



No. 08-127736-00003-0000

Fecha: 2009-07-31 14:59:23 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 62

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- ☒ Patente de Invención.
☐ Patente de Modelo de Utilidad.
☐ Diseño Industrial.
☐ Esquema de Trazado para Circuitos Integrados.
☐ Marcas de Productos o Servicios.
☐ Marca Colectiva.
☐ Marca de Certificación.
☐ Lema Comercial.

②

Número del expediente: 08 127736

Solicitante: SCHERING CORPORATION

SOLICITUD
PUBLICADA

Apoderado: CARLOS REYNALDO OLARTE GARCIA

Título de la nueva creación o denominación del signo: FORMULACIONES DE

LIBERACION PULSADA DE FENILEFRINA Y COMPOSICIONES FARMACEUTICAS

Gaceta: 603

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: GYNOPHARM S.A.	IDENTIFICACIÓN	
	Dirección: Carrera 14 N° 94-44 Piso 7 Torre b	C.C. ☐	NIT ☒
	Nacionalidad o Domicilio: COLOMBIA	C.E. ☐	Otro ☐
	Lugar de Constitución: BARRANQUILLA	Cual ☐	
	Teléfono: 2 36 84 95 Fax:	Número 802,006,279-4	
	E-mail:		
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ	IDENTIFICACIÓN	
	Dirección: CARRERA 13 No. 119-95	C.C. ☒	NIT ☐
	Teléfono: (571)213 12 13 Fax: (571)612 19 79	C.E. ☐	Otro ☐
	E-mail: negocios@optimum-co.com	Cual ☐	
		Número 51.975.664 TP 83823	

④

FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal:

No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. _____

Fecha _____

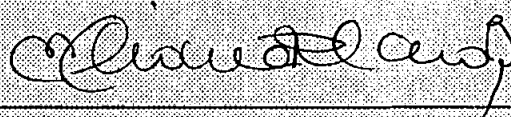
⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA: _____



C.C. 51.975.664

TP. 83823



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 08 127736
Asunto : Oposición a la solicitud de patente de Invención titulada
**"FORMULACIONES DE LIBERACIÓN PULSADA DE
FENILEFRINA Y COMPOSICIONES
FARMACÉUTICA"**
Solicitante : SCHERING CORPORATION
Opositora : GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 603 del 30 de Abril de 2009

Yo, *ELIANA ISaura MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad *GYNOPHARM S.A.* conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada **"FORMULACIONES DE LIBERACION PULSADA DE FENILEFRINA Y COMPOSICIONES FARMACÉUTICA"**, cuyo titular es SCHERING

CORPORATION., y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular FENILEFRINA. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente fue presentada el 1 de enero de 2009 reivindicando prioridad bajo la solicitud US20060810018P del 2006-06-01; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 603 del 30 de Abril de 2009, cuya publicación internacional corresponde a la WO2007143156 del 2007-12-13.
- 2.2. La solicitud colombiana 08 127736 objeto de la presente oposición, se refiere a una formulación de liberación pulsada o una composición farmacéutica que comprende fenilefrina. La composición farmacéutica comprende un componente de liberación

inmediata y un componente con recubrimiento entérico formulados conjuntamente ya sea en forma sólida o en una suspensión. El componente de la cubierta entérica comprende microcristales sembrados con fenilefrina como componente activo y recubierto con una cubierta sensible al pH para retardar la liberación de la fenilefrina. La composición farmacéutica puede comprender además por lo menos un componente activo seleccionado del grupo que consiste en un antihistamínico, un analgésico, un antipirético, un anti-inflamatorio no esteroide y mezclas de dos o más de dichos componentes activos.

2.3. En primera instancia, se debe advertir que algunas reivindicaciones también se refieren a un método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)"*, los usos no están contemplados como patentables; y, Artículo 20.- *"No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:



- D1: US2005266032 publicada el 1 de diciembre de 2005.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela un dosis específica a partir de una solución o suspensión la cual comprende un primer fármaco y un segundo fármaco, donde ambas están seleccionadas a partir de cantidades de descongestionantes donde uno de estos es fenileprina y donde se define que el primer fármaco es de inmediata entrega mientras que el segundo pues comprender un activo de liberación controlada, donde el activo de liberación controlada está recubierta de hidroxipropilcelulosa o copolímeros con ácidos metacrilatos y metacrilicos tal como Eudragit. Particularmente en los párrafos 007, 008, 0017, 0024 y 0067 define que puede comprender una solución o una suspensión en la que la fenileprina puede entregarse de manera controlada en una forma de liberación controlada y donde el activo de liberación controlada esta recubierto a partir de hidroxipropilcelulosa. Para cualquier persona versada en la materia a partir de esto puede desarrollar y encontrar que la forma pueda incluir microcristales pues estos pueden ser meramente una forma alternativa para obtener polvo o granulado. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud no comprende ALTURA O NIVEL INVENTIVO pues lo revelado se deriva de manera evidente del estado de la técnica

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08 127736 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.7. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.7.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”* A la fecha de prioridad, 1 de junio de 2006, a partir del documento D1, puede llegar de manera evidente a una formulación de liberación que puede comprender una solución o una suspensión en la que la fenileprina puede entregarse de manera controlada en una forma de liberación controlada y donde el activo de liberación controlada esta recubierto a partir de hidroxipropilcelulosa y que obviamente la forma pueda incluir microcristales pues estos pueden ser meramente una forma alternativa para obtener polvo o granulado, sobre el cual busca protección en el capítulo reivindicatorio.

2.7.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.



2.8. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.”* La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **“FORMULACIONES DE LIBERACIÓN PULSADA DE FENILEFRINA Y COMPOSICIONES FARMACÉUTICA”**, cuyo titular es SCHERING CORPORATION, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 603 del 30 de Abril de 2009.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: US2005266032 publicada el 1 de diciembre de 2005.

4. FUNDAMENTO DE DERECHO



Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **GYNOPHARM S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: US2005266032 publicada el 1 de diciembre de 2005.



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.



Gynopharm

The primary support
for the woman's health specialist

PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGÓN**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **GYNOPHARM S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHÓRQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 08 127736, titulada "**FORMULACIONES DE LIBERACION PULSADA DE FENILEERINA Y COMPOSICIONES FARMACEUTICAS**", cuyo titular es **SCHERING CORPORATION**, publicada en la gaceta No. 603 del 30 de abril de 2009.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los ____ días del mes de ____ de 2009.

GYNOPHARM S.A.

Cédula de Extranjería: No. 319788.
NIT: 802.006.2704
Representante Legal

Acepto:

ELIANA ISAURA MORENO BOHÓRQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.



RECONOCIMIENTO DE DOCUMENTO PRIVADO

Ante mí. LILIANA CONSTANZA BARBOSA PLATA,
Notaria Veinticinco del Circulo de Bogotá (E).
comparece Luis Palacios

Aragon
identificado con cedula de ciudadanía

cc 60.319.788 Bta
y declara que la firma puesta en el presente
instrumento privado es suya y que el contenido
del mismo es cierto.
Bogotá D.C.

30 JUL 2009

LILIANA CONSTANZA BARBOSA PLATA
NOTARIA VEINTICINCO DEL CIRCULO DE BOGOTA

PRESENTACION PERSONAL

El anterior escrito fue presentado ante el Notario Dieciocho del Circulo de Bogotá

personalmente por

DIANA TRAVEZA
MORENO BOHOLIVER

quien exhibió la c.c.

y Tarjeta Profesional No.

Fecha

0975664
83823
31 JUL 2009

C.S.J.

[Signature]



8-127736

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-127736-00003-0000

Fecha: 2009-07-31 14:59:23 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 62

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 59,592
FECHA : AGOSTO 12 DE 2009

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GYNOPHARM S.A.	RECIBO DE CAJA			56599	31/07/2009	540,000.00
GYNOPHARM S.A.	RECIBO DE CAJA			56600	31/07/2009	540,000.00
GYNOPHARM S.A.	RECIBO DE CAJA			56601	31/07/2009	540,000.00
GYNOPHARM S.A.	RECIBO DE CAJA			56602	31/07/2009	540,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEMAS COMERCIALES	287,000.00
		TOTAL :	\$ 287,000.00

SUN: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/07/30

HORA: 12:34:26

OPERACION: 10ERP0730125

PAGINA: 1

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 3,551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72,965 del libro respectivo, fue constituida la sociedad-----
anonima denominada GYNOPHARM S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
532	1999/03/25	Notaria 3a. de Barranquilla	80,373	1999/04/13

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

GYNOPHARM S.A.-----

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 802.006.279-4.

MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

Direccion para notificaciones judiciales:

CR 49.C No 80 - 125 OF 512.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 16 de Dic/bre de 2047.

C E R T I F I C A

OBJETO SOCIAL: a) La fabricacion de capsulas y otro productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/07/30

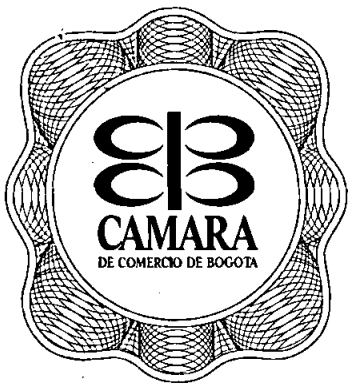
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OPERACION: 10ERP0730125

PAGINA: 2

uso y consumo humano y veterinario. b) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal. c) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos, medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. e) Actuar como representante o agente de personas naturales y juridicas nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualesquiera de las actividades descritas en los literales a), b), c) y d) antes transcritos. f) Prestar los servicios de asesoria y consultoria en las areas administrativa, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de GYNOPHARM S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial. g) Adquirir, operar, administrar y explotar, a cualquier titulo, empresas o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto; comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en

*** CONTINUA ***



01



* 8 3 6 9 7 3 8 3 *



14

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/07/30

HORA: 12:34:26

OPERACION: 10ERP0730125

PAGINA: 3

general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o lo de sus socios.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acci3n
Autorizado		
\$*****4,000,000,000	*****4,000,000	*****1,000
Suscrito		
\$*****2,672,646,000	*****2,672,646	*****1,000
Pagado		
\$*****2,672,646,000	*****2,672,646	*****1,000

C E R T I F I C A

ADMINISTRACION: Seran funciones de la junta directiva, entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion y para enajenar o gravar bienes inmuebles y demas activos fijos de la sociedad, cualquiera que sea la cuantia de la transaccion. Las demas que le sean propias y no esten atribuidas a otro organo social y las que le correspondan en virtud de la ley. la sociedad tendra un Gerente General, quien ejercera la administracion y representacion legal de la sociedad y tendra las siguientes atribuciones, entre otras: Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto. Para enajenar, a cualquier titulo, bienes inmuebles de la sociedad o constituir gravámenes sobre los mismos, debera obtener la aprobacion de la junta directiva, cualquiera que sea la cuantia de la transaccion; o las demas funciones que le corres-

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/07/30

HORA: 12:34:26

OPERACION: 10ERP0730125

PAGINA: 4

pondan como representante legal por disposicion de la ley, de estos estatutos o de la junta directiva. El Gerente General tendra un suplente, designado por la junta directiva, quien lo reemplazara con identicas facultades en sus faltas temporales, absolutas o meramente accidentales, sin que sea necesario para ello acreditar la ausencia del principal.-----

C E R T I F I C A

Que según Acta No. 15 del 18 de Febrero de 2008 correspondiente a la Asamblea de Accionistas en Bogota, de la sociedad:

GYNOPHARM S.A.-----

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 25 de Febrero de 2008 bajo el No. 137,919 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE:

JUNTA DIRECTIVA

Principales

- | | |
|---|--------------------|
| 1. Llobet Poal Manuel | CC.*****14,670,196 |
| 2. Zanatta Reherman Leonardo Andres | CC.*****2,760,271 |
| 3. Munoz Marroquin Diego | CC.*****7,688,292 |
| 4. Montealegre Gonzalez Andres Leonardo | CC.*****79,950,262 |

Suplentes

- | | |
|-----------------------------------|--------------------|
| 1. Agudelo Pelaez Luis Hernando | CC.*****14,238,997 |
| 2. Aroca Almanza Arleth Ayelina | CC.*****36,718,415 |
| 3. Penaranda Urbina Adriana Paola | CC.*****53,120,683 |
| 4. tovar Vasquez Ruth | CC.*****52,175,756 |

C E R T I F I C A

Que según Acta No. 18 del 30 de Octubre de 2003 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación

Gerente General.

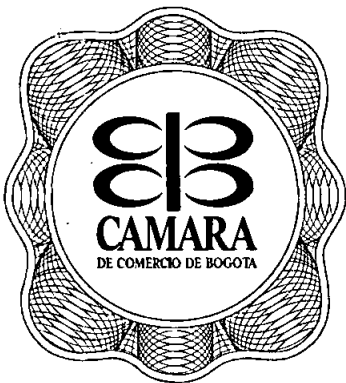
Palacios Aragon Luis Alberto

CE.*****319,788

C E R T I F I C A

Que según Acta No. 49 del 03 de Marzo de 2008 correspondiente a la

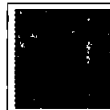
*** CONTINUA ***



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15

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/07/30

HORA: 12:34:26

OPERACION: 10ERP0730125

PAGINA: 5

Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Mollajoli Centurion Andres Fernando	CE.*****351,283

C E R T I F I C A

Que según Acta No. 19 del 30 de Abril de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el No. 149,314 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal.	
PENALOSA AUDITORES & ASOCIADOS S.A.	Ni.*****830,095,635

C E R T I F I C A

Que por Documento Privado del 11 de Mayo de 2009, otorgado en Bogota por Peñalosa Auditores & Asociados S.A. inscrito en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el Nro 149,315 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Designado: Revisor Fiscal Ppal	
Padilla Romero Ivan Dario	CC.*****80,025,798
Designado: Revisor Fiscal Suplente	
Gomez Preciado Clara Judith	CC.*****52,544,226

C E R T I F I C A

Que según Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 23 de Noviembre del 2.000 bajo el No. 1.872 del libro repectivo, consta que el señor RUBEN MINSKI GONTOVNIK C.C. No. 7.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficiente a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombre y representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/07/30

HORA: 12:34:26

OPERACION: 10ERP0730125

PAGINA: 6

S.A., en el giro normal de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 12 de junio del 2.002, bajo el 2.164 del libro respectivo, consta que el señor JORGE CASTELLANOS MARTINEZ, identificado con C.C.No.19.460.089, actuando como representante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Amplio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la cedula de ciudadanía No.32.732.070 de Barranquilla, mediante documento privado de octubre 10/2000, inscrito en la Camara de Comercio de Barranquilla bajo el No.1.872 del libro respectivo, para que en representacion de GYNOPHARM S.A, suscriba las declaraciones cambiarias a los que esta obligada GYNOPHARM S.A. en el giro ordinario de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que por Escritura Publica No. 2,404 del 28 de Mayo de 2009, otorgada en la Notaria 1a. de Bogota cuya parte pertinente se inscribió en esta Cámara de Comercio, el 02 de Julio de 2009 bajo el No. 3,948 del libro respectivo,-----
consta que el señor LUIS ALBERTO PALACIOS ARAGON con CE No.319788, en su calidad de Representante Legal de GYNOPHARM S.A., manifesto que confiere poder general, amplio y suficiente a la Doctora -----
CAROLINA MARIA ROMERO CERON, identificada con cedula de ciudadanía numero 52.352.190, para que en nombre de la sociedad GYNOPHARM -----
S.A., promueva y defienda los intereses de la sociedad judicial y extrajudicialmente, en toda especie de gestiones y actuaciones ante las autooridades administrativas o jurisdiccionales en especial ----
para: a) Recibir notificaciones de cualesquiera tipo de actos -----
emanados de las autoridades administrativas o judiciales. b) -----
Presentar recursos por la via administrativa o judicial, renunciar a terminos, desistir, conciliar, transigir y modificar. c) Elevar peticiones y solicitar informacion a las autoridades -----
administrativas y jurisdiccionales. d) Presentar demandas ante las autoridades administrativas y judiciales.-----

C E R T I F I C A

*** CONTINUA ***



16

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/07/30

HORA: 12:34:26

OPERACION: 10ERP0730125

PAGINA: 7

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 31 de Marzo de 2009.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco días hábiles después de la correspondiente inscripción, siempre que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad, y/o de apelación para ante la Superintendencia de Industria y Comercio.

mka...



US 20050266032A1

(19) **United States**(12) **Patent Application Publication****Srinivasan et al.**(10) **Pub. No.: US 2005/0266032 A1**(43) **Pub. Date: Dec. 1, 2005**(54) **DOSAGE FORM CONTAINING MULTIPLE DRUGS**

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(73) Assignee: **Sovereign Pharmaceuticals, Ltd.**, Fort Worth, TX(21) Appl. No.: **11/115,321**(22) Filed: **Apr. 27, 2005****Related U.S. Application Data**

(63) Continuation-in-part of application No. 10/736,902, filed on Dec. 17, 2003.

Continuation-in-part of application No. 10/798,884, filed on Mar. 12, 2004.

Continuation-in-part of application No. 10/910,806, filed on Aug. 4, 2004.

Continuation-in-part of application No. 10/939,351, filed on Sep. 14, 2004.

Continuation-in-part of application No. 11/012,264, filed on Dec. 16, 2004.

Publication Classification(51) Int. Cl.⁷ **A61K 31/485; A61K 31/137**(52) U.S. Cl. **424/400; 514/282; 514/649**(57) **ABSTRACT**

A pharmaceutical dosage form comprising a first drug and a second drug, both of which are selected from decongestants, antitussives, expectorants, analgesics and antihistamines. The dosage form provides a plasma concentration within a therapeutic range of the second drug over a period which is coextensive with at least about 70% of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug. This Abstract is neither intended to define the invention disclosed in this specification nor intended to limit the scope of the invention in any way.

DOSAGE FORM CONTAINING MULTIPLE DRUGS CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application is a continuation-in-part of U.S. patent application No. 10/736,902, filed Dec. 17, 2003, Ser. No. 10/798,884, filed Mar. 12, 2004, Ser. No. 10/910,806, filed Aug. 4, 2004, Ser. No. 10/939,351, filed Sep. 14, 2004, and Ser. No. 11/012,267, filed Dec. 16, 2004. The entire disclosures of these applications are expressly incorporated by reference herein.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The present invention relates to a pharmaceutical dosage form which comprises a first drug and a second drug, both of which are selected from decongestants, antitussives, expectorants, analgesics and antihistamines. The dosage form releases the first drug and the second drug so as to provide pharmaceutically effective plasma concentrations of these drugs over similar periods of time. The present invention also relates to a process for manufacturing the dosage form and to methods for alleviating conditions which can be alleviated by a combination of these drugs.

[0004] 2. Discussion of Background Information

[0005] Conditions such as colds and allergies are accompanied by a variety of symptoms which frequently can not satisfactorily be ameliorated or treated with a single drug but require the administration of two or more drugs. Drugs which are indicated for the amelioration of cold and allergy related symptoms often belong to at least one of the following classes: antihistamines, decongestants, antitussives, expectorants and analgesics. To facilitate and simplify the administration of the different drugs that are required for the amelioration of the various symptoms that a patient is experiencing it would be expedient to administer all of these drugs in a single dosage form, or at least in as few dosage forms as possible. However, in many cases these different drugs have significantly different pharmacokinetic properties. For example, a single dose of a first indicated drug may provide a therapeutically effective plasma concentration for a period of time which is significantly longer than the therapeutically effective plasma concentration that is provided by a single dose of a second indicated drug. As a result, there appears to be virtually no benefit in combining the first drug and the second drug in a single dosage form because with a corresponding combination, the first drug would still provide the desired therapeutic effect when the other drug has ceased to be effective and would have to be administered again.

[0006] Accordingly, it would be desirable if patients suffering from symptoms for which a first drug is indicated would also obtain relief, over a similar time period, from one or more symptoms for which one or more second drugs are indicated, by administering a single dose of a dosage form such as, e.g., a tablet, liquid, syrup, suspension, gel, capsule, suppository and the like. In other words, it would be desirable to have available a dosage form which provides the therapeutic effects of drugs with significantly different pharmacokinetic properties over a similar period of time.

SUMMARY OF THE INVENTION

[0007] The present invention provides a pharmaceutical dosage form which comprises a first drug and a second drug,

both of which are selected from decongestants, antitussives, expectorants, analgesics and antihistamines and preferably belong to different classes of drugs. The dosage form provides a plasma concentration within the therapeutic range of the second drug over a period which is coextensive with at least about 70% of the period over which the dosage form provides a plasma concentration within the therapeutic range of the first drug.

[0008] In one aspect of the dosage form, the first drug may comprise a decongestant. By way of non-limiting example, the decongestant may comprise phenylephrine and/or pseudoephedrine and/or one or more pharmaceutically acceptable salts of one or both of two decongestants.

[0009] In another aspect of the dosage form, the first drug may comprise an antitussive. By way of non-limiting example, the antitussive may comprise one or more of a morphine derivative such as, e.g., codeine, dihydrocodeine, hydrocodone and hydromorphone, dextromethorphan, carbapentane, chlorphedianol, benzonatate, caramiphen, nescapine and/or one or more pharmaceutically acceptable salts of one or more of these antitussive drugs.

[0010] In another aspect of the dosage form, the first drug may comprise an antihistamine. Non-limiting examples of antihistamines for use in the present invention include acrivastine, astemizole, azatadine, azelastine, bromodiphenhydramine, brompheniramine, carbinoxamine, carbastine, cetirizine, chlorphedianol, chlorcyclizine, clemastine, chlorothene, chlorpheniramine, cyclizine, cyproheptadine, des-carboethoxyloratadine, desloratadine, dextbrompheniramine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine, ebastine, epanastine, efeterizine, fexofenadine, hydroxyzine, isothipendyl, ketotifen, loratadine, meclizine, methapyrilene, mizolastine, mequitazine, mianserin, montelukast, noberastine, norastemizole, picumast, phenindamine, pheniramine, phenyltoloxamine, promethazine, propenpyridamine, pyrilamine, temelastine, terfenadine, thenylidamine, thonzylamine, trimeprazine, triphenennamine, triprolidine, and pharmaceutically acceptable salts thereof. By way of non-limiting example, the antihistamine may comprise at least one of promethazine, diphenhydramine, chlorpheniramine, carbinoxamine and pharmaceutically acceptable salts thereof.

[0011] In yet another aspect of the dosage form, the first drug may comprise an analgesic. By way of non-limiting example, the analgesic may comprise one or more of aspirin, acetaminophen, ibuprofen, ketoprofen, naproxen, sodium naproxen, meloxicam, hydrocodone, oxycodone, morphine, meperidine and fentanyl.

[0012] In a still further aspect of the dosage form of the present invention, the first drug may comprise an expectorant such as, e.g., guaifenesin and/or a pharmaceutically acceptable salt thereof.

[0013] In another aspect of the dosage form of the present invention, the second drug may comprise a decongestant and/or an antitussive and/or an antihistamine and/or an analgesic and/or an expectorant. Non-limiting specific examples of these drugs include those which are given above as non-limiting examples of the first drug.

[0014] In another aspect of the dosage form, the plasma half-life of the second drug may differ from the plasma

half-life of the first drug by at least about 2 hours, e.g., by at least about 3 hours, or by at least about 4 hours.

[0015] In yet another aspect of the dosage form of the present invention, the plasma concentration within the therapeutic range of the second drug may be coextensive with at least about 80%, e.g., at least about 90%, or at least about 95%, of the period of a plasma concentration within the therapeutic range of the first drug.

[0016] In a still further aspect of the dosage form, the dosage form may comprise a tablet such as, e.g., a bi-layered tablet. By way of non-limiting example, the tablet may comprise a matrix which comprises the first drug or the second drug and has dispersed therein particles which comprise the other one of the first drug and the second drug.

[0017] In another aspect of the dosage form, the dosage form may comprise a solution or a suspension.

[0018] The present invention also provides a bi-layered tablet which comprises a first layer and a second layer. The first layer comprises a first drug which is selected from decongestants, antitussives, expectorants, analgesics and antihistamines, and the second layer comprising a second drug which is also selected from decongestants, antitussives, expectorants, analgesics and antihistamines but is different from the first drug and preferably belongs to a different class than the first drug. The bi-layered tablet provides a plasma concentration within the therapeutic range of the second drug over a period which is coextensive with at least about 70% of the period over which the bi-layered tablet provides a plasma concentration within the therapeutic range of the first drug.

[0019] In one aspect of the bi-layered tablet of the present invention, the first layer and/or the second layer may comprise at least one drug that is selected from phenylephrine, pseudoephedrine, codeine, dihydrocodeine, hydrocodone, dextromethorphan, carbapentane, chlorpheniramine, benzonatate, caramiphen, norepinephrine, guaifenesin, acrivastine, astemizole, azatadine, azelastine, bromodiphenhydramine, brompheniramine, carbinoxamine, carbastine, cetirizine, chlorpheniramine, chlorcyclizine, clemastine, chlorpheniramine, cyclizine, cyproheptadine, descarboethoxyloratadine, desloratadine, dexbrompheniramine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine, ebastine, epanastine, efeterizine, fexofenadine, hydroxyzine, isothipendyl, ketotifen, loratadine, meclizine, methapyrilene, mizolastine, mequitazine, mianserin, montelukast, norepinephrine, norastemizole, picumast, phenindamine, pheniramine, phenyltoloxamine, promethazine, propenpyridamine, pyrilamine, temelastine, terfenadine, thenyldiamine, thonzylamine, trimetoprim, tripeleminamine, triprolidine and pharmaceutically acceptable salts thereof, aspirin, acetaminophen, ibuprofen, ketoprofen, naproxen, sodium naproxen, meloxicam, hydrocodone, oxycodone, morphine, meperidine and fentanyl.

[0020] In another aspect of the bi-layered tablet, the period of a plasma concentration within the therapeutic range of the second drug may be coextensive with at least about 80%, e.g., at least about 90%, or at least about 95%, of the period of a plasma concentration within the therapeutic range of the first drug.

[0021] In yet another aspect of the bi-layered tablet, the plasma half-life of the second drug may differ from the

plasma half-life of the first drug by at least about 2 hours, for example, by at least about 3 hours.

[0022] In a still further aspect of the bi-layered tablet, the first or the second layer may be an immediate release layer, or the first and the second layers may both be controlled release layers.

[0023] The present invention also provides a multi-layered tablet which comprises at least a first layer and a second layer. The first layer comprises a first drug which is selected from decongestants, antitussives, expectorants, analgesics and antihistamines and the second layer is a controlled release layer and comprises a second drug which is selected from decongestants, antitussives, expectorants, analgesics and antihistamines and is different from the first drug and preferably belongs to a different class than the first drug.

[0024] In one aspect of the multi-layered tablet, the first layer may be an immediate release layer and/or the second layer may be a controlled release layer.

[0025] In another aspect of the multi-layered tablet, the second drug may have a plasma half-life which differs from the plasma half-life of the first drug by at least about 2 hours, for example, by at least about 3 hours.

[0026] In yet another aspect of the multi-layered tablet, the tablet may provide a plasma concentration within the therapeutic range of the second drug over a period which is coextensive with at least about 90% of the period over which the tablet provides a plasma concentration within the therapeutic range of the first drug.

[0027] In a still further aspect of the multi-layered tablet, the layers thereof may be discrete zones which are arranged adjacent to each other, or one of the first and second layers may be partially or completely surrounded by the other one of the first and second layers.

[0028] The present invention also provides a pharmaceutical dosage form which comprises a first drug which is selected from antihistamines and has a first plasma half-life, and a second drug which is selected from decongestants, antitussives, analgesics and expectorants and has a second plasma half-life that differs from the first plasma half-life by at least about 3 hours. The dosage form provides a plasma concentration within the therapeutic range of the second drug over a period which is coextensive with at least about 80% of the period over which the dosage form provides a plasma concentration within the therapeutic range of the first drug.

[0029] In one aspect of the dosage form, the first plasma half-life may be longer by at least about 4 hours, e.g., longer by at least about 6 hours, than the second plasma half-life. In another aspect, the first plasma half-life may be at least about 8 hours.

[0030] In another aspect of the dosage form of the present invention, the period of a plasma concentration within the therapeutic range of the at least one second drug may be coextensive with at least about 90%, e.g., at least about 95%, or about 100% of the period of a plasma concentration within the therapeutic range of the first drug.

[0031] In yet another aspect, the dosage form may be associated with instructions to administer the dosage form three or fewer times per day, e.g., once or twice per day.

[0032] In a still further aspect, the dosage form may comprise a tablet.

[0033] In another aspect of the dosage form, the second drug may comprise a decongestant.

[0034] In another aspect, the antihistamine may be selected from acrivastine, astemizole, azatadine, azelastine, bromodiphenhydramine, brompheniramine, carbinoxamine, carebastine, cetirizine, chlorcyclizine, clemastine, chlorothene, chlorpheniramine, cyclizine, cyproheptadine, decarboethoxyloratadine, desloratadine, dexbrompheniramine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine, ebastine, epanastine, efletirizine, fexofenadine, hydroxyzine, isothipendyl, ketotifen, loratadine, meclizine, methapyrilene, mizolastine, mequitazine, mianserin, montelukast, naberastine, norastemizole, picumast, phenindamine, pheniramine, phenyltoloxamine, promethazine, propenpyridamine, pyrilamine, temelastine, terfenadine, thenyldiamine, thonzylamine, trimoprazine, tripeleminamine, triprolidine, and pharmaceutically acceptable salts thereof.

[0035] The present invention also provides dosage forms as set forth above, including the various aspects thereof, which dosage forms are substantially free of antihistamines (and/or contain less than therapeutically effective amounts thereof).

[0036] The present invention also provides a method of alleviating a condition which can be alleviated by administration of an antihistamine and at least one other condition which can be alleviated by administration of a drug which is at least one of a decongestant, an antitussive, an expectorant and an analgesic, wherein the method comprises administering a dosage form of the present invention, including the various aspects thereof, to a subject in need thereof.

[0037] The present invention also provides a process of making a pharmaceutical dosage form of the present invention, wherein the method comprises preparing a first composition which comprises the first drug and a second composition which comprises the second drug, and combining the first and the second compositions, for example, by using a tablet press.

[0038] The pharmaceutical dosage forms of the present invention comprise at least two drugs, i.e., a first drug and a second drug. It is noted that the terms "a first drug" and "a second drug" do not exclude, but rather include the presence of more than one first or second drug. For example, the dosage form may comprise one first drug and two or more (e.g., three, four, five, etc.) second drugs. In this case, the dosage form desirably provides plasma concentrations within the therapeutic ranges of all of the second drugs over periods of time which individually are coextensive with at least about 70% (e.g., at least about 80%, at least about 90%, at least about 95%, or at least about 100%) of the period of time over which the dosage form provides a plasma concentration within the therapeutic range of the first drug. Moreover, in cases where the dosage form comprises more than one first drug and more than one second drug, the first drug with the longest period of a plasma concentration with the therapeutic range is the standard, i.e., preferably all other drugs that are present in the dosage form show plasma concentrations within the therapeutic ranges thereof over periods of time which are coextensive with at least about

70% (e.g., at least about 80%, at least about 90%, at least about 95%, or at least about 100%) of the period for the first drug with the longest period of a plasma concentration with the therapeutic range.

[0039] The pharmaceutical dosage form which constitutes one aspect of the present invention comprises first and second drugs which may be present in the form of a pharmaceutically acceptable salt thereof. The term "pharmaceutically acceptable salt" as used herein and in the appended claims refers to those salts of a particular drug that are not substantially toxic at the dosage administered to achieve the desired effect and do not independently possess significant pharmacological activity. The salts included within the scope of this term are pharmaceutically acceptable acid addition salts of a suitable inorganic or organic acid. Non-limiting examples of suitable inorganic acids are, for example hydrochloric, hydrobromic, sulfuric and phosphoric acids. Non-limiting examples of suitable organic acids include carboxylic acids, such as acetic, propionic, tannic, glycolic, lactic, pyruvic, malonic, succinic, fumaric, malic, tartaric, citric, cyclamic, ascorbic, maleic, hydroxymaleic, benzoic, phenylacetic, 4-aminobenzoic, 4-hydroxybenzoic, anthranillic, cinnamic, salicylic, 4-aminosalicylic, 2-phenoxybenzoic, 2-acetoxybenzoic and mandelic acids, as well as sulfonic acids, such as methanesulfonic, ethanesulfonic, and β -hydroxyethanesulfonic acids.

[0040] Non-limiting examples of drugs for use in the present invention in the form of their pharmaceutically acceptable salts include codeine phosphate, codeine sulfate, hydrocodone bitartrate, dihydrocodeine bitartrate, carbapentane citrate, pseudoephedrine hydrochloride, phenephine hydrochloride, azatadine maleate, bromodiphenhydramine HCl, brompheniramine maleate, carbinoxamine maleate, cetirizine HCl, chlorcyclizine HCl, clemastine fumarate, chlorothene citrate, chlorpheniramine maleate, dimethindene maleate, diphenhydramine HCl, fexofenadine HCl, hydroxyzine HCl, isothipendyl HCl (teruhistin), methapyrilene fumarate, methapyrilene HCl, montelukast sodium, phenindamine tartrate, pheniramine maleate, phenyltoloxamine citrate, promethazine hydrochloride, propenpyridamine maleate, pyrilamine maleate, thenyldiamine HCl, trimoprazine tartrate, tripeleminamine HCl and triprolidine HCl.

[0041] The dosage form of the present invention will usually provide a plasma concentration within the therapeutic range of the second drug over a period which is coextensive with (overlaps) at least about 70%, more preferred at least about 80%, e.g., at least about 90%, at least about 95%, or about 100%, of the period over which the dosage form provides a plasma concentration within the therapeutic range of the first drug. The term "therapeutic range" as used herein and in the appended claims refers to the range of drug levels (including active metabolite levels) within which most patients will experience a significant therapeutic effect (including alleviation of symptoms) without an undesirable degree of adverse reactions. It is noted that the term "coextensive with" does not exclude, but rather includes, cases where a part of the period over which the plasma concentration of the second drug (and/or active metabolites thereof) is within the therapeutic range is outside the period over which the plasma concentration of the first drug is within the therapeutic range. In other words, even if the corresponding period for the second drug is to overlap, for example, 70% of the corresponding period of the first drug, a certain

percentage (preferably not more than about 30%, e.g., not more than about 20%, not more than about 10% or even not more than about 5%) of the total period over which the plasma concentration of the second drug is within the therapeutic range may be outside the period over which the plasma concentration of the first drug is within the therapeutic range.

[0042] The period over which the therapeutic range of a particular drug may be provided in a given case depends, at least in part, on the plasma half-life of the drug and/or active metabolites thereof. The term "plasma half-life" as used herein and in the appended claims refers to the time required for the plasma drug concentration to decline by 50%. The shorter the plasma half-life of a particular drug, the shorter will be the period within the therapeutic range of the drug which is provided by a single administered dose of the drug. In one preferred aspect of the dosage form of the present invention, the plasma half-life of the second drug will be shorter than the plasma half-life of the first drug by at least about 2 hours, e.g., by at least about 3 hours, by at least about 4 hours, by at least about 5 hours, by at least about 6 hours, by at least about 8 hours, or even by at least about 10 hours.

[0043] A preferred, although non-limiting, embodiment of the dosage form of the present invention is a tablet, in particular, a bi-layered tablet. Non-limiting examples of other embodiments of the dosage form of the invention are capsules, pills, chewable tablets, suspensions, solutions, syrups, and suppositories.

[0044] The bi-layered tablet which forms one of the aspects of the present invention comprises two layers. The first layer comprises a first drug which is selected from decongestants, antitussives, expectorants, analgesics and antihistamines. The second layer comprises a second drug which is different from the first drug and is selected from decongestants, antitussives, expectorants, analgesics and antihistamines. Specific and non-limiting examples of such drugs are given above. Particularly for the treatment of conditions which are associated with thick tenacious mucus exudates it is preferred for the bi-layered tablet or any other dosage form of the present invention to be substantially antihistamine-free, i.e., neither the first nor the second drug comprise more than insignificant amounts of antihistamines or any other drugs which have a substantial drying action.

[0045] The layers of the bi-layered tablet of the present invention may individually be immediate release layers or controlled release layers. The term "controlled release layer" as used herein and in the appended claims refers to any layer that is not an immediate release layer, i.e., does not release all of the active ingredients contained therein within a relatively short time (for example, within less than 1 hour, e.g., less than 0.5 hours, following ingestion of the dosage form). Accordingly, this term is a generic term which encompasses, e.g., sustained (extended) release layers, pulsed release layers, delayed release layers, and the like. Preferably, the controlled release layer releases the one or more drugs contained therein continuously or intermittently and, preferably, in approximately equal amounts per time unit (e.g., zero order release rate), over an extended period of time such as, e.g., at least about 2 hours, at least about 3 hours, at least about 4 hours, or at least about 6 hours. The desirable length of the time period of continuous or inter-

mittent (e.g., pulsed) release depends, inter alia, on the plasma half-life of the drug and/or an active metabolite thereof.

[0046] The first and second layers of the bi-layered tablet of the present invention will usually contain the first and second drugs in amounts which are commensurate with the intended duration of action but will not give rise to overdosing when present in the intended form (e.g., a particular pharmaceutically acceptable salt) and the intended release matrix (e.g., immediate release, controlled release, etc.). In this regard, it is noted that a drug may be present in both the first layer and the second layer (and any additional layer, if present), for example, in order to obtain an as fast as possible release and, thus action of the drug (e.g., by using an immediate release matrix) and to at the same time extend the duration of the action of the drug (e.g., by using a controlled release matrix that releases the drug at a lower rate and/or at a later time than the immediate release layer). In the following, preferred ranges of amounts of selected drugs for use in the bi-layered tablet and other dosage forms of the present invention are given for illustrative purposes only.

[0047] Promethazine: at least about 0.1 mg, e.g., at least about 5 mg, at least about 6 mg, at least about 8 mg, at least about 12 mg, or at least about 25 mg, but not more than about 90 mg, e.g., not more than about 75 mg, not more than about 70 mg, not more than about 60 mg, or not more than about 50 mg of promethazine hydrochloride, or an equivalent amount (on a molar basis) of promethazine and/or any other pharmaceutically acceptable salt thereof.

[0048] Chlorpheniramine: at least about 0.1 mg, e.g., at least about 2 mg, or at least about 4 mg, but not more than about 16 mg, e.g., not more than about 12 mg of chlorpheniramine maleate, or an equivalent amount of chlorpheniramine and/or any other pharmaceutically acceptable salt thereof.

[0049] Carbinoxamine: at least about 0.1 mg, e.g., at least about 6 mg, but not more than about 32 mg, e.g., not more than about 24 mg of carbinoxamine maleate, or an equivalent amount of carbinoxamine and/or any other pharmaceutically acceptable salt thereof.

[0050] Diphenhydramine: at least about 10 mg, e.g., at least about 15 mg, at least about 20 mg, at least about 40 mg, at least about 70 mg, or at least about 90 mg, but not more than about 200 mg, e.g., not more than about 150 mg, not more than about 120 mg, or not more than about 100 mg of diphenhydramine hydrochloride, or an equivalent amount of diphenhydramine and/or any other pharmaceutically acceptable salt thereof.

[0051] Carbetapentane: at least about 1 mg, e.g., at least about 5 mg, at least about 10 mg, at least about 25 mg, or at least about 50 mg, but not more than about 120 mg, e.g., not more than about 100 mg, not more than about 70 mg, or not more than about 60 mg, of carbetapentane citrate, or an equivalent amount of carbetapentane and/or any other pharmaceutically acceptable salt thereof.

[0052] Codeine: at least about 1 mg, e.g., at least about 10 mg, at least about 25 mg, or at least about 30 mg, but not more than about 120 mg, e.g., not more than about 80 mg, not more than about 60 mg, or not more than about 45 mg, of codeine phosphate, or an equivalent amount of codeine and/or any other pharmaceutically acceptable salt thereof.

[0053] Dihydrocodeine: at least about 1 mg, e.g., at least about 5 mg, but not more than about 30 mg, e.g., not more than about 20 mg, of dihydrocodeine bitartrate, or an equivalent amount of dihydrocodeine and/or any other pharmaceutically acceptable salt thereof.

[0054] Hydrocodone: at least about 1 mg, e.g., at least about 5 mg, but not more than about 20 mg, e.g., not more than about 15 mg, of hydrocodone bitartrate, or an equivalent amount of hydrocodone and/or any other pharmaceutically acceptable salt thereof.

[0055] Phenylephrine: at least about 1 mg, e.g., at least about 10 mg, or at least about 15 mg, but not more than about 125 mg, e.g., not more than about 100 mg, not more than about 90 mg, not more than about 75 mg, not more than about 50 mg, or not more than about 25 mg of phenylephrine hydrochloride, or an equivalent amount of phenylephrine and/or any other pharmaceutically acceptable salt thereof.

[0056] Pseudoephedrine: at least about 1 mg, e.g., at least about 10 mg, at least about 25 mg, or at least about 50 mg, but not more than about 240 mg, e.g., not more than about 150 mg, not more than about 100 mg, or not more than about 70 mg of pseudoephedrine hydrochloride, or an equivalent amount of pseudoephedrine and/or any other pharmaceutically acceptable salt thereof.

[0057] Guaifenesin: at least about 1 mg, e.g., at least about 10 mg, at least about 25 mg, at least about 50 mg, or at least about 100 mg, but not more than about 2400 mg, e.g., not more than about 1600 mg, not more than about 1500 mg, not more than about 1200 mg, not more than about 1000 mg, not more than about 600 mg, or not more than about 500 mg of guaifenesin, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[0058] Acetaminophen: at least about 10 mg, e.g., at least about 50 mg, or at least about 100 mg, but not more than about 1000 mg, e.g., not more than about 500 mg, or not more than about 250 mg of acetaminophen.

[0059] Another aspect of the present invention is a multi-layered tablet which comprises at least a first layer and a second layer, but may optionally comprise a third, fourth, fifth, etc. layer. The first layer may be an immediate release layer or a controlled release layer, depending on the drug(s) contained therein and the desired release characteristics thereof, and comprises at least one first drug which is selected from decongestants, antitussives, expectorants, analgesics and antihistamines. The mandatory second layer may also be an immediate release layer or a controlled release layer, depending on the drug(s) contained therein and the desired release characteristics thereof, and comprises at least one second drug which is different from the first drug and is selected from decongestants, antitussives, expectorants, analgesics and antihistamines. If more than two drugs are to be incorporated in the tablet, the first and/or the second layer may contain all of the additional drugs. Alternatively, separate additional layers may be provided for the additional drugs, for example, in cases where it would be difficult to design a controlled release layer which provides a desired release rate for both the first or second drug and/or the additional drug(s). Of course, a fourth, fifth, etc. layer may be provided for, e.g., a third or fourth additional drug, and so on. Alternatively and by way of non-limiting example, the second and a third layer may contain the same drug or drugs,

but in different (relative) concentrations and/or incorporated in a different controlled release formulation.

[0060] The multi-layered tablet of the present invention will usually be made up of two or more distinct layers or discrete zones of granulation compressed together with the individual layers lying on top of one another. Layered tablets have the appearance of a sandwich because the edges of each layer or zone are exposed. Such conventional layered tablets are generally prepared by compressing a granulation onto a previously compressed granulation. The operation may be repeated to produce multi-layered tablets of more than two layers. In a preferred embodiment of the multi-layered tablet of the present invention, the tablet consists of two layers.

[0061] It is to be noted that it is not necessary for the two or more individual layers of the multi-layered tablet of the present invention to lie on top of one another. By way of non-limiting example, a second layer (e.g., sustained release layer) may be partially or completely surrounded by a first layer (e.g., an immediate release layer). For example, the second layer may be coated with the first layer. In the case of three layers, for example, the third layer may be partially or completely coated with the second layer, which in turn may be partially or completely coated with the first layer. Of course, these are but a few examples of the many different ways in which the various layers of the multi-layered tablet of the present invention can be arranged relative to each other. Moreover, it is to be understood that the tablets of the present invention are not limited to such multi-layered tablets. By way of non-limiting example, the tablet may comprise an immediate release matrix which comprises one or more first drugs, which matrix has dispersed therein particles of one or more sustained release formulations which have the one or more second drugs and any of the additional desired drug(s) incorporated therein.

[0062] In another aspect of the multi-layered tablet, the at least one drug in the second layer (and/or in the additional layers) may have a plasma half-life which is shorter by at least about 3 hours, e.g., shorter by at least about 4 hours, or shorter by at least about 6 hours, than the plasma half-life of the first drug or the first drug with the longest plasma half-life, respectively.

[0063] In another aspect of the multi-layered tablet, the tablet may provide a plasma concentration within a therapeutic range of the drug(s) in the second layer over a period which is coextensive with at least about 80%, e.g., at least about 90%, of the period over which the multi-layered tablet provides a plasma concentration within the therapeutic range of the drug(s) in the first layer.

[0064] Another aspect of the present invention is formed by a liquid dosage form, preferably a suspension, which comprises (a) a first drug which is selected from decongestants, expectorants, antitussives, analgesics and antihistamines and (b) a second drug which is selected from decongestants, expectorants, antitussives, analgesics and antihistamines and is different from the first drug. This liquid dosage form provides a plasma concentration within the therapeutic range of component (b) over a period which is coextensive with at least about 70%, preferably at least 80%, e.g., at least 90%, of the period over which the liquid dosage form provides a plasma concentration within the therapeutic range of component (a). This may be accomplished in various ways. By way of non-limiting example, component

(b) may be incorporated into a solid controlled release formulation. For example, particles of component (b) may be provided with a controlled release coating (e.g. a controlled release coating comprising an organic polymer such as, e.g., a polyacrylate). This formulation may then be comminuted, if necessary, in an appropriate manner (e.g., by milling) to form particles of a size which is small enough to be suitable for being suspended in a pharmaceutically acceptable liquid carrier. Component (a), on the other hand, may be used as such or incorporated in a solid immediate release formulation, comminuted and incorporated into the liquid carrier as well. A non-limiting example of a corresponding procedure is described in the Examples below.

[0065] Prior to incorporating components (a) and (b) into a pharmaceutically acceptable liquid carrier to form a liquid dosage form according to the present invention, at least a part of component (a) and/or at least a part of component (b) may be converted into a complex with a complexing agent. Non-limiting examples of suitable complexing agents comprise ion-exchange resins such as, e.g., (sodium) polystyrene sulfonate.

[0066] The dosage forms of the present invention can be manufactured by processes which are well known to those of skill in the art. For example, for the manufacture of bi-layered tablets, the active ingredients may be dispersed uniformly into a mixture of excipients, for example, by high shear granulation, low shear granulation, fluid bed granulation, or by blending for direct compression. Excipients may include diluents, binders, disintegrants, dispersants, lubricants, glidants, stabilizers, surfactants and colorants. Diluents, also termed "fillers", are typically used to increase the bulk of a tablet so that a practical size is provided for compression. Non-limiting examples of diluents include lactose, cellulose, microcrystalline cellulose, mannitol, dry starch, hydrolyzed starches, powdered sugar, talc, sodium chloride, silicon dioxide, titanium oxide, dicalcium phosphate dihydrate, calcium sulfate, calcium carbonate, alumina and kaolin. Binders impart cohesive qualities to a tablet formulation and are used to ensure that a tablet remains intact after compression. Non-limiting examples of suitable binders include starch (including corn starch and pregelatinized starch), gelatin, sugars (e.g., glucose, dextrose, sucrose, lactose and sorbitol), celluloses, polyethylene glycol, waxes, natural and synthetic gums, e.g., acacia, tragacanth, sodium alginate, and synthetic polymers such as polymethacrylates and polyvinylpyrrolidone. Lubricants facilitate tablet manufacture; non-limiting examples thereof include magnesium stearate, calcium stearate, stearic acid, glyceryl behenate, and polyethylene glycol. Disintegrants facilitate tablet disintegration after administration, and non-limiting examples thereof include starches, alginic acid, crosslinked polymers such as, e.g., crosslinked polyvinylpyrrolidone, croscarmellose sodium, potassium or sodium starch glycolate, clays, celluloses, starches, gums and the like. Non-limiting examples of suitable glidants include silicon dioxide, talc and the like. Stabilizers inhibit or retard drug decomposition reactions, including oxidative reactions. Surfactants may be anionic, cationic, amphoteric or nonionic. If desired, the tablets may also contain minor amounts of nontoxic auxiliary substances such as pH buffering agents, preservatives, e.g., antioxidants, wetting or emulsifying agents, solubilizing agents, coating agents, flavoring agents, and the like.

[0067] Extended/sustained release formulations may be made by choosing the right combination of excipients that slow the release of the active ingredients by coating or temporarily bonding or decreasing the solubility of the active ingredients. Examples of these excipients include cellulose ethers such as hydroxypropylmethylcellulose (e.g., Methocel K4M), polyvinylacetate-based excipients such as, e.g., Kollidon SR, and polymers and copolymers based on methacrylates and methacrylic acid such as, e.g., Eudragit NE 30D.

[0068] There are several commercially available tablet presses capable of making bi-layered tablets. For example, Manesty RotaPress Diamond, a 45 station D tooling press, is capable of making bi-layered tablets described in this application. Non-limiting examples of presses for the manufacture of bi-layered tablets include Fette America Model No. PT 3090; Maneklal Global Exports (Mumbai, India) Models JD and DH series; Niro Pharma Systems, Model R292F; and Korsch AG Models XL 800 and XL 400.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

[0069] The particulars shown herein are by way of example and for purposes of illustrative discussion of the embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the present invention. In this regard, no attempt is made to show details of the present invention in more detail than is necessary for the fundamental understanding of the present invention, the description making apparent to those skilled in the art how the several forms of the present invention may be embodied in practice.

EXAMPLE 1

Liquid Formula

[0070] A liquid dosage form in accordance with the present invention which comprises promethazine hydrochloride, dihydrocodeine bitartrate and phenylephrine hydrochloride is illustrated as follows:

Ingredients	Per 5 mL	Per 425 L
Promethazine Hydrochloride USP	12.5 mg	1.063 kg
Dihydrocodeine Bitartrate USP	10.0 mg	0.850 kg
Phenylephrine Hydrochloride USP	10.0 mg	0.850 kg
Methyl Paraben USP	9.0 mg	0.765 kg
Propyl Paraben USP	1.0 mg	0.085 kg
Propylene Glycol USP	259 mg	22.016 kg
Saccharin Sodium USP	3.18 mg	0.270 kg
Citric Acid USP	5.0 mg	0.425 kg
Strawberry Flavor	10 mg	0.850 kg
Banana Flavor	10 mg	0.850 kg
Sorbitol Solution 70% USP	3212.5 mg	273.1 kg
Purified Water, as required to q.s. to	5.0 mL	425 L

[0071] Manufacturing process for 425 L batch size: In a suitably sized stainless steel vessel, dissolve methyl paraben and propyl paraben in approximately 50 L of warm (about 45° C.), purified water. Add about half of the propylene glycol and mix for about 1 hr. In a separate 1000 L stainless

steel tank equipped with a suitably sized agitator, add about 50 L of purified water. With the agitator on, add phenylephrine hydrochloride, promethazine hydrochloride, saccharin sodium and citric acid and dissolve. Add the previously prepared paraben/propylene glycol solution to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinsate to the 1000 L tank. Add the remaining propylene glycol to a suitably sized stainless steel vessel and dissolve the strawberry and banana flavors. Transfer this to the 1000 L tank. Rinse the container with 2 L of purified water and transfer to the 1000 L tank. With the agitator on, add the sorbitol solution 70% to the 1000 L tank. In a suitably sized stainless steel vessel, dissolve the dihydrocodeine bitartrate in about 5 L of purified water and transfer to the 1000 L tank. Rinse the container with about 2 L of purified water and transfer to the 1000 L tank. Stop the agitator and let the solution stand for 15 minutes. QS to 425 L with purified water. Filter product through a 1 micron filter and fill in appropriately sized containers.

[0072] To make products with other antihistamines, decongestants, antitussives, or expectorants, one or more combinations of each of the ingredients in a range as described in Table 1 below can be made depending on the specific therapeutic effect desired.

EXAMPLE 2

Suspension Formula

[0073] A suspension formula in accordance with the present invention which comprises promethazine hydrochloride and phenylephrine tannate is illustrated as follows:

Ingredients	g/100 mL = 120 g	kg/batch = 1000 kg
Promethazine Hydrochloride	0.500	4.167
Phenylephrine Tannate	0.800	6.667
Silica, colloidal anhydrous, NF	1.73	14.417
Hydroxyethylcellulose, NF	0.05	0.417
Sorbitol Solution 70% (non-crystallizing), NF	34.00	283.333
Glycerol	14.75	122.917
Xylitol, NF	16.00	133.333
Sodium Citrate, USP	2.00	16.667
Saccharin Sodium cryst., USP	0.01	0.083
Sodium Benzoate, NF	0.15	1.250
Citric Acid Monohydrate, USP	0.16	1.333
Strawberry Flavor	0.15	1.250
Banana Flavor	0.15	1.250
Purified Water	49.55	412.917
Total Amount	120.000 g	1000.000 kg

[0074] Manufacturing process for 1000 kg batch: In a suitably sized stainless steel vessel, dissolve saccharin sodium, sodium benzoate, citric acid, and sodium citrate in approximately 50 L of warm (about 45 deg C.), purified water. In another large stainless steel drum mix the silica, promethazine hydrochloride and micronized phenylephrine tannate until a uniform and consistent mixture is obtained. In a separate 1000 L stainless steel tank equipped with a suitably sized homogenizer/disperser add about 100 L of purified water. With the homogenizer on, add the silica mixture containing phenylephrine tannate and promethazine hydrochloride. Add the previously prepared solution of

saccharin sodium, sodium benzoate, citric acid, and sodium citrate to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinsate to the 1000 L tank. Add the remaining ingredients and homogenize for 15 minutes. Filter product through a 10 micron filter and fill in appropriately sized containers.

[0075] To make products with other antihistamines, decongestants, antitussives, or expectorants, one or more combinations of each of the ingredients in a range as described in Table 1 below can be made depending on the specific therapeutic effect desired.

EXAMPLE 3

Bi-Layered Tablet (Direct Compression)

[0076] A bi-layered tablet in accordance with the present invention which comprises promethazine hydrochloride in one layer and phenylephrine hydrochloride and chlorpheniramine maleate in the other layer is illustrated as follows:

Ingredients	Weight/Tablet (mg)	Weight/1 kg batch (in grams)
<u>Layer 1 (Immediate release)</u>		
Promethazine Hydrochloride	25.0	45.5
Silicified Microcrystalline Cellulose	114.0	297.3
Sodium Starch Glycolate	10.0	18.2
Magnesium Stearate	1.0	1.8
<u>Layer 2 (Sustained release)</u>		
Phenylephrine HCl	20.0	36.4
Chlorpheniramine Maleate	8.0	14.5
Lactose Monohydrate	50.0	90.9
Dicalcium Phosphate	50.0	90.9
Kollidon SR	252.0	458.2
Stearic acid	15.0	27.3
Magnesium Stearate	5.0	9.1
Total	550.0	1030.0

[0077] Manufacturing Process

[0078] (a) Immediate release layer: Screen all ingredients through a USP sieve size # 30. Blend promethazine hydrochloride (45.5 gms), silicified microcrystalline cellulose (297.3 gms) and sodium starch glycolate (18.2 gms) in a twin shell blender for 20 minutes. Add magnesium stearate (1.8 gms), which acts as a lubricant, to the above blend and mix for 3 minutes.

[0079] (b) Sustained release layer: Screen all ingredients through a USP sieve size # 30. Preblend a portion of the Kollidon SR (145 gms) and all the chlorpheniramine maleate (14.5 gms) for 15 minutes. Add the remaining Kollidon SR (313.2 gms), phenylephrine hydrochloride (36.4 gms), lactose monohydrate (90.9 gms) and dicalcium phosphate (90.9 gms) to the above preblend and mix for an additional 20 minutes. Add stearic acid (27.3 gms) and magnesium stearate (9.1 gms) to the above blend and mix for three minutes.

[0080] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet the immediate release layer is 150 mgs and the sustained release layer is 400 mgs.

[0081] By using the process described above, a bi-layered tablet of the following composition may be manufactured by using direct compression:

Ingredients	Weight/tablet (mgs)
<u>Layer 1 (Immediate Release)</u>	
Promethazine Hydrochloride	50
Silicified Microcrystalline Cellulose	133.5
Sodium Starch Glycolate	15
Magnesium Stearate	1.5
<u>Layer 2 (Sustained Release)</u>	
Phenylephrine HCl	20
Chlorpheniramine Maleate	8
Lactose Monohydrate	50
Dicalcium Phosphate	50
Kollidon SR	25.2
Stearic Acid	15
Magnesium Stearate	5
Total	600

EXAMPLE 4

Bi-Layered Tablet (Wet Granulation)

[0082] A bi-layered tablet in accordance with the present invention which comprises promethazine hydrochloride in one layer and pseudoephedrine hydrochloride and chlorpheniramine maleate in the other layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
<u>Layer 1 (Immediate release)</u>		
Promethazine Hydrochloride	25.0	35.7
Silicified Microcrystalline Cellulose	111.0	158.6
Povidone	3.0	4.3
Croscarmellose Sodium	10.0	14.3
Magnesium Stearate	1.0	1.4
<u>Layer 2 (Sustained release)</u>		
Pseudoephedrine HCl	60.0	85.7
Chlorpheniramine Maleate	8.0	11.4
Microcrystalline Cellulose (PH 102)	30.0	42.9
Lactose Monohydrate	100.0	142.9
Dicalcium Phosphate	100.0	142.9
Povidone	15.0	21.4
Methocel K4M Premium	212.0	302.9
Stearic Acid	20.0	28.6
Magnesium Stearate	5.0	7.1
Total	700.0	1000.0

[0083] Manufacturing Process

[0084] (a) Immediate release layer: Screen all ingredients through a USP sieve size # 30. Blend promethazine hydrochloride (35.7 gms), silicified microcrystalline cellulose (158.6 gms) and croscarmellose sodium (14.3 gms) in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (4.3 gms povidone in 14.3 gms purified water). Dry the granulation until the loss on drying (LOD) is less than 2.0%. Screen the dried granu-

lation through a USP sieve size # 14. Add the screened granulation and the prescreened magnesium stearate (1.4 gms) to the above blend and mix for 3 minutes.

[0085] (b) Sustained release layer: Screen all ingredients through a USP sieve size # 30. Blend the pseudoephedrine hydrochloride (87.5 gms), chlorpheniramine maleate (11.4 gms), microcrystalline cellulose PH 102 (42.9 gms), lactose monohydrate (142.9 gms), dicalcium phosphate (142.9 gms), Methocel K4M Premium (302.9 gms) and stearic acid (28.6 gms) in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (21.4 gms povidone in 71.3 gms purified water). Dry the granulation till the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add granules and the prescreened magnesium stearate (7.1 gms) to the above blend and mix for 3 minutes.

[0086] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet the immediate release layer is 150 mgs and the sustained release layer is 550 mgs.

[0087] By using the process described above, a bi-layered tablet of the following composition may be manufactured by using wet granulation:

Ingredients	Weight/tablet (mgs)
<u>Layer 1 (Immediate Release)</u>	
Promethazine Hydrochloride	50
Silicified Microcrystalline cellulose	129.5
Povidone	4
Croscarmellose sodium	15
Magnesium Stearate	1.5
<u>Layer 2 (Sustained Release)</u>	
Pseudoephedrine HCl	60
Chlorpheniramine Maleate	8
Microcrystalline Cellulose 102	30
Lactose Monohydrate	100
Dicalcium Phosphate	100
Povidone	15
Hydroxypropylmethylcellulose	212
Stearic Acid	20
Magnesium Stearate	5
Total	750

[0088] The above examples illustrate how to manufacture a bi-layered tablet containing an antihistamine, i.e., promethazine hydrochloride, in one layer and an antihistamine and/or a decongestant and/or an antitussive and/or an expectorant in the other layer. For the layer that does not contain promethazine hydrochloride, combinations of one or more of each of the non-limiting examples of possible ingredients in an exemplary range as described in the following Table 1 can be made depending on the specific therapeutic effect desired.

TABLE I

Active ingredient	Amount per Tablet	Preferred Amount per Tablet	OTC Daily Dosage
ANTIHISTAMINES			
Azelastine hydrochloride	0.1-2.0 mg	0.125 mg	
Azetadine hydrochloride	0.1-4.0 mg	1 mg	
Brompheniramine maleate	0.1-64 mg	2-16 mg	24 mg
Dexbrompheniramine maleate	0.1-24 mg	3-6 mg	12 mg
Carbinoxamine maleate	0.1-16 mg	4 mg	
Cetirizine hydrochloride	0.1-40 mg	5-10 mg	
Chlorcyclizine	0.1-300 mg		75 mg
Chlorpheniramine maleate	0.1-64 mg	2-16 mg	24 mg
Chlorpheniramine polistirex	0.1-32 mg	4-8 mg	
Clemastine	0.1-12 mg	0.5-2.68 mg	
Cyproheptadine	0.1-16 mg	2-4 mg	
Dexchlorpheniramine maleate	0.1-24 mg	2 mg	12 mg
Cyproheptadine hydrochloride	0.1-32 mg	2-4 mg	
Diphenhydramine hydrochloride	0.1-300 mg	10-50 mg	300 mg
Diphenhydramine citrate	0.1-2000 mg		450 mg
Bromodiphenhydramine hydrochloride	0.1-200 mg	12.5-25 mg	
Dexylamine succinate	0.1-200 mg	12.5-25 mg	75 mg
Pexofenadine hydrochloride	0.1-720 mg	30-180 mg	
Hydroxyzine hydrochloride	0.1-400 mg	10-100 mg	
Hydroxyzine pamoate	0.1-400 mg	25-100 mg	
Loratadine	0.1-80 mg	1-10 mg	
Desloratadine	0.1-40 mg	5 mg	
Phenindamine tartrate	0.1-750 mg		150 mg
Pheniramine maleate	0.1-750 mg		150 mg
Pyridamine maleate	0.1-200 mg	25 mg	200 mg
Terfenadine			
Taenylidamine			
Thonzylamine	0.1-3000 mg		600 mg
Thymol			
Triphenylamine hydrochloride	0.1-400 mg	25-50 mg	
Triprolidine hydrochloride	0.1-40 mg	1.25-5 mg	10 mg
ANITUSSIVES			
Chlophedianol hydrochloride	0.1-800 mg		100 mg
Codeine	0.1-240 mg	8.4-60 mg	120 mg
Codeine phosphate	0.1-240 mg	2.5-60 mg	120 mg
Codeine sulfate	0.1-480 mg		120 mg
Dextromethorphan	0.1-480 mg		120 mg
Dextromethorphan hydrobromide	0.1-240 mg	3.3-30 mg	120 mg
Dextromethorphan polistirex	0.1-240 mg	30 mg	
Diphenhydramine citrate	0.1-7000 mg		228 mg
Diphenhydramine hydrochloride	0.1-400 mg	10-50 mg	150 mg
Benzonate	0.1-800 mg	100-200 mg	
Hydrocodone bitartrate	0.1-40 mg	1.66-10 mg	
Dihydrocodeine	0.1-128 mg	16-32 mg	
Carbamiphen edisylate	0.1-160 mg	6.7-40 mg	
Carbetapentane tannate	0.1-480 mg	30-60 mg	
Carbetapentane citrate	0.1-160 mg	20 mg	
Hydromorphone	0.1-8 mg	1 mg	
Noscapine	0.1-200 mg		
EXPECTORANT			
Guaiifenesin	0.1-2000 mg	50-1200	2400 mg

EXAMPLE 5

Extended Release Suspension

[0089]

Ingredients	Amount/5 ml
Hydrocodone ion-exchange complex	Equivalent to 8 mgs Hydrocodone bitartrate

-continued

Ingredients	Amount/5 ml
Dexchlorpheniramine ion-exchange complex	Equivalent to 4 mgs Dexchlorpheniramine maleate
Phenylephrine ion-exchange complex	Equivalent to 10 mgs Phenylephrine HCl
Eudragit® L 100	0.2 to 2.8 grams
Glycerin	315 mgs
Polysorbate 80	1.5 mgs

-continued

Ingredients	Amount/5 ml
Carbomer (e.g., Carbopol 974)	15 mgs
Methyl Paraben	9 mgs
Propyl Paraben	1 mgs
Artificial grape flavor	5 mgs
FD&C red # 40 dye	0.5 mgs
Water	q.s.

[0090] The formula described above serves as a non-limiting example. Any active drug which is in the form of a salt, such as promethazine hydrochloride, codeine phosphate, pseudoephedrine hydrochloride, morphine sulfate, or meperidine hydrochloride can be incorporated as an ion-exchange resin complex.

[0091] Procedure:

[0092] (1) Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. Amberlite® IRP 69) to a hydrocodone bitartrate, dextchlorpheniramine maleate and phenylephrine HCl solution.

[0093] (2) Stir the mix for 12 hrs to allow complete drug/resin complex formation.

[0094] (3) Separate and dry the insoluble drug/resin complex.

[0095] (4) Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. Eudragit® L 100, Kollidon® MAE, Aquacoat® CPD) and dry the granules.

[0096] (5) Mill the granules, if needed.

[0097] (6) To an appropriate amount of water add the following ingredients and dissolve: Carbomer (e.g., Carbopol® 974), glycerin, polysorbate 80, methyl paraben, propyl paraben, artificial grape flavor, FD&C red # 40 dye.

[0098] (7) Add milled granules.

[0099] (8) Add water to make up to a final volume.

[0100] (9) Agitate at suitable rate to avoid settling of the suspension and maintain a homogeneous product mixture.

[0101] (10) Fill in suitable containers ensuring that the product is homogeneous throughout the filling operation

EXAMPLE 6

Bi-Layered Tablet (Wet Granulation)

[0102] A bi-layered tablet in accordance with the present invention which comprises guaifenesin in a first sustained release layer and codeine phosphate and pseudoephedrine hydrochloride in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
<u>Layer 1 (Sustained release)</u>		
Guaifenesin	600.0	510.6
Methocel K15M	100.0	85.1

-continued

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
Silicified Microcrystalline Cellulose	50	42.6
Eudragit NE	42	35.7
Magnesium Stearate	8.0	6.8
<u>Layer 2 (Sustained release)</u>		
Codeine Phosphate	30.0	25.5
Pseudoephedrine HCl	120.0	102.1
Microcrystalline Cellulose (PH 102)	45.0	38.3
Eudragit NE	15.0	12.8
Methocel K4M Premium	140.0	119.1
Stearic Acid	20.0	17.0
Magnesium Stearate	5.0	4.3
Total	1175.0	1020.0

[0103] Procedure:

[0104] (a) Sustained release layer #1: Mix the guaifenesin, Methocel®K15M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit®NE (30%). Dry the granulation until the LOD (weight loss on drying) is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0105] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the codeine phosphate, pseudoephedrine HCl, microcrystalline cellulose PH 102, and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Add the Methocel®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0106] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 800 mgs and layer #2 is 375 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 7

Bi-Layered Tablet (Wet Granulation)

[0107] A bi-layered tablet in accordance with the present invention which comprises promethazine hydrochloride in an immediate release layer and codeine phosphate and pseudoephedrine hydrochloride in a sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
<u>Layer 1 (Immediate release)</u>		
Promethazine HCl	25.0	37.0
Silicified Microcrystalline Cellulose	111.0	104.3
Povidone	3.0	4.4
Croscarmellose Sodium	10.0	14.8
Magnesium Stearate	1.0	1.5

-continued

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
<u>Layer 2 (Sustained release)</u>		
Codeine Phosphate	30.0	44.4
Pseudoephedrine HCl	120.0	177.6
Microcrystalline Cellulose (PH 102)	30.0	44.4
Dicalcium Phosphate	100.0	148.0
Povidone	15.0	22.2
Methocel K4M Premium	205.0	303.4
Stearic Acid	20.0	29.6
Magnesium Stearate	5.0	7.4
Total	675.0	1000.0

[0108] Procedure:

[0109] (a) Immediate release layer #1: Mix the promethazine HCl, silicified microcrystalline cellulose and croscarmellose sodium, in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (3.0 gms povidone in 10.0 gms purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0110] (b) Sustained release layer #2: Mix the codeine phosphate, pseudoephedrine HCl, microcrystalline cellulose PH 102, dicalcium phosphate, Methocel K4M Premium and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (15.0 gms povidone in 50.0 gms purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0111] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 150 mgs and layer #2 is 525 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 8

Bi-Layered Tablet (Wet Granulation)

[0112] A bi-layered tablet in accordance with the present invention which comprises phenylephrine hydrochloride and carbinoxamine maleate in a first sustained release layer and codeine phosphate in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
<u>Layer 1 (Sustained release)</u>		
Phenylephrine HCl	75.0	185.2
Carbinoxamine Maleate	8.0	19.8
Methocel K4M	59.0	145.7
Silicified Microcrystalline Cellulose	30.0	74.1
Eudragit NE	15.0	37.0
Magnesium Stearate	3.0	7.4

-continued

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
<u>Layer 2 (Sustained release)</u>		
Codeine Phosphate	30.0	74.1
Microcrystalline Cellulose (PH 102)	45.0	111.1
Eudragit NE	15.0	37.0
Methocel K4M Premium	107.0	246.9
Stearic Acid	20.0	49.4
Magnesium Stearate	5.0	12.3
Total	405.0	1000.0

[0113] Procedure:

[0114] (a) Sustained release layer #1: Mix the phenylephrine HCl, carbinoxamine maleate, Methocel K4M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit NE (30%). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0115] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the codeine phosphate, microcrystalline cellulose PH 102, and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit NE (30%). Add the Methocel K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0116] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 190 mgs and layer #2 is 215 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 9

Bi-Layered Tablet (Wet Granulation)

[0117] A bi-layered tablet in accordance with the present invention which comprises pseudoephedrine hydrochloride and chlorpheniramine maleate in a first sustained release layer and codeine phosphate in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
<u>Layer 1 (Sustained release)</u>		
Pseudoephedrine HCl	120.0	253.2
Chlorpheniramine Maleate	12.0	25.3
Methocel K4M	70.0	147.7
Silicified Microcrystalline Cellulose	35.0	73.9
Eudragit NE	20.0	42.2
Magnesium Stearate	3.0	6.3

-continued

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
<u>Layer 2 (Sustained release)</u>		
Codeine Phosphate	30.0	63.3
Microcrystalline Cellulose (PH 102)	45.0	95.0
Eudragit NE	15.0	31.7
Methocel K4M Premium	100.0	211.0
Stearic Acid	20.0	42.2
Magnesium Stearate	5.0	10.5
Total	475.0	1000.0

[0118] Procedure:

[0119] (a) Sustained release layer #1: Mix the pseudoephedrine HCl, chlorpheniramine maleate, Methocel®K4M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0120] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the codeine phosphate, microcrystalline cellulose PH 102, and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Add the Methocel®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0121] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 260 mgs and layer #2 is 215 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 10**Bi-Layered Tablet (Wet Granulation)**

[0122] A bi-layered tablet in accordance with the present invention which comprises carbinoxamine maleate in a first sustained release layer and codeine phosphate in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
<u>Layer 1 (Sustained release)</u>		
Carbinoxamine Maleate	8.0	19.3
Lactose Monohydrate	61.0	147.0
Methocel K4M	70.0	168.7
Silicified Microcrystalline Cellulose	39.0	94.0
Eudragit NE	20.0	48.2
Magnesium Stearate	2.0	4.82
<u>Layer 2 (Sustained release)</u>		
Codeine Phosphate	30.0	72.3
Microcrystalline Cellulose (PH 102)	45.0	108.5
Eudragit NE	15.0	36.2

-continued

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
Methocel K4M Premium	100.0	241.0
Stearic Acid	20.0	48.2
Magnesium Stearate	5.0	12.1
Total	415.0	1000.0

[0123] Procedure:

[0124] (a) Sustained release layer #1: Mix the carbinoxamine maleate, Methocel®K4M, lactose monohydrate and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0125] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the codeine phosphate, microcrystalline cellulose PH 102, and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Add the Methocel®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0126] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 200 mgs and layer #2 is 215 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 11**Bi-Layered Tablet (Direct Compression)**

[0127] A bi-layered tablet in accordance with the present invention which comprises promethazine hydrochloride (longer half-life drug) in an immediate release layer and codeine phosphate (shorter half-life drug) in a sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight/1 kg batch (in grams)
<u>Layer 1 (Immediate release)</u>		
Promethazine HCl	25	45.5
Silicified Microcrystalline Cellulose	114.0	207.5
Sodium Starch Glycolate	10.0	18.2
Magnesium Stearate	1.0	1.8
<u>Layer 2 (Sustained release)</u>		
Codeine Phosphate	60.0	109.2
Lactose Monohydrate	50.0	91.0
Dicalcium Phosphate	50.0	91.0
Kollidon SR	220.0	400.4
Stearic acid	15.0	27.3
Magnesium Stearate	5.0	9.1
Total	550.0	1000.0

[0128] Procedure:

[0129] (a) Immediate release layer #1: Screen all ingredients through a USP sieve size # 30. Blend the promethazine hydrochloride, microcrystalline cellulose and sodium starch glycolate for 20 minutes. Add magnesium stearate to the above blend and mix for an additional time of three minutes.

[0130] (b) Sustained release layer #2: Blend the codeine phosphate, lactose monohydrate, dicalcium phosphate and Kollidon® SR for 20 minutes. Add stearic acid and magnesium stearate to the above blend and mix for an additional time of three minutes.

[0131] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet the immediate release layer #1 is 150 mgs and the sustained release layer #2 is 400 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 12**Bi-Layered Tablet (Wet Granulation)**

[0132] A bi-layered tablet in accordance with the present invention which comprises pseudophedrine tannate and chlorpheniramine tannate in an immediate release layer and codeine phosphate in a sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
Layer 1 (Immediate release)		
Pseudoephedrine Tannate	60.0	85.7
Chlorpheniramine Tannate	8.0	11.4
Silicified Microcrystalline Cellulose	108.0	154.3
Povidone	3.0	4.3
Croscarmellose Sodium	10.0	14.3
Magnesium Stearate	1.0	1.4
Layer 2 (Sustained release)		
Codeine Phosphate	30.0	42.9
Microcrystalline Cellulose (PH 102)	30.0	42.9
Lactose Monohydrate	100.0	142.9
Dicalcium Phosphate	100.0	142.9
Povidone	15.0	21.4
Methocel K4M Premium	210.0	300.0
Stearic Acid	20.0	28.6
Magnesium Stearate	5.0	7.1
Total	700.0	1000.0

[0133] Procedure:

[0134] (a) Immediate release layer #1: Mix the pseudoephedrine tannate, chlorpheniramine tannate, silicified microcrystalline cellulose and croscarmellose sodium, in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (3.0 gms povidone in 10.0 gms purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0135] (b) Sustained release layer #2: Mix the codeine phosphate, microcrystalline cellulose PH 102, lactose mono-

hydrate, dicalcium phosphate, Methocel K4M Premium and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (15.0 gms povidone in 50.0 gms purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0136] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 190 mgs and layer #2 is 510 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 13**Bi-Layered Tablet (Wet Granulation)**

[0137] A bi-layered tablet in accordance with the present invention which comprises promethazine hydrochloride in an immediate release layer and codeine phosphate and phenylephrine hydrochloride in a sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
Layer 1 (Immediate release)		
Promethazine HCl	25	55.5
Silicified Microcrystalline Cellulose	86.0	190.0
Povidone	3.0	6.7
Croscarmellose Sodium	10.0	22.2
Magnesium Stearate	1.0	2.2
Layer 2 (Sustained release)		
Codeine Phosphate	30.0	66.6
Phenylephrine HCl	75.0	166.5
Microcrystalline Cellulose (PH 102)	30.0	66.6
Dicalcium Phosphate	30.0	66.6
Povidone	15.0	33.3
Methocel K4M Premium	120.0	266.4
Stearic Acid	20.0	44.4
Magnesium Stearate	5.0	11.1
Total	450.0	1000.0

[0138] Procedure:

[0139] (a) Immediate release layer #1: Mix the promethazine hydrochloride, silicified microcrystalline cellulose and croscarmellose sodium, in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (3.0 gms povidone in 10.0 gms purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0140] (b) Sustained release layer #2: Mix the codeine phosphate, phenylephrine HCl, microcrystalline cellulose PH 102, dicalcium phosphate, Methocel K4M Premium and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (15.0 gms povidone in 50.0 gms purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0141] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 125 mgs and layer #2 is 325 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 14

Bi-Layered Tablet (Direct Compression)

[0142] A bi-layered tablet in accordance with the present invention which comprises guaifenesin in a first sustained release layer and codeine phosphate in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight/1 kg batch (in grams)
<u>Layer 1 (Sustained release)</u>		
Guaifenesin	600.0	499.8
Methocel K15M	200.0	166.6
Silicified Microcrystalline Cellulose	72	60.0
Eudragit NE	42	39.1
Magnesium Stearate	8.0	7.4
<u>Layer 2 (Sustained release)</u>		
Codeine Phosphate	60.0	50.6
Lactose Monohydrate	35.0	29.2
Dicalcium Phosphate	35.0	29.2
Kollidon SR	170.0	141.6
Stearic acid	15.0	12.5
Magnesium Stearate	5.0	4.2
Total	1200.0	1000.0

[0143] Procedure:

[0144] (a) Sustained release layer #1: Screen all ingredients through a USP sieve size # 30. Blend the guaifenesin, Methocel® K15M and silicified microcrystalline cellulose for 25 minutes. Add magnesium stearate to the above blend and mix for an additional time of three minutes.

[0145] (b) Sustained release layer #2: Blend the codeine phosphate, lactose monohydrate, dicalcium phosphate and Kollidon® SR for 20 minutes. Add stearic acid and magnesium stearate to the above blend and mix for an additional time of three minutes.

[0146] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 880 mgs and layer #2 is 320 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 15

Bi-Layered Tablet (Wet Granulation)

[0147] A bi-layered tablet in accordance with the present invention which comprises guaifenesin in a first sustained release layer and codeine phosphate and phenylephrine hydrochloride in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
<u>Layer 1 (Sustained release)</u>		
Guaifenesin	600.0	558.0
Methocel K15M	100.0	93.0
Silicified Microcrystalline Cellulose	50	46.5
Eudragit NE	42	39.1
Magnesium Stearate	8.0	7.4
<u>Layer 2 (Sustained release)</u>		
Codeine Phosphate	30.0	27.9
Phenylephrine HCl	60.0	55.8
Microcrystalline Cellulose (PH 102)	45.0	41.9
Eudragit NE	15.0	14.0
Methocel K4M Premium	100.0	93.0
Stearic Acid	20.0	18.6
Magnesium Stearate	5.0	4.7
Total	1075.0	1000.0

[0148] Procedure:

[0149] (a) Sustained release layer #1: Mix the guaifenesin, Methocel®K15M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0150] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the codeine phosphate, phenylephrine HCl, microcrystalline cellulose PH 102, dicalcium phosphate and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Add the Methocel®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0151] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 800 mgs and layer #2 is 275 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 16

Bi-Layered Tablet (Wet Granulation)

[0152] A bi-layered tablet in accordance with the present invention which comprises guaifenesin in a first sustained release layer and codeine phosphate and phenylephrine hydrochloride in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
<u>Layer 1 (Sustained release)</u>		
Guaifenesin	1000.0	635.0
Methocel K15M	200.0	127.0

-continued

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
Silicified Microcrystalline Cellulose	40.0	25.4
Eudragit NE	50.0	31.8
Magnesium Stearate	10.0	6.4
<u>Layer 2 (Sustained release)</u>		
Codeine Phosphate	30.0	19.1
Phenylephrine HCl	60.0	38.1
Microcrystalline Cellulose (PH 102)	45.0	28.6
Eudragit NE	15.0	9.5
Methocel K4M Premium	100.0	63.5
Stearic Acid	20.0	12.7
Magnesium Stearate	5.0	3.2
Total	1575.0	1000.0

[0153] Procedure:

[0154] (a) Sustained release layer #1: Mix the guaifenesin, Methocel®K15M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0155] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the codeine phosphate, phenylephrine HCl, microcrystalline cellulose PH 102, dicalcium phosphate and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Add the Methocel®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0156] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 1300 mgs and layer #2 is 275 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 17**Bi-Layered Tablet (Direct Compression)**

[0157] A bi-layered tablet in accordance with the present invention which comprises codeine phosphate in a first sustained release layer and phenylephrine hydrochloride and chlorpheniramine maleate in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight/1 kg batch (in grams)
<u>Layer 1 (Sustained release)</u>		
Codeine Phosphate	30	54.5
Methocel® K4M	50	90.9

-continued

Ingredients	Weight/tablet (mg)	Weight/1 kg batch (in grams)
Silicified Microcrystalline Cellulose	100.0	181.8
Sodium Starch Glycolate	10.0	18.2
Magnesium Stearate	1.0	1.8
<u>Layer 2 (Sustained release)</u>		
Phenylephrine HCl	60	109
Chlorpheniramine Maleate	8.0	14.5
Lactose Monohydrate	50.0	90.9
Dicalcium Phosphate	50.0	90.9
Methocel K4M	181.0	329.1
Stearic acid	15.0	27.3
Magnesium Stearate	5.0	9.1
Total	550.0	1000.0

[0158] Procedure:

[0159] (a) Sustained release Layer #1: Screen all ingredients through a USP sieve size # 30. Preblend a portion of the Kollidon SR (145 gms) and all the codeine phosphate for 15 minutes. Add lactose monohydrate (90.9 gms) and dicalcium phosphate (90.9 gms) to the above preblend and mix for an additional 20 minutes. Add stearic acid (27.3 gms) and magnesium stearate (9.1 gms) to the above blend and mix for three minutes.

[0160] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Preblend a portion of the Kollidon SR (145 gms) and all the chlorpheniramine maleate (14.5 gms) for 15 minutes. Add the remaining Kollidon SR (313.2 gms), phenylephrine hydrochloride (36.4 gms), lactose monohydrate (90.9 gms) and dicalcium phosphate (90.9 gms) to the above preblend and mix for an additional 20 minutes. Add stearic acid (27.3 gms) and magnesium stearate (9.1 gms) to the above blend and mix for three minutes.

[0161] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet the immediate release layer is 150 mgs and the sustained release layer is 400 mgs.

EXAMPLE 18**Bi-Layered Tablet (Direct Compression)**

[0162] By using the process described in Example 17, a bi-layered tablet which contains codeine phosphate in an immediate release layer and codeine phosphate, phenylephrine hydrochloride and chlorpheniramine maleate in a sustained release layer may be manufactured by using direct compression:

Ingredients	Weight/tablet (mgs)
<u>Layer 1 (Immediate Release)</u>	
Codeine Phosphate	10
Silicified Microcrystalline Cellulose	133.5
Sodium Starch Glycolate	15
Magnesium Stearate	1.5

-continued

Ingredients	Weight/tablet (mgs)
<u>Layer 2 (Sustained Release)</u>	
Codeine Phosphate	40
Phenylephrine HCl	50
Chlorpheniramine Maleate	8
Lactose Monohydrate	50
Dicalcium Phosphate	50
Kollidon SR	252
Stearic Acid	15
Magnesium Stearate	5
Total	620

EXAMPLE 19

Bi-Layered Tablet (Wet Granulation)

[0163] A bi-layered tablet in accordance with the present invention which comprises codeine phosphate in an immediate release layer and codeine phosphate, pseudoephedrine hydrochloride and chlorpheniramine maleate in a sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/l kg batch (gms)
<u>Layer 1 (Immediate release)</u>		
Codeine Phosphate	10.0	11.9
Silicified Microcrystalline Cellulose	111.0	158.6
Povidone	3.0	4.3
Croscarmellose Sodium	16.5	14.3
Magnesium Stearate	1.0	1.4
<u>Layer 2 (Sustained release)</u>		
Codeine Phosphate	30	35.7
Pseudoephedrine HCl	60.0	85.7
Chlorpheniramine Maleate	8.0	11.4
Microcrystalline Cellulose (PH 102)	35.0	42.9
Lactose Monohydrate	100.0	142.9
Dicalcium Phosphate	100.0	142.9
Povidone	15.0	21.4
Methocel K4M Premium	212.0	302.9
Stearic Acid	20.0	28.6
Magnesium Stearate	5.0	7.1
Total	700.0	1012.0

[0164] Procedure:

[0165] (a) Immediate release layer #1: Screen all ingredients through a USP sieve size # 30. Blend the codeine phosphate (11.9 grams), silicified microcrystalline cellulose (158.6 grams), and croscarmellose sodium in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (4.3 gms povidone in 14.3 gms purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add granules and the prescreened magnesium stearate (1.4 gms) to the above blend and mix for 3 minutes.

[0166] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Blend the pseudoephedrine hydrochloride (87.5 gms), chlorpheniramine maleate (11.4 gms), codeine phosphate (37.5 gms), microcrystalline

cellulose PH 102 (42.9 gms), lactose monohydrate (142.9 gms), dicalcium phosphate (142.9 gms), Methocel K4M Premium (302.9 gms) and stearic acid (28.6 gms) in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (21.4 gms povidone in 71.3 gms purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add granules and the prescreened magnesium stearate (7.1 gms) to the above blend and mix for 3 minutes.

[0167] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet the immediate release layer is 150 mgs and the sustained release layer is 550 mgs.

EXAMPLE 20

Bi-Layered Tablet (Wet Granulation)

[0168] By using the process described in Example 19, a bi-layered tablet containing codeine phosphate in an immediate release layer and pseudoephedrine hydrochloride and chlorpheniramine maleate in a sustained release layer may be manufactured by using wet granulation:

Ingredients	Weight/tablet (mgs)
<u>Layer 1 (Immediate Release)</u>	
Codeine Phosphate	30
Silicified Microcrystalline cellulose	129.5
Povidone	4
Croscarmellose sodium	15
Magnesium Stearate	1.5
<u>Layer 2 (Sustained Release)</u>	
Pseudoephedrine HCl	60
Chlorpheniramine Maleate	8
Microcrystalline Cellulose 102	30
Lactose Monohydrate	100
Dicalcium Phosphate	100
Povidone	15
Hydroxypropylmethylcellulose	212
Stearic Acid	20
Magnesium Stearate	5
Total	750

[0169] The above examples 6-20 illustrate how to manufacture a bi-layered tablet containing an antitussive, i.e., codeine phosphate in (at least) a first layer and an antihistamine and/or a decongestant and/or an expectorant in (at least) a second layer. Non-limiting examples of possible active ingredients (in addition to the antitussive morphine derivative) in an exemplary range as described in the above Table 1 can be employed depending on the specific therapeutic effect desired.

EXAMPLE 21

Extended Release Suspension (Gel)

[0170] An extended release suspension (in the form of a gel) in accordance with the present invention which contains a codeine phosphate ion-exchange complex and promethazine hydrochloride is illustrated as follows (note that the codeine phosphate is used in a controlled release form since it has a shorter half-life than the promethazine hydrochloride):

Ingredients	Amount/5 ml
Codeine Phosphate Ion-Exchange Complex	Equivalent to 30 mgs of Codeine Phosphate
Promethazine HCl	25 mgs
Eudragit® L 100	0.2 to 2.8 grams
Glycerin	315 mgs
Polysorbate 80	1.5 mgs
Carbomer (e.g., Carbopol® 974)	37.5 mgs
Methyl Paraben	9 mgs
Propyl Paraben	1 mgs
Saccharin Sodium cryst., USP	0.1 mg
Artificial Grape Flavor	5 mgs
FD&C Red # 40 Dye	0.5 mgs
Sodium Hydroxide	q.s.
Water	q.s.

[0171] Procedure:

[0172] (1) Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. Amberlite® IRP 69) to a codeine phosphate solution.

[0173] (2) Stir the mix for 12 hrs to allow complete drug/resin complex formation.

[0174] (3) Separate and dry the insoluble drug/resin complex.

[0175] (4) Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. Eudragit® L 100, Kollidon® MAE, Aquacoat® CPD) and dry the granules.

[0176] (5) Mill the granules, if needed.

[0177] (6) To an appropriate amount of water add the following ingredients and dissolve: promethazine hydrochloride, Carbomer (e.g., Carbopol® 974), glycerin, polysorbate 80, methyl paraben, propyl paraben, artificial grape flavor, FD&C red # 40 dye.

[0178] (7) Add milled granules.

[0179] (8) Add water to 95% of final volume.

[0180] (9) Agitate at suitable rate to avoid settling of the suspension and maintain a homogeneous product mixture.

[0181] (10) Neutralize the solution to form a gel using a 1N sodium hydroxide solution. Add water to make final volume.

[0182] (11) Fill in suitable containers ensuring that the product is homogeneous throughout the filling operation.

EXAMPLE 22

Extended Release Suspension (Liquid)

[0183] An extended release suspension (in the form of a liquid) in accordance with the present invention which contains a codeine phosphate ion-exchange complex and promethazine hydrochloride is illustrated as follows:

Ingredients	Amount/5 ml
Codeine Phosphate Ion-Exchange Complex	Equivalent to 45 mgs of Codeine Phosphate
Promethazine HCl	25 mgs
Eudragit® L 100	0.2 to 2.8 grams
Silica, colloidal anhydrous, NF	100 mgs

-continued

Ingredients	Amount/5 ml
Glycerin	740 mgs
Xylitol, NF	800 mgs
Sodium Citrate, USP	100 mgs
Saccharin Sodium cryst., USP	0.1 mg
Sodium Benzoate	7.5 mgs
Citric Acid Monohydrate, USP	8.0 mgs
Artificial Grape Flavor	5 mgs
FD&C Red # 40 Dye	0.5 mgs
Water	q.s.

[0184] Manufacturing Process for 1000 L Batch:

[0185] Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. Amberlite® IRP 69) to a codeine phosphate solution. Stir the mix for 12 hrs to allow complete drug/resin complex formation. Separate and dry the insoluble drug/resin complex. Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. Eudragit® L 100, Kollidon® MAE, Aquacoat® CPD) and dry the granules. Mill the granules, if needed.

[0186] In a suitably sized stainless steel vessel, dissolve saccharin sodium, sodium benzoate, citric acid, and sodium citrate in approximately 50 L of warm (about 45° C.), purified water. In another large stainless steel drum mix the silica, codeine phosphate ion-exchange complex, and promethazine hydrochloride until a uniform and consistent mixture is obtained. In a separate 1000 L stainless steel tank equipped with a suitably sized homogenizer/disperser add about 100 L of purified water. With the homogenizer on, add the silica mixture containing codeine phosphate ion-exchange complex, and promethazine hydrochloride. Add the previously prepared solution of saccharin sodium, sodium benzoate, citric acid, and sodium citrate to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinsate to the 1000 L tank. Add the remaining ingredients and homogenize for 15 minutes.

EXAMPLE 23

Extended Release Suspension (Liquid)

[0187] An extended release suspension (in the form of a liquid) in accordance with the present invention which contains a codeine phosphate ion-exchange complex, pseudoephedrine tannate and chlorpheniramine tannate is illustrated as follows:

Ingredients	Amount/5 ml
Codeine Phosphate Ion-Exchange Complex	Equivalent to 45 mgs of Codeine Phosphate
Pseudoephedrine Tannate	75.0
Chlorpheniramine Tannate	4.5
Eudragit® L 100	0.2 to 2.8 grams
Silica, colloidal anhydrous, NF	100 mgs
Glycerin	740 mgs
Xylitol, NF	800 mgs
Sodium Citrate, USP	100 mgs
Saccharin Sodium cryst., USP	0.1 mg
Sodium Benzoate	7.5 mgs
Citric Acid Monohydrate, USP	8.0 mgs
Artificial Grape Flavor	5 mgs

US 2005/0266032 A1

Dec. 1, 2005

18

-continued

Ingredients	Amount/5 ml
FD&C Red # 40 Dye	0.5 mgs
Water	q.s

[0188] Manufacturing Process for 1000 kg Batch:

[0189] Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. Amberlite® IRP 69) to a codeine phosphate solution. Stir the mix for 12 hrs to allow complete drug/resin complex formation. Separate and dry the insoluble drug/resin complex. Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. Eudragit® L 100, Kollidon® MAE, Aquacoat® CPD) and dry the granules. Mill the granules, if needed.

[0190] In a suitably sized stainless steel vessel, dissolve saccharin sodium, sodium benzoate, citric acid, and sodium citrate in approximately 50 L of warm (about 45° C.), purified water. In another large stainless steel drum mix the silica, codeine phosphate ion-exchange complex, pseudoephedrine tannate, and the chlorpheniramine tannate until a uniform and consistent mixture is obtained. In a separate 1000 L stainless steel tank equipped with a suitably sized homogenizer/disperser add about 100 L of purified water. With the homogenizer on, add the silica mixture containing codeine phosphate ion-exchange complex, pseudoephedrine tannate, and the chlorpheniramine tannate. Add the previously prepared solution of saccharin sodium, sodium benzoate, citric acid, and sodium citrate to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinsate to the 1000 L tank. Add the remaining ingredients and homogenize for 15 minutes.

EXAMPLE 24

Extended Release Suspension

[0191] An extended release suspension which contains a hydrocodone bitartrate ion-exchange complex, a dexchlorpheniramine maleate ion-exchange complex and a phenylephrine hydrochloride ion-exchange complex is illustrated as follows:

Ingredients	Amount/5 ml
Hydrocodone Bitartrate Ion-Exchange Complex	Equivalent to 8 mgs of Hydrocodone bitartrate
Dexchlorpheniramine Maleate Ion-Exchange Complex	Equivalent to 4 mgs of Dexchlorpheniramine Maleate
Phenylephrine HCl Ion-Exchange Complex	Equivalent to 10 mgs of Phenylephrine HCl
Eudragit® L 100	0.2 to 2.8 grams
Glycerin	2.5 mgs
Polysorbate 80	1.5 mgs
Carbomer (e.g., Carbopol® 974)	15 mgs
Methyl Paraben	9 mgs
Propyl Paraben	1 mgs
Artificial Grape Flavor	5 mgs
FD&C Red # 40 Dye	0.5 mgs
Water	q.s

[0192] The formula described above serves as a non-limiting example. Any active drug which is in the form of a

salt, such as codeine, or dihydrocodeine, or hydrocodone can be incorporated as an ion-exchange resin complex.

[0193] Procedure:

[0194] (1) Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. Amberlite® IRP 69) to a codeine phosphate, dexchlorpheniramine maleate and phenylephrine HCl solution.

[0195] (2) Stir the mix for 12 hrs to allow complete drug/resin complex formation.

[0196] (3) Separate and dry the insoluble drug/resin complex.

[0197] (4) Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. Eudragit® L 100, Kollidon® MAE, Aquacoat® CPD) and dry the granules.

[0198] (5) Mill the granules, if needed.

[0199] (6) To an appropriate amount of water add the following ingredients and dissolve: Carbomer (e.g., Carbopol® 974), glycerin, polysorbate 80, methyl paraben, propyl paraben, artificial grape flavor, FD&C red # 40 dye.

[0200] (7) Add milled granules.

[0201] (8) Add water to make up to a final volume.

[0202] (9) Agitate at suitable rate to avoid settling of the suspension and maintain a homogeneous product mixture.

[0203] (10) Fill in suitable containers ensuring that the product is homogeneous throughout the filling operation.

EXAMPLE 25

Suspension Formula

[0204] A suspension formula which comprises codeine phosphate and phenylephrine tannate is illustrated as follows:

Ingredients	g/100 ml. = 120 g	kg/batch = 1000 kg
Codeine Phosphate	0.500	4.167
Phenylephrine Tannate	0.800	6.667
Silica, colloidal anhydrous, NF	1.73	14.417
Hydroxyethylcellulose, NF	0.65	0.417
Sorbitol Solution 70% (non-crystallizing), NF	34.00	283.333
Glycerol	14.75	122.917
Xylitol, NF	16.00	133.333
Sodium Citrate, USP	2.00	16.667
Saccharin Sodium cryst., USP	0.01	0.083
Sodium Benzoate, NF	0.15	1.250
Citric Acid Monohydrate, USP	0.16	1.333
Strawberry Flavor	0.15	1.250
Banana Flavor	0.15	1.250
Purified Water	49.55	412.917
Total Amount	120.000 g	1000.000 kg

[0205] Manufacturing Process for 1000 kg Batch:

[0206] In a suitably sized stainless steel vessel, dissolve saccharin sodium, sodium benzoate, citric acid, and sodium citrate in approximately 50 L of warm (about 45° C.), purified water. In another large stainless steel drum mix the

silica, codeine phosphate, and micronized phenylephrine tannate until a uniform and consistent mixture is obtained. In a separate 1000 L stainless steel tank equipped with a suitably sized homogenizer/disperser add about 100 L of purified water. With the homogenizer on, add the silica mixture containing phenylephrine tannate and codeine phosphate. Add the previously prepared solution of saccharin sodium, sodium benzoate, citric acid, and sodium citrate to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinsate to the 1000 L tank. Add the remaining ingredients and homogenize for 15 minutes. Filter product through a 10 micron filter and fill in appropriately sized containers.

[0207] To make products with other agents such as antihistamines, decongestants, or expectorants, one or more combinations of each of the ingredients in a range as described in Table 1 below can be made depending on the specific therapeutic effect desired.

EXAMPLE 26

Liquid Formula

[0208] A liquid dosage form which comprises codeine phosphate and phenylephrine hydrochloride is illustrated as follows:

Ingredients	Per 5 mL	Per 425 L
Codeine Phosphate USP	30 mg	2,550 kg
Phenylephrine Hydrochloride USP	10.0 mg	0.850 kg
Methyl Paraben USP	2.0 mg	0.765 kg
Propyl Paraben USP	1.0 mg	0.085 kg
Propylene Glycol USP	259 mg	22.016 kg
Saccharin Sodium USP	3.18 mg	0.270 kg
Citric Acid USP	5.0 mg	0.425 kg
Strawberry Flavor	10 mg	0.850 kg
Banana Flavor	10 mg	0.850 kg
Sorbitol Solution 70% USP	2212.5 mg	273.1 kg
Purified Water, as required to q.s. to	5.0 mL	425 L

[0209] Manufacturing Process for 425 L Batch Size:

[0210] In a suitably sized stainless steel vessel, dissolve methyl paraben and propyl paraben in approximately 50 L of warm (about 45° C.), purified water. Add about half of the propylene glycol and mix for about 1 hr. In a separate 1000 L stainless steel tank equipped with a suitably sized agitator, add about 50 L of purified water. With the agitator on, add phenylephrine hydrochloride, codeine phosphate, saccharin sodium and citric acid and dissolve. Add the previously prepared paraben/propylene glycol solution to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinsate to the 1000 L tank. Add the remaining propylene glycol to a suitably sized stainless steel vessel and dissolve the strawberry and banana flavors. Transfer this to the 1000 L tank. Rinse the container with 2 L of purified water and transfer to the 1000 L tank. With the agitator on, add the sorbitol solution 70% to the 1000 L tank. In a suitably sized stainless steel vessel, dissolve the codeine phosphate in about 5 L of purified water and transfer to the 1000 L tank. Rinse the container with about 2 L of purified water and transfer to the 1000 L tank. Stop the agitator and let the solution stand for 15 minutes. QS to 425 L with

purified water. Filter product through a 1 micron filter and fill in appropriately sized containers.

[0211] To make products with other antihistamines, decongestants, or expectorants, one or more combinations of each of the ingredients in a range as described in Table 1 above can be made depending on the specific therapeutic effect desired.

EXAMPLE 27

Bi-Layered Tablet (Wet Granulation)

[0212] A bi-layered tablet in accordance with the present invention which comprises guaifenesin in a first sustained release layer and carbetapentane citrate and pseudoephedrine hydrochloride in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
Layer 1 (Sustained release)		
Guaifenesin	600.0	510.6
Methocel K15M	100.0	85.1
Silicified Microcrystalline Cellulose	50	42.6
Eudragit NE	42	35.7
Magnesium Stearate	8.0	6.8
Layer 2 (Sustained release)		
Carbetapentane Citrate	30.0	25.5
Pseudoephedrine HCl	120.0	102.1
Microcrystalline Cellulose (PH 102)	45.0	38.4
Eudragit NE	15.0	12.8
Methocel K4M Premium	140.0	119.1
Stearic Acid	20.0	17.0
Magnesium Stearate	5.0	4.3
Total	1175.0	1000.0

[0213] Procedure:

[0214] (a) Sustained release layer #1: Mix the guaifenesin, Methocel®K15M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using the Eudragit® NE (30%). Dry the granulation until the LOD (weight loss on drying) is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0215] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size# 30. Mix the carbetapentane citrate, pseudoephedrine HCl, microcrystalline cellulose PH 102, and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using the Eudragit® NE (30%). Add the Methocel®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0216] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 800 mgs and layer #2 is 375 mgs. Capsules may be manufactured by filling the same proportions into capsules.

US 2005/0266032 A1

20

Dec. 1, 2005

EXAMPLE 28

Bi-Layered Tablet (Wet Granulation)

[0217] A bi-layered tablet in accordance with the present invention which comprises promethazine hydrochloride in an immediate release layer and carbetapentane citrate and pseudoephedrine hydrochloride in a sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
<u>Layer 1 (Immediate release)</u>		
Promethazine HCl	25.0	37.0
Silicified Microcrystalline Cellulose	113.0	164.3
Povidone	3.0	4.4
Croscarmellose Sodium	10.0	14.8
Magnesium Stearate	1.0	1.5
<u>Layer 2 (Sustained release)</u>		
Carbetapentane Citrate	30.0	44.4
Pseudoephedrine HCl	123.0	177.6
Microcrystalline Cellulose (PH 102)	50.0	44.4
Dicalcium Citrate	109.0	148.0
Povidone	15.0	22.2
Methocel K4M Premium	205.0	304.4
Stearic Acid	20.0	29.6
Magnesium Stearate	5.0	7.4
Total	675.0	1000.0

[0218] Procedure:

[0219] (a) Immediate release layer #1: Mix the promethazine HCl, silicified microcrystalline cellulose and croscarmellose sodium, in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (3.0 gms povidone in 10.0 gms purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0220] (b) Sustained release layer #2: Mix the carbetapentane citrate, pseudoephedrine HCl, microcrystalline cellulose PH 102, dicalcium phosphate, Methocel K4M Premium and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (15.0 gms povidone in 50.0 gms purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0221] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 150 mgs and layer #2 is 525 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 29

Bi-Layered Tablet (Wet Granulation)

[0222] A bi-layered tablet in accordance with the present invention which comprises phenylephrine hydrochloride and carbinoxamine maleate in a first sustained release layer and carbetapentane citrate in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
<u>Layer 1 (Sustained release)</u>		
Phenylephrine HCl	75.0	185.2
Carbinoxamine Maleate	8.0	19.8
Methocel K4M	59.0	145.7
Silicified Microcrystalline Cellulose	30.0	74.1
Eudragit NE	15.0	37.0
Magnesium Stearate	3.0	7.4
<u>Layer 2 (Sustained release)</u>		
Carbetapentane Citrate	30.0	74.1
Microcrystalline Cellulose (PH 102)	45.0	111.1
Eudragit NE	15.0	37.0
Methocel K4M Premium	103.0	246.9
Stearic Acid	20.0	49.4
Magnesium Stearate	5.0	12.3
Total	405.0	1000.0

[0223] Procedure:

[0224] (a) Sustained release layer #1: Mix the phenylephrine HCl, carbinoxamine maleate, Methocel®K4M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using the Eudragit® NE (30%). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0225] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the carbetapentane citrate, microcrystalline cellulose PH 102, and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using the Eudragit® NE (30%). Add the Methocel®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0226] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 190 mgs and layer #2 is 215 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 30

Bi-Layered Tablet (Wet Granulation)

[0227] A bi-layered tablet in accordance with the present invention which comprises pseudoephedrine hydrochloride and chlorpheniramine maleate in a first sustained release layer and carbetapentane citrate in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
<u>Layer 1 (Sustained release)</u>		
Pseudoephedrine HCl	120.0	253.2
Chlorpheniramine Maleate	12.0	25.3
Methocel K4M	70.0	146.7

-continued		
Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
Silicified Microcrystalline Cellulose	35.0	73.9
Eudragit NE	20.0	42.2
Magnesium Stearate	5.0	6.3
Layer 2 (Sustained release)		
Carbetapentane Citrate	30.0	63.4
Microcrystalline Cellulose (PH 102)	45.0	95.0
Eudragit NE	15.0	31.7
Methocel K4M Premium	60.0	209.5
Stearic Acid	20.0	42.2
Magnesium Stearate	5.0	10.6
Total	475.0	1000.0

[0228] Procedure:

[0229] (a) Sustained release layer #1: Mix the pseudoephedrine HCl, chlorpheniramine maleate, Methocel®K4M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using the Eudragit® NE (30%). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0230] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the carbetapentane citrate, microcrystalline cellulose PH 102, and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using the Eudragit® NE (30%). Add the Methocel®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0231] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 260 mgs and layer #2 is 215 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 31

Bi-Layered Tablet (Wet Granulation)

[0232] A bi-layered tablet in accordance with the present invention which comprises carbinoxamine maleate in a first sustained release layer and carbetapentane citrate in a second sustained release layer is illustrated as follows:

Layer 1 (Sustained release)		
Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
Carbinoxamine Maleate	8.0	19.3
Lactose Monohydrate	61.0	147.0
Methocel K4M	70.0	168.7
Silicified Microcrystalline Cellulose	34.0	94.0
Eudragit NE	20.0	48.2
Magnesium Stearate	2.0	4.82

-continued		
Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
Layer 2 (Sustained release)		
Carbetapentane Citrate	30.0	72.4
Microcrystalline Cellulose (PH 102)	45.0	108.5
Eudragit NE	15.0	36.2
Methocel K4M Premium	100.0	241.0
Stearic Acid	20.0	48.2
Magnesium Stearate	5.0	12.1
Total	415.0	1000.0

[0233] Procedure:

[0234] (a) Sustained release layer #1: Mix the carbinoxamine maleate, Methocel®K4M, lactose monohydrate and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using the Eudragit® NE (30%). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0235] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the carbetapentane citrate, microcrystalline cellulose PH 102, and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using the Eudragit® NE (30%). Add the Methocel®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0236] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 200 mgs and layer #2 is 215 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 32

Bi-Layered Tablet (Direct Compression)

[0237] A bi-layered tablet in accordance with the present invention which comprises promethazine hydrochloride (longer half-life drug) in an immediate release layer and carbetapentane citrate (shorter half-life drug) in a sustained release layer is illustrated as follows:

Layer 1 (Immediate release)		
Ingredients	Weight/tablet (mg)	Weight/1 kg batch (in grams)
Promethazine HCl	25	45.5
Silicified Microcrystalline Cellulose	114.0	207.5
Sodium Starch Glycolate	10.0	18.2
Magnesium Stearate	1.0	1.8
Layer 2 (Sustained release)		
Carbetapentane Citrate	60.0	109.2
Lactose Monohydrate	50.0	91.0

-continued

Ingredients	Weight/tablet (mg)	Weight/1 kg batch (in grams)
Dicalcium Citrate	50.0	91.0
Kollidon SR	220.0	399.4
Stearic acid	15.0	27.3
Magnesium Stearate	5.0	9.1
Total	850.0	1000.0

[0238] Procedure:

[0239] (a) Immediate release layer #1: Screen all ingredients through a USP sieve size # 30. Blend the promethazine hydrochloride, microcrystalline cellulose and sodium starch glycolate for 20 minutes. Add magnesium stearate to the above blend and mix for an additional time of three minutes.

[0240] (b) Sustained release layer #2: Blend the carbapentane citrate, lactose monohydrate, dicalcium citrate and Kollidon® SR for 20 minutes. Add stearic acid and magnesium stearate to the above blend and mix for an additional time of three minutes.

[0241] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet the immediate release layer #1 is 150 mgs and the sustained release layer #2 is 400 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 33

Bi-Layered Tablet (Wet Granulation)

[0242] A bi-layered tablet in accordance with the present invention which comprises pseudoephedrine tannate and chlorpheniramine tannate in an immediate release layer and carbapentane tannate in a sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
Layer 1 (Immediate release)		
Pseudoephedrine Tannate	66.0	85.7
Chlorpheniramine Tannate	8.0	11.4
Silicified Microcrystalline Cellulose	106.0	154.3
Povidone	3.0	4.3
Croscarmellose Sodium	10.0	14.3
Magnesium Stearate	1.0	1.4
Layer 2 (Sustained release)		
Carbetapentane Tannate	30.0	42.9
Microcrystalline Cellulose (PH 102)	30.0	42.9
Lactose Monohydrate	100.0	142.9
Dicalcium Citrate	100.0	142.9
Povidone	15.0	21.4
Methocel K4M Premium	210.0	300.0
Stearic Acid	20.0	28.6
Magnesium Stearate	5.0	7.1
Total	700.0	1000.0

[0243] Procedure:

[0244] (a) Immediate release layer #1: Mix the pseudoephedrine tannate, chlorpheniramine tannate, silicified

microcrystalline cellulose and croscarmellose sodium, in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (3.0 gms povidone in 10.0 gms purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0245] (b) Sustained release layer #2: Mix the carbapentane tannate, microcrystalline cellulose PH 102, lactose monohydrate, dicalcium phosphate, Methocel K4M Premium and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (15.0 gms povidone in 50.0 gms purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0246] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 190 mgs and layer #2 is 510 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 34

Bi-Layered Tablet (Wet Granulation)

[0247] A bi-layered tablet in accordance with the present invention which comprises diphenhydramine hydrochloride in an immediate release layer and carbapentane citrate and phenylephrine hydrochloride in a sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
Layer 1 (Immediate release)		
Diphenhydramine HCl	100	181.8
Silicified Microcrystalline Cellulose	86.0	156.4
Povidone	3.0	5.5
Croscarmellose Sodium	10.0	18.2
Magnesium Stearate	1.0	1.8
Layer 2 (Sustained release)		
Carbetapentane Citrate	60.0	109.1
Phenylephrine HCl	75.0	136.4
Microcrystalline Cellulose (PH 102)	30.0	54.5
Dicalcium Citrate	30.0	54.5
Povidone	15.0	27.3
Methocel K4M Premium	115.0	209.1
Stearic Acid	20.0	36.4
Magnesium Stearate	5.0	9.1
Total	450.0	1000.0

[0248] Procedure:

[0249] (a) Immediate release layer #1: Mix the diphenhydramine hydrochloride, silicified microcrystalline cellulose and croscarmellose sodium in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (3.0 gms povidone in 10.0 gms purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0250] (b) Sustained release layer #2: Mix the carbetapentane citrate, phenylephrine HCl, microcrystalline cellulose PH 102, dicalcium phosphate, Methocel K4M Premium and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (15.0 gms povidone in 50.0 gms purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0251] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 125 mgs and layer #2 is 325 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 35

Bi-Layered Tablet (Direct Compression)

[0252] A bi-layered tablet in accordance with the present invention which comprises guaifenesin in a first sustained release layer and carbetapentane citrate in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight/1 kg batch (in grams)
<u>Layer 1 (Sustained release)</u>		
Guaifenesin	600.0	499.8
Methocel K15M	200.0	166.6
Silicified Microcrystalline Cellulose	72	60.0
Magnesium Stearate	8.0	6.7
<u>Layer 2 (Sustained release)</u>		
Carbetapentane Citrate	60.0	50
Lactose Monohydrate	35.0	29.2
Dicalcium Citrate	35.0	29.2
Kollidon SR	170.0	141.6
Stearic acid	15.0	12.5
Magnesium Stearate	5.0	4.2
Total	1200.0	1000.0

[0253] Procedure:

[0254] (a) Sustained release layer #1: Screen all ingredients through a USP sieve size # 30. Blend the guaifenesin, Methocel® K15M and silicified microcrystalline cellulose for 25 minutes. Add magnesium stearate to the above blend and mix for an additional time of three minutes.

[0255] (b) Sustained release layer #2: Blend the carbetapentane citrate, lactose monohydrate, dicalcium citrate and Kollidon® SR for 20 minutes. Add stearic acid and magnesium stearate to the above blend and mix for an additional time of three minutes.

[0256] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 880 mgs and layer #2 is 320 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 36

Bi-Layered Tablet (Wet Granulation)

[0257] A bi-layered tablet in accordance with the present invention which comprises guaifenesin in a first sustained

release layer and carbetapentane citrate and phenylephrine hydrochloride in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
<u>Layer 1 (Sustained release)</u>		
Guaifenesin	600.0	545.5
Methocel K15M	100.0	90.9
Silicified Microcrystalline Cellulose	50	45.5
Eudragit NE	42	38.2
Magnesium Stearate	8.0	7.3
<u>Layer 2 (Sustained release)</u>		
Carbetapentane Citrate	60.0	54.6
Phenylephrine HCl	60.0	54.6
Microcrystalline Cellulose (PH 102)	45.0	40.9
Eudragit NE	15.0	13.6
Methocel K4M Premium	100.0	90.9
Stearic Acid	20.0	13.6
Magnesium Stearate	5.0	4.5
Total	1100	1000

[0258] Procedure:

[0259] (a) Sustained release layer #1: Mix the guaifenesin, Methocel® K15M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using the Eudragit® NE (30%). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0260] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the carbetapentane citrate, phenylephrine HCl, microcrystalline cellulose PH 102, dicalcium phosphate and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using the Eudragit® NE (30%). Add the Methocel® K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0261] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 800 mgs and layer #2 is 275 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 37

Bi-Layered Tablet (Wet Granulation)

[0262] A bi-layered tablet in accordance with the present invention which comprises guaifenesin in a first sustained release layer and carbetapentane citrate and phenylephrine hydrochloride in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
Layer 1 (Sustained release)		
Guaifenesin	1000.0	625.0
Methocel K15M	200.0	208.3
Silicified Microcrystalline Cellulose	40.0	41.7
Eudragit NE	50.0	31.3
Magnesium Stearate	10.0	6.3
Layer 2 (Sustained release)		
Carbetapentane Citrate	40.0	37.5
Phenylephrine HCl	60.0	37.5
Microcrystalline Cellulose (PH 102)	45.0	25
Eudragit NE	15.0	9.4
Methocel K4M Premium	100.0	62.5
Stearic Acid	20.0	12.5
Magnesium Stearate	5.0	3.1
Total	1600.0	1000.0

[0263] Procedure:

[0264] (a) Sustained release layer #1: Mix the guaifenesin, Methocel®K15M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using the Eudragit® NE (30%). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 5 minutes.

[0265] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the carbetapentane citrate, phenylephrine HCl, microcrystalline cellulose PH 102, dicalcium phosphate and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using the Eudragit® NE (30%). Add the Methocel®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 5 minutes.

[0266] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 1300 mgs and layer #2 is 300 mgs. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 38**Bi-Layered Tablet (Direct Compression)**

[0267] By using the process described in Example 37, a bi-layered tablet which contains carbetapentane citrate in an immediate release layer and carbetapentane citrate, phenylephrine hydrochloride and chlorpheniramine maleate in a sustained release layer may be manufactured by using direct compression:

Ingredients	Weight/tablet (mgs)
Layer 1 (Immediate Release)	
Carbetapentane Citrate	10
Silicified Microcrystalline Cellulose	133.5
Sodium Starch Glycolate	15
Magnesium Stearate	1.5
Layer 2 (Sustained Release)	
Carbetapentane Citrate	40
Phenylephrine HCl	50
Chlorpheniramine Maleate	8
Lactose Monohydrate	50
Dicalcium Citrate	50
Kollidon SR	252
Stearic Acid	15
Magnesium Stearate	5
Total	630

EXAMPLE 39**Bi-Layered Tablet (Wet Granulation)**

[0268] A bi-layered tablet in accordance with the present invention which comprises carbetapentane citrate in an immediate release layer and carbetapentane citrate, pseudoephedrine hydrochloride and chlorpheniramine maleate in a sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mgs)	Weight/1 kg batch (gms)
Layer 1 (Immediate release)		
Carbetapentane Citrate	10.0	13.8
Silicified Microcrystalline Cellulose	111.0	153.1
Povidone	3.0	4.1
Croscarmellose Sodium	10.0	13.8
Magnesium Stearate	1.0	1.4
Layer 2 (Sustained release)		
Carbetapentane Citrate	40	55.2
Pseudoephedrine HCl	60.0	82.8
Chlorpheniramine Maleate	8.0	11
Microcrystalline Cellulose (PH 102)	30.0	41.4
Lactose Monohydrate	100.0	137.9
Dicalcium Citrate	100.0	137.9
Povidone	15.0	20.7
Methocel K4M Premium	212.0	292.4
Stearic Acid	20.0	27.6
Magnesium Stearate	5.0	6.9
Total	725.0	1000.0

[0269] Procedure:

[0270] (a) Immediate release layer #1: Screen all ingredients through a USP sieve size # 30. Blend the carbetapentane citrate, silicified microcrystalline cellulose, and croscarmellose sodium in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (1.1 gms povidone in 13.7 gms of solution). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add granules and the prescreened magnesium stearate (1.4 gms) to the above blend and mix for 3 minutes.

[0271] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Blend the pseudoephedrine hydrochloride (87.5 gms), chlorpheniramine maleate, carbetapentane citrate, microcrystalline cellulose PH 102, lactose monohydrate, dicalcium citrate, Methocel K4M Premium and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (20.7 gms povidone in 69 gms of solution). Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add granules and the prescreened magnesium stearate (6.9 gms) to the above blend and mix for 3 minutes.

[0272] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet the immediate release layer is 135 mgs and the sustained release layer is 590 mgs.

EXAMPLE 40

Bi-Layered Tablet (Wet Granulation)

[0273] By using the process described in Example 39, a bi-layered tablet containing carbetapentane citrate in an immediate release layer and carbetapentane citrate, pseudoephedrine hydrochloride and chlorpheniramine maleate in a sustained release layer may be manufactured by using wet granulation:

Ingredients	Wgtg./tablet (mgs)
<u>Layer 1 (Immediate Release)</u>	
Carbetapentane Citrate	30
Silicified Microcrystalline cellulose	125
Povidone	3
Croscarmellose sodium	10
Magnesium Stearate	1
<u>Layer 2 (Sustained Release)</u>	
Carbetapentane Citrate	30
Pseudoephedrine HCl	60
Chlorpheniramine Maleate	8
Microcrystalline Cellulose 102	30
Lactose Monohydrate	100
Dicalcium Citrate	100
Povidone	15
Hydroxypropylmethylcellulose	2.7
Stearic Acid	20
Magnesium Stearate	5
Total	750

[0274] The above examples 21-40 illustrate how to manufacture a bi-layered tablet containing an antitussive, i.e., carbetapentane citrate, in (at least) a first layer and an antihistamine and/or a decongestant and/or an expectorant in (at least) a second layer. Non-limiting examples of possible active ingredients (in addition to carbetapentane) in an exemplary range as described in the above Table 1 can be employed depending on the specific therapeutic effect desired.

EXAMPLE 41

Extended Release Suspension (Gel)

[0275] An extended release suspension (in the form of a gel) in accordance with the present invention which contains

a carbetapentane citrate ion-exchange complex and promethazine hydrochloride is illustrated as follows (note that the carbetapentane citrate is used in a controlled release form since it has a shorter half-life than the promethazine hydrochloride):

Ingredients	Amount/5 ml
Carbetapentane Citrate Ion-Exchange Complex	Equivalent to 60 mgs of Carbetapentane Citrate
Promethazine HCl	25 mgs
Eudragit® L 100	0.2 to 2.8 grams
Glycerin	315 mgs
Polysorbate 80	1.5 mgs
Carbomer (e.g., Carbopol® 974)	37.5 mgs
Methyl Paraben	9 mgs
Propyl Paraben	1 mgs
Saccharin Sodium cryst., USP	0.1 mg
Artificial Grape Flavor	5 mgs
FD&C Red # 40 Dye	0.5 mgs
Sodium Hydroxid.	q.s.
Water	q.s.

[0276] Procedure:

[0277] (1) Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. Amberlite® IRP 69) to a carbetapentane citrate solution.

[0278] (2) Stir the mix for 12 hrs to allow complete drug/resin complex formation.

[0279] (3) Separate and dry the insoluble drug/resin complex.

[0280] (4) Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. Eudragit® L 100, Kollidon® MAE, Aquacoat® CPD) and dry the granules.

[0281] (5) Mill the granules, if needed.

[0282] (6) To an appropriate amount of water add the following ingredients and dissolve: promethazine hydrochloride, Carbomer (e.g., Carbopol® 974), glycerin, polysorbate 80, methyl paraben, propyl paraben, artificial grape flavor, FD&C red # 40 dye.

[0283] (7) Add milled granules.

[0284] (8) Add water to 95% of final volume.

[0285] (9) Agitate at suitable rate to avoid settling of the suspension and maintain a homogeneous product mixture.

[0286] (10) Neutralize the solution to form a gel using a 1N sodium hydroxide solution to a pH of 5 to 8. Add water to make final volume.

[0287] (11) Fill in suitable containers ensuring that the product is homogeneous throughout the filling operation.

EXAMPLE 42

Extended Release Suspension (Liquid)

[0288] An extended release suspension (in the form of a liquid) in accordance with the present invention which contains a carbetapentane tannate ion-exchange complex and promethazine hydrochloride is illustrated as follows:

Ingredients	Amount/5 ml
Carbetapentane Tannate Ion-Exchange Complex	Equivalent to 30 mgs of Carbetapentane Tannate
Promethazine HCl	25 mgs
Eudragit® L 100	0.2 to 2.8 grams
Silica, colloidal anhydrous, NF	650 mgs
Glycerin	740 mgs
Xylitol, NF	800 mgs
Sodium Citrate, USP	100 mgs
Saccharin Sodium cryst., USP	0.1 mg
Sodium Benzoate	7.5 mgs
Citric Acid Monohydrate, USP	8.0 mgs
Artificial Grape Flavor	5 mgs
FD&C Red # 40 Dye	0.5 mgs
Water	q.s.

[0289] Manufacturing Process for 1000 L. Batch:

[0290] Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. Amberlite® IRP 69 or Amberlite® 88N) to a carbetapentane tannate solution. Stir the mix for 12 hrs to allow complete drug/resin complex formation. Separate and dry the insoluble drug/resin complex. Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. Eudragit® L 100, Kollidon® MAE, Aqua-coat® CPD) and dry the granules. Mill the granules, if needed.

[0291] In a suitably sized stainless steel vessel, dissolve saccharin sodium, sodium benzoate, citric acid, and sodium citrate in approximately 50 L of warm (about 45° C.), purified water. In another large stainless steel drum mix the silica, carbetapentane tannate ion-exchange complex, and promethazine hydrochloride until a uniform and consistent mixture is obtained. In a separate 1000 L stainless steel tank equipped with a suitably sized homogenizer/disperser add about 100 L of purified water. With the homogenizer on, add the silica mixture containing carbetapentane tannate ion-exchange complex, and promethazine hydrochloride. Add the previously prepared solution of saccharin sodium, sodium benzoate, citric acid, and sodium citrate to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinsate to the 1000 L tank. Add the remaining ingredients and homogenize for 15 minutes.

EXAMPLE 43

Extended Release Suspension (Liquid)

[0292] An extended release suspension (in the form of a liquid) in accordance with the present invention which contains a carbetapentane citrate ion-exchange complex, pseudoephedrine tannate and chlorpheniramine tannate is illustrated as follows:

Ingredients	Amount/5 ml
Carbetapentane Citrate Ion-Exchange Complex	Equivalent to 20 mgs of Carbetapentane Citrate
Pseudoephedrine Tannate	75.0
Chlorpheniramine Tannate	4.5
Eudragit® L 100	0.2 to 2.8 grams
Silica, colloidal anhydrous, NF	100 mgs

--continued

Ingredients	Amount/5 ml
Glycerin	740 mgs
Xylitol, NF	800 mgs
Sodium Citrate, USP	100 mgs
Saccharin Sodium cryst., USP	0.1 mg
Sodium Benzoate	7.5 mgs
Citric Acid Monohydrate, USP	8.0 mgs
Artificial Grape Flavor	5 mgs
FD&C Red # 40 Dye	0.5 mgs
Water	q.s.

[0293] Manufacturing Process for 1000 kg Batch:

[0294] Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. Amberlite® IRP 69 or Amberlite® 188N) to a carbetapentane citrate solution. Stir the mix for 12 hrs to allow complete drug/resin complex formation. Separate and dry the insoluble drug/resin complex. Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. Eudragit® L 100, Kollidon® MAE, Aqua-coat® CPD) and dry the granules. Mill the granules, if needed.

[0295] In a suitably sized stainless steel vessel, dissolve saccharin sodium, sodium benzoate, citric acid, and sodium citrate in approximately 50 L of warm (about 45° C.), purified water. In another large stainless steel drum mix the silica, carbetapentane citrate ion-exchange complex, pseudoephedrine tannate, and the chlorpheniramine tannate until a uniform and consistent mixture is obtained. In a separate 1000 L stainless steel tank equipped with a suitably sized homogenizer/disperser add about 100 L of purified water. With the homogenizer on, add the silica mixture containing carbetapentane citrate ion-exchange complex, pseudoephedrine tannate, and the chlorpheniramine tannate. Add the previously prepared solution of saccharin sodium, sodium benzoate, citric acid, and sodium citrate to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinsate to the 1000 L tank. Add the remaining ingredients and homogenize for 15 minutes.

EXAMPLE 44

Extended Release Gel

[0296] An extended release suspension which contains a carbetapentane citrate ion-exchange complex, a dexchlorpheniramine maleate ion-exchange complex and a phenylephrine hydrochloride ion-exchange complex is illustrated as follows:

Ingredients	Amount/5 ml
Carbetapentane Citrate Ion-Exchange Complex	Equivalent to 20 mgs of Carbetapentane Citrate
Dexchlorpheniramine Maleate Ion-Exchange Complex	Equivalent to 4 mgs of Dexchlorpheniramine Maleate
Phenylephrine HCl Ion-Exchange Complex	Equivalent to 10 mgs of Phenylephrine HCl
Eudragit® L 100	0.2 to 2.8 grams
Glycerin	315 mgs
Polysorbate 80	1.5 mgs
Carbomer (e.g., Carbopol® 974)	15 mgs

US 2005/0256032 A1

27

Dec. 1, 2005

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Ingredients	Amount/5 ml
Methyl Paraben	9 mgs
Propyl Paraben	1 mgs
Artificial Grape Flavor	5 mgs
FD&C Red #40 Dye	0.5 mgs
Water	0.5

[0297] The formula described above serves as a non-limiting example. Any active drug which is in the form of a salt can be incorporated as an ion-exchange resin complex.

[0298] Procedure:

[0299] (1) Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. Amberlite® IRP 69 or Amberlite® 188N) to a carbetapentane citrate, dexchlorpheniramine maleate and phenylephrine HCl solution.

[0300] (2) Stir the mix for 12 hrs to allow complete drug/resin complex formation.

[0301] (3) Separate and dry the insoluble drug/resin complex.

[0302] (4) Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. Eudragit® L 100, Kollidon® MAE, Aquacoat® CPD) and dry the granules.

[0303] (5) Mill the granules, if needed.

[0304] (6) To an appropriate amount of water add the following ingredients and dissolve: Carbomer (e.g., Carbopol® 974), glycerin, polysorbate 80, methyl paraben, propyl paraben, artificial grape flavor, FD&C red #40 dye.

[0305] (7) Add milled granules.

[0306] (8) Add water to 95% of the final volume.

[0307] (9) Agitate at suitable rate to avoid settling of the suspension and maintain a homogeneous product mixture.

[0308] (10) Neutralize the solution to form a gel using a 1N sodium hydroxide solution to a pH of 5 to 8. Add enough water to make up to the final volume.

[0309] (11) Fill in suitable containers ensuring that the product is homogeneous throughout the filling operation.

EXAMPLE 45

Suspension Formula

[0310] A suspension formula which comprises carbetapentane citrate and phenylephrine tannate is illustrated as follows:

Ingredients	g/100 mL = 120 g	kg/batch = 1000 kg
Carbetapentane Citrate	0.500	
Phenylephrine Tannate	0.800	6.667
Silica, colloidal anhydrous, NF	1.73	14.417
Hydroxyethylcellulose, NF	0.05	0.417
Sorbitol Solution 70% (non-crystallizing), NF	34.00	283.333
Glycerol	14.75	122.917

-continued

Ingredients	g/100 mL = 120 g	kg/batch = 1000 kg
Xylitol, NF	16.00	133.333
Sodium Citrate, USP	2.00	16.667
Saccharin Sodium cryst., USP	0.01	0.083
Sodium Benzoate, NF	0.15	1.250
Citric Acid Monohydrate, USP	0.16	1.333
Strawberry Flavor	0.15	1.250
Banana Flavor	0.15	1.250
Purified Water	49.55	412.917
Total Amount	120.000 g	1000.000 kg

[0311] Manufacturing Process for 1000 kg Batch: bbb

[0312] In a suitably sized stainless steel vessel, dissolve saccharin sodium, sodium benzoate, citric acid, and sodium citrate in approximately 50 L of warm (about 45° C.), purified water. In another large stainless steel drum mix the silica, carbetapentane citrate, and micronized phenylephrine tannate until a uniform and consistent mixture is obtained. In a separate 1000 L stainless steel tank equipped with a suitably sized homogenizer/disperser add about 100 L of purified water. With the homogenizer on, add the silica mixture containing phenylephrine tannate and carbetapentane citrate. Add the previously prepared solution of saccharin sodium, sodium benzoate, citric acid, and sodium citrate to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinsate to the 1000 L tank. Add the remaining ingredients and homogenize for 15 minutes. Filter product through a 10 micron filter and fill in appropriately sized containers.

[0313] To make products with other agents such as antihistamines, decongestants, or expectorants, one or more combinations of each of the ingredients in a range as described in Table 1 above can be made depending on the specific therapeutic effect desired.

EXAMPLE 46

Liquid Formula

[0314] A liquid dosage form which comprises carbetapentane citrate and phenylephrine hydrochloride is illustrated as follows:

Ingredients	Per 5 mL	Per 425 L
Carbetapentane Citrate USP	30 mg	2.55 kg
Phenylephrine Hydrochloride USP	10.0 mg	0.850 kg
Methyl Paraben USP	9.0 mg	0.765 kg
Propyl Paraben USP	1.0 mg	0.085 kg
Propylene Glycol USP	259 mg	22.016 kg
Saccharin Sodium USP	5.18 mg	0.270 kg
Citric Acid USP	5.0 mg	0.425 kg
Strawberry Flavor	10 mg	0.850 kg
Banana Flavor	10 mg	0.850 kg
Sorbitol Solution 70% USP	3212.5 mg	273.1 kg
Purified Water, as required to q.s. to	5.0 mL	425 L

[0315] Manufacturing Process for 425 L Batch Size:

[0316] In a suitably sized stainless steel vessel, dissolve methyl paraben and propyl paraben in approximately 50 L of

warm (about 45° C.), purified water. Add about half of the propylene glycol and mix for about 1 hr. In a separate 1000 L stainless steel tank equipped with a suitably sized agitator, add about 50 L of purified water. With the agitator on, add phenylephrine hydrochloride, carbapentane citrate, saccharin sodium and citric acid and dissolve. Add the previously prepared paraben/propylene glycol solution to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinsate to the 1000 L tank. Add the remaining propylene glycol to a suitably sized stainless steel vessel and dissolve the strawberry and banana flavors. Transfer this to the 1000 L tank. Rinse the container with 2 L of purified water and transfer to the 1000 L tank. With the agitator on, add the alcohol solution 70% to the 1000 L tank. In a suitably sized stainless steel vessel dissolve the carbapentane citrate in about 5 L of purified water and transfer to the 1000 L tank. Rinse the container with about 2 L of purified water and transfer to the 1000 L tank. Stop the agitator and let the solution stand for 15 minutes. QS to 425 L with purified water. Filter product through a 1 micron filter and fill in appropriately sized containers.

[0317] To make products with other antihistamines, decongestants, or expectorants, one or more combinations of each of the ingredients in a range as described in Table 1 above can be made depending on the specific therapeutic effect desired.

EXAMPLE 47

Bi-Layered Tablet (Wet Granulation)

[0318] A bi-layered tablet in accordance with the present invention which comprises phenylephrine hydrochloride in a first sustained release layer and guaifenesin in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight (kg)
Layer 1 (Sustained release)		
Phenylephrine HCl	60.0	6.0
Methocel K15M	100.0	10.0
Silicified Microcrystalline Cellulose	50.0	5.0
Eudragit NE	42.0	4.2
Magnesium Stearate	5.0	0.5
Layer 2 (Sustained release)		
Guaifenesin	60.0	6.0
Microcrystalline Cellulose (PH 102)	25.0	2.5
Eudragit NE	15.0	1.5
Methocel K4M Premium	14.0	1.4
Stearic Acid	2.0	0.2
Magnesium Stearate	5.0	0.5
Total	1,450	145.5

[0319] Procedure:

[0320] (a) Sustained release layer #1: Mix phenylephrine hydrochloride in Methocel®K15M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Dry the granulation until the LOD (weight loss on drying) is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0321] (b) Sustained release layer #2: Screen all ingredients through a US sieve size # 30. Mix guaifenesin, microcrystalline cellulose PH 102, and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Add the Methocel®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0322] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 260 mg and layer #2 is 825 mg. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 48

Bi-Layered Tablet (Wet Granulation)

[0323] A bi-layered tablet in accordance with the present invention which comprises promethazine hydrochloride in an immediate release layer and phenylephrine hydrochloride in a sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight batch (Kg)
Layer 1 (Immediate release)		
Promethazine HCl	25.0	25.0
Silicified Microcrystalline Cellulose	161.0	161.0
Povidone	3.0	3.0
Crosscarmellose Sodium	10.0	10.0
Magnesium Stearate	1.0	1.0
Layer 2 (Sustained release)		
Phenylephrine hydrochloride	30.0	30.0
Microcrystalline Cellulose (PH 102)	25.0	25.0
Dicalcium Phosphate	50.0	50.0
Povidone	15.0	15.0
Methocel K4M Premium	205.0	205.0
Stearic Acid	20.0	20.0
Magnesium Stearate	5.0	5.0
Total	550.0	550.0

[0324] Procedure:

[0325] (a) Immediate release layer #1: Mix the promethazine HCl, silicified microcrystalline cellulose and crosscarmellose sodium, in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (3.0 g povidone in 10.0 g purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0326] (b) Sustained release layer #2: Mix the phenylephrine hydrochloride, microcrystalline cellulose PH 102, dicalcium phosphate, Methocel K4M Premium and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (15.0 g povidone in 50.0 g purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0327] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 200 mg and layer #2 is 350 mg. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 49

Bi-Layered Tablet (Wet Granulation)

[0328] A bi-layered tablet in accordance with the present invention which comprises phenylephrine hydrochloride and carbinoxamine maleate in a first sustained release layer and phenylephrine hydrochloride in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight batch (Kg)
<u>Layer 1 (Sustained release)</u>		
Phenylephrine HCl	75.0	75.0
Carbinoxamine Maleate	8.0	8.0
Methocel K4M	120.0	120.0
Silicified Microcrystalline Cellulose	30.0	30.0
Eudragit NE	15.0	15.0
Magnesium Stearate	3.0	3.0
<u>Layer 2 (Sustained release)</u>		
Phenylephrine hydrochloride	30.0	30.0
Microcrystalline Cellulose (PH 102)	65.0	65.0
Eudragit NE	20.0	20.0
Methocel K4M Premium	115.0	115.0
Stearic Acid	2.0	2.0
Magnesium stearate	5.0	5.0
Total	500.0	500.0

[0329] Procedure:

[0330] (a) Sustained release layer #1: Mix the phenylephrine HCl, carbinoxamine maleate, Methocel®K4M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0331] (b) Sustained release layer #2: Screen all ingredients through a US sieve size # 30. Mix the phenylephrine hydrochloride, microcrystalline cellulose PH 102, and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Add the Methocel®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0332] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 250 mg and layer #2 is 250 mg. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 50

Bi-Layered Tablet (Wet Granulation)

[0333] A bi-layered tablet in accordance with the present invention which comprises phenylephrine hydrochloride and diphenhydramine hydrochloride in a first sustained release layer and codeine phosphate in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight batch (Kg)
<u>Layer 1 (Sustained release)</u>		
Phenylephrine HCl	120.0	120.0
Diphenhydramine HCl	12.0	12.0
Methocel K4M	200.0	200.0
Silicified Microcrystalline Cellulose	35.0	35.0
Eudragit NE	20.0	20.0
Magnesium Stearate	3.0	3.0
<u>Layer 2 (Sustained release)</u>		
Codeine Phosphate	30.0	30.0
Microcrystalline Cellulose (PH 102)	55.0	55.0
Eudragit NE	15.0	15.0
Methocel K4M Premium	138.0	138.0
Stearic Acid	20.0	20.0
Magnesium Stearate	2.0	2.0
Total	650.0	650.0

[0334] Procedure:

[0335] (a) Sustained release layer #1: Mix the phenylephrine HCl, diphenhydramine hydrochloride, Methocel®K4M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0336] (b) Sustained release layer #2: Screen all ingredients through a US sieve size # 30. Mix the codeine phosphate, microcrystalline cellulose PH 102, and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Add the Methocel®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0337] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 390 mg and layer #2 is 260 mg. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 51

Bi-Layered Tablet (Wet Granulation)

[0338] A bi-layered tablet in accordance with the present invention which comprises carbinoxamine maleate in a first sustained release layer and phenylephrine hydrochloride in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight batch (Kg)
Layer 1 (Sustained release)		
Carbinoxamine Maleate	8.0	8.0
Lactose Monohydrate	61.0	61.0
Methocel K4M	70.0	70.0
Silicified Microcrystalline Cellulose	39.0	39.0
Eudragit NE	20.0	20.0
Magnesium Stearate	2.0	2.0
Layer 2 (Sustained release)		
Phenylephrine hydrochloride	30.0	30.0
Microcrystalline Cellulose (PH 102)	45.0	45.0
Eudragit NE	15.0	15.0
Methocel K4M Premium	103.0	103.0
Stearic Acid	20.0	20.0
Magnesium Stearate	2.0	2.0
Total	415.0	415.0

[0339] Procedure:

[0340] (a) Sustained release layer # 1: Mix the carbinoxamine maleate, Methocel®K4M, lactose monohydrate and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0341] (b) Sustained release layer #2: Screen all ingredients through a US sieve size # 20. Mix the phenylephrine hydrochloride, microcrystalline cellulose PH 102, and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Add the Methocel®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0342] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 200 mg and layer #2 is 215 mg. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 52

Bi-Layered Tablet (Direct Compression)

[0343] A bi-layered tablet in accordance with the present invention which comprises promethazine hydrochloride (longer half-life drug) in an immediate release layer and phenylephrine hydrochloride (shorter half-life drug) in a sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight batch (Kg)
Layer 1 (Immediate release)		
Promethazine HCl	25.0	25.0
Silicified Microcrystalline Cellulose	114.0	114.0

-continued

Ingredients	Weight/tablet (mg)	Weight batch (Kg)
Layer 2 (Sustained release)		
Sodium Starch Glycolate	10.0	10.0
Magnesium Stearate	1.0	1.0
Layer 2 (Sustained release)		
Phenylephrine hydrochloride	60.0	60.0
Lactose Monohydrate	50.0	50.0
Dicalcium Phosphate	50.0	50.0
Kollidon SR	220.0	220.0
Stearic acid	15.0	15.0
Magnesium Stearate	5.0	5.0
Total	550.0	550.0

[0344] Procedure:

[0345] (a) Immediate release layer #1: Screen all ingredients through a US sieve size # 30. Blend the promethazine hydrochloride, microcrystalline cellulose and sodium starch glycolate for 20 minutes. Add magnesium stearate to the above blend and mix for an additional time of three minutes.

[0346] (b) Sustained release layer #2: Blend the phenylephrine hydrochloride, lactose monohydrate, dicalcium phosphate and Kollidon® SR for 20 minutes. Add stearic acid and magnesium stearate to the above blend and mix for an additional time of three minutes.

[0347] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet the immediate release layer #1 is 150 mg and the sustained release layer #2 is 400 mg. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 53

Bi-Layered Tablet (Wet Granulation)

[0348] A bi-layered tablet in accordance with the present invention which comprises phenylephrine tannate and chlorpheniramine tannate in an immediate release layer and phenylephrine tannate in a sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight batch (Kg)
Layer 1 (Immediate release)		
Phenylephrine Tannate	60.0	60.0
Chlorpheniramine Tannate	8.0	8.0
Silicified Microcrystalline Cellulose	208.0	208.0
Povidone	3.0	3.0
Croscarmellose Sodium	10.0	10.0
Magnesium Stearate	1.0	1.0
Layer 2 (Sustained release)		
Phenylephrine tannate	30.0	30.0
Microcrystalline Cellulose (PH 102)	30.0	30.0
Dicalcium Phosphate	100.0	100.0
Povidone	15.0	15.0
Methocel K4M Premium	210.0	210.0
Stearic Acid	20.0	20.0
Magnesium Stearate	5.0	5.0
Total	700.0	700.0

[0349] Procedure:

[0350] (a) Immediate release layer #1: Mix the phenylephrine tannate, chlorpheniramine tannate, silicified microcrystalline cellulose and croscarmellose sodium, in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (3.0 Kg povidone in 7.0 Kg purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0351] (b) Sustained release layer #2: Mix the Phenylephrine tannate, microcrystalline cellulose PH 102, dicalcium phosphate, Methocel K4M Premium and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (15.0 Kg povidone in 35.0 Kg purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0352] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 290 mg and layer #2 is 40 mg. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 54**Bi-Layered Tablet (Wet Granulation)**

[0353] A bi-layered tablet in accordance with the present invention which comprises diphenhydramine hydrochloride in an immediate release layer and phenylephrine hydrochloride in a sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight batch (Kg)
Layer 1 (Immediate release)		
Diphenhydramine HCl	290.0	100.0
Silicified Microcrystalline Cellulose	86.0	86.0
Povidone	2.0	2.0
Croscarmellose Sodium	10.0	10.0
Magnesium Stearate	1.0	1.0
Layer 2 (Sustained release)		
Phenylephrine HCl	75.0	75.0
Microcrystalline Cellulose (PH 102)	30.0	30.0
Dicalcium Phosphate	30.0	30.0
Povidone	15.0	15.0
Methocel K4M Premium	175.0	175.0
Stearic Acid	20.0	20.0
Magnesium Stearate	2.0	2.0
Total	550.0	550.0

[0354] Procedure:

[0355] (a) Immediate release layer #1: Mix the diphenhydramine hydrochloride, silicified microcrystalline cellulose and croscarmellose sodium, in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (3.0 g povidone in 10.0 g purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0356] (b) Sustained release layer #2: Mix the phenylephrine hydrochloride, microcrystalline cellulose PH 102, dical-

cium phosphate, Methocel K4M Premium and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (15.0 g povidone in 50.0 g purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0357] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 200 mg and layer #2 is 350 mg. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 55**Bi-Layered Tablet (Direct Compression)**

[0358] A bi-layered tablet in accordance with the present invention which comprises guaifenesin in a first sustained release layer and phenylephrine hydrochloride in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight batch (Kg)
Layer 1 (Sustained release)		
Guaifenesin	600.0	300.0
Methocel K15M	200.0	100.0
Silicified Microcrystalline Cellulose	72.0	36.0
Magnesium Stearate	8.0	4.0
Layer 2 (Sustained release)		
Phenylephrine hydrochloride	60.0	30.0
Dicalcium Phosphate	70.0	35.0
Kollidon SR	172.0	86.0
Stearic acid	15.0	7.5
Magnesium Stearate	3.0	1.5
Total	1200.0	600.0

[0359] Procedure:

[0360] (a) Sustained release layer #1: Screen all ingredients through a US sieve size # 30. Blend the guaifenesin, Methocel® K15M and silicified microcrystalline cellulose for 25 minutes. Add magnesium stearate to the above blend and mix for an additional time of three minutes.

[0361] (b) Sustained release layer #2: Blend the phenylephrine hydrochloride, dicalcium phosphate and Kollidon® SR for 20 minutes. Add stearic acid and magnesium stearate to the above blend and mix for an additional time of three minutes.

[0362] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 880 mg and layer #2 is 320 mg. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 56**Bi-Layered Tablet (Wet Granulation)**

[0363] A bi-layered tablet in accordance with the present invention which comprises brompheniramine maleate in a first sustained release layer and phenylephrine hydrochloride in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight/batch (Kg)
Layer 1 (Sustained release)		
Brompheniramine Maleate	6.0	6.0
Methocel® K15M	94.0	94.0
Silicified Microcrystalline Cellulose	50.0	50.0
Eudragit® NE	42.0	42.0
Magnesium Stearate	8.0	8.0
Layer 2 (Sustained release)		
Phenylephrine HCl	60.0	60.0
Microcrystalline Cellulose (PH 102)	45.0	45.0
Eudragit® NE	15.0	15.0
Methocel® K4M Premium	108.0	108.0
Stearic Acid	20.0	20.0
Magnesium Stearate	2.0	2.0
Total	450.0	450.0

[0364] Procedure:

[0365] (a) Sustained release layer #1: Mix the brompheniramine maleate, Methocel®K15M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0366] (b) Sustained release layer #2: Screen all ingredients through a US sieve size # 30. Mix the phenylephrine hydrochloride, microcrystalline cellulose PH 102, dicalcium phosphate and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Add the Methocel®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0367] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 200 mg and layer #2 is 250 mg. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 57

Bi-Layered Tablet (Wet Granulation)

[0368] A bi-layered tablet in accordance with the present invention which comprises guaifenesin in a first sustained release layer and phenylephrine hydrochloride in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight/batch (Kg)
Layer 1 (Sustained release)		
Guaifenesin	100.0	400.0
Methocel® K15M	20.0	80.0
Silicified Microcrystalline Cellulose	40.0	160.0
Eudragit® NE	5.0	20.0
Magnesium Stearate	1.0	4.0

-continued

Ingredients	Weight/tablet (mg)	Weight/batch (Kg)
Layer 2 (Sustained release)		
Phenylephrine hydrochloride	30.0	12.0
Microcrystalline Cellulose (PH 102)	45.0	18.0
Eudragit® NE	15.0	6.0
Methocel® K4M Premium	100.0	40.0
Stearic Acid	20.0	8.0
Magnesium Stearate	2.0	0.5
Total	150.0	604.0

[0369] Procedure:

[0370] (a) Sustained release layer #1: Mix the guaifenesin, Methocel®K15M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0371] (b) Sustained release layer #2: Screen all ingredients through a US sieve size # 30. Mix the phenylephrine HCl, microcrystalline cellulose PH 102 and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a Eudragit® NE (30%). Add the Methocel®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0372] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 1300 mg and layer #2 is 210 mg. Capsules may be manufactured by filling the same proportions into capsules.

EXAMPLE 58

Bi-Layered Tablet (Direct Compression)

[0373] A bi-layered tablet in accordance with the present invention which comprises phenylephrine hydrochloride in a first immediate release layer and phenylephrine hydrochloride and diphenhydramine hydrochloride in a second sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight/batch (Kg)
Layer 1 (Immediate release)		
Phenylephrine hydrochloride	30.0	30.0
Silicified Microcrystalline Cellulose	160.0	160.0
Sodium Starch Glycolate	9.0	9.0
Magnesium Stearate	1.0	1.0
Layer 2 (Sustained release)		
Phenylephrine HCl	60.0	60.0
Diphenhydramine HCl	60.0	60.0

-continued

Ingredients	Weight/tablet (mg)	Weight batch (Kg)
Dicalcium Phosphate	100.0	100.0
Kollidon SR	220.0	220.0
Stearic acid	16.0	16.0
Magnesium Stearate	4.0	4.0
Total	660.0	660.0

[0374] Procedure:

[0375] (a) Immediate release Layer #1: Screen all ingredients through a US sieve size # 30. Preblend a portion (about a third of the total) of the silicified microcrystalline cellulose and all the phenylephrine hydrochloride for the immediate release layer for 15 minutes. Add sodium starch glycolate and mix for additional 10 minutes. Add magnesium stearate to the above blend and mix for three minutes.

[0376] (b) Sustained release layer #2: Screen all ingredients through a US sieve size # 30. Preblend a portion of the Kollidon SR (about a third of the total) and all the diphenhydramine hydrochloride for 15 minutes. Add the remaining Kollidon SR, phenylephrine hydrochloride and dicalcium phosphate to the above preblend and mix for additional 20 minutes. Add stearic acid and magnesium stearate to the above blend and mix for three minutes.

[0377] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet the immediate release layer is 200 mg and the sustained release layer is 460 mg.

EXAMPLE 59

Bi-Layered Tablet (Direct Compression)

[0378] By using the process described in Example 58, a bi-layered tablet which contains phenylephrine hydrochloride in an immediate release layer and phenylephrine hydrochloride and dexbrompheniramine maleate in a sustained release layer (see the formula below) may be manufactured by using direct compression:

Ingredients	Weight/tablet (mg)
<u>Layer 1 (Immediate Release)</u>	
Phenylephrine hydrochloride	9.0
Silicified Microcrystalline Cellulose	133.5
Sodium Starch Glycolate	15.0
Magnesium Stearate	1.5
<u>Layer 2 (Sustained Release)</u>	
Phenylephrine hydrochloride	46.0
Dexbrompheniramine maleate	5.0
Dicalcium Phosphate	60.0
Kollidon SR	245.0
Stearic Acid	7.0
Magnesium Stearate	3.0
Total	660.0

EXAMPLE 60

Bi-Layered Tablet (Wet Granulation)

[0379] A bi-layered tablet in accordance with the present invention which comprises phenylephrine hydrochloride in

an immediate release layer and phenylephrine hydrochloride and chlorpheniramine maleate in a sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight batch (Kg)
<u>Layer 1 (Immediate release)</u>		
Phenylephrine hydrochloride	10.0	10.0
Silicified Microcrystalline Cellulose	111.0	111.0
Povidone	3.0	3.0
Croscarmellose Sodium	10.0	10.0
Magnesium Stearate	1.0	1.0
<u>Layer 2 (Sustained release)</u>		
Phenylephrine HCl	60.0	60.0
Chlorpheniramine Maleate	8.0	8.0
Microcrystalline Cellulose (PH 102)	30.0	30.0
Dicalcium Phosphate	100.0	100.0
Povidone	15.0	15.0
Methocel K4M Premium	212.0	212.0
Stearic Acid	20.0	20.0
Magnesium Stearate	5.0	5.0
Total	585.0	585.0

[0380] Procedure:

[0381] (a) Immediate release layer #1: Screen all ingredients through a US sieve size # 30. Blend the phenylephrine hydrochloride, silicified microcrystalline cellulose, and croscarmellose sodium in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (4.3 Kg povidone in 10.0 Kg purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add granules and the prescreened magnesium stearate to the above blend and mix for 3 minutes.

[0382] (b) Sustained release layer #2: Screen all ingredients through a US sieve size # 30. Blend the phenylephrine hydrochloride, chlorpheniramine maleate, microcrystalline cellulose PH 102, dicalcium phosphate and Methocel K4M Premium and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (15.0 Kg povidone in 35.0 Kg purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add granules and the prescreened magnesium stearate to the above blend and mix for 3 minutes.

[0383] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet the immediate release layer is 135 mg and the sustained release layer is 450 mg.

EXAMPLE 61

Bi-Layered Tablet (Wet Granulation)

[0384] By using the process described in Example 60, a bi-layered tablet containing phenylephrine hydrochloride in an immediate release layer and phenylephrine hydrochloride and chlorpheniramine maleate in a sustained release layer may be manufactured by using wet granulation:

-continued

Ingredients	Weight/tablet (mg)	Ingredients	Weight/tablet (mg)
<u>Layer 1 (Immediate Release)</u>		Hydroxypropylmethylcellulose	212.0
Phenylephrine hydrochloride	30.0	Stearic Acid	20.0
Silified Microcrystalline Cellulose	129.5	Magnesium Stearate	5.0
Povidone	4.0	Total	730.0
Crosscarmellose sodium	15.0		
Magnesium Stearate	1.5		
<u>Layer 2 (Sustained Release)</u>			
Phenylephrine HCl	30.0		
Chlorpheniramine Maleate	3.0		
Microcrystalline Cellulose 102	33.0		
Lactose Monohydrate	100.0		
Dicalcium Phosphate	100.0		
Povidone	15.0		

EXAMPLE 62

Bi-Layered Tablet (Wet Granulation)

[0385] A bi-layered tablet in accordance with the present invention which comprises phenylephrine hydrochloride in a sustained release layer and carbethapentane citrate in an immediate release layer is illustrated as follows:

<u>Formula</u>		<u>Amounts</u>	
Process Steps	Ingredients	Dose (mg)	Scale-Up
<u>Sustained Release Layer</u>			
Wet Mix	RMI - PURIFIED WATER	48.000	15.000 kg
Wet Mix	RMI - POVIDONE K-30 USP	12.000	3.750 kg
Pre-blend	RMI - PHENYLEPHRINE HCl USP	40.000	12.500 kg
	UNMIC		
Pre-blend	RMI - CAL PHOSPHATE DIBASIC DIHYD	25.000	7.813 kg
Pre-blend	RMI - PROSOLV SMCC 90	125.000	39.063 kg
Pre-blend	RMI - METHOCEL K4M PREMIUM USP	50.000	15.625 kg
Final blend	RMI - METHOCEL K4M PREMIUM USP	144.000	45.000 kg
Lube blend	RMI - MAGNESIUM STEARATE NF	4.000	1.250 kg
Layer Weight:		400.000	
<u>Immediate Release Layer</u>			
Wet Mix	RMI - PURIFIED WATER	24.000	7.500 kg
Wet Mix	RMI - POVIDONE K-30 USP	6.000	1.875 kg
Pre-blend	RMA - CARBETAPENTANE CITRATE	40.000	12.500 kg
Pre-blend	RMI - PROSOLV SMCC 90	100.000	31.250 kg
Pre-blend	RMI - LACTOSE MONOHYDRATE #316	40.000	12.500 kg
Pre-blend	RMI - SODIUM STARCH GLYCOLATE	8.000	2.500 kg
Pre-blend	DYE - FD&C BLUE #1 ALUMINUM LAKE	0.156	0.048 kg
Final blend	RMI - PROSOLV SMCC 90	145.688	45.528 kg
Final blend	RMI - LACTOSE MONOHYDRATE #316	40.000	12.500 kg
Final blend	RMI - SODIUM STARCH GLYCOLATE	16.000	5.000 kg
Final blend	DYE - FD&C BLUE #1 ALUMINUM LAKE	0.156	0.048 kg
Lube blend	RMI - MAGNESIUM STEARATE NF	4.000	1.250 kg
Layer Weight:		400.000	
Totals(wt)		800.00	250.000 kg
Totals (tablets)		1	312.500

[0386] Procedure**[0387]** Sustained Release Layer (Layer 1)

[0388] 1. Set aside 0.5 kg of Purified Water to be used in step 4.

[0389] 2. Prepare a solution using the scale up amounts of Povidone K-30, and the remaining Purified Water from step 1.

[0390] 3. Blend the pre-blend scale up amounts of Phenylephrine HCl USP, Calcium Phosphate Dibasic Dihydrate, and Prosolv SMCC 90 with a high shear mixer/granulator for 10 minutes.

[0391] 4. With the mixer/granulator on, pump the solution prepared in step 2 in to the mixer/granulator. After completion, stop the mixer/granulator and rinse the container with the Purified water set aside in step 1. Pump the rinse water to the mixer/granulator with mixer on. Turn off mixer when completed.

[0392] 5. Charge the pre-blend scale up amount of Methocel K4M premium to the mixer/granulator and mix for 1 minute.

[0393] 6. Dry the granulation until the LOD is 4% or less.

[0394] 7. Pass the dried granulation through a Fitzpatrick Fitzmill fitted with a 14 mesh screen.

[0395] 8. Screen the final blend scale up amount of Methocel K4M premium through a 14 mesh screen.

[0396] 9. Blend the milled granulation from step 7 and the screened materials from step 8 using a V-blender for 20 minutes.

[0397] 10. Screen the lube scale up amount of Magnesium Stearate using a 30 mesh screen.

[0398] 11. Transfer the screened Magnesium Stearate to the V-blender and blend for 3 minutes. When completed discharge into drums double lined with polyethylene bags.

[0399] Immediate Release Layer (Layer 2)

[0400] 1. Set aside 0.5 kg of Purified Water to be used in step 4.

[0401] 2. Prepare a solution using the scale up amounts Povidone K-30, and the remaining Purified Water from step 1.

[0402] 3. Blend the pre-blend scale up amounts of Carbetapentane Citrate, Prosolv SMCC 90, Lactose Monohydrate #316, Sodium Starch Glycolate, and FD&C Blue #1 Aluminum Lake using a high shear mixer/granulator for 10 minutes.

[0403] 4. With the mixer/granulator on, pump the solution prepared in step 2 in to the mixer/granulator. After completion, stop the mixer/granulator and rinse the container with the Purified Water set aside in step 1. Pump the rinse water to the mixer/granulator with mixer on. Allow mixture to mix for an additional minute then turn mixer/granulator off.

[0404] 5. Dry the granulation until the LOD is 4% or less.

[0405] 6. Pass the dried granulation through a Fitzpatrick Fitzmill fitted with a 14 mesh screen.

[0406] 7. Screen the final blend scale up amounts of Prosolv SMCC 90, Lactose Monohydrate #316, Sodium Starch Glycolate, and FD&C Blue #1 Aluminum Lake through a 14 mesh screen.

[0407] 8. Blend the milled granulation from step 6 and the screened materials from step 7 using a V-blender for 20 minutes.

[0408] 9. Screen the lube scale up amount of Magnesium Stearate using a 30 mesh screen.

[0409] 10. Transfer the screened Magnesium Stearate to the V-blender and blend for 3 minutes. When completed discharge into proper drums double lined with polyethylene bags.

[0410] Compress bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer 1 is 400.0 mg and layer 2 is 400 mg.

[0411] The above examples 41-62 illustrate how to manufacture a bi-layered tablet containing a decongestant, i.e., phenylephrine hydrochloride, in (at least) a first layer and an antihistamine and/or a decongestant and/or an expectorant in (at least) a second layer. Non-limiting examples of other possible active ingredients in an exemplary range as described in the above Table 1 can be employed depending on the specific therapeutic effect desired.

EXAMPLE 63**Bi-Layered Tablet (Wet Granulation)**

[0412] A bi-layered tablet in accordance with the present invention which contains phenylephrine hydrochloride in both an immediate release layer and a sustained release layer and carbetapentane citrate in both an immediate release layer and a sustained release layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight batch (Kg)
Layer 1 (Immediate release)		
Carbetapentane citrate	15.0	22.5
Phenylephrine hydrochloride	15.0	22.5
Silicified Microcrystalline Cellulose	74.2	111.3
Croscarmellose Sodium	10.0	15.0
Magnesium Stearate	0.8	1.2
Layer 2 (Sustained release)		
Carbetapentane citrate	45.0	67.5
Phenylephrine hydrochloride	45.0	67.5
Microcrystalline Cellulose (PH 102)	20.0	30.0
Povidone	8.0	12.0
Methocel K4M Premium	150.0	225.0
Magnesium Stearate	2.0	3.0
Total	385.0	577.5

[0413] Procedure:

[0414] (a) Immediate release layer #1: Mix the pre-screened (# 30 mesh) phenylephrine hydrochloride, carbetapentane citrate, silicified microcrystalline cellulose and croscarmellose sodium, in a V shaped blender for 20 minutes. Add prescreened (# 40 mesh) magnesium stearate in a V shaped blender and mix for 3 minutes.

[0415] (b) Sustained release layer #2: Mix the phenylephrine hydrochloride, carnitapentane citrate, Methocel K4M Premium and microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (12.0 Kg povidone in 28.0 Kg purified water). Dry the granulation until the LOD is less than 2.0%. Screen granules through a US sieve size # 14. Add the granules and the prescreened magnesium stearate in a V-shaped blender and mix for 3 minutes.

[0416] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 115 mg and layer #2 is 270 mg.

EXAMPLE 64

Bi-Layered Tablet (Wet granulation)

[0417] A bi-layered tablet in accordance with the present invention which comprises phenylephrine hydrochloride and guaifenesin in two different sustained release layers is illustrated as follows:

Process Steps	Ingredients	Formula	
		Amounts	
		Dose(mg)	Scale-Up
Wet Mix	RMI - PURIFIED WATER	55.000	17.148 kg
Wet Mix	RMI - Povidone K-30 USP	15.000	4.148 kg
Pre-blend	RMA - GUAIFENESIN USP	80.000	187.100 kg
Pre-blend	RMA - PHENYLEPHRINE HCL USP	40.000	12.500 kg
Pre-blend	RMI - CALCIUM PHOSPHATE DIBASIC ANHYD	40.000	12.500 kg
Pre-blend	RMI - METHOCEL K4M PREMIUM USP	16.000	5.900 kg
Final blend	RMI - STEARIC ACID NF	4.500	1.06 kg
Final blend	RMI - METHOCEL K4M PREMIUM USP	79.700	24.06 kg
Lube blend	RMI - MAGNESIUM STEARATE NF	4.500	1.06 kg
Color blend	DYE - FD&C BLUE #1 ALUM LAKES	0.300	0.04 kg
Total (wt)		830.000	250.00 kg
Total (tablets)			317,500

[0418] Procedure

[0419] 1. Set aside 0.5 kg of purified water to be used as a rinse in step 4.

[0420] 2. Prepare a solution using the scale up amounts of Povidone K-30, and the remaining Purified Water.

[0421] 3. Blend the pre-blend scale up amounts of Guaifenesin USP, Phenylephrine HCL USP, and Calcium Phosphate Dibasic Anhydrous using a high shear mixer/granulator for 10 minutes.

[0422] 4. With the mixer/granulator on, pump the solution prepared in step 2 in to the mixer/granulator. After completion, stop the mixer/granulator and rinse the container with the 0.5 kg of Purified water set aside in step 1. Pump the rinse water to the mixer/granulator with mixer on. Turn off mixer when completed.

[0423] 5. Charge the pre-blend scale up amount of Methocel K4M premium to the mixer/granulator and mix for 1 minute.

[0424] 6. Dry the granulation until the LOD is 1% or less.

[0425] 7. Pass the dried granulation through a Fitzpatrick Fitzmill fitted with a 109 screen.

[0426] 8. Screen the final blend raw materials through a 12 mesh screen.

[0427] 9. Blend the milled granulation from step 7 and the screened materials from step 8 using a V-blender for 20 minutes.

[0428] 10. Screen the lube blend material through a 30 mesh screen.

[0429] 11. Charge the screened material from step 10 to the V-blender and blend for 2 minutes.

[0430] 12. Discharge half of the blended product into proper drums double lined with polyethylene bags and set aside for step 16.

[0431] 13. Screen the color blend material through a 30 mesh screen.

[0432] 14. Charge the screened color blend material to the V-blender and blend for 1 minute.

[0433] 15. Discharge into proper drums double lined with polyethylene bags and set aside for step 16.

[0434] 16. Compress bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer 1 is 400.0 mg's and layer 2 is 400.0 mg's.

EXAMPLE 65

Extended Release Suspension (Gel)

[0435] An extended release suspension (in the form of a gel) in accordance with the present invention which contains phenylephrine hydrochloride ion-exchange complex and promethazine hydrochloride is illustrated as follows (the phenylephrine hydrochloride is used in a controlled release form since it has a shorter half-life than the promethazine hydrochloride):

-continued

Ingredients	Amount/5 ml
Phenylephrine hydrochloride Ion-Exchange Complex	Equivalent to 30 mg of Phenylephrine
Promethazine HCl	25 mg
Eudragit® L 100	0.2 to 2.8 g
Glycerin	315 mg
Polysorbate 80	1.5 mg
Carbomer (e.g., Carbopol® 974)	37.5 mg
Methyl Paraben	9 mg
Propyl Paraben	1 mg
Saccharin Sodium cryst., USP	0.1 mg
Artificial Grape Flavor	5 mg
FD&C Red # 40 Dye	0.5 mg
Sodium Hydroxide	to pH 4 to 5
Water	to 5 ml

[0436] Procedure:

[0437] (1) Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. Amberlite® IRP 69) to a phenylephrine hydrochloride solution.

[0438] (2) Stir the mix for 12 hrs to allow complete drug/resin complex formation.

[0439] (3) Separate and dry the insoluble drug/resin complex.

[0440] (4) Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. Eudragit® L 100, Kollidon® MAE, Aquacoat® V CPD) and dry the granules.

[0441] (5) Mill the granules, if needed.

[0442] (6) To an appropriate amount of water add the following ingredients and dissolve: promethazine hydrochloride, Carbomer (e.g., Carbopol® 974), glycerin, polysorbate 80, methyl paraben, propyl paraben, artificial grape flavor, FD&C red # 40 dye.

[0443] (7) Add milled granules.

[0444] (8) Add water to 80% of final volume.

[0445] (9) Agitate at suitable rate to avoid settling of the suspension and maintain a homogeneous product mixture.

[0446] (10) Neutralize the solution to a pH of 6.5 (range 5.5 to 7.5) to form a gel using a 1N sodium hydroxide solution. QS with water to make final volume of 5 ml per dose.

[0447] (11) Fill in suitable containers.

EXAMPLE 65**Extended Release Suspension (Liquid)**

[0448] An extended release suspension (in the form of a liquid) in accordance with the present invention which contains a phenylephrine hydrochloride ion-exchange complex and promethazine hydrochloride is illustrated as follows:

Ingredients	Amount/5 ml
Phenylephrine hydrochloride Ion-Exchange Complex	Equivalent to 45 mg of Phenylephrine hydrochloride
Promethazine HCl	25 mg
Eudragit® L 100	0.2 to 2.8 g

Ingredients	Amount/5 ml
Silica, colloidal anhydrous, NF	100 mg
Glycerin	740 mg
Xylitol, NF	800 mg
Sodium Citrate, USP	100 mg
Saccharin Sodium cryst., USP	0.1 mg
Sodium Benzoate	7.5 mg
Citric Acid Monohydrate, USP	8.0 mg
Artificial Grape Flavor	5 mg
FD&C Red # 40 Dye	0.5 mg
Water	q.s to 5 ml

[0449] Manufacturing Process for 1000 L Batch:

[0450] Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. Amberlite® IRP 69) to a phenylephrine hydrochloride solution. Stir the mix for 12 hrs to allow complete drug/resin complex formation. Separate and dry the insoluble drug/resin complex. Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. Eudragit® L 100, Kollidon® MAE, Aquacoat® CPD) and dry the granules. Mill the granules, if needed.

[0451] In a suitably sized stainless steel vessel, dissolve saccharin sodium, sodium benzoate, citric acid, and sodium citrate in approximately 50 L of warm (about 45° C.), purified water. In another large stainless steel drum mix the silica, phenylephrine hydrochloride ion-exchange complex, and promethazine hydrochloride until a uniform and consistent mixture is obtained. In a separate 1000 L stainless steel tank equipped with a suitably sized homogenizer/disperser add about 100 L of purified water. With the homogenizer on, add the silica mixture containing phenylephrine hydrochloride ion-exchange complex, and promethazine hydrochloride. Add the previously prepared solution of saccharin sodium, sodium benzoate, citric acid, and sodium citrate to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinsate to the 1000 L tank. Add the remaining ingredients and homogenize for 15 minutes.

EXAMPLE 67**Extended Release Suspension (Liquid)**

[0452] An extended release suspension (in the form of a liquid) in accordance with the present invention which contains a codeine phosphate ion-exchange complex, phenylephrine tannate and chlorpheniramine tannate is illustrated as follows:

Ingredients	Amount/5 ml
Codeine phosphate Ion-exchange complex	Equivalent to 45 mg Codeine phosphate
Phenylephrine Tannate	75.0
Chlorpheniramine Tannate	4.5
Eudragit® L 100	0.2 to 2.8 grams
Silica, colloidal anhydrous, NF	100 mg
Glycerin	740 mg
Xylitol, NF	800 mg
Sodium Citrate, USP	100 mg
Saccharin Sodium cryst., USP	0.1 mg

-continued

Ingredients	Amount 5 ml
Sodium Benzoate	7.5 mg
Citric Acid Monohydrate, USP	8.0 mg
Artificial Grape Flavor	5 mg
FD&C Red # 40 Dye	0.5 mg
Water	q.s to 5 ml

[0453] Manufacturing Process for 1000 Kg Batch:

[0454] Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. Amberlite® IRP 69) to a codeine phosphate solution. Stir the mix for 12 hrs to allow complete drug/resin complex formation. Separate and dry the insoluble drug/resin complex. Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. Eudragit® L 100, Kollidon® MAE, Aquacoat® CPD) and dry the granules. Mill the granules, if needed.

[0455] In a suitably sized stainless steel vessel, dissolve saccharin sodium, sodium benzoate, citric acid, and sodium citrate in approximately 50 L of warm (about 45° C.), purified water. In another large stainless steel drum mix the silica and the codeine phosphate ion-exchange complex, phenylephrine tannate, and the chlorpheniramine tannate until a uniform and consistent mixture is obtained. In a separate 1000 L stainless steel tank equipped with a suitably sized homogenizer/dispenser add about 100 L of purified water. With the homogenizer on, add the silica mixture containing the codeine phosphate ion-exchange complex, the phenylephrine tannate, and the chlorpheniramine tannate. Add the previously prepared solution of saccharin sodium, sodium benzoate, citric acid, and sodium citrate to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinse to the 1000 L tank. Add the remaining ingredients and homogenize for 15 minutes.

EXAMPLE 63**Extended Release Suspension**

[0456] An extended release suspension which contains a hydrocodone bitartrate ion-exchange complex, a dexchlorpheniramine maleate ion-exchange complex and a phenylephrine hydrochloride ion-exchange complex is illustrated as follows:

Ingredients	Amount 5 ml
Hydrocodone Bitartrate Ion-Exchange Complex	Equivalent to 8 mg of Hydrocodone bitartrate
Dexchlorpheniramine Maleate Ion-Exchange Complex	Equivalent to 6 mg of Dexchlorpheniramine Maleate
Phenylephrine HCl Ion-Exchange Complex	Equivalent to 70 mg of Phenylephrine HCl
Eudragit® L 100	0.2 to 2.5 g
Glycerin	0.5 mg
Polysorbate 80	1.5 mg
Carbomer (e.g., Carbopol® 974)	1.5 mg
Methyl Paraben	1 mg
Propyl Paraben	1 mg
Artificial Grape Flavor	5 mg
FD&C Red # 40 Dye	0.5 mg
Water	q.s

[0457] The formula described above serves as a non-limiting example. Any active drug which is in the form of a

salt, such as an antihistamine, codeine, or dihydrocodeine, can be incorporated as an ion-exchange resin complex.

[0458] Procedure:

[0459] (1) Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. Amberlite® IRP 69) to a dexchlorpheniramine maleate, hydrocodone bitartrate and phenylephrine HCl solution.

[0460] (2) Stir the mix for 12 hrs to allow complete drug/resin complex formation.

[0461] (3) Separate and dry the insoluble drug/resin complex.

[0462] (4) Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. Eudragit® L 100, Kollidon® MAE, Aquacoat® CPD) and dry the granules.

[0463] (5) Mill the granules, if needed.

[0464] (6) To an appropriate amount of water add the following ingredients and dissolve: Carbomer (e.g., Carbopol® 974), glycerin, polysorbate 80, methyl paraben, propyl paraben, artificial grape flavor, FD&C red # 40 dye.

[0465] (7) Add milled granules.

[0466] (8) Add water to make up to a final volume.

[0467] (9) Agitate at suitable rate to avoid settling of the suspension and maintain a homogeneous product mixture.

[0468] (10) Fill in suitable containers ensuring that the product is homogeneous throughout the filling operation.

EXAMPLE 69**Suspension Formula**

[0469] A suspension formula which comprises codeine phosphate and phenylephrine tannate is illustrated as follows:

Ingredients	g/100 ml	kg/batch
Codeine Phosphate	0.20	1.567
Phenylephrine Tannate	0.80	6.867
Silica, colloidal anhydrous, NF	1.73	14.417
Hydroxyethylcellulose, NF	0.05	0.417
Gorbitol Solution 70% (non-crystallizing), NF	34.00	283.333
Glycerol	14.75	122.917
Sorbitol, NF	16.00	133.333
Sodium Citrate, USP	2.00	16.667
Saccharin Sodium cryst., USP	0.01	0.083
Sodium Benzoate, NF	0.15	1.250
Citric Acid Monohydrate, USP	0.16	1.333
Strawberry Flavor	0.15	1.250
Banana Flavor	0.15	1.250
Purified Water	49.55	412.917
Total Amount	120.00	1000.000

[0470] Manufacturing Process for 1000 kg Batch:

[0471] In a suitably sized stainless steel vessel, dissolve saccharin sodium, sodium benzoate, citric acid, and sodium citrate in approximately 50 L of warm (about 45° C.), purified water. In another large stainless steel drum mix the silica, codeine phosphate and micronized phenylephrine tannate until a uniform and consistent mixture is obtained. In

a separate 1000 L stainless steel tank equipped with a suitably sized homogenizer/dispenser add about 100 L of purified water. With the homogenizer on, add the silica mixture containing phenylephrine tannate and codeine phosphate. Add the previously prepared solution of saccharin sodium, sodium benzoate, citric acid, and sodium citrate to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinse to the 1000 L tank. Add the remaining ingredients and homogenize for 15 minutes. Filter product through a 10 micron filter and fill in appropriately sized containers.

[0472] To make products with other agents such as anti-histamines, decongestants, or expectorants, one or more combinations of each of the ingredients in a range as described in Table 1 below can be made depending on the specific therapeutic effect desired.

EXAMPLE 70

Liquid Formula

[0473] A liquid dosage form which comprises phenylephrine hydrochloride is illustrated as follows:

Ingredients	Per 5 mL	Per 425 L
Codeine Phosphate USP	30 mg	2.550 kg
Phenylephrine Hydrochloride USP	10.0 mg	0.850 kg
Methyl Paraben USP	9.0 mg	0.765 kg
Propyl Paraben USP	1.0 mg	0.085 kg
Propylene Glycol USP	259 mg	22.016 kg
Saccharin Sodium USP	3.18 mg	0.270 kg
Citric Acid USP	5.0 mg	0.425 kg
Strawberry Flavor	10 mg	0.850 kg
Banana Flavor	10 mg	0.850 kg
Sorbitol Solution 70% USP	3212.5 mg	273.1 kg
Purified Water, as required to q.s. to	5.0 mL	425 L

[0474] Manufacturing Process for 425 L Batch Size:

[0475] In a suitably sized stainless steel vessel, dissolve methyl paraben and propyl paraben in approximately 50 L of warm (about 45° C.), purified water. Add about half of the propylene glycol and mix for about 1 hr. In a separate 1000 L stainless steel tank equipped with a suitably sized agitator, add about 50 L of purified water. With the agitator on, add phenylephrine hydrochloride, codeine phosphate, saccharin sodium and citric acid and dissolve. Add the previously prepared paraben/propylene glycol solution to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinsate to the 1000 L tank. Add the remaining propylene glycol to a suitably sized stainless steel vessel and dissolve the strawberry and banana flavors. Transfer this to the 1000 L tank. Rinse the container with 2 L of purified water and transfer to the 1000 L tank. With the agitator on, add the sorbitol solution 70% to the 1000 L tank. In a suitably sized stainless steel vessel, dissolve the codeine phosphate in about 5 L of purified water and transfer to the 1000 L tank. Rinse the container with about 2 L of purified water and transfer to the 1000 L tank. Stop the agitator and let the solution stand for 15 minutes. QS to 425 L with purified water. Filter product through a 1 micron filter and fill in appropriately sized containers.

[0476] To make products with other anti-histamines, decongestants, or expectorants, one or more combinations of each of the ingredients in a range as described in Table 1 above can be made depending on the specific therapeutic effect desired.

EXAMPLE 71

Liquid Formula

[0477] A liquid dosage form in accordance with the present invention which comprises diphenhydramine hydrochloride, dihydrocodeine bitartrate and phenylephrine hydrochloride is illustrated as follows:

Ingredients	Per 5 mL	Per 425 L
Diphenhydramine Hydrochloride USP	12.5 mg	1.063 kg
Dihydrocodeine Bitartrate USP	10.0 mg	0.850 kg
Phenylephrine Hydrochloride USP	10.0 mg	0.850 kg
Methyl Paraben USP	9.0 mg	0.765 kg
Propyl Paraben USP	1.0 mg	0.085 kg
Propylene Glycol USP	259 mg	22.016 kg
Saccharin Sodium USP	3.18 mg	0.270 kg
Citric Acid USP	5.0 mg	0.425 kg
Strawberry Flavor	10 mg	0.850 kg
Banana Flavor	10 mg	0.850 kg
Sorbitol Solution 70% USP	3212.5 mg	273.1 kg
Purified Water, as required to q.s. to	5.0 mL	425 L

[0478] Manufacturing process for 425 L batch size: In a suitably sized stainless steel vessel, dissolve methyl paraben and propyl paraben in approximately 50 L of warm (about 45° C.), purified water. Add about half of the propylene glycol and mix for about 1 hr. In a separate 1000 L stainless steel tank equipped with a suitably sized agitator, add about 50 L of purified water. With the agitator on, add phenylephrine hydrochloride, diphenhydramine hydrochloride, saccharin sodium and citric acid and dissolve. Add the previously prepared paraben/propylene glycol solution to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinsate to the 1000 L tank. Add the remaining propylene glycol to a suitably sized stainless steel vessel and dissolve the strawberry and banana flavors. Transfer this to the 1000 L tank. Rinse the container with 2 L of purified water and transfer to the 1000 L tank. With the agitator on, add the sorbitol solution 70% to the 1000 L tank. In a suitably sized stainless steel vessel, dissolve the dihydrocodeine bitartrate in about 5 L of purified water and transfer to the 1000 L tank. Rinse the container with about 2 L of purified water and transfer to the 1000 L tank. Stop the agitator and let the solution stand for 15 minutes. Adjust pH to 3.5 to 5.5 with either HCl or NaOH, qs to 425 L with purified water. Filter product through a 1 micron filter and fill in appropriately sized containers.

[0479] To make products with other analgesics, decongestants, antitussives or expectorants, one or more combinations of each of the ingredients in a range as described in Table 1 below can be made depending on the specific therapeutic effect desired.

EXAMPLE 72

Suspension Formula

[0480] A suspension formula in accordance with the present invention which comprises diphenhydramine hydrochloride and phenylephrine tannate is illustrated as follows:

Ingredients	100 ml	833.33 l
Diphenhydramine Hydrochloride	0.25%	2.083
Phenylephrine Hinnate	0.04%	0.667
Silica, colloidal anhydrous, NF	1.73	14.117
Hydroxyethylcellulose, NF	0.05	0.417
Sorbitol Solution 70% (non-crystallizing) NF	34.00	283.333
Glycerol	15.00	125.000
Xanthol, NF	16.00	133.333
Sodium Citrate, USP	2.00	16.667
Saccharin Sodium Cryst., USP	0.01	0.083
Sodium Benzoate, NF	0.15	1.250
Citric Acid Monohydrate, USP	0.15	1.333
Strawberry Flavor	0.15	1.250
Banana Flavor	0.15	1.250
Purified Water	QS	QS
Total Amount	100 ml	833.33 l

[0481] Manufacturing process for 833.33 l batch: In a suitably sized stainless steel vessel, dissolve saccharin sodium, sodium benzoate, citric acid, and sodium citrate in approximately 50 L of water (about 45° C.), purified water. In another large stainless steel drum mix the silica, diphenhydramine hydrochloride and micronized phenylephrine tannate until a uniform and consistent mixture is obtained. In a separate 1000 L stainless steel tank equipped with a suitably sized homogenizer/disperser add about 100 L of purified water. With the homogenizer on, add the silica mixture containing phenylephrine tannate and diphenhydramine hydrochloride. Add the previously prepared solution of saccharin sodium, sodium benzoate, citric acid, and sodium citrate to the 1000 L tank. Raise the final vessel with about 2 L of water and transfer the slurry to the 1000 L tank. Add the remaining ingredients, qs to 833.33 l and homogenize for 15 minutes. Filter product through a 10 micron filter and fill in appropriately sized containers.

[0482] To make products with other antihistamines, decongestants, antitussives, or expectorants, one or more combinations of each of the ingredients in a range as described in Table 1 below can be made depending on the specific therapeutic effect desired.

EXAMPLE 75

Bi-Layered Tablet (Direct Compression)

[0483] A bi-layered tablet in accordance with the present invention which comprises diphenhydramine hydrochloride in one layer and phenylephrine hydrochloride and diphenhydramine hydrochloride in the other layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight/kg batch (in grams)
Layer 1 (Immediate Release)		
Diphenhydramine Hydrochloride	100.0	137.9
Silicified Microcrystalline Cellulose	1.5	157.2
Sodium Starch Glycolate	10.0	13.8
Magnesium Stearate	1	1.58

-continued

Ingredients	Weight/tablet (mg)	Weight/kg batch (in grams)
Layer 2 (Sustained release)		
Phenylephrine HCl	20.0	27.6
Diphenhydramine Hydrochloride	100.0	137.9
Lactose Monohydrate	50.0	68.97
Dicalcium Phosphate	50.0	68.97
Kollidon SR	260.0	358.6
Stearic acid	15.0	20.7
Magnesium Stearate	5.0	6.9
Total	725.00	1000.0

[0484] Manufacturing Process

[0485] (a) Immediate release layer: Screen all ingredients through a USP sieve size # 30. Blend diphenhydramine hydrochloride, silicified microcrystalline cellulose and sodium starch glycolate in a twin shell blender for 20 minutes. Add magnesium stearate which acts as a lubricant, to the above blend and mix for 3 minutes.

[0486] (b) Sustained release layer: Screen all ingredients through a USP sieve size # 30. Preblend a portion (about 1/3) of the Kollidon SR and all the diphenhydramine hydrochloride for 15 minutes. Add the remaining Kollidon SR, phenylephrine hydrochloride, lactose monohydrate and dicalcium phosphate to the above preblend and mix for an additional 20 minutes. Add stearic acid and magnesium stearate to the above blend and mix for three minutes.

[0487] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet the immediate release layer is 225 mg and the sustained release layer is 500 mg.

[0488] By using the process described above, a bi-layered tablet of the following composition may be manufactured through direct compression:

Ingredients	Weight/tablet (mgs)
Layer 1 (Immediate Release)	
Diphenhydramine Hydrochloride	50
Silicified Microcrystalline Cellulose	133.5
Sodium Starch Glycolate	15
Magnesium Stearate	1.5
Layer 2 (Sustained Release)	
Phenylephrine HCl	30
Diphenhydramine Hydrochloride	50
Dicalcium Phosphate	100
Kollidon SR	260
Stearic Acid	15
Magnesium Stearate	5
Total	650

EXAMPLE 74

Bi-Layered Tablet (Wet Granulation)

[0489] A bi-layered tablet in accordance with the present invention which comprises diphenhydramine hydrochloride in one layer and pseudoephedrine hydrochloride and diphen-

hydramine hydrochloride in the other layer is illustrated as follows:

Ingredients	Weight/tablet (mg)	Weight/kg batch (gms)
Layer 1 (Immediate Release)		
Diphenhydramine Hydrochloride	100.0	100.0
Sulfified Microcrystalline Cellulose	11.0	11.0
Povidone	3.0	3.0
Croscarmellose Sodium	10.0	10.0
Magnesium Stearate	1.0	1.0
Layer 2 (Sustained Release)		
Pseudoephedrine HCl	120.0	120.0
Diphenhydramine Hydrochloride	100.0	100.0
Microcrystalline Cellulose (PH 102)	100.0	100.0
Lactose Monohydrate	100.0	100.0
Dicalcium Phosphate	10.0	10.0
Povidone	15.0	15.0
Methocel K4M Premium	10.0	20.0
Stearic Acid	20.0	20.0
Magnesium Stearate	5.0	5.0
Total	800.0	800.0

[0490] Manufacturing Process

[0491] (a) Immediate release layer: Screen all ingredients through a USP sieve size # 30. Blend diphenhydramine hydrochloride, sulfified microcrystalline cellulose and croscarmellose sodium in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution (4.3 gms povidone in 14.3 gms purified water). Dry the granulation until the loss on drying (LOD) is less than 2.0%. Screen the dried granulation through a USP sieve size # 14. Add the screened granulation and the prescreened magnesium stearate to the above blend and mix for 3 minutes.

[0492] (b) Sustained release layer: Screen all ingredients through a USP sieve size # 30. Blend the pseudoephedrine hydrochloride, diphenhydramine hydrochloride, Prosolv® (sulfified microcrystalline cellulose), lactose monohydrate, dicalcium phosphate, Methocel K4M Premium and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30% povidone solution. Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add granules and the prescreened magnesium stearate to the above blend and mix for 3 minutes.

[0493] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet the immediate release layer is 225 mgs and the sustained release layer is 575 mgs.

[0494] By using the process described above, a bi-layered tablet of the following composition may be manufactured through wet granulation:

Ingredients	Weight/tablet (mg)
Layer 1 (Immediate Release)	
Diphenhydramine Hydrochloride	100
Sulfified Microcrystalline Cellulose	29.5
Povidone	3

-continued

Ingredients	Weight/tablet (mgs)
Croscarmellose sodium	15
Magnesium Stearate	1.5
Layer 2 (Sustained Release)	
Pseudoephedrine HCl	120
Diphenhydramine Hydrochloride	100
Microcrystalline Cellulose 102	30
Lactose Monohydrate	100
Dicalcium Phosphate	100
Povidone	15
Hydroxypropylmethylcellulose	210
Stearic Acid	20
Magnesium Stearate	5
Total	950

[0495] The above examples 63-74 illustrate how to manufacture a bi-layered tablet containing an antihistamine, i.e., diphenhydramine hydrochloride in one layer and a decongestant and/or an antitussive and/or an expectorant and/or an analgesic in the other layer (optionally in combination with diphenhydramine hydrochloride). One or more of the non-limiting examples of active ingredients which may be used in combination with diphenhydramine hydrochloride depending on the specific therapeutic effect desired are listed in the above Table 1 together with exemplary ranges thereof.

EXAMPLE 75

Extended Release Suspension

[0496]

Ingredients	Amount/5 ml
Diphenhydramine hydrochloride	Equivalent to 12.5 mg
Ion-exchange complex	Diphenhydramine hydrochloride
Phenylephrine ion-exchange complex	Equivalent to 10 mg
	Phenylephrine HCl
Hydragrit® L 100	0.2 to 2.8 grams
Glycerin	315 mg
Sorbitate 80	1.5 mg
Carbomer (e.g., Carbopol® 974)	15 mg
Methyl Paraben	9 mg
Propyl Paraben	1 mg
Artificial grape flavor	5 mg
D&C red # 40 dye	0.5 mg
Water	q.s. to 5 mL

[0497] The formula described above serves as a non-limiting example. Any active drug which is in the form of a salt, such as diphenhydramine hydrochloride, codeine phosphate, pseudoephedrine hydrochloride, morphine sulfate, or neperidine hydrochloride can be incorporated as an ion-exchange resin complex.

[0498] Procedure:

[0499] (1) Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. Amberlite® IRP 88N) to a diphenhydramine hydrochloride and phenylephrine HCl solution.

[0500] (2) Stir the mix for 12 hrs to allow complete drug/resin complex formation.

- [0501] (3) Separate and dry the insoluble drug-resin complex.
- [0502] (4) Granulate the drug-resin complex with a delayed release/meric polymer (e.g., Eudragit® L 100, Kollidon® MAE, Aquacoat® PF) and dry the granules.
- [0503] (5) Mill the granules, if needed.
- [0504] (6) To an appropriate amount of water add the following ingredients and dissolve: Carbomer (e.g., Carbopol® 974), glycerin, polysorbate 80, methyl paraben, propyl paraben, artificial grape flavor, FD&C red # 40 dye.
- [0505] (7) Add milled granules.
- [0506] (8) Add water to make up to a final volume.
- [0507] (9) Adjust pH to the desired viscosity to keep all the solid materials in suspension.
- [0508] (10) Agitate at suitable rate to avoid settling of the suspension and maintain a homogeneous product mixture.
- [0509] (11) Fill in suitable containers ensuring that the product is homogeneous throughout the filling operation.

EXAMPLE 76

Bi-Layered Tablet (Wet Granulation)

[0510] A bilayered tablet in accordance with the present invention which comprises diphenhydramine hydrochloride and guaifenesin in both layers as sustained release layers is illustrated as follows.

Ingredients		Amounts	
Process Steps	Ingredients	Dose (mg)	Scale Up
Wet Mix	PURIFIED WATER	55.00	13.75 kg
Wet Mix	POVIDONE K-30 USP	15.00	3.75 kg
Pre-Blend	GUAFENESIN USP	100.00	150.00 kg
Pre-Blend	DIPHENHYDRAMINE HCL USP	100.00	25.00 kg
Pre-Blend	CAL. PHOSPHATE DIBASIC ANHYD	50.00	10.00 kg
Pre-Blend	METHOCEL K4M PREMIUM USP	16.00	4.00 kg
Final Blend	STEARIC ACID NF	4.50	1.13 kg
Final Blend	METHOCEL K4M PREMIUM USP	89.00	22.43 kg
Lube Blend	MAGNESIUM STEARATE NF	4.50	1.13 kg
Color Blend	FD&C BLUE # 2 LUMULAF	0.30	0.07 kg
	Total (wt.)	919.00 g	231 kg
	Total (tablets)	1	250.00

- [0511] Procedure
- [0512] 12. Set aside 0.5 kg of purified water to be used as a rinse in step 4.
- [0513] 13. Prepare a solution using the scale up amounts of Povidone K-30, and its remaining Purified Water.
- [0514] 14. Blend the pre-blend scale up amounts of Guaifenesin USP, Diphenhydramine HCL USP, and Calcium Phosphate Dibasic Anhydrous using a high shear mixer/granulator for 10 minutes.
- [0515] 15. With the mixer/granulator on, pump the solution prepared in step 12 in to the mixer/granulator. After completion, stop the mixer/granulator and rinse the con-

- tainer with the 0.5 kg of purified water set aside in step 12. Pump the rinse water to the mixer/granulator with mixer on. Turn off mixer when completed.
- [0516] 16. Charge the pre-blend scale up amount of Methocel K4M premium to the mixer/granulator and mix for 1 minute.
- [0517] 17. Dry the granulation until the LOD is 1% or less.
- [0518] 18. Pass the dried granulation through a Fitzpatrick Fitzmill fitted with a 109 screen.
- [0519] 19. Screen the final blend raw materials through a 12 mesh screen.
- [0520] 20. Blend the milled granulation from step 7 and the screened materials from step 8 using a V-blender for 20 minutes.
- [0521] 21. Screen the lube blend material through a 30 mesh screen.
- [0522] 22. Charge the screened material from step 10 to the V-blender and blend for 2 minutes.
- [0523] 23. Discharge half of the blended product into properly labeled drums double lined with polyethylene bags and set aside for step 16.
- [0524] 24. Screen the color blend material through a 30 mesh screen.
- [0525] 25. Charge the screened color blend material to the V-blender and blend for 1 minute.

- [0526] 26. Discharge into properly labeled drums double lined with polyethylene bags and set aside for step 16.
- [0527] 27. Compress bi-layered tablets using a rotary 4-layer tablet press where in each tablet layer 1 is 450 mg and layer 2 is 475 mg.

EXAMPLE 77

Bi-Layered Tablet (Wet Granulation)

[0528] A bilayered tablet in accordance with the present invention which comprises diphenhydramine hydrochloride in a sustained release layer and carbetapentane in an immediate release layer is illustrated as follows.

Formula		Amounts	
Process Steps	Ingredients	Dose (mg)	Scale-Up
<u>Sustained Release Layer</u>			
Wet Mix	PURIFIED WATER	48.00	15,000 kg
Wet Mix	POVIDONE K-30 USP	12.00	3,750 kg
Pre-blend	DIPHENHYDRAMINE HCl USP	50.00	15,630 kg
Pre-blend	CALCIUM PHOSPHATE TRIBASIC DIHYD	15.00	4,690 kg
Pre-blend	PROSOLV® SMCC 90	125.00	39,063 kg
Pre-blend	METHOCEL K4M PREMIUM USP	50.00	15,625 kg
Final blend	METHOCEL K4M PREMIUM USP	144.00	45,000 kg
Lube blend	MAGNESIUM STEARATE NF	4.00	1,250 kg
Layer Weight		400.00	
<u>Immediate Release Layer</u>			
Wet Mix	PURIFIED WATER	24.00	7,500 kg
Wet Mix	POVIDONE K-30 USP	6.00	1,875 kg
Pre-blend	CARBENPENTANE CITRATE NF	40.00	12,500 kg
Pre-blend	PROSOLV SMCC 90	100.00	31,250 kg
Pre-blend	LACTOSE MONOHYDRATE #316	40.00	12,500 kg
Pre-blend	SODIUM STARCH GLYCOLATE	8.00	2,500 kg
Pre-blend	FD&C BLUE #1 ALUMINUM LAKE	0.15	0,048 kg
Final blend	PROSOLV SMCC 90	145.68	45,528 kg
Final blend	LACTOSE MONOHYDRATE #316	40.00	12,500 kg
Final blend	SODIUM STARCH GLYCOLATE	16.00	5,000 kg
Final blend	FD&C BLUE #1 ALUMINUM LAKE	0.15	0,048 kg
Lube blend	MAGNESIUM STEARATE NF	4.00	1,250 kg
Layer Weight		400.00	
Totals (mg)		800.00	250,000 kg
Totals (kg)		1	312,500

[0529] Procedure

[0530] Sustained Release Layer (Layer 1)

[0531] 1. Set aside 0.5 kg of purified water to be used in step 4.

[0532] 2. Prepare a solution using the scale up amounts of Povidone K-30, and the remaining Purified Water from step 1.

[0533] 3. Blend the pre-blend scale up amounts of Diphenhydramine HCl USP, Calcium Phosphate Dibasic Dihydrate, and Prosolv SMCC 90 with a high shear mixer/granulator for 10 minutes.

[0534] 4. With the mixer/granulator on, pump the solution prepared in step 2 in to the mixer/granulator. After completion, stop the mixer/granulator and rinse the container with the purified water set aside in step 1. Pump the rinse water to the mixer/granulator with mixer on. Turn off mixer when completed.

[0535] 5. Charge the pre-blend scale up amount of Methocel K4M premium to the mixer/granulator and mix for 1 minute.

[0536] 6. Dry the granulation until the LOD is 2% or less.

[0537] 7. Pass the dried granulation through a Fitzpatrick Fitzmill fitted with a 14 mesh screen.

[0538] 8. Screen the final blend scale up amount of Methocel K4M premium through a 14 mesh screen.

[0539] 9. Blend the milled granulation from step 7 and the screened materials from step 8 using a V-blender for 20 minutes.

[0540] 10. Screen the lube scale up amount of Magnesium Stearate using a 30 mesh screen.

[0541] 11. Transfer the screened Magnesium Stearate to the V-blender and blend for 3 minutes. When completed discharge into properly identified drums double lined with polyethylene bags.

[0542] Immediate Release Layer (Layer 2)

[0543] 1. Set aside 0.5 kg of purified water to be used in step 4.

[0544] 2. Prepare a solution using the scale up amount of Povidone K-30, and the remaining purified water from step

[0545] 3. Blend the pre-blend scale up amounts of Carbenpentane Citrate, Prosolv SMCC 90, Lactose Monohydrate 316, Sodium Starch Glycolate, and FD&C Blue #1 Aluminum Lake using a high shear mixer/granulator for 10 minutes.

[0546] 4. With the mixer/granulator on, pump the solution prepared in step 2 in to the mixer/granulator. After completion, stop the mixer/granulator and rinse the container with the purified water set aside in step 1. Pump the rinse water to the mixer/granulator with mixer on. Allow mixture to mix for an additional minute then turn mixer/granulator off.

[0547] 5. Dry the granulation until the LOD is 4% or less.

[0548] 6. Pass the dried granulation through a Fitzpatrick Fitzmill fitted with a 14 mesh screen.

[0549] 7. Screen the final blend scale up amounts of Prosolv SMCC 90, Lactose Monohydrate #710, Sodium Starch Glycolate, and BD&C Blue #1 Aluminum Lake through a 14 mesh screen.

[0550] 8. Blend the milled granulation from step 5 and the screened materials from step 7 using a V-blender for 20 minutes.

[0551] 9. Screen the lobe scale up amount of Magnesium Stearate using a 20 mesh screen.

[0552] 10. Transfer the screened Magnesium Stearate to the V-blender and blend for 3 minutes. When completed discharge into properly identified 30 liter double lined with polyethylene bags.

[0553] 11. Compress bi-layered tablets using a rotary bi-layer tablet press wherein each tablet layer 1 is 400.0 mg and layer 2 is 400 mg.

[0554] It is noted that the foregoing examples have been provided merely for the purpose of explanation and are in no way to be construed as limiting of the present invention. While the present invention has been described with reference to exemplary embodiments, it is understood that the words which have been used herein are words of description and illustration, rather than words of limitation. Changes may be made, within the purview of the appended claims, as presently stated and as amended, without departing from the scope and spirit of the present invention in its aspects. Although the present invention has been described herein with reference to particular means, materials and embodiments, the present invention is not intended to be limited to the particulars disclosed herein; rather, the present invention extends to all functionally equivalent structures, methods and uses, such as are within the scope of the appended claims.

What is claimed is:

1. A pharmaceutical dosage form comprising (a) a first drug which is selected from decongestants, antitussives, expectorants, analgesics and antihistamines, and (b) a second drug which is selected from decongestants, antitussives, expectorants, analgesics and antihistamines, wherein the dosage form provides a plasma concentration within a therapeutic range of the second drug over a period which is coextensive with at least about 70% of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

2. The dosage form of claim 1, wherein the first drug comprises a decongestant.

3. The dosage form of claim 2, wherein the decongestant comprises at least one of phenylephrine, pseudoephedrine and pharmaceutically acceptable salts thereof.

4. The dosage form of claim 3, wherein the decongestant comprises at least one of phenylephrine and a pharmaceutically acceptable salt thereof.

5. The dosage form of claim 3, wherein the decongestant comprises at least one of pseudoephedrine and a pharmaceutically acceptable salt thereof.

6. The dosage form of claim 1, wherein the first drug comprises an antitussive.

7. The dosage form of claim 6, wherein the antitussive comprises at least one of a morphine derivative, dextromethorphan, carbetapentane, chlophedianol, benzonatate, daramiphen, noscapine and pharmaceutically acceptable salts thereof.

8. The dosage form of claim 7, wherein the antitussive comprises at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

9. The dosage form of claim 7, wherein the antitussive comprises at least one of carbetapentane and a pharmaceutically acceptable salt thereof.

10. The dosage form of claim 7, wherein the antitussive comprises at least one of chlophedianol and a pharmaceutically acceptable salt thereof.

11. The dosage form of claim 1, wherein the first drug comprises an antihistamine.

12. The dosage form of claim 11, wherein the antihistamine comprises at least one of astemizole, azatadine, azelastine, bromodiphenhydramine, brompheniramine, carbinoxamine, cetirizine, chlorcyclizine, clemastine, chlorothene, chlorpheniramine, cyclizine, cyproheptadine, desloratadine, dexbrompheniramine, dexbrompheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine, fexofenadine, hydroxyzine, isothipendyl, loratadine, methapyrilene, montelukast, phenindamine, pheniramine, phenyltoloxamine, promethazine, prophenpyridamine, pyrilamine, terfenadine, thenyldiamine, thonzylamine, trimetoprim, triprolidine, and pharmaceutically acceptable salts thereof.

13. The dosage form of claim 11, wherein the antihistamine comprises at least one of promethazine, diphenhydramine, chlorpheniramine and pharmaceutically acceptable salts thereof.

14. The dosage form of claim 11, wherein the antihistamine comprises at least one of carbinoxamine and a pharmaceutically acceptable salt thereof.

15. The dosage form of claim 1, wherein the first drug comprises an analgesic.

16. The dosage form of claim 15, wherein the analgesic comprises at least one of aspirin, acetaminophen, ibuprofen, etopirofen, naproxen, sodium naproxen, meloxicam, hydrocodone, oxycodone, morphine, meperidine, and fentanyl.

17. The dosage form of claim 1, wherein the first drug comprises an expectorant.

18. The dosage form of claim 17, wherein the expectorant comprises at least one of guaifenesin and a pharmaceutically acceptable salt thereof.

19. The dosage form of claim 2, wherein the second drug comprises an antitussive.

20. The dosage form of claim 19, wherein the antitussive comprises at least one of a morphine derivative, dextromethorphan, carbetapentane, chlophedianol, benzonatate, daramiphen, noscapine and pharmaceutically acceptable salts thereof.

21. The dosage form of claim 19, wherein the antitussive comprises at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

22. The dosage form of claim 2, wherein the second drug comprises an antihistamine.

23. The dosage form of claim 22, wherein the antihistamine comprises at least one of astemizole, azatadine, azelastine, bromodiphenhydramine, brompheniramine, carbinoxamine, cetirizine, chlorcyclizine, clemastine, chlorothene, chlorpheniramine, cyclizine, cyproheptadine, desloratadine, dexbrompheniramine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine, fexofenadine, hydroxyzine, isothipendyl, loratadine, methapyrilene, montelukast, phenindamine, pheniramine, phenyltoloxamine, promethazine, prophepyridamine, pyrilamine, terfenadine, triethylamine, thonzamine, trimetopazine, triphenylamine, triprolidine, and pharmaceutically acceptable salts thereof.

24. The dosage form of claim 22, wherein the antihistamine comprises at least one of promethazine, diphenhydramine, chlorpheniramine and pharmaceutically acceptable salts thereof.

25. The dosage form of claim 23, wherein the antihistamine comprises at least one of carbinoxamine and a pharmaceutically acceptable salt thereof.

26. The dosage form of claim 2, wherein the second drug comprises an analgesic.

27. The dosage form of claim 26, wherein the analgesic comprises at least one of aspirin, acetaminophen, ibuprofen, ketoprofen, naproxen, sodium naproxen, meloxicam, hydrocodone, oxycodone, morphine, meperidine, and fentanyl.

28. The dosage form of claim 2, wherein the second drug comprises an expectorant.

29. The dosage form of claim 28, wherein the expectorant comprises at least one of guaifenesin and a pharmaceutically acceptable salt thereof.

30. The dosage form of claim 2, wherein the second drug comprises a decongestant.

31. The dosage form of claim 30, wherein the decongestant comprises at least one of phenylephrine, pseudoephedrine and pharmaceutically acceptable salts thereof.

32. The dosage form of claim 2, wherein the second drug comprises an antihistamine.

33. The dosage form of claim 32, wherein the antihistamine comprises at least one of astemizole, azatadine, azelastine, bromodiphenhydramine, brompheniramine, carbinoxamine, cetirizine, chlorcyclizine, clemastine, chlorothene, chlorpheniramine, cyclizine, cyproheptadine, desloratadine, dexbrompheniramine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine, fexofenadine, hydroxyzine, isothipendyl, loratadine, methapyrilene, montelukast, phenindamine, pheniramine, phenyltoloxamine, promethazine, prophepyridamine, pyrilamine, terfenadine, triethylamine, thonzamine, trimetopazine, triphenylamine, triprolidine, and pharmaceutically acceptable salts thereof.

34. The dosage form of claim 32, wherein the antihistamine comprises at least one of promethazine, diphenhydramine, chlorpheniramine and pharmaceutically acceptable salts thereof.

35. The dosage form of claim 32, wherein the antihistamine comprises at least one of carbinoxamine and a pharmaceutically acceptable salt thereof.

36. The dosage form of claim 6, wherein the second drug comprises an analgesic.

37. The dosage form of claim 36, wherein the analgesic comprises at least one of aspirin, acetaminophen, ibuprofen, etopirofen, naproxen, sodium naproxen, meloxicam, hydrocodone, oxycodone, morphine, meperidine, and fentanyl.

38. The dosage form of claim 6, wherein the second drug comprises an expectorant.

39. The dosage form of claim 38, wherein the expectorant comprises at least one of guaifenesin and a pharmaceutically acceptable salt thereof.

40. The dosage form of claim 12, wherein the second drug comprises a decongestant.

41. The dosage form of claim 40, wherein the decongestant comprises at least one of phenylephrine, pseudoephedrine and pharmaceutically acceptable salts thereof.

42. The dosage form of claim 12, wherein the second drug comprises an antitussive.

43. The dosage form of claim 42, wherein the antitussive comprises at least one of a morphine derivative, dextromethorphan, carbetapentane, chlorphedianol, benzonatate, caramiphen, noscapine and pharmaceutically acceptable salts thereof.

44. The dosage form of claim 42, wherein the antitussive comprises at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

45. The dosage form of claim 11, wherein the second drug comprises an analgesic.

46. The dosage form of claim 45, wherein the analgesic comprises at least one of aspirin, acetaminophen, ibuprofen, etopirofen, naproxen, sodium naproxen, meloxicam, hydrocodone, oxycodone, morphine, meperidine, and fentanyl.

47. The dosage form of claim 11, wherein the second drug comprises an expectorant.

48. The dosage form of claim 47, wherein the expectorant comprises at least one of guaifenesin and a pharmaceutically acceptable salt thereof.

49. The dosage form of claim 16, wherein the second drug comprises a decongestant.

50. The dosage form of claim 49, wherein the decongestant comprises at least one of phenylephrine, pseudoephedrine and pharmaceutically acceptable salts thereof.

51. The dosage form of claim 16, wherein the second drug comprises an antitussive.

52. The dosage form of claim 51, wherein the antitussive comprises at least one of a morphine derivative, dextromethorphan, carbetapentane, chlorphedianol, benzonatate, caramiphen, noscapine and pharmaceutically acceptable salts thereof.

53. The dosage form of claim 51, wherein the antitussive comprises at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

54. The dosage form of claim 16, wherein the second drug comprises an antihistamine.

55. The dosage form of claim 54, wherein the antihistamine comprises at least one of astemizole, azatadine, azelastine, bromodiphenhydramine, brompheniramine, carbinoxamine, cetirizine, chlorcyclizine, clemastine, chlorothene, chlorpheniramine, cyclizine, cyproheptadine, desloratadine, dexbrompheniramine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine, fexofenadine, hydroxyzine, isothipendyl, loratadine, methapyrilene, montelukast, phenindamine, pheniramine, phenyltoloxamine, promethazine, prophepyridamine, pyrilamine, terfenadine, triethylamine, thonzamine, trimetopazine, triphenylamine, triprolidine, and pharmaceutically acceptable salts thereof.

dine, thenyldiamine, thonzylamine, trimeprazine, tripelenamine, triprolidine, and pharmaceutically acceptable salts thereof.

56. The dosage form of claim 54, wherein the antihistamine comprises at least one of promethazine, diphenhydramine, chlorpheniramine and pharmaceutically acceptable salts thereof.

57. The dosage form of claim 54, wherein the antihistamine comprises promethazine.

58. The dosage form of claim 15, wherein the second drug comprises at least one of carmentidine and a pharmaceutically acceptable salt thereof.

59. The dosage form of claim 58, wherein the expectorant comprises at least one of guaifenesin and a pharmaceutically acceptable salt thereof.

60. The dosage form of claim 1, wherein a plasma half-life of the second drug differs from a plasma half-life of the first drug by at least about 2 hours.

61. The dosage form of claim 1, wherein a plasma half-life of the second drug differs from a plasma half-life of the first drug by at least about 3 hours.

62. The dosage form of claim 1, wherein a plasma half-life of the second drug differs from a plasma half-life of the first drug by at least about 4 hours.

63. The dosage form of claim 1, wherein the period of a plasma concentration within the therapeutic range of the second drug is coextensive with at least about 80% of the period of a plasma concentration within the therapeutic range of the first drug.

64. The dosage form of claim 1, wherein the period of a plasma concentration within the therapeutic range of the second drug is coextensive with at least about 90% of the period of a plasma concentration within the therapeutic range of the first drug.

65. The dosage form of claim 1, wherein the period of a plasma concentration within the therapeutic range of the second drug is coextensive with at least about 95% of the period of a plasma concentration within the therapeutic range of the first drug.

66. The dosage form of claim 1, wherein the period of a plasma concentration within the therapeutic range of the second drug is substantially coextensive with the period of a plasma concentration within the therapeutic range of the first drug.

67. The dosage form of claim 1, wherein the dosage form comprises a tablet.

68. The dosage form of claim 67, wherein the tablet comprises a matrix which comprises one of the first drug and the second drug and has dispersed therein particles which comprise the other one of the first drug and the second drug.

69. The dosage form of claim 1, wherein the dosage form comprises one of a solution and a suspension.

70. A bi-layered tablet which comprises a first layer and a second layer, the first layer comprising a first drug which is selected from decongestants, antitussives, expectorants, analgesics and antihistamines, and the second layer comprising a second drug which is selected from decongestants, antitussives, expectorants, analgesics and antihistamines and is different from the first drug, wherein the bi-layered tablet provides a plasma concentration within a therapeutic range of the second drug over a period which is coextensive with at least about 70% of a period over which the bi-layered tablet provides a plasma concentration within a therapeutic range of the first drug.

71. The bi-layered tablet of claim 70, wherein the first drug is selected from one or more of phenylephrine, pseudoephedrine, codeine, dihydrocodeine, hydrocodone, dextromethorphan, carbetapentane, chlorphedianol, benzonatate, caramiphen, noscapine, guaifenesin, astemizole, azatadine, azelastine, bromodiphenhydramine, brompheniramine, carbinoxamine, cetirizine, chlorcyclizine, clemastine, chlorothene, chlorpheniramine, cyclizine, cyproheptadine, desloratadine, dexbrompheniramine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine, fexofenadine, hydroxyzine, isothipendyl, loratadine, methapyrilene, montelukast, phenindamine, pheniramine, phenyltoloxamine, promethazine, propenpyridamine, pyrillamine, terfenadine, thenyldiamine, thonzylamine, trimeprazine, tripelenamine, triprolidine, and pharmaceutically acceptable salts thereof, aspirin, acetaminophen, ibuprofen, ketoprofen, naproxen, sodium naproxen, meloxicam, hydrocodone, oxycodone, morphine, meperidine, and fentanyl.

72. The bi-layered tablet of claim 71, wherein the second drug is different from the first drug and is selected from one or more of phenylephrine, pseudoephedrine, codeine, dihydrocodeine, hydrocodone, dextromethorphan, carbetapentane, chlorphedianol, benzonatate, caramiphen, noscapine, guaifenesin, astemizole, azatadine, azelastine, bromodiphenhydramine, brompheniramine, carbinoxamine, cetirizine, chlorcyclizine, clemastine, chlorothene, chlorpheniramine, cyclizine, cyproheptadine, desloratadine, dexbrompheniramine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine, fexofenadine, hydroxyzine, isothipendyl, loratadine, methapyrilene, montelukast, phenindamine, pheniramine, phenyltoloxamine, promethazine, propenpyridamine, pyrillamine, terfenadine, thenyldiamine, thonzylamine, trimeprazine, tripelenamine, triprolidine, and pharmaceutically acceptable salts thereof, aspirin, acetaminophen, ibuprofen, ketoprofen, naproxen, sodium naproxen, meloxicam, hydrocodone, oxycodone, morphine, meperidine, and fentanyl.

73. The bi-layered tablet of claim 71, wherein the period of a plasma concentration within the therapeutic range of the second drug is coextensive with at least about 80% of the period of a plasma concentration within the therapeutic range of the first drug.

74. The bi-layered tablet of claim 72, wherein the period of a plasma concentration within the therapeutic range of the second drug is coextensive with at least about 90% of the period of a plasma concentration within the therapeutic range of the first drug.

75. The bi-layered tablet of claim 74, wherein the period of a plasma concentration within the therapeutic range of the second drug is coextensive with at least about 95% of the period of a plasma concentration within the therapeutic range of the first drug.

76. The bi-layered tablet of claim 70, wherein the period of a plasma concentration within the therapeutic range of the second drug is substantially coextensive with the period of a plasma concentration within the therapeutic range of the first drug.

77. The bi-layered tablet of claim 76, wherein a plasma half-life of the second drug differs from a plasma half-life of the first drug by at least about 2 hours.

78. The bi-layered tablet of claim 74, wherein a plasma half-life of the second drug differs from a plasma half-life of the first drug by at least about 3 hours.

79. The bi-layered tablet of claim 70, wherein one of the first and second layers is an immediate release layer.

80. The bi-layered tablet of claim 79, wherein the first and second layers are controlled release layers.

81. A multi-layered tablet which comprises at least a first layer and a second layer, wherein the first layer comprises a first drug which is selected from decongestants, antitussives, expectorants, analgesics and antihistamines and the second layer is a controlled release layer and comprises a second drug which is selected from decongestants, antitussives, expectorants, analgesics and antihistamines and is different from the first drug.

82. The multi-layered tablet of claim 81, wherein the first layer is an immediate release layer.

83. The multi-layered tablet of claim 82, wherein the second layer is a controlled release layer.

84. The multi-layered tablet of claim 82, wherein the second drug has a plasma half-life which differs from the plasma half-life of the first drug by at least about 3 hours.

85. The multi-layered tablet of claim 84, wherein the tablet provides a plasma concentration within a therapeutic range of the second drug over a period which is coextensive with at least about 90% of a period over which the tablet provides a plasma concentration within a therapeutic range of the first drug.

86. The multi-layered tablet of claim 81, wherein the layers are discrete zones which are arranged adjacent to each other.

87. The multi-layered tablet of claim 81, wherein one of the first and second layers is partially or completely surrounded by the other one of the first and second layers.

88. A pharmaceutical dosage form which comprises (a) a first drug which is selected from antihistamines and has a first plasma half-life and (b) a second drug which is selected from decongestants, antitussives, analgesics and expectorants and has a second plasma half-life that differs from the first plasma half-life by at least about 3 hours, wherein the dosage form provides a plasma concentration within a therapeutic range of the second drug over a period which is coextensive with at least about 80% of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

89. The dosage form of claim 88, wherein the first plasma half-life is longer by at least about 4 hours than the second plasma half-life.

90. The dosage form of claim 88, wherein the first plasma half-life is longer by at least about 3 hours than the second plasma half-life.

91. The dosage form of claim 88, wherein the first plasma half-life is at least about 3 hours.

92. The dosage form of claim 88, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 90% of the period of a plasma concentration within the therapeutic range of the first drug.

93. The dosage form of claim 88, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 95% of the period of a plasma concentration within the therapeutic range of the first drug.

94. The dosage form of claim 88, wherein the period of a plasma concentration within the therapeutic range of the at

least one second drug is substantially coextensive with the period of a plasma concentration within the therapeutic range of the first drug.

95. The dosage form of claim 88, wherein the dosage form is associated with instructions to administer the dosage form once or fewer times per day.

96. The dosage form of claim 88, wherein the dosage form is associated with instructions to administer the dosage form once or twice per day.

97. The dosage form of claim 88, wherein the dosage form comprises a tablet.

98. The dosage form of claim 97, wherein the second drug comprises a decongestant.

99. The dosage form of claim 98, wherein the antihistamine is selected from astemizole, azatadine, azelastine, bromodiphenhydramine, brompheniramine, carbinoxamine, cetirizine, chlorcyclizine, clemastine, chlorpheniramine, cyclizine, cyproheptadine, desloratadine, dexbrompheniramine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine, fexofenadine, hydroxyzine, isohipendyl, loratadine, methapyrilene, montelukast, phenindamine, pheniramine, phenyltoloxamine, promethazine, propenpyridamine, pyrilamine, terfenadine, thenyldiamine, thonzylamine, trimetopazine, triphenylamine, triprolidine, and pharmaceutically acceptable salts thereof.

100. The dosage form of claim 98, wherein the antihistamine comprises at least one of promethazine, diphenhydramine, chlorpheniramine and pharmaceutically acceptable salts thereof.

101. The dosage form of claim 98, wherein the antihistamine comprises carbinoxamine.

102. The dosage form of claim 99, wherein the second drug comprises a decongestant.

103. The dosage form of claim 102, wherein the decongestant comprises at least one of phenylephrine, pseudoephedrine and pharmaceutically acceptable salts thereof.

104. The dosage form of claim 99, wherein the second drug comprises an antitussive.

105. The dosage form of claim 104, wherein the antitussive comprises at least one of a morphine derivative, dextromethorphan, carbetapentane, chlorphedianol, benzonatate, tramiphen, noscapine and pharmaceutically acceptable salts thereof.

106. The dosage form of claim 104, wherein the antitussive comprises at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

107. The dosage form of claim 99, wherein the second drug comprises an analgesic.

108. The dosage form of claim 107, wherein the analgesic comprises at least one of aspirin, acetaminophen, ibuprofen, etopirofen, naproxen, sodium naproxen, meloxicam, hydrocodone, oxycodone, morphine, meperidine, and fentanyl.

109. The dosage form of claim 99, wherein the second drug comprises an expectorant.

110. The dosage form of claim 109, wherein the expectorant comprises at least one of guaifenesin and a pharmaceutically acceptable salt thereof.

111. A method of alleviating a condition which can be alleviated by administration of an antihistamine and at least one other condition which can be alleviated by administration of a drug which is at least one of a decongestant,

antitussive, expectorant, and analgesic, wherein the method comprises administering the dosage form of claim 88 to a subject in need thereof.

112. A process of making the pharmaceutical dosage form of claim 1, wherein the method comprises preparing a first composition which comprises the first drug and a second composition which comprises the second drug, and combining the first and the second compositions.

113. The process of claim 112, wherein the first and second compositions are combined by using a tablet press.

114. A pharmaceutical dosage form comprising (a) a first drug which is selected from decongestants, antitussives, expectorants and analgesics, and (b) a second drug which is selected from decongestants, antitussives, expectorants and analgesics and is different from the first drug, wherein the dosage form provides a plasma concentration within a therapeutic range of the second drug over a period which is coextensive with at least about 70% of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug and wherein the dosage form is substantially free of antihistamines.

115. The dosage form of claim 114, wherein the first drug comprises a decongestant.

116. The dosage form of claim 115, wherein the decongestant comprises at least one of phenylephrine, pseudoephedrine and pharmaceutically acceptable salts thereof.

117. The dosage form of claim 114, wherein the first drug comprises an antitussive.

118. The dosage form of claim 117, wherein the antitussive comprises at least one of a morphine derivative, dextromethorphan, carbapentane, codeine, lisdexamfetamine, ephedrine, pseudoephedrine, and pharmaceutically acceptable salts thereof.

119. The dosage form of claim 117, wherein the antitussive comprises at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

120. The dosage form of claim 117, wherein the antitussive comprises at least one of carbapentane and a pharmaceutically acceptable salt thereof.

121. The dosage form of claim 114, wherein the first drug comprises an analgesic.

122. The dosage form of claim 121, wherein the analgesic comprises at least one of aspirin, acetaminophen, ibuprofen, ketoprofen, naproxen, sodium naproxen, meloxicam, hydrocodone, oxycodone, morphine, meperidine, and fentanyl.

123. The dosage form of claim 121, wherein the analgesic comprises a NSAID.

124. The dosage form of claim 114, wherein the first drug comprises an expectorant.

125. The dosage form of claim 124, wherein the expectorant comprises at least one of guaifenesin and a pharmaceutically acceptable salt thereof.

126. The dosage form of claim 115, wherein the second drug comprises an antitussive.

127. The dosage form of claim 126, wherein the antitussive comprises at least one of a morphine derivative, dextromethorphan, carbapentane, codeine, lisdexamfetamine, ephedrine, pseudoephedrine, and pharmaceutically acceptable salts thereof.

128. The dosage form of claim 127, wherein the antitussive comprises at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

129. The dosage form of claim 115, wherein the second drug comprises an analgesic.

130. The dosage form of claim 129, wherein the analgesic comprises at least one of aspirin, acetaminophen, ibuprofen, ketoprofen, naproxen, sodium naproxen, meloxicam, hydrocodone, oxycodone, morphine, meperidine, and fentanyl.

131. The dosage form of claim 129, wherein the analgesic comprises a NSAID.

132. The dosage form of claim 115, wherein the second drug comprises an expectorant.

133. The dosage form of claim 132, wherein the expectorant comprises at least one of guaifenesin and a pharmaceutically acceptable salt thereof.

134. The dosage form of claim 117, wherein the second drug comprises an analgesic.

135. The dosage form of claim 134, wherein the analgesic comprises at least one of aspirin, acetaminophen, ibuprofen, ketoprofen, naproxen, sodium naproxen, meloxicam, hydrocodone, oxycodone, morphine, meperidine, and fentanyl.

136. The dosage form of claim 134, wherein the analgesic comprises a NSAID.

137. The dosage form of claim 117, wherein the second drug comprises an expectorant.

138. The dosage form of claim 137, wherein the expectorant comprises at least one of guaifenesin and a pharmaceutically acceptable salt thereof.

139. The dosage form of claim 121, wherein the second drug comprises an expectorant.

140. The dosage form of claim 139, wherein the expectorant comprises at least one of guaifenesin and a pharmaceutically acceptable salt thereof.

141. The dosage form of claim 114, wherein a plasma half-life of the second drug differs from a plasma half-life of the first drug by at least about 2 hours.

142. The dosage form of claim 141, wherein the period of a plasma concentration within the therapeutic range of the second drug is substantially coextensive with the period of plasma concentration within the therapeutic range of the first drug.

143. The dosage form of claim 114, wherein the dosage form comprises a tablet.

144. A bi-layered tablet which comprises a first layer and second layer, the first layer comprising a first drug which is selected from decongestants, antitussives, expectorants and analgesics, and the second layer comprising a second drug which is different from the first drug and is selected from decongestants, antitussives, expectorants and analgesics, wherein the bi-layered tablet provides a plasma concentration within a therapeutic range of the second drug over a period which is coextensive with at least about 70% of a period over which the bi-layered tablet provides a plasma concentration within a therapeutic range of the first drug and wherein the bi-layered tablet is substantially free of antihistamines.

145. The bi-layered tablet of claim 144, wherein the first drug is selected from one or more of phenylephrine, pseudoephedrine, codeine, dihydrocodeine, hydrocodone, dextromethorphan, carbapentane, chlorpheniramine, benzonate, ephedrine, pseudoephedrine, and pharmaceutically acceptable salts thereof, aspirin, acetaminophen, ibuprofen, ketoprofen, naproxen, sodium naproxen, meloxicam, hydrocodone, oxycodone, morphine, meperidine, and fentanyl.

146. The bi-layered tablet of claim 145, wherein the second drug is different from the first drug and is selected from one or more of phenylephrine, pseudoephedrine, codeine, dihydrocodeine, hydrocodone, dextromethorphan,

carbetapentane, chlorpheniramine, benzonatate, ephedrine, nescapine, guaifenesin, and pharmaceutically acceptable salts thereof, aspirin, acetaminophen, ibuprofen, ketoprofen, naproxen, sodium naproxen, hydrocodone, hydrocodone, morphine, meperidine, and fentanyl.

147. The bi-layered tablet of claim 144, wherein the period of a plasma concentration within the therapeutic range of the second drug is substantially coextensive with the period of a plasma concentration within the therapeutic range of the first drug.

148. The bi-layered tablet of claim 147, wherein a plasma half-life of the second drug differs from a plasma half-life of the first drug by at least about 2 hours.

149. The bi-layered tablet of claim 144, wherein one of the first and second layers is an immediate release layer.

150. The bi-layered tablet of claim 144, wherein the first and second layers are controlled release layers.

151. A method of alleviating a condition which can be alleviated by administration of at least two drugs which are selected from decongestants, antitussives, expectorants and analgesics, wherein the method comprises administering the dosage form of claim 114 to a subject in need thereof.

152. The dosage form of claim 1, wherein the dosage form comprises at least one of carbinexamine and a pharmaceutically acceptable salt thereof as a first drug and at least one of pseudoephedrine and a pharmaceutically acceptable salt thereof as a second drug.

153. The bi-layered tablet of claim 70, wherein the dosage form comprises at least one of carbinexamine and a pharmaceutically acceptable salt thereof as a first drug and at least one of pseudoephedrine and a pharmaceutically acceptable salt thereof as a second drug.

154. The dosage form of claim 114, wherein the dosage form comprises an NSAID as a first drug and at least one of pseudoephedrine, phenylephrine, guaifenesin, codeine, dihydrocodeine, hydrocodone, carbetapentane and pharmaceutically acceptable salts thereof as a second drug.

155. The dosage form of claim 154, wherein the NSAID comprises at least one of ibuprofen, ketoprofen, naproxen and sodium naproxen.

156. The bi-layered tablet of claim 144, wherein the dosage form comprises an NSAID as a first drug and at least one of pseudoephedrine, phenylephrine, guaifenesin, codeine, dihydrocodeine, hydrocodone, carbetapentane and pharmaceutically acceptable salts thereof as a second drug.

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