol. The dry granules were milled and blended with ingredient 7. Finally, ingredient 10 was mixed with the blend. The final blend was compressed into tablets of 0.625 inch diameter. These tablets were then heated at 65°C under vacuum for 18 hours to remove ammonium bicarbonate by thermal decomposition. A 75% porous structure was formed.

INGREDIENTS OF TABLET L		MG/TABLET
1	Ammonium bicarbonate (pore former)	(600) later removed
2	Mannitol	29
3	PVP-XL	10
4	Avicel PH 105	35
5	PEG 3350	5
6	Klucel EF	5
7	Microencapsulated fluconazole	71
8	Banana flavor	15
9	Aspartame	15
10	Sodium stearyl fumarate	15
	TOTAL	(800) 200

The friability of Tablet L was 0.0% after 10 revolutions in the Vanderkamp friabilator.

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Example 8

Tablets Not Containing Volatilizable Component

Tablet M: The following ingredients were blended and compressed into tablets of 0.5 inch diameter and 0.104 inch thickness.

Tablet N: These tablets were made by further heating Tablet M at 83°C for one hour.

INGREDIENTS OF TABLETS M AND N		MG/TABLET
1	Xylitol	322
2	Carnauba wax	40
3	Doxylamine succinate	25
4	Grape flavor	5
5	Magnesium stearate	8
	TOTAL	400

The physical characterization of these two tablets is shown in Table 6.

TABLE 6

	Diameter (inch)	Thickness (inch)	Hardness (kp)	Friability (%) 100 revolutions
Tablet M	0.5	0.104	3 kp	0.96
Tablet N	0.5	0.104	8 kp	0.00

Both hardness and friability of Tablet N were improved because of the melting and solidifying of carnauba wax.

Example 9

Tablets Not Containing Volatilizable Component

Tablet O: The following ingredients were blended and compressed into tablets of 0.5 inch diameter and 0.090 inch thickness.

Tablet P: These tablets were made further heating Tablet M at 60°C for one hour.

INGREDIENTS OF TABLETS M AND N		MG/TABLET
1	Lactose	241.4
2	PEG 3350	40
3	Tenidap	90.6
4	Explotab (sodium starch glycolate)	20
5	Magnesium stearate	8
	TOTAL	400

The physical characterization of these two tablets is shown in Table 7.

TABLE 7

	Diameter (inch)	Thickness (inch)	Hardness (kp)	Friability (%) 100 revolutions
Tablet O	0.5	0.104	3 kp	failed at 10 rev
Tablet P	0.5	0.104	8 kp	0.02

Both hardness and friability of Tablet K were improved because of the melting and solidifying of PEG 3350.

CLAIMS

1. A method for the preparation of a tablet of increased strength which comprises the steps of

(a) combining and compressing a meltable binder, at least one excipient and a pharmaceutically active agent into a tablet,

(b) melting said binder in said tablet, and

(c) solidifying said binder.

2. A method according to claim 1 wherein said binder is polyethylene glycol, a sucrose ester, an ethoxylated fatty acid, an ethoxylated alcohol, or an ethoxylated fatty ester.

3. A method according to claim 1 wherein said binder is a wax, a natural fat or a glyceride.

4. A method according to claim 1 wherein said binder has a melting point ranging from about 20°C to about 100°C.

5. A method according to claim 1 wherein step (a) includes combining with a volatilizable material which is removed after said compressing step.

6. A method according to claim 5 wherein said volatilizable material is ammonium bicarbonate.

7. A tablet when made according to the method of claim 1.

8. A tablet according to claim 7 wherein said binder is polyethylene glycol, a sucrose ester, an ethoxylated fatty acid, an ethoxylated alcohol or an ethoxylated fatty ester.

9. A tablet according to claim 7 wherein said binder is a wax, a natural fat or a glyceride.

10. A porous tablet when made according to the method of claim 6.

11. A tablet according to claim 7 having a porosity of 50% to 90%.

12. A tablet according to claim 7 wherein said pharmaceutically active agent is fluconazole, piroxicam, tenidap or doxylamine succinate.

FIG. 1

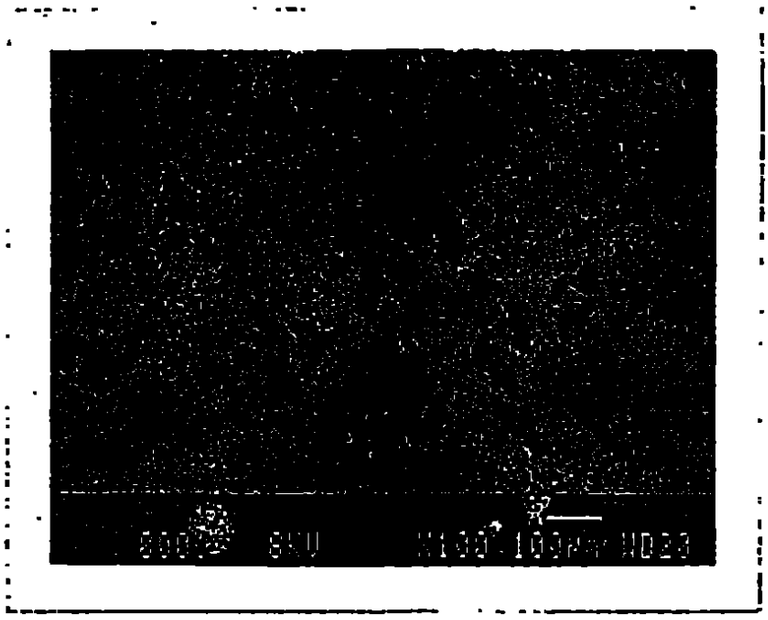

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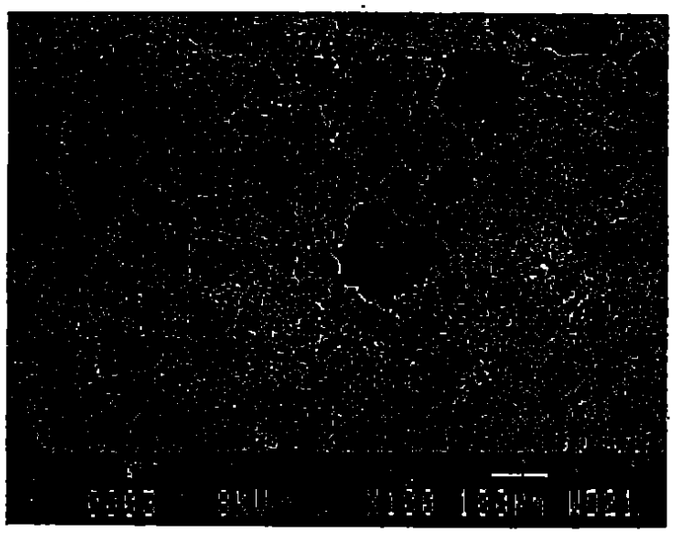
FIG. 2



INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/07497

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/20

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	FR,A,2 231 365 (HOFFMANN LA ROCHE & CIE) 27 December 1974	1,3,4,7, 9
Y	see claims 1,5	2,8,12
X	BE,A,688 121 (LOVENS KEMISKE FABRIK PRODUKTIONSAKTIEBOLAGET) 12 April 1967	1,3,7,9
Y	see claims 1,6	2,8,12
Y	EP,A,0 349 509 (PHARLYSE) 3 January 1990 see claims 1,4 see page 3, line 6 - line 16	2,8,12

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[10] Special categories of cited documents :[10]

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

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IV. CERTIFICATION

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EUROPEAN PATENT OFFICE	Dagmar Frank

Form PCT/ISA/210 (second sheet) (January 1985)

Mme Dagmar FRANK

ENSDOCID: <WO___9313788A1_I_>

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	DATABASE WPI Derwent Publications Ltd., London, GB; AN 74-56811V & DD,A,105 560 (BERGNER H.) 5 May 1974 see abstract	5,6,10, 11

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9207497 SA 64618

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 23/10/92
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR-A-2231365	27-12-74	DE-A-	2425764	02-01-75
		GB-A-	1422768	28-01-76
		JP-A-	50031022	27-03-75
BE-A-688121	12-04-67	CA-A-	983393	10-02-76
		DE-A-	1617593	29-04-71
		FR-A-	1602625	04-01-71
		GB-A-	1137156	
		NL-A-	6614357	13-04-67
		SE-C-	337281	09-10-75
EP-A-0349509	03-01-90	LU-A-	87233	28-02-90

EPO FORM P0759

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ENSDOCID: <WO___9313758A1_I_>

IN THE INTERNATIONAL BUREAU

International Appln S. N.:	PCT/CA 01/00951
Filed:	June 21, 2001
Applicant:	Duchesnay Inc.
Title:	RAPID ONSET FORMULATION
Agent's file ref:	AML/11621.23

April 17, 2002

THE INTERNATIONAL BUREAU OF WIPO
34, Chemin des Comlombettes
1211 Geneva 20, Switzerland

Dear Sir or Madam:

In response to the International Search Report dated February 21, 2002, please substitute the enclosed set of Claims for the corresponding set of Claims presently on file.

remarks:

Claims 1 to 18 are now in the case.

Claims 14 and 15 are amended to claim the "use" of the rapid onset formulation of claim 1. New claims 17 and 18 are added. The claims are directed to the process for obtaining the novel rapid onset formulation of claim 1. Thus claims 17 and 18 are necessarily novel. Support is found in Figure 2 and pages 3 to 6 of the disclosure.

Respectfully submitted,

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AMENDED CLAIMS

1. An enterically-coated pyridoxine HCl and doxylamine succinate rapid onset formulation comprising a disintegrating agent such that the following dissolution profiles are satisfied when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm:

(a) at least about 40% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 30 minutes of measurement;

(b) at least about 70% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 60 minutes of measurement;

(c) at least about 80% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 90 minutes of measurement;

(d) at least about 90% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 120 minutes of measurement.

2. An enterically-coated pyridoxine HCl and doxylamine succinate rapid onset formulation as in claim 1, wherein the following dissolution characteristics are also satisfied when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm:

(a) at least about 20% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 15 minutes of measurement;

(b) at least about 60% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 45 minutes of measurement;

(c) at least about 80% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 75 minutes of measurement.

3. The rapid onset formulation of claims 1 or 2, wherein at least about 40% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved within 5 minutes when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm.

4. The rapid onset formulation of claims 1 or 2, wherein said formulation contains a core coated with at least one enteric coating, said core comprising pyridoxine HCl, doxylamine succinate and the following non-active excipients: a filler or binder, a disintegrating agent, a lubricant, a silica flow conditioner and a stabilizing agent.

5. The rapid onset formulation of claim 4, wherein said filler or binder consists of microcrystalline cellulose.

6. The rapid onset formulation of claim 4, wherein said disintegrating agent consists of sodium crosscarmellose.

7. The rapid onset formulation of claim 4, wherein said lubricant consists of magnesium stearate.

8. The rapid onset formulation of claim 4, wherein said silica flow conditioner consists of silicon dioxide.

9. The rapid onset formulation of claim 4, wherein said stabilizing agent consists of magnesium trisilicate.

10. The rapid onset formulation of claims 1 or 2, wherein said core comprises:

(a) about 4-10% by weight of pyridoxine HCl;

(b) about 4-10% by weight of doxylamine succinate;

(c) about 40-80% by weight of microcrystalline cellulose;

(d) about 10-30% by weight of magnesium trisilicate;

(e) about 0.5-5% by weight of silicon dioxide;

(f) about 0.5-5% by weight of sodium croscarmellose; and

(g) about 0.5-5% by weight of magnesium stearate.

11. The rapid onset formulation of claim 10, wherein said core comprises:

(a) about 7% by weight of pyridoxine HCl;

(b) about 7% by weight of doxylamine succinate;

(c) about 62% by weight of microcrystalline cellulose;

(d) about 18% by weight of magnesium trisilicate;

(e) about 0.7% by weight of silicon dioxide;

(f) about 2.5% by weight of sodium croscarmellose; and

(g) about 2.8% by weight of magnesium stearate.

12. The rapid onset formulation of claim 4, wherein said at least one enteric coating is aqueous based.

13. The rapid onset formulation of claim 12, wherein said enteric coating consists of a seal coat applied to the core, an enteric coating *per se* applied on the seal coat and an aesthetic top coat applied on the enteric coating *per se*.

14. The use of the rapid onset formulation of claims 1 or 2 for alleviating the symptoms of nausea and vomiting in a mammal.

15. The use of the rapid onset formulation of claims 1 or 2 for alleviating the symptoms of nausea and vomiting during human pregnancy.

16. A medicament for attenuating the symptoms associated with nausea and vomiting consisting essentially of the formulation of claim 4.

17. A process for preparing the rapid onset formulation of claim 4, said process comprising the steps of:

- blending said doxylamine succinate and said silica flow conditioner to obtain a pre-blend;
- mixing said preblend with said pyridoxine HCl to obtain an active ingredient blend;
- mixing said active ingredient blend with said remaining non-active excipients, namely: a filler or binder, a disintegrating agent, a lubricant, and a stabilizing agent to obtain a final blend; and
- tabletting and coating said final blend.

18. A process in accordance with claim 17 wherein said final tabletting and coating step comprises compression of said final into a tablet shape, seal coating of said tablet shape, followed by enteric coating, followed by colour coating.

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Radicación : 09052756 Folios: 134
Fecha (DCO): 2012-06-19 16:54:07
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

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