



No. 06-057410-00004-0000

 Fecha: 2008-02-26 15:10:23 Dep. 2020 NUECREACIONE
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 Industria y Comercio
 SUPERINTENDENCIA

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

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

②

Número del expediente: 06-53410Solicitante: PFIZER PRODUCTS, INCSOLICITUD
PUBLICADAApoderado: CARLOS REINALDO OLARTE GARCIA
 Título de la nueva creación o denominación del signo: "FORMAS DE DOSIFICACIÓN MULTIPARTICULADAS DE AZITROMICINA MEJORADAS OBTENIDAS MEDIANTE PROCEDIMIENTOS DE COAGULACIÓN EN ESTADO PENDING"
Gaceta: 582

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: <u>PROCAPS S.A</u>	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Número <u>890.106.527-5</u>
	Dirección: <u>CALLE 80 No. 78B -201</u> Nacionalidad o Domicilio: <u>COLOMBIA</u> Lugar de Constitución: <u>BARRANQUILLA</u> Teléfono: <u>(571)3719900</u> Fax: <u>(571)3730818</u> E-mail: _____	
REPRESENTANTE O APODERADO	Nombre: <u>ELIANA ISaura MORENO BOHORQUEZ</u> Dirección: <u>CARRERA 13 No. 119-95 OF 104</u> Teléfono: <u>(571)2131213</u> Fax: <u>(571)6121979</u> E-mail: <u>negocios@optimum-co.com</u>	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Número <u>51.975.664 TP 83823</u>

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

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Señora Jefe,
DIVISIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Referencia : Expediente N° 06.053.410
Asunto : Oposición a la solicitud de patente de Invención titulada
"FORMAS DE DOSIFICACIÓN MULTIPARTÍCULADAS
DE AZITROMICINA MEJORADAS OBTENIDAS
MEDIANTE PROCEDIMIENTOS DE COAGULACIÓN EN
ESTADO FUNDIDO"
Solicitante : PFIZER PRODUCTS, INC.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 582 del 30 de noviembre de 2007

Yo, **ELLANA 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 **PROCAPS 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 **FORMAS DE DOSIFICACIÓN MULTIPARTÍCULADAS DE AZITROMICINA MEJORADAS OBTENIDAS MEDIANTE PROCEDIMIENTOS DE COAGULACIÓN EN ESTADO**

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FUNDIDO", cuyo titular es PFIZER PRODUCTS, INC, 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 azitromicina. 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 8 de marzo de 2006, reivindicando prioridad bajo las solicitudes US20030527244P del 20040204; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 5821 del 30 de noviembre de 2007, cuya publicación internacional corresponde a la WO2005075454 del 20031204.

2.2. La solicitud colombiana 06.53410 objeto de la presente oposición, se refiere a un procedimiento para la formación de multiparticulados que comprende las etapas de: (a) formar en un extrusor una mezcla en estado fundido que comprende

azitromicina y un vehículo farmacéuticamente aceptable; (b) suministrar dicha mezcla en estado fundido de la etapa (a) a un medio de atomización para formar gotas a partir de dicha mezcla; y (c) coagular dichas gotas de la etapa (b) para formar dichos multiparticulados; donde el procedimiento para la formación de multiparticulados que comprende las etapas de: (a) formar una mezcla en estado fundido que comprende azitromicina y un vehículo farmacéuticamente aceptable; (b) suministrar dicha mezcla en estado fundido de la etapa (a) a un medio de atomización para formar gotas a partir de dicha mezcla; y (c) coagular dichas gotas de la etapa (b) para formar dichos multiparticulados, en el que la concentración de ésteres de azitromicina en dichos multiparticulados es menor de aproximadamente un 1 % en peso; donde dicha mezcla en estado fundido se forma en un extrusor; en el que dicha mezcla en estado fundido se forma a una temperatura de procesamiento que es al menos 10°C superior al punto de fusión de dicho vehículo; en el que dicha mezcla en estado fundido comprende una suspensión de azitromicina dihidrato cristalina en dicho vehículo; en el que dicha mezcla en estado fundido está a una temperatura de al menos aproximadamente 70°C y menor de aproximadamente 130°C; en el que dicha mezcla en estado fundido está en estado fundido durante al menos 5 segundos y durante menos de aproximadamente 20 minutos antes de la formación de dichas gotas en la etapa (b).

2.3. 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 parentabilidad de la presente solicitud:

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- D1: WO03063833 publicada el 7 de agosto de 2003.
- D2: US5824342 publicada el 20 de octubre de 1998.
- D3: US4086346 publicada el 25 de abril de 1978.
- D4: US6139872 publicada el 31 de octubre de 2000.

2.4. Ahora bien, el documento D1, particularmente en la descripción, particularmente en la página 13, líneas 23 a página 16 línea 5; página 22, líneas 8 a 23; y, reivindicaciones 3 y 14, revela un proceso para preparar multi-partículas de un fármaco que tiene alta y baja solubilidad, con una concentración de un polímero tal como un poloxámero y un material formador de microfase lipofílico tal como un derivado glicérido el cual comprende los pasos de formar una mezcla fundida que comprende un fármaco inestable y un portador (ver página 21, líneas 36 a página 22 líneas 33); entregando dicha mezcla fundida a medios de atomización tal como de disco rotativo (ver página 23 línea 14) para conformar gotas de dicha mezcla fundida; y, finalmente enfriar dichas gotas para conformar micro-partículas. Dicho documento D1, revela a partir de la página 38, línea 8, la azitromicina como activo de uso en la invención. De igual forma, este documento D1, enseña que el orden para reducir la degradación, los excipientes convenientes así como diseños especiales de extrusión, particularmente en las páginas 21, líneas 36 a página 22 línea 2 y página 22 líneas 29 a 33, así como página 27 líneas 10 a 12. Así, las cosas, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica, particularmente en el documento D1.

2.5. El documento D2, revela en la descripción, particularmente en la columna 8, líneas 8 a 10, columna 17 línea 62 a columna 19 línea 46, multi-partículas que consisten en una suspensión sólida de un sustrato sólido no graso que comprende un ingrediente activo asociado con el mismo, donde el sustrato no graso y el activo están dispersos no uniformemente en un portador sólido no graso el cual puede ser

un derivado glicérido, donde la mezcla fue extruida (ver columna 18, líneas 15 a 42); donde la mezcla extruida después fue procesada a través de un atomizador para obtener multi-partículas de grasa solidificada a temperatura ambiente. Por su parte, D2, define que dichos procesos son particularmente admisibles para sustancias sensibles al calor, donde el tiempo de residencia a altas temperaturas es reducido, tal y como se evidencia en la columna 3, líneas 22 a 33 de dicho documento D2. Como tal, dicho documento D2, define que para evitar largas exposiciones a excesiva temperatura, la velocidad del proceso (velocidad del proceso referida al transporte del material tal como un tornillo sinfin) podrá incrementarse en el orden necesario para acelerar el ingreso a la etapa de extrusión y consecuentemente reducir el tiempo de residencia a altas temperaturas, conforme se revela en la columna 18, líneas 22 a 25. Por lo tanto, en el documento D2, se anticipa a la solución propuesta en la presente solicitud objeto de oposición, de tal forma que la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica, particularmente con base en el documento D2.

2.6. Por su parte el documento D3, revela en la descripción, particularmente en la columna 4 línea 20 a columna 5 línea 25, un método de manufactura de multi-partículas térmicamente sensibles, que comprenden fenacetina, donde dicho proceso comprende fundir la fenacetina usando un extrusor de tornillo; atomizar dicha mezcla extruida; solidificar las micro-partículas usando un gas o un líquido. Por su parte, el documento D4, revela en la descripción, particularmente en la columna 8 línea 4 a columna 9 línea 67, ejemplo 6 y reivindicaciones, un proceso de extrusión para conformar micro-partículas que comprende formar una mezcla extruida, atomizarla con una boquilla de rocío para obtener partículas; y, enfriar dichas partículas con un líquido tal como nitrógeno. Por lo tanto, a partir de estos documentos D3 y D4, en combinación con la materia definida en los documentos D1 y D2, cualquier persona versada en la materia puede llegar de manera obvia a

conformar un procedimiento para la formación de multiparticulados que comprende las etapas de: (a) formar en un extrusor una mezcla en estado fundido que comprende un activo y un vehículo farmacéuticamente aceptable; (b) suministrar dicha mezcla en estado fundido de la etapa (a) a un medio de atomización para formar gotas a partir de dicha mezcla; y (c) coagular dichas gotas de la etapa (b) para formar dichos multiparticulados. Por lo tanto, a los ojos de estos documentos D3 y D4, en combinación con la materia definida en los documentos D1 y D2, la presente solicitud carece evidentemente de altura inventiva.

2.7. Por lo tanto, este documento objeto de oposición a la luz del documento D1 y D2 carece de NOVEDAD y a partir de los documentos D3 y D4, en combinación con la materia definida en los documentos D1 y D2, la presente solicitud carece de ALTURA INVENTIVA.

2.8. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 06-053410 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.

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

2.9.1. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."* A la fecha de prioridad, 4 de diciembre de 2003 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1 y D2, un procedimiento para la

formación de multiparticulados que comprende las etapas de: (a) formar en un extrusor una mezcla en estado fundido que comprende un azitromicina y un vehículo farmacéuticamente aceptable; (b) suministrar dicha mezcla en estado fundido de la etapa (a) a un medio de atomización para formar gotas a partir de dicha mezcla; y (c) coagular dichas gotas de la etapa (b) para formar dichos multiparticulados. Por lo tanto, a los ojos de estos documentos D1 y D2, la presente solicitud carece evidentemente de novedad, sobre el cual busca protección en el capítulo reivindicatorio.

2.9.2. 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, 4 de diciembre de 2003, a partir de los documentos D3 y D4 en combinación con D1 y D2, es posible deducir la conformación de un procedimiento para la formación de multiparticulados que comprende las etapas de: (a) formar en un extrusor una mezcla en estado fundido que comprende un activo y un vehículo farmacéuticamente aceptable; (b) suministrar dicha mezcla en estado fundido de la etapa (a) a un medio de atomización para formar gotas a partir de dicha mezcla; y (c) coagular dichas gotas de la etapa (b) para formar dichos multiparticulados. Por lo tanto, a los ojos de estos documentos D3 y D4, en combinación con la materia definida en los documentos D1 y D2, la presente solicitud carece evidentemente de altura inventiva, sobre el cual busca protección en el capítulo reivindicatorio.

2.10. 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*

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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.

2.11. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"FORMAS DE DOSIFICACIÓN MULTIPARTÍCULADAS DE AZITROMICINA MEJORADAS OBTENIDAS MEDIANTE PROCEDIMIENTOS DE COAGULACIÓN EN ESTADO FUNDIDO"**, cuyo titular es **PFIZER PRODUCTS, INC.**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 582.

3. PRUEBAS

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

- D1: WO03063833 publicada el 7 de agosto de 2003.
- D2: US5824342 publicada el 20 de octubre de 1998.
- D3: US4086346 publicada el 25 de abril de 1978.
- D4: US6139872 publicada el 31 de octubre de 2000.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

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- 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:

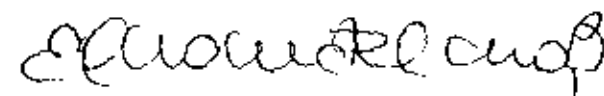
1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de PROCAPS S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: WO03063833 publicada el 7 de agosto de 2003.
 - D2: US5824342 publicada el 20 de octubre de 1998.
 - D3: US4086346 publicada el 25 de abril de 1978.
 - D4: US6139872 publicada el 31 de octubre de 2000.

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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.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800175089-2

RECIBO OFICIAL DE CAJA : 08 - 16,757
FECHA : FEBRERO 26 DE 2008

COMERCIO
N.º 08-284111-00004-0000
DIRECCION DE REGISTRO Y MARCAS
DIRECCION DE PROTECCION DE DISEÑOS INDUSTRIALES
DIRECCION DE PROTECCION DE PATENTES
DIRECCION DE PROTECCION DE SECRETOS INDUSTRIALES
DIRECCION DE PROTECCION DE DISEÑOS INDUSTRIALES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Gr. PAGO
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	83556	30/01/2008	1,882,000.00
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	2131825	15/02/2008	1,546,000.00

***** CONCEPTO *****

NT. MENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	266,000.00
	TOTAL :	\$ 266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



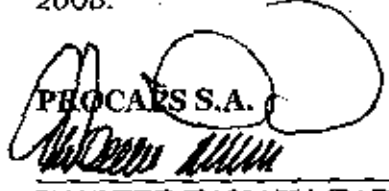
PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, 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 **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, 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. **06.053.410**, titulada "**FORMAS DE DOSIFICACIÓN MULTIPARTÍCULADAS DE AZITROMICINA MEJORADAS OBTENIDAS MEDIANTE PROCEDIMIENTOS DE COAGULACIÓN EN ESTADO FUNDIDO**", cuyo titular es **PFIZER PRODUCTS, INC.**, publicada en la gaceta No. 582 del 30 de Noviembre de 2007.

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.

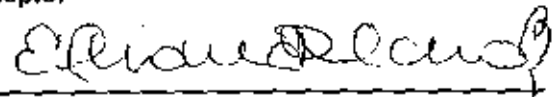
De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 20 días del mes de febrero de 2008.


PROCAPS S.A.

WALTER TANAKA TATEKAWA
C.C. N° 16'251.923
Representante Legal

Acepto:


ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.864 de Bogotá
T.P.A. 83823 del C.S. de la J.

DILIGENCIA DE RECONOCIMIENTO ANTE EL
SUSCRITO NOTARIO SEÑOR DE BARRANQUILLA
COMPARECIO Walter Tatekawa
IDENTIFICADO CON C.C. 16.251.923 Palmira (Velle)
y declaró que es cierto el contenido del documento
anterior y alzó la firma
Barranquilla **22 FEB. 2008**

[Handwritten signature]

NOTARIA 6A DE BARRANQUILLA
JORGE DEL ROSARIO FLOEZ DE CASTRO
N. 403 ENCARGADO

PRESENTACION PERSONAL
El suscrito es el que fue presentado ante el
NOTARIO DUEÑO DEL CIRCULO DE BODIA, C.C.

Permanente por Eliana J
Moeno Bohorquez

Quien exhibió la c.c. 51975664

y Tarjeta Profesional No. 83873

Fecha 26 FEB. 2008

[Handwritten signature]

[Handwritten signature]



***** Pag. 1
CAMARA DE COMERCIO
DE BARRANQUILLA
05*****

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

PROCAPS S.A.-----
NIT: 890.106.527-5.

EN JUNIO DE ESTE AÑO SE ELEGIRÁ JUNTA DIRECTIVA DE LA CÁMARA DE COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA QUINCENA DE MAYO. PARA INFORMACIÓN DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL O COMUNICARSE AL SIGUIENTE TELEFONO: 3303911.

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. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad-----
limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA
"PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada-----
se transformo en sociedad anonima bajo la denominacion social de
"PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada-----
se transformo en sociedad de responsabilidad limitada bajo al razon
social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI -
MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada-----
se transformo en sociedad anonima bajo la denominacion social de
"PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

***** C O N T I N U A *****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A.

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion PROCAPS 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
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18

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:

PROCAPS S.A.-----

SIGLA: PROCAPS.

***** C O N T I N U A *****



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NIT: 890.106.527-5.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.

C E R T I F I C A

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

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 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabricacion de capsulas y otros 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 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, alimenticias 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) La compra, venta, exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) 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 cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, 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 PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o in-

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dustrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa 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 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 la de sus socios. La sociedad podra garantizar el cumplimiento de obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,224,500,000	*****1,224,500	*****1,000
Pagado		
\$*****1,229,071,000	*****1,229,071	*****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. 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. Constituir

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apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. 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. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta

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Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades 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), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE:

JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben	CC.*****7,463,982
2. Minski Gontovnik Meyer	CC.*****7,461,324
3. Minski Gontovnik Jose	CC.*****8,671,834

Suplentes

1. Minski Zilberblum Elliot	CC.*****72,219,541
2. Minski Deitel Daniel	*****
3. Minski Sharon	PA.*990,212,082,805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS

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S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	
Minski Gontovnik Ruben	CC.*****7,463,982
Suplente del Presidente	
Minski Minski Abraham	CC.*****802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.*****70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Tanaka Tatekawa Walter	CC.*****16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Ppal.	
Vargas Pertuz Ana Isabel	CC.*****32,696,645

***** C O N T I N U A *****

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C E R T I F I C A

Que según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal.	
Lozada Villareal Milena	CC.*****32,748,111

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo, y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, 3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, 3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, obrando como Presidente y Representante Legal de la sociedad C.I. NATURMEGA S.A., que obrando en su condicion de Presidente y Representante Legal de la sociedad PROCAPS S.A., el presidente debidamente facultado por los Estatutos Sociales y por el Maximo Organo Social, otorga los siguientes poderes: Otorgar poder general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con las facultades que se transcriben a continuacion: a.- Para que representen a la sociedad PROCAPS S.A, ante todo tipo de autoridades administrativas y jurisdiccionales, en asuntos de naturaleza civil, laboral, comercial, penal, aduanera, cambiaria, tributaria, policiva, administrativa y fiscal. b.- Contestar y presentar demandas, requerimientos, recursos, pedir y aportar pruebas, recibir, notificarse, ejercer la accion de tutela, tramitar incidente de desacato, comparecer en los procesos que cursen contra la sociedad, allanarse en nombre de la sociedad en los asuntos que sean necesarios, transigir, desistir, sustituir, renunciar y reasumir el poder. c.- La facultad expresa de conciliar, por tanto pueden llegar a acuerdos conciliatorios, transaccionales, judiciales o extrajudiciales o extrajudiciales, cualquiera que sea su cuantia, para lo cual las apoderadas deben aportar la autorizacion simple y escrita del Representante legal de la sociedad. d.- Podran presentar solicitudes de devolucion y/o compensacion de impuestos, ventas y rentas, recibir los pagos por las devoluciones y adelantar todo tramite o proceso administrativo ante la DIAN, de tal forma que en ningun momento quede sin representacion legal de la sociedad. PODERES ESPECIALES: a.- Se confiere poder especial amplio y suficiente a las personas que se determinan seguidamente, que conforman el grupo A y B, para, para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS

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MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), -----
liquidados a la tasa representativa del mercado vigente en el dia
que se realice la respectiva transaccion. Grupo A. WALTER NANAKA
TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO -----
CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN -----
VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA -----
DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO -----
CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME
FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial ----
amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA -----
CC.No.8.715.941, y al señor ANTONIO VARELA DIAZ CC.No.72.004.699,
para que en nombre y representacion de PROCAPS S.A., suscriban ----
declaraciones cambiarias, aduaneras y tributarias a que este -----
obligada la sociedad, en el giro normal de sus negocios y -----
operaciones sociales, por tanto quedan facultados para firmarlas,
como tambien los demas documentos relacionados con ellas, -----
notificarse, aportar y solicitar las pruebas que sean necesarias.
c.- Otorgar poder especial amplio y suficiente al señor MARLON ----
TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS
CERRA CC.No.8.715.941, para que en nombre y representacion de ----
PROCAPS S.A., suscriban las declaraciones, reportes y cualquier
documento relacionado con los tramites o registros de Comercio ----
Exterior y o cualquier entidad del Estado que haga sus veces: d)
Otorgar poder especial amplio y suficiente a la doctora CARMEN ----
ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER
TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y -----
representacion de PROCAPS S.A.; endosen los titulos valores de la
sociedad hasta por la suma de UN MIL MILLONES DE PESOS -----
(1.000.000.000.00) M.L. CUARTO: El representante legal de la ----
sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta
que la presente reforma fue aprobada por la Asamblea General ----
Extraordinaria de Accionista de PROCAPS S.A., con observancia de
las disposiciones legales y estatutarias.-----

C E R T I F I C A

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: 20 de Marzo de 2007.

La información sobre embargos de establecimiento se suministra en

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

(19) World Intellectual Property Organization
International Bureau



INTERNATIONAL BUREAU OF PATENT COOPERATION
35, rue de la Harpe, CH-1015, Yverdon, Suisse
P.O. Box 6809, CH-1000, Lausanne, Suisse
Patent Cooperation Treaty, 1977

(43) International Publication Date
7 August 2003 (07.08.2003)

PCT

(10) International Publication Number
WO 03/063833 A1

(51) International Patent Classification: **A61K 9/16, 9/14**

Daniel, Tod [US/US]; Bend Research, Inc., 64550 Research Road, Bend, OR 97701 (US).

(23) International Application Number: **PCT/US03/00335**

(22) International Filing Date: 28 January 2003 (28.01.2003)

(74) Agents: **LUMB, J., Trevor et al.; c/o Simpson, Allison, Urquhart-Dykes & Lord, 30 Welbeck Street, London, W1G 8HR (GB).**

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/354,081 1 February 2002 (01.02.2002) US

(80) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GR, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

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

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Published:

with international search report

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



WO 03/063833 A1

(54) Title: **PHARMACEUTICAL COMPOSITIONS OF AMORPHOUS DISPERSIONS OF DRUGS AND LIPOPHILIC MICROPHASE-FORMING MATERIALS**

(57) Abstract: A pharmaceutical composition comprises a solid amorphous dispersion comprising a low-solubility drug and a concentration-enhancing polymer and a lipophilic microphase-forming material. Alternatively, a solid amorphous dispersion comprising a low-solubility drug and a concentration-enhancing polymer is co-administered with a lipophilic microphase-forming material to an in vivo use environment.

PHARMACEUTICAL COMPOSITIONS OF AMORPHOUS DISPERSIONS
OF DRUGS AND LIPOPHILIC MICROPHASE-FORMING MATERIALS

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The priority of Provisional Application Serial No. 60/354,081 filed February 1, 2002 is claimed.

BACKGROUND OF THE INVENTION

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The invention relates to pharmaceutical compositions comprising (1) a solid amorphous dispersion comprising a low-solubility drug and a concentration-enhancing polymer and (2) a lipophilic microphase-forming material that enhances the concentration of the drug in a use environment.

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Low-solubility drugs often show poor bioavailability or irregular absorption, the degree of irregularity being affected by factors such as dose level, fed state of the patient, and form of the drug. Increasing the bioavailability of low-solubility drugs has been the subject of much research. Increasing bioavailability depends on improving the concentration of dissolved drug in solution to improve absorption.

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It is well known that the amorphous form of a low-solubility drug that is capable of existing in either the crystalline or amorphous form may temporarily provide a greater aqueous concentration of drug relative to the equilibrium concentration obtained by dissolution of the drug in a use environment. Such amorphous forms may consist of the amorphous drug alone, a dispersion of the drug in a matrix material, or the drug adsorbed onto a substrate. It is believed that such amorphous forms of the drug may dissolve more rapidly than the crystalline form, often dissolving faster than the drug can precipitate from solution. As a result, the amorphous form may temporarily provide a greater-than-equilibrium concentration of drug.

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While such amorphous forms may show initially enhanced concentration of the drug in a use environment, nevertheless the improved concentration is often short-lived. Typically, the initially enhanced drug concentration is only temporary and quickly returns to the lower equilibrium concentration.

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One approach to increase the bioavailability of low-solubility drugs has involved forming amorphous dispersions of drugs with polymers. Examples of attempts to increase drug concentration by forming a dispersion of the drug with a polymer include Nakamichi *et al.*, U.S. Patent No. 5,456,923, and Curatolo *et al.*, EP 0901786A2.

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It is known to mix surfactants with solid amorphous dispersions. Curatolo *et al.*, EP 0901786A2 disclose that a component of the dispersion may be a surface-

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active agent such as a fatty acid and alkyl sulfonate, commercial surfactants such as benzethonium chloride, docusate sodium, and polyoxyethylene sorbitan fatty acid esters, and natural surfactants. Curatolo et al. state that such materials can advantageously be employed to increase the rate of dissolution by facilitating wetting, thereby increasing the maximum drug concentration and the degree of supersaturation attained, and also to inhibit crystallization or precipitation of drug by interacting with dissolved drug by mechanisms such as complexation, formation of inclusion complexes, formation of micelles or adsorbing to the surface of solid drug, crystalline or amorphous. Curatolo et al. state that these surface active agents may comprise up to 25% of the dispersion. In addition, Curatolo et al. also disclose that surface active agents may be present in compositions containing dispersions.

Nevertheless, what is still desired is a composition that may enhance the dissolution and/or bioavailability of poorly soluble drugs. These needs and others that will become apparent to one of ordinary skill are met by the present invention, which is summarized and described in detail below.

BRIEF SUMMARY OF THE INVENTION

The present invention overcomes the drawbacks of the prior art by providing a composition comprising (1) a solid amorphous dispersion comprising a low-solubility drug and a concentration-enhancing polymer and (2) a lipophilic microphase-forming material. The combination of a solid amorphous dispersion and a lipophilic microphase-forming material results in improved dissolved concentration of the drug in the aqueous use environment, and in some embodiments a surprising synergy. For a given dose of drug, the combination may either provide higher bioavailability with the same amount of concentration-enhancing polymer, or may provide the same bioavailability but with less concentration-enhancing polymer.

In another aspect of the invention, a solid amorphous dispersion comprising a low-solubility drug and a concentration-enhancing polymer is co-administered with a lipophilic microphase-forming material to an *in vivo* use environment. Another aspect of the invention comprises a kit comprising a solid amorphous dispersion comprising a low-solubility drug and a concentration-enhancing polymer and a lipophilic microphase-forming material.

The present inventors have found that the ability of a solid amorphous dispersion to enhance the concentration of drug in a use environment may be significantly improved by the addition of certain lipophilic microphase-forming materials. These lipophilic microphase-forming materials, when administered to an aqueous use environment such as the GI tract, form a plurality of small microphases, or so-called

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"lipophilic microphases." The lipophilic microphase-forming materials are chosen (1) to be water immiscible, (2) so that the drug has a high partition coefficient with respect to the lipophilic microphases, and (3) so that the resulting lipophilic microphases in the aqueous use environment are small.

5 Without wishing to be bound by any particular theory, the present inventors believe that when a composition of the present invention comprising a solid amorphous dispersion comprising a low-solubility drug and a concentration-enhancing polymer and a lipophilic microphase-forming material are introduced to a use environment such as the GI tract, the drug may be present in several different species.

10 When the aqueous use environment is either the GI tract of an animal, or an *in vitro* use environment that simulates the GI tract of an animal, it is believed that at least five different drug species are formed: (1) free drug; (2) drug present within bile salt micelles that are naturally occurring in the GI tract; (3) polymer/drug assemblies; (4) precipitate; and (5) drug in lipophilic microphases.

15 As used herein, the term "free drug" refers to drug molecules which are dissolved in the aqueous solution and are generally either monomeric or clusters of no more than about 100 molecules. A "polymer/drug assembly" refers to a collection of polymer molecules and drug molecules which are physically associated to form an assembly or aggregate that is sufficiently small that it remains suspended in solution.

20 "Precipitate" is a general term for any relatively large particulates that form and fall out of solution, either naturally or upon centrifugation. Such precipitate may comprise one or more or all of the following forms: (1) crystalline drug; (2) amorphous drug; and/or (3) a mixture of drug and polymer that is present as particles that are sufficiently large so as to drop out of solution (typically greater than about 5 to 10 microns in average diameter).

25 As used herein, the term "total dissolved drug" refers to the concentration of drug in a use environment that is not present in precipitate. Thus, "total dissolved drug" refers to drug that is present as free drug, drug within bile salt micelles, drug in polymer/drug assemblies, and drug in the lipophilic microphases.

It is desired to increase the free drug concentration in the GI tract

30 because, in general, primarily free drug is directly absorbed from the GI tract into the blood. The absorption rate of a drug from the GI tract to the blood is therefore generally proportional to the free drug concentration at the intestinal membrane surface. Drug present in the other species generally must first convert to the free drug form in order to be absorbed.

35 The present invention provides one or more of the following advantages over prior methods for enhancing the concentration and bioavailability of low-solubility drugs. The lipophilic microphases are capable of sufficiently solubilizing the drug in the

use environment to enhance bioavailability. In some cases, the lipophilic microphases are thought to be (1) highly mobile, meaning that they may diffuse more rapidly throughout the use environment than precipitate; and (2) labile, meaning that the drug may rapidly convert back and forth between the lipophilic microphases and free drug. It is believed that the lipophilic microphases may be more mobile than the polymer/drug assemblies. Because the lipophilic microphases solubilize the drug, the lipophilic microphases may reduce the formation of drug precipitate and increase the amount of total dissolved drug. The lability of the lipophilic microphases may also increase the rate of resupply of free drug in the use environment. As free drug is absorbed, drug present in the lipophilic microphases may rapidly convert to free drug, thus maintaining a sustained free drug concentration. When the lipophilic microphases are small, their high mobility may also increase the rate of drug absorption by the intestines by increasing the transport rate of the drug through the unstirred boundary layer adjacent to the intestinal wall. In combination, these properties may greatly enhance the rate and extent of drug absorption (e.g., bioavailability).

In addition, the compositions may also have the advantage of providing more regular absorption between the fed and fasted state of a patient. A problem when dosing low-solubility, lipophilic drugs is that the absorption of the drug may vary widely between the fed and fasted state of the patient. As previously noted, bile-salt micelles may be present in the GI tract. These micelles can behave in a similar way as the lipophilic microphase-forming materials of the present invention. It is believed that drug can readily partition into such bile-salt micelles, and drug in bile-salt micelles is readily absorbable because it is labile and the micelles are highly mobile.

It is well known in the art that in the fed state, the concentration of bile-salt micelles present in the GI tract is greater than the concentration present in the fasted state. The inventors believe that this difference in the concentration of bile-salt micelles in the GI tract in the fed versus fasted state may account, at least in part, for the fed/fasted differences in bioavailability observed for many pharmaceutical compositions. The compositions of the present invention comprising a solid amorphous dispersion and a lipophilic microphase-forming material may minimize this fed/fasted difference in bioavailability. The compositions tend to equalize the amount of drug present in highly labile, highly mobile species between the fed and fasted state, and thus provide a more uniform bioavailability between the fed and fasted state.

The foregoing and other objectives, features, and advantages of the invention will be more readily understood upon consideration of the following detailed description of the invention.

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DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides in one aspect a composition comprising (1) a solid amorphous dispersion comprising a low-solubility drug and a concentration-enhancing polymer, and (2) a lipophilic microphase-forming material. The lipophilic microphase-forming material may either be present in the dispersion itself, may be mixed with the dispersion, or may be separate from but co-administered with the dispersion. Suitable lipophilic microphase-forming materials, drugs and polymers, and methods for making the compositions, are discussed in more detail below.

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LIPOPHILIC MICROPHASE-FORMING MATERIALS

The lipophilic microphase-forming material may comprise a surfactant and/or a lipophilic material. Thus, as used herein, the "lipophilic microphase-forming material" is intended to include blends of materials in addition to a single material. The lipophilic microphase-forming material must (1) be water immiscible (2) be capable of forming a plurality of small lipophilic microphases in the use environment and (3) have a relatively high partition coefficient for the drug in the use environment.

The lipophilic microphase-forming material must be "water immiscible," meaning that the material when administered as prescribed herein to an *in vivo* aqueous use environment exceeds its solubility as solvated molecules thus requiring the formation of a second phase. Ideally such a second phase takes the form of a large number of small phases such as micelles or a microemulsion. The lipophilic microphase is a separate phase in the aqueous use environment; the separate phase ranging from extremely small aggregates such as micelles or as large droplets up to a few microns in size. Thus, the lipophilic microphase-forming material is not completely water soluble. The lipophilic microphase-forming material also is capable of forming a plurality of small lipophilic microphases in an *in vivo* aqueous use environment without the need for stirring, agitation or other mechanical energy. The material need not be self-emulsifying. Nevertheless, preferably the lipophilic microphase-forming material should not agglomerate into a single phase within the use environment, but should remain as a plurality of microphases for at least 1 hour and preferably longer. When the composition is administered to an *in vitro* aqueous use environment, the lipophilic microphase-forming material should form a plurality of microphases with at most only slight agitation of the use environment. The microphases remain small for at least 1 hour, and more preferably at least 4 hours, after administration to the use environment.

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It should be noted that some lipophilic materials that do not form a plurality of microphases when administered alone may often form such phases when administered with the polymer/drug solid amorphous dispersions. This is particularly true

when the lipophilic microphase-forming material is dispersed, along with the drug and the polymer in the solid amorphous dispersion.

The resulting lipophilic microphases formed in the aqueous use environment are small. By "small" is meant that the lipophilic microphase-forming material forms lipophilic microphases that are generally less than about 10 μm in characteristic diameter. By "characteristic diameter" is meant the volume average diameter of the microphase in the use environment. The characteristic diameter may be determined by standard measurement techniques, such as dynamic light scattering and static light scattering, or by examination via optical- or scanning-electron microscopy, transmission-electron microscopy, coulter-counting methods, and size-exclusion field-flow fractionation. The resulting particles may be smaller, such as less than 1 μm in characteristic diameter, less than 100 nm in characteristic diameter, and less than 50 nm in characteristic diameter. The size of the microphases depends on the other components of the composition, such as the drug and polymer, the manner in which the components of the composition are combined, (such as having the lipophilic microphase-forming material dispersed within the polymer/drug dispersion), as well as the components of the use environment. This is particularly true in an *in vivo* use environment where the presence of proteins, bile salts, and other surface active agents may cause some compositions to form suitably small lipophilic microphases even though they do not form such microphases in *in vitro* tests. In addition, it is well known that, in the *in vivo* environment, many lipophilic microphase-forming materials such as mono-, di-, and tri-glycerides may undergo chemical conversion to other species that in time form the microphases. Thus the ultimate test of an appropriate lipophilic microphase-forming material and composition is best conducted in the *in vivo* use environment.

The lability of a drug from the free drug phase into and out of the lipophilic microphase is generally a function of the microphase size. By "lability" is meant the kinetics or rate of drug release or drug partitioning into or out of the microphase. Generally, for a given mass of lipophilic microphase-forming material, lability increases as the size of the microphase decreases. As the solubility of the drug decreases, it is preferable for the characteristic size of the microphase to be smaller. Thus, when the solubility of the drug is extremely low, such as about 1 $\mu\text{g/ml}$ or less, preferred compositions generally form microphases less than about 1 μm in characteristic diameter when dosed to the *in vivo* use environment.

The drug should also have a relatively high partition coefficient in the lipophilic microphase-forming material. By partition coefficient is meant the ratio of the concentration of drug present in the lipophilic microphases to the free drug concentration as follows:

$$K_p = \frac{[Drug]_{lipophile}}{[Drug]_{free}} \quad (I)$$

where K_p is the partition coefficient, $[Drug]_{lipophile}$ is the concentration of the drug in the lipophilic microphases, and $[Drug]_{free}$ is the free drug concentration.

In a given volume of the aqueous use environment, the total amount of drug in the lipophilic microphases is also dependent on the amount of lipophilic microphase present. Thus the concentration of drug in the lipophilic microphase per unit volume of the aqueous use environment, $[Drug]_{aqueous, lipophile}$, is given by:

$$[Drug]_{aqueous, lipophile} = X_{lipophile} \cdot K_p \cdot [Drug]_{free}$$

where $X_{lipophile}$ is the volume fraction of the lipophilic microphase in the use environment.

In situations where the drug is only present as free drug and drug within the lipophilic microphase, the total dissolved drug concentration $[Drug]_{aqueous, total}$ is given by:

$$[D]_{aqueous, total} = [Drug]_{free} + [Drug]_{aqueous, lipophile} \quad (II)$$

$$[Drug]_{aqueous, total} = [Drug]_{free} \cdot [1 + X_{lipophile} \cdot K_p]$$

In order for the presence of the lipophile to have a large impact on the bioavailability of a composition, there generally must be a significant fraction of the total drug dosed that is within the lipophilic microphase. By significant fraction it is generally meant that at least about 0.1% and preferably at least about 1% of the total drug dosed is present in the use environment within the lipophilic microphase-forming material. According to the above equations, the fraction of the total drug present within the lipophilic microphases generally increases with: (1) increasing K_p , (2) increasing $X_{lipophile}$, (3) increasing $[Drug]_{free}$.

Since there are practical limits to the size of oral dosage forms that may be administered, it is generally undesirable to have large values of $X_{lipophile}$. For example, when the compositions of the present invention are formed into an oral tablet or capsule for administration, the mass of the tablet or capsule is generally less than about 1000 mg and preferably less than about 700 mg. Since a significant portion of the dosage form

must also comprise the active drug and other excipients, the maximum amount of lipophilic microphase-forming material in a single oral dosage form is about 500 mg. When dosed orally to the GI tract of a human, the aqueous volume into which the lipophilic microphase-forming material composition disperses is generally about 50 ml up to about 500 ml, depending on the fed state of the subject. Thus, the maximum practical value for $X_{\text{lipophile}}$ is about 0.001 to 0.01. Thus, for example, when the dose of the drug is 100 mg, it is desirable to have at least 0.1 wt% (0.1 mg) and preferably at least 1 wt% (1 mg) of the drug be present in the lipophilic microphase-forming material. This generally means that the concentration of drug in the lipophilic microphase-forming material (in wt%) when the composition is dosed orally to a human is at least about 0.1 mg/500 mg or 0.02 wt% and preferably at least about 0.2 wt% (1 mg/500 mg).

The minimum K_p may be determined by determining the K_p necessary to achieve the desired concentration of drug in the lipophilic microphase forming material. Since the concentration of drug in the lipophilic microphase-forming material at equilibrium is given by:

$$[\text{Drug}]_{\text{lipophile}} = [\text{Drug}]_{\text{free}} \cdot K_p$$

then the minimum K_p may be determined by setting the free drug concentration, $[\text{Drug}]_{\text{free}}$, to the maximum aqueous solubility of the drug, S_{xtal} . The minimum K_p should generally be at least about 0.02 wt%/S_{xtal}, preferably greater than about 0.2 wt%/S_{xtal}, more preferably greater than about 0.5 wt%/S_{xtal}, even more preferably greater than about 1 wt%/S_{xtal}, and most preferably greater than about 2 wt%/S_{xtal}. (The maximum aqueous solubility, S_{xtal} , is the maximum solubility of the thermodynamically most stable crystalline form of the drug, or the undispersed amorphous form if the crystalline form is unknown, over the physiologically pH range of 1-8.) Thus, when the maximum aqueous solubility of the drug is about 100 µg/ml or about 0.01 wt%, then K_p should be greater than about 2 (0.02 wt%/0.01 wt%), preferably greater than about 20 (0.2 wt%/0.01 wt%), more preferably greater than about 50 (0.5 wt%/0.01 wt%), even more preferably greater than 100 (1 wt%/0.01 wt%), and most preferably greater than 200 (2 wt%/0.01 wt%). Thus, the minimum and preferred minimum values for K_p for various drug solubilities are given as follows:

S_{xtal} (µg/ml)[wt%]	Minimum	Preferred Minimum	More Preferred Minimum	Even More Preferred Minimum	Most Preferred Minimum
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	K_p	K_p	K_p	K_p	K_p
100 [0.01]	2	20	50	100	200
10 [0.001]	20	200	500	1,000	2,000
1.0 [1×10^{-4}]	200	2,000	5,000	10,000	20,000
0.1 [1×10^{-5}]	2,000	20,000	50,000	100,000	200,000
0.01 [1×10^{-6}]	20,000	200,000	500,000	1,000,000	2,000,000

The partition coefficient K_p for a drug in a particular lipophilic microphase-forming material may be determined by any method or series of experiments in which the concentration of drug present as free drug and drug present in lipophilic microphases can be determined. One exemplary method is as follows. Crystalline drug (or amorphous drug if the crystalline form of the drug is not known) is added to an appropriate buffer solution such as PBS (described below) at an amount such that if all of the drug dissolved the concentration would be greater than the equilibrium solubility of the drug. The concentration of free drug in the solution is then determined by any technique that can quantitatively measure the amount of dissolved drug in solution, such as high-performance liquid chromatography (HPLC) or nuclear magnetic resonance (NMR) spectroscopy. Typically, this is accomplished by collecting a sample of the solution containing the drug and either filtering or centrifuging the sample to remove undissolved drug species, and then analyzing the concentration of the remaining dissolved drug. This technique provides the value of $[\text{Drug}]_{\text{free}}$ in Equation 1. Next, crystalline drug is added to an appropriate buffer solution to which various amounts of the lipophilic microphase-forming material had been added, such as 1 vol%, 2 vol% and 3 vol%, again at an amount such that if all of the drug dissolved the concentration of drug either present as free drug or in the lipophilic microphase would be greater than the equilibrium solubility of the drug with the lipophilic microphase-forming material present. The total concentration of total dissolved drug, that is the sum of drug present as free drug plus drug present in lipophilic microphases, (as given in Equation 1)—is determined using the same techniques described above. The total dissolved drug concentration $[\text{Drug}]_{\text{aqueous, total}}$ is then plotted versus the vol% lipophilic microphase-forming material in the solution. The slope of the line for this graph is equal to the product of the free drug concentration (which is normally assumed to be equal to the solubility of the drug in the absence of the lipophilic microphase-forming material, or S_{xlat}) and K_p . Thus, $K_p = \text{slope}/S_{\text{xlat}}$. When the aqueous solubility of the lipophilic microphase-forming material or the "critical micelle concentration" (CMC) of the lipophilic microphase-forming material is very small relative to the amount of lipophilic microphase-forming material used in the above experiment, the y-intercept of the line through the data points is approximately equal to the crystalline drug solubility, S_{xlat} . When the amount of lipophilic

microphase-forming material used is only slightly larger than the CMC or the lipophilic microphase-forming material aqueous solubility, then the values of $X_{lipophilic}$ should be corrected by subtracting the CMC or solubility from the total volume fraction of lipophilic microphase-forming material added to the solution.

5 In a preferred embodiment of this invention, the lipophilic microphase-forming material is part of the solid amorphous dispersion of drug and polymer. In such cases, it is preferred that the dispersion comprise no greater than 50 wt% lipophilic microphase-forming material, preferably no greater than 40 wt%, more preferably no greater than 30 wt%. When the lipophilic microphase-forming material is included in the
10 dispersion, the glass-transition temperature (T_g) of the dispersion may be reduced if the melting point of the lipophilic microphase-forming material is low, potentially leading to reduced stability of the drug in the dispersion. However, in many cases the addition of the lipophilic microphase-forming material also increases the solubility of the drug in the polymer plus lipophilic microphase-forming material matrix. As a result its addition may
15 improve the stability of the dispersion regardless of its effect on T_g . In cases where it is necessary to keep the T_g of the dispersion high and the lipophilic microphase-forming material is part of the dispersion, it is generally preferable for the material, if crystalline, to have a relatively high melting point and if amorphous to have a relatively high T_g . Thus, the melt temperature or T_g of the lipophilic microphase-forming material should be
20 sufficiently high such that the T_g of the dispersion is at least 50°C when tested under ambient humidity conditions (e.g., 50% relative humidity). More preferably, the T_g of the dispersion is at least 70°C at 50% relative humidity, and most preferably at least 100°C at 50% relative humidity. Other factors, such as the T_g of the drug, the T_g of the concentration-enhancing polymer, the drug:polymer ratio, and the amount of lipophilic
25 microphase-forming material included in the dispersion may affect the T_g of the dispersion, and these factors should be considered when selecting a lipophilic microphase-forming material to use in a composition.

Another preferred embodiment of the present invention is a solid oral dosage form comprising the novel compositions. The solid dosage form may take the
30 form of one or more tablets or capsules or a multiplicity of particles or granules. When the solid dosage form is one or more tablets or capsules, the dosage form may be taken orally by swallowing whole, chewed and then swallowed, or the dosage form may disintegrate and optionally dissolve in the mouth and then be swallowed. When the solid dosage form is a multiplicity of small particles or granules the powder or granules may be
35 ingested by any known method, including first dispersing in an aqueous vehicle and then swallowing, or mixing with food and then ingesting along with the food.

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In order for the compositions of the present invention to be efficiently formed into solid dosage forms it is generally desirable for the lipophilic microphase-forming materials to have relatively high melting points and relatively high T_g values. However, even lipophilic microphase-forming materials that are liquid at room temperature may be formed into solid dosage forms as long as the amount incorporated into the dosage form is not too high.

When the lipophilic microphase-forming material is either a liquid at room temperature or becomes liquid at a temperature of about 50°C or less, a preferred embodiment is to disperse the lipophilic microphase-forming material in a solid excipient. The lipophilic microphase-forming material may be adsorbed to the surface of a solid material such as microcrystalline cellulose; silica; dibasic calcium phosphate; calcium silicate (Zeodur™); clays, such as kaolin (hydrated aluminum silicate), bentonite (hydrated aluminum silicate), hectorite and Veegum®; Na-, Al-, and Fe-montmorillonite; silicon dioxide (Cab-O-Sil® or Aerosil®); magnesium trisilicate; aluminum hydroxide; magnesium hydroxide, magnesium oxide or talc. Highly porous materials such as calcium silicate are preferred. This embodiment has the advantage of separating the lipophilic microphase-forming material from the solid amorphous dispersion, thus minimizing the effect of the lipophilic microphase-forming material on the glass transition temperature of the dispersion. As described in more detail below, it is desired that the dispersion have a high glass transition temperature in order to provide good physical stability.

Alternatively, it may be dispersed in a water soluble or water dispersible polymer, as either a separate phase, or homogeneously throughout the polymer. In one preferred embodiment, the lipophilic microphase-forming material is dispersed in a concentration-enhancing polymer. Such lipophilic microphase-forming material dispersions serve to (1) render the lipophilic microphase-forming material solid to aid in incorporation into solid dosage forms, (2) aid in dispersing of the lipophilic microphase-forming material as a microphase, and (3) provide additional concentration-enhancing polymer for generating and sustaining high concentrations of dissolved drug. In an often particularly preferred embodiment, the lipophilic microphase-forming material is dispersed, along with the drug, in one or more concentration enhancing polymers to form a single dispersion comprising the drug, the one or more concentration-enhancing polymers, and the lipophilic microphase-forming material. Such lipophilic microphase-forming material dispersions are often preferred even when the lipophilic microphase-forming material is a solid below about 50°C.

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The lipophilic microphase-forming material may be either hydrophobic, amphiphilic, or a mixture of a hydrophobic and an amphiphilic material. By "amphiphilic" material is meant a material that has both hydrophobic and hydrophilic portions. Since hydrophobic materials alone tend not to form small microphases in an aqueous use environment, amphiphilic and mixtures of amphiphilic and hydrophobic materials are preferred. However, it is known that some such hydrophobic materials will form microphases due to the influence of (1) other excipients such as the concentration-enhancing polymer, (2) the drug itself, or (3) naturally occurring components of the GI tract. Thus, hydrophobic materials alone form a part of the invention as long as they form suitably small microphases when the compositions or dosage forms are administered to a use environment. The use of a mixture of hydrophobic and amphiphilic material may be preferred because the hydrophobic material often provides a higher partition coefficient, while the amphiphilic material may limit or reduce the size of the lipophilic microphases in the use environment. Thus, such mixtures may have higher lability and higher partition coefficients.

Generally, the lipophilic microphase-forming materials have a molecular weight of less than about 20,000 daltons. However, most lipophilic microphase-forming materials have molecular weights below about 2,000 daltons. Additionally, the lipophilic microphase-forming materials are water immiscible and form lipophilic microphases. The lipophilic microphase-forming material is therefore distinct from the concentration-enhancing polymer. The concentration-enhancing polymers generally have molecular weights of greater than about 10,000 daltons, are more soluble or dispersible in the use environment, and are generally less hydrophobic.

Examples of amphiphilic materials suitable for use as the lipophilic microphase-forming material include: sulfonated hydrocarbons and their salts, such as sodium 1,4-bis(2-ethylhexyl) sulfosuccinate, also known as docusate sodium (CROPOL) and sodium lauryl sulfate (SLS); poloxamers, also referred to as polyoxyethylene-polyoxypropylene block copolymers (PLURONICS, LUTROLs); polyoxyethylene alkyl ethers (CREMOPHOR A, BRIJ); polyoxyethylene sorbitan fatty acid esters (polysorbates, TWEEN); short-chain glyceryl mono-alkylates (HODAG, IMWITTOR, MYRJ); polyglycolized glycerides (GELUCIREs); mono- and di-alkylate esters of polyols, such as glycerol; nonionic surfactants such as polyoxyethylene 20 sorbitan monooleate, (polysorbate 80, sold under the trademark TWEEN 80, available commercially from ICI); polyoxyethylene 20 sorbitan monolaurate (Polysorbate 20, TWEEN 20); polyethylene (40 or 60) hydrogenated castor oil (available under the trademarks CREMOPHOR® RH40 and RH60 from BASF); polyoxyethylene (35) castor oil (CREMOPHOR® EL);

polyethylene (60) hydrogenated castor oil (Nikkol HCO-60); alpha tocopheryl
polyethylene glycol 1000 succinate (Vitamin E TPGS); glyceryl PEG 8 caprylate/caprate
(available commercially under the registered trademark LABRASOL® from Gattefosse);
PEG 32 glyceryl laurate (sold commercially under the registered trademark GELUCIRE
5 44/14 by Gattefosse), polyoxyethylene fatty acid esters (available commercially under
the registered trademark MYRJ from ICI), polyoxyethylene fatty acid ethers (available
commercially under the registered trademark BRIJ from ICI). Alkylate esters of polyols
may be considered amphiphilic or hydrophobic depending on the number of alkylates per
molecule and the number of carbons in the alkylate. When the polyol is glycerol, mono-
10 and di-alkylates are often considered amphiphilic while trialkylates of glycerol are
generally considered hydrophobic. However, some scientists classify even medium
chain mono- and di-glycerides as hydrophobic. See for example Patel et al US Patent
No. 6,294,192 (B1), which is incorporated herein in its entirety by reference. Regardless
of the classification, compositions comprising mono- and di-glycerides are preferred
15 compositions of this invention. Other suitable amphiphilic materials may be found in
Patel, Patent No. 6,294,192 and are listed as "hydrophobic non-ionic surfactants and
hydrophilic ionic surfactants."

It should be noted that some amphiphilic materials may not be water
immiscible by themselves, but instead are at least somewhat water soluble. Such
20 amphiphilic materials may nevertheless be used in mixtures to form the lipophilic
microphase, particularly when used as mixtures with hydrophobic materials.

Examples of hydrophobic materials suitable for use as the lipophilic
microphase-forming material include: medium-chain glyceryl mono-, di-, and tri-alkylates
(CAPMUL MCM, MIGLYOL 810, MYVEROL 18-92, ARLACEL 186, fractionated coconut
25 oil, light vegetable oils); sorbitan esters (ARLACEL 20, ARLACEL 40); long-chain fatty
alcohols (stearyl alcohol, cetyl alcohol, cetostearyl alcohol); long-chain fatty-acids
(stearic acid); and phospholipids (egg lecithin, soybean lecithin, vegetable lecithin,
sodium taurocholic acid, and 1,2-diacyl-sn-glycero-3-phosphocholine, such as 1-
palmitoyl-2-oleyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycero-3-
30 phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphocholine, 1-palmitoyl-2-stearoyl-sn-
glycero-3-phosphocholine, and other natural or synthetic phosphatidyl cholines); mono
and diglycerides of capric and caprylic acid under the following registered trademarks:
Capmul® MCM, MCM 8, and MCM 10, available commercially from Abitec, and
Imwitor® 988, 742 or 308, available commercially from Condea Vista; polyoxyethylene 6
35 apricot kernel oil, available under the registered trademark Labrafil® M 1944 CS from
Gattefosse; polyoxyethylene corn oil, available commercially as Labrafil® M 2125;

propylene glycol monolaurate, available commercially as Lauroglycol from Gattefosse; propylene glycol dicaprylate/caprate available commercially as Captex® 200 from Abitec or Miglyol® 840 from Condea Vista, polyglyceryl oleate available commercially as Plurol oleique from Gattefosse, sorbitan esters of fatty acids (e.g., Span® 20, Crill® 1, Crill® 4, available commercially from ICI and Croda), and glyceryl monooleate (Maisine, Pecanol); medium chain triglycerides (MCT, C6-C12) and long chain triglycerides (LCT, C14-C20) and mixtures of mono-, di-, and triglycerides, or lipophilic derivatives of fatty acids such as esters with alkyl alcohols; fractionated coconut oils, such as Miglyol® 812 which is a 56% caprylic (C8) and 36% capric (C10) triglyceride, Miglyol® 810 (68% C8 and 28% C10), Neobee® M5, Captex® 300, Captex® 355, and Crodamol® GTCC; (Miglyols are supplied by Condea Vista Inc. (Huls), Neobee® by Stepan Europe, Voreppe, France, Captex by Abitec Corp., and Crodamol by Croda Corp); vegetable oils such as soybean, safflower, corn, olive, cottonseed, arachis, sunflowerseed, palm, or rapeseed; fatty acid esters of alkyl alcohols such as ethyl oleate and glyceryl monooleate. Other hydrophobic materials suitable for use as the lipophilic microphase-forming material include those listed in Patel, U.S. Patent No. 6,294,192 as "hydrophobic surfactants." Exemplary classes of hydrophobic materials include: fatty alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty acid monoesters; glycerol fatty acid diesters; acetylated glycerol fatty acid monoesters; acetylated glycerol fatty acid diesters, lower alcohol fatty acid esters; polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof. Mixtures of relatively hydrophilic materials, such as those termed herein as "amphiphilic" or in Patel as "hydrophilic surfactants" and the above hydrophobic materials are particularly suitable. Specifically, the mixtures of hydrophobic surfactants and hydrophilic surfactants disclosed by Patel are suitable and for many compositions, preferred. However, unlike Patel, mixtures that include triglycerides as a hydrophobic component are also suitable.

In one embodiment, the lipophilic microphase-forming material is selected from the group consisting of polyglycolized glycerides (GELUCIREs); polyethylene (40 or 60) hydrogenated castor oil (available under the trademarks CREMOPHOR® RH40 and

RH60 from BASF); polyoxyethylene (35) castor oil (CREMOPHOR® EL); polyethylene
 (60) hydrogenated castor oil (Nikkol HCO-60); alpha tocopheryl polyethylene glycol 1000
 succinate (Vitamin E TPGS); glyceryl PEG 8 caprylate/caprate (available commercially
 under the registered trademark LABRASOL® from Gattefosse); PEG 32 glyceryl laurate
 5 (sold commercially under the registered trademark GELUCIRE 44/14 by Gattefosse);
 polyoxyethylene fatty acid esters (available commercially under the registered trademark
 MYRJ from ICI); polyoxyethylene fatty acid ethers (available commercially under the
 registered trademark BRIJ from ICI); polyoxyethylene-polyoxypropylene block
 copolymers (PLURONICs, LUTROLs); polyoxyethylene alkyl ethers (CREMOPHOR A,
 10 BRIJ); long-chain fatty alcohols (stearyl alcohol, cetyl alcohol, cetostearyl alcohol); long-
 chain fatty-acids (stearic acid); polyoxyethylene 6 apricot kernel oil, available under the
 registered trademark Labrafil® M 1944 CS from Gattefosse; polyoxyethylene corn oil,
 available commercially as Labrafil® M 2125; propylene glycol monolaurate, available
 commercially as Lauroglycol from Gattefosse; polyglyceryl oleate available commercially
 15 as Plurol oleique from Gattefosse; triglycerides, including medium chain triglycerides
 (MCT, C₈-C₁₂) and long chain triglycerides (LCT, C₁₄-C₂₀); fractionated coconut oils, such
 as Miglyol® 812 which is a 56% caprylic (C₈) and 36% capric (C₁₀) triglyceride, Miglyol®
 810 (68% C₈ and 28% C₁₀), Neobee® M5, Captex® 300, Captex® 355, and Crodamol®
 GTCC; (Miglyols are supplied by Condea Vista Inc. [Huls], Neobee® by Stepan Europe,
 20 Voreppe, France, Captex by Abitec Corp., and Crodamol by Croda Corp); vegetable oils
 such as soybean, safflower, corn, olive, cottonseed, arachis, sunflowerseed, palm, or
 rapeseed; polyoxyethylene alkylethers; fatty acids; lower alcohol fatty acid esters;
 polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters;
 polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives
 25 of monoglycerides; lactic acid derivatives of diglycerides; propylene glycol diglycerides;
 transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers;
 sucroglycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated
 vegetable oils; reaction products of polyols and at least one member of the group
 consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and
 30 sterols; and mixtures thereof.

Especially preferred lipophilic microphase-forming materials include
 mixtures of polyethoxylated castor oils and medium-chain glyceryl mono-, di-, and/or tri-
 alkylates, (such as mixtures of CREMOPHOR RH40 and CAPMUL MCM), mixtures of
 polyoxyethylene sorbitan fatty acid esters and medium-chain glyceryl mono-, di-, and/or
 35 tri-alkylates, (such as mixtures of TWEEN 80 and CAPMUL MCM), mixtures of
 polyethoxylated castor oils and medium-chain glyceryl mono-, di-, and/or tri- alkylates,

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(such as mixtures of CREMOPHOR RH40 and ARLACEL 20), mixtures of sodium taurocholic acid and palmitoyl-2-oleyl-sn-glycero-3-phosphocholine and other natural or synthetic phosphatidylcholines, and mixtures of polyglycolized glycerides and medium-chain glyceryl mono-, di-, and/or tri-alkylates, (such as mixtures of Gelucire 44/14 and CAPMUL MCM).

The lipophilic microphase-forming material is present in a sufficient amount so that the combination of the solid amorphous dispersion and lipophilic microphase-forming material provides concentration enhancement, as described more fully below. In general, the lipophilic microphase-forming material is either present in the composition or co-administered with the solid amorphous dispersion such that the weight ratio of the lipophilic microphase-forming material to drug (hereinafter referred to as the lipophile:drug ratio) ranges from 0.1 to 100 (wt/wt), and more typically from 0.2 to 50.

The optimum amount of the lipophilic microphase-forming material depends on the mass of the dose of the drug, the partition coefficient, and the solubility of the drug. The optimum mass of the lipophilic microphase-forming material increases as the mass of the dose increases. The optimum mass of the lipophilic microphase-forming material decreases as the partition coefficient increases and as the solubility increases.

Nevertheless, in general, the amount of lipophilic microphase forming material present in the composition should not be so high that the concentration of free drug obtained in the use environment is much lower than that obtained when less lipophilic microphase-forming material is combined with the solid amorphous dispersion and is introduced to the use environment. Generally, when the amount of lipophilic microphase-forming material that is added to the composition is greater than the amount such that all of the drug introduced to the use environment is either present as free drug or is in the lipophilic microphases, then the performance, in terms of improving drug absorption, will be reduced relative to lower levels of the lipophilic microphase-forming material. Thus, it is preferred for compositions to contain less than this "maximum preferred level." Nonetheless, levels of lipophilic microphase-forming material somewhat above this level may still improve drug absorption relative to the dispersion alone. This maximum preferred level will depend on the free drug concentration ($[Drug]_{free}$, typically given in mg/ml), the density of the lipophilic microphase-forming material ($\rho_{lipophile}$, typically given in mg/ml), and the partition coefficient (K_p). The maximum preferred lipophile:drug ratio is given by the following equation:

$$\text{Maximum lipophile:drug ratio} = \rho_{lipophile} / (K_p * [Drug]_{free})$$

It should be noted that for some values of K_p and $[\text{Drug}]_{\text{free}}$, the maximum preferred lipophile:drug ratio will be quite large. For example, when $\rho_{\text{lipophile}} = 1000 \text{ mg/mL}$, $K_p = 100$, and $[\text{Drug}]_{\text{free}} = 0.001 \text{ mg/mL}$, the maximum preferred lipophile:drug ratio is calculated to be 10,000. If the drug dose is, for example 100 mg, this results in a maximum preferred lipophile dose of 1000 g. Such high doses of lipophile are impractical. Thus when the value of K_p and/or $[\text{Drug}]_{\text{free}}$ are low, the maximum preferred lipophile:drug ratio may be limited by practical considerations such as the maximum dose well tolerated by the subject or the maximum practical size of the dosage form.

PREPARATION OF COMPOSITIONS

Compositions of the present invention may be prepared according to any technique that results in a mixture comprising (1) a solid amorphous dispersion comprising a low-solubility drug and a concentration-enhancing polymer and (2) a lipophilic microphase-forming material. In one method, a solid amorphous dispersion of the drug, polymer and lipophilic microphase-forming material is formed so that the lipophilic microphase-forming material is included in the dispersion itself. Alternatively, a solid amorphous dispersion of drug and polymer may be formed and then mixed with the lipophilic microphase-forming material so that the lipophilic microphase-forming material is mixed with but not included within the dispersion. As yet another alternative, the solid amorphous dispersion of the drug and polymer may be prepared and then co-administered with a lipophilic microphase-forming material to a use environment, so that the dispersion and lipophilic microphase-forming material are both present in the use environment.

Dispersions of a low-solubility drug and polymer may be made according to any known process which results in at least a "major portion" (meaning at least 60 wt%) of the drug being in the amorphous state. While the drug in its pure state may be crystalline or amorphous, at least a major portion of the drug in the dispersion is amorphous. By "amorphous" is meant simply that the drug is in a non-crystalline state. As used herein, the term "a major portion" of the drug means that at least 60 wt% of the drug in the dispersion is in the amorphous form. It has also been found that the aqueous concentration of the drug in a use environment tends to improve as the fraction of drug present in the amorphous state in the dispersion increases. Accordingly the drug in the dispersion may be substantially amorphous, and preferably may be almost completely amorphous. As used herein, "substantially amorphous" means that at least 75 wt% of the drug is amorphous and "almost completely amorphous" means that at least 90 wt% of the drug is amorphous. The amount of drug in the dispersion which is amorphous or

crystalline may be measured by powder X-ray diffraction, Scanning Electron Microscope (SEM) analysis, differential scanning calorimetry (DSC), or any other standard quantitative measurement.

The amorphous drug can exist as a pure phase, as a solid solution of drug
5 homogeneously distributed throughout the polymer or any combination of these states or those states that lie intermediate between them. The dispersion is preferably "substantially homogeneous" so that the amorphous drug is dispersed as homogeneously as possible throughout the polymer. Dispersions of the present invention that are substantially homogeneous generally have improved concentration-
10 enhancing properties and, in turn improved bioavailability, relative to nonhomogeneous dispersions. As used herein, "substantially homogeneous" means that the drug present in relatively pure amorphous domains within the solid dispersion is relatively small, on the order of less than 20%, and preferably less than 10% of the total amount of drug.

While the dispersion may have some drug-rich domains, it is preferred
15 that the dispersion itself have a single glass transition temperature (T_g) which demonstrates that the dispersion is substantially homogeneous. This contrasts with a simple physical mixture of pure amorphous drug particles and pure amorphous polymer particles which generally displays two distinct T_g s, one that of the drug and one that of the polymer. T_g as used herein is the characteristic temperature where a glassy
20 material, upon gradual heating, undergoes a relatively rapid (e.g., 10 to 100 seconds) physical change from a glass state to a rubber state. Dispersions with more than one T_g , indicating at least partial amorphous phase separation, may also function well, particularly when neither amorphous phase is comprised only of amorphous drug, but rather also contains a significant amount of concentration-enhancing polymer.

When the lipophilic microphase-forming material is included in the
25 dispersion, it may exist as a pure lipophilic phase, as a solid solution of the lipophilic microphase-forming material homogeneously distributed throughout the dispersion, or any combination of these states or those states that lie intermediate between them. Generally, it is preferred that the lipophilic microphase-forming material be well
30 distributed throughout the dispersion, either as small, preferably less than 1 μ m in diameter, relatively pure domains of lipophilic microphase-forming material, or more preferably, dispersed such that it is at least partially dissolved in the drug and polymer solid amorphous dispersion.

The solid amorphous dispersions of the drug and polymer may be made
35 according to any conventional process for forming dispersions. When the lipophilic microphase-forming material is included in the dispersion, such dispersions may also be made according to any conventional process for forming dispersions. Such processes

include mechanical, thermal and solvent processes. Exemplary mechanical processes include milling and extrusion; melt processes include high temperature fusion, solvent modified fusion and melt-congeal processes; and solvent processes include non-solvent precipitation, spray coating and spray-drying. See, for example, U.S. Patent No.

5 5,456,923 and U.S. Patent No. 5,939,099 which describe formation of dispersions via extrusion processes; U.S. Patent No. 5,340,591 and U.S. Patent No. 4,673,564 which describe forming dispersions by milling processes; and U.S. Patent No. 5,707,646 and U.S. Patent No. 4,894,235 which describe the formation of dispersions via melt/congeal processes, the disclosures of which are incorporated by reference.

10 In one embodiment, the solid amorphous dispersion of drug and concentration-enhancing polymer may be formed via a melt-congeal or melt-extrusion process. Such processes are particularly suitable when the drug has a relatively low melting point, typically less than about 200°C and preferably less than about 150°C. In such processes, a molten mixture comprising the drug and concentration-enhancing
15 polymer, and optionally, lipophilic microphase-forming material, is rapidly cooled such that the molten mixture solidifies to form a solid amorphous dispersion. By "molten mixture" is meant that the mixture comprising the drug and concentration-enhancing polymer is about 10°C or more above the melting point of the lowest melting point component in the composition. The drug may exist in the molten mixture as a pure phase, as a solution of
20 drug homogeneously distributed throughout the molten mixture, or any combination of these states or those states that lie intermediate between them. The molten mixture is preferably substantially homogeneous so that the drug is dispersed as homogeneously as possible throughout the molten mixture. As mentioned above, it is also desirable that the lipophilic microphase-forming material be dispersed as homogeneously as possible
25 throughout the molten mixture. When the temperature of the molten mixture is below the melting point of both the drug and the concentration-enhancing polymer, the molten excipients, concentration-enhancing polymer, and drug are preferably sufficiently soluble in each other that a substantial portion of the drug disperses in the concentration-enhancing polymer or excipients. It is often preferred that the mixture be heated above
30 the lower of the melting point of the concentration-enhancing polymer, the drug, and the lipophilic microphase-forming material, if present.

Generally, the processing temperature may vary from 50°C up to about 200°C or higher, depending on the melting point of the drug and polymer, which is a function of the polymer grade selected, and the lipophilic microphase-forming material, if
35 present. However, the processing temperature should not be so high that an unacceptably high level of degradation of the drug or polymer occurs. In some cases,

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the molten mixture should be formed under an inert atmosphere to prevent degradation of the drug and/or polymer at the processing temperature. When relatively high temperatures are used, it is often preferable to minimize the time that the mixture is at the elevated temperature to minimize degradation.

5 The molten mixture may also comprise an excipient that will reduce the melting temperature of the composition (either the drug and/or the polymer), allowing processing at lower temperature. When such excipients have low volatility and substantially remain in the mixture upon solidification, they generally can comprise up to 30 wt% of the molten mixture. For example, a plasticizer may be added to the
10 composition to reduce the melting temperature of the polymer. Examples of plasticizers include water, triethylcitrate, triacetin, and dibutyl sebacate. Volatile agents that dissolve or swell the polymer, such as acetone, water, methanol, and ethyl acetate, may also be added in low quantities to reduce the melting point of the composition. When such
15 volatile excipients are added, at least a portion, up to essentially all of such excipients, may evaporate in the process of or following conversion of the molten mixture to a solid mixture. In such cases, the processing may be considered to be a combination of solvent processing and melt-congealing or melt-extrusion. Removal of such volatile excipients from the molten mixture can be accomplished by breaking up or atomizing the molten mixture into small droplets and contacting the droplets with a fluid such that the
20 droplets both cool and lose all or part of the volatile excipient. Examples of other excipients that can be added to the composition to reduce the processing temperature include low molecular weight polymers or oligomers, such as polyethylene glycol, polyvinylpyrrolidone, and poloxamers; fats and oils, including mono-, di-, and triglycerides; natural and synthetic waxes, such as carnauba wax, beeswax,
25 microcrystalline wax, castor wax, and paraffin wax; long-chain alcohols, such as cetyl alcohol and stearyl alcohol; and long-chain fatty acids, such as stearic acid. When the lipophilic microphase-forming material is added to the molten mixture, the lipophilic microphase-forming material may act to reduce the melting temperature of the composition. As mentioned above, when the excipient added is volatile, it may be
30 removed from the mixture while still molten or following solidification to form the solid amorphous dispersion.

 Virtually any process may be used to form the molten mixture. One method involves melting the concentration-enhancing polymer in a vessel and then adding the drug, and optionally, the lipophilic microphase-forming material, to the molten
35 polymer. Another method involves melting the drug, and optionally, the lipophilic microphase-forming material, in a vessel and then adding the concentration-enhancing polymer. As the lipophilic microphase-forming material may often be a liquid at room

temperature or may have a low melting point relative to the polymer, it is often preferred to use this last method. In yet another method, a solid blend of the drug, concentration-enhancing polymer, and optionally, the lipophilic microphase-forming material, may be added to a vessel and the blend heated to form the molten mixture. When the lipophilic microphase-forming material is included in the dispersion, it may be mixed with the drug and polymer before or after forming the molten mixture. Alternatively, the lipophilic microphase-forming material may first be melted, if it is not already liquid, and the drug and polymer added to the molten lipophilic microphase-forming material to form the molten mixture.

Once the molten mixture is formed, it may be mixed to ensure the drug is homogeneously distributed throughout the molten mixture. Such mixing may be done using mechanical means, such as overhead mixers, magnetically driven mixers and stir bars, planetary mixers, and homogenizers. Optionally, when the molten mixture is formed in a vessel, the contents of the vessel can be pumped out of the vessel and through an in-line or static mixer and then returned to the vessel. The amount of shear used to mix the molten mixture should be sufficiently high to ensure uniform distribution of the drug in the molten mixture. The molten mixture can be mixed from a few minutes to several hours, the mixing time being dependent on the viscosity of the mixture and the solubility of the drug and any optional excipients in the concentration-enhancing polymer.

An alternative method of preparing the molten mixture is to use two vessels, melting the drug and optionally, the lipophilic microphase-forming material in the first vessel and the concentration-enhancing polymer and optionally, lipophilic microphase-forming material in a second vessel. The two melts are then pumped through an in-line static mixer or extruder to produce the molten mixture that is then rapidly solidified.

Alternatively, the molten mixture can be generated using an extruder, such as a single-screw or twin-screw extruder, both well known in the art. In such devices, a solid, or semi-solid mixture of the composition is fed to the extruder whereby the combination of heat and shear forces within the extruder produce a uniformly mixed molten mixture, which can then be rapidly solidified to form the solid amorphous dispersion. The solid feed can be prepared using methods well known in the art for obtaining solid mixtures with high content uniformity. Alternatively, the extruder may be equipped with two or more feeders, allowing the drug, and optionally the lipophilic microphase-forming material, to be fed to the extruder through one feeder and the polymer, and optionally the lipophilic microphase-forming material, through the other. Other excipients to reduce the processing temperature as described above may be

included in the solid feed, or in the case of liquid excipients, such as water, may be injected into the extruder using methods well-known in the art.

5 The extruder should be designed such that it produces a molten mixture with the drug uniformly distributed throughout the composition. The various zones in the extruder should be heated to appropriate temperatures to obtain the desired extrudate temperature as well as the desired degree of mixing or shear, using procedures well known in the art.

10 When the drug has a high solubility in the concentration-enhancing polymer, and optionally the lipophilic microphase-forming material, a lower amount of mechanical energy will be required to form the dispersion. In such cases, when the melting point of the undispersed drug is greater than the melting point of the undispersed concentration-enhancing polymer, and optionally the lipophilic microphase-forming material, the processing temperature may be below the melting temperature of the undispersed drug but greater than the melting point of the polymer, and optionally the lipophilic microphase-forming material, since the drug will dissolve into the molten polymer, and if present, the lipophilic microphase-forming material. When the melting point of the undispersed drug is less than the melting point of the undispersed concentration-enhancing polymer, and optionally the lipophilic microphase-forming material, the processing temperature may be above the melting point of the undispersed drug but below the melting point of the undispersed concentration-enhancing polymer since the molten drug will dissolve in the polymer, and optionally the lipophilic microphase-forming material, or be absorbed into the polymer.

25 When the drug has a low solubility in the polymer and optional lipophilic microphase-forming material, a higher amount of mechanical energy may be required to form the dispersion. Here, the processing temperature may need to be above the melting point of the drug and the polymer. As mentioned above, alternatively, a liquid or low-melting point excipient may be added that promotes melting or the mutual solubility of the concentration-enhancing polymer and the drug. A high amount of mechanical energy may be needed to mix the drug and the polymer to form a dispersion. Typically, 30 the lowest processing temperature and an extruder design that imparts the lowest amount of mechanical energy (e.g., shear) that produces a satisfactory dispersion (substantially amorphous and substantially homogeneous) is chosen in order to minimize the exposure of the drug to harsh conditions.

35 Once the molten mixture of drug, concentration-enhancing polymer, and optionally the lipophilic microphase-forming material is formed, the mixture should be rapidly solidified to form the solid amorphous dispersion. Rapid solidification is only necessary when the drug and other materials in the molten mixture are not miscible. By

"rapidly solidified" is meant that the molten mixture is solidified sufficiently fast such that substantial phase separation of the drug from the other materials does not occur.

Typically, this means that the mixture should be solidified in less than about 10 minutes, preferably less than about 5 minutes, more preferably less than about 1 minute. If the mixture is not rapidly solidified, phase separation can occur, if the materials are not miscible at storage temperatures, resulting in the formation of drug-rich phases.

Solidification often takes place primarily by cooling the molten mixture to at least about 10°C and preferably at least about 30°C below its melting point. As mentioned above, solidification can be additionally promoted by evaporation of all or part of one or more volatile excipients or solvents. To promote rapid cooling and evaporation of volatile excipients, the molten mixture is often formed into a high surface area shape such as a rod or fiber or droplets. For example, the molten mixture can be forced through one or more small holes to form long thin fibers or rods or may be fed to a device, such as an atomizer such as a rotating disk, that breaks the molten mixture up into droplets from 1 µm to 1 cm in diameter. The droplets are then contacted with a relatively cool fluid such as air or nitrogen to promote cooling and evaporation.

Another method for forming solid amorphous dispersions is by "solvent processing," which consists of dissolution of the drug and one or more concentration-enhancing polymers, as well as, optionally, the one or more materials that make up the lipophilic microphase-forming material, in a common solvent. Optionally, the lipophilic microphase-forming material may also be dissolved or suspended in the solvent.

"Common" here means that the solvent, which can be a mixture of compounds, will dissolve the drug and the polymer(s). Although it need not completely dissolve the lipophilic microphase-forming material, it is often preferred to use a solvent in which the lipophilic microphase-forming material is also soluble. After both the drug, the polymer, and optionally the lipophilic microphase-forming material have been dissolved, the solvent is rapidly removed by evaporation or by mixing with a non-solvent. Exemplary processes are spray-drying, spray-coating (pan-coating, fluidized bed coating, etc.), and precipitation by rapid mixing of the polymer and drug solution with CO₂, water, or some other non-solvent.

The solvent may be removed through the process of spray-drying. The term spray-drying is used conventionally and broadly refers to processes involving breaking up liquid mixtures into small droplets (atomization) and rapidly removing solvent from the mixture in a container (spray-drying apparatus) where there is a strong driving force for evaporation of solvent from the droplets. The strong driving force for solvent evaporation is generally provided by maintaining the partial pressure of solvent in the spray-drying apparatus well below the vapor pressure of the solvent at the temperature

of the drying droplets. This is accomplished by either (1) maintaining the pressure in the spray-drying apparatus at a partial vacuum (e.g., 0.01 to 0.50 atm); (2) mixing the liquid droplets with a warm drying gas; or (3) both. In addition, a portion of the heat required for evaporation of solvent may be provided by heating the spray solution.

5 Solvents suitable for spray-drying can be any compound in which the drug and polymer are mutually soluble. If the lipophilic microphase-forming material is part of the dispersion, it may be soluble in the solvent or may be suspended in the solvent. Preferably, the solvent is volatile with a boiling point of 150°C or less. In addition, the solvent should have relatively low toxicity and be removed from the dispersion to a level
10 that is acceptable according to The International Committee on Harmonization (ICH) guidelines. Removal of solvent to this level may require a processing step such as tray-drying subsequent to the spray-drying or spray-coating process. Preferred solvents include alcohols such as methanol, ethanol, n-propanol, iso-propanol, and butanol; ketones such as acetone, methyl ethyl ketone and methyl iso-butyl ketone; esters such
15 as ethyl acetate and propylacetate; and various other solvents such as acetonitrile, methylene chloride, toluene, and 1,1,1-trichloroethane. Lower volatility solvents such as dimethyl acetamide or dimethylsulfoxide can also be used. Mixtures of solvents, such as 50% methanol and 50% acetone, can also be used, as can mixtures with water as long as the polymer and drug are sufficiently soluble to make the spray-drying process
20 practicable.

Generally, the temperature and flow rate of the drying gas is chosen so that the polymer/drug-solution droplets are dry enough by the time they reach the wall of the apparatus that they are essentially solid, and so that they form a fine powder and do not stick to the apparatus wall. The actual length of time to achieve this level of dryness
25 depends on the size of the droplets. Droplet sizes generally range from 1 µm to 500 µm in diameter, with 5 µm to 100 µm being more typical. The large surface-to-volume ratio of the droplets and the large driving force for evaporation of solvent leads to actual drying times of a few seconds or less, and more typically less than 0.1 second. Solidification times should be less than 100 seconds, preferably less than a few seconds,
30 and more preferably less than 1 second. The size of droplets formed during the spray-drying process are typically less than about 200 µm in diameter. The resultant solid particles thus formed are generally less than about 200 µm in diameter.

Following solidification, the solid powder typically stays in the spray-drying chamber for about 5 to 60 seconds, further evaporating solvent from the solid powder.
35 The final solvent content of the solid dispersion as it exits the dryer should be low, since this reduces the mobility of the drug molecules in the dispersion, thereby improving its

stability. Generally, the solvent content of the dispersion as it leaves the spray-drying chamber should be less than 10 wt% and preferably less than 2 wt%. In some cases, it may be preferable to spray a solvent or a solution of a polymer or other excipient into the spray-drying chamber to form granules, so long as the dispersion is not adversely affected.

Spray-drying processes and spray-drying equipment are described generally in Perry's *Chemical Engineers' Handbook*, Sixth Edition (R. H. Perry, D. W. Green, J. O. Maloney, eds.) McGraw-Hill Book Co. 1984, pages 20-54 to 20-57. More details on spray-drying processes and equipment are reviewed by Marshall "Atomization and Spray-Drying," 50 *Chem. Eng. Prog. Monogr. Series 2* (1954). Further details of the spray drying procedure are disclosed in commonly owned Provisional U.S. Patent Applications Serial Nos. 60/354,080 and 60/353,986, the disclosures of which are incorporated herein by reference (Attorney Docket Nos. PC23195 and PC23203).

The amount of polymer relative to the amount of drug present in the solid amorphous dispersion depends on the drug and polymer and may vary widely from a drug-to-polymer weight ratio of from 0.01 to about 4 (e.g., 1 wt% drug to 80 wt% drug in the absence of other excipients in the dispersion). However, in most cases it is preferred that the drug-to-polymer ratio is greater than about 0.05 (4.8 wt% drug in the absence of other excipients) and less than about 2.5 (71 wt% drug in the absence of other excipients). In some embodiments, the addition of the lipophilic microphase-forming material allows for higher drug loadings. Thus, the drug:polymer ratio may be at least 1.

The dispersion is usually in the form of small particles. The particles may be less than 500 μm in diameter, less than 100 μm in diameter, less than 50 μm in diameter, or less than 25 μm in diameter. When the dispersion is formed by spray-drying, the resulting dispersion is in the form of such small particles. When the dispersion is formed by other methods such by melt-congeal or melt-extrusion processes, the resulting dispersion may be sieved, ground, milled, or otherwise processed to yield a plurality of small particles.

In cases where the composition of the present invention is prepared by mixing the previously formed solid amorphous dispersion with the lipophilic microphase-forming material, the mixture can be prepared by any method that results in a uniform mixture of the dispersion and the lipophilic microphase-forming material. Mixing processes include physical mixing as well as wet- and dry-granulation and coating processes. The resulting mixture may be a solid composition comprising the dispersion suspended in the lipophilic microphase-forming material, a mixture of separate dispersion particles and lipophilic microphase-forming material particles interspersed with one another, a series of respective layers of dispersion and lipophilic microphase-

forming material, or any other mixture of dispersion and lipophilic microphase-forming material.

In many cases, to aid the dispersing of the lipophilic microphase-forming material in the use environment, it is often desirable to disperse the lipophilic microphase-forming material in a water soluble or water dispersable matrix prior to forming the mixture. Alternatively, the lipophilic microphase-forming material may be adsorbed to a water insoluble substrate such as dibasic calcium phosphate, calcium carbonate, microcrystalline cellulose, silicon dioxide calcium silicate; clays, such as kaolin (hydrated aluminum silicate), bentonite (hydrated aluminum silicate), hectorite and Veegum®; silicon dioxide (Cab-O-Sil® or Aerosil®); magnesium trisilicate; aluminum hydroxide; magnesium hydroxide, magnesium oxide or talc. Highly porous materials such as calcium silicate are preferred. When the lipophilic microphase-forming material is dispersed in a water dispersable matrix, the dispersion may be formed by any of the processes described previously for forming the polymer/drug dispersion including melt processes such as extrusion, solvent processes such as spray-drying, as well as conventional wet and dry granulation processes. Following forming the adsorbate dispersion or granule of lipophilic microphase-forming material the dispersion or granule containing the lipophilic microphase-forming material may then be blended with the polymer/drug dispersion.

When it is desired to adsorb (or absorb) the lipophilic microphase-forming material onto a solid substrate, the lipophilic microphase-forming material may be adsorbed onto the solid substrate using any conventional method. In one exemplary method, the substrate is initially dried to remove water. The lipophilic microphase-forming material is then combined with the substrate. The lipophilic microphase-forming material may be combined with the substrate by the use of a planetary mixer, a Z-blade mixer, a rotogranulator or similar equipment. Preferably, the amount of lipophilic microphase-forming material is kept sufficiently low so that the mixture of lipophilic microphase-forming material and solid substrate forms a free-flowing powder. The proportion of lipophilic microphase-forming material to solid substrate preferably is less than about 4:1 (wt:wt) lipophilic microphase-forming material to solid substrate. As the weight ratio of lipophilic microphase-forming material to substrate increases, the material becomes cake-like, and then oily or slurry-like. The particular ratio will depend on the porosity of the substrate and the nature of the lipophilic microphase-forming material. The lipophilic microphase-forming material may be diluted in a solvent such as methanol prior to adsorbing the lipophilic microphase-forming material to the solid substrate. The resulting slurry is dried, for example in a vacuum desiccator, to form a solid material

comprising the lipophilic microphase-forming material and substrate. This solid material may then be combined with the solid amorphous dispersion.

Mixing methods include convective mixing, shear mixing, or diffusive mixing. Convective mixing involves moving a relatively large mass of material from one part of a powder bed to another, by means of blades or paddles, revolving screw, or an inversion of the powder bed. Shear mixing occurs when slip planes are formed in the material to be mixed. Diffusive mixing involves an exchange of position by single particles. These mixing processes can be performed using equipment in batch or continuous mode. Tumbling mixers (e.g., twin-shell) are commonly used equipment for batch processing. Continuous mixing can be used to improve composition uniformity. Continuous mixers include "in-line" mixers and extruders. Extruders may be single screw or twin-screw. Twin-screw extruders may turn in the same or opposite direction.

Milling may also be employed to combine the dispersion and the lipophilic microphase-forming material. Milling is the mechanical process of reducing the particle size of solids (comminution). Because in some cases milling may alter crystalline structure and cause chemical changes for some materials, milling conditions are generally chosen which do not alter the physical form of the dispersion in the sense that the drug in the dispersion is no longer amorphous. The most common types of milling equipment are the rotary cutter, the hammer, the roller, and fluid energy mills. Equipment choice depends on the characteristics of the ingredients in the composition (e.g., soft, abrasive, or friable). Wet- or dry-milling techniques can be chosen for several of these processes, also depending on the characteristics of the ingredients (e.g. dispersion stability in solvent). The milling process may serve simultaneously as a mixing process if the feed materials are heterogeneous. Conventional mixing and milling processes suitable for use in the present invention are discussed more fully in Lachman, et al., *The Theory and Practice of Industrial Pharmacy* (3d Ed. 1986).

The dispersion and lipophilic microphase-forming material may also be combined by dry- or wet-granulating processes as long as granulating conditions are chosen such that the dispersion remains a solid amorphous dispersion. In addition to the physical mixtures described above, the compositions of the present invention may constitute any device or collection of devices that accomplishes the objective of delivering to the use environment both the dispersion and the lipophilic microphase-forming material.

In a particularly preferred embodiment, the polymer/drug dispersion in lipophilic microphase-forming material, or alternatively, a solid amorphous dispersion of polymer, drug and lipophilic microphase-forming material, are incorporated into the same solid dosage form such as a capsule or tablet. In order to deliver the desired dose of

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drug to the use environment, more than one such capsule or tablet may be dosed. A solid amorphous dispersion of drug and polymer, together with the lipophilic microphase-forming material, may both be delivered "immediately" to the use environment, meaning that both are substantially released from the dosage form in less than about 30 minutes, or one or both of the dispersion and lipophilic microphase-forming material may be delivered over a period of 1 to 20 hours in a sustained, delayed or pulsatile fashion. Thus, the dosage form may be considered a controlled release dosage form in which the dispersion, the lipophilic microphase-forming material or both the dispersion and the lipophilic microphase-forming material are delivered to the use environment over a 1- to 20-hour period.

Thus, in the case of oral administration to an animal, the dosage form may constitute a layered tablet wherein one or more layers comprise the dispersion and one or more other layers comprise the lipophilic microphase-forming material. Alternatively, the dosage form may be a coated tablet wherein the tablet core comprises the dispersion and the coating comprises the lipophilic microphase-forming material or wherein the tablet core comprises the lipophilic microphase-forming material and the coating comprises the dispersion (which may be formed during the coating process). In addition, the dispersion and the lipophilic microphase-forming material may even be present in different dosage forms such as tablets or beads and may be administered simultaneously or separately as long as both the dispersion and lipophilic microphase-forming material are administered in such a way that the dispersion and lipophilic microphase-forming material are both present in the use environment. In yet another specific embodiment, the polymer/drug dispersion may be dissolved or suspended in an aqueous vehicle containing the lipophilic microphase-forming material and the aqueous suspension subsequently dosed to the use environment.

CONCENTRATION-ENHANCEMENT

The compositions of the present invention provide concentration-enhancement in a use environment relative to one or more control compositions. The compositions of the present invention may provide concentration-enhancement relative to a first control composition consisting essentially of the solid amorphous dispersion of the drug and polymer but without any lipophilic microphase forming material present. Thus, the lipophilic microphase forming material is either present in the composition or co-administered in a sufficient amount to provide concentration enhancement (as described more fully below) relative to a first control consisting essentially of an equivalent amount of the solid amorphous dispersion of drug and concentration-enhancing polymer but with no lipophilic microphase forming material present. That is,

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the first control composition is identical to the composition comprising the solid amorphous dispersion and the lipophilic microphase-forming material except for the absence of the lipophilic microphase-forming material.

Alternatively, the compositions of the present invention provide
5 concentration enhancement relative to a second control composition consisting essentially of the same lipophilic microphase-forming material combined with undispersed crystalline drug in an amount equivalent to the amount of drug in the dispersion of the test composition, but with no concentration-enhancing polymer present. Thus, the second control composition is identical to the composition of the invention
10 except that (1) the drug is in the form of undispersed crystalline drug rather than dispersed in the concentration-enhancing polymer and (2) there is no concentration-enhancing polymer present. In cases where more than one crystal form of the drug is known, the control composition consists of the crystalline form that is most thermodynamically stable at ambient conditions (25°C and 50% relative humidity). In
15 cases where no crystalline form of the drug is known, undispersed amorphous drug may be substituted for crystalline drug.

At a minimum, compositions of the present invention provide concentration enhancement in a use environment relative to at least one of the two above controls. Preferably, compositions of the present invention will provide
20 concentration enhancement in a use environment relative to both of the above two controls.

Compositions comprising an amorphous dispersion and lipophilic microphase-forming material provide concentration-enhancement in either an *in vivo* or *in vitro* use environment. In an *in vivo* use environment, the concentration-enhancement
25 may result in either enhanced relative bioavailability and/or a more regular fed/fasted bioavailability ratio (that is, a fed/fasted bioavailability ratio closer to 1). In an *in vitro* use environment, concentration enhancement may be either enhanced drug concentration in highly mobile drug species, reduced precipitate, enhanced maximum drug concentration, or enhanced dissolution area under the concentration versus time curve (AUC).

As used herein, a "use environment" can be either the *in vivo* environment
30 of the GI tract, subdermal, intranasal, buccal, intrathecal, ocular, Intraaural, subcutaneous spaces, vaginal tract, arterial and venous blood vessels, pulmonary tract or intramuscular tissue of an animal, such as a mammal and particularly a human, or the *in vitro* environment of a test solution, such as phosphate buffered saline (PBS).
35 Concentration enhancement may be determined through either *in vivo* tests or through *in vitro* dissolution tests. A composition of the present invention meets the concentration enhancement criteria in at least one of the above test environments.

In one aspect, the compositions comprising an amorphous dispersion and lipophilic microphase-forming material provide improved relative bioavailability relative to either the first control composition, the second control composition, or preferably both. Relative bioavailability may be tested *in vivo* in animals or humans using conventional methods for making such a determination. An *in vivo* test, such as a crossover study, may be used to determine whether a test composition provides an enhanced relative bioavailability compared with one or both control compositions. It is to be understood by those skilled in the art that such *in vivo* tests are conventionally carried out under fasted conditions. In an *in vivo* crossover study a "test composition" of dispersion and lipophilic microphase-forming material is dosed to half a group of test subjects and, after an appropriate washout period (e.g., one week) the same subjects are dosed with a control composition. As described above, the control composition may be either the first control composition which consists of the amorphous dispersion with no lipophilic microphase-forming material present, or the second control composition, which consists of an equivalent amount of the drug in undispersed crystalline form and an equivalent amount of the lipophilic microphase-forming material but with no concentration-enhancing polymer present. The other half of the group is dosed with the control composition first, followed by the test composition. The relative bioavailability is measured as the concentration in the blood (serum or plasma) versus time area under the curve (AUC) determined for the test group divided by the AUC in the blood provided by the control composition. Preferably, this test/control ratio is determined for each subject, and then the ratios are averaged over all subjects in the study. *In vivo* determinations of AUC can be made by plotting the serum or plasma concentration of drug along the ordinate (y-axis) against time along the abscissa (x-axis).

To demonstrate improved bioavailability relative to the first control composition and the second control composition, a "three-way *in vivo* crossover" study may be conducted where the three compositions are the test composition, the first control composition and the second composition.

A preferred embodiment is one in which the relative bioavailability of the test composition is at least 1.25 relative to either the first control composition or the second control composition. (That is, the AUC in the blood provided by the test composition is at least 1.25-fold the AUC provided by the control composition.) The relative bioavailability may be at least 2.0, and more preferably at least 3.0, relative to either control composition. The determination of AUCs is a well-known procedure and is described, for example, in Welling, "Pharmacokinetics Processes and Mathematics," ACS Monograph 185 (1986). An even more preferred embodiment of the present invention is one for which the relative bioavailability of the test composition is at least

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1.25-fold relative to both the first control composition and the second control composition.

Alternatively, in another separate aspect, the compositions comprising an amorphous dispersion and lipophilic microphase-forming material provide more regular absorption. In this aspect, the compositions provide a fed/fasted bioavailability ratio that is near 1.0. By "fed/fasted bioavailability ratio" is meant the AUC in the blood provided by a composition dosed to a subject in the fed state, divided by the AUC in the blood provided by the same composition dosed to a subject in the fasted state. By "subject in the fed state" is meant a subject who has eaten a Food and Drug Administration (FDA)-recommended standard high fat breakfast within a period of twenty minutes, and then ingested (i.e., swallowed) the test dosage form essentially immediately thereafter. A standard high-fat breakfast consists of, for example, two eggs fried in one tablespoon of butter, two strips of bacon, six ounces of hash brown potatoes, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces of whole milk. This standard high-fat breakfast contains approximately 964 calories, 54% supplied as fat (58 gm) and 12% supplied as protein, calculated using the monograph "Nutritive Value of Foods", U.S. Department of Agriculture Home and Garden Bulletin Number 72. Additional food can also be consumed within the twenty-minute period and the subject still qualifies as "fed". A "subject in the fasted state" for purposes of definition is one who has not eaten for at least eight hours, typically overnight, prior to ingestion of the dosage form.

Thus, a preferred composition of the present invention comprising a dispersion and a lipophilic microphase forming material provides a fed/fasted bioavailability ratio of from 0.5 to 2.0. Preferably, the compositions provide a fed/fasted bioavailability ratio of from 0.67 to 1.5, and more preferably of from 0.8 to 1.25. Preferably, the composition of the present invention provides a fed/fasted bioavailability ratio that is closer to 1 than at least one of the first control compositions and the second composition, more preferably both compositions.

Alternatively, the concentration-enhancement provided by the compositions of the present invention may be determined in *in vitro* dissolution tests in an appropriate use environment. It has been determined that enhanced drug concentration in *in vitro* dissolution tests in PBS solution is a good indicator of *in vivo* performance and bioavailability. By "PBS solution" is meant an aqueous solution comprising 20 mM sodium phosphate (Na_2HPO_4), 47 mM potassium phosphate (KH_2PO_4), 87 mM NaCl, and 0.2 mM KCl, adjusted to pH 6.5 with NaOH. In particular, a composition of the present invention may be dissolution-tested by adding it to PBS

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solution and agitating to promote dissolution. A composition of the invention is one which meets the criteria set out below when dosed to PBS solution.

In one aspect, the compositions comprising a dispersion and a lipophilic microphase forming material, following introduction to an aqueous use environment, provide a concentration of "highly mobile" drug that is at least 2-fold the concentration of highly mobile drug provided by either the first control composition or the second control composition. Preferably, the concentration of highly mobile drug provided by the composition is at least 3-fold, more preferably at least 4-fold the concentration of highly mobile drug provided by either the first control composition or the second control composition. Preferred embodiments meet these criteria with both the first control composition and the second control composition.

By "highly mobile" is meant drug that is present either as free drug or in a lipophilic microphase. Drug that is highly mobile may be quantified using analytical techniques capable of measuring the concentration of drug in solution that is not in the form of polymer/drug assemblies or in precipitate. For example, a nuclear magnetic resonance (NMR) technique may be used, since the NMR measurement only yields a well-resolved signal for species that are sufficiently small or mobile that they may rapidly rotate. In particular, the NMR signal has been found to be proportional to the amount of highly mobile drug; that is, free drug and any drug that may be present in a mobile, solvated non-aggregated state such as in lipophilic microphases but not drug present in large polymer/drug assemblies. Highly mobile drug may also be quantified through permeation analysis in which the rate of drug transport through a dialysis or other suitable membrane is proportional to the free drug concentration.

Alternatively, the compositions comprising a dispersion and a lipophilic microphase forming material provide concentration enhancement by reducing the mass of precipitate formed in the use environment relative to the control composition. Reducing the mass of precipitate results in an increase in the amount of drug present in drug forms that are more labile and mobile, resulting in an increase in relative bioavailability. As used herein, the "precipitate ratio" is defined as the mass of drug present in the precipitate obtained when a first control composition (e.g., the solid amorphous dispersion alone) is administered to an aqueous use environment divided by the mass of drug present in the precipitate obtained when a test composition comprising the solid amorphous dispersion and lipophilic microphase-forming material is administered to an equivalent amount of the same use environment. Thus, if 30 mg of drug is present in the precipitate formed when a control composition is administered to a test medium and 20 mg of drug is present in the precipitate formed when a test composition is administered to the same test medium, the precipitate ratio is equal to 1.5

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(30/20). The compositions comprising a dispersion and a lipophilic microphase forming material, following introduction to an aqueous environment of use, provide a precipitate ratio that is at least 1.25 relative to the first control composition previously described. Preferably, the composition of the present invention provides a precipitate ratio that is at least 2-fold, more preferably at least 3-fold relative to the control composition.

The amount of drug present in precipitate may be determined by any analytical technique that can quantitatively make such a determination. In one method, the amount of drug present in precipitate is determined by subtracting the total dissolved drug concentration from the theoretical concentration of drug if all of the drug added to the test medium had dissolved. As used herein, the term "total dissolved drug" refers to the total amount of drug dissolved in the aqueous solution, and includes drug present in the form of free drug, micelles, lipophilic microphases and polymer/drug assemblies. Specifically, this means that total dissolved drug may be determined by separating out any undissolved drug by centrifugation or filtration and then measuring the amount of drug remaining in the supernatant or filtrate. Total dissolved drug is typically taken as that material that either passes a 0.45 μ m syringe filter or, alternatively, the material that remains in the supernatant following centrifugation. Filtration can be conducted using a 13 mm, 0.45 μ m polyvinylidene difluoride syringe filter sold by Scientific Resources under the trademark TITAN®. Centrifugation is typically carried out in a polypropylene microcentrifuge tube by centrifuging at 13,000 G for 60 seconds. Other similar filtration or centrifugation methods can be employed and useful results obtained. For example, using other types of microfilters may yield values somewhat higher or lower ($\sim$ 10-40%) than that obtained with the filter specified above but will still allow identification of preferred compositions.

Alternatively, drug in precipitate may be determined by collecting the solids obtained upon centrifugation or filtration of the aqueous solution, dissolution of the solids in an appropriate solvent, such as methanol, dimethylsulfoxide, or dimethylacetamide, and then analyzing for the drug using any quantitative analytical technique such as HPLC or NMR.

In another alternative aspect, the composition comprising a solid amorphous dispersion and a lipophilic microphase forming material may provide a Maximum total dissolved Drug Concentration (MDC) that is at least 1.25-fold the MDC of either the first control composition or the second control composition. In other words, if the MDC provided by either control composition is 100 μ g/mL, then a composition comprising a dispersion and lipophilic microphase-forming material provides an MDC of at least 125 μ g/mL. More preferably, the MDC of drug achieved with the compositions of

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the present invention are at least 2-fold, and even more preferably at least 3-fold, that of either control composition. To facilitate testing, the maximum drug concentration may be taken as the maximum concentration achieved within 90 to 180 minutes following administration of the drug. Preferred compositions meet these criteria for both the first
5 control composition and the second control composition.

Alternatively, the compositions comprising a dispersion and a lipophilic microphase-forming material may provide in an aqueous use environment a total dissolved drug concentration versus time Area Under The Curve (AUC), for any period of at least 90 minutes between the time of introduction into the use environment and about
10 270 minutes following introduction to the use environment that is at least 1.25-fold that of either the first control composition or the second control composition. More preferably, the AUC achieved with the compositions of the present invention are at least 2-fold and more preferably at least 3-fold that of either control composition. Preferred compositions meet these criteria for both the first control composition and the second control
15 composition.

In a particularly preferred embodiment of the present invention, the inventors have found that certain compositions provide a surprisingly "synergistic enhancement" in the various concentration and bioavailability criteria described above. The "synergistic enhancement" is determined by comparing the performance of the test
20 composition of solid amorphous dispersion and lipophilic microphase-forming material to a "third control composition." The third control composition consists essentially of the undispersed drug alone in its thermodynamically lowest energy state, typically the most stable crystalline form or its amorphous form if a crystalline form is unknown. Preferred compositions of solid amorphous dispersions of drug and polymer and lipophilic
25 microphase-forming material exhibit synergistic enhancement by performing better than would be expected by simply adding the enhancement provided by a dispersion with the enhancement provided by the lipophilic microphase-forming material.

To determine synergy, it is necessary to determine the performance of the first control composition, the second control composition, and the third control
30 composition either in *in vivo* or in *in vitro* dissolution tests. The relative enhancement of the first control composition (e.g., the solid amorphous dispersion but with no lipophilic microphase-forming material) is determined with respect to the third control composition. For example, if the first control composition provides an AUC₉₀ (that is, the AUC obtained during the first 90 minutes following introduction of the composition to a use
35 environment) of 20,000 min*µg/ml and the third control composition provides an AUC₉₀ of 1,000 min*µg/ml, the first control composition has a relative enhancement of 20-fold.

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Likewise, the relative enhancement of the second control composition (e.g., the undispersed crystalline drug with lipophilic microphase-forming material but no concentration-enhancing polymer) is determined with respect to the third control composition. For example, if the second control composition provides an AUC_{90} of 40,000 $\text{min} \cdot \mu\text{g/ml}$ and the third control composition provides an AUC_{90} of 1,000 $\text{min} \cdot \mu\text{g/ml}$, the second control composition has a relative enhancement of 40-fold.

Compositions of the present invention provide synergistic enhancement when the relative enhancement provided by the test composition compared with the third control composition is greater than the sum of the relative enhancement provided by the first control composition and the relative enhancement provided by second control composition. Returning to the examples described above, if the first control composition provided a relative enhancement of 20-fold, and the second control composition provided a relative enhancement of 40-fold, the sum of their relative enhancements would be 60-fold. Thus, a test composition provides synergistic enhancement when it provides a relative enhancement of greater than 60-fold compared with the third control composition.

The synergistic enhancement may also be determined by comparing the relative bioavailability of the test composition, first control composition, and second control composition relative to the third control composition. Synergistic enhancement would be shown where the relative bioavailability of the test composition is greater than the sum of the relative bioavailability of the first control composition and the relative bioavailability of the second control composition. For example, if the first control composition provides a relative bioavailability of 1.5 with respect to the third control composition, and the second control composition provides a relative bioavailability of 2.0 with respect to the third control composition, the test composition shows synergistic enhancement when it has a relative bioavailability relative to the third control composition greater than 3.5.

In particular, the inventors have noted that synergistic enhancements in concentration are often obtained by compositions in which the lipophilic microphase-forming material is dispersed, along with the drug, in the concentration-enhancing polymer. Such compositions are highly preferred.

LOW-SOLUBILITY DRUGS

The drug is a "low-solubility drug," meaning that the drug may be either "substantially water-insoluble," which means that the drug has a minimum aqueous solubility at physiologically relevant pH (e.g., pH 1-8) of less than 0.01 mg/mL, "sparingly

water-soluble," that is, has an aqueous solubility up to about 1 to 2 mg/mL, or even low to moderate aqueous-solubility, having an aqueous-solubility from about 1 mg/mL to as high as about 20 to 40 mg/mL. In general, it may be said that the drug has a dose-to-aqueous solubility ratio greater than 10 mL, and more typically greater than 100 mL, where the drug solubility (mg/mL) is the minimum value observed in any physiologically relevant aqueous solution (e.g., those with pH values between 1 and 8) including USP simulated gastric and intestinal buffers, and dose is in mg. The dose-to-aqueous-solubility-ratio may be determined by simply dividing the dose (in mg) by the aqueous solubility (in mg/mL).

The use of the lipophilic microphase-forming material works particularly well for very low solubility drugs. Thus, the invention finds particular utility where the drug has a solubility of less than 100 $\mu\text{g/mL}$, and even greater utility where the solubility is less than 10 $\mu\text{g/mL}$.

In addition, the invention finds utility when the drug has a relatively high absorption rate constant. By "absorption rate constant" is meant a constant that describes the rate at which the drug is moved from the site of administration (e.g., the GI tract of an animal) to the extra-cellular compartment of the body. Absorption rate constants are generally described by zero-order or first-order models. See for example, Remington's *The Science and Practice of Pharmacy*, 20th Ed (2000). The invention finds particular utility when the drug has an absorption rate constant of at least 0.005 min^{-1} , more utility when the drug has an absorption rate constant of at least 0.01 min^{-1} , and even more utility when the drug has an absorption rate constant of at least 0.03 min^{-1} or higher.

Preferred classes of drugs include, but are not limited to, antihypertensives, antianxiety agents, anticoagulating agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, antineoplastics, beta blockers, anti-inflammatories, antipsychotic agents, cognitive enhancers, anti-atherosclerotic agents, cholesterol-reducing agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheimer's disease agents, antibiotics, anti-depressants, and antiviral agents, glycogen phosphorylase inhibitors, and cholesterol ester transfer protein inhibitors.

Each named drug should be understood to include the neutral form of the drug, pharmaceutically acceptable salts, as well as prodrugs. Specific examples of antihypertensives include prazosin, nifedipine, amlodipine besylate, trimazosin and doxazosin; specific examples of a blood glucose-lowering agent are glipizide and

chlorpropamide; a specific example of an anti-impotence agent is sildenafil and sildenafil citrate; specific examples of antineoplastics include chlorambucil, lomustine and echinomycin; a specific example of an imidazole-type antineoplastic is tubulazole; a specific example of an anti-hypercholesterolemic is atorvastatin calcium; specific examples of anxiolytics include hydroxyzine hydrochloride and doxepin hydrochloride; specific examples of anti-inflammatory agents include betamethasone, prednisolone, aspirin, piroxicam, valdecoxib, carprofen, celecoxib, flurbiprofen and (+)-N-(4-[3-(4-fluorophenoxy)phenoxy]-2-cyclopenten-1-yl)-N-hydroxyurea; a specific example of a barbiturate is phenobarbital; specific examples of antivirals include acyclovir, nelfinavir, and virazole; specific examples of vitamins/nutritional agents include retinol and vitamin E; specific examples of beta blockers include timolol and nadolol; a specific example of an emetic is apomorphine; specific examples of a diuretic include chlorthalidone and spironolactone; a specific example of an anticoagulant is dicumarol; specific examples of cardiotonics include digoxin and digitoxin; specific examples of androgens include 17-methyltestosterone and testosterone; a specific example of a mineral corticoid is desoxycorticosterone; a specific example of a steroidal hypnotic/anesthetic is alfaxalone; specific examples of anabolic agents include fluoxymesterone and methanstenolone; specific examples of antidepressant agents include sulpiride, [3,6-dimethyl-2-(2,4,6-trimethylphenoxy)pyridin-4-yl]-(1-ethylpropyl)-amine, 3,5-dimethyl-4-(3-pentoxyl-2-(2',4',6'-trimethylphenoxy)pyridine, pyroxidine, fluoxetine, paroxetine, venlafaxine and sertraline; specific examples of antibiotics include carbenicillin indanyl sodium, bacampicillin hydrochloride, troleandomycin, doxycycline hyclate, ampicillin and penicillin G; specific examples of anti-infectives include benzalkonium chloride and chlorhexidine; specific examples of coronary vasodilators include nitroglycerin and miflozine; a specific example of a hypnotic is etomidate; specific examples of carbonic anhydrase inhibitors include acetazolamide and chlorzamide; specific examples of antifungals include econazole, terconazole, fluconazole, voriconazole, and griseofulvin; a specific example of an antiprotozoal is metronidazole; specific examples of anthelmintic agents include thiabendazole and oxfendazole and morantel; specific examples of antihistamines include astemizole, levocabastine, cetirizine, decarboethoxylopatadine and cinnarizine; specific examples of antipsychotics include ziprasidone, olanzapine, thiothixene hydrochloride, fluspirilene, risperidone and penfluridol; specific examples of gastrointestinal agents include loperamide and cisapride; specific examples of serotonin antagonists include ketanserin and mianserin; a specific example of an anesthetic is lidocaine; a specific example of a hypoglycemic agent is acetohexamide; a specific example of an anti-emetic is dimenhydrinate; a specific example of an antibacterial is cotrimoxazole; a specific example of a dopaminergic agent is L-DOPA; specific

examples of anti-Alzheimer's Disease agents are THA and donepezil; a specific example of an anti-ulcer agent/H2 antagonist is famotidine; specific examples of sedative/hypnotic agents include chlordiazepoxide and triazolam; a specific example of a vasodilator is alprostadil; a specific example of a platelet inhibitor is prostacyclin; specific examples of ACE inhibitor/antihypertensive agents include enalaprilic acid, quinapril, and lisinopril; specific examples of tetracycline antibiotics include oxytetracycline and minocycline; specific examples of macrolide antibiotics include erythromycin, clarithromycin, and spiramycin; a specific example of an azalide antibiotic is azithromycin; specific examples of glycogen phosphorylase inhibitors include [R-(R'S')] 5-chloro-N-[2-hydroxy-3-(methoxymethylamino)-3-oxo-1-(phenylmethyl)propyl-1H-indole-2-carboxamide and 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-3-oxopropyl]amide; and specific examples of cholesterol ester transfer protein inhibitors include [2R,4S]-4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester, [2R,4S]-4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester, and [2R,4S]-4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.

CONCENTRATION-ENHANCING POLYMERS

The composition also includes a concentration-enhancing polymer. By "concentration-enhancing" is meant a polymer present in a sufficient amount so that the dispersion provides, at a minimum, either improved AUC, maximum drug concentration, or relative bioavailability relative to a control consisting of an equivalent amount of crystalline drug but with no concentration-enhancing polymer. (Concentration enhancement may be evaluated as described above, except that the dispersion would be the test composition and crystalline drug without any polymer present would be the control composition). Concentration-enhancing polymers should be pharmaceutically acceptable, and should have at least some solubility in aqueous solution at physiologically relevant pHs (e.g., 1-8). Almost any neutral or ionizable polymer that has an aqueous-solubility of at least 0.1 mg/mL over at least a portion of the pH range of 1-8 may be suitable.

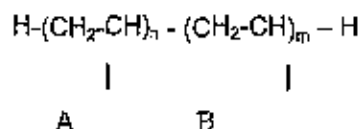
It is preferred that the concentration-enhancing polymer be "amphiphilic" in nature, meaning that the polymer has hydrophobic and hydrophilic portions. Amphiphilic polymers are preferred because it is believed that such polymers tend to have relatively strong interactions with the drug and may promote the formation of various types of polymer/drug assemblies in solution.

A particularly preferred class of amphiphilic polymers are those that are ionizable, the ionizable portions of such polymers, when ionized, constituting at least a portion of the hydrophilic portions of the polymer. For example, while not wishing to be bound by a particular theory, such polymer/drug assemblies may comprise hydrophobic drug clusters surrounded by the concentration-enhancing polymer with the polymer's hydrophobic regions turned inward towards the drug and the hydrophilic regions of the polymer turned outward toward the aqueous environment. Alternatively, depending on the specific chemical nature of the drug, the ionized functional groups of the polymer may associate, for example, via ion pairing or hydrogen bonds, with ionic or polar groups of the drug. In the case of ionizable polymers, the hydrophilic regions of the polymer would include the ionized functional groups. In addition, the repulsion of the like charges of the ionized groups of such polymers (where the polymer is ionizable) may serve to limit the size of the polymer/drug assemblies to the nanometer or submicron scale. Such drug/concentration-enhancing polymer assemblies in solution may well resemble charged polymeric micellar-like structures. In any case, regardless of the mechanism of action, the inventors have observed that such amphiphilic polymers, particularly ionizable cellulosic polymers such as those listed below, have been shown to interact with drug so as to maintain a higher concentration of drug in an aqueous use environment.

One class of polymers suitable for use with the present invention comprises non-ionizable (neutral) non-cellulosic polymers. Exemplary polymers include: vinyl polymers and copolymers having at least one substituent selected from the group consisting of hydroxyl, alkylacyloxy, and cyclicamido; polyvinyl alcohols that have at least a portion of their repeat units in the unhydrolyzed (vinyl acetate) form; polyvinyl alcohol polyvinyl acetate copolymers; polyvinyl pyrrolidone; polyoxyethylene-polyoxypropylene copolymers, also known as poloxamers; and polyethylene polyvinyl alcohol copolymers.

A preferred class of neutral non-cellulosic polymers comprises vinyl copolymers of at least one hydrophilic, hydroxyl-containing repeat unit and at least one hydrophobic, alkyl- or aryl-containing repeat unit. Such neutral vinyl copolymers are termed "amphiphilic hydroxyl-functional vinyl copolymers." Amphiphilic hydroxyl-functional vinyl copolymers are believed to provide high concentration enhancements due to the amphiphilicity of these copolymers which provide both sufficient hydrophobic groups to interact with the hydrophobic, low-solubility drugs and also sufficient hydrophilic groups to have sufficient aqueous solubility for good dissolution. The copolymeric structure of the amphiphilic hydroxyl-functional vinyl copolymers also allows their hydrophilicity and hydrophobicity to be adjusted to maximize performance with a specific low-solubility drug.

The preferred copolymers have the general structure:

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where A and B represent "hydrophilic, hydroxyl-containing" and "hydrophobic" substituents, respectively, and n and m represent the average number of hydrophilic vinyl repeat units and average number of hydrophobic vinyl repeat units respectively per polymer molecule. Copolymers may be block copolymers, random copolymers or they may have structures anywhere between these two extremes. The sum of n and m is generally from about 50 to about 20,000 and therefore the polymers have molecular weights from about 2,500 to about 1,000,000 daltons.

The hydrophilic, hydroxyl-containing repeat units, "A," may simply be hydroxyl (-OH) or it may be any short-chain, 1 to 6 carbon, alkyl with one or more hydroxyls attached thereto. The hydroxyl-substituted alkyl may be attached to the vinyl backbone via carbon-carbon or ether linkages. Thus exemplary "A" structures include, in addition to hydroxyl itself, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxymethoxy, hydroxyethoxy and hydroxypropoxy.

The hydrophobic substituent, "B," may simply be: hydrogen (-H), in which case the hydrophobic repeat unit is ethylene; an alkyl or aryl substituent with up to 12 carbons attached via a carbon-carbon bond such as methyl, ethyl or phenyl; an alkyl or aryl substituent with up to 12 carbons attached via an ether linkage such as methoxy, ethoxy or phenoxy; an alkyl or aryl substituent with up to 12 carbons attached via an ester linkage such as acetate, propionate, butyrate or benzoate. The amphiphilic hydroxyl-functional vinyl copolymers of the present invention may be synthesized by any conventional method used to prepare substituted vinyl copolymers. Some substituted vinyl copolymers such as polyvinyl alcohol/polyvinyl acetate are well known and commercially available.

A particularly convenient subclass of amphiphilic hydroxyl-functional vinyl copolymers to synthesize are those where the hydrophobic substituent "B" comprises the hydrophilic substituent "A" to which an alkylate or arylate group is attached via an ester linkage to one or more of the hydroxyls of A. Such copolymers may be synthesized by first forming the homopolymer of the hydrophobic vinyl repeat unit having the substituent B, followed by hydrolysis of a portion of the ester groups to convert a portion of the hydrophobic repeat units to hydrophilic, hydroxyl-containing repeat units having the substituent A. For example, partial hydrolysis of the homopolymer, polyvinylbutyrate,

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yields the copolymer, vinylalcohol/vinylbutyrate copolymer for which A is hydroxyl (-OH) and B is butyrate (-OOC-CH₂-CH₂-CH₃).

For all types of copolymers, the value of n must be sufficiently large relative to the value of m that the resulting copolymer is at least partially water soluble.

- 5 Although the value of the ratio, n/m varies depending on the identity of A and B, it is generally at least about 1 and more commonly about 2 or more. The ratio n/m can be as high as 200. When the copolymer is formed by hydrolysis of the hydrophobic homopolymer, the relative values of n and m are typically reported in "percent hydrolysis," which is the fraction (expressed as a percent) of the total repeat units of the
- 10 copolymer that are in the hydrolyzed or hydroxyl form. The percent hydrolysis, H, is given as

$$H = 100 \times \left(\frac{n}{n + m} \right)$$

- 15 Thus, vinylbutyrate/vinylalcohol copolymer (formed by hydrolysis of a portion of the butyrate groups) having a percent hydrolysis of 75% has an n/m ratio of 3. A particularly preferred family of amphiphilic hydroxyl-functional vinyl copolymers are those where A is hydroxyl and B is acetate. Such copolymers are termed vinylacetate/vinylalcohol copolymers. Some commercial grades are also sometimes
- 20 referred to simply as polyvinylalcohol. However, the true homopolymer, polyvinylalcohol is not amphiphilic and is almost entirely water insoluble. Preferred vinylacetate/vinylalcohol copolymers are those where H is between about 67% and 99.5%, or n/m has a value between about 2 and 200. The preferred average molecular weight is between about 2500 and 1,000,000 daltons and more preferably between
- 25 about 3000 and about 100,000 daltons.

- Another class of polymers suitable for use with the present invention comprises ionizable non-cellulosic polymers. Exemplary polymers include: carboxylic acid-functionalized vinyl polymers, such as the carboxylic acid functionalized polymethacrylates and carboxylic acid functionalized polyacrylates such as the
- 30 EUDRAGITS manufactured by Rohm Tech Inc., of Malden, Massachusetts; amine-functionalized polyacrylates and polymethacrylates; proteins such as gelatin and albumin; and carboxylic acid functionalized starches such as starch glycolate. Non-cellulosic polymers that are amphiphilic are copolymers of a relatively hydrophilic and a relatively hydrophobic monomer. Examples include acrylate and methacrylate

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copolymers. Exemplary commercial grades of such copolymers include the EUDRAGITS, which are copolymers of methacrylates and acrylates.

A preferred class of polymers comprises ionizable and neutral (or non-ionizable) cellulosic polymers with at least one ester- and/or ether-linked substituent in which the polymer has a degree of substitution of at least 0.05 for each substituent. It should be noted that in the polymer nomenclature used herein, ether-linked substituents are recited prior to "cellulose" as the moiety attached to the ether group; for example, "ethylbenzoic acid cellulose" has ethoxybenzoic acid substituents. Analogously, ester-linked substituents are recited after "cellulose" as the carboxylate; for example, "cellulose phthalate" has one carboxylic acid of each phthalate moiety ester-linked to the polymer and the other carboxylic acid unreacted.

It should also be noted that a polymer name such as "cellulose acetate phthalate" (CAP) refers to any of the family of cellulosic polymers that have acetate and phthalate groups attached via ester linkages to a significant fraction of the cellulosic polymer's hydroxyl groups. Generally, the degree of substitution of each substituent group can range from 0.05 to 2.9 as long as the other criteria of the polymer are met. "Degree of substitution" refers to the average number of the three hydroxyls per saccharide repeat unit on the cellulose chain that have been substituted. For example, if all of the hydroxyls on the cellulose chain have been phthalate substituted, the phthalate degree of substitution is 3. Also included within each polymer family type are cellulosic polymers that have additional substituents added in relatively small amounts that do not substantially alter the performance of the polymer.

Amphiphilic celluloses comprise polymers in which the parent cellulosic polymer has been substituted at any or all of the 3 hydroxyl groups present on each saccharide repeat unit with at least one relatively hydrophobic substituent. Hydrophobic substituents may be essentially any substituent that, if substituted to a high enough level or degree of substitution, can render the cellulosic polymer essentially aqueous insoluble. Examples of hydrophobic substituents include ether-linked alkyl groups such as methyl, ethyl, propyl, butyl, etc.; or ester-linked alkyl groups such as acetate, propionate, butyrate, etc.; and ether- and/or ester-linked aryl groups such as phenyl, benzoate, or phenylate. Hydrophilic regions of the polymer can be either those portions that are relatively unsubstituted, since the unsubstituted hydroxyls are themselves relatively hydrophilic, or those regions that are substituted with hydrophilic substituents. Hydrophilic substituents include ether- or ester-linked nonionizable groups such as the hydroxy alkyl substituents hydroxyethyl, hydroxypropyl, and the alkyl ether groups such as ethoxyethoxy or methoxyethoxy. Particularly preferred hydrophilic substituents are

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3A

those that are ether- or ester-linked ionizable groups such as carboxylic acids, thiocarboxylic acids, substituted phenoxy groups, amines, phosphates or sulfonates.

One class of cellulosic polymers comprises neutral polymers, meaning that the polymers are substantially non-ionizable in aqueous solution. Such polymers contain non-ionizable substituents, which may be either ether-linked or ester-linked. Exemplary ether-linked non-ionizable substituents include: alkyl groups, such as methyl, ethyl, propyl, butyl, etc.; hydroxy alkyl groups such as hydroxymethyl, hydroxyethyl, hydroxypropyl, etc.; and aryl groups such as phenyl. Exemplary ester-linked non-ionizable substituents include: alkyl groups, such as acetate, propionate, butyrate, etc.; and aryl groups such as phenylate. However, when aryl groups are included, the polymer may need to include a sufficient amount of a hydrophilic substituent so that the polymer has at least some water solubility at any physiologically relevant pH of from 1 to 8.

Exemplary non-ionizable (neutral) cellulosic polymers that may be used as the polymer include: hydroxypropyl methyl cellulose acetate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, and hydroxyethyl ethyl cellulose.

A preferred set of neutral cellulosic polymers are those that are amphiphilic. Exemplary polymers include hydroxypropyl methyl cellulose and hydroxypropyl cellulose acetate, where cellulosic repeat units that have relatively high numbers of methyl or acetate substituents relative to the unsubstituted hydroxyl or hydroxypropyl substituents constitute hydrophobic regions relative to other repeat units on the polymer.

A preferred class of cellulosic polymers comprises polymers that are at least partially ionizable at physiologically relevant pH and include at least one ionizable substituent, which may be either ether-linked or ester-linked. Exemplary ether-linked ionizable substituents include: carboxylic acids, such as acetic acid, propionic acid, benzoic acid, salicylic acid, alkoxybenzoic acids such as ethoxybenzoic acid or propoxybenzoic acid, the various isomers of alkoxyphthalic acid such as ethoxyphthalic acid and ethoxysophthalic acid, the various isomers of alkoxy nicotinic acid such as ethoxynicotinic acid, and the various isomers of picolinic acid such as ethoxypicolinic acid, etc.; thiocarboxylic acids, such as thioacetic acid; substituted phenoxy groups, such as hydroxyphenoxy, etc.; amines, such as aminoethoxy, diethylaminoethoxy, trimethylaminoethoxy, etc.; phosphates, such as phosphate ethoxy; and sulfonates, such as sulphonate ethoxy. Exemplary ester linked ionizable substituents include: carboxylic acids, such as succinate, citrate, phthalate, terephthalate, isophthalate, trimellitate, and the various isomers of pyridinedicarboxylic acid, etc.; thiocarboxylic acids, such as

thiosuccinate; substituted phenoxy groups, such as amino salicylic acid; amines, such as natural or synthetic amino acids, such as alanine or phenylalanine; phosphates, such as acetyl phosphate; and sulfonates, such as acetyl sulfonate. For aromatic-substituted polymers to also have the requisite aqueous solubility, it is also desirable that sufficient hydrophilic groups such as hydroxypropyl or carboxylic acid functional groups be attached to the polymer to render the polymer aqueous soluble at least at pH values where any ionizable groups are ionized. In some cases, the aromatic substituent may itself be ionizable, such as phthalate or trimellitate substituents.

Exemplary cellulosic polymers that are at least partially ionized at physiologically relevant pHs include: hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose succinate, hydroxypropyl cellulose acetate succinate, hydroxyethyl methyl cellulose succinate, hydroxyethyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, hydroxyethyl methyl cellulose acetate succinate, hydroxyethyl methyl cellulose acetate phthalate, carboxyethyl cellulose, carboxymethyl cellulose, carboxymethyl ethyl cellulose, cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, hydroxypropyl methyl cellulose acetate succinate phthalate, hydroxypropyl methyl cellulose succinate phthalate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, and ethyl picolinic acid cellulose acetate.

Exemplary cellulosic polymers that meet the definition of amphiphilic, having hydrophilic and hydrophobic regions include polymers such as cellulose acetate phthalate and cellulose acetate trimellitate where the cellulosic repeat units that have one or more acetate substituents are hydrophobic relative to those that have no acetate substituents or have one or more ionized phthalate or trimellitate substituents.

A particularly desirable subset of cellulosic ionizable polymers are those that possess both a carboxylic acid functional aromatic substituent and an alkylate substituent and thus are amphiphilic. Exemplary polymers include cellulose acetate

phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, and ethyl picolinic acid cellulose acetate.

Another particularly desirable subset of cellulosic ionizable polymers are those that possess a non-aromatic carboxylate substituent. Exemplary polymers include hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose succinate, hydroxypropyl cellulose acetate succinate, hydroxyethyl methyl cellulose acetate succinate, hydroxyethyl methyl cellulose succinate, hydroxyethyl cellulose acetate succinate and carboxymethyl ethyl cellulose. Of these cellulosic polymers that are at least partially ionized at physiologically relevant pHs, the inventors have found the following to be most preferred: hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate and carboxymethyl ethyl cellulose. The most preferred is hydroxypropyl methyl cellulose acetate succinate.

Another preferred class of polymers consists of neutralized acidic polymers. By "neutralized acidic polymer" is meant any acidic polymer for which a significant fraction of the "acidic moieties" or "acidic substituents" have been "neutralized"; that is, exist in their deprotonated form. By "neutralized acidic cellulosic polymers" is meant any cellulosic "acidic polymer" for which a significant fraction of the "acidic moieties" or "acidic substituents" have been "neutralized." By "acidic polymer" is meant any polymer that possesses a significant number of acidic moieties. In general, a significant number of acidic moieties would be greater than or equal to about 0.1 milliequivalents of acidic moieties per gram of polymer. "Acidic moieties" include any functional groups that are sufficiently acidic that, in contact with or dissolved in water, can at least partially donate a hydrogen cation to water and thus increase the hydrogen-ion concentration. This definition includes any functional group or "substituent," as it is termed when the functional group is covalently attached to a

polymer, that has a pK_a of less than about 10. Exemplary classes of functional groups that are included in the above description include carboxylic acids, thiocarboxylic acids, phosphates, phenolic groups, and sulfonates. Such functional groups may make up the primary structure of the polymer such as for polyacrylic acid, but more generally are covalently attached to the backbone of the parent polymer and thus are termed "substituents." Neutralized acidic polymers are described in more detail in commonly assigned copending provisional patent application U.S. Serial No. 60/300,256 entitled "Pharmaceutical Compositions of Drugs and Neutralized Acidic Polymers" filed June 22, 2001, the relevant disclosure of which is incorporated by reference.

The glass transition temperature of the dispersion is dependent on the glass transition temperatures of the materials comprising the dispersion. Since one of the primary materials used to form the dispersion is the concentration-enhancing polymer, and since the glass transition temperature of the drug is often relatively low, the concentration-enhancing polymer may be chosen so as to have a relatively high glass transition temperature. Thus, the polymer may have, when equilibrated with humid air having a relative humidity of about 50%, a glass transition temperature of at least 40°C, at least 70°C, or even greater than 100°C.

While specific polymers have been discussed as being suitable for use in the mixtures of the present invention, blends of such polymers may also be suitable.

Thus, the term "concentration-enhancing polymer" is intended to include blends of polymers in addition to a single species of polymer.

EXCIPIENTS AND DOSAGE FORMS

Although the key ingredient present in the compositions is simply the mixture of (1) the dispersion of drug and the concentration-enhancing polymer, and (2) the lipophilic microphase-forming material, the inclusion of other excipients in the composition may be useful. These excipients may be utilized in order to formulate the composition into tablets, capsules, suppositories, suspensions, powders for suspension, creams, transdermal patches, depots, and the like. The mixture may be added to other dosage form ingredients in essentially any manner that does not substantially alter the drug. The excipients may be either separate from the mixture and/or included within the mixture.

The addition of pH modifiers such as acids, bases, or buffers may be beneficial, retarding the dissolution of the composition (e.g., acids such as citric acid or succinic acid when the concentration-enhancing polymer is anionic) or, alternatively,

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enhancing the rate of dissolution of the composition (e.g., bases such as sodium acetate or amines when the polymer is anionic).

Conventional matrix materials, complexing agents, solubilizers, fillers, disintegrating agents (disintegrants), or binders may also be added as part of the composition itself or added by granulation via wet or mechanical or other means. These materials may comprise up to 90 wt% of the composition.

Examples of matrix materials, fillers, or diluents include lactose, mannitol, xylitol, microcrystalline cellulose, dibasic calcium phosphate (dihydrate and anhydrous), and starch.

Examples of disintegrants include sodium starch glycolate, sodium alginate, carboxy methyl cellulose sodium, methyl cellulose, and croscarmellose sodium, and crosslinked forms of polyvinyl pyrrolidone such as those sold under the trade name CROSPVIDONE (available from BASF Corporation).

Examples of binders include methyl cellulose, microcrystalline cellulose, starch, and gums such as guar gum, and tragacanth.

Examples of lubricants include magnesium stearate, calcium stearate, and stearic acid.

Examples of preservatives include sulfites (an antioxidant), benzalkonium chloride, methyl paraben, propyl paraben, benzyl alcohol and sodium benzoate.

Examples of suspending agents or thickeners include xanthan gum, starch, guar gum, sodium alginate, carboxymethyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, hydroxypropyl methyl cellulose, polyacrylic acid, silica gel, aluminum silicate, magnesium silicate, and titanium dioxide.

Examples of anticaking agents or fillers include silicon oxide and lactose.

Examples of solubilizers include ethanol, propylene glycol or polyethylene glycol.

Other conventional excipients may be employed in the compositions of this invention, including those excipients well-known in the art. Generally, excipients such as pigments, lubricants, flavorants, and so forth may be used for customary purposes and in typical amounts without adversely affecting the properties of the compositions. These excipients may be utilized in order to formulate the composition into tablets, capsules, suspensions, powders for suspension, creams, transdermal patches, and the like.

In particular, solid dosage forms such as immediate release tablets, controlled release tablets, delayed release tablets, chewable tablets and analogous capsules containing solid material are a preferred embodiment of this invention. Preferred dosage forms of this type generally comprise from 10 wt% lipophilic

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microphase-forming material up to 80 wt% lipophilic microphase-forming material as well as the solid amorphous dispersion of drug and concentration-enhancing polymer, together with other optional excipients.

It is conventionally thought that because lipophilic microphase-forming material are typically either low melting point or low T_g solids, or even liquids at room temperature, that they are not considered appropriate additives for such solid dosage forms except at low levels, typically less than about 5 wt% or less to promote wetting and dissolution of the tablet. However, the inventors have found that, contrary to such conventional wisdom, solid dosage forms with excellent properties can be made that have relatively high levels of lipophilic microphase-forming material. In order for such high lipophilic microphase-forming material levels to be utilized in such solid dosage forms, the inventors have found it desirable to adsorb at least a portion of the lipophilic microphase-forming material on a solid substrate or disperse the lipophilic microphase-forming material in a water soluble or water dispersible matrix. As mentioned earlier, appropriate adsorption substrates include materials such as silicon oxide, dibasic calcium phosphate, microcrystalline cellulose, and calcium silicate. Appropriate water soluble or water dispersible dispersion matrix materials include sugars such as sucrose and xylitol, organic acids such as citric acid or lactic acid, water soluble polymers such as polydextrose, polyethylene oxide, or dextrin. Particularly preferred dispersion matrix materials are the concentration-enhancing polymers previously described. In a particularly preferred embodiment, the lipophilic microphase-forming material is dispersed along with drug in the concentration-enhancing polymer. An added advantage of this embodiment, particularly when the lipophilic microphase-forming material is liquid at temperatures below about 50°C, is that relatively high levels of lipophilic microphase-forming material, up to about 50 wt% or in some cases even more, can often be added to the drug/polymer solid amorphous dispersion while still having the resulting material be a solid powder or granule at ambient conditions.

The compositions of the present invention may be delivered by a wide variety of routes, including, but not limited to, oral, nasal, rectal, vaginal, subcutaneous, intravenous, and pulmonary. Generally, the oral route is preferred.

Compositions of this invention may also be used in a wide variety of dosage forms for administration of drugs. Exemplary dosage forms are powders or granules that may be taken orally either dry or reconstituted by addition of water or other liquids to form a paste, slurry, suspension or solution; tablets; capsules; multiparticulates; and pills. Various additives may be mixed, ground, or granulated with the compositions of this invention to form a material suitable for the above dosage forms. In one preferred embodiment, the solid amorphous dispersion of drug and concentration-enhancing

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polymer is formulated as a dry powder and then, prior to administration, is dispersed in a vehicle that contains the lipophilic microphase-forming material.

The compositions of the present invention may be formulated in various forms such that they are delivered as a suspension of particles in a liquid vehicle. Such suspensions may be formulated as a liquid or paste at the time of manufacture, or they may be formulated as a dry powder with a liquid, typically water, added at a later time but prior to oral administration. Such powders that are constituted into a suspension are often termed sachets or oral powder for constitution (OPC) formulations. Such dosage forms can be formulated and reconstituted via any known procedure. The simplest approach is to formulate the dosage form as a dry powder that is reconstituted by simply adding water and agitating. Alternatively, the dosage form may be formulated as a liquid and a dry powder that are combined and agitated to form the oral suspension. In yet another embodiment, the dosage form can be formulated as two powders which are reconstituted by first adding water to one powder to form a solution to which the second powder is combined with agitation to form the suspension.

Generally, it is preferred that the dispersion of drug be formulated for long-term storage in the dry state as this promotes the chemical and physical stability of the drug.

Yet another method to deliver the dispersion and lipophilic microphase-forming material is to co-administer the dispersion and lipophilic microphase-forming material to an *in vivo* use environment. The solid amorphous dispersion and lipophilic microphase-forming material may each be added separately to the *in vivo* use environment. Thus, when dosed orally, the dispersion may be taken orally prior to the lipophilic microphase-forming material, at the same time, or after the lipophilic microphase-forming material has been taken orally. In general, if administered separately to an *in vivo* use environment, the solid amorphous dispersion and the lipophilic microphase-forming material should be administered within 15 minutes of each other.

Since the present invention has an aspect that relates to the treatment of a condition or disorder by treatment with a combination of a polymer/drug solid amorphous dispersion and a lipophilic microphase-forming material which may be co-administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: (1) a composition comprising a solid amorphous dispersion of drug and concentration-enhancing polymer; and (2) a composition comprising a lipophilic microphase-forming material. The amounts of (1) and (2) are such that, when co-administered separately, the condition or disorder is treated and/or remediated. The kit

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comprises a container for containing the separate compositions such as a divided bottle or a divided foil packet, wherein each compartment contains a plurality of dosage forms (e.g., tablets) comprising (1) or (2). Alternatively, rather than separating the active ingredient-containing dosage forms, the kit may contain separate compartments each of which contains a whole dosage which in turn comprises separate dosage forms. An example of this type of kit is a blister pack wherein each individual blister contains two (or more) tablets, one (or more) tablet(s) comprising pharmaceutical composition (1), and the second (or more) tablet(s) comprising pharmaceutical composition (2). Typically the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician. In the case of the instant invention a kit therefore comprises

(1) a therapeutically effective amount of a composition comprising a solid amorphous dispersion of a low-solubility drug and a concentration-enhancing polymer, in a first dosage form;

(2) a therapeutically effective amount of a composition comprising a lipophilic microphase-forming material, in a second dosage form; and

(3) a container for containing said first and second dosage forms.

An example of such a kit, alluded to above, is a so-called blister pack. Blister packs are well known in the packaging industry and are widely used for the packaging of pharmaceutical unit dosage forms such as tablets, capsules, and the like. Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably, the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. Tablet(s) or capsule(s) can then be removed via said opening.

It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen during which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, e.g., as follows

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"First Week, Monday, Tuesday, ...etc.... Second Week, Monday, Tuesday,...", etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also a daily dose of the first compound can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

Compositions of the present invention may be used to treat any condition which is subject to treatment by administering a drug.

Other features and embodiments of the invention will become apparent from the following examples which are given for illustration of the invention rather than for limiting its intended scope.

EXAMPLES

Dispersions 1-12

Solid amorphous dispersions of drugs and various concentration-enhancing polymers were prepared by spray-drying each solution of drug and polymer, using either a Niro PSD-1 spray drier or a "mini" spray drier. For Dispersions 1, 2, 9, 10, 11, and 12 the drug was [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester ("Drug 1"). For Dispersions 3 and 4, the drug was the hydrochloride salt form of ziprazidone ("Drug 2A"), while for Dispersion 5, the drug was the free base form of ziprazidone ("Drug 2B"). For Dispersions 6 and 7, the drug was 2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(3,3,3-trifluoropropyl)-, (4bS,7S,8aR) ("Drug 3"). For Dispersion 8, the drug was 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-3-[(3R,4S)-dihydroxypyrrolidin-1-yl)-(2R)-hydroxy-3-oxopropyl] amide ("Drug 4").

For Dispersion 1, an amorphous dispersion of Drug 1 and HPMCAS-MF was prepared using a Niro PSD-1 spray drier. First, a spray solution was formed containing 2.5 wt% Drug 1, 7.5 wt% HPMCAS-MF, and 90% acetone. The solution was spray-dried by directing a Niro two-fluid external-mix spray nozzle at 2.7 bar with a feed rate of 190 g/min into the stainless-steel chamber of a Niro PSD-1 spray-dryer, using nitrogen as the drying gas, maintained at a temperature of 137°C at the inlet; the drying gas and evaporated solvent exited the drier at 49°C.

The resulting solid amorphous dispersion was collected via a cyclone and then dried in a Gruenberg solvent tray-drier by spreading the spray-dried particles onto polyethylene-lined trays to a depth of not more than 1 cm and then drying them at 40°C

for 26 hours. After drying, Dispersion 1 contained 25 wt% Drug 1. The mean diameter of the dispersion particles was 15 Dm.

Dispersions 2, 3, 8, 10, and 12 were prepared using the same process as described for Dispersion 1, with the exception of the variables noted in Table 1, which summarizes the process conditions. Dispersion 12 was spray-dried using a Niro PSD-4 spray drier and a pressure nozzle (Delvan SDX111 (SA-38)).

Table 1

Disp No.	Drug No.	Drug Mass (g)	Polymer	Polymer Mass (g)	Solvent	Solvent Mass (g)	Nozzle Pressure (bar)	Feed Rate (g/min.)	T _{in} (°C)	T _{out} (°C)
1	1	8	HPMCAS-MF	24	Acetone	288	2.7	190	137	49
2	1	40	HPMCAS-MF	120.4	Acetone	840	2.7	200	139	50
3	2A	1	HPMCAS-HF	9	Methanol	490	7.7	50	120	60
8	4	150	HPMCAS-MF	150	Acetone	11,700	1.9	200	180	70
10	1	4.2	CMEC	7.8	Acetone	138	6.7	200	110	45
12	1	144	HPMCAS-MG	432	Acetone	3024	48	1867	110	45

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For Dispersion 4, an amorphous dispersion of ziprazidone, in the hydrochloride salt form, ("Drug 2A"), was prepared using the mini spray drier. The spray solution consisted of 0.14 wt% Drug 2A, 0.14 wt% HPMCAS-HF, and 99.72 wt% methanol. The solution was pumped into a "mini" spray-drying apparatus via a Cole Parmer 74900 series rate-controlling syringe pump at a rate of 1.3 mL/min. The drug/polymer solution was atomized through a Spraying Systems Co. two-fluid nozzle, Module No. SU1A using a heated stream of nitrogen (100°C). The spray solution was sprayed into an 11-cm diameter stainless steel chamber. The resulting solid amorphous dispersion was collected on filter paper, dried under vacuum, and stored in a desiccator. After drying, Dispersion 4 contained 50 wt% Drug 2 form A.

Dispersions 5, 6, 7, 9 and 11 were prepared using the same process as described for Dispersion 4, with the exception of the variables noted in Table 2, which summarizes the process conditions. Note that for Dispersion 11 the lipophilic microphase-forming material (Capmul MCM) was included in the solvent solution used to form the dispersion.

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Table 2

Disp. No.	Drug No.	Drug Mass (mg)	Polymer	Polymer Mass (mg)	Solvent	Solvent Mass (g)	Feed Rate (mL/min)	T _{in} (°C)
4	2A	500.2	HPMCAS-HF	500.2	Methanol	356.0	1.3	100
5	2B	500.2	HPMCAS-HF	500.1	Methanol	166.0	1.3	100
6	3	25.4	CAP	225.6	Acetone	25	1.3	100
7	3	25.3	HPMCAS-MF	225.0	Acetone	25	1.3	100
9	1	3.0	HPMC	27	MeOH/ Acetone 1/1	10	1.3	100
11	1	40	HPMCAS-MF	120	Acetone	12	1.0	90

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Table 3 summarizes the various dispersions used in the Examples which follow.

Table 3

Dispersion No.	Drug No.	Drug Conc. in Dispersion (active, wt%)	Polymer	Spray-drier Used to Prepare Dispersion
1	1	25	HPMCAS-MF	Niro PSD-1
2	1	25	HPMCAS-MF	Niro PSD-1
3	2A	10	HPMCAS-HF	Niro PSD-1
4	2A	50	HPMCAS-HF	Mini
5	2B	50	HPMCAS-HF	Mini
6	3	10	CAP	Mini
7	3	10	HPMCAS-MF	Mini
8	4	50	HPMCAS-MF	Niro PSD-1
9	1	10	HPMC	Mini
10	1	35	CMEC	Niro PSD-1
11	1	20	HPMCAS-MF	Mini
12	1	25	HPMCAS-MG	Niro PSD-1

- 5 HPMCAS-MF = medium fine grade (AQUAT-MF, Shin Etsu)
 HPMCAS-HF = high, fine grade (AQUAT-HF, Shin Etsu)
 HPMCAS-MG = medium, granular grade (AQUAT-MG, Shin Etsu)
 CAP = cellulose acetate phthalate (NF grade, Eastman Chemical Co.)
 1.0 HPMC = hydroxypropyl methyl cellulose (Methocel®) Dow Chemical Co.
 CMEC = carboxy methyl ethyl cellulose (Freund Industrial Co. Ltd., Tokyo, Japan)

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Example 1

In this example, a method is used to screen a candidate lipophilic microphase-forming material for suitability in providing concentration-enhancement. A simulated intestinal buffer solution was prepared by dissolving 6.8 g of potassium phosphate monobasic in 750 mL of deionized water with 85 mL 0.2 M sodium hydroxide. Water was added for a final volume of 1 L. The pH was adjusted to 6.8 ± 0.1 using 0.2 M sodium hydroxide.

Next, a lipophilic microphase-forming material was added to the buffer solution. 0.069 wt% polyethoxylated castor oil (CREMOPHOR RH40) and 0.031 wt% glyceryl mono- and di-caprylate (CAPMUL MCM) were added to the buffer to form the lipophilic microphase. 250 mL of the resulting solution was then added to a vessel in a VanKel dissolution testing apparatus with automatic sampling. The solution temperature was maintained at 37°C, and stirred with a paddle speed of 50 rpm.

After equilibration to 37°C, 120.3 mg of Dispersion 1 was added to the buffer containing the lipophilic microphase, resulting in a theoretical Drug 1 concentration of 120 µg/mL, if all of the drug had dissolved. Samples were collected at 5, 15, 20, 35, 45, 60, 75, 90, 120, 180 and 1200 minutes, centrifuged for 1 minute at 13,000 G, and then analyzed by high-performance liquid chromatography (HPLC) using a Waters Symmetry C₈ column. The mobile phase consisted of 0.2 vol% H₃PO₄ (in water)/methanol in the ratio of 15/85 vol/vol. Drug concentration was calculated by comparing UV absorbance at 256 nm to the absorbance of Drug 1 standards. Drug measured by HPLC includes free drug in solution, drug present in drug/polymer aggregates, and drug in the lipophilic microphase. The results are shown in Table 4.

Control 1

Control 1 consisted of dissolution of Dispersion 1 in intestinal buffer without the lipophilic microphase-forming material.

Table 4

Example No.	Dispersion	Time (min)	Drug 1 Concentration ($\mu\text{g/mL}$)	AUC ($\text{min} \cdot \mu\text{g/mL}$)
1	1	0	0	0
		5	42	100
		15	75	700
		20	85	1,100
		35	86	2,400
		45	87	3,200
		60	84	4,500
		75	85	5,800
		90	81	7,000
		120	78	9,400
		180	74	14,000
		1200	68	86,100
Control 1	1	0	0	0
		5	13	0
		15	21	200
		20	29	300
		35	39	800
		45	43	1,300
		60	45	1,900
		75	55	2,700
		90	59	3,500
		120	64	5,400
		180	59	9,000
		1200	40	59,400

5 The concentrations of drug obtained in these samples were used to determine the maximum concentration of drug (" $C_{\text{max}180}$ ") and the area under the concentration-versus-time curve (" AUC_{180} ") during the initial one hundred eighty minutes. The results are shown in Table 5.

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Table 5

Exp. No.	Dispersion	Drug	Lipophilic Microphase	Lipophile/ Drug Ratio	$C_{\text{max}180}$ ($\mu\text{g/mL}$)	AUC_{180} ($\text{min} \cdot \mu\text{g/mL}$)
1	1	1	Cremophor & Capmul	8.3	87	14,000
Control 1	1	1	none	--	64	9,000

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As can be seen from the data, the test performed with the lipophilic microphase-forming material (Example 1) provided a C_{max180} that was 1.4-fold that of the control, and an AUC_{180} that was 1.6-fold that of the control, indicating that the lipophilic microphase-forming material is suitable for use in the invention.

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Example 2

This example demonstrates that the lipophilic microphase forming material results in a significant amount of drug being present in lipophilic microphases and decreases the amount of drug present as precipitate. For Example 2, 4.0 mg of Dispersion 2 was added to Eppendorf tubes (in duplicate) containing 1.0 mL of deuterated PBS with the following lipophilic microphase-forming material: 1.09 mg Cremophore RH40 and 0.50 mg Capmul MCM. The solution also contained 0.11 mg 3-(trimethylsilyl)propionic-2,2,3,3- d_4 acid, sodium salt ("TSP"; a deuterated NMR reference standard). Next, 10 μ L of a 1.11 mg/mL ^{19} F trifluoroacetic acid standard solution ("TFA") was added to each tube. The solutions in the tubes were vortexed 1 minute, centrifuged 1 minute to remove bubbles, resuspended using a pipette, and transferred to an 8 mm NMR tube. Proton and ^{19} F spectra were recorded for separate identical samples using a Varian Gemini 2000 NMR instrument. By comparing the drug NMR spectra to the TFA standard, these spectra were used to determine the total amount of Drug 1 present as free drug in solution and drug in the lipophilic microphase. Drug in polymer/drug assemblies was determined by subtracting the concentration of highly mobile drug from the concentration of total dissolved drug. Free drug and drug in the lipophilic microphase together are referred to as "highly mobile" drug.

The precipitate was analyzed by centrifuging the solution and decanting the supernatant. The pellet was dried, then dissolved in DMSO and analyzed by NMR. The proton spectra was used to measure the polymer:drug ratio, and the concentration of drug in the precipitate was calculated from standards.

HPLC was used to determine the amount of total dissolved drug in the supernatant following centrifugation. The drug observed by HPLC consisted of free drug in solution, drug present in polymer/drug assemblies, and drug in the lipophilic microphase.

The results of these tests were used to determine the amount of Drug 1 in precipitate, in highly mobile species, or in polymer/drug assemblies in a solution of Example 2. The results are shown in Table 6.

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Control 2 consisted of Dispersion 2 in deuterated PBS without the lipophilic microphase.

Table 6

Exp. No.	Dispersion	Drug	Lipophilic Microphase	Lipophile/Drug Ratio	Drug in Precipitate (µg/mL)	Highly Mobile Drug (µg/mL)	Drug in Polymer/Drug Assemblies (µg/mL)
2	2	1	Cremophor & Capmul	1.59	50	400	550
Control 2	2	1	none	—	270	<3	730

These data show that the composition of the present invention provided concentration enhancement over the control. Specifically, the concentration of drug that is highly mobile, meaning either present as free drug or present in lipophilic microphases, for Example 2 was at least 133-fold that provided by Control 2. In addition, the precipitate ratio was 5.4 (270/50).

Examples 3-8

These examples show concentration-enhancement provided by several candidate lipophilic microphase-forming materials. For each of Examples 3-8, Dispersion 2 was added to a solution containing a lipophilic microphase-forming material. Example 3 consisted of Dispersion 2 in solution with a mixture of sodium taurocholic acid and 1-palmitoyl-2-oleyl-sn-glycero-3-phosphocholine ("NaTC/POPC"; 4/1 wt/wt). Example 4 consisted of Dispersion 2 in solution with NaTC/POPC and a mixture of Tween 80 and Capmul MCM (40/60 wt/wt). Example 5 consisted of Dispersion 2 in solution with NaTC/POPC and a mixture of Cremophor RH40 and Capmul MCM (40/60 wt/wt). Example 6 consisted of Dispersion 2 in solution with NaTC/POPC and a mixture of Cremophor RH40 and Capmul MCM (72/28 wt/wt). Example 7 consisted of Dispersion 2 in solution with NaTC/POPC and a mixture of Cremophor RH40 and Arlacel 20 (75/25 wt/wt). Example 8 consisted of Dispersion 2 in solution with NaTC/POPC and sodium lauryl sulfate (SLS).

For Example 3, to analyze the concentration of Drug 1 that was highly mobile using NMR, 18 mg of Dispersion 2 was added to 1.8 mLs of deuterated PBS containing 0.5 wt% NaTC/POPC, and the reference standards TSP and ¹⁹F TFA. For

Examples 4 through 8, 0.1 wt% of additional lipophilic microphase-forming materials were added. The results are shown in Table 7. Control 2 (Dispersion 2 in deuterated PBS without the lipophilic microphase) is shown again for comparison.

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Table 7

Ex. No.	Dispersion	Drug	Lipophilic Microphase	Lipophile/ Drug Ratio	Highly Mobile Drug ($\mu\text{g/mL}$)
3	2	1	NaTC/POPC	2.0	13.0
4	2	1	NaTC/POPC + Tween 80 & Capmul	2.4	24.9
5	2	1	NaTC/POPC + Cremophor & Capmul (40/60)	2.4	32.9
6	2	1	NaTC/POPC + Cremophor & Capmul (72/28)	2.4	86.7
7	2	1	NaTC/POPC + Cremophor & Arlacel	2.4	78.4
8	2	1	NaTC/POPC + SLS	2.4	22.8
Control 2	2	1	none	--	<1

The results show that addition of the lipophilic microphase results in greater than 13- to 86-fold increases in highly mobile drug concentrations compared with the control consisting of the dispersion alone. In addition, formulations with a lipophilic microphase-forming material in addition to NaTC/POPC (examples 4 to 8), showed concentration enhancement over the use of NaTC/POPC alone (Example 3), with concentrations of highly mobile drug 1.7-fold to 6.7-fold that provided by Example 3.

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Examples 9-12

These examples demonstrate concentration enhancement using several different candidate lipophilic microphase-forming materials. In these examples, Dispersion 1 was co-administered to PBS containing the lipophilic microphase-forming material TWEEN 80 (Example 9), Capmul MCM (Example 10), Cremophor RH40 (Example 11), or a 69/31 (wt/wt) mixture of Cremophor RH40/Capmul MCM (Example 12).

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For each of these tests, approximately 120 mg of Dispersion 1 was added to 250 mLs of PBS containing 0.5 wt% of the lipophilic microphase-forming material.

Table 8

Example No.	Dispersion	Time (min)	Drug 1 Concentration ($\mu\text{g/mL}$)	AUC ($\text{min} \cdot \mu\text{g/mL}$)
9	1	0	0	0
		5	11	0
		15	28	200
		20	33	400
		35	52	1,000
		45	64	1,600
		60	78	2,700
		75	86	3,900
		90	93	5,200
		120	97	8,100
		180	97	13,900
		1200	91	110,000
10	1	0	0	0
		5	73	200
		15	89	1,000
		20	90	1,400
		35	94	2,800
		45	94	3,800
		60	94	5,200
		75	91	6,600
		90	90	7,900
		120	84	10,500
		180	75	15,300
		1200	45	76,700
11	1	0	0	0
		5	9	0
		15	24	200
		20	32	300
		35	50	900
		45	62	1,500
		60	76	2,500
		75	89	3,800
		90	103	5,200
		120	114	8,500
		180	127	15,700
		1200	144	153,800

Table 8 (continued)

Example No.	Dispersion	Time (min)	Drug 1 Concentration ($\mu\text{g/mL}$)	AUC ($\text{min} \cdot \mu\text{g/mL}$)
12	1	0	0	0
		5	49	100
		15	92	800
		20	101	1,300
		35	111	2,900
		45	112	4,000
		60	113	5,700
		75	112	7,400
		90	112	9,100
		120	113	12,500
		180	111	19,200
		1200	125	139,700

- The concentrations of drug obtained in these samples were used to determine the $C_{\text{max}180}$ and the AUC_{180} during the initial one hundred eighty minutes. The results are shown in Table 9. The results for Control 1 are shown again for comparison.

Table 9

Exp. No.	Dispersion	Drug	Lipophilic Microphase	Lipophile/Drug Ratio	$C_{\text{max}180}$ ($\mu\text{g/mL}$)	AUC_{180} ($\text{min} \cdot \mu\text{g/mL}$)
9	1	1	Tween 80	41.7	97	13,900
10	1	1	Capmul	41.7	94	15,300
11	1	1	Cremophor	41.7	127	15,700
12	1	1	Cremophor & Capmul	41.7	113	19,200
Control 1	1	1	none	—	64	9,000

As can be seen from the data, Examples 9 through 12 provided $C_{\text{max}180}$ from 1.5-fold to 2.0-fold that of the control, and AUC_{180} from 1.5-fold to 2.1-fold that of the control.

Examples 13-15

These examples demonstrate concentration enhancement using Drug 2. The dispersions used in these Examples contained ziprazidone in either the hydrochloride salt form (Drug 2A), or the free base form (Drug 2B). Table 3 shows the compositions of Dispersions 3, 4, and 5 with Drug 2A or 2B. Examples 13 through 15

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consisted of Dispersions 3 through 5 in solutions with NaTC/POPC as the lipophilic microphase.

For these tests, 3.6 mg of Dispersion 3, 0.78 mg of Dispersion 4, or 0.72 mg of Dispersion 5, was added to microcentrifuge tubes in duplicate. A sufficient amount of each dispersion was added so that the concentration of drug would have been approximately 200 µg/mL, if all of the drug had dissolved. The tubes were placed in a 37°C temperature-controlled chamber, and 1.8 mL PBS containing 0.5 wt% NaTC/POPC was added to each respective tube. The samples were quickly mixed using a vortex mixer for about 60 seconds. The samples were centrifuged at 13,000 G at 37°C for 1 minute. The resulting supernatant solution was then sampled and diluted 1:6 (by volume) with water/methanol (1/4) and then analyzed by high-performance liquid chromatography (HPLC) using a Phenomenex QDS 20 column. The mobile phase consisted of 0.02 M KH₂PO₄, pH 3.0/acetonitrile in the ratio of 60/40 vol/vol. Drug concentration was calculated by comparing UV absorbance at 254 nm to the absorbance of Drug 2A or 2B standards. The contents of each respective tube were mixed on the vortex mixer and allowed to stand undisturbed at 37°C until the next sample was taken. Samples were collected at 4, 10, 20, 40, 90, and 1200 minutes. The results are shown in Table 10.

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Controls 3-5

Controls 3 through 5 consisted of Dispersions 3 through 5, respectively, in PBS without the lipophilic microphase.

Table 10

Example No.	Dispersion	Time (min)	Drug 2 Concentration ($\mu\text{g/mL}$)	AUC ($\text{min} \cdot \mu\text{g/mL}$)
13	3	0	0	0
		4	173	300
		10	168	1,400
		20	133	2,900
		40	108	5,300
		90	59	9,500
		1200	249	180,200
14	4	0	0	0
		4	12	0
		10	24	100
		20	43	500
		40	47	1,400
		90	26	3,200
		1200	15	26,800
15	5	0	0	0
		4	74	100
		10	42	500
		20	37	900
		40	21	1,500
		90	16	2,400
		1200	13	18,500
Control 3	3	0	0	0
		4	23	100
		10	21	200
		20	24	400
		40	20	900
		90	8	1,600
		1200	8	10,900
Control 4	4	0	0	0
		4	10	0
		10	13	100
		20	16	200
		40	13	500
		90	9	1,100
		1200	4	8,000
Control 5	5	0	0	0
		4	27	100
		10	23	200
		20	18	400
		40	13	700
		90	7	1,200
		1200	7	8,500

The concentrations of drug obtained in these samples were used to determine the $C_{\text{max}90}$ and the AUC_{90} during the initial ninety minutes. The results are shown in Table 11.

Table 11

Ex. No.	Dispersion	Drug	Lipophilic Microphase	Lipophile/ Drug Ratio	C _{max90} (µg/mL)	AUC ₉₀ (min*µg/mL)
13	3	2A	NaTC/POPC	25	173	9500
Control 3	3	2A	none	--	24	1600
14	4	2A	NaTC/POPC	25	47	3200
Control 4	4	2A	none	--	16	1100
15	5	2A	NaTC/POPC	25	74	2400
Control 5	5	2A	none	--	27	1200

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As can be seen from the data, Examples 3, 4, and 5 provided C_{max90} were 7.2-, 2.9-, and 2.7-fold that provided by each respective control. Examples 3, 4, and 5 provided AUC₉₀ values that were 5.9-, 2.9-, and 2.0-fold that provided by each respective control.

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- Examples 16-19

Examples 16 through 19 evaluate several lipophilic microphase-forming materials with dispersions containing different drugs and different polymers.

Examples 16 through 19 consisted of Dispersions 6 through 9 in solutions with NaTC/POPC or Tween 80 as the lipophilic microphase material. Table 3 shows the compositions of Dispersions 6 through 9.

For Examples 16 and 17, 3.6 mg of Dispersion 6 or Dispersion 7 was added to PBS containing 2 wt% Tween 80 (the Drug 3 concentration would have been 200 µg/mL if all of the drug dissolved). For Example 18, 3.6 mg of Dispersion 8 was added to PBS containing 0.5 wt% NaTC/POPC (the Drug 4 concentration would have been 1000 µg/mL if all of the drug dissolved). For Example 19, 1.8 mg of Dispersion 9 was added to PBS containing 0.5 wt% NaTC/POPC (the Drug 1 concentration would have been 100 µg/mL if all of the drug dissolved). Dissolution tests were performed as described above for Examples 13 through 15. Drug 3 was analyzed by HPLC using a Waters Symmetry C₁₈ column. The mobile phase consisted of 0.02 M KH₂PO₄, pH 3.0/acetonitrile in the ratio of 60/40 vol/vol. Drug concentration was calculated by comparing UV absorbance at 208 nm to the absorbance of Drug 3 standards. Drug 4 was analyzed by HPLC using a Zorbax SB C₁₈ column. The mobile phase consisted of water/ methanol in the ratio of 35/65 vol/vol. Drug concentration was calculated by

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Table 12

Example No.	Dispersion	Time (min)	Drug Concentration ($\mu\text{g/mL}$)	AUC ($\text{min} \cdot \mu\text{g/mL}$)
16	6	0	0	0
		4	143	300
		10	193	1300
		20	206	3300
		40	212	7500
		90	207	18,000
		1200	207	247,800
17	7	0	0	0
		4	174	300
		10	193	1,400
		20	198	3,400
		40	212	7,500
		90	205	17,900
		1200	217	252,200
18	8	0	0	0
		4	1019	2,000
		10	982	8,000
		20	1004	18,000
		40	970	37,700
		90	961	88,000
		1200	288	779,400
19	9	0	0	0
		4	94	200
		10	95	800
		20	85	1,600
		40	80	3,300
		90	66	7,200
		1200	28	63,800
Control 6	6	0	0	0
		4	159	300
		10	149	1,200
		20	148	2,700
		40	130	5,500
		90	117	11,700
		1200	82	122,300
Control 7	7	0	0	0
		4	21	0
		10	31	200
		20	43	600
		40	58	1,600
		90	86	5,200
		1200	173	148,900

Table 12 (continued)

Example No.	Dispersion	Time (min)	Drug Concentration ($\mu\text{g/mL}$)	AUC ($\text{min} \cdot \mu\text{g/mL}$)
Control 8	8	0	0	0
		4	540	1,100
		10	582	4,400
		20	601	10,400
		40	620	22,600
		90	594	52,900
		1200	276	536,000
Control 11	11	0	0	0
		4	70	100
		10	64	500
		20	59	1,200
		40	50	2,200
		90	42	4,600
		1200	18	37,800

- 5 The concentrations of drug obtained in these samples were used to determine the $C_{\text{max}90}$ and the AUC_{90} during the initial ninety minutes. The results are shown in Table 13.

Table 13

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Ex. No.	Dispersion	Drug	Polymer	Lipophilic Microphase	Lipophile/Drug Ratio	$C_{\text{max}90}$ ($\mu\text{g/mL}$)	AUC_{90} ($\text{min} \cdot \mu\text{g/mL}$)
16	6	3	CAP	Tween	100	212	18,000
Control 6	6	3	CAP	none	--	159	11,700
17	7	3	HPMCAS-MF	Tween	100	212	17,900
Control 7	7	3	HPMCAS-MF	none	--	86	5200
18	8	4	HPMCAS-MF	NaTC/PO PC	5	1019	86,000
Control 8	8	4	HPMCAS-MF	none	--	620	52,900
19	9	1	HPMC	NaTC/PO PC	50	95	7200
Control 9	9	1	HPMC	none	--	70	4600

Example 20

Partition coefficients were measured for Drug 1 in PBS with the lipophilic microphase-forming materials Capmul MCM, a 2.2:1 (wt:wt) mixture of Cremophore RH40/Capmul MCM, Pluronic F127, TWEEN 80, sodium lauryl sulfate (SLS), PEG 6000 distearate, MYRJ 59, Cremophore A25, and NaTC/POPC, using the following method. First, highly mobile Drug 1 concentration was measured for solutions of crystalline Drug 1 and varying concentrations of the lipophilic microphase material, or with Dispersion 2 (25 wt% Drug 1 with HPMCAS-MF). The concentration of Drug 1 versus concentration of lipophilic microphase material was graphed, and the slope was used to determine the partition coefficient of Drug 1 in the lipophilic microphase material from the equation

$$[\text{Drug}]_{\text{lipophile}} = [\text{Drug}]_{\text{free}} \cdot K_p \cdot \%_{\text{lipophile}}$$

For example, to determine the partition coefficient for Drug 1 in a 2.2:1 w/w mixture of Cremophore RH40/Capmul MCM, 2.0 mg of crystalline Drug 1 was added to 2.0 mL of deuterated PBS containing ^{19}F TFA standard and 0.047 wt%, 0.089 wt%, or 0.164 wt% of a Cremophore RH40/Capmul MCM mixture (2.2:1 wt:wt). Each solution was stirred overnight at 37°C. Highly mobile Drug 1 concentration (free drug and drug in lipophilic microphases) was measured using NMR. The results are shown below in Table 14.

Table 14

Cremophore/Capmul (wt%)	Highly-Mobile Drug 1 Concentration ($\mu\text{g/mL}$)
0.047	9
0.089	23
0.164	53

The slope of the data in Table 14, $[\text{Drug}]_{\text{lipophile}} = [\text{Drug}]_{\text{free}} \cdot K_p \cdot \%_{\text{lipophile}}$, is 38,000. Dividing this by $[\text{Drug}]_{\text{free}}$, 0.010 $\mu\text{g/mL}$, gives a partition coefficient, K_p , of 3,800,000. Partition coefficients for the remaining lipophilic microphase materials were calculated using similar procedures. The summary of partition coefficients is shown in Table 15.

Table 15

	Partition Coefficient K_p
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Lipophilic Microphase Material	Determined Using Crystalline Drug 1	Determined Using Dispersion 2
Capmul MCM	--	11,000,000
Cremophor RH40/Capmul MCM (2.2/1 wt/wt)	3,800,000	4,700,000
PEG 6000 distearate	--	1,400,000
Cremophore RH40	--	740,000
Pluronic F127	400,000	
Tween 80	320,000	
MYRJ 59	--	300,000
Cremophor A25	--	200,000
SLS	63,000	
NaTC/POPC	33,000	

The data in Table 15 show that lipophilic microphase-forming materials with a wide range of partition coefficients with Drug 1 are available. The data also show that the partition coefficient measured for Drug 1 and a 2.2/1 (wt/wt) mixture of Cremophor RH40/Capmul MCM when using Dispersion 2 was greater than that measured when using crystalline Drug 1. This is because Dispersion 2 provides an enhanced free drug concentration ($[Drug]_{free}$) over crystalline Drug 1.

Example 21

Solutions containing Drug 1 in PBS with lipophilic microphase-forming materials were analyzed using light scattering to determine the size of the lipophilic microphases. To form these solutions, 3 mg Drug 1 was added to 10 mL PBS containing 0.1 wt% Capmul MCM/Tween 80 (3/2), or 0.1 wt% Cremophor RH40/ Capmul MCM (5/2), and equilibrated overnight. Solutions were filtered using a 0.45 μ m PTFE syringe filter to remove any undissolved species. Dynamic light-scattering of each of the solutions was measured using a PSS-NICOMP 380 Submicron Particle Sizer, and the size of lipophilic microphases in the solution was calculated. The mean particle sizes (characteristic diameter) for the bulk of particles in solution are shown in Table 16. (The value reported is a volume-weighted mean, assuming a gaussian size distribution, with approximately 85% of the particle volume being within about 30% of the reported size.)

Table 16

Lipophilic Microphase (0.1 wt%)	Lipophile/ Drug Ratio	DLS Mean Particle Size (nm)
Capmul MCM/ Tween 80 (3/2)	3.33	14.8
Cremophor RH40/	3.33	17.9

34693
2/5

Capmul MCM (5/2)		
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Example 22

The concentration-enhancement provided by Dispersion 11, comprising 20 wt% Drug 1, 20 wt% Capmul MCM, and 60 wt% HPMCAS-MF, was determined using NMR analysis as follows. A 9.0 mg sample of Dispersion was added to 1.8 mL of deuterated PBS, and the reference standards TSP and ^{19}F TFA, as described in Example 2. The concentration of highly mobile drug provided by Dispersion 11 as determined by NMR is shown in Table 17. For comparison, the results for Control 2 (Dispersion 2 comprising 25 wt% Drug 1 and 75 wt% HPMCAS-MF) is included in the table. These data show that the concentration of highly mobile Drug 1 provided by Dispersion 11, containing the lipophilic microphase-forming material Capmul MCM, was greater than 980-fold that provided by the control composition that did not contain the lipophilic microphase-forming material.

Table 17

Example No.	Dispersion	Lipophilic Microphase-Forming Material	Lipophile/Drug Ratio	Highly Mobile Drug 1 ($\mu\text{g/mL}$)
22	11	Capmul MCM (Included in dispersion)	1	980
Control 2	2	none	--	<1

Examples 23-25

The concentration-enhancement provided by Dispersion 2, comprising 25 wt% Drug 1 and 75 wt% HPMCAS when co-administered with various lipophilic microphase-forming materials was determined as follows. A 7.2 mg sample of Dispersion 2 was added to 1.8 mL of deuterated PBS, and the reference standards TSP and ^{19}F TFA to which had been added 1.8 mg of the lipophilic microphase-forming materials shown in Table 18. The concentration of highly mobile drug provided by Dispersion 2 co-administered with these lipophilic microphase-forming materials was determined by NMR using the procedures outlined in Example 2. The results are presented in Table 18, as is the result for Control 2. These data show that the concentration of highly mobile Drug 1 provided by Dispersion 2 and the various lipophilic microphase-forming materials was greater than 2.4- to 360-fold that provided by the control composition that did not contain the lipophilic microphase-forming material.

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Table 18

Example No.	Dispersion	Lipophilic Microphase-Forming Material	Lipophile/Drug Ratio	Highly Mobile Drug 1 ($\mu\text{g/mL}$)
23	2	PEG Distearate	1	2.4
24	2	Cremophor/Capmul (5/2 wt/wt)	1	170
25	2	Capmul MCM	1	360
Control 2	2	None	--	<1

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Examples 26-28

The concentration-enhancement provided by Dispersion 10, comprising 35 wt% Drug 1 and 65 wt% CMEC when co-administered with various lipophilic microphase-forming materials was determined as follows. A 5.1 mg sample of Dispersion 10 was added to 1.8 mL of deuterated PBS, and the reference standards TSP and ^{19}F TFA to which had been added 1.8 mg of the lipophilic microphase-forming materials shown in Table 19. The concentration of highly mobile drug provided by Dispersion 10 co-administered with these lipophilic microphase-forming materials was determined by NMR using the procedures outlined in Example 2. The results are presented in Table 18, as is the result for Control 3, which comprised Dispersion 10 without a lipophilic microphase-forming material. These data show that the concentration of highly mobile Drug 1 provided by Dispersion 10 when co-administered with various lipophilic microphase-forming materials was greater than 3.4-fold to 210-fold that provided by the control composition that did not contain the lipophilic microphase-forming material.

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Table 19

Example No.	Dispersion	Lipophilic Microphase-Forming Material	Lipophile/Drug Ratio	Highly Mobile Drug 1 ($\mu\text{g/mL}$)
26	10	PEG Distearate	1	3.4
24	10	Cremophor/Capmul (5/2 wt/wt)	1	120
28	10	Capmul MCM	1	210
Control 3	10	none	--	<1

Example 29

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This example demonstrates a lipophilic microphase-forming material adsorbed to a solid substrate.

The lipophilic microphase-forming material was adsorbed to a solid substrate as follows. First, a quantity of calcium silicate (Zeopharm® 800, available from JM Huber Corporation) was dried in a vacuum oven at a temperature of about 100°C for 5 hours. Next a 69:31 (wt/wt) mixture of Cremophore RH 40:Capmul MCM was prepared. The materials were warmed sufficiently to become liquid, and 6.9 g of Cremophore RH 40 and 3.1 g of Capmul MCM was added to a vial. The mixture was warmed to 37°C with constant stirring. The mixture was diluted by adding 10 g of methanol (1:1 mass ratio). The resulting solution was agitated and then stirred at room temperature. 1.1952 g of the Cremophore RH 40:Capmul MCM solution and 0.2015 g of calcium silicate were next added to a vial. The materials were mixed to form a slurry and then allowed to dry in a fume hood at room temperature overnight. The vials were then placed in a vacuum desiccator and allowed to dry for about five hours to remove residual methanol. The resulting material was a dry, freely flowing powder having a weight ratio of lipophilic microphase forming material to solid substrate of about 3/1.

Examples 30 - 31

Compositions comprising a solid amorphous dispersion and lipophilic-microphase forming material adsorbed onto a solid substrate were dissolution tested to determine whether the composition provided concentration-enhancement.

For Example 30, 7.2 mg of Dispersion 12 and 12 mg of the adsorbed lipophilic microphase-forming material of Example 29 was added to microcentrifuge tubes.

For Example 31, 3.6 mg of Dispersion 12 and 12 mg of the adsorbed lipophilic microphase-forming material of Example 29 was added to microcentrifuge tubes.

For Example 30, a sufficient amount of dispersion was added so that the concentration of drug would have been approximately 980 µg/mL, if all of the drug had dissolved. For Example 31, a sufficient amount of dispersion was added so that the concentration of drug would have been approximately 490 µg/mL, if all of the drug had dissolved. The tubes were placed in a 37°C temperature-controlled chamber, and 1.8 mL MFDS was added to each respective tube. The samples were quickly mixed using a vortex mixer for about 90 seconds. The samples were centrifuged at 13,000 G at 37°C for 2 minutes. The resulting supernatant solution was then sampled and diluted

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1:5 (by volume) with methanol and then analyzed by HPLC. The contents of each respective tube were mixed on the vortex mixer and allowed to stand undisturbed at 37°C until the next sample was taken. Samples were collected at 4, 10, 20, 40, 90, and 1200 minutes. The results are shown in Table 20.

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Controls 10 - 13

Control 10 consisted of 7.2 mg of Dispersion 12 but no lipophilic microphase-forming material.

Control 11 consisted of 3.6 mg of Dispersion 12 but no lipophilic microphase-forming material.

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Control 12 consisted of 1.8 mg of crystalline Drug 1 and 12 mg of the adsorbed lipophilic microphase-forming material of Example 29.

Control 13 consisted of 0.9 mg of crystalline Drug 1 and 12 mg of the adsorbed lipophilic microphase-forming material of Example 29.

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Table 20

Example No.	Dispersion	Time (min)	Drug 1 Concentration ($\mu\text{g/mL}$)	AUC ($\text{min} \cdot \mu\text{g/mL}$)
30	12	0	0	0
		4	850	1,710
		10	817	6,710
		20	775	14,600
		40	741	29,700
		90	731	66,500
31	12	0	0	0
		4	407	821
		10	392	3,220
		20	377	7,070
		40	362	14,500
		90	357	32,800
Control 10	12	0	0	0
		4	189	364
		10	432	2,200
		20	726	7,960
		40	769	23,000
		90	681	59,800
Control 11	12	0	0	0
		4	92	194
		10	227	1,170
		20	354	4,080
		40	369	11,300
		90	307	28,200
Control 12	none	0	0	0
		4	5	11
		10	5	37
		20	5	83
		40	5	182
		90	6	453
Control 13	none	0	0	0
		4	3	8
		10	3	27
		20	3	61
		40	4	137
		90	4	333

5 The concentrations of drug obtained in these samples were used to determine the C_{max} and the AUC_{90} during the initial ninety minutes. The results are shown in Table 21.

Table 21

Ex. No.	Dispersion	Drug	Lipophilic Microphase	Lipophile/ Drug Ratio	C _{max90} (μg/mL)	AUC ₉₀ (min*μg/mL)
30	12	1	Cremophor/ Capmul	5	850	66,600
Control 10	12	1	none	--	770	59,300
Control 12	none	1	Cremophor/ Capmul	5	6	450
31	12	1	Cremophor/ Capmul	10	410	32,400
Control 11	12	1	none	--	370	28,200
Control 13	none	1	Cremophor/ Capmul	10	4	330

Combining a solid amorphous dispersion and adsorbed lipophilic microphase-forming material provided greatly enhanced drug concentration relative to controls consisting of equivalent amounts of crystalline drug and lipophilic microphase-forming material. As can be seen from the data, Example 30 provided a C_{max90} that was 1.1- and 142-fold that provided by Controls 10 and 12 respectively. Example 31 provided a C_{max90} that was 1.1- and 102-fold that provided by Controls 11 and 13, respectively. Example 30 provided an AUC₉₀ that was 1.1- and 148-fold that provided by Controls 10 and 12 respectively. Example 31 provided an AUC₉₀ that was 1.1- and 98-fold that provided by Controls 10 and 12 respectively.

Example 32

A combination of a solid amorphous dispersion and adsorbed lipophilic-microphase forming material was dosed to aqueous solution and analyzed by NMR using the procedure of Example 2 to determine the amount of highly mobile drug that was present in aqueous solution, compared with dosing a dispersion alone.

For Example 32, 7.2 mg of Dispersion 12 and 12 mg of the adsorbed lipophilic microphase-forming material of Example 29 were added to 1.8 ml of partially deuterated PBS containing 0.5 wt% NaTC/POPC and a TFA standard (0.0013M ¹⁹F). Samples were held at 37°C and vortexed for one minute and then transferred to an 8mm NMR tube. The concentration of drug was determined through integration of drug peaks and comparison with the TFA peaks.

Control 14 was the same as Example 32 but contained no adsorbed lipophilic microphase-forming material.

Results are shown in Table 22.

Table 22

Ex. No.	Dispersion	Drug	Lipophilic Microphase	Lipophile/ Drug Ratio	Highly Mobile Drug (µg/mL)
32	12	1	Cremophor/Capmul	5	614
Control 14	12	1	none	—	14

5 The results showed that addition of the lipophilic microphase forming material resulted in a 45-fold increase in highly mobile drug concentration compared with the control consisting of the dispersion alone.

10 The terms and descriptions which have been employed in the foregoing specification are used therein as terms of description and not of limitation, and there is no intention, in the use of such terms and expressions, of excluding equivalents of the features shown and described or portions thereof, it being recognized that the scope of the invention is defined and limited by the claims which follow.

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CLAIMS

1. A composition comprising:
- (a) a solid amorphous dispersion comprising a low-solubility drug and a concentration-enhancing polymer;
 - (b) a lipophilic microphase-forming material, said composition having a mass ratio of said lipophilic microphase-forming material to said low-solubility drug of from 0.1 to 100;
 - (c) said lipophilic microphase-forming material being present in a sufficient amount so that said composition provides concentration enhancement of said drug in a use environment relative to at least one of a first control composition and a second control composition; wherein
 - (i) said first control composition consists essentially of an equivalent amount of said solid amorphous dispersion with no lipophilic microphase-forming material present;
 - (ii) said second control composition consists essentially of an equivalent amount of said low-solubility drug in undispersed form with an equivalent amount of said lipophilic, microphase-forming material but with no concentration-enhancing polymer; and

wherein said lipophilic microphase-forming material is water immiscible and said low-solubility drug has a partition coefficient K_p between said use environment and said lipophilic microphase-forming material of at least 0.02 wt% / $S_{x\%al}$, where $S_{x\%al}$ is the maximum aqueous solubility of said low-solubility drug in wt%.

2. The composition of claim 1 wherein said lipophilic microphase-forming material forms lipophilic microphases in said use environment having a characteristic diameter of less than about 10 μm .

3. The composition of claim 1 wherein said lipophilic microphase-forming material is selected from the group consisting of medium-chain glyceryl mono-, di-, and tri-alkylates, sorbitan esters, long-chain fatty alcohols, long-chain fatty-acids, phospholipids, mono and diglycerides of capric and caprylic acid, polyoxyethylene 6 apricot kernel oil, polyoxyethylene com oil, propylene glycol monolaurate, propylene glycol dicaprylate/caprate, polyglyceryl, sorbitan esters of fatty acids, glyceryl monooleate, medium chain triglycerides and long chain triglycerides, and mixtures of

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mono-, di-, and triglycerides, or lipophilic derivatives of fatty acids such as esters with alkyl alcohols, fractionated coconut oils, vegetable oils, fatty acid esters of alkyl alcohols, alcohols, polyoxyethylene alkylethers, fatty acids, glycerol fatty acid monoesters, glycerol fatty acid diesters, acetylated glycerol fatty acid monoesters, acetylated glycerol fatty acid diesters, lower alcohol fatty acid esters, polyethylene glycol fatty acid esters, polyethylene glycol glycerol fatty acid esters, polypropylene glycol fatty acid esters, polyoxyethylene glycerides, lactic acid derivatives of monoglycerides, lactic acid derivatives of diglycerides, propylene glycol diglycerides, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block copolymers, transesterified vegetable oils, sterols, sterol derivatives, sugar esters, sugar ethers, sucroglycerides, polyoxyethylene vegetable oils, polyoxyethylene hydrogenated vegetable oils, reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

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4. The composition of claim 1 wherein said solid amorphous dispersion and said lipophilic microphase-forming material are both present in a single dosage form.

5. The composition of claim 1 wherein said low-solubility drug has an absorption rate constant of at least 0.005 min^{-1} .

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6. The composition of claim 1 wherein said lipophilic microphase-forming material is present in a sufficient amount so as to provide a concentration of highly mobile drug that is at least 2-fold that provided by at least one of said first control composition and said second control composition.

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7. The composition of claim 1 wherein said composition provides a maximum concentration of dissolved drug in said use environment that is at least 1.25-fold that provided by at least one of said first control composition and said second control composition.

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8. The composition of claim 1 wherein said composition provides a dissolution area under the curve in a use environment for any 90-minute period between the time of introduction to the use environment and 270 minutes following introduction to the use environment that is at least 1.25-fold that provided by at least one of said first control composition and said second control composition.

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9. The composition of claim 1 wherein said composition provides a relative bioavailability of at least 1.25-fold relative to at least one of said first control composition and said second control composition.

5 10. The composition of claim 1 wherein said composition provides a fed/fasted relative bioavailability ratio of from 0.5 to 2.0.

10 11. The composition of claim 1 wherein said composition provides a precipitate ratio of at least 1.25-fold relative to at least one of said first control composition and said second control composition.

12. The composition of claim 1 wherein said composition provides concentration enhancement of said low-solubility drug in said use environment relative to both said first control composition and said second control composition.

15 13. The composition of claim 1 wherein said drug is selected from the group consisting of antihypertensives, antianxiety agents, antidiabetic agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, antineoplastics, beta blockers, anti-inflammatories, antipsychotic agents, cognitive
20 enhancers, anti-atherosclerotic agents, cholesterol-reducing agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheimer's disease agents, antibiotics, anti-depressants, and antiviral agents, glycogen phosphorylase inhibitors, and cholesterol ester transfer protein inhibitors.

25 14. The composition of claim 1 wherein said concentration-enhancing polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, carboxymethyl ethyl cellulose, and hydroxypropyl methyl
30 cellulose, poloxamers, polyvinylpyrrolidone, polyvinyl alcohols that have at least a portion of their repeat units in hydrolyzed form, and mixtures thereof.

15. A method for co-administering a solid amorphous dispersion and a lipophilic microphase-forming material *in vivo*, comprising:

35 (a) forming a solid amorphous dispersion comprising a low-solubility drug and a concentration-enhancing polymer;

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- 5 (b) providing a lipophilic microphase-forming material, wherein a mass ratio of said lipophilic microphase-forming material to said low-solubility drug is from 0.1 to 100;
- (c) administering said solid amorphous dispersion and said lipophilic microphase-forming material in a sufficient amount so as to provide concentration enhancement of said drug in a use environment relative to at least one of a first control composition and a second control composition; wherein
- 10 (i) said first control composition consists essentially of an equivalent amount of said solid amorphous dispersion with no lipophilic microphase-forming material present;
- (ii) said second control composition consists essentially of an equivalent amount of said low-solubility drug in undispersed form with an equivalent amount of said lipophilic, microphase-forming material but with no concentration-enhancing polymer; and
- 15 wherein said lipophilic microphase-forming material is water immiscible and said low-solubility drug has a partition coefficient K_o between said use environment and said lipophilic microphase-forming material of at least $0.02 \text{ wt\%/} S_{\text{total}}$, where S_{total} is the maximum aqueous solubility of said low-solubility drug in wt%.
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US005824342A

United States Patent [19]

Cherukuri et al.

[11] **Patent Number:** 5,824,342
 [45] **Date of Patent:** Oct. 20, 1998

[54] **FLASH FLOW FORMED SOLLOID DELIVERY SYSTEMS**

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[21] **Appl. No.:** 629,780

[22] **Filed:** Apr. 9, 1996

Related U.S. Application Data

[62] **Division of Ser. No. 484,794, Jun. 7, 1995, Pat. No. 5,549, 917, which is a division of Ser. No. 269,679, Jul. 1, 1994.**

[51] **Int. Cl.⁶** A61K 9/00

[52] **U.S. Cl.** 424/484; 426/454; 424/48; 424/49

[58] **Field of Search** 426/3-6, 454; 424/48, 49, 484, 457, 464, 468, 489

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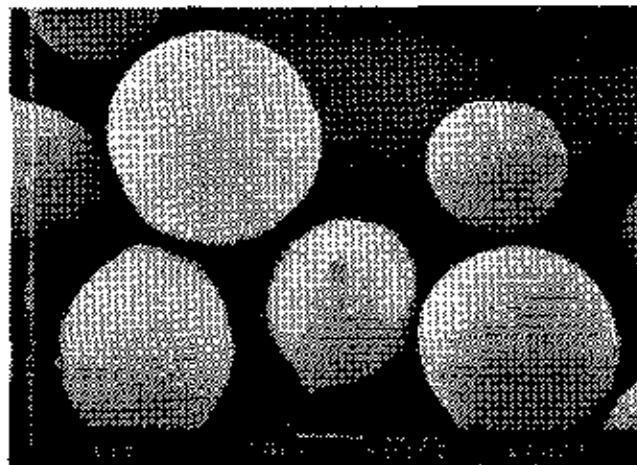
Primary Examiner—Jeanette Hunter

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[57] ABSTRACT

Discrete entities of a solid suspension are made from a solid fat matrix and a non-fat solid substrate having an active associated with said substrate. These entities are spheroidal in shape, have uniform size and substantially the same active content due to the flash flow process used to make them. They are especially useful as delivery systems for comestibles, pharmaceuticals and personal products.

1 Claim, 2 Drawing Sheets



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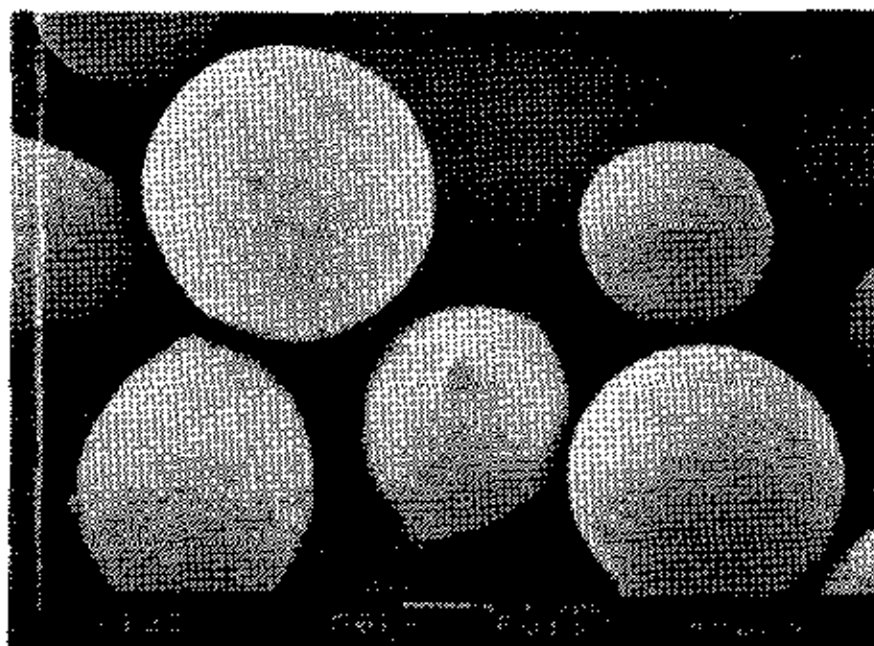


FIG. 1A

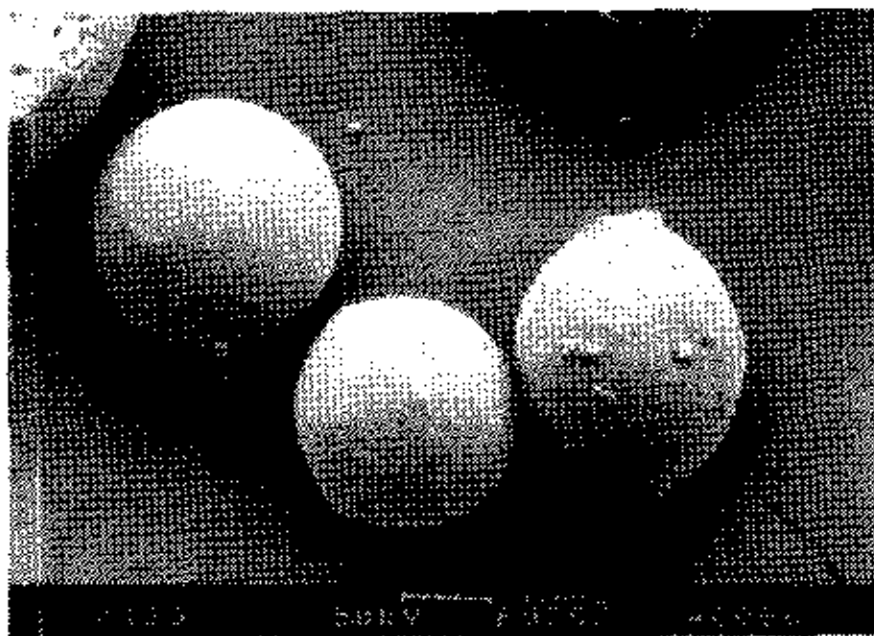


FIG. 1B

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FIG. 2

FLASH FLOW FORMED SOLLOID DELIVERY SYSTEMS

This is a division of U.S. Ser. No. 08/487,794, filed Jun. 7, 1995 now U.S. Pat. No. 5,549,917, which in turn is a division of U.S. Ser. No. 08/269,679, filed Jul. 1, 1994 now pending.

FIELD OF THE INVENTION

The present invention relates to delivery systems for actives in the form of discrete entities which comprise a solid suspension of a non-fat solid substrate in a solid fat. These entities are formed using flash flow processing in combination with a fluid disruptive force to form discrete spheroids of a solid suspension.

BACKGROUND OF THE INVENTION

The processing of materials using extrusion techniques and spray nozzles has been used for many years. In particular, in the food, cosmetic and pharmaceutical industry, ingestible ingredients have been subjected to a number of different processing techniques whereby the ingredients are transformed from their original structure into a new form. Such transformation is usually through the application of pressure and heat, as well as various solvents.

There are many forms of spray drying which have been used over the years for a variety of applications. In general, spray drying involves the atomization of a feedstock in aqueous solution into a spray, followed by contact with a drying medium, e.g. air, which results in moisture evaporation and dried particles. The atomization of a feed into a spray results in the breakup of the liquid into droplets which are then dried as they are suspended in a medium of warm or hot air. The nozzles from which the spray emanates can be selected from a variety of different shapes and configurations and can produce a number of different effects. For example, the forces emanating from the spray nozzle can be centrifugal, pressure, kinetic or sonic. Nozzles, which are generally conical in shape, can have grooved cores, swirled chambers or other geometric designs which impart a specific effect or character on the liquid as it is forced through the orifice.

These different designs have been studied extensively, with the result being that little is actually understood with respect to the subtleties of droplet formation in spray drying equipment. While a number of theories have been advanced to explain the formation of droplets and their variation, the complexity of droplet formation has defied precise empirical correlation. In fact, depending on the pressure, type of liquid used and nozzle type, only general conclusions have been reported in the literature. Such conclusions include the observation that the discharge velocity of the droplet from the nozzle greatly impacts the fineness and size distribution of the resultant droplets. Additionally, it is recommended by some experts that the best atomization is obtained by keeping the discharge velocity of the liquid from the nozzle above a certain minimum.

In addition to the drying steps involved in standard spray drying processing, spray chilling or spray congealing of materials has also been widely used. For example, it is known to take fats which are solid at room temperature, melt them to a liquid and spray them from a nozzle into a cooled chamber where the droplets solidify. In these processes, the fat is subjected to temperatures for a relatively significant amount of time such that the fat is above its melting point and in the molten state. These conditions are necessary to

properly process the fat into congealed droplets and to prevent clogging of the processing equipment.

There are several drawbacks to conventional spray drying or spray congealing methods. First, these processes result in subjecting the material to be processed to a significant heat history, which in the case of heat sensitive materials is unacceptable. For example, in the case of highly volatile flavor oils or heat sensitive sweeteners such as aspartame, exposure to heat causes loss of their ability to fully perform. The same applies to pharmaceuticals which lose their activity if exposed to excessive heat. Additionally, the heating chambers which are required to evaporate the water or other solvent in conventional spray drying methods are costly and inefficient.

Second, spray drying is commonly conducted in aqueous media whereby the water is removed during the drying process. The use of water or other solvents requires extra measures with respect to processing and disposal equipment, all of which also add to the cost of the process and system, and prevents the incorporation of water sensitive materials. Additionally, spray drying is a relatively low output process, requiring high amounts of energy to evaporate the water. This, of course is energy inefficient.

In spray drying and spray congealing processes, the feedstock material is heated to its molten state in a mixing vat and pumped into a feedline which is connected to a nozzle. The feedline and nozzle must be kept at elevated temperature to keep the feed material flowing.

In the case of fats which are solid at room temperature, sufficient heat must be applied to keep the fat in the liquid state, both in the mixing vat as well as during its transport to the nozzle head. In the case of spray drying, heat is further applied in the form of hot air which is used to dry the droplets as they emanate from the nozzle.

The application of heat throughout all phases of the conventional spray drying and spray congealing processes is costly and requires control features which must be monitored. Additionally, the amount of space required to conduct the conventional processes is large and therefore costly. This is due to the need for a large volume used to dry or cool the particles, typical of the fluidized bed type processes.

Furthermore, conventional spray drying or spray congealing processes require the feed material to sit for relatively long periods, i.e. hours, in the liquid state while they are waiting to be pumped into the feedlines and subsequently sprayed. This waiting period creates a heat history which, as previously discussed, is deleterious to heat sensitive materials which may be present in the feed material, e.g. volatile flavor oils, heat sensitive sweeteners and pharmaceuticals. Furthermore, the conventional processes require dispersing agents to keep components in the molten mixture from settling out prior to and during pumping to the nozzle.

Additionally, in prior art spray drying or congealing methods variables such as pressure, temperature, nozzle type and material type must be balanced to produce a consistent particle size. These variables are such that it makes predictability of the character of the final product difficult at best to determine. Additionally, even under the best of conditions, uniformity of content of the particles is not necessarily controllable. Particles formed from spray drying or spray congealing can only have uniformity of content if they are the same size and are made from a homogenous mixture of ingredients, i.e. a blend of materials.

More recently, an apparatus and method for processing feedstock has been described by Dr. Richard Fuisz in copending U.S. Ser. No. 07/965,804 entitled "Process For

Making Shearform Matrix". This application relates to a unique process and apparatus for making a matrix using fluid shear force. The process involves controlling the temperature of a feedstock which includes a solid non-solubilized carrier material to the point where the feedstock undergoes internal flow. The flowing material is then ejected as a stream under pressure from an orifice which is then disrupted by a fluid shear force as it emanates from the orifice. The fluid shear force is preferably air. This application describes apparatus which is useful in the present invention and is incorporated herein by reference.

The present invention seeks to improve on the prior art techniques of spray drying or spray congealing and overcome the disadvantages associated with these techniques. A new form of product has been discovered using flash flow processing techniques. This new form has been termed a "solloid", the definition of which is discussed further herein. The solloids of the present invention are solid suspensions, i.e. a solid suspended in a solid, which are formed by using flash flow processing and disruptive fluid shear forces to form discrete, uniform spheroids under extremely low pressures as compared to the prior art processes, and with minimal exposure to heat. The present invention seeks to avoid temperatures above those which are necessary to achieve a flow condition of the matrix material being processed, which in most instances will be below or close to the melting point temperature. The temperature required to create the flow condition, however, must not be such that it reaches the melting point of the non-fat solid substrate in the fat matrix. Additionally, the time period during which the feedstock material is subjected to these temperatures is very short, i.e. on the order of tenths of a second in the flash heat method and on the order of seconds in the flash shear method.

SUMMARY OF THE INVENTION

The present invention relates to a method of forming a solid suspension hereinafter termed a "solloid" for delivering actives. The method includes: a) providing a mixture of a non-fat solid substrate having an active associated therewith and a solid fat which is solidifiable at room temperature and having a flow point lower than the melting point of said non-fat solid substrate; and b) subjecting such mixture to conditions of flash flow wherein such mixture is heated to at least a temperature sufficient to cause said fat to undergo intraparticle flow but below the melting point of the solid substrate and a disruptive force is applied to said heated mixture to cause said mixture to form discrete solloids.

For purposes of the present invention, the term "solloid" will refer to the resultant product formed by subjecting a composition, i.e. a solid non-fat substrate in a solid fat, which has been flash flow processed, to a disruptive force, such as the frictional forces of gas, which disrupts the continuity of the material into discrete spheroidal shaped entities. The term also refers to the product formed by subjecting the above-mentioned composition to conditions of force and temperature sufficient to create intraparticle flow of the fat and applying sufficient fluid disruptive force to create and maintain discrete spheroidal shaped entities of a solid suspension. The solloid is used as a delivery system for actives and is particularly useful in ingestible products such as comestibles and pharmaceuticals, and the like, as well as cosmetics. The compositions of the present invention are of particular use as a delivery system for flavors, sweeteners and acidulants in chewing gum and confectionery compositions.

Additionally, the present invention is directed to a composition of matter which comprises a plurality of solloids.

The solloids comprise a solid suspension of a solid non-fat substrate having an active associated therewith dispersed in the material which is solidifiable at room temperature and having an intraparticle flow point lower than the melting point of said solid non-fat substrate. A predominant amount of the solloids have substantially the same active content and at least about 60% or more and preferably about 80% of these solloids have a mean diameter particle size, less than about 300 to about 400 microns.

The process of the present invention utilizes flash flow processing in combination with the application of separate disruptive fluid shear forces which are applied to the feedstock immediately upon reaching the flow condition. It is an important feature of this invention that an intimate mixture of the solid non-fat substrate and the fat be maintained and preserved throughout the process in order to result in the production of solloids. Thus, the application of temperature and initial force are such as to create an internal flow condition of the fat. The disruptive force applied subsequently to create solloids must not be so great as to destroy or separate the solid non-fat substrate suspended in the flowable fat material.

The term flash flow has become recognized in the art as referring to conditions of temperature and force required to transform a solid feedstock having a certain morphological and/or chemical structure, to a new solid having a different morphological and/or chemical structure without subjecting the solids to a heat history or other requirements inherent in extrusion processing. The term flash flow is described in co-owned U.S. Pat. Nos. 5,236,734, issued Aug. 17, 1993 and 5,238,696, issued Aug. 24, 1993, as well as co-pending U.S. Ser. No. 07/787,245 filed Nov. 4, 1991 and U.S. Ser. No. 07/893,238.

The term flash flow refers to subjecting an appropriate feedstock to conditions of temperature and force which induce a solid feedstock to undergo rapidly such physical and/or chemical transformation. The flash flow of the feedstock may be accomplished either by a flash heat process or by a flash shear process.

In the flash heat process a shearform matrix can be formed by spinning a feedstock in a "cotton candy" fabricating type machine. The spinning machine used to achieve a flash heat process can be a cotton candy type machine, such as the Econo Floss Model 3017 manufactured by Gold Metal Products Company of Cincinnati, Ohio, a machine having a coiled heater element as disclosed in U.S. Ser. No. 954,257 filed Sep. 30, 1992 (herein incorporated by reference) and the like. It will be appreciated by those skilled in the art that any apparatus or physical process which provides similar forces and temperature gradient conditions can also be used. For simplicity in disclosing and describing this invention, the term flash heat will be understood to mean a process which includes subjecting a feedstock to the combination of temperature, thermal gradients, flow, flow rates, and mechanical forces of the type produced in a cotton candy machine or the above-referenced U.S. Ser. No. 954,257. The apparatus is operated at the temperature and speed which permits flash heat of the feedstock without deterioration of any of its ingredients.

In the flash heat process, the feedstock material is heated sufficiently to create an internal flow condition which permits part of the feedstock to move at a subparticle level with respect to the rest of the mass and exit openings provided in the perimeter of the spinning head. The centrifugal force created in the spinning head flings the flowing feedstock material outwardly from the head so that it reforms with a

changed structure. The force required to discharge flowable feedstock is provided by the forces which result from the spinning head. The flash heat process has been used to produce an amorphous matrix from a crystalline material as disclosed in the aforementioned Puitsz patents. In the present invention, the feedstock comprises a mixture of a solid non-fat substrate and solid fat, which is then subjected to heat sufficient to permit intraparticle flow of the fat. The centrifugal force flings the feedstock material undergoing intraparticle flow into the air where the frictional forces provided by the ambient air disrupt the stream of such material and the newly formed masses and lock the new morphological structure in place. The resultant product is the spheroidal shaped solid suspension referred to as a solloid.

In the flash shear process, a shearform matrix is formed by raising the temperature of the feedstock material, which includes a non-solubilized fat, to a point where said fat undergoes intraparticle flow. The feedstock is advanced and ejected from an extruder or similar type of machinery while the fat is undergoing intraparticle flow and is then subjected to disruptive fluid shear forces to form multiple parts or masses which comprise the individual spheroidal solloids.

The solloids are substantially cooled immediately after contact with the fluid shear force and are permitted to continue in a free-flow or free-fall condition, whereby they are further cooled to prevent individual solloids from adhering to each other and to maintain a free-flow condition.

The feedstock material which can be used in a flash shear process includes but is not limited to a carrier such as fats and other oleaginous materials.

It is important that the feedstock selected for the flash flow process have the ability to be processed without reliance upon dissolution. In the case of fat based materials, the feedstock is a solid material at room temperature, which is then subjected to the flash shear or flash heat process. No solvents or liquids are required to obtain the solloid form in either of the flash shear or flash heat processes. These processes are solid to solid processes which occur rapidly, with little or no heat history during processing.

The flash shear process can be carried out in an apparatus which has means for increasing the temperature of a non-solubilized feedstock and means for simultaneously advancing it for ejection. A multiple heating zone twin extruder can be used for increasing the temperature and advancing feedstock. The second element of the apparatus is a means for ejecting the feedstock in a condition for shearing it to provide the shearform matrix. The means for ejecting is in fluid communication with the means for increasing the temperature and is arranged at the point to receive the feedstock while it is in the internal flow condition. The means for ejecting the feedstock is preferably a nozzle which provides sufficient frictional gas force applied to the ejected feedstock stream to disrupt the stream and form and maintain a solloid.

Apparatus for flash shear processing of the feedstock is described in co-pending U.S. Ser. No. 965,804, filed Oct. 23, 1992. The means for shearing is arranged proximately to the ejector and is disposed to effect the shear of the feedstock while it is in the internal flow condition. Preferably, the means for shearing is the means for delivering fluid such as air at sufficient velocity and at elevated temperature against the feedstock stream as it exits a nozzle. Such a device can be an external atomizing nozzle. The means for shearing can also be a chamber in which the environment can be maintained to induce shear upon the collision of a high velocity of a stream of feedstock directed against a preselected and maintained environment.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows microphotographs of solloids made in accordance with the present invention.

FIG. 2 is a microphotograph of a cross-section of a solloid made in accordance with the present invention.

DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

As previously discussed, the solloids of the present invention are discrete uniformly shaped spheroidal solid suspension delivery systems. The solid suspension includes a non-fat solid substrate having an active agent associated therewith. The non-fat solid substrate is suspended in a solid fat matrix. The discrete solloids can be used in a variety of products such as pharmaceuticals, comestibles, personal products and the like. The solloids are achievable through flash flow processing which may be either flash shear or flash heat as further described herein. The advantages of the present invention allow for both uniform delivery and controlled release of the active.

The active is generally associated with the non-fat solid substrate usually by simple mixing means. The term "associated with" includes the imbibing of the active into, coating onto or uniting with the non-fat solid substrate. In cases where the substrate is a porous material, the active may be a fluid such as a flavor oil or other oleaginous material which is capable of being imbibed into the porous substrate. As will be further described herein, the substrate need not necessarily be porous in the sense of having micro-channels, but may be capable of imbibing or carrying the active, which is preferably a material which is sensitive to heat and aqueous processing conditions.

The solloid form and the flash flow process are designed to be protective of heat and solvent sensitive actives, i.e., materials such as volatile flavor oils, artificial sweeteners and drugs. The flash shear and flash heat process allow for formation of solloids which have substantially uniform shape and size as well as content of active agent. The active agent is preserved because the flash shear and flash heat processes used to produce the solloid employ conditions of temperature and force which do not jeopardize the integrity or effectiveness of the active. Compositions of the present invention are processed with little or no heat history and processing time is substantially decreased as compared to conventional spray drying and spray congealing processes. The temperatures in the flash flow process are kept as low as possible and the required heat is only that which is necessary to achieve a flowable condition of the solid fat, but insufficiently high to melt the non-fat solid substrate.

The flash flow process has distinct advantages over extrusion techniques used for spray drying and spray congealing. The present process not only eliminates the disadvantages associated with a heat history, but also eliminates the settling out of components in the mixture prior to extrusion and eliminates the dispersion agents required to prevent settling out, which are common to spray drying and congealing processes due to the melting and mixing tanks which are required. Additionally, conventional spray drying and spray congealing processes require a significant amount of physical processing room to be properly conducted. This is because since the molten fluid from the holding and mixing tank must be pumped under pressure up to a tower height such that it can be sprayed downwardly into a cool environment and allowed to dry or congeal during the free-fall. Not only is such equipment and need for larger quantities of space eliminated in the present invention, but the time period

required to carry out the process is also significantly decreased. Whereas the conventional processing was batch oriented and required significant waiting times before a certain quantity of the feedstock would be pumped upward into the nozzle area, the present invention is a continuous process which has no requirement for pre-mixing and melting of the solid fat with the non-solid, substrate. Mixtures of the inventive composition can be immediately processed in tenths of a second in the case of flash heat processing and in seconds or at most minutes in the case of flash shear processing.

The advantages of processing from solid to solid without long melting residence times are extremely important. The inventive compositions are added into either the spinning head or the extrusion barrel and processed at temperatures sufficient to allow the fat to flow. A positive pressure is maintained during the process of flash shear. This positive pressure promotes the mixture to remain stable, i.e. prevent any settling-out of the non-fat solid substrate in the fat matrix. Settling-out of mixture components is a common occurrence in spray drying and spray congealing processes. To overcome this problem, mixers are used in the holding vat. Additionally, the positive pressure in the extruder serves to promote and maintain the intimate contact between the non-fat solid substrate and the solid fat during the brief time it is in the extrusion barrel. In the case of flash heat, the process occurs under centrifugal force in essentially fractions of a second and no settling-out is likely to occur.

In the case of flash shear processing, once the composition has travelled through the extrusion barrel, it is exited through a nozzle designed to direct a disruptive force sufficient to form and maintain solloids from the flowing mixture. This force is preferably a gas stream, such as air, which is directed at the flowing mass as it exits the extruder. The disruptive force is sufficient to create the flowing stream into discrete, spheroidal particles which are substantially uniform in size and contain substantially uniform content of the active. Forces which are too great so as to strip or separate the non-fat solid substrate from the flowing fat are not contemplated as part of this invention. The force should be sufficiently great to form the solloid entity but not so great as to separate the solloid components.

In the case of flash heat processing, the spinning head is equipped with a heating element which provides sufficient temperature to cause the solid fat to flow through the apertures of the spinning head, carrying with it the non-fat solid substrate containing the active. The flowable mass deforms sufficiently to be flung from the spinning head under centrifugal force and into the ambient atmosphere. The exiting mass is subjected to the frictional forces of ambient air as it travels from the spinning head. These frictional forces of air are sufficient to form and maintain the solloid as described herein.

The following general compositions are useful in the inventive solloid compositions and process:

Component	% by Weight of Composition
Fat	40-94
Non-fat Substrate	5-30
Active	0.01-35

FIGS. 1 and 2 depict microphotographs of the present invention. FIG. 1 shows the uniformity of size and shape. FIG. 2 shows the solid non-fat substrate inside the solid fat matrix. Interstices within the fat matrix crystals are apparent from the cross-section.

Fats which are useful in the present invention are those which are substantially solid at room temperature. Hydrogenated and partially hydrogenated vegetable and animal fats are among those useful. For example, a partial listing of vegetable fats include hydrogenated or partially hydrogenated cottonseed oils, hydrogenated or partially hydrogenated soybean oils, hydrogenated or partially hydrogenated palm oils and mixtures thereof. In addition, these fats may be supplemented with the mono-, di- and triglycerides of fatty acids as well as the propylene glycol mono and diesters of fats and fatty acids. Animal fats such as tallow, lard and other hydrogenated or partially hydrogenated versions of animal fats may also be employed in the present invention.

Other matrix materials which are useful include waxes which are solid at room temperature. For example, petroleum waxes such as paraffin and microcrystalline waxes and the like may be used. These materials may be used alone or combined with the fat matrix.

Other materials may be added to the solloid compositions to modify the flow properties, texture and taste. For example, medium chain triglycerides, emulsifiers, softeners and the like may be employed. Vapor depressant additives may be added to volatile flavor oils to aid in loss of flavor components. Medium chain triglycerides have been found to be particularly useful in suppressing vaporization of menthol.

The non-fat solid substrates may be selected from a wide variety of materials which are capable of binding to, being coated with, united with or inhibiting an active substance. One limitation, however, is that the melting point of the material chosen for the non-fat solid substrate must be such that it does not melt during the flash flow process. This means that the melting point of the non-fat solid substrate must be beyond the flow point temperature of the solid fat. There are several reasons for this requirement, one being that the ultimate product derived from the compositions and process of the invention is a solloid, i.e., a solid suspension of the solid substrate in the solid fat. If the substrate were allowed to melt, a blend would occur and the solid suspension would not be a solloid as defined herein. Additionally, the active agent which is associated with the solid substrate would also blend into the fat. It is the intention of the present invention to carry the active on the substrate such that it remains substantially united with the solid substrate in the solloid form. While it is entirely possible that a certain amount of active may leach out of the substrate or otherwise migrate into the flowable fat during processing, it is believed that a substantial amount of the active remains intimately associated with the substrate. The resultant solloids benefit from this characteristic in that it provides for uniformity and content of the active for each solloid, as well as a controlled release of the active therefrom. Each solloid must be disrupted by mastication, ingestion or other force such as rubbing on the skin, to release the active from the individual solloid and make it available for its intended purpose.

Representative non-fat solid substrates include, without limitation, those materials which are adsorbent as well as absorbent. For example, cellulosic materials such as alkyl celluloses, hydroxyalkyl celluloses and hydroxyalkylalkyl celluloses are contemplated. These include methylecellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose, hydroxybutylmethyl cellulose, cellulose esters and hydroxyalkyl cellulose esters. Cellulose acetylphthalate and hydroxypropylmethyl cellulose are among those useful. Additionally, carboxyalkyl celluloses and their esters, as well as carboxyalkylalkyl celluloses and their esters are also useful. One example is carboxymethyl cellulose.

Other non-fat solid substrates include water swellable gums and mucilages, algal polysaccharides, pectin and lignin. For example, karaya gum, acacia gum, tragacanth, sodium alginate, calcium alginate, carageenan and its salts, as well as mixtures thereof may be employed. Starches, including chemically and biologically modified starches are also contemplated as being useful. Additionally, protein materials such as zein, sorghum and other prolamines may also be employed.

Various silicas and microcrystalline substances are also useful as the solid non-fat substrate. For example, silicas are well known for their ability to absorb or otherwise capture liquids and certain silicas are extremely porous in nature. For example, synthetic amorphous silica has been particularly useful since it has a unique combination of uniformity, chemical inertness, large surface area and porosity which makes it very adsorptive. These silicas are manufactured with precisely controlled surface area, porosity and particle size distribution. This makes them particularly useful in the inventive compositions. Commercially available silicas of this kind are sold under the trademarks SYLOID® and SYLOX® by W.R. Grace & Company, Baltimore, Md. These materials are specifically intended for conventional liquid dispersions and suspensions. However, they are also useful in the solid suspension of the present invention.

It is preferred that the non-fat solid substrate have mucosal adhesive properties. This means that the substrate has an affinity for adhering to the mucosal membranes of the body, particularly in the mouth, such that the active can be either absorbed quickly or in the case of flavorants, perceived for long periods of time in the oral cavity, since the active agents are carried by the substrate. These substrate materials adhere when subjected to the moist conditions of the mouth, largely because of their physical and chemical affinity to the mucosal membrane structure. The carboxyl and hydroxyl hydrophilic groups on the substrates, as well as other hydrophilic groups which may be present, are believed to be largely responsible for the affinity and adhesion of these classes of materials to the mucosal membrane. These materials also have the capability of being smooth and devoid of any unpleasant texture in the mouth. For this reason, their lubricious mouth-feel allows for them to be virtually imperceptible when bound to the mucosal surface, thereby allowing the active to be slowly released in the mouth, in the case of flavorants, or in the bloodstream in the case of drugs.

The preferred non-fat solid substrate of the present invention is hydroxypropylmethyl cellulose. This particular substrate has found to be especially useful in chewing gum compositions and other confectionery products. Flavorants such as flavor oils are generally admixed with the hydroxypropylmethyl cellulose and added to the solid fat matrix in compositions of the present invention. Since the flavor oils are readily imbibed by the cellulose, the oils are carried into the final solloid product with virtually no volatilization of the is flavor components during processing.

The actives which are useful in the present invention can be chosen from any number of actives which are capable of being associated and therefore carried by the non-fat solid substrate. For example, liquids are particularly useful since they can be coated onto or imbibed by the non-fat solid substrate. However, nonliquid forms may be possible if the non-solid substrate is first flash flow processed, i.e. taking solid substrate and combining it in a flash flow process (such as described in copending U.S. Ser. No. 07/787,245, filed Nov. 4, 1991,) with solid active to form a united solid non-fat substrate/active particle.

For purposes of the present invention, however, liquids are preferred. The examples of liquid actives include drugs

and oleagenous materials such as flavor oils and the like. The liquid active may be a combination of materials, such as a sweetener dissolved or dispersed in the flavor oil or a blend of two liquids. For example, artificial sweeteners can be added to the flavor oil and then imbibed onto the substrate. Alternatively, a blend of flavor oils or drug materials may be made and combined with the substrate.

In one embodiment, fish oil is coated or imbibed onto the solid non-fat substrate, e.g. starch, and incorporated into the inventive delivery system.

Flavor oils which may be useful in the present invention may be selected from a wide variety of natural or artificial oils or essences. These oils are generally derived from plant extracts, although they may alternatively be synthetically derived. Peppermint oil, spearmint oil, cinnamon oil, oil of wintergreen, menthol, citrus oils and other fruit essences are the most commonly used flavor oils which are employed in the present invention. The solloids of the present invention give the perception that a greater quantity of flavor is present than the actual amount, thereby enhancing both the organoleptic impact with less flavor oil and eliminating the need for higher amounts of flavor oil or active. This is particularly useful in applications such as chewing gum compositions, where the addition of flavor oil at high concentrations to achieve a more intense flavor impact results in plasticization of the gum base components and sloppy chew characteristics. Additionally, flavor oils such as peppermint oil, spearmint oil, menthol and cinnamon oil are particularly harsh and create a burning sensation in the mouth if ingested in too high a quantity. The present invention allows for the use of smaller quantities than in typically comestible applications if desired, with the perception that greater quantities are present.

Alternatively, because the process allows for precision in the amount of active in the solloid, higher loading of the active than in prior methods is possible. In essence, the processes of the present invention allow for precise control of the quantity of active in the solloid.

Examples of citrus or fruit oils and/or essences which are useful include a host of materials such as apple, apricot, banana, blueberry, cherry, grape, grapefruit, lemon, lime, orange, pear, peaches, pineapple, plum, raspberry, strawberry and the like. Mixtures and derivatives of these materials are contemplated.

Additional flavoring agents may be chosen from synthetic flavor oils and flavoring aromatics, and/or oils, oleo resins and extracts derived from plants, leaves, flowers, fruits and so forth, and combinations thereof. For example, clove oil, bay oil, anise oil, eucalyptus oil, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, oil of bitter almonds and cassia oil may be used. Commonly used flavors include menthol, artificial vanilla, cinnamon derivatives, and various fruit flavors, whether employed individually or in admixture.

Flavorings such as aldehydes and esters including cinnamyl acetate, cinnamaldehyde, citral (diethylacetal, dihydrocarvyl acetate, eugenyl formate, p-methylatmosol, and so forth may also be used. Generally any flavoring or food additive such as those described in "Chemicals Used in Food Processing," pub 1274 by the National Academy of Sciences, pages 63-258 may be used.

Further examples of aldehyde flavorings include, but are not limited to acetaldehyde (apple); benzaldehyde (cherry, almond); anisic aldehyde (licorice, anise); cinnamic aldehyde (cinnamon); citral, i.e., alpha citral (lemon, lime); neral, i.e. beta citral (lemon, lime); decanal (orange, lemon); ethyl vanillin (vanilla, cream); hellotropine, i.e., pipernonal

(vanilla, cream); vanillin (vanilla, cream); alpha-amyl cinnamaldehyde (spicy fruity flavors); butyraldehyde (butter cheese); valeraldehyde (butter, cheese); citronellal; decanall (citrus fruits); aldehyde C-8 (citrus fruits); aldehyde C-9 (citrus fruits); aldehyde C-12 (citrus fruits); 2-ethylbutyraldehyde (berry fruits); hexenal, i.e., trans-2 (berry fruits); tolyl aldehyde (cherry, almond); veratraldehyde (vanilla); 2,6-dimethyl-5-heptenal, i.e. melonal (melon); 2,6-dimethyloctanal (greenfruit); and 2-dodecenal (citrus, mandarin), mixtures thereof and the like.

Other specific flavor compounds such as ethylacetate, thiophene, ethylpropionate, ethyl butyrate, 2-hexanoate, 2-methylpyrazine, heptaldehyde, 2-octanone, limonene, and eugenol are also useful.

The flavor oil content of the present delivery systems is generally in the range of about 0.02% to about 40% by weight of the delivery system. However, deviations from this range are certainly possible provided that the solloid is formed as a result of the flash flow process. Preferably, the oils are present in amounts of about 0.5% to about 20% by weight of the solloid delivery system and most preferably about 2% to about 12%.

Those drugs which may be useful in the present invention include either solid or liquid drugs which may be combined with the non-fat solid substrate. Liquids are preferred since they can be imbibed or otherwise coated onto the substrate. However, as previously discussed above, solids may be combined with the non-fat solid substrate via flash flow processing to form a new solid form which can be incorporated in the compositions of the present invention.

The drugs useful may be selected from a wide range of drugs and their acid addition salts. These drugs can be used either singly or in combination. Both inorganic and organic salts may be used provided the drug maintains its medicinal value. Exemplary acid salts include hydrochloride, hydrobromide, orthophosphate, benzoate, maleate, tartrate, succinates, citrate, salicylate, sulfate, and acetate. The weight percent of the drug in the mixture which is formed into solloids is up to about 30% by weight.

One advantage of the present invention is that the active in the solloid product is in substantially the same proportion as it is in the mixture. This is particularly useful in dosage forms where the active content is critical. For example, the solloids containing the active can be used to fill a pharmaceutical capsule.

Final dosage forms in which the solloids may be present can be selected from any number of vehicles or dosage forms. For example, food products, medicaments, baked goods, pharmaceutical preparations, lozenges, capsules, nuggets, chewing gum, liquids and gels may be employed among others.

Once prepared, the solloids may be stored for future use or formulated with conventional additives such as pharmaceutically acceptable carriers and confectionery ingredients to prepare compositions which offer a variety of textures to suit particular applications. Pharmaceutically acceptable carriers may be selected from a wide range of materials. Without being limited thereto, such materials include diluents, binders and adhesives, lubricants, disintegrants, colorants, flavorings, sweeteners and other miscellaneous materials such as buffers and adsorbents used to prepare a particular medicated composition. In addition, elixirs, and syrups whereby the solloids are suspended therein are also contemplated.

Among the drugs which are useful, include the following:

(a) Antitussives, such as dextromethorphan, dextromethorphan hydrobromide, noscapine, carbatapentane citrate, and chlorpheniramine hydrochloride;

(b) Antihistamines, such as chlorpheniramine maleate, phenindamine tartrate, pyrilamine maleate, doxylamine succinate, and phenyltoloxamine citrate;

(c) Decongestants, such as phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine, hydrochloride ephedrine;

(d) Various alkaloids, such as codeine phosphate, codeine sulfate and morphine;

(e) Mineral and nutritional supplements such as potassium chloride and calcium carbonates, magnesium oxide and other alkali metal and alkaline earth metal salts;

(f) Laxatives, vitamins and antacids;

(g) Ion exchange resins such as cholestyramine;

(h) Anti-cholesterolemic and anti-lipid agents;

(i) Antiarrhythmics such as N-acetylprocainamide;

(j) Antipyretics and analgesics such as acetaminophen, aspirin and ibuprofen;

(k) Appetite suppressants such as phenylpropanolamine hydrochloride or caffeine; and

(l) Expectorants such as guaifenesin; and

(m) H₂ inhibitors.

Additional useful active medicaments include anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, anti-infectives, psychotropics, anemias, stimulants, gastro-intestinal sedatives, antidiarrheal preparations, anti-anginal drugs, vasodilators, anti-hypertensive drugs, vasoconstrictors and migraine treatments, antibiotics, tranquilizers, antipsychotics, antitumor drugs, anticoagulants and antithrombotic drugs, hypnotics, sedatives, antiemetics, anti-nauseants, anticonvulsants, neuromuscular drugs, hyper- and hypoglycemic agents, thyroid treatment preparations, diuretics, antispasmodics, uterine relaxants, antiobesity drugs, anabolic drugs, erythropoietic drugs, antiasthmatics, expectorants, mucolytics, anti-uricemic drugs, and the like.

Mixtures of the drugs and medicaments may also be used.

The present invention contemplates the inclusion of those sweeteners well known in the art, including both natural and artificial sweeteners. Thus, sweeteners may be chosen from the following non-limiting list: sugars such as sucrose, glucose (corn syrup), dextrose, invert sugar, fructose, and mixtures thereof; saccharin and its various salts such as the sodium or calcium salt; cyclamic acid and its various salts such as the sodium or calcium salt; the dipeptide sweeteners such as aspartame and alitame; chlorinated sugar derivatives such as sucralose; natural sweeteners such as dihydrochalcone; glycyrrhin; *Stevia rebaudiana* (Stevioside); and sugar alcohols such as sorbitol, sorbitol syrup, mannitol, xylitol, and the like. Also contemplated as a sweetener is the nonfermentable sugar substitute hydrogenated starch hydrolysate (Iycasin) which is described in U.S. Pat. No. Re. 26,959. Also contemplated is the synthetic sweetener 3,6-dihydro-6-methyl-1,1,2,3-oxathiazin-4-one-2, 2-dioxide particularly the potassium (Acesulfame-K), sodium and calcium salts thereof as described in German Patent No. 2,001,017.7.

The sweeteners may be incorporated as the active agent, per se, i.e., flash flow processed with the non-fat solid substrate to form a substrate/active combined solid, combined with a flavor oil as the active or incorporated directly in the fat matrix.

The delivery system can be incorporated in conventional chewing gum compositions. These compositions typically contain a sweetener, a gum base and a flavor. Additionally

sources of flavor and/or sweetener can of course be combined with the solloid delivery system and incorporated in the chewing gum composition.

In the present invention, the flavor, sweetener and optionally acidulants can be incorporated into the solloid. For example, in one embodiment a flavorant selected from the group consisting of flavor oils, sweeteners, food acids (also referred to as acidulants) and mixtures thereof may be united with the solid non-fat substrate. Preferably a mixture of all three are present. In another embodiment, one or more of the flavorant materials may additionally be incorporated into the solid fat matrix such that it remains in the solid fat portion of the solloid.

Chewing gum compositions incorporating the novel solloid delivery systems have distinct advantages in terms of sustained flavorant perception. Due to the physical structure of the solloid, the flavorant materials are protected during processing as well as in the bulk storage form subsequent to processing. The fat surrounding the non-fat solid substrate serves to prevent volatilization of the flavorant materials from the discrete solloid particles as well as to prevent moisture from prematurely attacking the sweetener and/or

other flavorant material. Once incorporated into a chewing gum composition, the solloid form serves to protect the flavorants from other components in the chewing gum as well as preventing migration of the flavorant from the gum base onto the surface of the gum.

One particular advantage to the inventive delivery systems relates to their ability to sustain the flavor and sweetness perception of the chewing gum. The non-fat solid substrate preferably has a muco-adhesive property which serves to adhere the solloids to the mucous membranes of the mouth. The solloids slowly release their flavorant materials through a delayed hydration process. The perception of flavor and sweetness is significantly increased due to the presence of the solloids in the mouth during mastication.

As a demonstration of the comparative sustained release of flavor and sweetness of the present inventive chewing gum compositions containing the novel solloids as compared to commercially available chewing gum compositions can be demonstrated by the following data. This data was developed by an expert chewing panel and ratings were based on a scale of 1-10 with 1 being the lowest rating and 10 being the highest rating.

FLAVOR AND SWEETNESS DURATION EVALUATION
COMMERCIALY AVAILABLE PRODUCTS vs. INVENTIVE PRODUCT

Time	Amount of Flavor			Amount of Sweetness		
	Wrigley's Peppermint	Extra 00 Peppermint	Inventive Peppermint	Wrigley's Peppermint	Extra 00 Peppermint	Inventive Peppermint
0.30 Seconds	8.00	7.42	8.86	8.14	8.29	8.71
5.0 Minutes	5.43	5.86	8.57	5.29	5.57	8.00
10.0 Minutes	5.43	4.86	7.71	3.00	3.86	6.43
15.0 Minutes	2.00	4.12	7.00	1.29	3.14	5.29
20.0 Minutes	0.86	3.14	5.57	0.57	2.71	4.14
25.0 Minutes	0.29	2.14	4.00	0.29	2.14	3.57
30.0 Minutes	0.14	1.86	3.86	0.14	1.43	3.00
40.0 Minutes	0.00	0.86	3.43	0.00	0.57	2.71
50.0 Minutes	0.00	0.29	2.86	0.00	0.29	2.00
60.0 Minutes	0.00	0.29	2.29	0.00	0.14	1.71

FLAVOR AND SWEETNESS LIKING EVALUATION
COMMERCIALY AVAILABLE PRODUCTS vs. INVENTIVE PRODUCT

Time	Flavor Liking			Sweetness Liking		
	Wrigley's Peppermint	Extra 00 Peppermint	Inventive Peppermint	Wrigley's Peppermint	Extra 00 Peppermint	Inventive Peppermint
0.30 Seconds	7.43	6.71	8.29	7.71	6.57	8.29
05.0 Minutes	4.86	5.43	8.43	5.57	5.14	8.00
10.0 Minutes	3.14	4.14	7.43	2.86	4.00	7.29
15.0 Minutes	1.43	3.00	6.71	1.00	3.00	6.29
20.0 Minutes	0.43	2.43	5.14	0.43	2.57	4.86
25.0 Minutes	0.14	1.86	4.29	0.14	1.86	4.14
30.0 Minutes	0.14	1.57	3.86	0.14	1.43	3.71
40.0 Minutes	0.00	0.86	3.57	0.00	0.57	2.86
50.0 Minutes	0.00	0.29	2.86	0.00	0.29	2.00
60.0 Minutes	0.00	0.14	2.14	0.00	0.14	1.71

The first evaluation table above relates to the sweetness and flavor duration. The expert panel was given samples of commercially available chewing gum products, namely Wrigley's Peppermint and Wrigley's Extra® Peppermint chewing gums and asked to compare these to the inventive peppermint chewing gums. Samples of each of the chewing gum products were chewed by all members of the panel. The gums were masticated for a sixty minute period, with ratings taken at the intervals listed in the tables. It is abundantly clear from the duration evaluation table that while the commercially available chewing gum products have flavor and sweetness duration at the 30 second level which is substantially similar to those of the inventive products, the ratings for the commercially available products drop significantly even after 5 minutes. At the 10 minute mark, the ratings for the two commercially available products with respect to both flavor and sweetness were only half as good as the flavor ratings given to the inventive products. The ratings were substantially greater in the inventive compositions after 30-60 minutes of chew. More specifically, at the 60 minute level, the inventive products were ten times or more greater in flavor and sweetness, as evidenced from the tables.

With respect to the flavor and sweetness liking evaluation, reference is made to the second table above. "Liking" is the term used for overall pleasure sensation received during chew. Liking substantially dropped off in the commercially available products after 5 minutes of chewing. This is compared to the liking ratings for the inventive products which stayed substantially the same even after 10-15 minutes of chewing. At the 25 minute mark, the inventive compositions showed ratings of 4.29 (flavor) and 4.14 (sweetness), while the commercially available chewing gum products were only 0.14 and 1.57 for flavor and 0.14 and 1.43 for sweetness. No substantial flavor or sweetness was perceived at the 40 minute mark for the original Wrigley's Peppermint gum, and liking ratings of 0.86 and 0.57 were given for the Extra Peppermint gum at those time periods. However, the present inventive compositions produced chewing gums which produced ratings substantially higher at the 30-60 minute mark, 2.14-3.86 (flavor) and 1.71-2.86 (sweetness), indicating perception of the flavor and sweetness was clearly present and still enjoyable.

The ability of chewing gum to retain its flavor and sweetness after 60 minutes or more of chewing is believed to be due in part to the ability of the solloids to be retained in the mouth, allowing the sensation and perception of the flavorants to be prolonged.

With regard to chewing gum compositions, the amount of gum base employed will vary greatly depending on various factors such as the type of base, consistency desired and other components used to make the final product. In general, amounts of about 5% to about 85% by weight of the final chewing gum compositions are acceptable, with amounts of about 15% to about 30% by weight being preferred. The gum base may be any water-insoluble gum base well known in the art. Illustrative examples of suitable polymers in gum bases include both natural and synthetic elastomers and rubbers. For example, those polymers which are suitable in gum bases include, without limitation, substances of vegetable origin such as chicle, jelutong, gutta percha and crown gum. Synthetic elastomers such as butadiene-styrene copolymers, isobutylene-isoprene copolymers, polyethylene, polyisobutylene, polyvinylacetate and mixtures thereof are particularly useful.

The gum base composition may contain elastomer solvents to aid in softening the rubber component. Such elas-

tomers solvents may comprise methyl, glycerol or pentaerythritol esters of rosins or modified rosins, such as hydrogenated, dimerized or polymerized rosins or mixtures thereof. Examples of elastomer solvents suitable for use herein include the pentaerythritol ester of partially hydrogenated wood rosin, pentaerythritol ester of wood rosin, glycerol ester of wood rosin, glycerol ester of partially dimerized rosin, glycerol ester of polymerized rosin, glycerol ester of tall oil rosin, glycerol ester of wood rosin and partially hydrogenated wood rosin and partially hydrogenated methyl ester of rosin, such as polymers of alpha-pinene or beta-pinene; terpene resins including polyterpene and mixtures thereof. The solvent may be employed in an amount ranging from about 10% to about 75% and preferably about 45% to about 70% by weight of the gum base.

A variety of traditional ingredients such as plasticizers or softeners such as lanolin, stearic acid, sodium stearate, potassium stearate, glycerol triacetate, glycerin and the like, including, natural waxes, such as paraffin waxes and microcrystalline waxes may also be incorporated into the gum base to obtain a variety of desirable textures and consistency properties. In accordance with the invention, however, these ingredients may be reduced in amount or in some cases, may be eliminated entirely. When present, these individual additional materials are generally employed in amounts of up to about 15% by weight and preferably in amounts of from about 3% to about 10% by weight of the final gum base composition.

The chewing gum may additionally include the conventional additives of coloring agents such as titanium dioxide; emulsifiers such as lecithin and glycerol monostearate; additional fillers such as aluminum hydroxide, alumina, aluminum silicates; calcium carbonate, and talc and combinations thereof; and additional flavoring agents. These fillers may also be used in the gum base in various amounts. Preferably, the amount of fillers when used will vary from about 4% to about 35% by weight of the final chewing gum.

The amount of solloid delivery system used in the chewing gum composition will largely be a matter of preference. It is contemplated that the delivery system will be included in amounts of from about 0.25% to about 40% by weight of the final gum composition, with amounts of from about 1% to about 30% being preferred, and amounts of from about 1% to about 20% being most preferred.

In addition to the inventive delivery system, the chewing gum composition may also optionally include one or more additional ingredients such as conventional polysaccharide-based bulking agents including sugars or sugar alcohols, flavor delivery systems, spray-dried flavors, liquid flavors, natural and/or artificial sweeteners and the like.

The chewing gum compositions of the present invention may be prepared by combining the water-insoluble gum base portion and the water-soluble flavor portion including the novel flavor/sweetener delivery system according to conventional chewing gum processing techniques.

For illustrative purposes, a method of preparing the novel chewing gum compositions is as follows:

A suitable chewing gum base is first melted. Softeners and bulking agents such as sugars or sugar alcohols if desired may be added slowly with stirring thereafter. The inventive delivery system is then added and mixing is continued until a homogeneous mass is achieved. Optionally, additional flavor oils or spray dried flavors may be added as well. The mass may then be rolled, scored, dusted and wrapped in any manner known in the art.

With regard to the preparation of other types of conestibles, the inventive solloid delivery system may also

be added in a conventional manner. For example, in the case of pressed tablets, the delivery system may be dry blended with the remaining tablet ingredients and the mixture thereafter compressed into final tablet form. In the case of dentifrices, denture creams and cleansers, the products also benefit from incorporation of the delivery system in their formulations. In short, the matrix may be added to various comestibles in a manner similar to that which the skilled artisan currently uses to add conventional comestible ingredients.

In one particular embodiment, a micron-sized synthetic, amorphous silica has been used as the non-fat solid substrate for liquid actives. Using these materials, flavor oils can be adsorbed onto their surfaces and into their pores and the added to the feedstock of matrix material in form the inventive delivery systems. In this manner, additional controlled release characteristics can be imparted to the delivery systems, as well as adding further stabilization and protective features to the oils against volatilization and oxidation. These silica compounds also have ionic and hydrogen bond affinity for certain flavor component chemical groups, which affinity serves to strengthen flavor retention and consequently allows for increased delayed release capabilities and stabilization characteristics.

In another embodiment, polyunsaturated fatty acids such as fish oil are combined with a starch non-fat solid substrate and added to the fat matrix.

Additional materials which can be used as carriers for the flavor oils prior to incorporation with the inventive delivery system include maltodextrins, such as spray-dried maltodextrin marketed under the tradename M100 (10 DE) by Grain Processing Corporation, Muscatine, Iowa, as well as agglomerated maltodextrin (10 DE) sold under the tradename Micropor Buds 101SA, by E. Staley Manufacturing Co., Decatur, Ill. These materials are also porous and allow for flavor retention. Polydextrose and microcrystalline cellulose are also useful in this regard, as are a number of other adsorbent materials.

EXAMPLES

The following examples serve to provide further appreciation of the invention, but are not meant in any way to restrict the effective scope of the invention.

The following compositions were used to produce solloids in both the flash shear and flash heat processes

Solloid Delivery System Composition (% wt)			
Component	A	B	C
Partially Hydrogenated Soybean Oil	58.08	66.00	66.00
HPMC ¹	15.00	10.00	10.00
Flavor Oil	12.50*	10.00*	10.00**
Artificial Sweetener	10.42	10.00	10.00
Optional Ingredients ¹	4.00	4.00	4.00

¹hydroxypropylmethyl cellulose

²emulsifier and fillers

*spearmint/peppermint blend

**peppermint oil/menthol blend

Flash Shear Process

Each of the above compositions were processed using flash shear processing to yield the inventive solloid delivery system. Each composition was prepared as a mixture. The respective composition mixtures were then individually processed using an extruder where the extrudate was subjected

to disrupted air flow, with an atomizing nozzle. The compositions were fed into a twin screw extruder and the feed rate adjusted to maximize product quality.

The flash shear parameters of compositions A-C are shown in the following table.

Composition	Extruder System Temp °C.	Screw Speed rpm	Nozzle Air Pressure psig	Nozzle Air Temp °C.
A	62-70	309	2.25	75
B	70	310	2.5	79
C	70	300	2.5	80

The compositions were exposed to temperatures sufficient to cause them to flow, which as shown in the table below was about 62°-70° C. for partially hydrogenated soybean oil. The screw speed used was between about 300-310 rpm's, but this speed is only limited by the speed capacity of the machine. Higher speeds such as 500 rpm's or more have been successfully run. As a general principal, the higher the screw speed, the faster the throughput of the extrudate, and the shorter the residence time. In the compositions below, the residence time of the mixture in the extruder was between about 60-83 seconds. Residence time will of course vary depending on a number of factors, but for purposes of the present invention, the residence time of the composition need only be long enough for the fat to reach its intraparticle flow point. As described in the specification above, this will vary depending on the fat used. With small extrusion machines, the residence time may be as short as 5 seconds, whereas with large production equipment it may be closer to 160 seconds. In the above compositions the temperature of the fat while in the extruder system was between about 62°-70° C., but the inventive process need only use temperatures which are sufficient to cause the fat to undergo intraparticle flow which for some materials, depending upon the pressure and other parameters, may be lower than its melting point. In any event, this temperature must be below the melting point of the non-fat solid substrate and preferably no greater than about 10° C. above the fat melting point.

The material processed in the extruder is ejected through a nozzle which has air streams directed against it to disrupt the extrudate into small solloid particles. A nozzle which provides a concentric flow of air around the flow of extrudate and two banks of three opposed air jets directed at the extrudate and the concentric air flow have been used to provide a uniform size distribution of solloid particles when the air pressure is as set forth in the above table.

As compared to conventional spray congealing and spray drying processes, the process of the present invention may be considered a "cold flow" process, devoid of the long residence time in mixing and holding tanks and the various problems associated therewith. The screw speed was operated at full throttle which was between 300-310 rpm's. The air pressure was about 2.25 to about 2.5 psig.

The compositions while in the extruder system were always under a positive pressure which served to prevent settling of the non-fat solid substrate which remained in the solid state during mixing and transformation of the solid fat into the flowable state. The extruder was in this respect effectively a closed system.

The air pressure employed in process runs of the above compositions was extremely low (2.25-2.5 psig) compared to conventional spray drying or spray congealing. As mentioned above, the air pressure may be increased proportionate to nozzle orifice size. In other words, the larger the mass

of flowing extrudate exiting the extruder, the more pressure which may be used and still obtain the solloid product. Although the pressures of the inventive process have been found to be extraordinarily low as compared to conventional spray drying and congealing processes, the only limitations on the quantity of disruptive force used is that it not separate the non-fat solid substrate from the fat and that it produce a solloid as defined herein. Air pressures of from 2 to 11 psig have been used successfully, although the lower pressures are preferred.

While the mass of exiting extrudate may be a relatively dense stream of flowable material, in certain instances, i.e. certain compositions and high speed production equipment, it is preferable to design the nozzle head such that the flowable extrudate exits the extruder in the form of a hollow tube. This was accomplished in the present invention using a mandrel in the nozzle orifice to direct the flowable material between the nozzle wall and mandrel in much the same manner co-extrusion extruder heads operate. The hollow "tube" of flowable extrudate was then disrupted with a stream of gas in the same manner as described herein to form solloids.

Flash Heat Process

The following example describes the flash heat process which was used to make solloids in accordance with the present invention.

A mixture of solloid Composition A above was fed into a spinning machine equipped with a heated spinning head having a heating element including a plurality of elongate openings having a height between about 0.005 and about 0.01 inches. The rotational speed of the seven inch spinning head was 3,500 rpm. Depending on the size of the spinning head and the selection of the solid fat, the rotational speed can be from about 400 to 5,000 rpm. The heating element of the spinning head was at a temperature sufficient to cause flash heat of the fat whereby the fat underwent intraparticle flow. The flow temperature for Composition A was about 70° C.

As the solid composition was flash heat processed and flung through the openings of the spinning head into ambient air, discrete spheroidal solloids formed. As the solloids cooled in free flight the solid suspension and shape was locked-in. A sample of the solloids formed showed substantial uniformity in size and shape, with about 60% or more having a diameter in the ranges of less than about 300 to about 400 microns.

Chewing gum compositions were made in accordance with the present invention as shown in the table below. Each of the gums exhibited significant flavor and sweetness duration for periods of 60 minutes or longer.

CHewing GUM COMPOSITIONS
(% wt)

	1	2	3	4	5	6
Gum Base	27.00	26.00	26.00	24.00	26.00	24.00
Polym. Bulk Agent	59.83	58.78	56.15	59.35	58.74	60.275
Softener/Emulsifiers	4.55	9.75	9.75	11.10	10.50	10.50
Artificial Sweetener	0.17	0.17	0.20	0.05	0.16	0.225
Flavor	4.95	2.00	4.90	1.50	1.60	1.75
Soilicide Delivery System ¹	3.50*	3.30**	3.00**	4.00**	3.00**	2.75**

*Spearmint

**Peppermint

¹HPMC substrate/partially hydrogenated soybean oil (fat matrix)

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

While there have been described what are presently believed to be the preferred embodiments of the present invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention, and it is intended to claim all such changes and modifications as fall within the true scope of the invention.

What is claimed is:

1. A pharmaceutical product comprising:

a plurality of solloids, said solloids comprising a solid suspension of a solid non-fat substrate having an active associated therewith dispersed in a solid fat which is solidifiable at room temperature and having a flow point lower than the melting point of said non-fat solloid substrate, wherein a predominant amount of said solloids have substantially the active content and at least about 60% of said solloids in said plurality have a particle size less than about 300 to about 400 microns.

* * * * *

United States Patent [19]

Böcker et al.

[11] 4,086,346

[45] Apr. 25, 1978

[54] PREPARATION OF MELT-SPRAYED SPHERICAL PHENACETIN GRANULES

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[21] Appl. No.: 720,650

[22] Filed: Sep. 7, 1976

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 564,168, Apr. 1, 1975, abandoned, and Ser. No. 564,169, Apr. 1, 1975, abandoned.

[30] Foreign Application Priority Data

Apr. 6, 1974 Germany 2416903
Apr. 6, 1974 Germany 2416904

[51] Int. Cl.² A61K 9/16; A61K 31/32; A61K 31/165

[52] U.S. Cl. 424/253; 264/5; 264/13; 264/109; 264/117; 264/123; 264/319; 264/345; 264/349; 424/324

[58] Field of Search 264/5, 13, 109-117, 264/123, 319, 345, 349; 424/14, 253, 324

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[57] ABSTRACT

Substantially spherical granules of phenacetin are prepared by spraying liquid phenacetin which has been melted without decomposition by means of rapid passage through a melting device in which superheating is minimized. The resultant melt-sprayed granules are superior to crystalline phenacetin in the formulation of pharmaceutical tablets.

15 Claims, 6 Drawing Figures

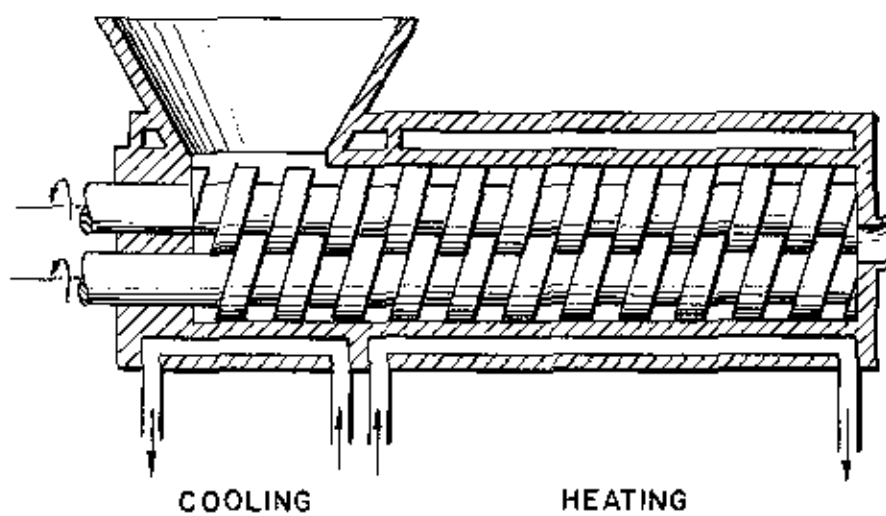
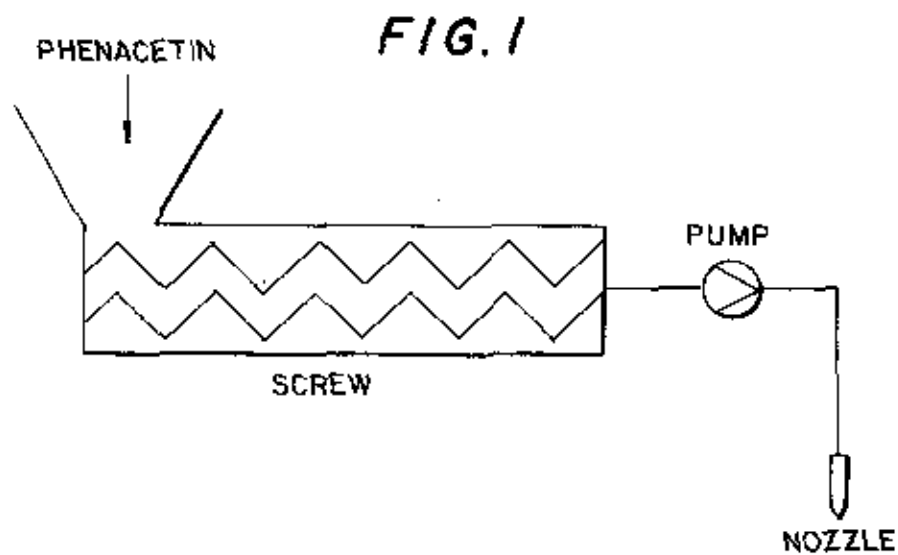
124
374**FIG. 2**



FIG. 3A

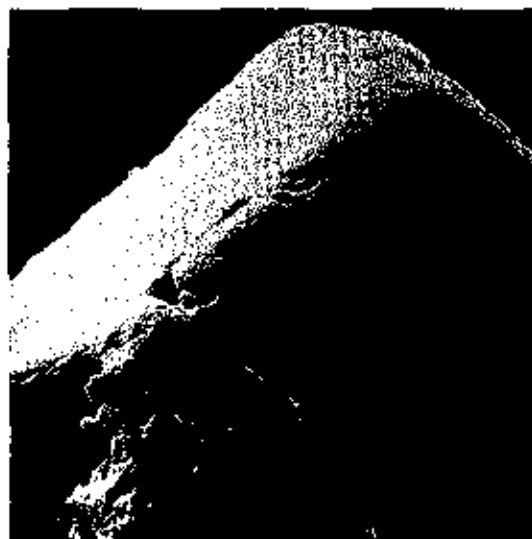


FIG. 3B



FIG. 4A



FIG. 4B

PREPARATION OF MELT-SPRAYED SPHERICAL PHENACETIN GRANULES

CROSS-REFERENCE

This is a continuation-in-part of Ser. Nos. 364,168 and 364,169, both filed Apr. 1, 1975, both now abandoned.

DETAILED DESCRIPTION

The present invention is concerned with melt-sprayed spherical phenacetin granules, their preparation and the formation of tablets therefrom.

A substance can be tableted directly if it can be compressed into tablets of good mechanical strength without the interposition of customary granulating processes; i.e., the formation by interrupted crystallization or precipitation of a finely crystalline granular powder. The ability to undergo direct compression is of importance in the production of tablets since a substance which is capable of being tableted directly should produce tablets of good mechanical properties even when tableted with auxiliaries on high speed tableting machines.

There are however few substances which can be compressed into tablets without prior granulation. These include ammonium bromide, ammonium chloride, ammonium iodide, potassium bromide, potassium chlorate, potassium chloride, potassium bichromate, potassium permanganate, sodium bromide, sodium chloride, sodium cyclamate, sodium thiosulphate, sodium citrate, hexamethylenetetramine, ipecacuanha powder and licorice extract [see W. A. Ritschel: "Die Tablette", Ed. Cantor Verlag, Aulendorf, 1966, page 217 and 218]. Other substances can be rendered directly compressible and tableted by means of additives. These include, inter alia, potassium aluminium sulphate, potassium aluminium iodide, potassium aluminium nitrate, calcium chloride, sodium tetraborate, aminophenazone, acetylsalicylic acid, chloral hydrate, camphor monobromate, pancreatin, pepsin and phenolphthalein.

A majority of other biologically active substances must be subjected to known granulating techniques in order to produce a finely crystalline granular powder capable of being compressed into tablets.

Phenacetin is known to be a substance which is distinctly difficult to convert to tablets. Thus attempts to tablet crystalline phenacetin having varied shape and particle size distribution results in tablets of poor mechanical strength which exhibit extensive capping and layer formation [see, e.g. Jaffe et al., J. Am. Pharm. Ass., 48, 26-29 (1959); Blacy et al., Pharm. Ind., 33, 897-900 (1971)]. To prepare suitable tablets from phenacetin, it has been necessary to granulate crystalline material having a particle size of 100 to 500 μ m or to granulate material which has been ground to a particle size of 20 to 60 μ m.

The production of phenacetin tablets can be produced by moist granulation as described in the British Pharmaceutical Codex of 1968. An auxiliary, such as sugar or starch, is admixed to the crystalline phenacetin powder and the mixture is moistened with an aqueous or alcoholic binder solution, such as starch, gluten, gelatin or sugar solution and then granulated. Thereafter, disintegrating agents and lubricants are admixed to the dried granules. After these expensive mixing, granulating and drying processes have been carried out, the thus treated phenacetin can then be compressed to give tablets.

F. Biedenbach, in *Pharmaz. Ztg.* 103, 104, 1958 similarly describes a preliminary treatment with polyvinyl pyrrolidone to convert phenacetin into crystalline granules which can be tableted.

It has now been found that melt-sprayed, substantially noncrystalline, phenacetin granules which are spherical in configuration have improved compressibility and in fact can be tableted directly by compressing the granules.

In this specification the word "tablet" means a compressed body which is composed of a plurality of discrete particles, and includes pills, lozenges and dragee cores. "Phenacetin" includes simple substituted derivatives of phenacetin. Tablets prepared from melt-sprayed spherical phenacetin granules have improved physical properties compared with conventional phenacetin tablets.

It is surprising that the phenacetin granules produced in accordance with the present invention exhibit such improved properties. According to the state of the art, it was not to be expected that an active compound in a spherical form would be easier to convert to tablets than an active compound in a crystalline form. Thus the literature contains very little experimentally verified information on the influence of particle geometry on compacting behavior. For pharmaceutical substances, apparently only the tableting behavior of crystalline and spherically spray-dried lactose has been studied. Indeed it has been suggested that the absence of a crystalline structure reduces the prospects of direct tableting [see, e.g. Ezuzian, *Pharm. Acta Helv.* 47, 323 (1972)]. Rounded crystal shapes, on the other hand, while showing better flow properties, at the same time reduce the hardness of the tablets so that irregular and sharp-edged crystals, coupled with relatively large crystal size, have been suggested as being necessary to obtain, on compression, a branched and multi-cross-linked tablet lattice which is rich in internal jagged points and spikes and therefore mechanically resistant. Hüttenrauch et al., *Die Pharmazie*, 23 475 (1968).

It has also been found that particles of potassium chloride having a rounded shape and a lower particle size distribution exhibit poorer compressive property than crystalline particles. [See, Lazarus et al., *J. Pharm. Sci.* 55, 1121-1127 (1966)].

The phenacetin granules of this invention are generally spherical in shape and are produced by melting the crystalline phenacetin, preferably in a special multi-screw extruder as described hereafter, and subsequently spraying the melt in a gaseous or liquid medium.

In the drawings,

FIG. 1 is a schematic presentation of the manufacturing elements utilized in the process and

FIG. 2 is a schematic cross section of the melting device.

FIGS. 3A-3B are scanning electron microscopic photographs of a commercial phenacetin crystal and

FIGS. 4A-4B are corresponding scanning electron microscopic photographs of a spherical granule according to the invention, respectively.

The phenacetin granules which can be used according to the invention preferably comprise at least 80% by weight of particles of size 20 - 500 μ m.

The phenacetin granules have good flow properties and do not tend to acquire an excessive electrostatic charge in the way that the previously commercially available material does. The granules can therefore be compressed into tablets either as a single substance or in

combination with further active compounds, and together with pharmaceutically acceptable excipients.

The ability of these granules to be compressed directly is of significant theoretical interest since it reflects the improved compressibility of the material. In practice such a tablet demonstrates insufficient disintegration to be of much therapeutic value.

Typical pharmaceutical excipients or auxiliaries include (a) fillers and extenders, as for example, edible carbohydrates such as starches, lactose, sucrose or glucose, mannitol and silica, (b) binders, such as for example, carboxymethylcellulose, alginates, gelatine, polyvinylpyrrolidone, lactose, glucose, sucrose, mannitol, calcium carbonate, calcium phosphate, polyethylene glycol, polyethylene oxides, cellulose, methylcellulose, hydroxyethylcellulose, amylose, pectins and sodium amylopectin glycolate, (c) humectants, such as for example, glycerol, (d) disintegrating agents, such as for example, agar-agar, calcium carbonate, sodium bicarbonate, starches, silicas, methylcellulose, alginic acid, alginates, formaldehyde-cascin, pectins, magnesium aluminium silicates, sodium bicarbonate, calcium carbonate, magnesium oxide and sodium amylopectin glycolate, (e) sustained release agents, such as for example, paraffin, (f) absorption enhancing agents, such as for example, quaternary ammonium compounds, (g) wetting agents, such as for example, cetyl alcohol and glycerol monostearate, (h) adsorbents, such as for example, kaolin and bentonite and (i) lubricants, for example talc, calcium stearate, magnesium stearate and solid polyethylene glycols. Mixtures of these materials can of course be present. Furthermore, anti-static agents, dyestuffs and flavoring agents, such as for example, aromas and sweeteners, can also be added to the tablet mixture.

The present invention includes a process for the preparation of these spherical phenacetin granules from the melt phase, and a device for carrying out the process.

It is well known that molten organic materials can be converted into granules by passing the molten material through a single nozzle, twin nozzle, or spinning disc atomiser and allowing subsequent solidification in a gas or a liquid; see, e.g. W. Boretzky, in "Fette-Öle-Anstrichmittel," No. 4, 1967, pp. 263-268 and G. Matz "Kristallisation in der Verfahrenstechnik" Springer 1957, pp. 284-291. These processes are preferably carried out with materials which are not sensitive to heat. Thus, W. Boretzky reports that stearic acids, paraffins and synthetic resins can be granulated in this way.

This procedure is unsuitable for heat-sensitive substances since these tend to discolor and decompose on heating to, or above, their melting points. Previously, such substances have been processed in the melt phase without degradation only if suitable reducing agents were added. German Offenlegungsschrift No. 1,617,933 discloses for example that pharmaceutically active compounds can be fused without decomposition if mixed with reducing agents, such as aqueous hydrazine solutions or ammonium formate solutions.

In the case of medicaments such as phenacetin, however, any such reducing agents which are used in the preparation of granules must be completely removed in order to meet purity requirements. The latter process is therefore disadvantageous in that pure active compound is contaminated in order to fuse it, and a further purification step is thus necessary.

In accordance with this invention, it has been found that phenacetic granules can be prepared from molten phenacetin without reducing agents. Broadly, the phe-

nacetin is melted, while preventing local superheating, to temperatures more than 15° F, preferably 10° C, above its melting point, and subsequently atomized, the phenacetin being maintained in a molten condition for a period not longer than 20 minutes, preferably not more than 10 minutes, prior to atomization.

More specifically, crystalline phenacetin is fused, without addition of a reducing agent or other auxiliary, in a continuously operating melting device which provides a low residence time and a narrow residence time spectrum, and subsequently atomizing the molten phenacetin. The melting device has heated surfaces maintained at temperatures of from 150° to 300° C and preferably comprises a plurality of intermeshing self-cleaning screws.

Although it has been reported that phenacetin can be heated above its melting point without decomposition [see Zaputisav et al., *Khim. Farm. Zh.*, 3, No. 5, 1969, pp. 51-54], according to Offenlegungsschrift No. 1,617,933, phenacetin decomposes even near the melting point if no suitable reducing agent is present. It was thus surprising that phenacetin which has been reported as being heat-sensitive, is not discolored or decomposed in a melting device having wall temperatures more than 100° C above the melting point.

The melting device used is preferably a heated intermeshing and self-cleaning multi-screw device with a narrow residence time spectrum and little play between both the screw crests and housing, and the screw flanks. A twin-screw device in which the screws rotate in the same direction and the play, relative to the diameter of one of the screws, is preferably from about 4×10^{-3} to about 30×10^{-3} is particularly suitable for gently melting the material. Such a twin-screw device was high heat transfer indices because of its particularly intense mixing effect, and therefore has a small volume filled with product. Additionally, because of its self-cleaning kinematics, deviations from the means residence time, which in any case is very short, are only slight. For example, the mean residence time is desirably no longer than ten minutes, and the total residence time is desirably no more than 20 minutes.

The intake zone of this melting screw should preferably be cooled to prevent difficult to handle pasty states of the material, formed by premature incipient melting, from hindering the flow of the crystalline phenacetin powder in the hopper zone. This intake zone is followed, in the feed direction, by a sealed, externally heated housing zone. Here, the powder is warmed to the melting point and undergoes intense forced convection. It then passes through a melting zone in which the consistency of the powder changes via pasty states to a mobile melt. It is particularly because of these states of the material, which are difficult to handle, that the use of the screw system described is of advantage. The screw shafts themselves can also be heated, in addition to the external heating of the housing, which has been mentioned.

The twin screw mentioned makes it possible to use very large temperature differences between the heating medium and the phenacetin without the latter issuing from the screw at temperatures which, on average, are more than 2° to 3° C above the melting point and without local superheating of the phenacetin to temperatures more than 10° C above its melting point. With a view to a short residence time and slight heat exposure, it is desirable to locate the end of the melting zone as close as possible to the exit from the screw. The melt

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2/6

issuing from the screw is fed, either directly or via a small intermediate container, to a heated pump and is brought to the atomizing pressure by this pump. Any components of the apparatus located between the screw and the atomizing device, as a precautionary measure, should only be heated to a few degrees above the melting point. The total residence time in the liquid phase should not exceed 20 minutes and desirably throughout the melting device such that 95% of any batch of phenacetin is passed through the device within 15 minutes.

The solidification of the atomized phenacetin takes place in a known manner in a gas, such as air, nitrogen, an inert gas or carbon dioxide, or a liquid such as water. When solidified in a gas, the product is obtained in its final form while when solidified in a liquid, it must be subsequently dried. As will be seen from FIGS. 3A, 3B, 4A and 4B the surfaces of crystalline phenacetin are substantially less structured and have a comparably more uniform surface. The spherical-granulate particle on the other hand shows a cracked surface which, under the stronger magnification of FIG. 4B, reveals itself to be fissured and structured. The cracks presumably are stress cracks, produced upon the cooling of the molten material and can be influenced by the spraying and cooling conditions.

The spherical phenacetin granules thus obtained in contrast to crystalline phenacetin, can be tableted directly; i.e., after simple admixture with customary tableting auxiliaries, it can be molded on high output tableting presses to yield tablets having good mechanical properties.

When the ultimate strength of tablets (two fractions of 250/500 μ m and 63/160 μ m, for each of phenacetin crystals and phenacetin spherical granules) is measured as a function of the pressure of the upper punch, there can be noted an initial increase in the strength with an increase in the compacting pressure. After a critical maximum compacting pressure has been reached, all the tablets show lamination and a tendency towards capping. In the low-pressure range (below 40 MN/M²), tablets of phenacetin crystals exhibit higher strength than tablets of phenacetin spherical granules. In the case of crystals, the compacting pressure for the 63/160 μ m fraction cannot be increased beyond about 35 MN/M² (about 350 kg/cm²) without extensive lamination of the tablets occurring. In the case of the 250/500 μ m fraction, it cannot be increased beyond about 45 MN/M² (about 450 kg/cm²). The maximum strength of tablets of phenacetin crystals lies in the range from just below 2 to just above 2 kg.

In the case of the coarse fraction (250/500 μ m) of the spherical granules, the maximum strength of the tablets which can be obtained is 1½ times as great as that of crystals. The difference is even clearer in the case of the fine fraction. With the 63/160 μ m fraction of the spherical granules, a 2½ times greater strength could be obtained than is observed for the corresponding fraction of the crystal.

The influence of the compacting pressure on the porosity of the tablet of phenacetin crystals and phenacetin spherical granules of the same screen fractions can also be seen. With an increase in the pressure, the material is more strongly compacted in the form of the tablet compacts, while the porosity decreases. For both crystal fractions, critical limit values of porosity are reached at a relatively low compacting pressure (around 40 MN/M²) and further increase in pressure results in lamination of the tablets. Phenacetin spherical granules can

be compacted at substantially higher pressure (about 80 MN/M²) before lamination occurs in the tablet. Thus this material can be compacted to substantially lower values of porosity. When comparing the two fine fractions, a porosity of about 17% is obtained for phenacetin crystals and a porosity of about 8% for the spherical granules. With the crystals and spherical granules, stronger compacting and therefore lower porosity is obtained in each case with the coarser fraction than when employing a comparable compacting pressure with the finer fraction.

Typical tablets are prepared, for example, by using melt-sprayed spherical phenacetin granules in which 80% by weight have a particle size range of from about 20 to about 500 μ m, adding 5-40% of micro-crystalline cellulose, 5-30% of starch and 0.05-1% of highly disperse silica (the percentages in each case being by weight, relative to phenacetin), mixing these constituents and compressing on a suitable tableting machine.

The following examples will serve to further typify the invention without being a limitation on the scope thereof. Examples 1-4 describe the preparation of granules. Example 5 is a comparative example utilizing crystalline phenacetin and Examples 6-8 describe tablets which were produced by direct compressing that is to say without dry granulation or moist granulation. The comparison of the results with crystalline phenacetin and melt-sprayed spherical phenacetin granules clearly shows that when using the granules and products with substantially improved properties result, in addition to the technical advantages provided by direct tableting compared to conventional working with crystalline phenacetin.

The tableting machines used in Examples 5-8 included various customary rotary machines and also high speed rotary machines.

EXAMPLE 1

Crystalline phenacetin was fused in an intermeshing twin screw device in which the screws rotate in the same direction, having a 32 mm external screw diameter, 17 mm root diameter and 770 mm screw length, with wall temperatures of 190° C. The residence time was 3.2 minutes in the screw and the throughput rate was 8 kg/hour. The melt was atomized at temperatures of about 140°, by means of a piston pump, with a vortex chamber nozzle in air at 20° C. The total residence time during which the product was exposed to heat was 13 minutes. The product was of requisite purity according to USP XVII, and had the following particle size distribution:

- 10% < 126 μ m
- 50% < 242 μ m
- 90% < 332 μ m

It was very free-flowing and non-dusting.

EXAMPLE 2

Crystalline phenacetin was fused in the twin screw described in Example 1, at wall temperatures of 210° C, using a residence time of 1.4 minute in the screw. The throughput rate was 18 kg/hour. The material was atomized at temperatures of about 140° C by means of a piston pump with a vortex chamber nozzle, in air at 20° C. The total residence time of the product was 6 minutes. The product conformed to the purity requirements of USP XVIII and had the following particle size distribution:

- 10% < 80 μ m

50% < 160 μ m
90% < 212 μ m

EXAMPLE 3

Crystalline phenacetin was fused in the twin screw described in Example 1, at wall temperatures of 270° C. The residence time in the screw was 1 minute and the throughput rate was 26 kg/hour. The melt was atomized at temperatures of about 140° C by means of a piston pump with a vortex chamber nozzle, in air at 20° C. The total residence time during which the product was exposed to heat was 4 minutes. The solidified product had the requisite purity and the following particle size distribution:

10% < 91 μ m
50% < 168 μ m
90% < 247 μ m

EXAMPLE 4

Crystalline phenacetin was fused in the twin screw described in Example 1, at wall temperatures of 210° C. The residence time in the screw was 1.5 minute. The throughput rate was 17 kg/hour. The melt was atomized at a temperature of 142° C by means of a piston pump, with a vortex chamber nozzle, in water at 20° C. The total residence time during which the product was exposed to heat was 6 minutes. The solidified and dried product had the requisite purity and the following particle size distribution:

10% < 38 μ m
50% < 104 μ m
90% < 230 μ m

EXAMPLE 5

(Comparative)

Crystalline phenacetin	500 g
Micro-crystalline cellulose	50 g
Maize starch	28 g
Highly disperse silica	2 g

The mixed constituents are converted to tablets weighing 580 mg on a 20-stamp rotary press with one compression station, at a machine output of 25,000 tablets per hour.

The tablets have a low hardness and show marked layering and capping.

The example confirms statements in the literature that crystalline phenacetin cannot be compressed directly into tablets.

EXAMPLE 6

Melt-sprayed phenacetin	500 g
Micro-crystalline cellulose	50 g
Maize starch	28 g
Highly disperse silica	2 g

As a result of replacing the crystalline phenacetin by melt-sprayed phenacetin, tableting under the same conditions as in Example 5 gives tablets which show no layering, no capping and good hardness. The tablets of Example 5 have a hardness of 1-1.5 kg while the tablets of Example 6 have a hardness of 5-6 kg.

EXAMPLE 7

Melt-sprayed phenacetin	250 g
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-continued

Caffeine	50 g
Micro-crystalline cellulose	30 g
Maize starch	19 g
Highly disperse silica	1 g

A mixture of the constituents in the stated ratios is converted to tablets weighing 350 mg on a high speed press. Tablets of hardness 3-4 kg, which show no capping and no layering, are obtained at an output of 100,000-150,000 tablets per hour.

EXAMPLE 8

Melt-sprayed phenacetin	250 g
Caffeine	50 g
Micro-crystalline cellulose	30 g
Maize starch	18.7 g
Highly disperse silica	10.1 g
Magnesium stearate	0.3 g

The composition of Example 8 differs from that of Example 7 in that magnesium stearate is added as lubricant. The addition of lubricant can largely be omitted if the desired tablet is flat faced and has no marks imprinted in it. If the melt-sprayed phenacetin is replaced by crystalline phenacetin in Examples 7 and 8, tablets of hardness 0.5-1 kg and which show severe capping are obtained.

The superiority of the melt-sprayed phenacetin granules over crystalline phenacetin manifests itself not only in conjunction with further additives, as in the preceding examples 6 to 8, but also when the material is pressed by itself, without additives. The maximum achievable crushing strength of a test tablet of 20 mm diameter and weighing 2 g is approximately 1.9 kg for crystalline phenacetin and approximately 4.4 kg for the melt-sprayed phenacetin according to the invention. In these experiments, the same particle size range (63-160 μ m) and the same compressing speed (4 strokes/minute with a reciprocating tableting machine) were used for both types of phenacetin.

What is claimed is:

1. A process for preparing melt-sprayed spherical phenacetin granules which comprises passing crystalline phenacetin through a melting device having heated surfaces maintained at temperatures of from 150° to 300° C at such a rate that the total residence time of the molten phenacetin in the melting device does not exceed 20 minutes and the average residence time does not exceed 10 minutes, and atomizing the melted phenacetin thus produced.

2. A process according to claim 1 wherein the melting device comprises a plurality of intermeshing self-cleaning screws.

3. A process according to claim 2 wherein the melting device comprises two like intermeshing self-cleaning screws arranged in a housing for rotation in the same direction and having clearances between the screw flanks and between the screw crests and the housing of less than 30×10^{-3} times the diameter of the screw.

4. A process according to claim 4 wherein the phenacetin is heated to a temperature not more than 10° C above its melting point.

5. A process according to claim 4 wherein the phenacetin is fused by passage through a melting chamber having walls maintained at a temperature of from 150°

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to 300° C at such a rate that the phenacetin is in molten state no more than 10 minutes.

6. Substantially spherical melt-sprayed granules consisting essentially of pure phenacetin produced in accordance with the process of claim 1.

7. Spherical melt-sprayed granules of phenacetin according to claim 6 in which about 80% by weight have particle sizes of from about 20 to about 500 μ m.

8. In the process of preparing compressed pharmaceutical tablets containing phenacetin produced in accordance with the process of claim 1 as a therapeutic agent the improvement which comprises tableting a composition in which the phenacetin is in the form of substantially spherical melt-sprayed granules of pure phenacetin.

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9. The process according to claim 8 wherein about 80% by weight of said granules have particle sizes of from about 20 to about 500 μ m.

10. A compressed pharmaceutical tablet comprising phenacetin as a therapeutic agent wherein the phenacetin which is compressed is in the form of substantially spherical melt-sprayed granules produced in accordance with the process of claim 1.

11. A tablet according to claim 10 which additionally contains at least one filler and at least one binder.

12. A tablet according to claim 11 wherein the filler includes at least one member selected from the group consisting of an edible carbohydrate, mannitol or silica.

13. A tablet according to claim 12 wherein the filler is starch and highly dispersed silica.

14. A tablet according to claim 12 which additionally contains a lubricant.

15. A tablet according to claim 10 which additionally contains caffeine.

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United States Patent [19]**Walsh**[11] **Patent Number:** **6,139,872**[45] **Date of Patent:** **Oct. 31, 2000**[54] **METHOD OF PRODUCING A VITAMIN PRODUCT**[75] **Inventor:** Leo Walsh, Lisle, Ill.[73] **Assignee:** Henkel Corporation, Gtlfh Mills, Pa.[21] **Appl. No.:** 08/917,049[22] **Filed:** Aug. 13, 1997**Related U.S. Application Data**[63] **Continuation-in-part of application No. 08/096,767, Aug. 14, 1996. Pat. No. 5,686,632.**[51] **Int. Cl.** A61K 9/14; A61K 9/20[52] **U.S. Cl.** 424/464; 424/465; 424/489; 424/195.1; 514/951[58] **Field of Search** 424/464, 465, 424/489, 195.1[56] **References Cited****U.S. PATENT DOCUMENTS**

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[57] **ABSTRACT**

A process for producing a nutrient supplement powder is provided. The process forms a powder into a plastic mass which is not completely molten. The plastic mass is then formed into an elongated shape and allowed to cool to set to a solid state. The solid is then comminuted to obtain a powder having a desirable particle size, e.g. not more than 5% by weight through a 120-mesh sieve and not more than 5% by weight retained on a 14-mesh sieve.

41 Claims, No Drawings

METHOD OF PRODUCING A VITAMIN PRODUCT

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 08/696,767, filed Aug. 14, 1996 U.S. Pat. No. 5,686,632, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to a method of producing a particulate material tablet from heat sensitive nutritional supplement materials. The particulate materials have a desirable particle size.

BACKGROUND OF THE INVENTION

Nutritional supplements such as tocopherol compounds, also designated as vitamin E, are active components in vegetable oils. Vitamin E activity refers to the physiological activity of this group of nutritional materials. Materials having a vitamin E activity all belong to a distinct series of compounds which are all derivatives of chroman-6-ol. These compounds are all tocopherol derivatives having an isoprenoid C16-sidechain. The term "tocopherol" is used to mean 2-methyl-2-(4',8',12'-trimethyltridecyl)chroman-6-ol. These compounds are alpha-, beta-, gamma-, and delta-tocopherol, and are of primary importance for vitamin E activity. Of these, alpha-tocopherol has the highest vitamin E activity and is the most valuable. The invention also relates to other nutrient supplements, such as phyosterols vitamins, which have relatively low melting points and are difficult to form into particulate materials.

The naturally occurring tocopherol homologs are generally isolated from natural products such as vegetable oil sources by various combinations of procedures such as esterification, saponification, extraction, distillation, ion exchange, adsorption chromatography, precipitation of sterols, and crystallization. The tocopherol concentrate isolated will vary depending on the particular separation technique used in addition to the vegetable source. One such concentrate, for example, contains mixtures of tocopherol with approximately 40% by weight residual sterols and hydrocarbons.

A well known commercial activity is the conversion of tocopherol, and especially α -tocopherol, into a solid form for convenient human consumption. One of the best methods commercially used to solidify tocopherol is to prepare tocopheryl succinate. Typically, tocopheryl succinate is prepared by reacting tocopherol with succinic anhydride, and then isolating the half ester product by crystallization. References describing methods of this nature are described in U.S. Pat. No. 3,538,119 and in British Patent No. 866,489. Another reference which describes both the preparation of alpha-tocopheryl succinate and its recovery is British Patent No. 1,114,150.

For medicinal and health applications requiring tocopherol, solid tocopherol derivatives are preferred. It is desired that such tocopherol derivatives be capable of dissolving in an aqueous solution and be highly potent with a high degree of vitamin E biological activity per unit. The preparation of tocopherol derivatives is described in U.S. Pat. No. 2,680,749, which describes, as a preferred method, reacting tocopherol with a suitable polybasic acid anhydride such as succinic acid anhydride under usual esterification conditions.

Tocopheryl succinate, which is a vitamin E, melts at about 73°-78° C. It is a white solid material which at room temperature is waxy and tacky and which has poor flow properties. Furthermore, the commercially available tocopheryl succinate ordinarily has a broad particle size distribution with many fine particles which causes the powder to be cohesive and to form lumps.

A number of attempts have been made to prepare free-flowing tocopheryl succinate with and without additives. A prior art method is disclosed in U.S. Pat. No. 3,551,457. In this method tocopheryl succinate is heated to melt it, i.e., to about 85° C., and the melt is poured into a shallow pan so as to form a layer having a thickness of between 0.3 and 2.5 cm, after which the melt is allowed to harden and crystallize over a period of 12-24 hours. The resulting mass is then ground at a low temperature, preferably at a temperature of about -80° C.

British Patent No. 1,007,161 discloses another method of preparing free-flowing, powdered tocopheryl succinate having a high bulk density. In the method tocopheryl succinate is melted and the melt is dispersed in an aqueous solution containing a thickening agent in the form of methyl cellulose, and subsequently the dispersion formed is quickly cooled so as to cause the tocopheryl succinate to crystallize to form fine particles which are separated and dried. A product thus prepared has a relatively broad particle size distribution which causes problems in the treatment of the product in known tableting machines. Furthermore, the use of methyl cellulose as thickening agent results in a certain tackiness which imparts to the product a tendency to adhere to e.g., parts of the tableting machine.

U.S. Pat. No. 4,870,196 (Thorengaard) discloses a method of preparing powdered, free-flowing tocopheryl succinate having a high bulk density comprising melting a mixture of tocopheryl succinate and wax, spraying the melt in a spraying zone containing a cloud of a powdering agent consisting of fine tocopheryl succinate and an additional powdering agent, and maintaining the product formed in a fluidized state by introducing cooling air until the tocopheryl succinate particles have hardened, and separating the product formed into a product fraction and a fine fraction, and recycling the fine fraction to the spraying zone.

Thorengaard reports that attempts to prepare tocopheryl succinate in the form of particles coated with other agents that the ones described above have not produced satisfactory results as these attempts have resulted in the reduction of the tocopheryl succinate content of the final product. It is stated that this is undesirable because of the subsequent preparation of high-dosed capsules and tablets since for such use it is desirable that the starting material contains as much tocopheryl succinate as possible and that it also has a high bulk density.

Phyosterols may be used in the present invention and are also derived from the plant kingdom, and some of them are desirable nutritional supplements because they are believed to reduce cholesterol.

SUMMARY OF THE INVENTION

This invention relates to a method of producing a particulate nutritional supplement comprising heating a mass of the nutritional supplement to an elevated temperature to form a plastic mass and cooling said plastic mass to form a solid. The elevated temperature is low enough that a plastic mass is formed but the nutritional supplement composition is not completely melted. Thus, the temperature of the entire mass will not exceed the melting point of the nutritional

supplement. The mass is typically divided into discrete portions, e.g. multiple ropes of extrudate, prior to cooling and setting. The extruder may be fit with an injection molding head to form tablets directly or with an atomizer head to form particulates. The mass is preferably essentially free of added physiologically inert binders, e.g. natural or synthetic polymers that are added thereto. The material can comprise mixtures of materials, the nutritional supplement acting as a nutritionally active matrix for other nutritional supplements (vitamins minerals and the like) not capable of behaving plastically, and thus less desirable as a nutritionally active matrix. The preferred active matrix nutritional supplements are tocopheryl succinate and phytosterols. Unexpectedly, these materials are believed to exhibit plastic behavior upon heating and are defined as "plastic nutritional supplements" to avoid the awkward "nutritional supplements that are capable of becoming plastic upon heating."

Generally the method is useful for providing particulate materials from relatively low melting point materials which are slow to crystallize. The mixture is mixed and heated to form a plastic mass. The plastic mass is preferably extruded and cooled, then ground to form the particulate material. All quantities herein, except in the examples, are understood to be modified by "about."

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to a method for producing particulate materials. The starting material is a solid material and at no point in this process of size enlargement is the mass of material heated above its melting point so as to melt the entire mass of material. Thus, the plastic mass of material is a shapeable, e.g. moldable or extrudable, material as opposed to a fully liquid melt. The product of the process is, in a sense, agglomerated particles of the nutritional supplement material and the process may be characterized as an agglomeration process. The nutritional supplement materials which can be processed by the method of the invention comprise materials which are solid at 40° C. and are molten by 170° C. Preferably, materials which are solid at 45° C. and are molten at 100–125° C. and most preferably materials that are solid at 50° C. and are molten at 90° C., when using tocopheryl succinate.

Examples of the above include organic materials such as tocopheryl succinate and phytosterols and their derivatives such as sterols, stanols (hydrogenated sterols), sterol esters and stanol esters. Specific examples of these phytosterols and their melting points include: alpha-sitosterol (164–166° C.), beta-sitosterol (140° C.), gamma-sitosterol (no data), campesterol (157–158° C.), stigmasterol (170° C.), stigmasterol (144–145° C.), brassicasterol (151–152° C.) and ergosterol (144–145° C.). Blends of phytosterols based on plant extracts that melt between 135–141° C. are 43–53 wt. % beta-sitosterol, 23–26 wt. % campesterol, 17–19 wt. % stigmasterol, less than 2 wt. % stigmasterol (a.k.a. beta-sitosterol), less than 2 wt. % campestanol, 2 wt. % brassicasterol. At least 80 wt. % active sterol and stanol in the plant extract is desired, the balance being tocopherol, squalene and other plant wax impurities.

To the above active matrices may be added nutritional supplements with less plastic behavior as solid state solutions or insoluble particulate filler and oils.

These nutritional supplement additives of lesser plasticity include vitamins such as: vitamin A (retinol, retinyl palmitate and retinol acetate), vitamin B1 (thiamin, thiamin hydrochloride and thiamin mononitrate), vitamin B2

(riboflavin), vitamin B3 (niacin, nicotinic acid and niacinamide) vitamin B5 (pantothenic acid, calcium pantothenate, d-pantothenol and d-calcium pantothenate), vitamin B6 (pyridoxine, pyridoxal, pyridoxamine and pyridoxine hydrochloride), vitamin B12 (cobalamin and cyanocobalamin), folic acid, folate, folacin, vitamin H (biotin), vitamin C (ascorbic acid, sodium ascorbate and calcium ascorbate), vitamin D (cholecalciferol, calciferol and ergocalciferol), vitamin E (d-alpha-tocopherol, d-beta-tocopherol, d-gamma-tocopherol, d-delta-tocopherol and d-alpha-tocopheryl acetate) and vitamin K (phyloquinone and phytonadione).

Nutritional supplement additives also include minerals such as boron (sodium tetraborate decahydrate), calcium (calcium carbonate, calcium caseinate, calcium citrate, calcium gluconate, calcium lactate, calcium phosphate, dibasic calcium phosphate and tribasic calcium phosphate), chromium (gift chromium from yeast, chromium acetate, chromium chloride, chromium trichloride and chromium picolinate) copper (copper gluconate and copper sulfate), fluorine (fluoride and calcium fluoride), iodine (potassium iodide), iron (ferrous fumarate, ferrous gluconate and ferrous sulfate), magnesium (magnesium carbonate, magnesium gluconate, magnesium hydroxide and magnesium oxide), manganese (manganese gluconate and manganese sulfate), molybdenum (sodium molybdate), phosphorus (dibasic calcium phosphate, sodium phosphate), potassium (potassium aspartate, potassium citrate, potassium chloride and potassium gluconate), selenium (sodium selenite and selenium from yeast), silicon (sodium metasilicate), sodium (sodium chloride), strontium, vanadium (vanadium sulfate) and zinc (zinc acetate, zinc citrate, zinc gluconate and zinc sulfate).

Nutritional supplement additives also include amino acids such as: alanine, arginine, asparagine, aspartic acid, carnitine, citrulline, cysteine, cystine, dimethylglycine, gamma-aminobutyric acid, glutamic acid, glutamine, glutathione, glycine, histidine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine and valine.

Nutritional supplement additives also include animal extracts such as: cod liver oil, marine lipids, shark cartilage, oyster shell, bee pollen and d-glucosamine sulfate.

Nutritional supplement additives also include unsaturated free fatty acids such as: linoleic, arachidonic and linolenic.

Nutritional supplement additives also include herbs and plant extracts such as: kelp, pectin, Spirulina, fiber, lecithin, wheat germ oil, safflower seed oil, flax seed, evening primrose, borage oil, black currant, pumpkin seed oil, grape extract, grape seed extract, bark extract, pine bark extract, french maritime pine bark extract, muira puama extract, fennel seed extract, dong quai extract, chaste tree berry extract, alfalfa, saw palmetto berry extract, green tea extracts, angelica, catnip, cayenne, comfrey, garlic, ginger, ginseng, goldensal, juniper berries, licorice, olive oil, parsley, peppermint, valerian, white willow, yellow dock and yerba mate.

Nutritional supplement additives also include enzymes such as: amylase, protease, lipase and papain as well as miscellaneous substances such as: menaquinone, choline (choline bitartrate), inositol, carotenoids (beta-carotene, alpha-carotene, zeaxanthin, cryptoxanthin and lutein), para-aminobenzoic acid, betaine HCl, eicosapentaenoic acid, omega-3 fatty acids, alpha-lipoic acid, thiolic acid, 1,2-dithiolane-3-pentanoic acid, 1,2-dithiolane-3-valeric acid, flavanoids, flavanones, flavones, flavonols, isoflavones,

proanthocyanidins, oligomeric proanthocyanidins, vitamin A aldehyde, a mixture of the components of vitamin A₂, the D Vitamins (D₁, D₂, D₃ and D₄) which can be treated as a mixture, ascorbyl palmitate and vitamin K₂.

Some vitamins such as trans vitamin A₂, 9, 13 di-cis vitamin A₂, and d-alpha tocopherol are liquids at room temperature. However, they can be treated by the method of the invention if they are heated in a mixture with other vitamins having melting points within the required range as long as the mixture can be solidified at room temperature. The method of the invention can be utilized to form particulate materials from vitamins which have melting points above 170° C. if they are mixed with the plastic nutrient supplements, tocopheryl succinate and phytosterols, having melting points within a 40° C. to 170° C. range.

The method of the invention is particularly useful for providing mixtures of vitamins in particulate form which can be easily tableted or used to fill capsules.

Vitamins which are liquid at room temperature such as vitamin E (α-tocopherol), vitamin K, or vitamin E acetate can be mixed with the plastic nutrient supplements and formed as particulate materials by the method of the invention.

Nutritional supplements with melting points higher than 170° C. can be mixed with plastic nutritional supplements. When the nutritional supplements have a melting point far above 170° C., the particles of any additional supplements are supported in a matrix of the lower melting plastic supplements. The mixture can also contain vitamins which are liquid at room temperature as long as the mixture (high melting point vitamins, vitamins which are molten at temperatures from 40° C. to 170° C., and liquid vitamins) is a solid at room temperature.

The process will be described in relation to the vitamin tocopheryl succinate but it is realized that the method can be applied to phytosterols as well and mixtures of plastic and less plastic nutritional supplements. The present invention permits the manufacture of multiple vitamin formulations in particulate form which can be easily fed to machines for automatically forming tablets and filling capsules. Also, the extruder can be fitted with an injection molding head comprising a die with runners and tablet shaped cavities to form tablets or pills directly or fitted with an atomizer head to form particulates.

The materials which can be processed by the method of the invention include single nutritional supplements and mixtures of supplements in variable proportions. The proportions are dependent upon the physical properties of the materials in the mixture and in particular their melting points. Generally liquid supplements can only be mixed in small portions with materials which are liquid in themselves at 40° C. or 50° C. High melting point materials (melting point above 170° C.) can be mixed with lower melting point materials in higher amounts as long as the product has sufficient strength to be comminuted without crumbling or producing unacceptable amounts of fine particles.

The invention will be described in relation to the preparation of powder tocopheryl succinate but the method can be applied to other plastic nutritional supplements which melt in the range of 40° C. to 170° C. alone, in admixture with each other or in admixture with vitamins which are liquid at temperatures below 40° C.

The vitamin materials which have melting points from 40° C. to 170° C. can be difficult to prepare in a particulate form on a commercial scale due to the difficulty with solidifying some of the compositions if they are melted. The present method does not form a melt of the material but only heats the material to a temperature at which a plastic mass which can be extruded is formed. Formation of a plastic

mass permits rapid solidification of the material after the material is forced from the extruder.

The temperature of the material in the extruder is below the melting point of the plastic nutritional supplements but at a temperature at which a plastic mass is formed. Generally the temperature of the plastic mass in the extruder will be from 2° C. to 25° C. and preferably at least 5° C. below the melting point of the plastic supplements which melt within the range of 40° C. to 170° C. The temperature is controlled at the point where the mass in the extruder is plastic not molten. The products of the invention are substantially free of nutritionally inactive binders for the plastic nutrient supplement which forms the particulate material. While not wishing to be held to any theory, it is possible for a material to be at its melting temperature but yet not completely liquified.

The invention will be described in relation to forming a powder from the partial succinic acid ester of a tocopherol (hereinafter tocopheryl succinate); however, the method can be applied to form particulate material from the plastic nutritional supplements, mixtures and other compositions heretofore described.

In typical embodiments, the process can be characterized as extrusion of a plastic mass of particulate tocopheryl succinate (preferably the starting material comprises a substantial portion, e.g. at least 5% by weight, of particles which pass through an 80-mesh (U.S. standard) sieve) wherein the temperature of the particulate material is sufficient to plasticify the mass, but insufficient to melt all of the solid particles of said tocopheryl succinate. The tocopheryl succinate to be used in the practice of the invention is typically in the free acid form. However, pharmaceutically acceptable salts, e.g. the sodium or potassium salts may also be useful.

The tocopheryl succinate or other plastic nutritional supplement used as a starting material in this invention are, typically, initially in the form of particulate material which can be mixed with other vitamins some of which may be liquid.

The tocopheryl succinate is preferably free of added inactive binders. Examples of binders include water-soluble celluloses, pregelatinized starches, and water-soluble macromolecules. The water-soluble celluloses include hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose and methylcellulose. A pregelatinized starch is a product obtained, for example, by heating a dispersion of starch in water, followed, as desired, by drying. Examples of water-soluble macromolecules includes polyvinylpyrrolidone (e.g. M.W. 10,000-100,000), polyvinyl alcohol (e.g. M.W. 10,000-50,000), dextrin, gum arabic, gum acacia, and gelatin. The tocopheryl succinate is also typically essentially free of solvents such as water or organic solvents, e.g. alcohols (e.g. methyl alcohol, ethyl alcohol, isopropyl alcohol) and ketones (e.g. acetone) and hydrocarbons, (e.g. hexane).

The tocopheryl succinate particulate material is subjected to sufficient heat and pressure to render it plastic. However, the temperature must be low enough that the entire mass does not melt. Without wishing to be bound by any particular theory, unless otherwise expressly noted, it is believed that the predominant portion by weight of the mass remains as solid particles, but that these particles are mixed with a phase of the tocopheryl succinate that is rendered fluid as a result of the heat and/or pressure. Upon exit of the resulting plastic mass from the zone of heat and/or pressure, the fluid phase reverts to solid form much more quickly than a fully melted liquid of tocopheryl succinate.

An extruder has been found to be particularly useful in forming and shaping the plastic mass of tocopheryl succinate. Extruders are generally described in *Encyclopedia of*

Polymer Science and Engineering, vol. 11, pp. 262-267 (John Wiley & Sons, Inc., N.Y., N.Y. 1988) the disclosure of which is incorporated herein by reference. The extruders useful herein may vary. Although single screw extruders can be employed, preferred extruders are the twin screw extruders of which the co-rotating twin screw extruders are especially preferred. Of particular interest are the so-called "cooker extruders" which provide for heating of the materials which are introduced within the extruder. Various screw configurations can be employed. For example, screws having combinations of elements for feeding, mixing, pumping, shearing, and the like, can be selected as desired for optimum results. Screws having sections or elements which provide relatively large output capacities, which have interrupted or nonconjugated flights, or which are "counter-flighted" or "reversing" also can be employed. Typical screw elements as well as screws having combinations of such elements are available from extruder manufacturers. The length to diameter ratio of the extruder will typically range from 10:1 to 50:1. The plastic mass is preferably divided into discrete portions, typically by passage through a die having a plurality of openings therein. Thus, dies for practicing the invention have a multiplicity of very small die openings or holes. All openings for any one die are preferably of equal size (i.e. equal in area dimension). The openings may vary from 0.1 to 4 millimeter diameter for different dies. Square or multi-sided openings may be used, but ideally, the openings are circular to give a cylindrical shape to resulting extrusions. The die is preferably oriented in a horizontal plane for vertical passage of the extruded material through the die. Such vertical discharge helps to prevent the initial material through the die from fouling the die openings. A heated die plate, i.e. one heated to the temperature of the last extruder zone, is also preferred.

A particularly useful extruder is the Wenger TX-52 extruder, commercialized by Wenger Manufacturing, Inc. of Sabetha, Kans., provided with two rotatable, flighted material advancing screws (screw elements of 52-mm diameter) with a total of 5 barrel sections and terminated in a spacer plate die. The screws will typically be inter-meshing and co-rotating. The die plate typically will have six die inserts, typically arranged in a hexagonal design, with a number of holes of the desired diameter in each insert, typically from 25 to 100 holes, each hole typically having a diameter of 0.1 mm to 2 mm, preferably from 0.4 mm to 0.6 mm. The design of the Wenger TX line of extruders is described in U.S. Pat. No. 4,875,847, which is incorporated by reference herein. The extruder is designed to heat the contents thereof and to expose the contents to significant compaction and shear. The temperature of the contents of the extruder should be maintained sufficiently low such that the entire mass of tocopherol succinate is not melted. Thus, the temperature of the entire contents of the extruder should not be allowed to exceed a temperature of 72° C. Typically, the temperature of the mass will be below 70° C., more typically below 65° C. Typically, the tocopheryl succinate will be fed into the extruder at ambient temperature, and will be gradually heated to a temperature of 55° C. to 65° C., more typically to a temperature of 60° C. to 63° C., just prior to exit of the material from the extruder. With a five section extruder, the set temperature of the heating medium will typically be 45° C. to 55° C., in the first two sections (e.g. contents in these two sections typically at 30° C. to 35° C.), 50° C. to 60° C. in the third and fourth sections (e.g. contents in third section typically 52° C. to 56° C. and in the fourth section 55° C. to 60° C.) and 58° C. to 62° C. in the last section (e.g. contents in last section 60° C. to 62° C.). It may be desirable to expose portions of the plastic mass to, e.g. that portion of the mass in contact or close proximity with the interior wall of the barrel of the extruder or the die plate, to temperatures that are in excess of 72° C., e.g. 75° C., to provide lubri-

cation of the wall or die plate. In such a case, however, one should ensure that the entire mass will not reach a temperature above 72° C. the melting temperature of tocopherol succinate. The maximum preferred temperature when using tocopheryl succinate and its mixtures with non-plastic supplements, is 125° C. The product will typically be fed to an extruder such as the Wenger TX-52 at a rate of 70 to 75 kg/hr and the screw speed will typically be between 160 rpm and 165 rpm.

The product of the extrusion will be a material which, upon cooling, sets to form a solid product within a matter of minutes, typically less than 1 hour, more typically at most 30 minutes, and more preferably at most 10 minutes. Preferably, the mass sets to a solid form in a matter of a few seconds, typically from 1 second to 30 seconds. It has been found that the material which takes a relatively longer time to set (which typically results when the plastic mass is heated to a relatively high temperature) appears to be harder after setting than the material which sets more quickly. The material which sets more quickly is thus, more fragile and friable than the material which takes a longer time to set. For materials which melt at temperatures of 40° C. it may be necessary to use cooling means to form a solid from the plastic material more quickly. Cooling means such as a cooled belt or cooled gases passing over the material can be used. Liquid nitrogen or carbon dioxide can be useful.

The extrudate will typically be in the form of a rope or plurality of ropes which can then be subjected to size reduction to obtain a product having the desired particle size. Size reduction is discussed in *Encyclopedia of Chemical Technology*, vol. 21, pp. 132-162 (John Wiley & Sons, Inc., N.Y., N.Y. 1983) the disclosure of which is incorporated herein by reference. The apparatus chosen for size reduction is preferably one which accomplishes size reduction by impact, and with minimal, if any, shear or compaction. Examples of preferred size reduction apparatus include a disk mill or pin mill. In such mills, the tocopheryl succinate will come into contact with striking members, e.g. bars or pins, attached perpendicularly to the plane of a rotating member, e.g. a disk or plate. The impact of the tocopheryl succinate will cause a reduction in the size of the particles thereof. There is preferably no surface in contact with or within close tolerance of the striking members so that there will be little or no shear or compaction, as opposed to free impact, applied to the particles. The chamber of such a mill is typically bounded with a screen with openings therein which will allow material of the desired size to exit the chamber therethrough. An example of a preferred impact mill is the model SM-18 Prema Mill, Praet Industries, Inc., Chicago, Ill. Such a grinder can typically produce 60 pounds/hr when operated at a tip speed of 10 meters/second.

In preferred embodiments, the extrudate will be in an elongated form, e.g. ropes, which have a diameter of roughly the size desired of the powdered particle, e.g. from 0.4 mm to 0.6 mm. Thus, the size reduction will serve largely to reduce the elongated dimension of the ropes to roughly the size of the diameter of the rope. Of course, the size reduction process will also serve to break the particles along the axial direction as well, so that the average diameter of the resulting product will be less than the diameter of the elongated starting material.

During size reduction, the tocopheryl succinate should be maintained below the melting point of the product, preferably at or below ambient temperature of 25° C. Cooling air or other cooling fluid, e.g. liquid nitrogen, can be introduced into the milling chamber to cool the product during size reduction.

In typical operation, the process will entail dropping tocopherol succinate powder into a feeder which in turn feeds the powder to an extruder at a controlled rate. The

extruder heats the powder with shear and pressure to form a plastic mass of material that is not fully melted. The pressure generated by the extruder forces the plastic material through die openings at the end of the extruder barrel. Upon exiting the extruder, the extruded material is vertically discharged onto a belt. The belt conveys the extruded material for sufficient time for the material to harden to a solid form. The hardened material then falls off the end of the belt into coarse crushing wheels which break the strands of extrudate into shorter, but still elongated pieces. The size reduced material falls into a holding bin prior to passing to a feeder. The feeder then feeds the size reduced material to a grinder at a controlled rate. The grinder is cooled to prevent material from melting. The grinder reduces the particle size of the material to a desired range. The ground material is then screened to remove particles considered too large (e.g. those retained on a 14-mesh screen) and too small (those passed by a 120-mesh screen). The material which is too small can be added to the feed of the extruder and the material which is too large can be added to the feed of the grinder.

The product can be characterized as a powdered composition. If desired, it can be sieved in order to obtain a desired grain size distribution. An excessively fine composition is undesirable because of its poor flowability in charging into dies in tabletting. An excessively coarse composition is unsuited for admixture with some other composition and moreover causes weight fluctuation in tablet manufacture. A typical lower limit on grain size is typically a maximum of 5% by weight of the grains through a 120-mesh sieve. Typically, the product will have less than 5% retained on a 14-mesh sieve. Preferably at least 85% of the material will pass a 25-mesh sieve, but will be retained on a 60-mesh sieve.

The mesh sizes as defined in this specification are those specified in the relevant U.S. standard (as published in *Handbook of Chemistry and Physics*, p. I-158 (57th ed., CRC Press, Cleveland Ohio, 1976)). Said mesh sizes and the corresponding sieve opening sizes are shown below.

Mesh	Sieve opening size (micrometers)
10	2,000
20	850
80	180
120	125

In another embodiment of the invention the tocopheryl succinate or the phytylsterol plastic nutritional supplements may be atomized. Extrusion involves turning the tocopheryl succinate or the phytylsterol into a fluid mass without fully melting it, atomizing it into spherical particles and allowing the particles to harden into a free flowing powder.

In extrusion the heating and shear in the extruder forms a plastic mass of material. The viscosity of the plastic material can be controlled in the extruder to allow it to be more fluid (less viscous). The plastic, flowable mass can be extruded directly into a spray nozzle with sufficient viscosity to allow it to be atomized. The nozzle atomizes the material into droplets. These droplets are allowed to fall for a time sufficient to allow them to harden and lose their plasticity. The hard particles are collected as a free flowing powder.

The spray nozzle of choice in this case is a two fluid or three fluid spray nozzle. In a two fluid nozzle the one fluid is the plastic, flowable material and the second fluid is air or steam for external atomization. In the three fluid nozzle air or steam is mixed inside the nozzle with the plastic, flowable material and the third fluid is air or steam for external atomization. An inert gas like nitrogen or a fluid like liquid

nitrogen may also be used. A centrifugal wheel atomizer may also be used.

This process is similar to prilling but the material being prilled is not fully melted.

A desirable attribute of this process is that it forms a more spherical particle which has better flow properties than cylindrical particles and it eliminates the necessity of a grinding step.

Details of industrial atomization of this type may be found in U.S. Pat. No. 5,549,917 to Cherukuri et al., incorporated herein in its entirety as if it set forth in full.

The tocopheryl succinate and phytylsterols according to the invention can be used as raw materials in the manufacture of tocopheryl succinate and phytylsterol-containing tablets and capsules. Tabletting of the powder is carried out by a conventional method in the presence of a lubricant and, if necessary, some other drug substance and/or an excipient (e.g. lactose, sucrose, mannitol). As said lubricant, there may be mentioned those lubricants which are used in conventional tablet manufacture, such as stearic acid and stearates (e.g. magnesium stearate, calcium stearate) and talc. The amount and kind of the lubricant are selected within such a range as to give tablets which are practical from the strength and disintegration viewpoint. Typically, it is used in an amount of 0.1 to 7 percent by weight based on the main active substance. Of the lubricants, a stearate or stearic acid is typically added in an amount of at least 0.5 percent by weight based on the main active substance. The above-mentioned other drug substance can include a variety of vitamins, mineral, and other dietary supplements. The compression is normally carried out under the condition of 1 to 2 ton/cm².

The following examples will illustrate the invention and should not be construed to limit the invention, except as expressly noted in the appended claims. All parts, ratios and percentages stated herein are by weight unless noted otherwise in context.

EXAMPLES

Example 1

Tocopheryl succinate powder (available from Henkel Corp., Ambler, Pa., as Covitol 1210) is charged to a Wenger TX-53 extruder. The extruder had five barrel sections, the set temperature and actual temperature of the contents of each section being set forth below. The die consisted of a die plate with six inserts each having 61 openings, each opening 0.5 mm in diameter. A 90° elbow was attached to the end of the extruder. A six insert die plate was attached to the end of the elbow. Throughout the trial Covitol 1210 (TM Henkel Corp., LaGrange Ill.) was used as the feed for the extruder. The extruded material was discharged vertically downward. The 0.5 mm die inserts were the only inserts used during the trial. The running conditions of the trial are listed in the following Table 1.

TABLE 1

Run	1	2	3
Feed Set/Rev Spd (rpm)	20	—	—
Extruder Shaft Speed (rpm)	100	162	175
Extr. Motor Load (%)	24	31	30
Zone #1 Set/Act. (°C)	50/38	50/32	50/32
Zone #2 Set/Act. (°C)	50/38	50/32	50/32
Zone #3 Set/Act. (°C)	55/57	55/56	55/56
Zone #4 Set/Act. (°C)	60/60	60/60	60/60
Zone #5 Set/Act. (°C)	60/60	60/60	60/60

TABLE 1-continued

Run	1	2	3
Die Config. & Dia.	6 x 62 x 0.5 mm	6 x 61 x 0.5 mm	6 x 61 x 0.5 mm
Total Die Opening (cm ²)	2.875	2.875	2.875
Zone #4 Press. (kPa)	0	4830	4830
Zone #5 Press. (kPa)	5170	6210	6210
Rate (kg/hr.)	36	72	78

The product of run 2 of the above extrusion was then ground in a Pyuma SM-18 impact mill, Prater Industries, Chicago, Ill. For each run the material was loaded into a bin and fed into the grinder using a vibrating feeder. The screen surrounding the impeller had holes of approximately 2.4 mm. (This size is larger than the particles which pass through the screen because the angle at which the particles typically approach the screen causes the apparent diameter of the holes to be smaller than 2.4 mm.) The running conditions and screening results of each trial are listed in Table 2.

TABLE 2

Run #	1	2	3
Rotor Tip Speed (rpm)	19	16	27
No Load/Rotor Load (inches)	9.61/8.8	0.6/1.0	1.0/2.3
Feed Rate (lb/hr.)	60	112	112
% on 14 Mesh Screen	—	—	—
% on 25 Mesh Screen	5.4	2.3	0.4
% on 30 Mesh Screen	31.8	13.2	7.3
% on 40 Mesh Screen	53.3	45.8	50.8
% on 60 Mesh Screen	8.4	38.3	33.3
% on 120 Mesh Screen	0.2	0.9	3.0
% on 140 Mesh Screen	—	0.3	1.4
% Less Than 140 Mesh Screen	0.2	1.2	3.5

The process has been described in relation to forming particulate incoferol succinate (vitamin E succinate). The method can be applied to other plastic nutrient supplement compositions.

Example 2

As in Example 1, however the extrudate was blasted with liquid nitrogen as it left the extruder to atomize the extrudate into particulates.

Example 3

The extruder of Example 1 is fitted with an injection molding head in order to mold tablets directly.

Example 4

A blend of sterols as described above (comprising beta-sitosterol, campesterol, stigmasterol and brassicasterol) and available as General 122 (TM Henkel Corp., LaGrange, Ill.) is extruded in a manner similar to Example 1.

Example 5

A blend of sterols as described above (comprising beta-sitosterol, campesterol, stigmasterol and brassicasterol) and available as General 300 (TM Henkel Corp., LaGrange, Ill.) is extruded in a manner similar to Example 1.

Example 6

The extruder of Example 1 is fitted with an atomizing nozzle that atomizes the extrudate to form a free flowing powder.

The present invention requires that the material to be treated, whether it is a single nutritional supplement or a mixture of nutrition supplements to a temperature at which the mixture is a plastic mass but not molten and cooling the material to a solid form. The solidified material can be comminuted to form particles within a prescribed size range.

It is critical that the entire composition not be melted. Melting the entire composition makes the material difficult to cool and solidify. The composition is heated and mixed at a temperature at which the mixture is plastic mass but not completely melted. It is not known whether the composition becomes plastic without any portion of the composition being melted or a portion of the composition becomes molten and causes agglomeration and plastification of the composition. Both effects may occur depending on the composition.

If the composition is an unseparated mixture of several different materials, the composition may exhibit a broad softening range rather than a sharp melting point. These compositions are preferably heated to a temperature at the low end of the softening range so that the composition can be cooled and solidified more rapidly.

If the composition is a mixture of particles of different compositions, it can be processed directly by the process of the invention or the mixture can be homogenized by known methods before being treated by the process of the invention. Homogenization is particularly useful when one of the materials in the composition is a liquid at room temperature.

What is claimed is:

1. A process for producing a substantially physiologically inert binder free, particulate composition wherein the binder consists essentially of a plastic nutritional supplement which process comprises:

heating a mass of the plastic nutritional supplement to a temperature not above about 170° C., effective to form a plastic but not completely molten, mass of material; extruding the plastic mass of material into at least one elongated form;

cooling the elongated form for a sufficient time for the elongated form to set to a solid form; and

comminuting the solid form.

2. A process of producing a substantially binder free particulate composition comprising a plastic nutritional supplement which comprises:

heating a mass of the plastic nutritional supplement to an elevated temperature effective to form a plastic, but not completely molten, mass of material;

extruding the plastic mass of material into an atomizer head; and

atomizing the plastic mass of material into particles.

3. The process of claim 1 wherein the heating is accomplished in an extrusion zone.

4. The process of claim 1 wherein the elongated form is a rope having a diameter of from about 0.1 mm to about 2 mm.

5. The process of claim 4 wherein the diameter is from about 0.4 mm to about 0.6 mm.

6. The process of claim 1 wherein the elongated form sets to a solid form within one hour of the beginning of the cooling of the elongated form.

7. The process of claim 1 wherein the elongated form sets to a solid form within about 30 minutes of the beginning of cooling the elongated form.

8. The process of claim 1 wherein the elongated form sets to a solid form within about 10 minutes of the beginning of cooling the elongated form.

9. The process of claim 1 wherein the elongated form sets to a solid form in less than about 30 seconds of the beginning of cooling the elongated form.

10. The process of claim 1 wherein the solid form is comminuted by impacting the solid form.

11. The process of claim 10 wherein the comminuting does not compact the particles.

12. The process of claim 1 wherein the solid form is comminuted in an impact zone where there is no contact of impacting members of the impact zone with an opposing surface of the impact zone.

13. The process of claim 1 wherein the comminuted product has a particle size distribution wherein not more than 5% by weight passes through a 120-mesh sieve.

14. The process of claim 1 wherein the comminuted product has a particle size distribution wherein less than 5% by weight is retained on a 14 mesh sieve.

15. The process of claim 1 wherein the comminuted product has a particle size distribution wherein at least about 25% by weight of the comminuted product passes through a 25 mesh sieve and is retained on a 60-mesh sieve.

16. The process of claim 1 wherein the plastic nutritional supplement is selected from the group consisting of tocopheryl succinate, phytosterols and mixtures thereof.

17. The process of claim 16 wherein the phytosterols are selected from the group consisting of sterols, sterol esters, stanols, stanol esters and mixtures thereof.

18. The process of claim 17 wherein the sterols are selected from the group consisting of alpha-sitosterol, beta-sitosterol, gamma-sitosterol, campesterol, stigmasterol, brassicasterol and mixtures thereof.

19. The process of claim 17 wherein the stanols are selected from the group consisting of stigmastanol, ergostanol, campestanol and mixtures thereof.

20. The process of claim 17 wherein the phytosterols comprise:

beta-sitosterol;
campesterol;
stigmasterol; and
brassicasterol.

21. The process of claim 17 wherein the phytosterols comprise:

about 43 to about 53 wt. % beta-sitosterol;
about 22 to about 26 wt. % campesterol;
about 17 to about 19 wt. % stigmasterol; and
about 2 wt. % brassicasterol, wherein wt % is based on the total plant extract.

22. The product of the process of claim 1, wherein said product comprises phytosterols.

23. A process of producing a substantially physiologically inert binder free, particulate composition wherein the binder consists essentially of a plastic nutritional supplement which comprises:

heating a mass of the plastic nutritional supplement to an elevated temperature effective to form a plastic, but not completely molten, mass of material;
extruding the plastic mass of material into an injection molding head; and
molding tablets of said plastic nutritional supplement.

24. The process of claim 23 wherein the elevated temperature is not above about 170° C.

25. The process of claim 23 wherein the heating is accomplished in an extruding zone.

26. The process of claim 23 wherein the plastic nutritional supplement is selected from the group consisting of tocopheryl succinate, phytosterols and mixtures thereof.

27. The process of claim 26 wherein the phytosterols are selected from the group consisting of sterols, sterol esters, stanols, stanol esters and mixtures thereof.

28. The process of claim 27 wherein the sterols are selected from the group consisting of alpha-sitosterol, beta-sitosterol, gamma-sitosterol, campesterol, stigmasterol, brassicasterol and mixtures thereof.

29. The process of claim 27 wherein the stanols are selected from the group consisting of stigmastanol, campestanol, ergostanol and mixtures thereof.

30. The process of claim 26 wherein the phytosterols comprise:

beta-sitosterol;
campesterol;
stigmasterol; and
brassicasterol.

31. The process of claim 26 wherein the phytosterols comprise:

about 43 to about 53 wt. % beta-sitosterol;
about 22 to about 26 wt. % campesterol;
about 17 to about 19 wt. % stigmasterol; and
about 2 wt. % brassicasterol, wherein wt. % is based on the total plant extract.

32. The tablets of the process of claim 23.

33. The particles of the process of claim 2, wherein said particles comprise phytosterols.

34. The process of claim 2 wherein the elevated temperature is not above about 170° C.

35. The process of claim 2 wherein the heating is accomplished in an extrusion zone.

36. The process of claim 2 wherein the plastic nutritional supplement is selected from the group consisting of tocopheryl succinate, phytosterols and mixtures thereof.

37. The process of claim 36 wherein the phytosterols are selected from the group consisting of sterols, sterol esters, stanols, stanol esters and mixtures thereof.

38. The process of claim 37 wherein the sterols are selected from the group consisting of alpha-sitosterol, beta-sitosterol, gamma-sitosterol, campesterol, stigmasterol, brassicasterol and mixtures thereof.

39. The process of claim 37 wherein the stanols are selected from the group consisting of stigmastanol, ergostanol, campestanol and mixtures thereof.

40. The process of claim 37 wherein the phytosterols comprise:

beta-sitosterol;
campesterol;
stigmasterol; and
brassicasterol.

41. The process of claim 37 wherein the phytosterols comprise:

about 43 to about 53 wt. % beta-sitosterol;
about 22 to about 26 wt. % campesterol;
about 17 to about 19 wt. % stigmasterol; and
about 2 wt. % brassicasterol, wherein the wt. % is based on the total plant extract.

135
387
390

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 06-053410

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 582 DE

FECHA 30 DE NOVIEMBRE DE 2007 EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL 27 DE FEBRERO DEL 2008.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ☐ _____

NO ☒ X _____

2020
Bogotá, D.C.,

Doctor:
Carlos Reinaldo Olarte García
Apoderado

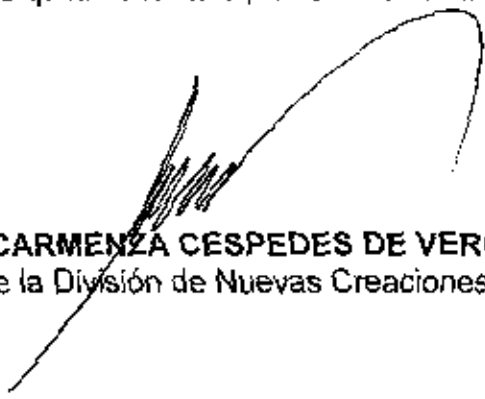
Oficio N°: 5464

ASUNTO: Radicación PCT N° 06-53410
Trámite 011
Evento 379
Actuación 440
Folios 011

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Eliana Isaura Moreno Bohórquez, en su calidad de apoderada de Procaps S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, 2020 2021.

202021