REYES & REYES
A B O G A D O S

SEÑOR
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E. S. D.

REF:	**Expediente 09-149-222.**
TÍTULO SOLICITADO:	**MICROESFERAS CON ESTRUCTURA DE MEDULA/CORAZA.**
PUBLICACIÓN:	**Gaceta 627 de 20/04/2011, número de publicación 208.**
PRIORIDAD:	**JP 2007-166183 de 25/06/2007**
SOLICITANTE:	**OTSUKA PHARMACEUTICAL CO., LTD.**
APODERADO:	**HUMBERTO RUBIO CAMACHO.**
TRÁMITE:	**SUSTENTACION DE OPOSICIÓN.**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LAFRANCOL S.A.,** sociedad constituida y vigente de conformidad con las leyes colombianas, con domicilio en Cali, Valle, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, y por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 21 de julio de 2011, en los siguientes términos:

I. RATIFICACIÓN

Comedidamente me permito insistir en que la solicitud de la referencia, que se refiere a un tipo de formulación farmacéutica o sistema de entrega de fármaco que corresponde a las características de una formulación inyectable por suspensión acuosa que conformada a su vez por las microesferas definidas dentro de del mismo capítulo reivindicatorio; carece de los requisitos de patentabilidad establecidos por los artículos 14, 16, 18 y 20 literal d), de la Decisión 486 y que como tal, no merece recibir el beneficio patentario.

II. COMPLEMENTO DE INFORMACIÓN

En primer lugar, y ante la reivindicación textual de un método para tratar la esquizofrenia, que comprende suministrar la formulación inyectable por suspensión acuosa de acuerdo con las reivindicaciones 15 a 17 de la solicitud colombiana en cuestión, es importante indicar que esto contraviene lo dispuesto en la Decisión 486 de 2000 que literalmente refiere a que *"No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnostico aplicados a los seres humanos o a animales."*

En un segundo aspecto y dado que la solicitud colombiana en trámite reivindica en general la inclusión de aripiprazol, un principio activo reconocido en el estado de la técnica[1], y que además ha sido manipulado tecnológicamente así como involucrado dentro de diversas clases de sistemas de entregas de fármacos[2]:

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[1] Patente Americana US 5006528 de 09/04/1991.
[2] http://www.google.com/patents?id=IZITAAAAEBAJ&printsec=frontcover&dq=US5006528&hl=en&ei=P2mOTuHdFsjo0QGo1LwS&sa=X&oi=book_result&ct=result&resnum=1&ved=0CDMQ6AEwAA

Patent Number	Filing date	Issue date	Original Assignee	Title
US6977257	Apr 24, 2002	Dec 20, 2005	Bristol-Myers Squibb Company	Aripiprazole oral solution
US7053092	Jan 28, 2002	May 30, 2006	Otsuka Pharmaceutical Co., Ltd.	5-HT1a receptor subtype agonist
US7115587	Aug 14, 2003	Oct 3, 2006	Bristol-Myers Squibb Company	Aripiprazole complex formulation and method
US7160888	Jul 28, 2004	Jan 9, 2007	Warner Lambert Company LLC	[1,8]naphthyridin-2-ones and related compounds for the treatment of schizophrenia
US7361756	Feb 7, 2005	Apr 22, 2008	Teva Pharmaceutical Industries Ltd.	Method of making 7-(4-bromobutoxy)-3,4-dihydrocarbostyril
US7456181	Jul 25, 2003	Nov 25, 2008	Hetero Drugs Limited	Aripiprazole crystalline forms
US7491726	Mar 21, 2003	Feb 17, 2009	Hetero Drugs Limited	Crystalline forms of aripiprazole
US7504504	Dec 16, 2004	Mar 17, 2009	Teva Pharmaceutical Industries Ltd.	Methods of preparing aripiprazole crystalline forms
US7507823	May 6, 2005	Mar 24, 2009	Bristol-Myers Squibb Company	Process of making aripiprazole particles
US7550445	Jun 14, 2006	Jun 23, 2009	Bristol-Myers Squibb Company	Aripiprazole complex formulation and method
US7642353	Nov 18, 2005	Jan 5, 2010	Synthon BV	Process of making crystalline aripiprazole
US7655798	Mar 17, 2006	Feb 2, 2010	Synthon BV	Process of making crystalline Type II aripiprazole
US7658998	Jan 21, 2004	Feb 9, 2010	Alkermes Controlled Therapeutics, Inc.	Method of preparing sustained release microparticles
US7714129	Sep 29, 2006	May 11, 2010	Teva Pharmaceutical Industries Ltd.	Methods of preparing anhydrous aripiprazole form II
US7732597	Sep 26, 2007	Jun 8, 2010	Symed Labs Limited	Crystalline form of linezolid
US7799790	Jun 2, 2008	Sep 21, 2010	Helm AG	Amorphous aripiprazole and process for the preparation thereof
US7807680	Oct 19, 2004	Oct 5, 2010	Otsuka Pharmaceutical Co., Ltd.	Controlled release sterile injectable aripiprazole formulation and method
US7825125	Aug 8, 2006	Nov 2, 2010	Helm AG	Amorphous aripiprazole and process for the preparation thereof
US7872132	Oct 8, 2004	Jan 18, 2011	Suven Life Sciences Limited	Intermediates useful for the preparation of aripiprazole and methods for the preparation of the novel intermediates and aripiprazole
US7884205	Jan 27, 2006	Feb 8, 2011	Sandoz AG	Salts of aripiprazole
US7902198	Nov 18, 2005	Mar 8, 2011	Synthon BV	Crystalline aripiprazole solvates
US7910589	Apr 26, 2007	Mar 22, 2011	Otsuka Pharmaceutical Co., Ltd.	Low hygroscopic aripiprazole drug substance and processes for the preparation thereof
US7964605	May 29, 2008	Jun 21, 2011	SK Holdings Co., Ltd.	Phenyl piperazine compounds, pharmaceutical composition comprising the same, and use thereof
US7985752	May 29, 2009	Jul 26, 2011	SK Holdings Co., Ltd.	Phenyl piperazine compounds, pharmaceutical composition including the same and use thereof

Y refiriéndose esta solicitud a un tipo de formulación farmacéutica o sistema de entrega de fármaco que corresponde a las características de una formulación inyectable por suspensión acuosa que está conformada a su vez por las microesferas definidas dentro del mismo capítulo reivindicatorio (que se describen como una estructura de médula/coraza que resulta siendo la estructura tradicional

resultante de un proceso convencional de microencapsulación[3],[4],4), podemos afirmar que cualquier persona medianamente versada en la formulación de productos farmacéuticos debe reconocer que el mismo principio activo se puede presentar en diferentes formas, por ejemplo, como comprimido, cápsula o solución acuosa, utilizando a su vez diferentes excipientes farmacéuticamente aceptables, y que reivindicar nuevas presentaciones farmacéuticas (SENFs) de fármacos ya descritos en el estado de la técnica y/o con excipientes o vehículos farmacéuticamente aceptables igualmente reconocidos, o reivindicar unas característica técnicas particulares que se asocian con ciertos efectos, como la liberación controlada por ejemplo, no pueden sustentar nivel inventivo alguno, dado que combinar dichos principios activos (bajo la realización de los respectivos ensayos de preformulación y formulación habituales) junto a dichos excipientes para conseguir dichos efectos técnicos, por lo general, forma parte de la capacidad habitual de dicha persona versada en formulación de productos farmacéuticos.

Finalmente, podemos demostrar que con anterioridad ya se habían descrito las características técnicas reivindicadas en la solicitud colombiana en cuestión, tanto para el sistema de fármaco como para el principio activo, veamos:

La publicación internacional WO 2005/016262 publicada el 24 de febrero de 2005 revela:

> The present invention relates, in part, to the discovery that a pharmaceutical composition comprising aripiprazole and a carrier administered in a bolus injection resulted in an extended release profile similar to that obtained by the injection of a poly lactide-co-glycolide microsphere formulation containing the active agent. This surprising result suggests that pharmacologically beneficial extended release formulations without the complexities and expense associated with the manufacture ofpolymeric microspheres can be achieved.
>
> (...)

[3] Vila Jato José Luis. Tecnología farmacéutica. Volumen II. Página 74.
[4] Diana ramos Picos, Martha Gómez Carril, Dianelis Fernández Mena. Métodos de obtención de microesferas biodegradables. Rev. Cubana Farm. 2001; 35(2):126-35.

In one embodiment, the aripiprazole or aripiprazole drug substance is injected as a mixture (including a suspension) of at least about 50 mg aripiprazole in an injection vehicle, such as at least about 70 to 210 mg or as much as about 900 to 2700 mg, e.g. less than 5400 mg. The aripiprazole can be present in an amount of at least about 10 mg/ml, preferably at least about 20 mg/ml or at least about 30 mg/ml. The invention also relates to methods for providing aripiprazole to an individual in an extended release injectable composition comprising administering a mixture of at least about 10 mg/ml aripiprazole in an injection vehicle comprising a viscosity enhancing agent and to compositions useful in such methods.

(...)

bioavailability of the active agent in the patient. A frequently used polymeric matrix is poly lactide-co-glycolide polymers. Thus, the aripiprazole drug substance and/or injectable compositions of the invention generally do not contain major amounts of PLGA polymer matrices.

(...)

solubility of the drug in the vehicle. The vehicle is preferably an aqueous vehicle

(...)

The aripiprazole drug substance can comprise, consist essentially of or consist of aripiprazole (in a crystalline, non-crystalline or amorphous form), an aripiprazole salt, an aripiprazole solvate (including ethanolates and hydrates), or other aripiprazole polymorphs. Preferred salts include those salts insoluble in an aqueous vehicle. Pharmaceutical salts such as the hydrochloride and hydrobromide salts are suitable.

(...)

7. The composition of Claim 6, wherein the surfactant is selected from the group consisting of polysorbate 20, polysorbate 40, and polysorbate 80.

(...)

35. The method of Claim 18, wherein the composition is administered by injection.

36. The method of Claim 18, wherein the composition is administered intramuscularly or subcutaneously.

(...)

Por su parte la patente americana US 2004/247870 publicada el 09 de diciembre de 2004 revela:

> The present invention relates to a method for preparing an injectable composition of microparticles for the sustained release of a biologically active agent. The microparticles include a biocompatible polymer and a biologically active agent. The invention provides an improved process for the preparation of microparticles, wherein the physical characteristics of the microparticles, for example, the morphology, density and size, are independent of the process used to prepare the initially formed polymer/drug matrix. The method includes the steps of (a) providing a polymer/biologically active agent matrix; (b) compressing the polymer/biologically active agent matrix, thereby forming a compressed matrix; and (c) fragmenting the compressed matrix, thereby forming an injectable microparticle composition. The polymer/drug matrix can be provided by any suitable method.
>
> (...)
>
> **[0009]** In one embodiment, the polymer/biologically active agent matrix is provided by (a) preparing a mixture of a biologically active agent, a biocompatible polymer and a solvent, e.g., a polymer solvent, and (b) removing the solvent, thereby forming the polymer/biologically active agent matrix. The biologically active agent can be suspended (e.g., completely or partially suspended) in the mixture and/or dissolved (e.g., completely or partially dissolved) in the mixture.
>
> **[0010]** As such, in one embodiment the invention relates to a method for preparing an injectable microparticle composition for the sustained release of a biologically active agent comprising the steps of (a) preparing a mixture comprising a biologically active agent, a biocompatible polymer, and a solvent, thereby forming a single phase solvent system; (b) removing the solvent from the solution, thereby forming a polymer/biologically active agent matrix; (c) compressing the matrix using confined pressure compaction, thereby forming a compressed matrix; and (d) fragmenting the matrix, thereby forming the injectable microparticle composition.
>
> (...)
>
> **[0012]** In a preferred embodiment, the biologically active agent is an antipsychotic drug such as aripiprazole, olanzapine or risperidone.
>
> (...)

[0036] In a particularly preferred embodiment, the microparticles prepared according the method of the invention include a biocompatible polymer and a drug used to treat affective disorders, such as schizophrenia, depression, and anxiety. Suitable drugs for treating affective disorders include, but are not limited to, risperidone, olanzapine and aripiprazole.

(...)

[0102] The injectable microparticles prepared according to the method described herein can be further modified to achieve a desired sustained release profile of the biologically active agent. In one embodiment, a substantial portion of the exterior surface of the injectable microparticles can be annealed or coated. Annealing is accomplished, for example, by the application of heat or an annealing solvent, wherein the annealing solvent is a solvent for the polymer of the injectable microparticle. The application of heat or an annealing solvent can be performed, for example, by using a fluidized bed system such as the Wurster process. Coating can be conducted using a suitable coating apparatus using a polymer or combination of polymers which can be the same or different from the polymer of the unmodified matrix.

(...)

6. The method of claim 1 wherein the biocompatible polymer is selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, polycarbonates, polyesteramides, polyanhydrides, poly(amino acids), polyorthoesters, polyacetals, polycyanoacrylates, polyetheresters, polycaprolactone, poly(dioxanone)s, poly(alkylene alkylate)s, polyurethanes, and blends and copolymers thereof.

(...)

40. The method of claim 39 wherein the biologically active agent is selected from the group consisting of aripiprazole, olanzapine and risperidone.

41. The method of claim 39 wherein the patient suffers from an affective disorder.

42. The method of claim 41 wherein the patient suffers from a condition selected from the group consisting of schizophrenia, depression, and anxiety.

(...)

Y finalmente la patente europea EP 0669128 publicada el 30 de agosto de 1995 revela:

With the aim of improvement in compliance at the time of maintenance therapy with hydrophobic antipsychotic drugs, the present inventors have conducted intensive studies on the development of a sustained release pharmaceutical preparation in which a drug itself is used as an active ingredient without modification. As the result, it was found that

a drug can be released at an almost constant rate extending over 1 week or more by including a hydrophobic antipsychotic drug into a base comprising a biodegradable high molecular weight polymer having *in vivo* histocompatibility to make a sustained release microsphere preparation and administrating it by subcutaneous or intramuscular injection, hence resulting in the accomplishment of the present invention.

(...)

having *in vivo* histocompatibility and (2) a process for producing an antipsychotic drug-containing sustained release microsphere preparation which comprises making an oil layer comprising a solution of a high molecular weight polymer having *in vivo* histocompatibility containing a hydrophobic antipsychotic drug, adding the oil layer to a water layer, subjecting the resulting mixture to an emulsification treatment to obtain an O/W type emulsion and subsequently removing the solvent in the oil layer by in-water drying method.

(...)

7. The antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 1 to 6, wherein said high molecular weight polymer having *in vivo* histocompatibility is one or more compounds selected from polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, poly(lactic-co-glycolic)acid, poly-α-cyanoacrylic ester, poly-β-hydroxybutyric acid, polytrimethylene oxalate, polyorthoester, polyorthocarbonate, polyethylene carbonate, poly-γ-benzyl-L-glutamic acid and poly-L-alanine.

(...)

9. The antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 1 to 8, wherein said antipsychotic drug-containing sustained release microsphere preparation is an aqueous suspension.

10. A process for producing an antipsychotic drug-containing sustained release microsphere preparation which comprises making an oil layer comprising a high molecular weight polymer having *in vivo* histocompatibility containing a hydrophobic antipsychotic drug, adding the oil layer to a water layer, subjecting the resulting mixture to an emulsification treatment to obtain an O/W type emulsion and subsequently removing the solvent in the oil layer by in-water drying method.

(...)

20. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 10 to 19, wherein said antipsychotic drug-containing sustained release microsphere preparation is an aqueous suspension.

Como bien se puede observar en estas tres anterioridades, absolutamente todas las características técnicas descritas para el sistema de macropartículas producidas e insertadas dentro de una suspensión acuosa inyectable, ya se habían revelado con anterioridad, específicamente en lo relacionado con la inserción de aripiprazol como principio activo dentro de las mismas, las clases de polímeros biodegradables (ácidos poli-lácticos y polímeros de acido láctico-acido-glicólico) la liberación extendida, un procedimiento de obtención que involucra la preparación de una emulsión O/W y la posterior evaporación del medio solvente acuoso, así como la utilización de dichas formulaciones en el tratamiento de la esquizofrenia.

En otras palabras, y a manera de conclusión, teniendo en cuenta la información expuesta con anterioridad, existen los suficientes lineamientos técnicos, para qué una persona medianamente versada en la formulación de productos farmacéuticos, pudiese obtener un sistema de entrega del fármaco o formulación

farmacéutica con todas las mismas características que las reivindicadas por la solicitud colombiana en trámite.

Por todo lo anterior, le solicito Señor Superintendente, que analice los argumentos citados con el rigor y detenimiento habituales y que decrete, además de la negación de la solicitud en comento, el archivo del citado expediente.

III. ANEXOS.

- Copia de todos los documentos citados en el acápite de Complemento de Información.

Señor Superintendente,

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C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.

Rev Cubana Farm 2001;35(2):126-35

Artículos de Revisión

Centro de Investigación y Desarrollo de Medicamentos

MÉTODOS DE OBTENCIÓN DE MICROESFERAS BIODEGRADABLES

Diana Ramos Picos,[1] Martha Gómez Carril[2] y Dianelis Fernández Mena[3]

RESUMEN

La liberación controlada de agentes terapéuticos desde microesferas biodegradables poliméricas ha sido extensamente estudiada. El ácido poliláctico y sus copolímeros con el ácido glicólico se han utilizado en la preparación de microesferas debido a su biodegradabilidad y biocompatibilidad. Estas microesferas han sido preparadas por varios métodos de obtención, los que son revisados en este trabajo. Se plantean las ventajas y desventajas de algunos de los métodos de obtención. En el caso del método de evaporación/extracción del solvente, que es el más usado, se plantean las variables que pueden influir en este y se discuten algunas de ellas.

DeCS: MICROESFERAS; POLIMEROS; POLIGLACTINAGIO; TECNOLOGIA FARMACEUTICA; BIODEGRADACION; COMPOSICION DE MEDICAMENTOS.

Recientemente han resultado útiles para formulaciones de liberación controlada de uso parenteral los sistemas de liberación consistentes en polímeros biodegradables, debido a sus posibilidades de controlar la liberación del fármaco de forma efectiva. Entre estos polímeros han desempeñado una función importante los de los ácidos láctico y glicólico teniendo en cuenta su disponibilidad, biodegradabilidad, no toxicidad y biocompatibilidad.[1]

Dentro de estas formulaciones se encuentran las microesferas que se han utilizado exitosamente para encapsular una amplia variedad de principios activos, incluyendo citostáticos, antiinflamatorios, péptidos y hormonas, entre otros.[2-5] Estas microesferas son partículas esféricas análogas de las microcápsulas pero sin una distinción clara entre núcleo y pared. Tiene una estructura monolítica preparada a partir de materiales biodegradables y con un gran

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espectro de velocidad de cesión y propiedades degradativas, donde el principio activo o agente terapéutico está distribuido a través de la matriz como una dispersión molecular o de partículas.

Se han usado varios métodos para la preparación de microesferas de diferentes polímeros biodegradables, incluyendo polímeros naturales y sintéticos. La selección de un método de preparación adecuado depende de las propiedades del polímero y el principio activo que se utilice y puede afectar las características de las microesferas.[6]

Este trabajo persigue el objetivo de revisar los métodos más empleados en la obtención de microesferas biodegradables obtenidas a partir del ácido poliláctico y/o glicólico.

MÉTODOS DE PREPARACIÓN

Existen varios métodos para la preparación de microesferas biodegradables preparadas de polímeros de ácido láctico y glicólico.

El método de evaporación/extracción del solvente y de separación de fases son los 2 principales métodos usados para estos fines.

La elección de la técnica de microencapsulación se hace principalmente sobre la base de las características físico-químicas del polímero y del principio activo a encapsular y se deben tener en cuenta los requerimientos siguientes:

- El rendimiento de microesferas con el intervalo de tamaños deseado debe ser alto.
- La eficiencia de encapsulación del principio activo debe ser alta.
- La actividad biológica del principio activo debe mantenerse durante el proceso de encapsulación.
- La reproducibilidad lote a lote en términos de un perfil cualitativo y de liberación del principio activo debe estar dentro de los límites especificados.
- El perfil de liberación debe ser ajustable mediante el control de la composición y las variables del proceso.
- Las microesferas no deben agregarse, deben ser un polvo fino que fluya libremente.

Por otra parte algunas de las propiedades de las microesferas deben ser optimizadas como son:

- Tamaño y distribución de tamaños.
- Propiedades de superficie.
- Carga de principio activo.
- Velocidad de liberación del principio activo.
- Velocidad de degradación de la matriz.

Otros aspectos como esterilidad, apirogenicidad y contenido de solvente residual tienen que ser satisfactorios.[8]

A continuación se discutirán varios métodos de preparación de microesferas obtenidas a partir de polímeros biodegradables.

1. Método de evaporación/extracción del solvente. En este método están incluidos todos los procesos en los que tiene lugar la eliminación del solvente, en el que está disuelto el polímero, ya sea por evaporación o por extracción de este. En todos los casos previamente tiene que formarse una emulsión. En dependencia de la naturaleza de la fase continua de la emulsión que se forme se clasificarán en técnicas de evaporación/extracción del solvente en fase acuosa o en fase oleosa.[9-11]

a) En fase acuosa:

– **Método de la emulsión aceite en agua (o/w).** En este método la fase orgánica que contiene el polímero y el principio activo se emulsifica en una fase acuosa que contiene un tensioactivo. Posteriormente las gotas orgánicas emulsificadas que contienen el polímero y el principio activo son endurecidas como microesferas por eliminación del solvente orgánico.[12]

En la figura 1 aparece representado el esquema de preparación de este método.

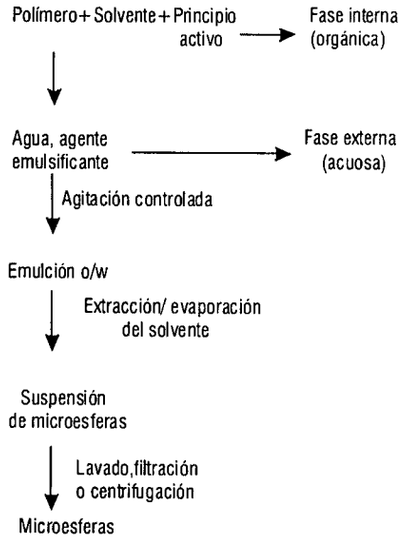

FIG.1. *Preparación del método de evaporación/extracción del solvente en fase acuosa o/w.*

Ventajas del método o/w:

- Es ampliamente usado en la encapsulación de p.a. liposolubles, debido a que se logra una eficiente incorporación de principio activo lipofílicos.
- Amplio rango de tamaños (desde grandes hasta pequeños) esencialmente controlados por la velocidad y las condiciones de agitación.
- Las microesferas tendrán propiedades superficiales hidrofílicas, lo que permite su resuspensión sin agregación.

Desventajas del método o/w:

- La incorporación de principios activos solubles en agua es muy baja debido a la repartición del principio activo en la fase acuosa externa de la emulsión.[9]

– **Método de la emulsión agua en aceite en agua (w/o/w).** También se conoce como método de la emulsión múltipe. Es una modificación del método o/w. Se utiliza para encapsular principios activos solubles en agua y se ha probado que es muy eficiente para encapsular este tipo de sustancia. En este método el principio activo se disuelve en agua (fase acuosa) y el polímero se disuelve en un solvente orgánico (fase orgánica). Ambas fases se mezclan obteniéndose la emulsión w/o, la que se adiciona lentamente sobre un medio acuoso que contiene un emulsificante como el alcohol polivi-nílico. Luego el solvente orgánico es eliminado y se obtienen las microesferas.[9] En la figura 2 se muestra el esquema de preparación de este método.

Jeffery y otros prepararon microesferas de albúmina de ácido poliláctico-co-glicólico usando este método y evaluaron el efecto de los parámetros de la formulación sobre las características de las microesferas obtenidas.[13-17]

b) En fase oleosa:

– **Emulsión o/o.** Este método es otra modificación de la emulsión o/w y la fase continua estará formada por un líquido orgánico como el aceite mineral[18,19] y se forma la emulsión o/o. Se usa para encapsular eficazmente principios activos solubles en agua.[1]

En la figura 3 aparece representado este método.

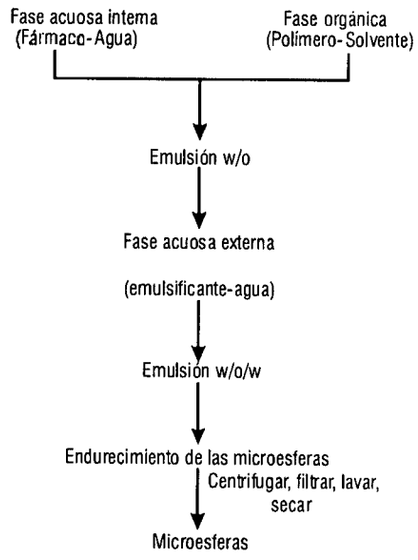

FIG. 2. *Flujo para la obtención de las microesferas por el método de emulsión múltiple w/o/w.*

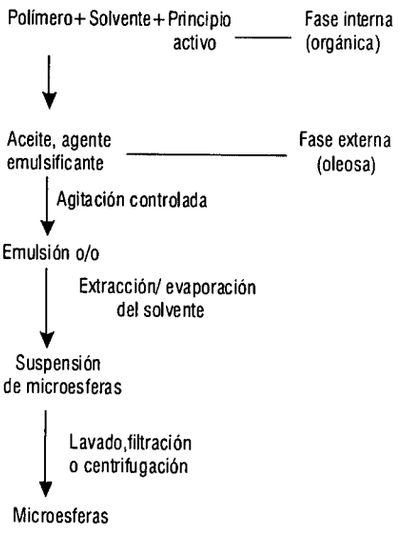

FIG. 3. *Preparación del método de evaporación/extracción del solvente en fase oleosa o/o.*

Tsai y otros usaron este método para encapsular mitomicina C en microesferas de ácido poliláctico.[20]

Desventajas del método o/o:

- Se hace difícil la obtención de microesferas pequeñas (menores de 50 μm).[21]
- Las microsferas tienden a agregarse cuando se resuspenden en vehículos acuosos debido a la naturaleza hidrófoba de su superficie y la ausencia de un estabilizador hidrofílico.[8]

c) Otros métodos de multifase. Más recientemente se han reportado los siguientes:

- Emulsión w/o/w/o.[22,23]
- Emulsión w/o/o.[23]
- Emulsión w/o/o/o.[24]

Aunque el método de evaporación/ /extracción del solvente es conceptualmente simple, existen muchas variables que pueden influir en las características de las microesferas obtenidas.[25-29] Estas variables son:

- Solvente orgánico.
- Naturaleza y cantidad de emulsificante.
- Naturaleza y solubilidad del principio activo.
- Temperatura de evaporación del solvente.
- Relación de volumen de las fases orgánica y acuosa.
- Relación principio activo y polímero.
- Estructura y masa molecular del polímero.
- Tipo y velocidad de agitación.

A continuación revisaremos las variables antes mencionadas:

Los solventes. Cuando se usa el proceso de evaporación/extracción del

solvente, el solvente para los polímeros de ácido láctico/glicólico debe ser inmiscible o solo ligeramente soluble en el medio de suspensión (acuoso u oleoso). *Bodmeier y Mcginity* evaluaron el efecto de diferentes solventes en la formación de microesferas de ácido poli (DL-láctico).[30-34] Ellos encontraron que los solventes miscibles en agua, como la acetona y el dimetilsulfóxido, no conducen a la formación de microesferas durante la emulsificación. Por el contrario, se forman aglomerados irregulares debido al rápido intercambio del solvente. Sin embargo, *Kawashina Y, Yamamoto H* y otros utilizan solventes como la acetona para realizar mezclas que contribuyen a mejorar el proceso de evaporación del solvente y así reducir el tiempo de formación de las microesferas.[10] Adicionalmente, el punto de ebullición del solvente debe ser más bajo que el del medio de suspensión si el solvente es eliminado por evaporación. Los solventes más comúnmente utilizados son el acetato de etilo y el diclorometano, por su baja toxicidad, su fácil eliminación y su excelente habilidad para disolver polímeros. Otros solventes que se han usado son el cloroformo y el acetonotrilo. Si se desea la disolución del principio activo en la solución del polímero, se necesita tener también en consideración la habilidad del disolvente para disolver el principio activo. También se han utilizado mezclas de solventes para disolver el polímero y el principio activo,[35] por ejemplo, diclorometano (inmiscible en agua) más metanol, etanol o propilenglicol (miscibles en agua). El uso de estos 3 últimos permite una rápida eliminación del solvente y una rápida precipitación del polímero.

Los emulsificantes. Los emulsificantes proporcionan una lámina fina protectora alrededor de las gotículas de aceite, polímero y principio activo, y de esta forma disminuyen la coalescencia y la coagulación y estabilizan el sistema emulsión. Frecuentemente, la dificultad inicial encontrada en el desarrollo de un procedimiento de microencapsulación es la aglomeración de las gotículas de aceite durante el proceso de fabricación. Cuando se está eliminando el solvente, el emulsificante continúa manteniendo las gotículas de aceite en su configuración esférica y las previene de la agregación hasta que el solvente es eliminado completamente y las microsferas son endurecidas como partículas discretas.[9]

Los emulsificantes más comúnmente empleados en el proceso de evaporación/ /extracción del solvente son los coloides poliméricos hidrofílicos y los surfactantes aniónicos o no iónicos. Ejemplos de ellos son el alcohol polivinílico,[36-38] la polivinilpirrolidona, los alginatos,[39] la gelatina,[40] la metilcelulosa,[41] la hidroxialquilcelulosa,[30] el polisorbato,[42,43] el span,[20] la lecitina,[43] etc. El emulsificante más comúnmente empleado en el método o/w es el alcohol polivinílico. La concentración requerida y la efectividad de cada emulsificante es diferente, y el mejor emulsificante para una aplicación en particular es determinado experimentalmente.

Las propiedades físico-químicas, las propiedades estructurales y la concentración del emulsificante influyen en las características de las microesferas.[41,43-45] Generalmente se dice que para un emulsificante dado, a mayor concentración se obtienen microesferas más pequeñas. Sin embargo, han aparecido concentraciones limitantes, por encima de las cuales el emulsificante no aumenta su efecto. Esto se debe probablemente a que se haya alcanzado la concentración óptima de empaquetamiento de la emulsión.

Los principios activos. Debido a que el método o/w involucra una emulsión acuosa, este se limita a encapsular en las

microesferas aquellos principios activos que presentan una baja solubilidad en agua, ya que si el principio activo es soluble en agua se repartirá desde la fase orgánica hacia la fase acuosa. Esta pérdida del principio activo traerá como resultado una pobre eficiencia de encapsulación.[41,42] Por el contrario, los principios activos liposolubles como los esteroides, pueden ser encapsulados exitosamente en microesferas usando este método o/w.[46]

Para minimizar la pérdida de principios activos ionizables hacia la fase acuosa durante el proceso de microencapsulación o/w, el pH de la fase acuosa puede ajustarse para suprimir la ionización del principio activo y consecuentemente reducir la solubilidad de este en dicha fase. Este resultado negativo puede también reducirse por la previa saturación de la fase acuosa con el mismo principio activo. *Wakiyama* y otros observaron que al presaturar la fase acuosa de una emulsión con el principio activo (tetracaína) a encapsular aumentaba el contenido de este en las microesferas formadas.

Si el principio activo a ser incorporado en las microesferas es insoluble en el solvente usado para disolver el polímero, este puede ser pulverizado o micronizado para proporcionar una distribución homogénea de partículas discretas mediante la emulsión y la microesfera resultante. Si el principio activo no es completamente soluble en el solvente orgánico empleado, este puede cristalizar dentro de la microesfera a ciertas concentraciones. En este sentido los cristales deben concentrarse en algunas regiones de las microesferas, como en la superficie, dando una distribución heterogénea del principio activo que alterará su perfil de liberación.[41,47]

Estructura y masa molecular. La naturaleza del polímero, la secuencia de los monómeros y de ahí su masa molecular permiten ajustar la liberación del fármaco al tiempo en que se alcanzan las concentraciones terapéuticas en sangre.

Los polímeros de diferentes masas moleculares varían en sus viscosidades intrínsecas, parámetro que determina en la eficiencia del proceso de obtención de las microesferas y en sus propiedades.

El resto de los parámetros influyen en el proceso de optimización del método de obtención y están íntimamente relacionados con el solvente, el polímero, el emulsificante y el principio activo.

2. Método de separación de fases (coacervación). Es un método no acuoso de preparación de microesferas y es utilizado fundamentalmente para principios activos solubles en agua. Consiste en disolver primeramente el polímero en el solvente orgánico y el principio activo en agua. Luego la emulsión microfina se obtiene por la adición de la solución acuosa a la solución orgánica. Un primer no solvente para el polímero se adiciona lentamente al sistema, formándose las gotículas de coaservado que son muy blandas para ser recolectadas, por lo que se hace necesaria la adición de una mayor cantidad de un segundo no solvente para endurecer las microgotas, las que ahora serán llamadas microesferas (fig. 4).[9]

Desventajas del método de separación de fases:

- Frecuente aglomeración porque no hay un estabilizador.
- La variación lote a lote ha causado problemas tanto en el proceso de coacervación como en el perfil de velocidad de liberación.[8]
- Más costoso comparado con los otros métodos debido a la gran cantidad de solventes que se necesitan aumentando la contaminación ambiental.

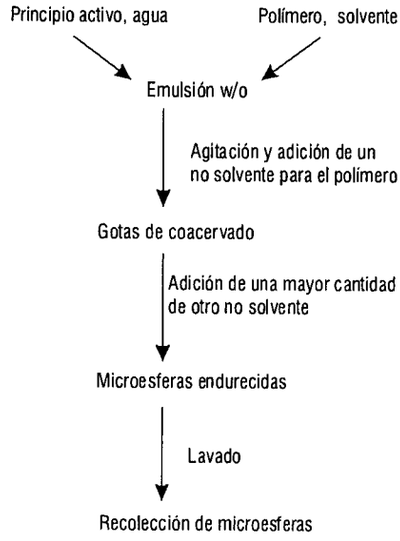

FIG. 4. *Método de separación de fases.*

Muchos solventes para el polímero pueden usarse en el proceso de separación de fases. En comparación con el método de evaporación/extracción del solvente, los requerimientos para el solvente del polímero son menos rigurosos. El solvente no tiene que ser inmiscible con el agua y el punto de ebullición puede ser mayor que el del agua. Sin embargo, el solvente debe disolver solo al polímero y no al p.a., es decir, se prefiere que el p.a. esté disperso en lugar de disuelto en la solución que contiene el polímero.[9]

Algunos de los ejemplos de solventes para el polímero usado en la separación de fases, son: diclorometano, acetato de etilo, acetonitrilo y tolueno.

Los no solventes influyen sobre la separación de fases y sobre el endurecimiento de las nuevas microesferas formadas. Además, debe tenerse mucho cuidado en su selección. El no solvente no debe disolver al polímero o al principio activo, pero debe ser inmiscible con el solvente para el polímero. El primer no solvente debe ser fácilmente removido por lavado con el segundo no solvente. El segundo no solvente debe ser relativamente volátil. Ejemplos del primer no solvente son líquidos viscosos polibutadienos líquidos de bajo peso molecular; polímeros metacrílicos líquidos de bajo peso molecular, aceite de silicona, aceites vegetales y aceite de parafina líquida.[7,48,49] Los hidrocarbones alifáticos como el heptano, hexano y éter de petróleo se han usado comúnmente como segundo no solvente.[50]

Fong patentó una única técnica de separación de fases que utiliza bajas temperaturas,[51] donde microencapsuló 2 principios activos en ácido poliláctico usando tolueno como solvente para el polímero e isopropanol como único no solvente.

Ruiz y otros también estudiaron el proceso de separación de fases usando ácido poliláctico-co-glicólico para formar microesferas que contenían triptorelina[53] y concluyeron que la naturaleza físico-química del polímero, la concentración del polímero, la viscosidad del aceite de silicona y la relación polímero-aceite de silicona afectaban la estabilidad del sistema emulsión en el proceso de separación de fases y por tanto la formación y calidad de la microesfera.

3. Otros métodos. A continuación mencionamos otros métodos que han sido utilizados para la obtención de microesferas biodegradables pero en una menor cuantía (Conti B, Pavanetto F, Genta I, Giunchedi P. Solvent evaporation, solvent extraction, and spray drying for polylactide microspheres preparation. Proc Pharm Technol Conf, bologna, 1991 (April 16-18):16-9).

- Secado por atomización.[53-55]
- Fusión en caliente.[56]
- Secado en frío.[57]
- Fluidización.[57]

De la presente revisión bibliográfica nos hemos propuesto el desarrollo de un medicamento de liberación modificada a base de microesferas como portadores de fármaco, con la utilización del método de evaporación/extracción del solvente en fase acuosa para la cual tendremos que optimizar todas las variables que influyen en el proceso discutidas en el texto.

La selección se fundamenta en las características del principio activo que se va a encapsular y por las ventajas que ofrece este método como son su reproducibilidad y bajo costo.

SUMMARY

The controlled release of therapeutic agents from polymeric biodegradable microspheres has been widely studied. Polylactic acid and its copolymers with glycolic acid have been used in the preparation of microspheres because of their biodegradability and biocompatibility. These microspheres have been prepared by various methods which are reviewed in this paper. As to their most used solvent evaporation-extraction method. The variables that might affect it are set forth here and some of them are also discussed.

Subject headings: MICROSPHERES; POLYMERS; POLYGHANTINGIO; TECHNOLOGY, PHARMACEUTICAL; BIODEGRADATION; DRUG COMPOUNDING.

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(54) Title: METHODS FOR ADMINISTERING ARIPIPRAZOLE

(57) Abstract: The present invention relates, in part, to the discovery that a pharmaceutical composition comprising aripiprazole and a carrier administered in a bolus injection resulted in an extended release profile similar to that obtained by the injection of a poly lactide-co-glycolide microsphere formulation containing the active agent. This surprising result suggests that pharmacologically beneficial extended release formulations without the complexities and expense associated with the manufacture microspheres.

METHODS FOR ADMINISTERING ARIPIPRAZOLE

BACKGROUND OF THE INVENTION

Aripiprazole, sold under the tradename Abilify®, is a dopamine D_2 and serotonin 5-HT_{1A} receptor agonist and antagonist of the serotonin 5-HT_{2A} receptor. Aripiprazole is used to treat schizophrenia and other psychotic and CNS disorders. See US Patent 5,006,528, for example. Abilify is currently sold as a tablet for oral administration. However, poor patient compliance with oral antipsychotics has been reported. As such, there exists a need for improved methods of delivering antipsychotics, such as aripiprazole, thereby improving patient compliance and maximizing the pharmacological profile of the active agent.

SUMMARY OF THE INVENTION

The present invention relates, in part, to the discovery that a pharmaceutical composition comprising aripiprazole and a carrier administered in a bolus injection resulted in an extended release profile similar to that obtained by the injection of a poly lactide-co-glycolide microsphere formulation containing the active agent. This surprising result suggests that pharmacologically beneficial extended release formulations without the complexities and expense associated with the manufacture ofpolymeric microspheres can be achieved.

Thus, the invention relates to an injectable composition for the extended release of aripiprazole comprising injecting or implanting a composition comprising aripiprazole wherein aripiprazole is present in the serum of the mammal for at least

about 7 days, preferably at least about 14 days, more preferably at least about 21 days, such as about three months. In a preferred embodiment, the composition comprises a suspension of aripiprazole in an injection vehicle, such as a suspension of an aripiprazole drug substance in an injection vehicle. The aripiprazole drug substance can comprise, consist essentially of or consist of aripiprazole (in a crystalline, non-crystalline or amorphous form), an aripiprazole salt, an aripiprazole solvate (including hydrates), or other aripiprazole polymorphs. The aripiprazole, or aripiprazole drug substance, can be added in a specified size. For example, the aripiprazole or aripiprazole drug substance can be added after being micronized to a mass mean diameter of less than about 100 microns, preferably between about 30 and 80 microns, as determined by Coulter counter.

In one embodiment, the aripiprazole or aripiprazole drug substance is injected as a mixture (including a suspension) of at least about 50 mg aripiprazole in an injection vehicle, such as at least about 70 to 210 mg or as much as about 900 to 2700 mg, e.g. less than 5400 mg. The aripiprazole can be present in an amount of at least about 10 mg/ml, preferably at least about 20 mg/ml or at least about 30 mg/ml. The invention also relates to methods for providing aripiprazole to an individual in an extended release injectable composition comprising administering a mixture of at least about 10 mg/ml aripiprazole in an injection vehicle comprising a viscosity enhancing agent and to compositions useful in such methods.

BRIEF DESCRIPTION OF THE DRAWINGS

The Figure compares the release profiles of subcutaneous injections (SC Bolus) according to the invention with injections of aripiprazole-containing microspheres.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to an injectable composition for the extended release of aripiprazole comprising a mixture of aripiprazole in an injection vehicle comprising an optional viscosity enhancing agent. The aripiprazole can be present in an amount of at least about 10 mg/ml, preferably at least about 20 mg/ml or at least about 30 mg/ml. The invention also relates to methods for providing aripiprazole to an

individual in an extended release injectable composition comprising administering a mixture of at least about 50 mg aripiprazole in an injection vehicle.

In general, the aripiprazole will be suspended in the injection vehicle. In one embodiment, the aripiprazole is supplied in a free flowing powder, substantially free of major amounts of pharmaceutical excipients or other compounds. For example, the aripiprazole can be supplied in a micronized state, consisting of or consisting essentially of aripiprazole. An aripiprazole drug substance can be said to consist essentially of aripiprazole if it contains, for example, 90% by weight or more aripiprazole and minor amounts (e.g., less than 10% by weight) of other materials that are, for example, residual to its process for manufacture. Compounds that may be found in a substantially pure aripiprazole drug substance can include wetting agents used, for example, to facilitate micronization, grinding or comminution, residual solvents, reaction by products or staring materials.

The compositions of the present invention are free of sustained release matrices. Sustained release matrices are polymers and other macromolecules (albumin), present in major amounts (e.g., 50% by weight or more of total solids), which when the active agent is dispersed therein, are used to slow the exposure or bioavailability of the active agent in the patient. A frequently used polymeric matrix is poly lactide-co-glycolide polymers. Thus, the aripiprazole drug substance and/or injectable compositions of the invention generally do not contain major amounts of PLGA polymer matrices.

Of course, polymers are often found in pharmaceutical compositions where the activity is not at all related to extending the release profile of the drug. For example, minor amounts of polysorbates, polyamines, polyvinylalcohol and polyethylene glycols are added to facilitate dispersibility of active agents in its vehicles. The inclusion of such polymers in amounts intended to accomplish these functions, and in amounts that do not permit the formation of substantial matrix formation, is permitted.

The aripiprazole drug substance is added to an injection vehicle. The drug substance can be dispersed or suspended in the vehicle, depending upon the solubility of the drug in the vehicle. The vehicle is preferably an aqueous vehicle

which suspends the drug substance. Preferably, the vehicle contains a viscosity enhancing agent.

Viscous vehicles can have, for example, a viscosity of at least 20 cp at 20° C. In other embodiments, the fluid phase of the suspension has a viscosity at 20° C. of at least about 30 cp, 40 cp, 50 cp, and 60 cp are preferred. The viscosity can be achieved by adding a viscosity enhancing agent, such as a carboxymethyl cellulose, such as sodium carboxy methylcellulose. In one embodiment, the injection vehicle comprises at least about 1% by volume sodium carboxymethyl cellulose, preferably about 3% by volume carboxymethyl cellulose.

The injection vehicle can advantageously contain a wetting agent, such as a polysorbate. Suitable polysorbates include polysorbate 20, polysorbate 40, and polysorbate 80, sold under the trademark Tween®. The wetting agent can be added in an amount that enhances the dispersibility of the active agent. An example of a suitable amount includes about 0.1 to 2% by weight of polysorbate 20.

The injection vehicle can also advantageously employ a density enhancing agent, such as a sugars, e.g. mannitol, or sorbitol and/or a tonicity adjusting agent, such as sodium chloride. In one embodiment, the tonicity adjusting agent is about 1% by weight, including 0.9% by weight.

In one embodiment, the composition consists of the aripiprazole drug substance and the injection vehicle, thereby providing a surprisingly simple and elegant formulation for obtaining an extended or sustained release profile.

The aripiprazole drug substance can comprise, consist essentially of or consist of aripiprazole (in a crystalline, non-crystalline or amorphous form), an aripiprazole salt, an aripiprazole solvate (including ethanolates and hydrates), or other aripiprazole polymorphs. Preferred salts include those salts insoluble in an aqueous vehicle. Pharmaceutical salts such as the hydrochloride and hydrobromide salts are suitable.

The methods of the invention include administering the compositions described herein, thereby obtaining an extended release or sustained release profile in the patient. An extended release profile includes deliveries that achieve a therapeutically effective amount of the aripiprazole is present in the plasma of the individual for at least about 7 days, preferably at least about 14 days, or more

preferably at least about 21 days alternatively for at least 2, 3, 4, 6 or 8 weeks or as much as three months.

In one embodiment, the formulations can be administered as a single or sole dose. However, the invention is particularly beneficial for those individuals that require constant or chronic therapy, such as those that receive repeated doses over several weeks or months or more. In such dosing regimens, the method can comprise a first administration of a first extended release formulation and a second administration of a second extended release formulation. The second formulation can be the same, substantially the same or different as the first and can include the same active agent or a different active agent. For example, the second formulation can be administered at about 7 days, or more, such as at least about 14 days, or at least about 17 days, after the first administration, where the first administration results in the release of agent for a period of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 days, or more.

The term "therapeutically effective amount" is further meant to define an amount resulting in the improvement of any parameters or clinical symptoms. The actual dose may vary with each patient and does not necessarily indicate a total elimination of all disease symptoms.

As used herein, the term "individual", "subject" or "patient" refers to a warm blooded animal, including but not limited to humans, such as a mammal which is afflicted with a particular disease state.

A therapeutically effective amount of the compound used in the treatment described herein can be readily determined by the attending diagnostician, as one skilled in the art, by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the therapeutically effective dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristic of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

The mode of administration will generally be by injection or implantation, such as intramuscularly or subcutaneously.

Preferred amounts according to the selected mode of administration are able to be determined by one skilled in the art. Pharmaceutical compositions can be manufactured utilizing techniques known in the art. Typically the therapeutically effective amount of the compound will be admixed with a pharmaceutically acceptable carrier.

For injection, the compounds may be in a physiologically acceptable pharmaceutical carrier and administered as a suspension. Illustrative pharmaceutical carriers also include water, aqueous methylcellulose solutions, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative, or synthetic origin. The pharmaceutical carrier may also contain preservatives, and buffers as are known in the art.

When the composition is to be used as an injectable material, including but not limited to needle-less injection, it can be formulated into a conventional injectable carrier. Suitable carriers include biocompatible and pharmaceutically acceptable solutions.

In a preferred embodiment, the size of the drug particle can be controlled. Often, the mass mean diameter of the drug particles is less than 100 microns, such as between about 1 and 100 microns, preferably about 10 and 100 microns, or about 20 and 60 microns.

In one embodiment, the unit dosage form can be stored as a dry powder, for example, to be mixed for injection prior to use, or as a stable suspension ready for use. Other methods for storing or administration using art recognized methods are also contemplated herein.

Experimental: Pharmacokinetic Evaluation of Aripiprazole in Rats following administration of single subcutaneous doses of Aripiprazole formulations.

Species and Strain: Sprague-Dawley rats. Male; 450 +/- 50 grams.

Study Groups: 5 Groups, 15 subjects

Group A: three rats injected once SC with 10 mg of Aripiprazole.

Group B: three rats injected once SC with 20 mg of Aripiprazole.

Group C: three rats injected once SC with 30 mg of Aripiprazole.

Group D: three rats injected once SC with ~67 mg of microparticles.

Group E: three rats injected once SC with ~40 mg of microparticles.

Group Conditions Table:

Rat Groups	Lot #	Polymer	Notes	% Load
A		N/A	Bulk Drug	100%
B		N/A	Bulk Drug	100%
C		N/A	Bulk Drug	100%
D	03-10-66-B	4A	Bulk Drug in microspheres	30%
E	03-10-66-C	4A	Bulk Drug in microspheres	50%

Route of Injection: Subcutaneous (SC) injection into the interscapular region.

Injection Vehicle: Aqueous diluent containing 3 % CMC (low viscosity), 0.1 % Tween 20, in 0.9 % NaCl and water.

Dose Volumes: Suspensions were formulated as follows:

Group A:	10mg powder in 0.75mL Diluent
Group B:	20mg powder in 0.75mL Diluent
Group C:	30mg powder in 0.75mL Diluent
Group D:	~67mg microparticles in 0.75mL Diluent
Group E:	40mg microparticles in 0.75mL Diluent

Blood Collection: Blood samples were collected via a lateral tail vein after anesthesia with Halothane. A syringe without an anticoagulant was used for the blood collection, then the whole blood was transferred to tubes containing K2 EDTA and mixing beads (Microtainer®; MFG# BD365974). The blood samples were processed (the tubes are inverted 15-20 times and centrifuged for 2 minutes at >14,000 g's) to separate plasma. The plasma samples prepared in this manner were transferred to labeled plain tubes (Microtainer®; MFG# BD5962) and stored frozen at < -70°C.

Blood Volumes: At least 250µL blood were collected at for each time point during the first 24 hours and 400µL for at each time point thereafter.

Time Points to obtain plasma :

2 h	24 h	3 d	10 d	21 d
4 h	32 h	4 d	14 d	24 d
8 h	2 d	7 d	17 d	28 d

Note: when plasma concentration was lower than the limitation of quantification, that group of ats were terminated.

The results obtained are reported in the Figure. Surprisingly, the rats that received bolus injections of aripiprazole and injection vehicle alone were substantially the same as those that received the aripiprazole dispersed within a PLGA microsphere.

Modifications and variations of the invention will be obvious to those skilled in the art from the foregoing detailed description of the invention. Such modifications and variations are intended to come within the scope of the appended claims.

All patents, patent application publications and articles cited herein are incorporated by reference in their entirety.

CLAIMS

We Claim:

1. An injectable composition for the extended release of aripiprazole comprising a mixture of at least about 10 mg/ml aripiprazole in an injection vehicle comprising an optional viscosity enhancing agent.

2. The composition of Claim 1, wherein the aripiprazole release is for at least 7 days.

3. The composition of Claim 2, wherein the viscosity enhancing agent comprises carboxymethyl cellulose.

4. The composition of Claim 3, wherein said injection vehicle comprises at least about 1% by volume sodium carboxymethyl cellulose.

5. The composition of Claim 4, wherein said injection vehicle comprises about 3% by volume carboxymethyl cellulose.

6. The composition of Claim 2, wherein the injection vehicle further comprises a wetting agent.

7. The composition of Claim 6, wherein the surfactant is selected from the group consisting of polysorbate 20, polysorbate 40, and polysorbate 80.

8. The composition of Claim 7, wherein the wetting agent is polysorbate 20.

9. The composition of Claim 8, wherein the injection vehicle comprises about 0.1 % by weight of polysorbate 20.

10. The composition of Claim 2, wherein said injection vehicle comprises a density enhancing agent.

11. The composition of Claim 10, wherein said density enhancing agent comprises sorbitol.

12. The composition of Claim 2, wherein said injection vehicle comprises a tonicity adjusting agent.

13. The composition of Claim 12, wherein said tonicity adjusting agent comprises sodium chloride.

14. The composition of Claim 1, wherein said injection vehicle comprises about 1% by weight of sodium chloride.

15. A composition comprising at least about 10 mg of aripiprazole and an aqueous injection vehicle comprising water, a viscosity enhancing agent, a wetting agent and a tonicity agent.

16. A composition comprising at least about 10 mg of aripiprazole and an aqueous injection vehicle comprising water, about 3 % by volume carboxymethylcellulose, about 0.1 % polysorbate 20 and about 1% by weight sodium chloride.

17. A composition comprising at least about 10 mg of aripiprazole and an aqueous injection vehicle consisting essentially of water, about 3 % by volume carboxymethylcellulose, about 0.1 % by weight polysorbate 20 and about 0.9% by weight sodium chloride.

18. A method for providing aripiprazole to an individual in an extended release injectable composition comprising administering a mixture of at least about

10 mg/ml aripiprazole in an injection vehicle comprising an optional viscosity enhancing agent.

19. The method of Claim 18, wherein the aripiprazole is present in an amount of at least about 20 mg/ml.

20. The method of Claim 19, wherein a therapeutically effective amount of the aripiprazole is present in the plasma of the individual for at least about 7 days.

21. The method of Claim 19, wherein a therapeutically effective amount of the aripiprazole is present in the plasma of the individual for at least about 14 days.

22. The method of Claim 19, wherein a therapeutically effective amount of the aripiprazole is present in the plasma of the individual for at least about 21 days.

23. The method of Claim 19, wherein the viscosity enhancing agent comprises carboxymethyl cellulose.

24. The method of Claim 23, wherein said injection vehicle comprises at least about 1% by volume sodium carboxymethyl cellulose.

25. The method of Claim 24, wherein said injection vehicle comprises about 3% by volume carboxymethyl cellulose.

26. The method of Claim 25, wherein the injection vehicle further comprises a wetting agent.

27. The method of Claim 26, wherein the surfactant is selected from the group consisting of polysorbate 20, polysorbate 40, and polysorbate 80.

28. The method of Claim 27, wherein the wetting agent is polysorbate 20.

29. The method of Claim 28, wherein the injection vehicle comprises about 0.1 % by weight of polysorbate 20.

30. The method of Claim 22, wherein said injection vehicle comprises a density enhancing agent.

31. The method of Claim 30, wherein said density enhancing agent comprises sorbitol.

32. The method of Claim 22, wherein said injection vehicle comprises a tonicity adjusting agent.

33. The method of Claim 32, wherein said tonicity adjusting agent comprises sodium chloride.

34. The method of Claim 21, wherein said injection vehicle comprises about 1% by weight of sodium chloride.

35. The method of Claim 18, wherein the composition is administered by injection.

36. The method of Claim 18, wherein the composition is administered intramuscularly or subcutaneously.

37. The method of Claim 18 further comprising a second administration of the composition at least about 7 days after the first administration.

38. The method of Claim18 further comprising a second administration of the composition at least about 14 days after the first administration.

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(54) **SUSTAINED-RELEASE MICROSPHERE CONTAINING ANTIPSYCHOTIC AND PROCESS FOR PRODUCING THE SAME.**

(57) A sustained-release microsphere produced by enclosing a hydrophobic antipsychotic such as bromperidol or haloperidol in a base comprising a biocompatible polymer such as polylactic acid or a lactic acid/glycolic acid copolymer. It can exhibit a desired pharmacological effect, where a long-term administration is necessary, by injecting once every 1 to 8 weeks instead of every day. As a result, a remarkable improvement can be expected in the compliance during maintenance therapy. In addition, the use of the biocompatible polymer serves to entirely dispense with surgical operations such as implantation, facilitates hypodermic and intramuscular injection just like the case of suspending injection, and can dispense with the widrawal of the microsphere. Furthermore, the microsphere can be administered with little aversion and pain.

EP 0 669 128 A1

Technical Field

This invention relates to a sustained release microsphere preparation which contains a hydrophobic antipsychotic drug and to a production process thereof.

Background Art

It is said that, in the drug therapy of mental diseases, maintenance therapy by continuous administration is effective in preventing recidivation of symptoms whereby it has come to be possible to guide patients in their daily life. However, since the current maintenance therapy with antipsychotic drugs is carried out by orally administering tablets or fine granules once a day or dividing the daily dose into several doses per day, decreased compliance during the maintenance therapy becomes a cause of recidivation of symptoms or re-hospitalization. Consequently, it has a drawback in that certain means must be employed to improve compliance after rehabilitation or during outpatient maintenance therapy.

In order to resolve this problem, long acting injections containing drugs in the form of decanoic acid ester or enanthic acid ester have been used. For example, decanoic acid esters of haloperidol and bromperidol are disclosed in JP-A-56-8318 (the term "JP-A" as used herein means "unexamined published Japanese Patent Application"), and decanoic acid ester or enanthic acid ester of fluphenazine is also known and used in the therapeutic field.

However, these prior long acting injections have drawbacks in that their administration route is limited to intramuscular injection, resistance at the time of administration is large because they are oil injections while the dispersibility of oil in muscular is small, and their administration gives patients severe pain. In addition, there is a possibility that their effects may vary depending on individuals and ages because, though the ester bodies of active ingredients show a sustained release effect in the living body by gradually releasing their active bodies due to the influence of esterase, release of drugs in the living body generally depends on their transition rate from the administered part into lymphoid system and also on the enzyme activity. Accordingly, it has been demanded to develop new long acting injections in which original drugs themselves are used.

On the other hand, each of JP-A-62-201816, JP-B-1-57087 and JP-B-2-124814 (the term "JP-B" as used herein means "examined Japanese Patent Publication") discloses sustained release microcapsules which make possible to administrate water soluble drugs at an interval of once a week or a month and production processes thereof. Also, JP-A-55-33414 discloses a so-called in-water drying method in which a hydrophobic drug and polylactic acid are dissolved in a common organic solvent, the resulting solution is emulsified by adding a phase separation agent and then the solvent is removed by evaporation to obtain fine particles.

Disclosure of the Invention

With the aim of improvement in compliance at the time of maintenance therapy with hydrophobic antipsychotic drugs, the present inventors have conducted intensive studies on the development of a sustained release pharmaceutical preparation in which a drug itself is used as an active ingredient without modification. As the result, it was found that a drug can be released at an almost constant rate extending over 1 week or more by including a hydrophobic antipsychotic drug into a base comprising a biodegradable high molecular weight polymer having *in vivo* histocompatibility to make a sustained release microsphere preparation and administrating it by subcutaneous or intramuscular injection, hence resulting in the accomplishment of the present invention.

Accordingly, the present invention relates to (1) an antipsychotic drug-containing sustained release microsphere preparation which is produced by including a hydrophobic antipsychotic drug into a base comprising a high molecular weight polymer having *in vivo* histocompatibility and (2) a process for producing an antipsychotic drug-containing sustained release microsphere preparation which comprises making an oil layer comprising a solution of a high molecular weight polymer having *in vivo* histocompatibility containing a hydrophobic antipsychotic drug, adding the oil layer to a water layer, subjecting the resulting mixture to an emulsification treatment to obtain an O/W type emulsion and subsequently removing the solvent in the oil layer by in-water drying method.

The hydrophobic antipsychotic drug to be applied to the present invention is selected from haloperidol, bromperidol, fluphenazine, chlorpromazine, sulpiride, carpipramine, clocapramine, mosapramine, risperidone, clozapine, oranzapine and sertindole and pharmaceutically acceptable acid addition salts thereof, preferably from the group consisting of haloperidol, bromperidol, fluphenazine maleate, chlorpromazine, chlorpromazine hibenzoate, sulpiride, carpipramine hydrochloride, carpipramine maleate, clocapramine hydrochloride, mosapramine hydrochloride, risperidone, clozapine, oranzapine and sertindole, of which haloperidol or bromperidol is particularly preferred.

The base that constitutes the sustained release microspheres of the present invention should have such a function that its concentration in blood plasma can be maintained at a constant level by a single administration whereby its effects can be obtained stably over a prolonged period of time. A biodegradable high molecular weight polymer having *in vivo* histocompatibility is used as a base having such a function. The sustained release microspheres of the present invention are constructed in the manner that the hydrophobic antipsychotic drug is included therein. Examples of such a high molecular weight polymer having *in vivo* histocompatibility include polymers of fatty acid esters or copolymers thereof, polyacrylic esters, polyhydroxybutyric acids, polyalkylene oxalates, polyorthoester, polycarbonate and polyamino acids, which may be used alone or as a mixture of two or more. Illustrative examples of the polymers of fatty acid esters or copolymers thereof include polylactic acid, polyglycolic acid, polycitric acid, polymalic acid and poly(lactic-co-glycolic)-acid, which may also be used alone or as a mixture of two or more. Another useful examples include poly-α-cyanoacrylic ester, poly-β-hydroxybutyric acid, polytrimethylene oxalate, polyorthoester, polyorthocarbonate, polyethylene carbonate, poly γ-benzyl-L-glutamic acid and poly L-alanine, which may be used alone or as a mixture of two or more. Of these polymers, polylactic acid, polyglycolic acid or poly(lactic-co-glycolic)acid may be used preferably.

These *in vivo* histocompatible high molecular weight polymers to be used in the present invention may have an average molecular weight of preferably from about 2,000 to about 80,000, more preferably from about 5,000 to about 20,000. When poly(lactic-co-glycolic)acid is used as the *in vivo* histocompatible high molecular weight polymer, compositional ratio of lactic acid and glycolic acid may be in the range of from about 100:0 to 50:50, preferably at 75:25 and 50:50.

Although the amount of the high molecular weight polymer(s) is decided by the drug-releasing rate, period and the like, and may be controlled within in a range of from about 0.2 to about 10,000 times by weight of the drug, it is preferred that the high molecular weight polymer is used as the base of the microsphere preparation of the present invention in an amount of from 1 to 1,000 times by weight of the drug.

A solution containing the above high molecular weight polymer (oil layer) is prepared by dissolving the high molecular weight polymer in a solvent. The concentration of the high molecular weight polymer in the oil layer may be in the range of preferably from about 0.5 to about 90% (w/w), more preferably from about 2 to about 60% (w/w).

Examples of the solvent include those which have a boiling point of about 120 °C or lower, do not show miscibility with water and can dissolve high molecular weight polymers, such as alkane halides (dichloromethane, chloroform, chloroethane, dichloroethane, trichloroethane and the like), ethyl acetate, ethyl ether, cyclohexane, benzene, n-hexane, toluene and the like, which may be used alone or as a mixture of two or more.

In the production process of the microsphere preparation, a hydrophobic antipsychotic drug is dissolved or dispersed in a solution prepared by dissolving a *in vivo* histocompatible high molecular weight polymer in a solvent to give an oil layer. The thus obtained oil layer is added to a water layer and subjected to an emulsification treatment to prepare an O/W type emulsion. Thereafter, the microsphere preparation is obtained by removing the solvent in the oil layer by means of in-water drying method.

When the oil layer is prepared by dispersing a drug, the drug may be used after making it into fine particles. By the use of microcrystals, the surface of microspheres becomes smooth and the drug release becomes close to 0 order. Such a releasing capacity close to 0 order seems to be accomplished due to decrease in the initial releasing rate resulting from the increased interaction between the afore-mentioned high molecular weight polymer and the drug effected by the increased contacting area and due to increase in the releasing rate in the late stage effected by the increased surface area of the drug. The finely ground drug may have a particle size of preferably within a range of 10 μm or less, more preferably within a range of 5 μm or less (about 0.1 to about 5 μm, preferably 0.5 to 5 μm). Fine particles of the drug can be obtained by usually used means. Examples of such means include jet mill, ball mill, vibrating mill, hammer mill, colloid mill and the like.

In preparing microspheres of the present invention, it is preferable to add an emulsifying agent to the water layer, and examples thereof include those which are able to form a stable O/W type emulsion, such as an anionic surfactant (sodium oleate, sodium stearate, sodium lauryl sulfate or the like), a nonionic surfactant (a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene castor oil derivative or the like), polyvinyl pyrrolidone, polyvinyl alcohol, carboxymethylcellulose, lecithin, gelatin and the like, which may be used alone or as a mixture of two or more. These agents may be used in a concentration of from about 0.01% to about 20%, more preferably from about 0.05% to about 10%.

Removal of the solvent from the oil layer is effected by a conventionally used means (in-water drying method: Tamotsu Kondo,

"Maikurokapuseru-sono kinou to ouyou (Microcapsules, Their Functions And Applications)", p.78, Japanese Standards Association, March 20, 1991). In this method, a solvent is removed by gradually reducing pressure while stirring using a propeller mixer, a magnetic stirrer or the like or by controlling the degree of vacuum using a rotary evaporator or the like.

The thus obtained microspheres are collected by centrifugation or filtration, washed several times with distilled water to remove free drug, the emulsifying agent and the like adhered to the surface of the microspheres and then treated under a reduced pressure, if necessary, with heating, to perfect removal of water and solvent in the microspheres.

If necessary, the thus obtained microspheres are gently ground and screened to remove oversized microspheres. When used as suspensions for injection use, the particle size of the microspheres may be a range which can satisfy their dispersibility and needle-passing property, for example, in the range of from about 0.5 to about 400 μm, more preferably from about 0.5 to about 200 μm, as an average particle size.

The microspheres of the present invention can be made into sustained release injections by preparing an aqueous suspension together with a dispersing agent (polysorbate 80, sodium carboxymethylcellulose, sodium alginate or the like), a preservative (methylparaben, propylparaben, benzyl alcohol, chlorobutanol or the like) and an isotonic agent (sodium chloride, glycerol, sorbitol, glucose or the like) or by preparing an oily suspension by dispersing the microspheres in a plant oil such as olive oil, sesame oil, peanut oil, cotton oil, corn oil or the like or in propylene glycol or the like. In this instance, in order to lessen resisting feeling at the time of injection, the sustained release microsphere preparation of the present invention may be used preferably in the form of aqueous suspension.

In addition, sustained release injections of microspheres of the present invention can be made into more stable sustained release injections by further mixing the above composition with a filler (mannitol, sorbitol, lactose, glucose or the like), dispersing the mixture and then subjecting the resulting dispersion to freeze drying or spray drying to obtain a solid preparation which is used by adding distilled water for injection use or an appropriate dispersion medium at the time of injection.

Dose of a hydrophobic antipsychotic drug as the active ingredient of the sustained release microsphere preparation of the present invention can be decided depending on each disease to be treated, symptoms and age of each patient and the like, and it may be in the range of generally from 5 to 5,000 mg, preferably from 10 to 2,000 mg, per adult per administration. Since the pharmaceutical preparation of the present invention releases its active ingredient depending on the hydrolysis of the high molecular weight polymer by water, it shows less individual difference and can be administered by not only intramuscular injection but also subcutaneous injection.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing remaining amount of bromperidol in the administered area of rat after intramuscular injection of each of the microsphere preparations obtained in Examples 1 to 3.

Fig. 2 is a graph showing periodical changes in the drug concentration in blood plasma of rat after intramuscular injection of the haloperidol-containing microsphere preparation obtained in Example 4.

Fig. 3 is a graph showing results of an *in vitro* drug release test of the microsphere preparation obtained in Test Example 3.

BEST MODE OF CARRYING OUT THE INVENTION

The following Examples and Test Examples are provided to illustrate the present invention further in detail.

EXAMPLE 1

Poly(lactic-co-glycolic)acid (50:50) (molecular weight: about 20,000) was dissolved in 3 ml of dichloromethane to prepare a 40% solution. In this was dissolved 190 mg of bromperidol (average particle size: 13.0 μm) to prepare a mixed solution. This was poured into 1,000 ml of 0.5% polyvinyl alcohol (Gosenol EG-40, manufactured by The Nippon Synthetic Chemical Industry) and dispersed using a homogenizer (manufactured by Tokushu Kika Kogyo) to prepare an O/W type emulsion. Thereafter, the O/W type emulsion was gently stirred using a conventional mixer to effect evaporation of dichloromethane and solidification of microspheres which were subsequently collected by centrifugation, simultaneously washing with distilled water. The thus recovered microspheres were made into a powder preparation by freeze drying.

EXAMPLE 2

dl-Polylactic acid (molecular weight: about 10,000) was dissolved in 3 ml of dichloromethane to prepare a 20% solution. In this was suspended 190 mg of bromperidol (average particle size: 2.5 μm) to obtain a mixed solution. Thereafter, a bromperidol-containing microsphere preparation was obtained in the same manner as described in Exam-

ple 1.

EXAMPLE 3

dl-Polylactic acid (molecular weight: about 20,000) was dissolved in 3 ml of dichloromethane to prepare a 20% solution. In this was dissolved 85 mg of bromperidol (average particle size, 13.0 μm) to obtain a mixed solution. Thereafter, a bromperidol-containing microsphere preparation was obtained in the same manner as described in Inventive Example 1.

EXAMPLE 4

dl-Polylactic acid (molecular weight, about 10,000) was dissolved in 4 ml of dichloromethane to prepare a 30% solution. In this was suspended 380 mg of haloperidol (average particle size: 3.0 μm) to obtain a mixed solution. Thereafter, a haloperidol-containing microsphere preparation was obtained in the same manner as described in Example 1.

EXAMPLE 5

A microsphere preparation is obtained in the same manner as described in the above Examples using fluphenazine maleate, chlorpromazine, chlorpromazine hibenzoate, sulpiride, carpipramine hydrochloride, carpipramine maleate, clocapramine hydrochloride, mosapramine hydrochloride, risperidone, clozapine, oranzapine or sertindole as the drug.

TEST EXAMPLE 1

Each of the bromperidol-containing microsphere preparations obtained in Examples 1 to 3 was suspended in physiological saline and administered into the femoral muscle of male SD rats (15 weeks of age) in a dose of 12.5 mg as bromperidol. After a predetermined period of time, microspheres remained in the administered area were periodically recovered to measure remaining amount of bromperidol. As the result, release of the drug at an almost constant rate was confirmed as shown in Fig. 1.

TEST EXAMPLE 2

The haloperidol-containing microsphere preparation obtained in Example 4 was suspended in a 0.5% sodium carboxymethylcellulose solution isotonized with mannitol and administered into the femoral muscle of male SD rats (13 weeks of age) in a dose of 25 mg as haloperidol. After a predetermined period of time, blood samples were periodically collected from ophthalmic veins to measure concentration of the drug in blood plasma. As the result, sustained concentration of haloperidol in blood plasma was confirmed as shown in Fig. 2.

TEST EXAMPLE 3

A 25 mg portion of each of the bromperidol-containing microsphere preparations obtained from the following formulations A and B was dispersed in 20 ml of physiological saline and shaken at 37°C and at 80 revolutions per minute using a constant temperature shaker (manufactured by Yamato Kagaku). Thereafter, samples were periodically collected to calculate drug releasing ratio by ultraviolet absorption photometry (245 nm). As shown in Fig. 3, it was confirmed that the microsphere preparation of formulation A which comprises finely ground bromperidol can release the drug at a rate of almost 0 order.

FORMULATION A

dl-Polylactic acid (molecular weight: about 5,000) was dissolved in 3 ml of dichloromethane to prepare a 12% solution. In this was suspended 190 mg of bromperidol (average particle size: 2.5 μm) to obtain a mixed solution. Thereafter, a bromperidol-containing microsphere preparation was obtained in the same manner as described in Example 1.

FORMULATION B

Bromperidol with no grinding (average particle size: 13.0 μm) was used in stead of the bromperidol of Formulation A having an average particle size of 2.5 μm.

INDUSTRIAL APPLICABILITY

According to the hydrophobic antipsychotic drug-containing sustained release microsphere preparation of the present invention, considerable improvement in compliance in maintenance therapy of mentally deranged persons can be expected because of the following features of the preparation of the present invention.

(1) When a long-term administration is required, desired pharmacological effects can be obtained continuously by one injection per 1 to 8 weeks, in stead of daily administration.

(2) Since a biodegradable high molecular weight polymer is used, surgical operations such as embedding and the like are not required at all, and subcutaneous and intramuscular administrations can be made easily absolutely in the same manner as the case of conventional suspension

injections so that recovery of the material is not required.
(3) Pain and resistance at the time of administration are small.

Claims

1. An antipsychotic drug-containing sustained release microsphere preparation which is produced by including a hydrophobic antipsychotic drug into a base comprising a high molecular weight polymer having *in vivo* histocompatibility.

2. The antipsychotic drug-containing sustained release microsphere preparation according to claim 1 wherein said hydrophobic antipsychotic drug is selected from haloperidol, bromperidol, fluphenazine, chlorpromazine, sulpiride, carpipramine, clocapramine, mosapramine, risperidone, clozapine, oranzapine and sertindole and pharmaceutically acceptable acid addition salts thereof.

3. The antipsychotic drug-containing sustained release microsphere preparation according to claim 1 or 2, wherein said hydrophobic antipsychotic drug is selected from haloperidol, bromperidol, fluphenazine maleate, chlorpromazine, chlorpromazine hibenzoate, sulpiride, carpipramine hydrochloride, carpipramine maleate, clocapramine hydrochloride, mosapramine hydrochloride, risperidone, clozapine, oranzapine and sertindole.

4. The antipsychotic drug-containing sustained release microsphere preparation according to claim 1, wherein said hydrophobic antipsychotic drug is selected from haloperidol and bromperidol.

5. The antipsychotic drug-containing sustained release microsphere preparation according to claim 1, wherein said high molecular weight polymer having *in vivo* histocompatibility is one or more compounds selected from polymers of fatty acid esters or copolymers thereof, polyacrylic esters, polyhydroxybutyric acids, polyalkylene oxalates, polyorthoester, polycarbonate and polyamino acids.

6. The antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 1 to 5, wherein said high molecular weight polymer having *in vivo* histocompatibility is one or more compounds selected from polylactic acid, polyglycolic acid, polycitric acid, polymalic acid and poly(lactic-co-glycolic)acid.

7. The antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 1 to 6, wherein said high molecular weight polymer having *in vivo* histocompatibility is one or more compounds selected from polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, poly(lactic-co-glycolic)acid, poly-α-cyanoacrylic ester, poly-β-hydroxybutyric acid, polytrimethylene oxalate, polyorthoester, polyorthocarbonate, polyethylene carbonate, poly-γ-benzyl-L-glutamic acid and poly-L-alanine.

8. The antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 1 to 7, wherein said hydrophobic antipsychotic drug is in the form of microcrystals having an average particle size of 5 μm or less.

9. The antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 1 to 8, wherein said antipsychotic drug-containing sustained release microsphere preparation is an aqueous suspension.

10. A process for producing an antipsychotic drug-containing sustained release microsphere preparation which comprises making an oil layer comprising a high molecular weight polymer having *in vivo* histocompatibility containing a hydrophobic antipsychotic drug, adding the oil layer to a water layer, subjecting the resulting mixture to an emulsification treatment to obtain an O/W type emulsion and subsequently removing the solvent in the oil layer by in-water drying method.

11. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to claim 10, wherein said hydrophobic antipsychotic drug is selected from haloperidol, bromperidol, fluphenazine, chlorpromazine, sulpiride, carpipramine, clocapramine, mosapramine, risperidone, clozapine, oranzapine and sertindole and pharmaceutically acceptable acid addition salts thereof.

12. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to claim 10 or 11, wherein said hydrophobic antipsychotic drug is selected from haloperidol, bromperidol, fluphenazine maleate, chlorpromazine, chlor-

promazine hibenzoate, sulpiride, carpipramine hydrochloride, carpipramine maleate, clocapramine hydrochloride, mosapramine hydrochloride, risperidone, clozapine, oranzapine and sertindole.

13. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to claim 10, wherein said hydrophobic antipsychotic drug is selected from haloperidol and bromperidol.

14. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to claim 10, wherein said high molecular weight polymer having *in vivo* histocompatibility is one or more compounds selected from polymers of fatty acid esters or copolymers thereof, polyacrylic esters, polyhydroxybutyric acids, polyalkylene oxalates, polyorthoester, polycarbonate and polyamino acids.

15. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 10 to 14, wherein said high molecular weight polymer having *in vivo* histocompatibility is one or more compounds selected from polylactic acid, polyglycolic acid, polycitric acid, polymalic acid and poly(lactic-co-glycolic)acid.

16. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 10 to 15, wherein said high molecular weight polymer having *in vivo* histocompatibility is one or more compounds selected from polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, poly(lactic-co-glycolic)acid, poly-α-cyanoacrylic ester, poly-β-hydroxybutyric acid, polytrimethylene oxalate, polyorthoester, polyorthocarbonate, polyethylene carbonate, poly-γ-benzyl-L-glutamic acid and poly-L-alanine.

17. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 10 to 16, wherein said hydrophobic antipsychotic drug is in the form of microcrystals having an average particle size of 5 μm or less.

18. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 10 to 17, wherein a solvent of said solution of high molecular weight polymer having *in vivo* histocompatibility is a solvent which has a boiling point of 120 °C or less and does not admix with water.

19. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 10 to 18, wherein one or more compounds selected from anionic surfactants, nonionic surfactants, polyvinyl pyrrolidone, polyvinyl alcohol, carboxymethylcellulose, lecithin and gelatin are added as emulsifying agents to said water layer.

20. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 10 to 19, wherein said antipsychotic drug-containing sustained release microsphere preparation is an aqueous suspension.

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(54) **METHOD OF PREPARING SUSTAINED RELEASE MICROPARTICLES**

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(57) **ABSTRACT**

The present invention relates to a method for preparing an injectable composition of microparticles for the sustained release of a biologically active agent. The microparticles include a biocompatible polymer and a biologically active agent. The invention provides an improved process for the preparation of microparticles, wherein the physical characteristics of the microparticles, for example, the morphology, density and size, are independent of the process used to prepare the initially formed polymer/drug matrix. The method includes the steps of (a) providing a polymer/biologically active agent matrix; (b) compressing the polymer/biologically active agent matrix, thereby forming a compressed matrix; and (c) fragmenting the compressed matrix, thereby forming an injectable microparticle composition. The polymer/drug matrix can be provided by any suitable method.

extracting the solvent present in the solid droplets into a non-solvent, thereby forming the polymer/biologically active agent matrix.

[0014] The present invention also relates to sustained release microparticles that are formed by the methods described herein. The microparticles include a biocompatible polymer such as, for example, poly(lactic acid) or a poly(lactic acid-co-glycolic acid) copolymer, and a biologically active agent, for example, a therapeutic, prophylactic or diagnostic agent such as a protein, peptide, nucleic acid or small organic molecule (e.g., an antipsychotic agent).

[0015] In a particularly preferred embodiment, the microparticles prepared according the method of the invention include a biocompatible polymer and a drug used to treat affective disorders, such as schizophrenia, depression, and anxiety. Suitable drugs for treating affective disorders include, but are not limited to, risperidone, olanzapine and aripiprazole.

[0016] In one embodiment, the microparticles can further include one or more excipients and/or release modifiers. The particles can include one or more additional drugs.

[0017] Practice of the present invention can be used to prepare microparticles by using any suitable method of preparing the polymer/biologically active agent matrix followed by downstream tailoring of the physical characteristics of the resulting injectable microparticles. For example, the morphology and/or size of the initially fabricated polymer/biologically active agent matrix is decoupled from the physical characteristics of the resulting microparticles, which can impact the injectability and release profile of the microparticles.

[0018] For example, the present invention allows the production of dense microparticles for drug delivery. In one embodiment, the porosity of the polymer/drug matrix is reduced and thus a given volume of microparticles formed in accordance with the processes described herein contains a higher drug load than an equivalent volume of polymer/biologically active agent matrix. Thus, practice of the present invention can be used to increase drug loads for a given dose volume.

[0019] Therefore, the improved method described herein provides for an efficient, facile and cost effective preparation of sustained release microparticles having desirable physical properties. For example, the microparticles prepared according to the methods described herein can exhibit a reduced initial release of biologically active agent, a higher sustained level of agent and/or a longer duration of release of the biologically active agent following administration.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] **FIG. 1** is a plot of olanzapine concentration in blood plasma (nanograms/milliliter) versus time (days) for an in vivo study of three polymer/drug microparticle compositions (50 milligrams olanzapine/kilogram normalized dose) administered subcutaneously to Sprague-Dawley rats.

[0021] **FIG. 2** is a plot of olanzapine concentration in blood plasma (nanograms/milliliter) versus time (days) for an in vivo study of two forms of a polymer/drug microparticle composition (50 milligrams olanzapine/kilogram normalized dose) administered subcutaneously to Sprague-Dawley rats. "Uncompacted" particles were produced by milling a cast film of a solution of polymer and drug. "Compacted" particles were further compacted and refragmented to produce injectable microparticles.

[0022] **FIG. 3** is a bar chart showing the results of an 18 hour in vitro study demonstrating the effect of various solvents on the molecular weight of poly(d,l-lactide-co-glycolide) in the presence of olanzapine.

[0023] **FIG. 4** is a plot showing the results of two in vitro studies measuring the cumulative release of insulin (as a percentage of total insulin) from three microparticle formulations in 0.1 M sodium phosphate, pH 7 at 37° C. and one microparticle formulation in Hepes buffer, pH 7 at 37° C. versus time (in days).

[0024] **FIG. 5** is a plot of naltrexone concentration in blood plasma (nanograms/milliliter) versus time (days) for an in vivo study of four polymer/drug microparticle compositions coated with various polymers and one uncoated control microparticle composition administered subcutaneously to Sprague-Dawley rats.

[0025] **FIG. 6** is a plot of Bovine Serum Albumin (herein "BSA") concentration in blood plasma (nanograms/milliliter) versus time (days) for an in vivo study of three polymer/drug compositions (15 milligrams BSA/kilogram normalized dose) administered to rats.

DETAILED DESCRIPTION OF THE INVENTION

[0026] The foregoing and other objects, features and advantages of the invention will be apparent from the following more particular description of preferred embodiments of the invention.

[0027] The present invention relates to a method for preparing an injectable composition of microparticles for the sustained release of a biologically active agent. The microparticles include a biocompatible polymer and a biologically active agent, for example, a therapeutic, prophylactic or diagnostic agent, also referred to herein as a "drug." The invention provides an improved process for the preparation of microparticles wherein the physical characteristics of the microparticles, for example, the morphology, density and size, are independent of the process used to prepare the initially formed polymer/biologically active agent matrix. That is, the method of the invention provides for the ability to decouple the fabrication of the polymer/biologically active agent matrix from subsequent steps used to impart the desired physical characteristics to the injectable microparticles.

[0028] The method includes the steps of: (a) providing a polymer/biologically active agent matrix; (b) compressing the polymer/biologically active agent matrix, thereby forming a compressed matrix; and (c) fragmenting the compressed matrix, thereby forming an injectable microparticle composition. The polymer/biologically active agent matrix can be provided by any suitable method. A suitable method should not result in a significant reduction of the biological activity of the incorporated drug. As such, in embodiments wherein the drug is a labile agent, for example, a biologically active agent that can undergo degradation when exposed to heat or solvent, the polymer/biologically active agent matrix can be prepared at a temperature which does

not significantly reduce the biological activity of the drug. The method can further include the step of fragmenting the polymer/biologically active agent matrix prior to compressing the matrix, referred to herein as "precompression fragmenting."

[0029] In one embodiment, the polymer/biologically active agent matrix is provided by (a) preparing a mixture of a biologically active agent, a biocompatible polymer and a solvent, e.g., a polymer solvent; and (b) removing the solvent, thereby forming the polymer/biologically active agent matrix. The biologically active agent can be suspended (e.g., completely or partially suspended) in the mixture and/or dissolved (e.g., completely or partially dissolved) in the mixture. For example, the solvent can be a solvent for both the biologically active agent and the biocompatible polymer, e.g., both the biologically active agent and the polymer are dissolved in the solvent. In one embodiment, the mixture constitutes a single phase solvent system.

[0030] As such, in one embodiment the invention relates to a method for preparing an injectable microparticle composition for the sustained release of a biologically active agent comprising the steps of: (a) preparing a mixture comprising a biologically active agent, a biocompatible polymer, and a solvent, thereby forming a single phase solvent system; (b) removing the solvent from the solution, thereby forming a polymer/biologically active agent matrix; (c) compressing the matrix using confined pressure compaction, thereby forming a compressed matrix; and (d) fragmenting the matrix, thereby forming the injectable microparticle composition.

[0031] The term "single phase solvent system," as used herein, refers to a mixture that includes one or more liquids, e.g., solvents, that are in a single phase and in which the polymer and biologically active agent are dissolved and/or suspended. When a combination of liquids is used, the liquids of the combination are miscible and when the liquids are mixed, a single phase, rather than separate phases, results. For example, when a combination of solvents is used, the solvents of the combination are miscible. A combination of liquids, e.g., solvents, can be formed prior to, following, or simultaneously with the mixing of the polymer and/or agent with the solvent or solvents to form a single phase solvent system. In a preferred embodiment, the solvent used is a single solvent.

[0032] In a preferred embodiment, compressing the polymer/biologically active agent matrix is conducted without the application of heat. For example, the compression can be conducted at or below the transition temperature of the matrix. In one embodiment, the matrix is compressed at about ambient temperature or room temperature (e.g., such as about 15° C. to about 30° C.). In one embodiment, fragmenting of the compressed matrix is conducted at or below the transition temperature of the polymer/biologically active agent matrix.

[0033] In a preferred embodiment, the biologically active agent is an antipsychotic drug such as aripiprazole, olanzapine or risperidone.

[0034] In one embodiment, the polymer/biologically active agent matrix is provided by (a) preparing a mixture of a biologically active agent, a biocompatible polymer, and a solvent, e.g., a polymer solvent; (b) forming droplets of the mixture; (c) solidifying the droplets (e.g., freezing), thereby forming solid droplets (e.g., frozen droplets); and (d) extracting the solvent present in the solid droplets into a non-solvent, thereby forming the polymer/biologically active agent matrix. The matrix can then be filtered and dried.

[0035] The present invention also relates to the sustained release microparticles that are formed by the methods described herein. The microparticles include a biocompatible polymer such as, for example, poly(lactic acid) or a poly(lactic acid-co-glycolic acid) copolymer, and a biologically active agent, for example, a therapeutic, prophylactic or diagnostic agent such as a protein, peptide, nucleic acid or small organic molecule.

[0036] In a particularly preferred embodiment, the microparticles prepared according the method of the invention include a biocompatible polymer and a drug used to treat affective disorders, such as schizophrenia, depression, and anxiety. Suitable drugs for treating affective disorders include, but are not limited to, risperidone, olanzapine and aripiprazole.

[0037] In one embodiment, the microparticles can further include one or more excipients and/or release modifiers. The particles can include one or more additional drugs.

[0038] The invention also relates to use of the microparticles prepared according to the described method for the manufacture of a medicament for use in therapy. For example, for use in treating affective disorders such as schizophrenia, depression and anxiety.

[0039] Preparation of Polymer/Drug Matrix

[0040] The terms "polymer/biologically active agent matrix" and "polymer/drug matrix," as used interchangeably herein, refer to a solid material comprising a biocompatible polymer (e.g., a homopolymer, copolymer or polymer blend) and drug molecules, which are dispersed throughout the polymer. The polymer/biologically active agent matrix can be of any size and shape prior to compression and fragmenting. For example, the polymer/biologically active agent matrix can be a film, pellet, cylinder, disc or particle (e.g., spherical, non-spherical or irregularly shaped). The polymer/drug matrix can be homogeneous or heterogeneous, for example, the polymer/drug matrix can have a homogeneous distribution of drug in the matrix or, alternatively, the distribution of drug in the matrix can be heterogeneous. The polymer/drug matrix can further comprise excipients such as, for example, surfactants, carbohydrates (e.g., monosaccharides and polysaccharides), release modifying agents, stabilizers, one or more additional biologically active agents and any combination thereof.

[0041] Any suitable method can be used to provide the polymer/drug matrix for subsequent fragmentation and compression to form an injectable microparticle composition.

[0042] In one embodiment, the polymer/biologically active agent matrix is provided by (a) forming a mixture of a biologically active agent, a biocompatible polymer and a solvent, e.g., a polymer solvent, and (b) removing the solvent, thereby forming a polymer/biologically active agent matrix. The biologically active agent can be in solution and/or suspended in the mixture. In one embodiment, the drug and polymer are dissolved and/or suspended in a single

phase solvent system. A number of methods are known for providing the polymer/drug matrix in this manner.

[0043] For example, methods for forming a composition for the sustained release of biologically active agent are described in U.S. Pat. No. 5,019,400, issued to Gombotz, et al., on May 28, 1991; U.S. Pat. No. 5,922,253 issued to Herbert, et al., on Jul. 13, 1999; and U.S. Pat. No. 6,455,074 issued to Tracy, et al., on Sep. 24, 2002, the entire contents of each of which are incorporated herein by reference.

[0044] In this method, a mixture comprising a biologically active agent, a biocompatible polymer and a polymer solvent is processed to create droplets, wherein at least a significant portion of the droplets contains polymer, polymer solvent and the active agent. These droplets are then frozen by a suitable means. Examples of means for processing the mixture to form droplets include directing the dispersion through an ultrasonic nozzle, pressure nozzle, Rayleigh jet, or by other known means for creating droplets from a solution.

[0045] Means suitable for freezing droplets include directing the droplets into or near a liquified gas such as liquid argon or liquid nitrogen to form frozen microdroplets which are then separated from the liquified gas. The frozen microdroplets are then exposed to a liquid or solid non-solvent such as ethanol, hexane, ethanol mixed with hexane, heptane, ethanol mixed with heptane, pentane or oil.

[0046] The solvent in the frozen microdroplets is extracted as a solid and/or liquid into the non-solvent to form a polymer/active agent matrix comprising a biocompatible polymer and a biologically active agent. Mixing ethanol with other non-solvents, such as hexane, heptane or pentane, can increase the rate of solvent extraction, above that achieved by ethanol alone, from certain polymers such as, for example, poly(lactide-co-glycolide) polymers.

[0047] A wide range of sizes of polymer/drug matrices can be made by varying the droplet size, for example, by changing the ultrasonic nozzle diameter. If the polymer/drug matrix is in the form of particles and very large particles are desired, the particles can be extruded, for example, through a syringe directly into the cold liquid. Increasing the viscosity of the polymer solution can also increase the polymer/drug matrix (e.g., particle) size. The size of the polymer/drug matrices (e.g., particles) which can be produced by this process ranges, for example, from about 1 micrometer to greater than about 1000 micrometers in diameter.

[0048] Yet another method of forming a polymer/drug matrix from a suspension or solution comprising a biocompatible polymer and a biologically active agent includes film casting, such as in a mold, to form a film or a shape. For instance, after putting the suspension into a mold, the polymer solvent is then removed (e.g., via evaporation or sublimation) or the temperature of the polymer suspension is reduced (e.g., the polymer suspension is frozen) until a film or shape is obtained. Means for removing the solvent from a cast film are known in the art and include vacuum drying, lyophilization, flash drying, and sublimation, among others. The solvent is removed until the residual solvent levels are brought to concentrations that are suitable for administration to a patient. One of ordinary skill in the art can determine the concentrations of residual solvent in particles administered to a patient that are acceptable or tolerated without undue experimentation.

[0049] A further example of a process for the production of a polymer/drug matrix, e.g., particles, is disclosed in U.S. Pat. No. 3,737,337, incorporated by reference herein in its entirety, wherein a solution of a wall or shell forming polymeric material in a solvent is prepared. The solvent is only partially miscible in water. A solid or core material is dissolved or dispersed in the polymer-containing mixture and, thereafter, the core material-containing mixture is dispersed in an aqueous liquid that is immiscible in the organic solvent in order to remove solvent from the polymer/drug matrix, e.g., particles.

[0050] Another example of a process in which solvent is removed from particles containing a substance is disclosed in U.S. Pat. No. 3,523,906, incorporated herein by reference in its entirety. In this process, a material to be encapsulated is emulsified in a solution of a polymeric material in a solvent that is immiscible in water and then the emulsion is emulsified in an aqueous solution containing a hydrophilic colloid. Solvent removal from the particles is then accomplished by evaporation and the product is obtained.

[0051] In still another process, as shown in U.S. Pat. No. 3,691,090, incorporated herein by reference in its entirety, organic solvent is evaporated from a dispersion of particles in an aqueous medium, preferably under reduced pressure.

[0052] Similarly, the disclosure of U.S. Pat. No. 3,891,570, incorporated herein by reference in its entirety, shows a method in which solvent from a dispersion of particles in a polyhydric alcohol medium is evaporated from the particles by the application of heat or by subjecting the particles to reduced pressure.

[0053] Another example of a solvent removal process is shown in U.S. Pat. No. 3,960,757, incorporated herein by reference in its entirety.

[0054] Tice et al., in U.S. Pat. No. 4,389,330, incorporated herein by reference in its entirety, describe the preparation of particles containing an active agent by a method including: (a) dissolving or dispersing an active agent in a solvent and dissolving a wall forming material in that solvent; (b) dispersing the solvent containing the active agent and wall forming material in a continuous-phase processing medium; (c) evaporating a portion of the solvent from the dispersion of step (b), thereby forming particles containing the active agent in the suspension; and (d) extracting the remainder of the solvent from the particles.

[0055] Solvent and/or solvent/nonsolvent systems suitable for production of a polymer/drug matrix can be determined via routine experimentation using techniques well known to those of ordinary skill in the art.

[0056] Suitable solvents for forming a poly(lactic acid-co-glycolic acid) polymer solution/drug mixture, for example, a dispersion of an agent in a polymer solution, or alternatively, a polymer/drug solution, e.g., an agent co-dissolved with polymer as a single phase solvent system, include methylene chloride, acetone, ethyl acetate, methyl acetate, tetrahydrofuran, dimethylsulfoxide (DMSO), acetonitrile, and chloroform.

[0057] In another embodiment, the polymer/drug matrix can be provided by mixing one or more dry polymers with one or more dry biologically active agents. In yet another

embodiment, the polymer/drug matrix may be supplied by purchasing the material from a commercial supplier.

[0058] As used herein, the terms "a" and "an" refer to one or more.

[0059] As used herein, the term "particle size" refers to a number median diameter as determined by conventional particle size measuring techniques known to those skilled in the art such as, for example, laser diffraction, photon correlation spectroscopy, sedimentation field flow fractionation, disk centrifugation or electrical sensing zone method. Laser diffraction is preferred. The "number median diameter" reflects the distribution of particles (by number) as a function of particle diameter. An alternative designation of particle size often used in the art is the "volume median diameter." The volume median diameter is the median diameter of the volume weighted size distribution, also referred to as $D_{v,50}$. The volume median diameter reflects the distribution of volume as a function of particle diameter.

[0060] An "injectable microparticle," as defined herein, comprises a biocompatible polymer component having a volume median particle size from about 1 to about 1000 microns and having a biologically active agent dispersed therein. For example, the particle size can be about 500 microns or less, such as about 400, 300, 200 or about 100 microns or less. The microparticles can be of any shape, for example, spherical, non-spherical or irregular shape, and are suitable for administration by any means (e.g., by needle, needle-free delivery, or inhalation). It is understood that injectable refers to a size range of the microparticle rather than the mode of administration employed to deliver the microparticles to a patient.

[0061] The term "release modifying agent," as used herein, refers to a material which, when incorporated into a polymer/drug matrix, modifies the drug-release characteristics of the matrix. A release modifying agent can, for example, either decrease or increase the rate of drug release from the matrix. One group of release modifying agents includes metal-containing salts, as disclosed in U.S. Pat. No. 5,656,297 issued to Bernstein, et al., on Aug. 12, 1997, the contents of which are incorporated herein by reference.

[0062] "Sustained release," as that term is used herein, is release of biologically active agent from the injectable microparticles which occurs over a period which is longer than the period during which a biologically significant amount of agent would be available following direct administration of a solution of agent. In one embodiment, a sustained release is a release of agent which occurs over a period of at least about one day such as, for example, at least about 2, 4, 6, 8, 10, 15, 20, 30, 60, or at least about 90 days. A sustained release of agent can be a continuous or a discontinuous release, with relatively constant or varying rates of release. The continuity of release and level of release can be affected by the type of polymer composition used (e.g., monomer ratios, molecular weight, block composition, and varying combinations of polymers), protein loading, and/or selection of excipients to produce the desired effect.

[0063] "Sustained release" is also referred to in the art as "modified release,""prolonged release,""long acting release ('LAR')," or "extended release."Sustained release," as used herein, also encompasses "sustained action" or "sustained effect."Sustained action" and "sustained effect," as those terms are used herein, refer to an increase in the time period over which an agent performs its therapeutic, prophylactic or diagnostic activity as compared to an appropriate control. "Sustained action" is also known to those experienced in the art as "prolonged action" or "extended action."

[0064] The sustained release profile of the injectable microparticles prepared according to the method described herein can exhibit a reduced initial release of biologically active agent, a higher sustained level of agent and/or a longer duration of release of the agent following administration.

[0065] Without being bound by a particular theory, it is believed that the release of the biologically active agent can occur by two different mechanisms. First, the biologically active agent can be released by diffusion through aqueous liquid-filled channels generated in the polymer matrix, such as by the dissolution of the biologically active agent or by voids created by the removal of the polymer solvent during the preparation of the sustained release composition. A second mechanism is the release of the biologically active agent due to degradation of the polymer.

[0066] The rate of polymer and/or particle degradation can be controlled, in part, by changing polymer properties that influence the rate of hydration of the polymer. These properties include, for example, the ratio of lactide to glycolide; the isomeric form of the polymer, e.g., the use of the L-isomer of a monomer instead of a racemic mixture; and the molecular weight of the polymer. These properties can affect hydrophilicity and crystallinity, which control the rate of hydration of the polymer.

[0067] By altering the properties of the polymer, the contributions of diffusion and/or polymer/particle degradation to biologically active agent release can be controlled. For example, increasing the glycolide content of a poly(lactide-co-glycolide) polymer and decreasing the molecular weight of the polymer can enhance the hydrolysis of the polymer and thus can provide an increased biologically active agent release from polymer erosion. Without being held to any particular theory, it is believed that the morphology and/or density of the polymer matrix can also effect the diffusion of an agent from the microparticles and/or the degradation of the microparticle or its constituent polymer.

[0068] Polymers which can be used in the formulation of polymer/drug matrix microparticles include any polymer which is biocompatible. Biocompatible polymers suitable for use in the present invention include biodegradable and non-biodegradable polymers and blends and copolymers thereof, as described herein. A polymer is biocompatible if the polymer and any degradation products of the polymer are non-toxic to the recipient and also possess no significant deleterious or untoward effects on the recipient's body, such as a significant immunological reaction at the injection site.

[0069] "Biodegradable," as defined herein, means the composition will degrade or erode in vivo to form smaller chemical species. Degradation can result, for example, by enzymatic, chemical and physical processes. Suitable biocompatible, biodegradable polymers include, for example, poly(lactides), poly(glycolides), poly(lactide-co-glycolides), poly(lactic acid)s, poly(glycolic acid)s, polycarbonates, polyesteramides, polyanydrides, poly(amino

acids), polyorthoesters, poly(dioxanone)s, poly(alkylene alkylate)s, copolymers or polyethylene glycol and polyorthoester, biodegradable polyurethane, blends thereof, and copolymers thereof.

[0070] Suitable biocompatible, non-biodegradable polymers include non-biodegradable polymers such as, for example, polyacrylates, polymers of ethylene-vinyl acetates and other acyl substituted cellulose acetates, non-degradable polyurethanes, polystyrenes, polyvinylchloride, polyvinyl flouride, poly(vinyl imidazole), chlorosulphonate polyolefins, polyethylene oxide, blends thereof, and copolymers thereof, such as PLG-co-EMPO described in copending U.S. patent application Ser. No. 09/886,394 entitled "Functionalized Degradable Polymer" and filed on Jun. 22, 2001, the entire contents of which is hereby incorporated by reference.

[0071] Further, the terminal functionalities or pendant groups of the polymers can be modified, for example, to modify hydrophobicity, hydrophilicity and/or to provide, remove or block moieties which can interact with the active agent via, for example, ionic or hydrogen bonding.

[0072] In a preferred embodiment of the present invention, the polymer used to produce the particles is a poly(lactic acid-co-glycolic acid) ("PLG") copolymer. The poly(lactic acid-co-glycolic acid) polymer includes d-, l-, or racemic forms of the polymer, for example, in some embodiments the polymer used is poly(d,l-lactic acid-co-glycolic acid). In some embodiments, the poly(lactic acid-co-glycolic acid) contains free carboxyl end groups. In other embodiments, the poly(lactic acid-co-glycolic acid) contains alkyl ester end groups such as methyl ester end groups.

[0073] Acceptable molecular weights for polymers used in this invention can be determined by a person of ordinary skill in the art taking into consideration factors such as the desired polymer degradation rate, physical properties such as mechanical strength, and rate of dissolution of polymer in solvent. Typically, an acceptable range of molecular weight is of about 2,000 Daltons to about 2,000,000 Daltons. In a preferred embodiment, the polymer is a biodegradable polymer or copolymer. In a more preferred embodiment, the polymer is a poly(lactide-co-glycolide) which can have a lactide:glycolide ratio of about 25:75 to about 85:15, e.g., about 25:75, about 50:50, about 75:25, or about 85:15, and a molecular weight of about 5,000 Daltons to about 150,000 Daltons. In an even more preferred embodiment, the molecular weight of the PLG used in the present invention has a molecular weight of about 5,000 Daltons to about 42,000 Daltons.

[0074] The term "biologically active agent," as used herein, is an agent or its pharmaceutically acceptable salt which, when released in vivo, possesses the desired biological activity, for example, therapeutic, diagnostic and/or prophylactic properties in vivo. It is understood that the term includes stabilized biologically active agents as described herein. The terms "biologically active agent,""therapeutic, prophylactic or diagnostic agent,""drug,""active agent," and "agent" are used interchangeably herein. Preferably, the drug is soluble in the solvent or combination of solvents that also dissolve the polymer.

[0075] Examples of suitable biologically active agents include, but are not limited to, antipsychotic agents such as aripiprazole, risperidone, and olanzapine; antitumor agents such as bleomycin hydrochloride, carboplatin, methotrexate and adriamycin; antibiotics such as gentamicin, tetracycline hydrochloride and ampicillin; antipyretic, analgesic and anti-inflammatory agents; antitussives and expectorants such as ephedrine hydrochloride, methylephedrine hydrochloride, noscapine hydrochloride and codeine phosphate; sedatives such as chlorpromazine hydrochloride, prochlorperazine hydrochloride and atropine sulfate; muscle relaxants such as tubocurarine chloride; antiepileptics such as sodium phenyloin and ethosuximide; antiulcer agents such as metoclopramide; antidepressants such as clomipramine; antiallergic agents such as diphenhydramine; cardiotonics such as theophillol; antiarrhythmic agents such as propranolol hydrochloride; vasodilators such as diltiazem hydrochloride and bamethan sulfate; hypotensive diuretics such as pentolinium and ecarazine hydrochloride; antidiuretic agents such as metformin; anticoagulants such as sodium citrate and sodium heparin; hemostatic agents such as thrombin, menadione sodium bisulfite and acetomenaphthone; antituberculous agents such as isoniazide and ethanbutol; hormones such as prednisolone sodium phosphate and methimazole; and narcotic antagonists such as nalorphine hydrochloride.

[0076] Additional biologically active agents suitable for use in the invention include, but are not limited to, proteins, muteins and active fragments thereof, such as immunoglobulins, antibodies, cytokines (e.g., lymphokines, monokines, chemokines), interleukins, interferons (β-IFN, α-IFN and γ-IFN), erythropoietin, nucleases, tumor necrosis factor, colony stimulating factors, insulin, enzymes (e.g., superoxide dismutase, tissue plasminogen activator), tumor suppressors, blood proteins, hormones and hormone analogs (e.g., growth hormone, adrenocorticotropic hormone and luteinizing hormone releasing hormone (LHRH)), vaccines (e.g., tumoral, bacterial and viral antigens), antigens, blood coagulation factors; growth factors; peptides such as protein inhibitors, protein antagonists, and protein agonists; nucleic acids, such as antisense molecules; oligonucleotides; and ribozymes.

[0077] In a particular embodiment, the biologically active agent is a labile drug. As used herein, "labile drug" refers to a drug which loses a substantial amount of activity when either warmed to elevated temperatures, such as temperatures greater than physiological temperatures (e.g., about 37° C.), or dissolved in an organic solvent or in solution at an aqueous/organic interface. Examples of labile drugs can include proteins, peptides and nucleic acids. By decoupling the process of forming the polymer/drug matrix from the final product morphology, the present processes enable formation of the polymer/drug matrix using variety of matrix formation techniques such as those that employ low temperatures, e.g., room temperature or below, while still producing injectable microparticles for sustained release of the labile agent. In addition, the instant processes enable the formation of the polymer/drug matrix using various solvent systems such as, for example, forming the matrix without mixing the drug with an organic solvent.

[0078] The microparticles prepared according to the invention can contain from about 0.01% (w/w) to about 90% (w/w) of the biologically active agent (dry weight of composition). The amount of agent can vary depending upon the desired effect of the agent, the planned release levels, and the time span over which the agent is to be released. A preferred

range of agent loading is about 0.1% (w/w) to about 75% (w/w), for example, about 0.1% (w/w) to about 60% (w/w). A more preferred range of agent loading is about 0.5% (w/w) to about 75% (w/w) agent, for example, about 0.5% (w/w) to about 60% (w/w).

[0079] In one embodiment, the biologically active agent is stabilized. The biologically active agent can be stabilized against degradation, loss of potency and/or loss of biological activity, all of which can occur during formation of the sustained release composition having the biologically active agent dispersed therein, and/or prior to and during in vivo release of the biologically active agent. In one embodiment, stabilization can result in a decrease in the solubility of the biologically active agent, the consequence of which is a reduction in the initial release of biologically active agent, in particular, when release is from a sustained release composition. In addition, the period of release of the biologically active agent can be prolonged.

[0080] Stabilization of the biologically active agent can be accomplished, for example, by the use of a stabilizing agent or a specific combination of stabilizing agents. The stabilizing agent can be present in the mixture. "Stabilizing agent," as that term is used herein, is any agent which binds or interacts in a covalent or non-covalent manner or is included with the biologically active agent. Stabilizing agents suitable for use in the invention are described in U.S. Pat. Nos. 5,716,644 and 5,674,534 to Zale, et al.; U.S. Pat. Nos. 5,654,010 and 5,667,808 to Johnson, et al.; U.S. Pat. No. 5,711,968 to Tracy, et al., and U.S. Pat. No. 6,265,389 to Burke, et al.; and in copending U.S. patent application Ser. No. 08/934,830 by Burke, et al., filed on Sep. 22, 1997, the entire teachings of each of which are incorporated herein by reference.

[0081] For example, a metal cation can be complexed with the biologically active agent, or the biologically active agent can be complexed with a polycationic complexing agent such as protamine, albumin, spermidine and spermine, or associated with a "salting-out" salt. In addition, a specific combination of stabilizing agents and/or excipients may be needed to optimize stabilization of the biologically active agent. For example, when the biologically active agent in the mixture is an acid-stable or free sulfhydryl-containing protein such as β-IFN, a particular combination of stabilizing agents which includes a disaccharide and an acidic excipient can be added to the mixture. This type of stabilizing formulation is described in detail in U.S. Pat. No. 6,465,425 issued to Tracy, et al., on Oct. 15, 2002, the entire contents of which is incorporated herein by reference.

[0082] Suitable metal cations include any metal cation capable of complexing with the biologically active agent. A metal cation-stabilized biologically active agent, as defined herein, comprises a biologically active agent and at least one type of metal cation wherein the cation is not significantly oxidizing to the biologically active agent. In a particular embodiment, the metal cation is multivalent, for example, having a valency of +2 or more. If the agent is metal cation-stabilized, it is preferred that the metal cation is complexed to the biologically active agent.

[0083] Suitable stabilizing metal cations include biocompatible metal cations. A metal cation is biocompatible if the cation is non-toxic to the recipient in the quantities used and also presents no significant deleterious or untoward effects on the recipient's body such as a significant immunological reaction at the injection site. The suitability of metal cations for stabilizing biologically active agents and the ratio of metal cation to biologically active agent needed can be determined by one of ordinary skill in the art by performing a variety of stability indicating techniques such as polyacrylamide gel electrophoresis, isoelectric focusing, reverse phase chromatography, and High Performance Liquid Chromatography (HPLC) analysis on particles of metal cation-stabilized biologically active agents prior to and following particle size reduction and/or encapsulation. The molar ratio of metal cation to biologically active agent is typically between about 1:2 and about 100:1, preferably between about 2:1 and about 12:1.

[0084] Examples of stabilizing metal cations include, but are not limited to, K^+, Zn^{+2}, Mg^{+2} and Ca^{+2}. Stabilizing metal cations also include cations of transition metals such as Cu^{+2}. Combinations of metal cations can also be employed. For example, in one embodiment, Zn^{+2} is used as a stabilizing metal cation for bovine serum albumin (herein "BSA") at a zinc cation component to BSA molar ratio of about 4:1 to about 100:1. In a preferred embodiment, the zinc cation component to BSA molar ratio is about 4:1 to about 12:1, and most preferably 10:1.

[0085] The biologically active agent can also be stabilized with at least one polycationic complexing agent. Suitable polycationic complexing agents include, but are not limited to, protamine, spermine, spermidine and albumin. The suitability of polycationic complexing agents for stabilizing biologically active agents can be determined by one of ordinary skill in the art in the manner described above for stabilization with a metal cation. An equal weight ratio of polycationic complexing agent to biologically active agent is suitable.

[0086] Further, excipients can be added to the compositions of the present invention such as, for example, to maintain the potency of the biologically active agent over the duration of release and to modify polymer degradation. One or more excipients can be added to the mixture which is then used to form the polymer/biologically active agent matrix. For example, an excipient may be suspended or dissolved along with polymer and agent in a solvent system prior to formation of the polymer drug matrix. Alternatively, excipient(s) can be mixed with the polymer/biologically active agent matrix from which the solvent has been removed either prior to or following fragmentation and/or compression of the matrix. For example, an excipient can be blended with the compressed and fragmented injectable microparticle composition.

[0087] Suitable excipients include, for example, carbohydrates, amino acids, fatty acids, surfactants, and bulking agents. Such excipients are known to those of ordinary skill in the art. An acidic or a basic excipient is also suitable. The amount of excipient used is based on its ratio to the biologically active agent, on a weight basis. For amino acids, fatty acids and carbohydrates, such as sucrose, trehalose, lactose, mannitol, dextran and heparin, the ratio of carbohydrate to biologically active agent, is typically between about 1:10 and about 20:1. For surfactants, the ratio of surfactant to biologically active agent is typically between about 1:1000 and about 2:1. Bulking agents typically comprise inert materials. Suitable bulking agents are known to those of ordinary skill in the art.

[0088] The excipient can comprise a metal cation component which is separately dispersed within the polymer matrix. This metal cation component acts to modulate the release of the biologically active agent and is not complexed with the biologically active agent. The metal cation component can optionally contain the same species of metal cation, as is contained in the metal cation stabilized biologically active agent, if present, and/or can contain one or more different species of metal cation. The metal cation component acts to modulate the release of the biologically active agent from the polymer matrix of the sustained release composition and can enhance the stability of the biologically active agent in the composition. A metal cation component used in modulating release typically comprises at least one type of multivalent metal cation. Examples of metal cation components suitable to modulate release include or contain, for example, $Mg(OH)_2$, $MgCO_3$ (such as $4MgCO_3.Mg(OH)_2 0.5H_2O$), $MgSO_4$, $Zn(OAc)_2$, $Mg(OAc)_2$, $ZnCO_3$ (such as $3Zn(OH)_2.2ZnCO_3)ZnSO_4$, $ZnCl_2$, $MgCl_2$, $CaCO_3$, $Zn_3(C_6H_5O_7)_2$ and $Mg_3(C_6H_5O_7)_2$. A suitable ratio of metal cation component to polymer is between about 1:99 to about 1:2 by weight. The optimum ratio depends upon the polymer and the metal cation component utilized and can be determined by one of ordinary skill in the art without undue experimentation. A polymer matrix containing a dispersed metal cation component to modulate the release of a biologically active agent from the polymer matrix is further described in U.S. Pat. No. 5,656,297 issued to Bernstein, et al., on Aug. 12, 1997, and U.S. Pat. No. 5,912,015 issued to Bernstein, et al., on Jun. 15, 1999, the entire contents of both of which are incorporated herein by reference.

[0089] In yet another embodiment, at least one pore forming agent, such as a water soluble salt, sugar or amino acid, is included in the sustained release composition to modify the microstructure of the particles. The proportion of pore forming agent added to the mixture, e.g., a dispersion or solution, comprising a biologically active agent, a biocompatible polymer, and a polymer solvent is between about 0.1% (w/w) to about 30% (w/w).

[0090] Compression

[0091] The polymer/drug matrix can be compressed using any suitable method. For example, the polymer/drug matrix can be compressed using confined pressure compaction, e.g., molding, tableting, and roll pressing, or by extrusion, e.g., pellet milling and screw extrusion. Preferably, the polymer/drug matrix is compressed using confined pressure compaction.

[0092] The term "confined pressure compaction," as used herein, refers to compaction of a material using a confined pressure device such as, for example, a device in which internal motion and shear of the polymer/drug matrix is incidental to consolidation of the matrix in a closed mold or between two surfaces. Preferably, the confined pressure compaction is conducted without the application of heat, e.g., the application of heat other than the heat generated by the act of compressing the matrix. For example, the compression of the matrix is conducted at ambient temperature. For example, compression of the matrix is conducted at about room temperature such as about 15° C. to about 30° C., about 17° C. to about 28° C., about 20° C. to about 25° C., or about 21° C. to about 22° C. In another embodiment, the matrix is compressed at or below room temperature.

[0093] Suitable equipment for compressing the polymer/drug matrix includes, but is not limited to, die and press systems, roll presses, and tableting presses. For example, hydraulic presses such as those produced by Carver, Inc. (Wabash, Ind.) can be used in conjunction with a die. In one embodiment, a Carver Model C Press is used. The die is of any shape or size that permits the formation of a compressed polymer/drug matrix having the desired physical characteristics (e.g., density and morphology). In one embodiment, a Carver Model C Press is used in conjunction with ¼ inch to 1 inch diameter cylindrical dies to compress the polymer/drug matrix.

[0094] Fragmentation

[0095] The polymer/drug matrix can be fragmented following compression or both prior to and following compression using any suitable method. Suitable fragmentation methods include, but are not limited to, grinding, shearing, shocking, shattering, granulating, pulverizing, shredding, crushing, and/or milling. Suitable equipment for fragmenting the polymer/drug matrix includes, but is not limited to, crushers, impact mills (e.g., hammer mills, impact breakers), roll crushers, roller mills, pin mills, tumbling mills, centrifugal mills, and fluid-energy mills (e.g., jet mills), among others that are well known to one of ordinary skill in the art. An example of a suitable mill for fragmenting the polymer/drug matrix is the 24-tooth Ultra Centrifugal Mill made by Retsch, Inc. (Newtown, Pa.). Another example is the Fluid Air Granumill Jr. (Fluid Air, Inc., Aurora, Ill.).

[0096] In one embodiment, multiple stage fragmentation is used to fragment the polymer/drug matrix, for example, two or more pieces of fragmentation equipment are used to produce particles having desired physical characteristics. A particle size classifier (e.g., an appropriately sized sieve) can be used in conjunction with the fragmentation apparatus to separate particles by size.

[0097] Fragmentation of the polymer/drug matrix can be performed under various conditions of temperature, for example, cooling or cryogenic cooling can be employed to reduce the temperature of the polymer/drug matrix during processing.

[0098] In a preferred embodiment, the temperature of the polymer/drug matrix is kept at or below the transition temperature of the polymer/drug matrix, e.g., below the phase transition temperature or below the glass transition temperature of the polymer/drug matrix. In another preferred embodiment, the temperature of the polymer/drug matrix is kept below any temperature at which the agent would be subject to substantial degradation of its therapeutic, prophylactic or diagnostic effect.

[0099] In a specific embodiment, the polymer/drug matrix is also fragmented prior to the step of compressing the matrix (referred to herein as "precompression fragmenting"). Precompression fragmenting of the polymer/drug matrix can facilitate transfer of the polymer/drug matrix to a compression apparatus. For example, a film, block, or particles comprising the polymer/drug matrix is fragmented to form a flowable powder to facilitate transfer of the material to a suitable compression apparatus.

[0100] The compression and fragmenting steps can be conducted multiple times. In one embodiment, the compressed matrix is fragmented and then again compressed.

The recompressed matrix is further fragmented and compressed as necessary to achieve a compressed polymer/drug matrix having a desired density and/or morphology. The resulting compressed polymer/drug matrix is then fragmented to produce the injectable microparticle composition product.

[0101] The size range of the injectable microparticles prepared by the present method can be controlled in the fragmentation step. For example, the final particle size distribution is typically a function of the total grinding or milling time, with shorter times producing, on average, larger particles and with longer grinding or milling times producing, on average, smaller particles. The size range of a sample of microparticles produced in this way can be further restricted by sorting, for example, sieving, thus achieving particles within a specified size range.

[0102] The injectable microparticles prepared according to the method described herein can be further modified to achieve a desired sustained release profile of the biologically active agent. In one embodiment, a substantial portion of the exterior surface of the injectable microparticles can be annealed or coated. Annealing is accomplished, for example, by the application of heat or an annealing solvent, wherein the annealing solvent is a solvent for the polymer of the injectable microparticle. The application of heat or an annealing solvent can be performed, for example, by using a fluidized bed system such as the Wurster process. Coating can be conducted using a suitable coating apparatus using a polymer or combination of polymers which can be the same or different from the polymer of the unmodified matrix.

[0103] "Annealing," as that term is used herein, refers to treating a substantial portion of the exterior surface of the injectable microparticles by the application of an external stress which increases the fluidity of the surface of the microparticles and upon rehardening results in a smoother and less porous outer layer.

[0104] Thus, in one embodiment, the sustained release composition of the invention comprises injectable microparticles comprising a biocompatible polymer and a biologically active agent and characterized by a porous center and a less porous outer layer, wherein the outer layer and the center consist of essentially the same materials, e.g., other components can be present either in the center or outer layer provided that the component does not function as a coating material. The variance in porosity can be achieved by annealing at least a substantial portion of the exterior surface of a solid polymer/active agent matrix. A process for annealing the surface of a sustained release composition comprising a polymer and an active agent is disclosed in U.S. Pat. No. 6,479,065 issued to Jaworowicz, et al., on Nov. 12, 2002, incorporated herein by reference in its entirety.

[0105] The present invention also includes microparticles produced according to the methods described herein. In addition, the invention is directed to pharmaceutical compositions comprising the microparticles. Pharmaceutical compositions comprising microparticles are suitable for administration to a patient. The pharmaceutical compositions described herein may also comprise pharmaceutically acceptable excipients such as, for example, diluents, stabilizers, and delivery vehicles. Pharmaceutically acceptable excipients can be selected by one of ordinary skill in the art without undue experimentation. Compositions for the delivery of microparticles are described, for example, in U.S. Pat. No. 6,495,164 issued to Ramstack, et al., on Dec. 17, 2002.

[0106] The composition of this invention can be administered in vivo, for example, to a human or to an animal, orally, or parenterally such as by injection, implantation (e.g., subcutaneously, intramuscularly, intraperitoneally, intracranially, and intradermally), administration to mucosal membranes (e.g., intranasally, intravaginally, intrapulmonary, buccally or by means of a suppository), or in situ delivery (e.g., by enema or aerosol spray) to provide the desired dosage of biologically active agent based on the known parameters for treatment with the particular agent of the various medical conditions.

[0107] The sustained release composition can be administered using any dosing schedule which achieves the desired therapeutic levels for the desired period of time. For example, the sustained release composition can be administered and the patient monitored until levels of the drug being delivered return to baseline. Following a return to baseline, the sustained release composition can be administered again. Alternatively, the subsequent administration of the sustained release composition can occur prior to achieving baseline levels in the patient.

[0108] The injectable microparticles of the present invention are used in a method for providing a therapeutically, prophylactically, or diagnostically effective amount of a biologically active agent to a subject for a sustained period. The injectable microparticle compositions described herein provide increased therapeutic benefits by reducing fluctuations in active agent concentration in blood, by providing a more desirable release profile and by potentially lowering the total amount of biologically active agent needed to provide a therapeutic benefit without the need for additional components in the composition.

[0109] As used herein, a "therapeutically effective amount,""prophylactically effective amount" or "diagnostically effective amount" is the amount of the biologically active agent or of the sustained release composition of biologically active agent needed to elicit the desired biological, prophylactic or diagnostic response following administration. For example, the desired response can be a reduction (complete or partial) of symptoms associated with affective disorders, such as, schizophrenia, depression and/or anxiety.

[0110] The present invention also includes microparticles produced according to the methods described herein. The invention is also directed to pharmaceutical compositions comprising the microparticles. Pharmaceutical compositions comprising microparticles are suitable for administration to a patient. The pharmaceutical compositions described herein may also comprise pharmaceutically acceptable excipients such as, for example, diluents, stabilizers, and delivery vehicles. Pharmaceutically acceptable excipients can be selected by one of ordinary skill in the art without undue experimentation.

[0111] Exemplification

[0112] The invention will now be further and specifically described by the following examples which are not intended to be limiting.

EXAMPLE 1

[0113] Injectable microparticles comprising polymer and olanzapine were prepared using an efficient and facile single

solvent process. PLG polymer and olanzapine were co-dissolved in a single solvent; (2) the solvent was removed by vacuum drying or sublimation to form a polymer/drug matrix; (3) the matrix was milled to produce a powder; (4) the resulting powder was compacted to form a compressed matrix; and (5) the compressed matrix was milled to form a dense, injectable microparticle formulation.

[0114] Specifically, an injectable microparticle composition comprising olanzapine (2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno [2,3-b][1,5]benzodiazepine) and poly(d, l-lactide-co-glycolide) polymer (herein referred to generically as "PLG") was prepared by co-dissolving olanzapine (Dr. Reddy's Laboratories, Ltd., Upper Saddle River, N.J.) and PLG in methylene chloride. The olanzapine loading was about 30% (w/w) of the final weight of the microparticle composition. However, it is understood that other solvents, for example, acetone, dimethylsulfoxide (DMSO), acetonitrile, and ethyl acetate are suitable for use. Table I shows specific polymer/olanzapine mixtures that were produced and which were processed into microparticles as described below.

TABLE I

Olanzapine/polymer/solvent mixtures

Formulation	Target Olanzapine Load	PLG Polymer Type [Lactide:Glycolide Ratio; Intrinsic Viscosity; End Group]	Solvent
A	30% (w/w)	50:50, 0.75 dL/g; Acid end group	CH_2Cl_2
B	30% (w/w)	75:25; 0.60 dL/g; Lauryl ester end group	CH_2Cl_2
C	30% (w/w)	50:50; 0.61 dL/g; Lauryl ester end group	CH_2Cl_2

[0115] The olanzapine/polymer/solvent mixtures were poured into either a polytetrafluoroethylene flat mold (approximately 1 inchx1 inchx½ inch deep) or a 3 inch diameter jar to form a film. The films were then dried either in an FTS Dura-Dry Lyophilizer (Kinetic Systems, Inc., Santa Clara, Calif.) or in a vacuum oven. Films were dried under various conditions including variation of vacuum, pressure, temperature, and drying time.

[0116] The films were milled using a 24-tooth Retsch Ultra Centrifugal Mill (Retsch, Inc., Newtown, Pa.) operating at 14,000 rpm. The collection pan was filled with liquid nitrogen prior to milling. The resulting powder, collected from the collection pan, was a flowable product that aided subsequent compaction steps.

[0117] A portion of the powders produced by milling the films were retained for analysis at this point. These powders were retained for comparison with the powders made by the subsequent compacting and re-milling of the film powders described below.

[0118] A portion of the milled powders was compacted using a Carver Model C Press (Carver, Inc., Wabash, Ind.) and either about ¼ inch or about ½ inch cylindrical dies. About 50 to about 300 milligrams of milled powder was filled into the dies and compacted at a machine setting of about 5000 pounds for about 30 seconds at room temperature to form pellets.

[0119] The compacted matrix was subsequently milled using a 24-tooth Retsch Ultra Centrifugal Mill (Retsch, Inc., Newtown, Pa.) operating at 14,000 rpm. The collection pan was filled with liquid nitrogen prior to milling. The final powder was collected from the collection pan and placed into vials for analysis.

[0120] The activity of olanzapine can be assessed based on interaction with three significant neurotransmitter receptor subtypes: the D_2 class of dopamine receptors; the $5HT_{2A}$ subtype of serotonin receptors; and the M_1 subtype of muscarinic receptors. Olanzapine activity was assessed both before and after incorporation into the matrix using suitable radioligand assays.

[0121] Specifically, competition radioligand binding assays for the D_2, $5HT_{2A}$ and M_1 receptors were performed using [^{3}H]raclopride, [^{3}H]ketanserin and [^{3}H]pirenzepine, respectively. Stock solutions of native olanzapine (10 mM) and olanzapine extracted from Formulation A (Table I) microparticles (10 mM, based on % olanzapine load) were made in ethanol. Subsequent dilutions were made into 50 mM Tris HCl, pH 7.4. Binding assays varied according to the receptor/radioligand combination investigated. All assays were done with the total and non-specific binding determined in triplicate with three different receptor preparations on three separate occasions. Table II shows K values (the concentration of competing ligand in a comparison assay which would occupy 50% of the receptors if no radioligand were present) for radioligand displacement by native olanzapine and olanzapine contained within microparticles formed from Formulation A as shown in Table I.

TABLE II

K_i values for radioligand displacement by native olanzapine and olanzapine contained within microparticles

Radioligand (Receptor)	K_i Native Olanzapine	K_i Olanzapine in Formulation A Microparticles
[^{3}H]raclopride (D_2)	13.6 ± 0.68 nM	11.5 ± 4.3 nM
[^{3}H]ketanserin (M_1)	12.8 ± 2.9 nM	14.9 ± 1.2 nM
[^{3}H]pirenzepine ($5HT_{2A}$)	1.32 ± 0.21 nM	1.55 + 0.32 nM

[0122] There was no significant difference between the inhibition constants of native olanzapine and olanzapine extracted from the Formulation A microparticles in terms of their potencies in displacing radioligands from D_2, M1 and $5HT_{2A}$ receptors.

EXAMPLE 2

[0123] In vivo studies were preformed to evaluate the pharmacokinetic profile of olanzapine in rats following administration of a single subcutaneous dose of formulated olanzapine as prepared in Example 1.

[0124] Male Sprague-Dawley rats (450±50 grams) were obtained from Charles River Laboratories, Inc. (Wilmington, Mass.). Animals were divided into four test groups. Groups 1-3 received the injectable microparticles prepared according to Example 1 and detailed in Table 1 as resulting Formulations A, B and C. Group 1 was injected subcutaneously once with nominal 83 milligrams of particles produced from Formulation A. Group 2 was injected subcutaneously once with nominal 83 milligrams of particles produced from Formulation B. Group 3 was injected subcutaneously once with nominal 83 milligrams of particles produced from

[0160] A portion of the polymer/drug microparticles thus formed were then compacted using a Carver Model C Press (Carver, Inc., Wabash, Ind.) at a machine setting of 4000 pounds to form wafers having a diameter of ⅜ inch and a thickness of about ⅛ of an inch. A portion of the wafers were fragmented by freezing the wafers in liquid nitrogen and then fracturing the frozen wafers using a razor blade thus forming implantable microparticles. The implantable microparticles had a size range of from about 200 to about 500 microns.

[0161] The compositions (polymer/drug microparticles, wafers and implantable microparticles) thus formed were administered to laboratory rats. Male Sprague-Dawley rats (400±50 grams) were obtained from Charles River Laboratories, Inc. (Wilmington, Mass.). The animals were immunosuppressed using cyclosporine (SANDIMMUNE®, Novartis Pharmaceuticals Corp., East Hanover, N.J.). Animals were divided into three test groups (n=3/group).

[0162] Animals in Group A were injected subcutaneously with the polymer/drug microparticles into the interscapular region. Each animal received a dose comprising approximately 50 milligrams of particles containing 7.5 milligrams BSA in a vehicle volume of 0.75 milliliters. The injection vehicle was 3% carboxymethylcellulose ('CMC') (low viscosity) and 0.1% TWEEN® 20 (i.e., polyoxyethylene 20 sorbitan monooleate, TWEEN® is a trademark of ICI Americas, Inc.) in 0.9% aqueous sodium chloride.

[0163] The animals in Group B were implanted subcutaneously with 50 milligrams compressed wafers (total amount of BSA administered was 7.5 mg) into the interscapular region.

[0164] The animals in Group C were implanted subcutaneously with 50 milligrams implantable microparticles (total amount of BSA administered was 7.5 mg) into the interscapular region.

[0165] Blood samples were collected via a lateral tail vein after anesthesia with halothane. Blood samples were collected at predose, at 2, 4, 6, 10, and 24 hours and then at 2, 4, 7, 10, 14, 17, 21, 24, and 28 days after administration. The blood was transferred to serum separator tubes and allowed to clot for 30 minutes at room temperature, centrifuged at 6000 g for 5 minutes at room temperature, and the serum stored at less than −70° C. Serum samples were analyzed using a BSA Enzyme-Linked Immuno-Sorbent Assay (ELISA) kit (Catalog #F030) provided by Cygnus Technologies (Wrentham, Mass.).

[0166] **FIG. 6** shows BSA concentration in blood serum, in nanograms/milliliter, versus time, in days. The data demonstrate that the implantable microparticles gave a release profile with a C_{MAX} (i.e., maximum BSA concentration in blood serum) lower than that of the uncompressed, unfragmented polymer/drug particles but higher than the implanted wafer. The implantable microparticles also showed higher sustained concentrations of BSA, and a longer duration of release than that provided by the uncompressed, unfragmented polymer/drug particles.

[0167] While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

We claim:

1. A method for preparing an injectable microparticle composition for the sustained release of a biologically active agent, comprising the steps of:

(a) preparing a mixture of a biologically active agent, a biocompatible polymer and a solvent, thereby forming a single phase solvent system;

(b) removing the solvent from the mixture, thereby forming a polymer/biologically active agent matrix;

(c) compressing the matrix using confined pressure compaction at ambient temperature, thereby forming a compressed matrix; and

(d) fragmenting the compressed matrix, thereby forming the injectable microparticle composition.

2. The method of claim 1 wherein the biologically active agent is dissolved in the mixture.

3. The method of claim 1 wherein the biologically active agent is suspended in the mixture.

4. The method of claim 1 further comprising the step of fragmenting the matrix prior to compressing the matrix.

5. The method of claim 1 wherein the biocompatible polymer is biodegradable.

6. The method of claim 1 wherein the biocompatible polymer is selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, polycarbonates, polyesteramides, polyanhydrides, poly(amino acids), polyorthoesters, polyacetals, polycyanoacrylates, polyetheresters, polycaprolactone, poly(dioxanone)s, poly(alkylene alkylate)s, polyurethanes, and blends and copolymers thereof.

7. The method of claim 6, wherein the polymer is poly(lactide-co-glycolide)-co-EMPO.

8. The method of claim 1 wherein the solvent is removed by evaporation.

9. The method of claim 1 wherein the solvent is removed by sublimation.

10. The method of claim 1 wherein the mixture is cast as a film prior to removal of the solvent.

11. The method of claim 1 wherein the matrix is compressed using a press and die apparatus.

12. The method of claim 1 wherein the compressed matrix is fragmented by milling.

13. The method of claim 12 wherein the milling is selected from the group consisting of jet milling, centrifugal milling and hammer milling.

14. The method of claim 1 wherein the compressed matrix is fragmented under cryogenic conditions.

15. The method of claim 1 wherein the compressed matrix is fragmented to produce microparticles having a volume median particle size of about 1 to about 1000 microns.

16. The method of claim 1 wherein the compressed matrix is fragmented to produce microparticles having a volume median particle size of about 500 microns or less.

17. A method for forming an injectable microparticle composition for the sustained release of a biologically active agent, comprising the steps of:

(a) forming a mixture of a biologically active agent, a biocompatible polymer and a polymer solvent;

(b) forming droplets of the mixture;

(c) freezing the droplets, thereby forming frozen droplets;

(d) extracting the polymer solvent from the frozen droplets into a non-solvent, thereby forming a polymer/biologically active agent matrix;

(e) compressing the matrix, thereby forming a compressed matrix; and

(f) fragmenting the compressed matrix, thereby forming the injectable microparticle composition.

18. The method of claim 17 wherein the biocompatible polymer is biodegradable.

19. The method of claim 17 wherein the biocompatible polymer is selected from the group consisting of poly(lactide)s, poly(glycolide)s, poly(lactide-co-glycolide)s, poly(lactic acid)s, poly(glycolic acid)s, polycarbonates, polyesteramides, polyanhydrides, poly(amino acids), polyorthoesters, polyacetals, polycyanoacrylates, polyetheresters, polycaprolactone, poly(dioxanone)s, poly(alkylene alkylate)s, polyurethanes, and blends and copolymers thereof.

20. The method of claim 17 wherein the droplets are frozen using a liquefied gas.

21. The method of claim 17 wherein the droplets are formed by atomizing the mixture.

22. The method of claim 17 wherein the droplets are microdroplets.

23. The method of claim 17 wherein the matrix is compressed using confined pressure compaction.

24. The method of claim 17 wherein the matrix is compressed using a press and die apparatus.

25. The method of claim 17 wherein the matrix is compressed in the presence of a coolant.

26. The method of claim 17 wherein the compressed matrix is fragmented by milling.

27. The method of claim 26 wherein the compressed matrix is fragmented by milling selected from the group consisting of jet, centrifugal and hammer milling.

28. The method of claim 17 wherein the compressed matrix is fragmented in the presence of a coolant.

29. The method of claim 17 wherein the compressed matrix is fragmented under cryogenic conditions.

30. The method of claim 17 wherein the compressed matrix is fragmented matrix is fragmented to produce microparticles having a volume median particle size of about 1 micron to about 1000 microns.

31. The method of claim 17 wherein the compressed matrix is fragmented to produce microparticles having a volume median particle size of about 500 microns or less.

32. The method of claim 17 wherein the biologically active agent is suspended in the mixture.

33. The method of claim 17 wherein the biologically active agent is dissolved in the mixture.

34. A method for treating a patient in need of therapy comprising:

administering to the patient a therapeutically effective amount of the injectable microparticle composition made by the method of claim 17.

35. A method for treating a patient in need of a sustained release of a biologically active agent, comprising:

administering to the patient a therapeutically effective amount of an injectable microparticle composition for sustained release of a biologically active agent prepared by a process including the steps of:

(a) preparing a mixture of a biologically active agent, a biocompatible polymer and a solvent, thereby forming a single phase solvent system;

(b) removing the solvent from the mixture, thereby forming a polymer/biologically active agent matrix;

(c) compressing the matrix using confined pressure compaction at ambient temperature, thereby forming a compressed matrix; and

(d) fragmenting the compressed matrix, thereby forming the injectable microparticle composition.

36. The method of claim 35 wherein the biologically active agent is dissolved in the mixture.

37. The method of claim 35 wherein the biologically active agent is suspended in the mixture.

38. The method of claim 35 wherein the process for preparing the injectable microparticle composition further comprises the step of fragmenting the polymer/biologically active agent matrix prior to compressing the matrix.

39. The method of claim 35 wherein the biologically active agent is an antipsychotic drug.

40. The method of claim 39 wherein the biologically active agent is selected from the group consisting of aripiprazole, olanzapine and risperidone.

41. The method of claim 39 wherein the patient suffers from an affective disorder.

42. The method of claim 41 wherein the patient suffers from a condition selected from the group consisting of schizophrenia, depression, and anxiety.

43. Microparticles produced by a process comprising the steps of:

(a) preparing a mixture of a biologically active agent, a biocompatible polymer and a solvent, thereby forming a single phase solvent system;

(b) removing the solvent from the mixture, thereby forming a polymer/biologically active agent matrix;

(c) compressing the matrix using confined pressure compaction at ambient temperature, thereby forming a compressed matrix; and

(d) fragmenting the compressed matrix, thereby forming the microparticles.

44. The method of claim 43 wherein the biologically active agent is dissolved in the mixture.

45. The method of claim 43 wherein the biologically active agent is suspended in the mixture

46. The microparticles of claim 43 wherein the process for preparing the microparticles further comprises the step of fragmenting the polymer/biologically active agent matrix prior to compressing the matrix.

47. The microparticles of claim 43 wherein the microparticles have a volume median particle size of about 1 micron to about 1000 microns.

48. The microparticles of claim 43 wherein the microparticles have a volume median particle size of about 500 microns or less.

49. A pharmaceutical composition comprising the microparticles of claim 43.

50. Microparticles produced by a process comprising the steps of:

(a) forming a mixture of a biologically active agent, a biocompatible polymer and a polymer solvent;

(b) forming droplets of the mixture;

(c) freezing the droplets, thereby forming frozen droplets;

(d) extracting the polymer solvent from the frozen droplets into a non-solvent, thereby forming a polymer/biologically active agent matrix;

(e) compressing the matrix, thereby forming a compressed matrix; and

(f) fragmenting the compressed matrix, thereby forming the microparticles.

51. The microparticles of claim 50 wherein the process for preparing the microparticles further comprises the step of fragmenting the polymer/biologically active agent matrix prior to compressing the matrix.

52. The microparticles of claim 50 wherein the microparticles have a volume median particle size of about 1 micron to about 1000 microns.

53. The microparticles of claim 50 wherein the microparticles have a volume median particle size of about 500 microns or less.

54. A pharmaceutical composition comprising the microparticles of claim 50 and a physiologically acceptable vehicle.

* * * * *

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Humberto Rubio Camacho.
Apoderado

Oficio N°: 16965

ASUNTO:

Radicación PCT Nº	09-149222
Trámite	011
Evento	378
Actuación	440
Folios	060

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 el doctor José Luis Reyes Villamizar, en su calidad de apoderado de LAFRANCOL 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 Nº 10 de 2001.

JOSÉ LUIS SALAZAR LÓPEZ.
Director de Nuevas Creaciones (C).

28 OCT. 2011

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

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