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Act. 329 CTOINFORMACION Folios: 63**SEÑOR****SUPERINTENDENTE DE INDUSTRIA Y COMERCIO****E. S. D.****REF: Expediente 06-064-910****TÍTULO SOLICITADO: PREPARACIÓN FARMACÉUTICA QUE CONTIENE GABAPENTIN.****PUBLICACIÓN: Gaceta 592 de 30 de Mayo de 2008, número de publicación 428.****PRIORIDAD: IT MI 2003A002399 de 09/12/2003****SOLICITANTE: ZAMBON GROUP S. P. A.****APODERADO: DILIA MARÍA RODRÍGUEZ D'ALEMÁN****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 **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada en los siguientes términos:

I. RATIFICACIÓN

Comedidamente me permito ratificar los argumentos que permitirán demostrar que la solicitud de la referencia, que reivindica un granulado de gabapentina obtenido mediante la granulación de gabapentina con polietileno glicol, que tiene un punto de fusión comprendido entre 50°C y 80°C, incumple los requisitos de

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Titre du document / Document title

Controlled-release of diclofenac sodium from wax matrix granule

Auteur(s) / Author(s)MIYAGAWA Y. ⁽¹⁾, OKABE T. ⁽¹⁾, YAMAGUCHI Y. ⁽¹⁾, MIYAJIMA M. ⁽¹⁾, SATO H. ⁽¹⁾, GUNADA H. ;**Affiliation(s) du ou des auteurs / Author(s) Affiliation(s)**⁽¹⁾ Central Research Laboratories, Zeria Pharmaceutical Co., Ltd., 2512-1 Oshikiri, Konan-machi, Osato-gun, Saitama 360-01, JAPON**Résumé / Abstract**

A twin-screw compounding extruder was used to prepare wax matrix granules (WMG) consisting of carnauba wax, diclofenac sodium (DS) as a model drug, and rate-controlling agents such as hydroxypropylcellulose (HPC-SL), methacrylic acid copolymer L (Eudragit L-100), and sodium chloride (NaCl). In this preparation, a wax matrix with high mechanical strength was obtained even at temperatures lower than the wax melting point. Dissolution behaviors of DS from WMG were strongly influenced by granule formulation, in which an increase in the content of HPC-SL or Eudragit L-100 brought a significant increase in the dissolution rate. The extent of this enhancing effect in HPC-SL was identical in two different dissolution mediums (pH 6.8 buffer solution and water), but in Eudragit L-100 was more significant in pH 6.8 buffer solution than in water. Only a small increase in the dissolution rate was observed in NaCl-containing WMG. These different behaviors were attributed to the physicochemical properties (i.e. swelling and solubility) of the rate-controlling agent in the dissolution medium. Further, mechanical strengths of the wetted WMG after dissolution studies were $> 70 \text{ g/mm}^2$, suggesting that burst release of DS in the gastrointestinal tract would be avoided.

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Mots-clés anglais / English Keywords

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Mots-clés français / French Keywords

Diclofénac ; Antiinflammatoire non stéroïde ; Forme libération contrôlée ; Cire carnauba ; Sodium chlorure ; Cellulose(hydroxypropyl) ; Méthacrylique acide copolymère ; Granule pharmaceutique ; Libération ; Principe actif ; Préparation ; Forma pharmaceutique ; Technologie pharmaceutique ; Eudragit L100 ; Arylacétique acide dérivé ;

Mots-clés espagnols / Spanish Keywords

Antiinflammatorio no esteroide ; Forma liberación controlada ; Cera carnauba ; Sodio cloruro ; Celulosa (hidroxipropil) ; Metacrílico ácido copolímero ; Gránulo farmacéutico ; Liberación ; Principio activo ; Preparación ; Forma farmacéutica ; Tecnología farmacéutica ;

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patentabilidad establecidos por los artículos 14 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario:

❖ Primero que todo, el proceso de granulación que describe la solicitud colombiana en trámite es ampliamente conocido en el estado de la técnica como "granulación por fusión" (melt granulation) y es un proceso ampliamente usado cuyo objetivo es transformar una mezcla de polvos en una masa o en conjunto compacto y homogéneo a través de la aplicación de calor y agitación a la mezcla de polvos, en donde al menos uno de ellos, tiene un punto de fusión bajo que permite formar una mezcla o dispersión fluida (fundida) que permite la unión de las partículas de la mezcla en gránulos que posteriormente se dejan enfriar, por lo menos, a temperatura ambiente.

Prueba del vasto conocimiento de esta técnica es expuesta en patentes como la US 3,263,006, US 3,405,208, US 3,601,847, ó US 3,700,364 que describen, desde la década de 1960 tanto el proceso como los equipos a través de los cuales se puede llevar cabo la formulación de granulados; así mismo, existen publicaciones de carácter científico que demuestran tanto las condiciones y las variables bajo las cuales se realizan dichos procesos de granulación, así como la utilidad de la misma en la elaboración de diversas formulaciones farmacéuticas con principios activos que presentan inconvenientes para la granulación por vía húmeda como son: *Advantages In Energy, Fuel, And Investment Savings By Melt-Type Granulation Processes*¹; *Alternative Granulation Technique: Melt Granulation*²; *Melt Granulation In A Laboratory Scale High Shear Mixer*³; *Preparation And Characterisation Of Ibuprofen-Poloxamer 188 Granules Obtained By Melt Granulation*⁴; *The Control Of Drug Release From Conventional Melt Granulation Matrices*⁵; y *Effect Of Crystallization Behavior Of Polyethylene Glycol 6000 On The Properties Of Granules Prepared By Fluidized Hot-Melt Granulation (FHMg)*⁶.

¹ Young, R.D. ; Lee, R.G. Technical conference of International Superphosphate and Compound Manufacturers Association Limited and the Fertilizer Association of India; 8 Dec 1975; New Delhi, India (Conference). Publication Date 1975 Jan 01.

² Alan Royce; Jiwaji Suryawanshi; Udayan Shah; Krishna Vishnupad. Drug Development and Industrial Pharmacy, Volume 22, Issue 9 & 10 September 1996, pages 917 - 924.

³ T. Schaefer; P. Holm; H. G. Kristensen. Drug Development and Industrial Pharmacy, Volume 16, Issue 8 May 1990, pages 1249 - 1277.

⁴ Passerini N, Albertini B, González-Rodríguez ML, Cavallari C, Rodríguez L. Eur J Pharm Sci. 2002 Feb;15(1):71-8.

⁵ P. Flanders; G. A. Dyer; D. Jordan. Drug Development and Industrial Pharmacy, Volume 13, Issue 6 May 1987, pages 1001 - 1022.

⁶ Motonori KIDOKORO, Kaoru SASAKI, Yasuo HARAMIISHI, and Norio MATAHIRA. Chem. Pharm. Bull. 51(5) 487-493 May 2003.

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En dos de las publicaciones se hace mención explícita del uso de polietilenglicoles, que es la clase de polímeros que reivindica la solicitud en trámite para la elaboración de sus respectivas formas farmacéuticas a través de esta técnica, si bien es cierto que no se hace mención del uso de pregabalina como principio activo, para cualquier persona medianamente versada en la materia queda claro que para aplicar esta técnica de granulación con cualquier otro principio activo, basta con someter los componentes de la formulación a los respectivos ensayos de formulación y preformulación que aseguren que dichos componentes bajo las condiciones del proceso, consigan las características finales de seguridad, estabilidad, eficacia y eficiencia que debe tener todo medicamento de este tipo.

También es útil resaltar que según el "Handbook of Pharmaceutical Excipients"⁷: que los Polietilenglicoles son ampliamente usados en distintos tipos de formulación entre ellos en formulaciones sólidas y en la formación de granulados y que son sustancias estables químicamente, lo que significa que son sustancias viables y ampliamente usadas en la industria farmacéutica como excipientes adecuados de granulación, en consecuencia, su empleo y su inclusión en las formulaciones -independientemente del activo- o como las reivindicadas en la solicitud colombiana en trámite carecería de nivel inventivo.

❖ La publicación internacional WO 03/035040 "METHODS OF TREATMENT USING A GASTRIC RETAINED GABAPENTIN DOSAGE", revela un método de tratamiento de la epilepsia que comprende administrar una cantidad terapéuticamente efectiva de gabapentina o una sal de la misma, en una forma de dosificación de retención gástrica, donde dicha forma de dosificación corresponde a tabletas que contienen Gabapentina y que están hechas mediante el uso de una técnica convencional de granulación en donde la formulación comprende gabapentina en una cantidad superior al 61% w/w, PEG o PolyOx® y otros agentes o aditivos necesarios. Si bien es cierto que en este ejemplo no se especifica si la granulación se hace o no con el PEG, no lo es menos que, los elementos principales revelados en la solicitud colombiana en trámite (Gabapentina, PEG, Granulación, otros agentes), son o fueron revelados en la anterioridad mencionada, lo que evidentemente desvirtúa al menos el nivel inventivo de la misma.

⁷ Arthur H. Kibbe. "Handbook of Pharmaceutical Excipients". Third Edition 2000. Pag 392, 393.

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❖ La publicación internacional WO 2003/068186 "PHARMACEUTICAL FORMULATIONS AND SYSTEMS FOR IMPROVED ABSORPTION AND MULTISTAGE RELEASE OF ACTIVE AGENTS" revela el uso de la técnica de granulado por fusión para la obtención de gránulos que posteriormente pueden convertirse en tabletas o cápsulas, además, se hace mención explícita del uso de polietilenglicol durante este proceso de obtención y se menciona la inclusión de gabapentina como principio activo de dichas formulaciones; con lo cual el nivel inventivo de la Rv 1 y otras (Rvs 5 a 18) de la solicitud colombiana en trámite quedan desvirtuados.

❖ La publicación internacional WO 2003/002151 "ORAL PHARMACEUTICAL COMPOSITIONS WITH MODIFIED RELEASE OF THE ACTIVE INGREDIENT" revela el uso de la técnica de granulado por fusión para la obtención de gránulos, en donde se hace mención explícita del uso de polietilenglicol en el proceso de fabricación y además se menciona la inclusión de gabapentina como principio activo de dichas formulaciones; con lo cual el nivel inventivo de lo reivindicado por la solicitud colombiana en trámite queda desvirtuado.

II. COMPLEMENTO DE INFORMACION.

En relación con los argumentos expuestos anteriormente, existen otros documentos que exponen la anterioridad en el uso de esta técnica de granulación por fusión de compuestos farmacéuticamente aceptables distintos a Polietileno glicol con bajo punto de fusión y que además permiten la liberación controlada del fármaco, veamos:

❖ La publicación internacional WO 00/01416 publicada el 13 de Junio de 2000 y titulada "PHARMACEUTICAL COMPOSITION CONTAINING LOW-MELTING WAXES" revela que este tipo de procesos donde se involucran materiales poliméricos de bajo punto de fusión para incluir de manera inmediata el principio activo (en este caso ceras tipo Witepsol que consisten en una mezcla de grasas sólidas de bajo punto de fusión que tienen índices de hidroxilo que oscilan entre 20 – 50, específicamente una mezcla de triglicéridos, diglicéridos y monoglicéridos en distintas proporciones), resulta ser un proceso reconocido con anterioridad en el estado de la técnica. También cabe resaltar que en esta publicación, las

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matrices obtenidas con las ceras tipo Witepsol no se limitan a la obtención de un granulado convencional, sino que además, y siendo su fundamento de invención el mismo que el propuesto por la solicitud colombiana en trámite, consigue composiciones que exhiben una liberación controlada del fármaco, lo que demuestra hasta que punto se ha desarrollado e implementado con anterioridad dicha técnica de granulación por fusión para obtener matrices monolíticas.

❖ La patente americana US 2002/0015730 publicada el 07 de febrero de 2002 y titulada "PHARMACEUTICAL FORMULATIONS AND METHOD FOR MAKING", revela una formulación farmacéutica oral que comprende gránulos de liberación extendida de diversos principios activos embebidos dentro de una matriz cerosa de uno o más ésteres de sucralosa de ácidos grasos como estearato de sucralosa o behenato de sucralosa (todos excipientes con bajo punto de fusión); su preparación se hace mediante el calentamiento (fundición) de una mezcla de el ingrediente activo y del éster de sucrosa de ácido graso, luego se granula o se peletiza dicho material fundido.

❖ La publicación internacional WO 03/082804 publicada el 29 de Octubre de 2003 y titulada "VENLAFAXINE BESYLATE"; la patente Americana US 4,443,428 publicada 17 de abril de 1984 y titulada "EXTENDED ACTION CONTROLLED RELEASE COMPOSITIONS"; la patente americana US 3,147,187 publicada el 01 de septiembre de 1964 y titulada "SUSTAINED RELEASE PHARMACEUTICAL" y la patente americana US 5,807,574 publicada el 15 de Septiembre de 1998 y titulada "HOMOGENEOUS MIXTURES OF LOW TEMPERATURE-MELTING DRUGS AND ADDITIVES FOR CONTROLLED RELEASE", revelan la inclusión de diversos tipos de fármacos en matrices constituidas entre otros compuestos, de ceras, explícitamente cera carnauba y ceras naturales (compuestos de bajo punto de fusión), para obtener granulados de liberación extendida a través de un proceso de previa fusión del compuesto que va a formar la matriz (la cera) y una posterior adición del principio activo.

Esto revela nuevamente que la granulación por fusión es una técnica de formulación reconocida y aplicada con anterioridad de una manera versátil, lo que demuestra las formulaciones de la solicitud colombiana en trámite carecen de nivel inventivo.

En el mismo sentido existen publicaciones de carácter científico que revelan la inclusión de diversos tipos de principios activos en este mismo tipo de matrices monolíticas, veamos:

Indomethacin Sustained Release From Alginate-Gelatin Or Pectin-Gelatin Coacervates⁸.

Abstract: Gastrointestinal side effects may interrupt essential therapy with indomethacin, a non-steroidal anti-inflammatory drug. Formulation of this drug into sustained release form may reduce some of these side effects by avoiding contact of drug crystals with gastrointestinal mucosa at high concentrations, as may happen with immediate release dosage forms. Indomethacin (IMC) sustained release microparticles (pellets) were prepared from pectin-gelatin or alginate-gelatin hydrocolloid coacervate systems under controlled pH and temperature conditions. Delayed release up to 14 h was obtained with pectin-gelatin or alginate-gelatin systems of varying composition. With the pectin-gelatin systems a low drug to hydrocolloid ratio and low pectin to gelatin ratio was the most optimal composition for sustained release. Incorporation of additives such as carnauba wax was essential for diffusion controlled mechanisms to operate in the alginate-gelatin systems. Additives also showed improvements in particle shape, size distribution and flow properties. The results of this study offer an inexpensive alternative form of sustained release IMC.

Controlled-Release Of Diclofenac Sodium From Wax Matrix Granule⁹.

Abstract: A twin-screw compounding extruder was used to prepare wax matrix granules (WMG) consisting of carnauba wax, diclofenac sodium (DS) as a model drug, and rate-controlling agents such as hydroxypropylcellulose (HPC-SL), methacrylic acid copolymer L (Eudragit L-100), and sodium chloride (NaCl). In this preparation, a wax matrix with high mechanical strength was obtained even at temperatures lower than the wax melting point. Dissolution behaviors of DS from WMG were strongly influenced by granule formulation, in which an increase in the content of HPC-SL or Eudragit L-100 brought a significant increase in the dissolution rate. The extent of this enhancing effect in HPC-SL was identical in two different dissolution mediums (pH 6.8 buffer solution and water), but in Eudragit L-100 was more significant in pH 6.8 buffer solution than in water. Only a small increase in the dissolution rate was observed in NaCl-containing WMG. These different behaviors were attributed to the physicochemical properties (i.e. swelling and solubility) of the rate-controlling agent in the dissolution medium. Further, mechanical strengths of the wetted WMG after dissolution studies were $> 70 \text{ g/mm}^2$ suggesting that burst release of DS in the gastrointestinal tract would be avoided.

Como se observa, diversos tipos de fármacos se pueden incluir en este tipo de matrices que bien pueden comprimirse finalmente para dar tabletas, tal como se pretende en la solicitud colombiana en tramite; así mismo se puede ver claramente que dichos artículos señalan el uso de cera de abeja y cera carnauba, ambos

⁸ JOSEPH I. ; SUREH VENKATARAM ; International journal of pharmaceutics ISSN 0378-5173 CODEN IJPHDE, 1995, vol. 126, no1-2, pp. 161-168 (1 p.)

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excipientes que cumplen con la característica esencial de tener bajos puntos de fusión.

En otras palabras, esta información evidencia que la inclusión de fármacos en este tipo de matrices, aparte de ser una estrategia reconocida en el estado de la técnica para procurar una formulación sencilla del fármaco, corresponde simplemente a la aplicación de los ensayos de preformulación y formulación pertinentes que permitan obtener las características de estabilidad, seguridad, eficacia y eficiencia que se espera para este tipo de medicamentos.

Por su parte, la patente americana US 5,169,645 publicada el 08 de Diciembre de 1992 y titulada "DIRECTLY COMPRESSIBLE GRANULES HAVING IMPROVED FLOW PROPERTIES" revela el uso de la cera de abejas y la cera carnauba (nuevamente excipientes con bajo punto de fusión) para la preparación de matrices monolíticas de liberación controlada, y finalmente un método de fabricación de tal formulación, que incluye la fusión inicial del material ceroso y la mezcla del ingrediente activo y demás excipientes con el material fundido, y que opcionalmente puede ser comprimido.

En conclusión, se evidencia nuevamente que la solicitud colombiana en trámite carece del requisito fundamental de nivel inventivo en primer lugar, porque reivindica sistemas o matrices obtenidas por granulación en fusión, que son sistemas reconocidos en el estado de la técnica y aplicables a una gran variedad de principios activos, y en segundo lugar porque como se ha demostrado con los argumentos anteriores, que esta técnica de formulación ha avanzado hasta el punto de no sólo obtener granulados convencionales como es el caso de la solicitud colombiana, sino que además ya es posible obtener sistemas de entrega controlada de fármaco con esta misma técnica.

❖ Ahora bien, si el fundamento de invención está dado porque la formulación está conformada por un granulado de Gabapentina con Polietilenoglicol que evita la degradación de dicho activo, es importante resaltar no solo la existencia en el mercado desde 1993 de formulaciones sólidas estabilizadas que contienen Gabapentina, sino lo revelado en la publicación internacional WO 99/59572 (25-

⁹ Yasuhiko Miyagawaa, Toshio Okabea, Yukiya Yamaguchia, Masaharu Miyajimaa, Hiroshi Satoa and Hisakazu Sunada. International Journal of Pharmaceutics Volume 138, Issue 2, 26 July 1996, Pages 215-224.

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11-1999) "GAMMA-AMINO BUTYRIC ACID DERIVATIVES CONTAINING, SOLID COMPOSITIONS AND PROCESS FOR PREPARING THE SAME" (equivalente a la solicitud colombiana 99-030-159), en donde el solicitante menciona:

We have made earnest studies to solve the prior art problems as stated above and, as a result, have now found that the degradation of 4-amino-3-substituted-butanoic acid derivatives including gabapentin owing to the lactam formation during the formulation and storage can be prevented by blocking the evaporation and movement of a very small amount of residual water in a solid composition containing the 4-amino-3-substituted-butanoic acid derivative manufactured, irrespective of formulation methods employed, that it is effective to add a humectant as a stabilizer

against degradation and that a solid composition containing the 4-amino-3-substituted-butanoic acid derivative stabilized by said humectant and a solid pharmaceutical preparation using said composition such as tablets, granules or the like have an excellent storage stability, on the basis of which this invention has been completed.

(...)

The humectant which may be employed in the invention in combination with a 4-amino-3-substituted-butanoic acid derivative is selected from ethylene glycol, propylene glycol, butylene glycol, sorbitol and glycerol and an aliphatic acid ester thereof, alone or in any combination of two or more thereof.

(...)

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The granulation of the 4-amino-3-substituted-butanoic acid derivative during the process for manufacturing pharmaceutical preparations as stated above such as gabapentin may be conducted by any granulation method well-known per se, for example, a fluidized granulation method, a high speed stirring granulation method, a melting granulation method and the like. In order

(...)

The granular powders thus obtained may be used as a pharmaceutical preparation of the 4-amino-3-substituted-butanoic acid derivative as such, or they may be also encapsulated under compression for capsules containing the 4-amino-3-substituted-butanoic acid derivative. Also, they may be further compressed to tablets.

(...)

preparation. And, in many cases, a total amount of the humectant may be preferably in the range of 0.02 - 20% by weight relative to the 4-amino-3-substituted-butanoic acid derivative, or it may preferably be in the range of 0.02 - 20% by weight relative to the total amount of the 4 amino-3-substituted-butanoic acid derivative and an auxiliary agent when added for manufacturing a pharmaceutical preparation.

(...)

Si bien es cierto que la anterioridad citada no hace mención del Polietilenglicol, si es claro que, desde 1999 -es decir casi 10 años-, se han venido planteando soluciones a los problemas que puede tener la Gabapentina como materia prima dentro de una formulación y entre ellas nos encontramos frente a la solución de la degradación de dicho activo en este caso, mediante la inclusión de un humectante; como es evidente, no es difícil, en consecuencia, realizar experimentos previos orientados a definir los auxiliares de formulación que deben estar presentes en una composición farmacéutica, máxime si en el arte previo ya se sabía de los inconvenientes que genera Gabapentina al momento de ser

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formulada. Por el contrario, esta escogencia es un paso previo y necesario en cualquier proceso de formulación farmacéutica, sin que su ejecución suponga nivel inventivo.

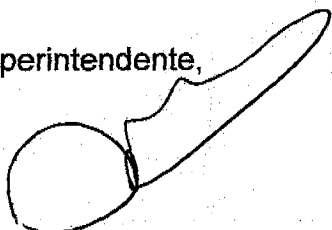
Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

III. ANEXOS.

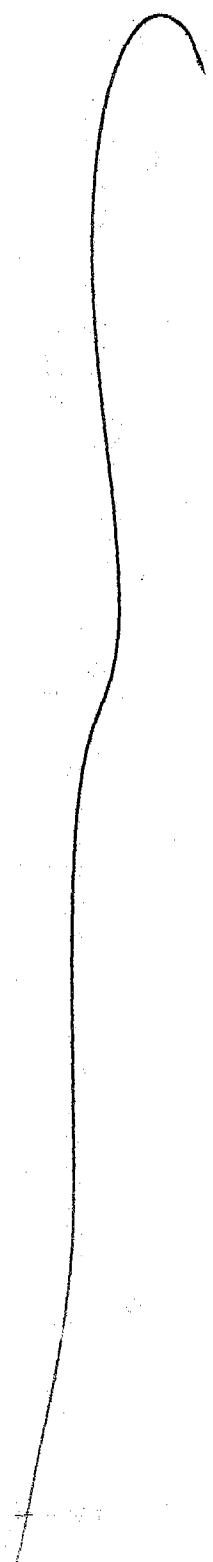
- La patente americana US 2002/0015730 publicada el 07 de febrero de 2002 y titulada "PHARMACEUTICAL FORMULATIONS AND METHOD FOR MAKING", páginas 3, 4, 7, 8 y capítulo reivindicatorio.
- La publicación internacional WO 03/082804 publicada el 29 de Octubre de 2003 y titulada "VENLAFAXINE BESYLATE" capítulo reivindicatorio.
- La patente Americana US 4,443,428 publicada 17 de abril de 1984 y titulada "EXTENDED ACTION CONTROLLED RELEASE COMPOSITIONS" capítulo reivindicatorio.
- La patente americana US 3,147,187 publicada el 01 de septiembre de 1964 y titulada "SUSTAINED RELEASE PHARMACEUTICAL".
- La patente americana US 5,807,574 publicada el 15 de Septiembre de 1998 y titulada "HOMOGENEOUS MIXTURES OF LOW TEMPERATURE-MELTING DRUGS AND ADDITIVES FOR CONTROLLED RELEASE".
- La publicación internacional WO 00/01416 publicada el 13 de Junio de 2000 y titulada "PHARMACEUTICAL COMPOSITION CONTAINING LOW-MELTING WAXES" paginas 1, 7, 8 y 9.
- La patente americana US 5,169,645 publicada el 08 de Diciembre de 1992 y titulada "DIRECTLY COMPRESSIBLE GRANULES HAVING IMPROVED FLOW PROPERTIES".
- Abstracts de todas las publicaciones científicas mencionadas en el acápite de Complemento de Información.
- La publicación internacional WO 99/59572- "GAMMA-AMINOBUTYRIC ACID DERIVATIVES CONTAINING, SOLID COMPOSITIONS AND PROCESS FOR PREPARING THE SAME" portada, páginas 1 a 9 y 41 a 43.

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Señor Superintendente,



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US 20020015730A1

(19) **United States**(12) **Patent Application Publication** (10) Pub. No.: US 2002/0015730 A1**Hoffmann et al.**(43) Pub. Date: **Feb. 7, 2002**(54) **PHARMACEUTICAL FORMULATIONS AND METHOD FOR MAKING**(76) Inventors: **Torsten Hoffmann, Radebeul (DE);
Michael Pflerth, Weisbach (DE);
Gerhard Zessin, Halle/Saale (DE);
Karl-Friedrich Landgraf, Dresden (DE)**Correspondence Address:
**Gabriel P. Katona L.L.P.
14th Floor
708 Third Avenue
New York, NY 10017 (US)**(21) Appl. No.: **09/793,936**(22) Filed: **Feb. 27, 2001****Related U.S. Application Data**

(63) Non-provisional of provisional application No. 60/187,962, filed on Mar. 9, 2000.

Publication Classification(51) Int. Cl.⁷ **A61K 9/26; A61K 31/7016**(52) U.S. Cl. **424/470; 514/53**(57) **ABSTRACT**

The invention relates to an oral pharmaceutical formulation with variably adjustable release rate, which comprises one or more active ingredients, and one or more sucrose ester of a fatty acid as the sole release-controlling agent for said active ingredient wherein when the dosage form is a granule or a pellet, the formulation is made by melting the oral formulation, and granulating or pelletizing the melt.

the dosage forms that are modified or retarded, is possible to produce non-disintegrating drug forms (so-called "single units") as well as suitably rapidly disintegrating and modified or retarded drug forms (so-called "multiple unit forms") from the granulates.

[0039] It is a further object of the present invention to provide methods for producing such retard or slow release formulations especially by melt granulation or melt pelletization.

[0040] According to the present invention, new oral pharmaceutical formulations with variably adjustable release behavior are provided which, in addition to one or more active ingredients, contain one or more sucrose esters of fatty acids as the sole release-controlling agent. The new pharmaceutical formulations are dosage forms, which release at various rates from immediate to controlled release.

[0041] As used throughout the disclosure and the claims, any reference to any active ingredient is meant also to include optionally more than one active ingredient, and reference to a sucrose ester of a fatty acid also includes optionally more than one sucrose ester of a fatty acid.

[0042] The pharmaceutical formulations of the present invention can be administered in the form of granules, pellets, tablets, film-coated tablets, microtablets, sugar-coated tablets and capsules and as therapeutic systems.

[0043] Surprisingly, sucrose esters of fatty acids are able to control the release of active ingredients in the desired manner and, moreover, to improve the technological properties during the preparation of the formulations of the invention by melt granulation or melt pelletization.

[0044] Sucrose esters of fatty acids are also suitable for granulating the active ingredient without the addition of other inert materials. By these means, a gross reduction in weight is possible in comparison to other methods, in which several feasible retarding agents or binders have to be used. At the same time, sucrose esters of fatty acids, particularly stearates with a low HLB value, such as from about 1 to about 16 can be suitably used as lubricants and as mold release agents.

[0045] Sucrose esters of fatty acids are nonionic surfactants, which are mono-, di-, tri- and polyesters of sucrose as the hydrophilic component and saturated or unsaturated fatty acids as the lipophilic component. By varying the degree of esterification and the nature of the fatty acids, sucrose esters of fatty acids can be produced with different HLB values, which have an effect on the biopharmaceutical properties, especially the release of active ingredient, the stability of the pharmaceutical formulation produced and its technological behavior. They are nontoxic, biodegradable, tasteless and odorless and have a long shelf life. The sucrose esters of fatty acids with a melting point higher than 30° C. are solid at room temperature and have an HLB value of from 1 to 16.

[0046] Sucrose esters of fatty acids are also sold under the name, for example, of sugar esters or sucrose esters by Mitsubishi (under the trade name of Ryoto), Gattefosse, or Sisterna and others.

[0047] Sucrose esters of fatty acids known from the literature are, for example, those of U.S. Pat. No. 4,844,067 used to improve the surface of silk fibers, and those of WO 93/17667 as taste improvers in pharmaceutical preparations.

[0048] Their main use is in the food industry. For example, sucrose esters of fatty acids are used to improve the mixing of chewing gum compositions, to counteract co-mixing and denaturing of finished beverages, for refining sugar, in condensed milk and in coffee creamers.

[0049] Sucrose esters of fatty acids are used for the production of wheat flour products, for example, as stabilizers to improve the texture and to avoid baking on and sticking on. In milk products they are used to stabilize emulsions and to avoid proteins and degradation, sucrose esters of fatty acids improve the crystallization behavior, and are effective emulsifiers and lower the viscosity during the production of all fats and oils.

[0050] In U.S. Pat. Nos. 3,896,238, 4,150,114, and 4,046,886, the use of sucrose esters of fatty acids in combination with alkyl sulfoxide or phosphorus oxides in pharmaceutical compositions is disclosed for improving the penetration of the active substance through the skin. Sucrose monododecanoate, monolaurate, monopalmitate and monostearate, as well as diesters and triesters of these compounds are named as special sucrose esters of fatty acids. In Japanese patent No. 8,175,437, the use of sucrose esters of fatty acids with an HLB value of 1 to 5 is disclosed as a base for suppositories.

[0051] In WO 88/06880, the use of sucrose esters of fatty acids in topical applications is disclosed, mixtures of mono- and dialkyl sucrose esters with an HLB value of 8 to 16 being used to improve the penetration through the skin. Preferably, sucrose cocoate, sucrose ricinoleate, sucrose laurate and sucrose stearate are used for that purpose.

[0052] Sucrose esters of fatty acids are also used, particularly, in cosmetic products (French patent No. 2,421,605, and Japanese patents Nos. 8,124,034 and 8,155,306).

[0053] In German patent No. 4,003,844, pharmaceutical compositions are described which, in addition to the active ingredient, cyclosporin, contain a sucrose monoester of a fatty acid and a diluent or carrier. These compositions enable the cyclosporin dosage level, required for achieving an effective therapy, to be reduced and, thus, lead to a reduction in undesirable side effects. As sucrose monoester of a fatty acid, monoesters of C₈₋₁₄ and C₈₋₁₈ fatty acids are particularly suitable for that purpose.

[0054] In WO 93/00093, a new controlled release formulation for Diltiazem in the form of spheroids is disclosed, which is composed of the active ingredient, a wetting agent and a polymer coating for controlling the release. Sucrose esters of fatty acids are used as a wetting agent. The actual retardation of active release takes place by a polymer. Moreover, the wetting agent is processed with the active ingredients by extrusion or by granulation with organic solvents. The extrudates are coated with conventional polymers. Sucrose or xylose esters of C₁₂₋₂₀ fatty acids, for example, are named as wetting agents.

[0055] In German patent No. 19,840,152, a retard formulation is disclosed, which contains calcium valproate, at least one acrylic polymer and at least one sugar ester, wherein the desired retarding effect being achieved by the acrylic polymer that is used. It is shown that the sugar ester, by itself, does not have any meaningful release retarding effect.

[0056] The suitability of sucrose esters of fatty acids to be the sole release-controlling agent in the pharmaceutical

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formulations of the present invention was all the more surprising, since these sucrose esters of fatty acids, on the one hand, have already been known for a long time per se, and now in accordance with the present invention can be employed in a simple manner in oral pharmaceutical formulations, with a variably adjustable release behavior.

[0057] The sucrose esters of fatty acids, used pursuant to the present invention, are esters of sucrose with saturated or unsaturated fatty acids or mixtures thereof. Particularly suitable are C₁₂₋₂₂ fatty acids. Sucrose stearates, sucrose palmitates, sucrose laurates, sucrose behenates and sucrose oleates, with an HLB value of about 1 to about 16, are suitably used. The melting point or melting range of the sucrose esters of fatty acids, which are used pursuant to the invention, lies between about 30° C. and about 200° C. Suitably, sucrose esters of fatty acids with a melting point or melting range of from about 40° C. to about 150° C. are used.

[0058] An essential advantage of the present invention is that the desired release behavior of the new pharmaceutical formulations can be controlled by the type and proportion of the sucrose fatty acid ester or esters used and by the parameters of the manufacturing process. Selection of an appropriate ester or combination of esters, and suitable processing parameters can be determined as the basis of guidelines disclosed herein and by routine experimentation.

[0059] Sucrose esters of fatty acids with a low HLB value are suitable for achieving a retarded release. Sucrose esters of fatty acids with a high HLB value are suitable for a more rapid or modified release behavior.

[0060] In the pharmaceutical formulations of the present invention, the sucrose esters of fatty acids can be used in amounts of from about 1% to about 95% by weight, based on the amount to be granulated (inner phase) in the formulation. More suitably, an amount of about 5% to about 50% by weight is used. Aside from sucrose esters of fatty acids, the active ingredient or mixtures of the active ingredient can also contain one or more inert excipients, such as are conventionally used in pharmaceutical preparations in the inner phase.

[0061] In further embodiments of the invention granules or pellets, which may or not contain sucrose esters of fatty acids in the granulate, can be coated instead with sucrose esters of fatty acids. The proportion of sucrose esters of fatty acids in the coating is from about 1% to about 60% by weight and suitably from about 5% to about 20% by weight, based on the coated form of the drug.

[0062] The sucrose esters of fatty acids can be used by themselves or optionally also in combination with other fusible inert ingredients. In some cases, the addition of one or more inert materials, such as plasticizers, can be of advantage for the process. A further modification of the release of active ingredient is possible by way of embedding suitably during the melt granulating or melt pelletizing process, a so-called pore-forming agent, an inert material with certain properties, such as having a characteristic solubility or swellability.

[0063] As active ingredients, the inventive, oral pharmaceutical formulations can contain compounds, the solubility of which in water ranges from good to practically insoluble.

[0064] For example, active ingredients of the following indication groups were found to be suitable for this purpose,

analeptic agents, antihypoxemic agents (such as caffeine), analgesics, antirheumatic agents (such as diclofenac, morphine, tramadol, tilidin, flupirtin), antiallergic agents (such as azelastin, pseudoephedrine), antiarrhythmic agents (such as quinaldine, disopyramide, diltiazem, verapamil), antimentia agents (nootropic agents) (such as piracetam, meergolin, xantho nicotinate, pentifyllin, vincaamin), antidiabetic agents (such as glibenclamide), antimetic agents, antiveriginous agents (such as betahistin dimesilate, dimenhydrinate), antiepileptic agents (such as carbamazepine, valproic acid, calcium valproate dihydrate, retigabine), antihypertensive agents (such as talinolol, fosinopril, doxazosin, metoprolol, nifedipine), antihypotensive agents (such as norfloxacin-HCl, dihydroergotamine mesilate), broncholytic agents, antiasthmatic agents (such as salbutamol, terbutalin sulfate, theophyllin), diuretics (such as furosemide, piretanide), circulation promoters (such as buflomedil, naftidrofuryl, pentoxifyllin), hypnotic agents, cardiac agents (such as trimetoprim, isosorbide mononitrate, isosorbide dinitrate, molsidomin), sedatives, lipid-lowering agents (such as bezafibrate, fenofibrate, xanthinol), antimigraine preparations (such as sumatriptan), muscle relaxants, anti-Parkinson agents and other agents against extrapyramidal disorders (such as levodopa, benserazide, carbidopa), psycho-pharmaceuticals (such as amitriptylin-HCl, venlafaxin-HCl, thioridazin-HCl, lithium carbonate, lithium acetate), or their pharmaceutically acceptable salts.

[0065] The pharmaceutical formulations of the present invention can suitably contain flupirtin, tramadol, nifedipine, carbamazepine, calcium valproate or retigabine.

[0066] Pursuant to the present invention, the pharmaceutical formulations of the invention can be suitably prepared by melt granulation or melt pelletization. For this purpose, for example, the mixture of active ingredient and one or more sucrose esters of fatty acids is heated with stirring in a high-speed mixer, optionally together with other inert materials. The heating can be accomplished by a heating jacket, with microwave, by radiation energy or by supplying energy by stirring. Granulation commences when the melting temperature of the sucrose ester of the fatty acids used in the mixture is reached or when the surface of the mixture softens or commences to melt. Because of the agglomeration that commences and the increase in friction associated therewith, the power increases that is taken up by the stirrer motor. As a rule, the granulation is terminated when the power uptake commences to rise exponentially. After that, the warm melt granulate is either discharged from the mixture and cooled in thin layers at room temperature or cooled with suitable cooling means (such as a cooling jacket) in the mixer, possibly with stirring. Pursuant to the invention, it is also possible to add the sucrose esters of the fatty acids in the molten state.

[0067] Surprisingly, a very narrow distribution of granulate sizes is achieved during this process. Depending on the manner, in which the process is carried out, the granulate or pellet particles have an almost rounded and smooth surface.

[0068] Likewise, it is possible to use other equipment, which can be heated, such as a fluidized bed granulator, or a rotor granulator.

[0069] The granules, so produced, can optionally be classified through a screen, possibly mixed with inert ingredients of the outer phase and, for example, pressed into tablets, or filled into capsules.

EXAMPLE 11

[0089]

Carbamazepine with 20% sucrose stearate of HLB 2	
Formulation:	
Substance	Amount
Carbamazepine	500 g
Sucrose stearate S-270	100 g
Parameters:	
Amount of formulation	500 g
Impeller speed	700 rpm
Chopper speed	3000 rpm
Heater jacket temp.	54° C.
Prepared as in Example 1	

EXAMPLE 13

[0090]

Tablets from each granulate of calcium valproate dihydrate and 10% sucrose stearate of HLB 1	
Formulation:	
Substance	Amount
Calcium valproate dihydrate	360 g
Sucrose stearate S-170	240 g
Parameters for granulation:	
Amount of formulation	500 g
Impeller speed	700 rpm
Chopper speed	3000 rpm
Heater jacket temp.	55° C.
Prepared according to Example 1	
Parameters for tableting:	
The granulate is pressed with an oblong tableting tool, 22 mm long, 9 mm wide into oblong tablets with a gross weight of 954 mg and each strength of 55 N.	
Evaluation: Active Ingredient Release	
Time in min	60 120 180 240 360 480
Release in % in pH 5.0	4.98 9.14 19.66
Release in % in pH 6.8	91.93 96.57 99.43
Prepared according to Example 10	

EXAMPLE 15

[0091]

Retigabine with 20% sucrose stearate of HLB 1	
Formulation:	
Substance	Amount
Retigabine	200 g
Sucrose stearate S-170	200 g

continued

Retigabine with 20% sucrose stearate of HLB 1	
Formulation:	
Amount of formulation	1000 g
Impeller speed	700 rpm
Chopper speed	3000 rpm
Heater jacket temp.	54° C.
Prepared according to Example 1	
Evaluation: Active Ingredient Release	
Time in min	30 60 120 180 240 360 480
Release in % in 0.1 N HCl	12.23 26.71 75.81
Release in a buffer at a pH of 6.71 6.77 15.82 15.79 23.60 27.99 35.62	
Active Ingredient Release: see FIG. 12	

EXAMPLE 16

[0092]

Retigabine with 20% sucrose stearate of HLB 2	
Formulation:	
Substance	Amount
Retigabine	400 g
Sucrose stearate S-270	200 g
Parameters:	
Amount of formulation	500 g
Impeller speed	700 rpm
Chopper speed	3000 rpm
Heater jacket temp.	55° C.
Prepared according to Example 1	
Evaluation: Active Ingredient Release	
Time in min	15 30 60 120 180 240 360 480
Release in % in 0.1 N HCl	2.28 32.53 43.93 100.97
Release in % in buffer of pH 7.8	11.82 24.77 34.41 44.94 52.74 61.63 76.37
Active Ingredient Release: see FIG. 16	

EXAMPLE 17

[0093]

Retigabine with 20% sucrose stearate of HLB 1 and 10% sucrose stearate of HLB 9	
Formulation:	
Substance	Amount
Retigabine	240 g
Sucrose stearate S-170	60 g
Sucrose stearate S-970	30 g

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with stirring at a heater jacket temperature of 52° C. At a product temperature of 30° C., sucrose stearate S-170 is added and granulated for a further 7 minutes with the chopper switched on (3000 rpm). The coated granulate was removed and screened through a 1.4 mm mesh screen.

Results: particle size distribution							
Particle size (µm)				Percentage (%)			
>1000				3.4			
>800				4.0			
>500				24.4			
>315				40.9			
>160				14.0			
>50				3.4			
<50				0			
Time in min	15	30	60	120	180	240	480
Release in % in 0.1 N HCl	23.8	43.6	71.4	94.4			
In a buffer of pH 7.5/2.5% SDS	7.2	13.2	19.8	25.4	31	40.2	47.4
Active ingredient Release in 0.1N HCl: see FIG. 21a							
Active ingredient Release in a buffer of pH 7.5, 2.5% SDS: see FIG. 21b							

We claim:

1. An oral pharmaceutical formulation with variably adjustable release rate, which comprises one or more active ingredients, and one or more sucrose ester of a fatty acid as the sole release-controlling agent for said active ingredient.
2. The oral pharmaceutical formulation of claim 1, wherein said release rate ranges from immediate release to a predetermined controlled release.
3. The oral pharmaceutical formulation of claim 1, wherein the release rate is controlled by the type or types and concentration of said sucrose fatty acid ester, and by predetermined process parameters of the manufacturing said formulation.
4. The oral pharmaceutical formulation of claim 1, wherein said formulation is a single unit, or a multiple unit dosage form.
5. The oral pharmaceutical formulation of claims 1, having a dosage form of granules, pellets, tablets, film tablets, microtablets, sugar coated tablets, capsules, or special therapeutic dosage forms.
6. The oral pharmaceutical formulation of claim 1, wherein said active ingredient is embedded in a matrix of said sucrose ester of fatty acid, or is coated with said sucrose ester.
7. The oral pharmaceutical formulation of claim 1, having a dosage form of granules or pellets, containing a mixture of said active ingredient or active ingredients with said sucrose ester or esters, said mixture being coated with said sucrose ester or esters.
8. The oral pharmaceutical formulation of claim 1 having a dosage form of granules or pellets of said active ingredient, said granules or pellets being coated with said sucrose ester.
9. The oral pharmaceutical formulation of claim 1, wherein said sucrose ester of a fatty acid is a mono-, di-, tri- or polyesters of sucrose with a saturated and/or unsaturated fatty acid of medium to long chain length.
10. The oral pharmaceutical formulation of claim 9, wherein said fatty acid is a C₁₂ to C₂₂ fatty acid.
11. The oral pharmaceutical formulation of claim 10, wherein said fatty acid is one or more of stearic acid, palmitic acid, lauric acid, behenic acid, and oleic acid.
12. The oral pharmaceutical formulation of claim 1, wherein said sucrose ester has an HLB value of from about 1 to about 16.
13. The oral pharmaceutical formulation of claim 1, wherein said sucrose ester has a melting point of from about 30° C. to about 200° C.
14. The oral pharmaceutical formulation of claim 13, wherein said melting point is from about 40° C. to about 150° C.
15. The oral pharmaceutical formulation of claim 1, having a dosage form of a granulate, said granulate containing from about 1 to about 95% wt. of said sucrose ester.
16. The oral pharmaceutical formulation of claim 1, wherein the concentration of said sucrose ester is from about 5 to about 50% wt.
17. The oral pharmaceutical formulation of claim 8, wherein the concentration of said sucrose ester in said coating is from about 1% to about 60% wt. based on the coated formulation.
18. The oral pharmaceutical formulation of claim 17, wherein the concentration of said sucrose ester in said coating is from about 3% to about 20% wt. based on the coated formulation.
19. The oral pharmaceutical formulation of claim 1, further comprising one or more inert materials.
20. The oral pharmaceutical formulation of claim 19, wherein said inert material is one or more of a pharmaceutically acceptable filler, fusible binder, disintegrant, flow regulating agent, mold release agent, and film former.
21. An oral pharmaceutical formulation with variably adjustable release rate, which comprises one or more active ingredients, one or more sucrose ester of a fatty acid, and a pore forming agent embedded in said formulation during the forming of a dosage form thereof.
22. The oral pharmaceutical formulation of claim 1, wherein said active ingredient ranges from a water soluble material to practically water insoluble material.
23. The oral pharmaceutical formulation of claim 1, wherein said active ingredient is one or more of an analeptic agent, antihypoxemic agent, analgesic, antirheumatic agent, antiallergic agent, antiarrhythmic agent, antidementia agent, antidiabetic agent, antiemetic agent, antiveriginous agent, antiepileptic agent, antihypertensive agent, anti-hypotensive agent, broncholytic agent, antiasthmatic agent, diuretic, circulation-promoter, hypnotic agent, sedative, cardiac agent, lipid-lowering agent, antimigraine preparation, muscle relaxants, agents against extrapyramidal disorders, antiParkinson agent, and psycho-pharmaceuticals.
24. The oral pharmaceutical formulation of claim 1 which contains as active ingredient one or more of caffeine, diclofenac, morphine, tramadol, tilidine, nicargoline, pentifylline, vincamine, flupirtine, azelastine, pseudoephedrine, calcium valproate, quinidine, disopyramide, diltiazem, verapamil, piracetam, nicergolin, xantine nicotinate, pentifyllin, vincamin, glibenclamide, betabistin dimesilate, dimeohydinate, carbamazepine, valproic acid, calcium valproate dihydrate, reitgabine, talinolol, furosemide, doxazosin, metoprolol, nifedipine, norfenefrine-HCl, dihydroergotamine mesilate, salbutamol, terbutaline sulfate, theophylline, furosemide, piretanide, bumetamide, nifedipine, pentoxifylline, trimethylglycerol, isosorbide mononitrate, isosorbide dinitrate,

molsidomine, bezafibrate, fenofibrate, zantidol, sumatriptan, levodopa benesazide mixture, levodopa carbidopa mixture, amitriptyline, venlafaxine HCl, thioridazine, lithium carbonate, lithium acetate, or pharmaceutically acceptable salts thereof.

25. The oral pharmaceutical formulation of claim 24, having the dosage form of a granule of retigabine with from about 1% to about 95% of said sucrose ester in said granule.

26. The oral pharmaceutical formulation of claim 25, wherein the concentration of said sucrose ester is from about 5% to about 50%.

27. A process for preparing the oral pharmaceutical formulation of claim 1, wherein the dosage form is a granule or a pellet, which comprises melting the oral formulation, and granulating or pelletizing the melt.

28. The method of claim 27, said melting comprising heating said formulation with stirring or in a fluidized bed to a temperature at which said sucrose ester softens, commences to melt at the surface, or completely melts, forming said granules or pellets, and cooling them.

29. The method of claim 28, which comprises heating said active ingredient in powder form, and adding said sucrose ester to the heated powder.

30. The method of claim 28, wherein said heating is carried out in a high speed mixer, a high shear mixer, fluidized bed, or a rotor granulator.

31. The method of claim 27, wherein said formulation further comprises a plasticizer.

32. The method of claim 29, wherein said formulation further comprises a plasticizer.

33. The method of claim 31, wherein said plasticizer is one or more of triethyl citrate, acetyl triethyl citrate, triacetin and dibutyl sebacate.

34. The method of claim 32, wherein said plasticizer is one or more of triethyl citrate, acetyl triethyl citrate, triacetin and dibutyl sebacate.

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We Claim:

1. A venlafaxine besylate compound.
2. The venlafaxine besylate compound according to claim 1, which is crystalline venlafaxine besylate.
- 5 3. The venlafaxine besylate compound according to claim 1 or 2, wherein said venlafaxine is (+/-)-venlafaxine.
4. The venlafaxine besylate compound according to claim 1-3, which is crystalline venlafaxine besylate
10 monohydrate.
5. The venlafaxine besylate compound according to claim 4, which is crystalline racemic-venlafaxine besylate monohydrate.
6. The venlafaxine besylate compound according to claim
15 2 or 3, which is crystalline venlafaxine besylate anhydrate.
7. The venlafaxine besylate compound according to claim 1-6, wherein said venlafaxine is pure or substantially pure (+) or (-) venlafaxine
20 enantiomer.
8. A pharmaceutical composition comprising a venlafaxine besylate compound of claim 1-7 and at least one pharmaceutically acceptable excipient.
9. The composition according to claim 8, wherein said
25 at least one excipient is selected from the group consisting of polymers, waxes, calcium phosphates, and sugars.

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10. The composition according to claim 8 or 9, wherein said at least one excipient is selected from the group consisting of HPMC, microcrystalline cellulose, and calcium phosphates.
- 5 11. The composition according to claim 8-10, which further comprises a lubricant.
12. The composition according to claim 8-11, wherein said at least one excipient is selected from the group consisting of hydrogenated castor oil,
10 glyceryl behenate, glycerylpalmito stearate, and saturated polyglycolized glycerate.
13. The composition according to claim 8-12, wherein said composition is in the form of granules, pellets, or a powder blend.
- 15 14. The composition according to claim 8-13, wherein said composition is in the form of a tablet.
15. The composition according to claim 8-14, wherein said composition is a unit dosage form and said venlafaxine besylate is contained in an amount
20 between 30 mg and 300 mg.
16. The composition according to claim 8-15, wherein said composition is an extended release composition.
17. The composition according to claim 16, wherein said composition has a dissolution profile such that less
25 than 30% of said venlafaxine besylate is released from said composition in 2 hours using either purified water or SGF at 37 °C with stirring at 100 r.p.m. in a basket apparatus.

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18. The composition according to claim 16 or 17, wherein said composition has a release profile that satisfies the following:

Time (hours)	Average % venlafaxine besylate released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

5 using USP Apparatus 1 (basket) at 100 rpm in purified water at 37 °C.

19. The composition according to claim 16-18, wherein said composition is a once daily dose tablet.
20. The composition according to claim 16-19, wherein
10 said composition is a tablet and said at least one excipient is a matrix material.
21. The composition according to claim 20, wherein said matrix material is a hydrophilic, lipophilic or biodegradable matrix material.
- 13 22. The composition according to claim 20 or 21, wherein said tablet is a hydrogel tablet.
23. The composition according to claim 21 or 22, wherein said tablet comprises hydroxypropylmethyl cellulose and venlafaxine besylate.

24. The composition according to claim 23, which further comprises a calcium phosphate, microcrystalline cellulose, or a lubricant.
25. The composition according to claim 23, wherein said tablet is a once daily dose tablet.
26. The composition according to claim 21, wherein said matrix material is a lipophilic matrix material.
27. The composition according to claim 26, wherein said matrix material is selected from the group consisting of glyceryl palmitostearate, glyceryl behenate, and hydrogenated castor oil.
28. The composition according to claim 26 or 27, wherein said tablet further comprises a calcium phosphate or a lubricant.
29. The composition according to claim 26-28, wherein said tablet is a once daily dose tablet.
30. The composition according to claim 16-29, wherein said composition is in the form of pellets.
31. The composition according to claim 30, wherein said pellets have a dissolution profile that satisfies the following criteria:

Time (hours)	Average % venlafaxine besylate released
2	<30
4	30-55

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8	55-80
12	65-90
24	>80

using USP Apparatus 1 (basket) at 100 rpm in purified water at 37 °C

32. The composition according to any one of claims 8-31, wherein said venlafaxine besylate is (+/-)-
5 venlafaxine besylate monohydrate.
33. A method for treating a venlafaxine-treatable disease or condition, which comprises administering to a patient in need thereof an effective amount of a venlafaxine besylate compound.
- 10 34. The method according to claim 33, wherein said venlafaxine besylate compound is administered in the form of a tablet.
35. The method according to claim 33 or 34, wherein said patient suffers from depression and said effective
15 amount of venlafaxine besylate is an antidepressant amount.
36. The method according to claim 33-35, wherein said venlafaxine besylate compound is administered once daily.
- 20 37. The method according to claim 36, wherein said venlafaxine besylate compound is administered orally in the form of one or two tablets once daily.
38. A process for making a venlafaxine besylate composition of claims 8-32, which comprises:
25 mixing venlafaxine besylate and a molten fusible

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carrier to form a partially melted mass; and
cooling said partially melted mass to form a
solidified product.

39. The process according to claim 38, wherein said
5 solidified product is in the form of granules or
pellets.
40. The process according to claim 38 or 39, which
further comprises milling said solidified product to
form granules.
- 10 41. The process according to claim 38-40, which further
comprises combining, prior to said mixing step, said
fusible carrier in a non-molten state with said
venlafaxine besylate and heating to render said
fusible carrier molten.
- 15 42. The process according to claim 38-41, wherein said
fusible carrier is a lipophilic matrix material.
43. The process according to claim 42, wherein said
fusible carrier is a wax.
- 20 44. The process according to claim 38-43, wherein said
mixing step further includes mixing at least
excipient selected from the group consisting of
calcium phosphates, microcrystalline cellulose, and
lactose.
- 25 45. The process according to claim 44, which further
comprises mixing said solidified product, optionally
after milling, with a lubricant to form a tableting
mixture and forming a tablet from said tableting
mixture.

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46. The process according to claim 38-45, which further comprises mixing said solidified product, optionally after milling, with a lubricant and at least one excipient selected from the group consisting of calcium phosphates, microcrystalline cellulose, and lactose.
47. The process according to claim 38-46, which further comprises converting said solidified product into a tablet.
48. The process according to claim 47, wherein said tablet is an extended release tablet.
49. The process according to claim 48, wherein said tablet has a release profile that satisfies the following:

Time (hours)	Average % venlafaxine besylate released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

using USP Apparatus 1 (basket) at 100 rpm in purified water at 37 °C.

50. Use of a venlafaxine besylate compound of claims 1-7 as a medicament.

United States Patent [19]

Oshlack et al.

[11] 4,443,428

[45] Apr. 17, 1984

[54] EXTENDED ACTION CONTROLLED RELEASE COMPOSITIONS

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Primary Examiner—Shep K. Rose
Attorney, Agent, or Firm—Steinberg & Raskin

[57] ABSTRACT

The action of controlled release medications is extended by incorporation into the controlled release matrix for a medication a mixture of the salt form of the medication with the free base form of the medication in a proportion of a 75-25% by weight of the salt form to 25-75% by weight of the free base form, the weight amounts being calculated with respect to the active base.

9 Claims, No Drawings

that satisfactory blood levels were maintained over a period of 7 hours thus confirming that extended bioavailability follows dissolution time.

EXAMPLE 5

In place of the hydroxyethylcellulose as used above, there may be substituted in equal amounts, hydroxymethylcellulose, hydroxypropylcellulose and mixtures of these.

In place of the fatty alcohol used as described above, there may be substituted in equivalent amounts any one of the higher aliphatic alcohols having from 10 to 18 carbon atoms in chain length and mixtures of these. Such aliphatic alcohols such as cetostearyl alcohol may be substituted in equal quantities for the cetyl alcohol as described above.

Lauryl alcohol, myristyl alcohol and stearyl alcohol are preferred alternate alcohols to the cetyl alcohol used as described above. In each and every instance wherein a fatty alcohol is used, an equivalent amount of paraffin wax may be substituted.

When these alternate hydrophilic and hydrophobic components are utilized in a slow release formulation, the manufacturing procedures described for the particular tablet remains the same and the resulting tablet will behave in essentially the same manner as described above.

EXAMPLE 6

The present method providing for the use of a pharmacologically active combination of a salt and base as an active ingredient to extend the dissolution time of slow release tablets provides a wide degree of flexibility in the therapeutic regimen for patients requiring extended bioavailability of a therapeutic agent. Thus, improved blood levels for extended periods of time results when the tablet compositions described in Examples 1-5 above are administered to a human or animal from 1 to 4 times daily after appropriate selection of the desired ratio of active base moiety to active pharmacologic salt as the active ingredient.

When the ratio of active base to salt is up to equal parts of each, the dissolution time extension is of a lesser magnitude than that obtained when the proportion of salt to base is greater than 50:50. The exact ratio to use to obtain a particular extension in dissolution time depends upon the particular active ingredient as well as the patients therapeutic needs.

While the invention has been described with respect to the production of certain specific compositions, it is apparent that variations and modifications of the invention can be made without departing from the spirit or scope of the invention.

What is claimed is:

1. On an extended action controlled release pharmaceutical composition for oral administration comprising

a hydrated hydroxyalkylcellulose and hydrophobic 10 to 18 carbon atoms higher aliphatic alcohol or paraffin wax balanced matrix melt granulation pharmaceutically acceptable controlled release core or matrix for the oral administration of pharmaceutically active agents, said controlled release core or matrix providing upon oral ingestion thereof slow release in the body of pharmaceutically active agents distributed therein, the improvement wherein said composition comprises said controlled release core or matrix for oral administration having distributed therethrough a pharmaceutically effective amount of a pharmacologically active substance in salt form thereof and in the free base form thereof, said pharmaceutically effective amount comprising between about 75% and 25% by weight of a pharmaceutically acceptable salt form of said pharmacologically active substance and between about 25% and 75% by weight of the free base form of said pharmacologically active substance, the amounts being based on the pharmacologically active moiety of said pharmacologically active substance.

2. Extended action controlled release composition according to claim 1 wherein said composition is in tablet form.

3. Extended action controlled release pharmaceutical composition according to claim 1 wherein said composition is in capsule form.

4. Extended action controlled release pharmaceutical composition according to claim 1 wherein the pharmacologically active substance is amitriptyline, atropine, chlorpheniramine, chlorpromazine, codeine, dexbrompheniramine, diphenylhydramine, doxilamine, ephedrine, hyoscyamine, morphine, oxycodone, papaverine, phenylpropanolamine, propranolol, quinidine, scopolamine, theophylline or thioridazine.

5. Composition according to claim 1 in tablet form.

6. Composition according to claim 5 in capsule form.

7. Composition according to claim 1 wherein the pharmaceutically effective amount of said pharmacologically active substance comprises between about 60% and 40% by weight of the salt form and about 40%-60% by weight of the free base form.

8. Extended action controlled release pharmaceutical composition according to claim 1 wherein said controlled release core or matrix for oral administration has distributed therethrough quinidine base and quinidine polygalacturonate or propranolol base and propranolol hydrochloride or theophylline and aminophylline or codeine base and codeine phosphate.

9. Extended action controlled release pharmaceutical composition according to claim 1 wherein said controlled release core or matrix for oral administration has distributed therethrough codeine base and codeine phosphate.

* * * * *

United States Patent Office

3,147,187

Patented Sept. 1, 1964

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3,147,187

SUSTAINED RELEASE PHARMACEUTICAL
Malcolm L. Playfair, Portland, Oreg., assignor to Don
Hall Laboratories, Portland, Oreg., a corporation of
Oregon

No Drawing. Filed Sept. 10, 1962, Ser. No. 222,704
2 Claims. (Cl. 167-82)

This invention pertains to pharmaceuticals, and relates particularly to a composition which affords controlled release of one or more drugs over a predetermined period of time.

This application is a continuation-in-part of my parent application Serial No. 845,077, filed October 8, 1959, and now abandoned.

Whereas sustained release pharmaceuticals have been prepared heretofore by the selective coating of drug particles with slowly soluble materials, it is a principal object of the present invention to provide a drug-containing composition in which all of the components are integrated, by a one step process, into a homogeneous mixture by means of an initial solution or melt.

Another important object of this invention is the provision of a drug-containing composition which may be formulated into compressed tablets or capsules by means of conventional equipment and procedures, to provide a pharmaceutical product of the sustained release type.

The foregoing and other objects and advantages of this invention will appear from the following detailed description.

In its basic concept, the present invention involves the formation, by solution or by melting, of a homogeneous mixture of drug, digestible fat or fat-soluble material, and swelling gum or swelling proteinaceous material. This liquid may be employed *per se* as a coating composition. Alternatively it may be solidified, by evaporation of the solvent or by cooling of the melt, and processed into tablets or capsules.

The foregoing basic composition may be modified by the inclusion of fats or fat-soluble materials which are resistant to digestion, for purposes of varying the rate of drug release. As explained more fully hereinafter, the proportions of ingredients may be varied over a considerable range to achieve the desired rate of drug release, the proportions being dependent in part upon such variables as the size of granule or tablet, the solubility and nature of the drug, the rate of digestion of the fat or fat-soluble material, the characteristics of the crystalline structure of the composition, and other factors.

The composition of this invention may include drugs of various types for various purposes where sustained release is desirable. In this respect, therefore, the type of drug employed in the composition does not form a part of this invention.

The drug is incorporated in one or more digestible fats or fat-soluble materials, or combinations thereof. These fatty materials function upon digestion in the body to release the drug to the system, and the rate of release is dependent in part upon the rate of digestion of the fatty materials. Examples of digestible fats are stearin, stearic acid, glyceryl mono stearate, diglycol stearate, oleic acid, and others. Examples of digestible fat-soluble materials are glyceryl-mono-oleate, glyceryl-trioleate, magnesium stearate, calcium stearate, and others.

The rate of digestion of the digestible fatty materials may be retarded by the incorporation of varying proportions of those types of fats and fat-soluble materials, or combinations thereof, which are resistant to digestion. Examples of such fats are cetyl alcohol, myristyl alcohol, and others. Examples of such fat-soluble materials are

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beeswax, carnauba wax, bayberry wax, palm wax, liquid and solid mineral oils, and others.

Also incorporated in the composition of this invention is a swelling agent comprising one or more swelling gums, or swelling proteinaceous materials, or combinations thereof. These materials function, upon digestion of the fatty material, to swell in the presence of body fluids or enzymes, thus causing the composition to disintegrate and to expose more surface area to digestion, thereupon releasing more drug to the system. Examples of swelling gums are such fibrous cellulose derivatives as methyl cellulose, carboxy methyl cellulose, hydroxy ethyl cellulose, and the sodium and other non-toxic metal salts thereof, and other fibrous gums. Examples of proteinaceous materials which are characterized by swelling in the presence of body enzymes are gluten, casein, and others.

A homogeneous mixture of the drug, fatty material and swelling agent may be prepared simply by heating the ingredients to form a melt. Alternatively, for example when the drug is thermolabile, one or more organic solvents may be employed to form a solution of the ingredients. Examples of such organic solvents are dichloroethylene, trichloroethylene, chloroform, carbon tetrachloride, ethyl alcohol, isopropyl alcohol, and others. It also may be found desirable to incorporate organic acids or bases for the purpose of overcoming incompatibilities of ingredients.

In some instances all of the ingredients may be liquified by heating or by solubilization, while in other instances some of the ingredients may remain as a homogeneous suspension of solids in the liquified portion of ingredients. In both instances there is produced a homogeneous mixture of the ingredients.

The foregoing basic composition may be employed in the liquid form as a coating composition. These coatings become solid either upon cooling or upon evaporation of the volatile solvent at a temperature below the decomposition temperature of the drug component.

The foregoing basic composition also may be employed in the production of compressed tablets or capsules, as desired. In the production of compressed tablets, for example, the solidified composition may be processed by granulation, preforming, etc., in accordance with well known practices. The granules may be compressed to tablet form and sugar coated and colored. Fillers or excipients, such as kaolin, dicalcium phosphate, sugar, starch, and others may be incorporated in the solid mixture as is well known. Alternatively, the granules may be coated and colored to form granules for encapsulation. As a further alternative, the granules or tablets may be coated with one or more successive layers of the liquified composition containing the same drug or different drug. Each successive layer may be formulated to provide the same or different release rate.

A still further alternative construction is to prepare a plurality of granules of the same drug but having different release rates, or of preparing a plurality of granules of different drugs and having the same or different release rates. These granules may be intermixed in desired proportions and compressed to tablet form, or encapsulated, as desired.

As stated hereinbefore, the proportions of ingredients may be varied over a considerable range to provide the desired release rate of drug. For example, for a given release rate the proportion of fatty material is greater when used with a highly water soluble drug than when used with a relatively insoluble drug, and the proportion of swelling agent is the inverse. The release rate also is dependent upon the crystalline characteristics of the composition, and this is influenced primarily by the type of fatty material. For example, faster release rates are

achieved with glyceryl mono stearate, as compared with an equal proportion of stearic acid, because of the more porous structure resulting from the use of the former.

The ultimate size of the granule or tablet also may determine the proportions of ingredients. For example, a tablet of relatively high potency but small size may require a larger proportion of fatty material, including indigestible fatty material, and lesser proportion of swelling agent, than a tablet of larger size. Desired proportions may vary with different release rates, drug solubilities, and other factors.

The following examples are illustrative, the proportions of ingredients being expressed in parts by weight:

EXAMPLE I

D-amphetamine hydrochloride	4
Stearic acid	8
Magnesium stearate	4
Cetyl alcohol	4
Carnauba wax	4
Dicalcium phosphate	38
Methyl cellulose	38

The above ingredients were mixed together and heated at about 205° F. to obtain a homogeneous melt, after which it was cooled and granulated by conventional procedure. Tablets were prepared of this granulation, and coated by conventional procedure. Alternatively, the granules were coated and encapsulated. Still further, the granules were melted or dissolved in appropriate solvents and employed as a coating for tablets containing other drugs.

To illustrate the effectiveness of the composition of Example I, it was tableted on 1/8" standard punches and the tablets were tested for drug release pattern in accordance with the Modified U.S.P. Pinaging Basket Method described in Drug Standards, volume 27, No. 4, July-August 1959. Comparative tests also were made on tablets in which the cellulose gum was replaced by varying percentages of corn starch. In these instances the parts by weight of active drug remained constant and the balance of the excipients were adjusted to total 100%. The results of these tests are set forth in the following table, in which the percentages of drug release represent the accumulated total drug released at the indicated time.

Table I

At end of—	Example I	10% corn starch	22% corn starch	50% cornstarch
1st hour	25.9	16.5	46.1	100.0 in less than 15 minutes
2nd hour	45.5	21.4	51.3	
3rd hour	57.1	24.5	55.0	
4th hour	57.5	25.1	100.0	
5th hour	86.0	32.7		
8th hour	100.0	38.4		

The composition using 10 percent corn starch had to be hand fed to the tablet die, and was tableted with considerable difficulty since it tended to extrude and stick. Moreover, drug release rate varied unpredictably with different samples by as much as plus or minus 50% from the average rate tabulated above, as compared with maximum variation of 15 percent in the samples of Example I.

EXAMPLE II

D-amphetamine hydrochloride	10
Glyceryl mono-stearate	21
Glyceryl di-stearate	34
Magnesium stearate	8
Carnauba wax	5
Methyl cellulose	22

The composition of Example II was prepared in the same manner as the composition of Example I, and utilized in the preparation of tablets and capsules.

The effectiveness of the composition of Example II and

its comparison with starch substitutions for the cellulose gum, as in Example I, are illustrated by the following test data:

Table II

At end of—	Example II	10% corn starch	22% corn starch	50% cornstarch
1st hour	25.9	20.0	22.1	100.0 in less than one hour
2nd hour	55.5	23.7	27.5	
3rd hour	55.7	30.0	35.0	
4th hour	73.4	34.1	42.0	
5th hour	91.0	43.0	45.9	
8th hour	100.0	51.1	63.0	

The problems of tableting and the unpredictability of drug release rate of different samples, as discussed in connection with Example I, also obtained with the above samples using 10% corn starch. The samples using 22% corn starch were somewhat less difficult to tablet, although still sufficiently difficult to render the manufacture economically unfeasible. Even with the highest degree of process control the drug release rate varied with different samples by more than plus or minus 25 percent.

EXAMPLE III

Amobarbital	50
Stearic acid	27
Sodium carboxymethyl cellulose	23

The composition of Example III was prepared in the same manner as Examples I and II, and utilized in the production of tablets and capsules. Alternatively, tablets of Example II were coated with the melt of Example III to provide a composite tablet in which amobarbital is first released to the system over a period of time, after which the amphetamine is released for a further extended period of time.

The following test data illustrate the effectiveness of the composition of Example III in comparison with starch substitutions, as in the preceding examples:

Table III

At end of—	Example III	10% corn starch	22% corn starch	50% cornstarch
1st hour	25.3	37.5	31.7	100.0 in less than 15 minutes
2nd hour	44.2	74.3	58.7	
3rd hour	51.6	100.0	100.0	
4th hour	83.4			
5th hour	85.5			
8th hour	100.0			

The same difficulties of tableting and unpredictability of drug release rate of different samples of the starch substituted compositions were experienced in this example as in the previous examples.

Moreover, it is to be observed by comparing the results of the three examples, that the drug release rate for the compositions containing 10 percent starch varied from as low as 20 percent in eight hours in Example I to 100 percent in three hours in Example III. The composition of Example II containing 22 percent starch exhibited as low as 47 percent drug release in eight hours, while the composition of Example III containing 23 percent starch effected 100 percent release in three hours. Thus, it is evident that starch is not a satisfactory substitute for cellulose gums in the compositions of the present invention.

From the foregoing it is believed to be apparent that the present invention provides a composition which may incorporate any desired drug or combinations of drugs and which may be employed effectively in the production of tablets and capsules which are characterized by yielding a sustained and accurately controlled release of the drug component over predetermined periods of time. The composition further enables this production to be carried

out in conventional equipment and according to conventional procedures.

It will be apparent to those skilled in the art that various changes in the types and proportions of ingredients exemplified heretofore may be made without departing from the spirit of this invention and the scope of the appended claims.

Having now described my invention and the manner in which the same may be used, what I claim as new and desire to secure by Letters Patent is:

1. A sustained release pharmaceutical composition consisting essentially of a homogeneous mixture of drug, digestible fatty material selected from the class consisting of fats and fat-soluble substances that are digestible by the human body, and swelling agent selected from the class consisting of those cellulose ethers and proteinaceous substances that are characterized by swelling in the presence of a substance selected from the group consisting of body fluids and enzymes.

2. The composition of claim 1 including fatty material selected from the class consisting of fats and fat-soluble

substances which are resistant to digestion by the human body.

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US005807574A

United States Patent [19]

Cheskin et al.

[11] Patent Number: **5,807,574**[45] Date of Patent: **Sep. 15, 1998**[54] **HOMOGENEOUS MIXTURES OF LOW TEMPERATURE-MELTING DRUGS AND ADDITIVES FOR CONTROLLED RELEASE**

5,164,193 11/1992 Okada et al. 424/468
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 5,455,045 10/1995 Samuels et al. 424/451

[75] Inventors: Howard Cheskin, Glenaceo; Thomas J. Hale, Chicago; Kurt G. Van Scoik, Ji Zhou, both of Grayslake, all of Ill.

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 WO 92/02145 2/1992 WIPO

[73] Assignee: **Abbott Laboratories, Abbott Park, Ill.****OTHER PUBLICATIONS**[21] Appl. No.: **879,468**[22] Filed: **Jun. 20, 1997****Related U.S. Application Data**

[63] Continuation of Ser. No. 415,401, Apr. 3, 1995, abandoned.

[51] Int. Cl.⁶ **A61K 9/48; A61K 9/52**[52] U.S. Cl. **424/451; 424/455; 424/457; 424/453; 424/452**[58] Field of Search **424/451, 452, 424/465, 453, 457, 489, 468, 453, 454, 456**[56] **References Cited****U.S. PATENT DOCUMENTS**

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 4,913,966 4/1990 Friedman et al. 424/499
 5,017,612 5/1991 Aubert et al. 514/557
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Primary Examiner—Thurman K. Page

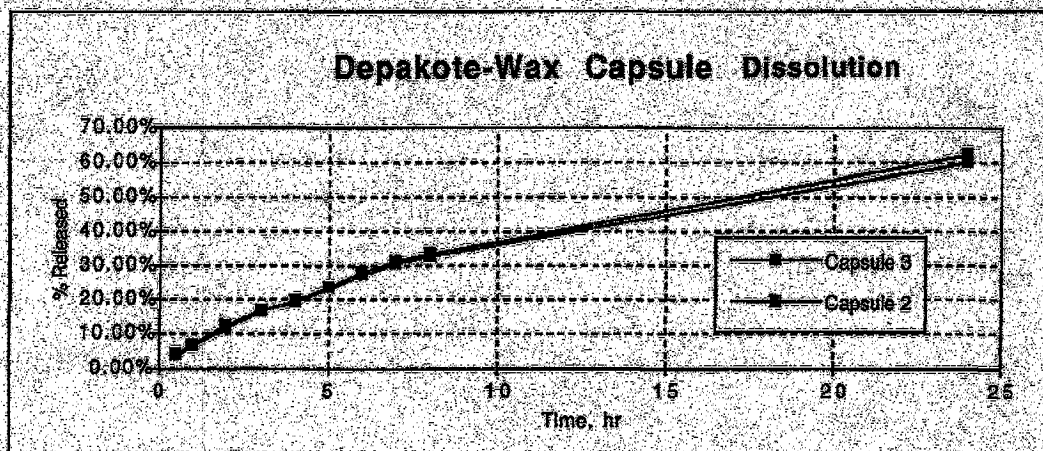
Assistant Examiner—James M. Spear

Attorney, Agent, or Firm—Michael J. Ward

[57]

ABSTRACT

The present invention relates to novel compositions of and methods of manufacture of controlled release formulations obtained by mixing molten drugs with molten additives to produce homogeneous drug-additive composites.

4 Claims, 3 Drawing Sheets

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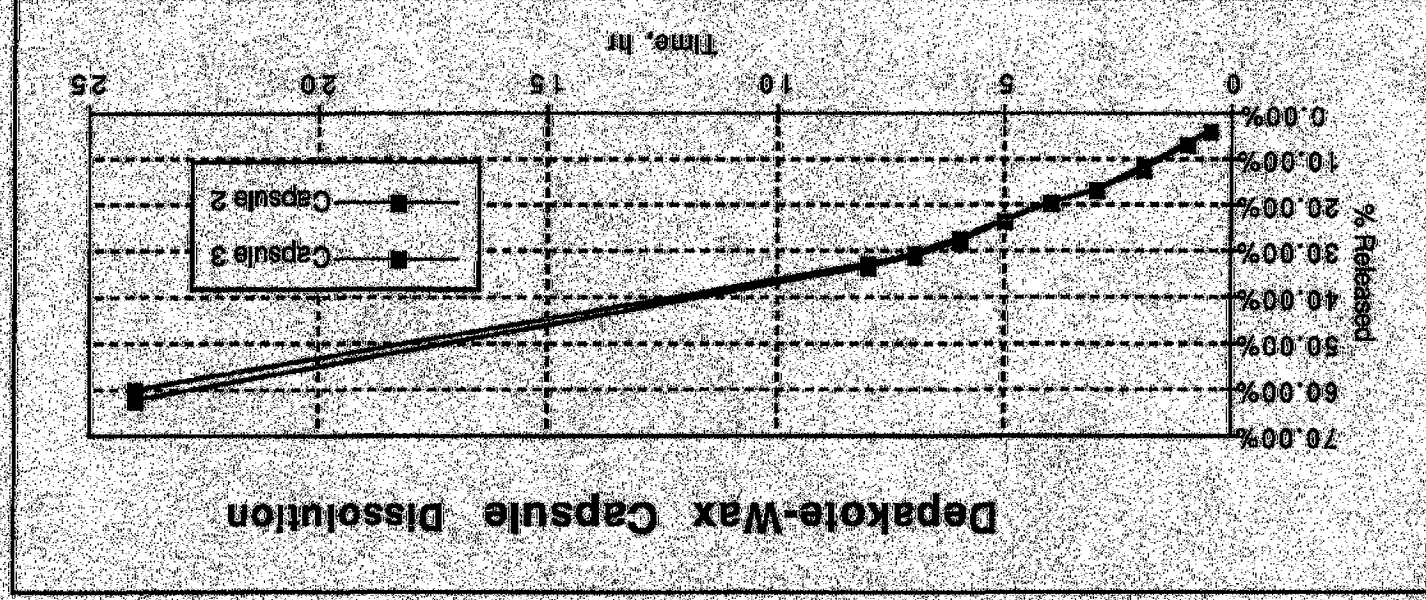


FIGURE 1

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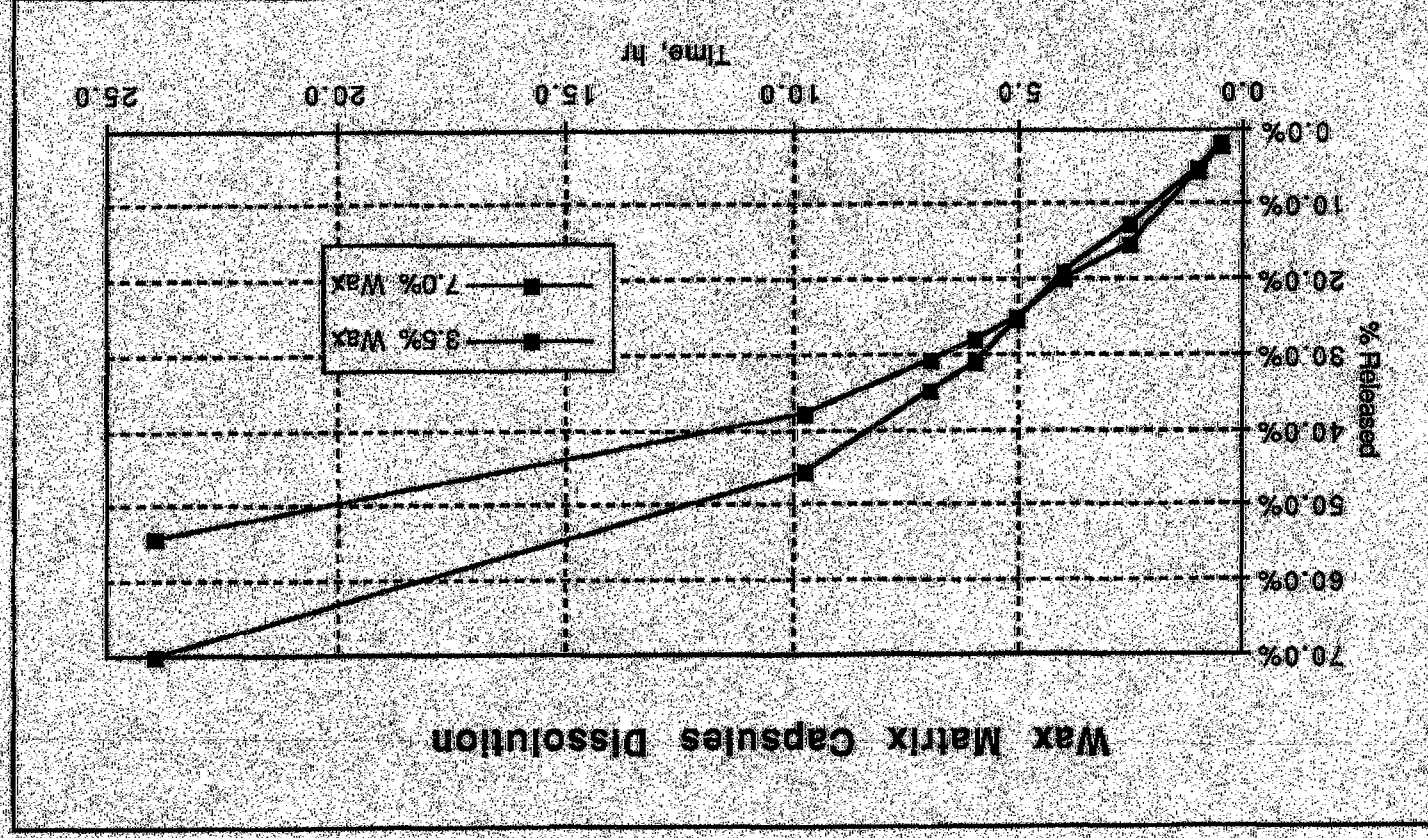


FIGURE 2

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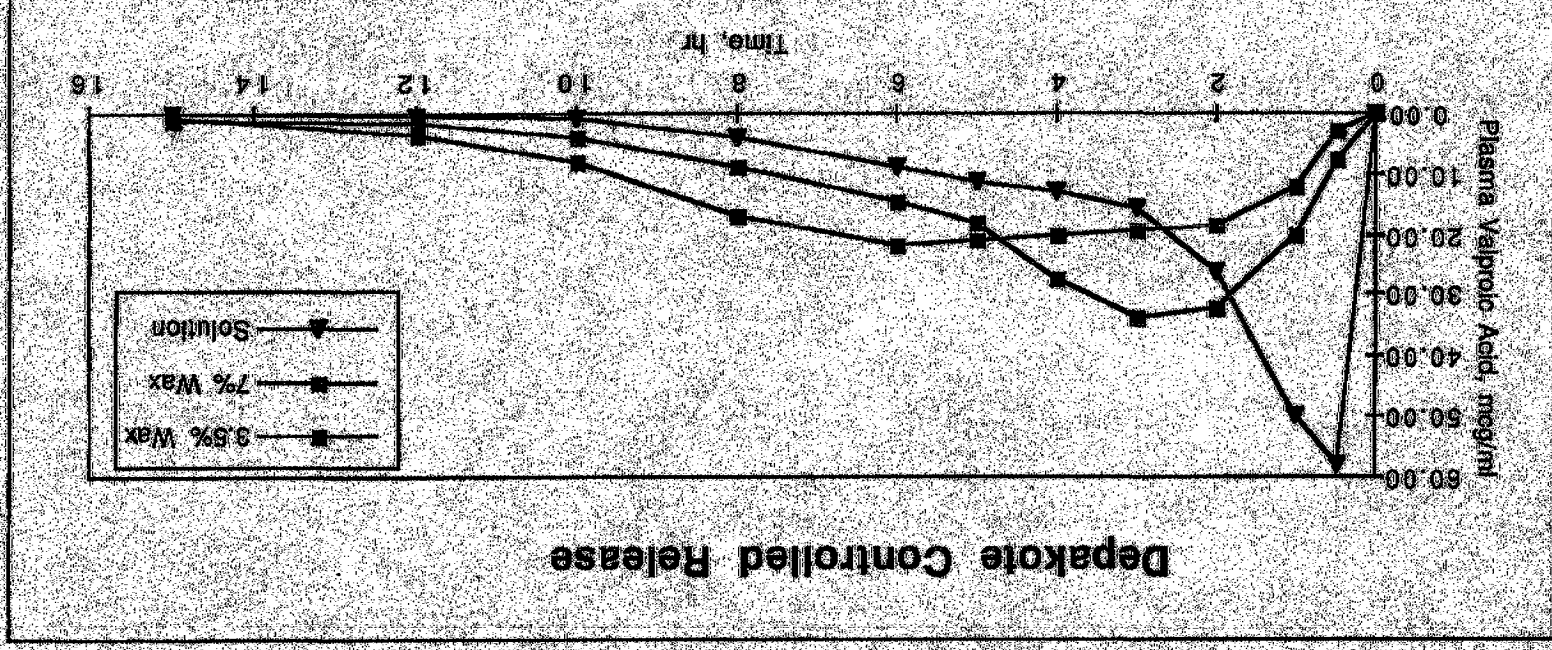


FIGURE 3

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HOMOGENEOUS MIXTURES OF LOW TEMPERATURE-MELTING DRUGS AND ADDITIVES FOR CONTROLLED RELEASE

This application is a continuation of U.S. patent application Ser. No. 08/415,401, filed Apr. 3, 1995, now abandoned.

FIELD OF THE INVENTION

The present invention provides novel compositions and methods of manufacturing controlled-release therapeutics comprising drugs which melt at low temperatures and an additive, such that the homogeneous composite contains 92-97% drug weight/weight (w/w).

BACKGROUND OF THE PRESENT INVENTION

Some medical conditions are best treated by administration of a pharmaceutical which is formulated to allow the active substance or ingredient to act as quickly as possible. Such a formulation may comprise an injectable solution or a readily-dissolvable tablet or capsule. This type of formulation is useful, for instance, for treating acute pain, such as headaches, or pain associated with sudden trauma resulting from an accident.

Other medical conditions are best treated by administration of a pharmaceutical in such a way as to sustain its action over an extended period of time. This type of administration is useful, for example, for treating chronic pain, such as that associated with rheumatic or arthritic conditions, or for the treatment of a chronic cardiovascular condition. It can be achieved by repeated administration of an immediate-release tablet or capsule at frequent intervals, for instance, every four to six hours. However, this is generally inconvenient, especially during the night, when it is often necessary to awaken a patient to administer the tablet or capsule. In addition, such multiple dosing may lead to undesirable fluctuations in the plasma concentration of the active substance.

It has previously been proposed to produce a formulation which will release the active substance therein at a controlled rate, such that the amount available in the body to treat the condition is maintained at a relatively constant level over an extended period of time. Particularly suitable periods are twelve hours and twenty-four hours, since such formulations need only be taken once or twice a day to maintain an effective treatment of the condition. Such formulations are generally known as "controlled-release formulations."

Many controlled-release formulations are already known, but there is no generally-applicable method by which such formulations can be designed. Each formulation is dependent on the particular active substance incorporated therein.

In designing a formulation, it is generally necessary to take into account many factors, including the rates of absorption and clearance of the active substance by the patient, the interaction of the active substance with the excipients and/or coatings to be used in the formulation, the solubility of the active substance and of the excipients and/or coatings, and the effects on the bioavailability of the active substance which may be caused by the excipients and/or coatings. It is, however, not readily possible to predict whether any particular formulation will provide the desired controlled-release, and it is generally found necessary to carry out substantial experimentation to produce a controlled-release formulation having the desired properties.

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Over the years, considerable effort has been directed toward the preparation of such controlled-release formulations in the pharmaceutical industry. Specifically, controlled-release compositions have been sought to deliver a controlled drug release over a long time without fragmentation of the composition in vivo.

WO 92/02145 to Warner-Lambert Corporation teaches a flavor delivery system by combining a flavor, resin and a polyalkylene wax in a liquid mixture. The resin and the wax protect, hold and mask the aroma of the flavor component. It is unclear what effect of mixing the wax with the resin has on the retention of the aroma of the flavor component.

U.S. Pat. No. 4,885,175 to Zibell teaches a chewing gum with delayed release which comprises macroscopic flavorer or sweetener mixed with a molten wax to produce a damp mix. The wax comprises 10-50% weight of the damp mix.

WO 92/01446 to APS Research Limited discloses application of a subcoat of a drug migration controlling agent (DMCA) to drug granules. The DMCA is a wax or wax-like material and is typically a long chain alcohol, acid or ester, paraffin wax, or a silicone wax. The DMCA is applied as a surface treatment on macroscopic drug granules.

U.S. Pat. No. 4,483,847 to Augart teaches using a high-melting and a low-melting lipid or lipoid material to produce a retarded liberation of active material. The solid active material and the high-melting lipid are embedded in the low-melting lipid at a temperature sufficient to melt the low-melting lipid but not the high-melting lipid. The mixture after cooling is ground to give a granulate which is then pressed into a tablet.

Pharmaceutical compositions comprising low-melting drugs are one such example wherein controlled-release formulations are already known, but there is no generally-applicable method by which such formulations can be designed.

In U.S. Pat. No. 5,017,613 to Aubert et al., liquid valproic acid (VPA) and solid ethyl cellulose are added slowly to a powdered sodium valproate to form a granular agglomeration. Precipitated silica is added to the granulate and compressed to tablets. The tablets are then lacquered.

The use of additives, particularly waxes, with low-melting drugs has had limited success in producing controlled-release formulations. An example of a low-melting drug is sodium hydrogen divalproex, an active ingredient in anti-epileptic drugs.

In formulations, VPA is a liquid at room temperature, thereby making it difficult to formulate a tablet. One way to tablet a form of VPA is to mix VPA with an equimolar amount of sodium to form sodium valproate. However, sodium valproate is difficult to work with due to its hygroscopic characteristics.

U.S. Pat. No. 4,913,906 to Friedman et al., discloses controlled-release formulations of VPA combined with an additive, such as carboxymethylcellulose, ethylcellulose or waxes, such as paraffin. The additives are added as solids and are used to granulate the VPA which is then pressed to a tablet. The active ingredient comprises 10-80% weight of the dosage form. The additives are formulated with VPA as solids.

What the prior art fails to teach is formulations of therapeutics where a liquid active ingredient is combined with a liquid additive to provide a homogeneous mixture which provides controlled-release of the active substance. The present invention relates to drug/additive compositions which give controlled-release of drug over a long time period after oral dosing.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts the results from a dissolution study. A sodium hydrogen divalproex and polyethylene wax mixture comprise a controlled-release capsule. Sodium hydrogen divalproex comprises 95.2% w/w of the drug-additive composite.

FIG. 2 depicts the results from a dissolution study with 93% w/w drug loaded composite capsules and 96.5% w/w drug loaded composite capsules.

FIG. 3 depicts in vivo studies in dogs with three separate formulations including a sodium valproate solution, a drug-additive composite comprising 93% w/w drug, and a drug-wax composite comprising 96.5% w/w drug.

SUMMARY OF THE INVENTION

The present invention relates to compositions of controlled-release therapeutics. The controlled-release therapeutics of the present invention comprise low temperature-melting drugs that are melted and mixed with a molten additive to give a homogeneous, liquid mixture. The drug comprises 92-97% w/w of the drug-additive composite.

The present invention also relates to methods of manufacturing controlled-release therapeutics comprising melting low temperature-melting drugs and an additive by mixing the drug and additive to provide a homogeneous drug-additive mixture, and allowing them to harden to form a drug-wax composite.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention is directed to compositions of and methods of manufacturing controlled-release orally administered drugs. The compositions are in a drug-additive composite, which show sustained release of the drug over time.

One embodiment of the present invention includes melting a low temperature-melting drug (a drug which melts below 150° Centigrade (C.)) and combining it in a liquid state with a molten additive. More preferably, the low temperature-melting drugs melt at 125° C. or below. Examples of drugs which melt at low temperatures include, but are not intended to be limited to, sodium hydrogen divalproex, ibuprofen, ranitidine, dibenzylamine, erythritol tetranitrate, isosorbide dinitrate, methosuximide, ketoprofen, gemfibrozil, paroxetine hydrochloride, and trimipramine maleate. Sodium hydrogen divalproex has a melting point of approximately 100° C. while ibuprofen has a melting point between 75° and 77° C.

The additives may be melted with the low temperature-melting drugs or they may be melted separately and later combined in liquid form with the molten drug. If the additive is melted with the low temperature-melting drug, the additive must have a melting point at or below the melting point of the drug. If the melting point temperature of the additive is higher than the melting point temperature of the drug, the melting point of the additive must be such that the higher temperature would not cause drug degradation. Similarly, if the additive is melted separately from the drug it must be at a temperature such that when combined with the molten drug, it does not cause drug degradation.

Additives that are acceptable for use with the present invention include derivatives of cellulose, such as ethyl cellulose, methylcellulose, hydroxypropyl cellulose, polyacrylamide, ethylene vinyl acetate copolymer,

polymethylmethacrylate, polyhydroxyethyl methacrylate and waxes. Preferably, the waxes are polyalkylene waxes, which can be natural or synthetic, such as polyethylene wax. Polyethylene wax has a melting point of approximately 97.8° C. and when molten, forms a homogeneous mixture with the molten drug without adversely affecting the drug. Polyethylene wax will also remain a solid in vivo thereby providing a matrix through which drug can diffuse. It is to be understood by those skilled in the art that the additives used in the drug-additive composite must be pharmaceutically acceptable for its intended use.

The additives must also not adversely affect the ability of the low-melting drug and the additive to form a homogeneous drug-additive composite. The homogeneous drug-additive composite provides for a more intimate mixture of drug and additive molecules, as opposed to simply dispersing solid drug particles in a liquid additive. For purposes of the present invention, the term "composite" refers to the homogeneous drug-additive mixture after it has solidified and is not meant to include the capsule which in some embodiments of the present invention contains the composite. Generally, the molten, homogeneous mixture may be added to a capsule wherein it cools and hardens. Cooling times can be from a few seconds minutes. However, the cooling time is fast enough so that a homogeneous drug-additive composite is produced. Other vehicles, which provide the same functions of the capsule, such as containment of and a site for cooling of the molten, homogeneous mixture, can be used as well. In addition, the molten, homogeneous mixture may be poured into molds where upon hardening, the drug-additive composite may be removed from the mold and further processed or used.

The homogeneous drug with additive composite allows for controlled release over time. The additive in the drug-additive composite provides a matrix structure, due to its ability to remain a solid in vivo, which allows drug to diffuse through the matrix over time.

Different types of capsules may be utilized with the formulations of the present invention. For example, Capill™ capsules are an injection-molded, starch-based hard shell which may be filled and sealed manually or by using specialized manufacturing equipment. Another example of a capsule that may be used with the formulations of the present invention are Vegicap™, a hydroxypropylmethylcellulose hard shell that is similar in size and shape with standard gelatin capsules and may be filled using standard capsule-filling equipment. In addition, soft or hard shell capsules may be used provided that the molten, homogeneous mixture does not melt the capsule. The composition of a soft elastic gelatin capsule typically comprises from about 30% to about 50% by weight of gelatin, from about 20% to about 30% by weight of a plasticizer, and from about 25% to about 40% by weight of water.

Various methods may be used for manufacturing and filling the capsules. For example, seamless capsule methods, rotary methods, methods using a Liner machine or an Accogel machine, and the like, may be used. Also various manufacturing machines may be used for manufacturing the capsules. The target filling volume/weight depends on the potency of the molten filling solution in combination with the desired dosage strength.

It is to be understood by those skilled in the art that a particular capsule is not a critical part of the present invention but is a vehicle for delivering a homogeneous drug-additive composite. However, if a capsule is used to deliver the drug-additive composite, it is necessary that the capsule

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maintain its structural integrity while the molten drug-additive mixture hardens. It is also necessary that the capsule dissolves after it is administered in vivo thereby facilitating drug release from the drug-additive composite.

Several advantages result from the present invention. First, complicated coatings of the drug-additive composite are not needed for a controlled-release of drug. Molten, homogeneous drug-additive mixture can be added to a capsule and allowed to harden by cooling. The capsule containing the drug-additive composite may then be capped.

Another advantage is there is no need for expensive tableting equipment because the molten, homogeneous drug-additive mixtures may be added directly to a preformed capsule.

Yet another advantage of the present invention is that the drug-additive composite allows slow, regular diffusion of drug out of the drug-additive composite due to the solid matrix from which diffusion of drug can occur over time.

Still yet another advantage of the present invention is that since both the drug and additive are mixed as liquids to form a homogeneous mixture, the drug and additive molecules are in a more intimate, uniform contact with each other, as opposed to where relatively large macroscopic drug particles are merely dispersed in a liquid additive. Macroscopic drug particles are relatively large particles which have their surfaces coated with liquid additive. The more intimate nature of the molten, homogeneous drug-additive mixture ensures a more uniform matrix upon cooling from which diffusion of drug can occur.

Still yet another advantage of the present invention is that the present invention allows for high drug loading with the additive. Drug loading of the drug-additive composite can comprise 92-97% drug (w/w).

Once the molten drug and molten additive are mixed it is added to a capsule, mold, or other suitable vehicle. The homogeneous mixture can be added by pipet, poured or added by more sophisticated instrumentation. Once the homogeneous mixture has hardened, it can be capped and sealed as the final product. Capping and sealing the final product may include using solvents such as ethanol.

The additive used in the method of the present invention are generally polyalkylene waxes. Preferably, polyethylene wax is used in the drug-wax composite.

The following Examples are used to illustrate the scope of the present invention and is not intended to be limited to the Examples themselves.

Example 1

A dissolution test was carried out to determine the quantity of sodium hydrogen divalproex which went into solution in an artificial medium with a phosphate buffer at pH 7.5. The quantity of VPA was determined by measuring VPA concentrations in samples taken from the dissolution medium.

A 25 gram (gm) sample of sodium hydrogen divalproex (Abbott Laboratories, Abbott Park, Ill. 60064) containing sodium hydrogen divalproex was melted in a beaker on a hot plate with 1.25 gm of polyethylene wax (S-390 C, Shamrock Technologies Inc., Newark, N.J. 07114) at approximately 115° C. The resulting sodium hydrogen divalproex-wax melt was mixed to form a sodium hydrogen divalproex-wax composite. Size 00 Capill™ capsules (Capsugel Corp., Greenwood, S.C. 29646), were filled with the molten sodium hydrogen divalproex-wax mixture by transferring the molten mixture using glass Pasteur pipets. The tip end of

the pipets were shortened to increase the flow of the molten mixture. The molten mixture was allowed to solidify by cooling for approximately 30 seconds. The Capill™ capsules were then capped and sealed with a 20% ethanol in water solution. Individual capsules were tested in USP Dissolution Apparatus II with a rotating paddle (VanKel Industries, Edison, N.J. 08820) for four hours in simulated gastric fluid without pepsin and then in simulated intestinal fluid without pancreatin, pH of 7.5. The gastric fluid without pepsin was made by dissolving 2.0 gm of sodium chloride (Sigma Chemical Co., St. Louis, Mo. 63178) in 7.0 milliliters (ml) of hydrochloric acid (Sigma) and adding water to 1000 ml. The simulated intestinal fluid without pancreatin was made by dissolving 6.8 gm of monobasic potassium phosphate in 250 ml of water and mixed. Added to the solution was 190 ml of 0.2 N sodium hydroxide to a pH of 7.5. The solution was diluted with water to 1000 ml.

Samples (2 ml) were removed at predetermined times and concentrations of VPA measured on the TDx® Analyzer (Abbott Laboratories, Abbott Park, Ill. 60064). Results are shown in Table 1. Percentages in Table 1 reflect the percent sodium hydrogen divalproex released from the composite based on VPA measurements. FIG. 1 is a graphic representation of the data showing controlled-release over 24 hours.

The capsules showed controlled release of sodium hydrogen divalproex such that only approximately 60% of the sodium hydrogen divalproex in the sodium hydrogen divalproex-wax composite was released over 24 hours.

TABLE 1

Time (hours)	Capsule 2	Capsule 3
0.5	3.80%	4.00%
1	6.70%	6.90%
2	11.50%	12.30%
3	17.00%	16.50%
4	19.60%	19.30%
5	23.80%	23.50%
6	27.60%	27.40%
7	31.00%	30.80%
8	33.80%	33.00%
24	62.60%	60.10%

Example 2

A dissolution test was done as in Example 1. 25 gm samples of sodium hydrogen divalproex (Abbott Laboratories), which were combined with 0.875 gm and 1.75 gm polyethylene wax (S-390 C, Shamrock Technologies Inc.). The sodium hydrogen divalproex and polyethylene wax were melted in a beaker on a hot plate at a temperature of approximately 115° C. The resultant sodium hydrogen divalproex-wax melt was mixed to form a homogeneous sodium hydrogen divalproex-wax mixture. The molten sodium hydrogen divalproex-wax composite was filled into Capill™ capsules. The molten mixture was transferred to the Capill™ capsules using glass Pasteur pipets which had been shortened at the tip end to increase flow of the molten mixture. The Capill™ capsules were then capped and sealed with a 20% ethanol in water solution.

The dissolution liquids were prepared as described in Example 1 and the procedure of Example 1 was followed. Samples (2 ml) were removed at predetermined times (0.5, 1, 2, 4, 5, 1, 6, 7, 9.8, and 24 hours) and concentrations of VPA measured on the TDx® Analyzer (Abbott Laboratories, Abbott Park, Ill. 60064). Results are shown in Table 2 and Table 3. Percentages in Table 2 and Table 3 reflect the percent sodium hydrogen divalproex released from the com-

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posite based on VPA measurements. FIG. 2 is a graphic representation of the data showing controlled-release over 24 hours.

The capsules showed controlled release of sodium hydrogen divalproex such that only 55% of the sodium hydrogen divalproex in the sodium hydrogen divalproex-wax composite was released in the 93% w/w drug loaded capsule over 24 hours while only 70% of the sodium hydrogen divalproex in the sodium hydrogen divalproex-wax composite was released in the 96.5% w/w drug loaded capsule for the same time period.

TABLE 2

96.5% Drug			
Time, hr	Capsule 1 % Release	Capsule 2 % Release	Capsule 3 % Release
0.5	5%	1.8%	1.4%
1.0	10%	5.2%	4.5%
2.5	13.4%	13.5%	11.4%
4.0	23.0%	18.4%	17.9%
5.1	26.9%	24.8%	24.6%
6.0	31.5%	30.9%	30.6%
7.0	35.0%	34.4%	33.0%
9.8	45.2%	44.9%	45.9%
24.0	70.0%	68.9%	70.7%

TABLE 3

93% Drug			
Time, hr	Capsule 1 % Release	Capsule 2 % Release	Capsule 3 % Release
1.0	2.2%	1.9%	2.0%
2.5	5.8%	5.2%	4.5%
4.0	13.9%	16.4%	13.1%
5.1	19.4%	20.4%	19.9%
6.0	25.4%	24.6%	25.0%
7.0	28.4%	27.6%	28.0%
9.8	31.4%	29.9%	30.7%
24.0	55.1%	53.1%	54.1%

Example 3

Nine beagle dogs were fasted overnight and fed prior to dosing. Each dog was tested with a capsule containing a 93% w/w sodium hydrogen divalproex-wax composite (approximately 515 milligrams (mg) of VPA equivalents), 96.5% w/w sodium hydrogen divalproex-wax composite (approximately 534 mg VPA equivalents), and a sodium valproate solution (approximately 500 mg of VPA equivalents). Each dog received each of the three formulations with a week between dosings for the drug to clear. Blood samples were drawn before dosing and at 30 minutes, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 15 hours post dosing. EDTA was used as an anticoagulant in the blood tubes. The plasma was isolated and frozen prior to measurement. Plasma VPA concentrations were measured with the TDR® Analyzer

(Abbott Laboratories, Abbott Park, Ill. 60064). The results are shown in FIG. 3. All determinations at each time point are the average of 9 measurements. As shown in FIG. 3, the sodium valproate solution peaks directly after administration and then shows a rapid decline of plasma VPA over time while the sodium hydrogen divalproex-wax composite formulations showed a delayed peak between 2-3 hours and consistently higher plasma VPA levels than the sodium valproate solution after 3 hours.

Capsules were made by taking 25 gm samples of sodium hydrogen divalproex (Abbott Laboratories) which were combined with 0.875 gm and 1.75 gm polyethylene wax (S-390 C, Shamrock Technologies Inc.). The sodium hydrogen divalproex and polyethylene wax were melted in a beaker on a hot plate at a temperature of approximately 115° C. The resultant sodium hydrogen divalproex-wax melt was mixed to form a homogeneous sodium hydrogen divalproex-wax mixture. The molten sodium hydrogen divalproex-wax composite was filled into Capill™ capsules. The molten mixture was transferred to the Capill™ capsules using glass Pasteur pipets which had been shortened at the tip end to decrease resistance to flow. After the homogeneous mixture had hardened, the Capill™ capsules were filled again with more of the homogeneous sodium hydrogen divalproex-wax mixture to a total of approximately 596 mg of sodium hydrogen divalproex-wax composite. The Capill™ capsules were then capped and sealed with a 20% ethanol in water solution.

We claim:

1. A controlled-release formulation comprising, in combination a therapeutically-effective dosage of drug which melts at low temperature and a polyethylene wax, such that the wax and drug form a homogeneous drug-additive composite with a 92-97 weight/weight of said drug.

2. The formulation of claim 1 where said drug is selected from the group consisting of sodium hydrogen divalproex, ibuprofen, ranitidine, dicyclanil, erythritol tetranitrate, isosorbide dinitrate, methosuximide, ketoprofen, gemfibrozil, paroxetine hydrochloride, and trimipramine maleate.

3. A method for manufacturing a controlled-release formulation comprising, in combination:

- melting a drug and additive at a temperature below 150° Centigrade, mixing said drug and said additive to produce a homogeneous mixture, said drug comprising 92-97% w/w of said said homogeneous mixture;
- adding said homogeneous mixture to a capsule;
- allowing said homogeneous mixture to harden to produce a drug-additive composite; and
- capping said capsule.

4. The method of claim 3 wherein said drug is selected from the group consisting of sodium hydrogen divalproex, ibuprofen, ranitidine, dicyclanil, erythritol tetranitrate, isosorbide dinitrate, methosuximide, ketoprofen, gemfibrozil, paroxetine hydrochloride, and trimipramine maleate.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/IL99/00365 (22) International Filing Date: 6 July 1999 (06.07.99) (30) Priority Data: 125244 7 July 1998 (07.07.98) IL (71) Applicant (for all designated States except US): YISSUM RESEARCH DEVELOPING COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM [IL/IL]; Jabotinsky Street 46, 91042 Jerusalem (IL). (71)(72) Applicant and Inventor: SINTOV, Amnon [IL/IL]; Oren Street 27, 84965 Omer (IL). (72) Inventors; and (73) Inventors/Applicants (for US only): VOLOSOV, Andrew [IL/IL]; Haarazim 21/14, 96181 Jerusalem (IL). BIALER, Meir [IL/IL]; Hahahutz Street 36, 96222 Jerusalem (IL). YAGEN, Boris [IL/IL]; Apt. 25, Neve Sheanan St. 18, 93707 Jerusalem (IL). (74) Agent: NOAM, Meir; P.O. Box 34335, 91342 Jerusalem (IL).	(51) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW. ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW). Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM). European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING LOW-MELTING WAXES		
(57) Abstract The present invention relates to pharmaceutical composition for oral administration comprising at least one active ingredient, and a low-melting wax or waxes of 30 °C to 40 °C melting point. The novel formulation is preferably applied as tablets or microspheres, providing an effective and easy mode of delivery for especially high drug-loaded systems. The composition has been found to exhibit unexpectedly enhanced drug absorption. The compositions of the present invention can further comprise any binder, glidant, lubricating compound, surfactant or any other excipients commonly-used in the art. The present invention is particularly useful for: (a) administration of less amount of drug than is required by the conventional methods while still maintaining the same activity; (b) loading more drug in smaller dispensing system; (c) a sustained drug release wherein the required rate of drug release is obtained by the percent of wax present in the composition or by combination of waxes with different melting points, all of them, or at least one of them, in the range of 30° to 40°; (d) protecting low pH-sensitive molecules in the gastric fluid and protecting proteins and peptide drugs from being degraded by the proteolytic enzymes in the intestinal lumen.		

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PHARMACEUTICAL COMPOSITIONS CONTAINING LOW-MELTING WAXES

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions for oral administration comprising any active ingredient and any low-melting wax of melting point in the range of 30° to 40°. The novel compositions exhibit unexpectedly enhanced drug absorption, thus, are useful to enhance gastric and intestinal absorption and providing an effective and easy mode of delivery for high drug-loaded systems. The said compositions exhibit controlled drug release wherein the control of the release rate is achieved by use of waxes with slightly different melting ranges. The said composition are also useful for protecting low pH-sensitive molecules in the gastric fluid, or for protecting proteins and peptide drugs from being degraded by the proteolytic enzymes in the intestinal lumen. The said novel compositions are preferably applied as tablets or microparticulate systems.

BACKGROUND OF THE INVENTION

The present invention relates to pharmaceutical compositions for oral controlled delivery and sustained drug release. These compositions can be any pharmaceutically accepted systems containing any active ingredient and characterized by a low-melting wax, or combination of such waxes, as excipients. More particularly, these compositions can be compressed tablets or particulate systems that assist in binding or coating the active material, and facilitate its penetration through the lipophilic strata of the intestinal mucosa at physiological temperature.

The term "controlled release", i.e., the release of an active agent in a controlled way over a predetermined period of time, has been the subject for considerable research over the past 30 years. The ultimate goal of controlled

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740
240**Example 1: In-Vitro Studies with Carbamazepine Epoxide (CBZ-E)****1.1 Materials and Methods**

- (a) CBZ-E was synthesized according to a procedure described in the literature (G. Bellucci et al. *J. Med. Chem.* 30, 768-773, (1987).), by epoxidation of CBZ with *m*-chloroperoxybenzoic acid. The yield of the process was about 60% (which was very close to the highest yield reported in ref. 8 for this procedure). Purified CBZ-E is a white crystalline compound with the empirical formula $C_{15}H_{12}N_2O_2$, a molecular weight of 252.27 and a melting point with decomposition at 200°C to 205°C. The final product (about 200g) obtained in our synthesis, was identified and analyzed by elemental microanalysis, IR spectrum, TLC, HPLC and melting point. The product appeared to be pure (mass balance 100.05% in the microanalysis), the melting point (with decomposition) was about 205°C.
- (b) Five Witepsol wax types (H5, H15, H37, H175 and W31, see page 9 for details) were chosen for this study. All of them had the melting range close to the body temperature and all of them represented conventional suppository bases, approved for clinical use. Witepsol is described in pharmacopoeia as hard fat based on glycerides of saturated C_{12} - C_{18} fatty acids. It is chemically and physically stable, broadly compatible with nearly all active compounds, neutral towards mucous membranes and has favorable processing properties.
- (c) The dissolution rates were determined by a conventional USP dissolution apparatus (Caleva). The standard dissolution conditions were as follows: 1000ml of distilled and degassed water, stirred with paddles at 50rpm. The temperature of the dissolution medium was 37°C, unless otherwise specified in text. Aliquots were taken manually in specified time intervals and the CBZ-E concentration was determined by HPLC.

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1.2 Results

1.2a Preliminary Experiments

(a) The first experiments were carried out in order to determine whether there was a substantial difference in the release (dissolution) rate of CBZ-E powder compared to that of the powder mixed with the wax. The preparation procedure for the powder-wax formulation was as follows: CBZ-E powder was dispersed in the Witepsol H15 melted wax at about 60°C in proportion 1:1 (w/w), mixed thoroughly, the mixture was poured into a gelatin capsule, solidified and the mold obtained was removed from the capsule. Dissolution of CBZ-E powder alone was performed after the powder was placed into a conventional gelatin capsules.

In these first experiments the dissolution conditions were varied (see Table. 1) in order to determine the most suitable procedure. After that, the standard conditions were set as specified in Materials and Methods.

The results obtained (as summarized in Fig.1 and Tab.1) clearly show a very significant difference both in the release rate and the release profile, namely, the dissolution rate of the wax-containing formulation was much slower than that of the powder.

(b) The next step was to determine whether and to what extent the amount of wax in the formulation affects the dissolution rate.

At this stage, it was decided to work with more pharmaceutically acceptable oral dosage forms. Therefore, compressed tablets of CBZ-E - wax mixture instead of molds were prepared. Tablets loaded with 60%, 66%, 70%, 75% and 80% of CBZ-E (w/w) were formulated by mixing Witepsol H15 with CBZ-E at approx. 60°C. The mixture was cooled to solidification, ground and the obtained granulate was compressed into tablets.

Interestingly, tablets containing more than two thirds (>70%) of CBZ-E did not liquify at 37°C, keeping its tablet form throughout the experiment. This fact proved to be very important for further investigation, providing an opportunity

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for more explicit evaluation of differences between the waxes, with respect to their influence on a release rate and also helping to determine the mechanism of release.

The experiments showed that in all cases the release rate was relatively slow (about 50% dissolved after twelve hours) and there was no significant difference between tablets containing around 80% (75%-85%) of CBZ-E. In light of these results it was decided to set the 80/20 ratio (w/w) between CBZ-E and a wax as a standard for further preparations.

1.2b INFLUENCE OF A WAX TYPE ON THE RELEASE RATE

At this stage a series of tests was carried out in order to determine the influence of a wax melting range on a release rate. As has been noted, five wax types were used:

Wax type	Melting range (°C)
Witepsol H37	36-38
Witepsol W31	35-37
Witepsol H175	34.5-36.5
Witepsol H5	34-36
Witepsol H15	33.5-35.5

Two types of experiments were carried out - one with molds (CBZ-E - wax 50/50 w/w) prepared as described earlier and the other with CBZ-E - wax (80/20 w/w) compressed tablets.

In both cases there was a dramatic difference in the release rates for different wax types (Figs. 2 and 3). Waxes with higher melting range caused much slower release rates than those with lower melting temperatures.

The two important conclusions drawn from these experiments were:

- (a) It was possible to control the release rate of CBZ-E by changing the wax type.



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United States Patent [19]

Shukla et al.

[11] Patent Number: 5,169,645

[45] Date of Patent: Dec. 8, 1992

[54] **DIRECTLY COMPRESSIBLE GRANULES
HAVING IMPROVED FLOW PROPERTIES**[75] Investors: Atul J. Shukla, Memphis, Tenn.;
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[21] Appl. No.: 429,858

[22] Filed: Oct. 31, 1989

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424/502[58] Field of Search 424/475, 476, 479, 489,
424/498, 502, 501, 499[56] **References Cited****U.S. PATENT DOCUMENTS**4,521,902 6/1983 Dunn 424/19
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Primary Examiner—Thurman K. Page

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Webb[57] **ABSTRACT**

Directly compressible, wax-containing granules having improved flow properties are obtained when waxes are admixed in the melt with certain flow improving additives, followed by cooling and granulation of the admixture. In certain embodiments of the invention, only the wax itself melts in the melt combination of the wax(es) and additives(s), and in other cases both the wax(es) and the additives(s) will both melt. In either case, the melt combination of the wax(es) with the additives(s) yields, upon cooling and granulation, a wax-containing particulate drug diluent having improved and unexpected flow properties.

2 Claims, No Drawings9A
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DIRECTLY COMPRESSIBLE GRANULES HAVING IMPROVED FLOW PROPERTIES

FIELD OF THE INVENTION

The present invention relates to methods and formulations for improving the flow properties of particulate waxes, including pharmaceutical waxes.

BACKGROUND OF THE INVENTION

Before the 1950's, most pharmaceutical tablets were manufactured by granulating the active ingredients and diluents together with suitable binders. The purpose of doing so was to produce free flowing compressible granules well suited for tableting in a tableting press. For many new formulations, this cumbersome and long traditional process of granulation is now being replaced by direct compression.

Early in the development of direct compression preparation of pharmaceutical dosage forms, only a few chemicals (NaCl, NaBr, KBr and methanamine) possessed the necessary flow, cohesion and lubricating properties to form tablets. Direct compression later evolved, however, to become a process by which tablets are compressed directly from a mixture of a wide variety of specially processed fillers, lubricants and disintegrants which can flow uniformly into a die cavity.

Some of the known direct compression diluents include sugars such as fructose, maltose, dextrose and other polysaccharides, calcium gluconate, calcium carbonate, powdered oyster shells, calcium phosphate, and polymers such as microcrystalline cellulose and other cellulose derivatives. Although most of these diluents are chemically inert, many of them have certain drawbacks. The sugar-based diluents are hygroscopic and their compression property is significantly dependent on the amount of moisture present in the diluents. The calcium salts are alkaline and may cause unwanted chemical reactions with certain types of acidic drugs.

Other direct compression diluents, including waxes, are also known. Several wax formulations have been widely accepted for use in drug dosage forms. These waxes include, for example, carnauba wax, beeswax, glyceride esters, hydrogenated vegetable as well as animal oils, stearyl alcohols and their derivatives, polyethylene glycols and their derivatives, esters of fatty acids such as palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, etc. These waxes are usually if not always chemically inert, can impart sustained release characteristics when required and, as drug diluents, provide a level of cohesion which approaches the ideal when active agents are combined with them and compressed into dosage forms.

The disadvantage with waxes inheres in their flow properties, however. Although melted waxes have satisfactory flow properties under some circumstances, most waxes tend to clump, not flow, and as such are generally inappropriate for use in tableting presses and similar production machinery even when attempts are made to grate or divide them. In fact, they are difficult to transfer, ship, store and dispense for this reason, also. In addition, of course, certain drugs should not be exposed even to the relatively low "melt heat" of a wax, for drug stability or other reasons. A free-flowing granulated wax is therefore the theoretical ideal as a diluent

for incorporation into a compressed drug-containing matrix.

U.S. Pat. No. 4,590,062 to Jang, entitled "Dry Direct Compression Compositions for Controlled Release Dosage Forms," discloses combinations of waxes and certain additional diluents which can be direct compressed with an active agent to prepare a controlled release tablet. The waxes and additional diluents may be slugged together and granulated, and flow aid materials such as finely divided silica or talc, in amounts between 0.5 and 2% by weight, may be included to improve the flow properties of the resulting wax granules. The diluent wax-containing granules are disclosed by Jang as suitable for combination with a wide range of biological and pharmaceutical active agents.

SUMMARY OF THE INVENTION

It has been identified that wax-containing granules having improved flow properties are obtained when one or more pharmaceutically-acceptable waxes are admixed in the melt with one or more flow improving additives, with cooling and granulation of the admixture. In some instances only the wax portion of the admixture actually melts; in other cases the wax(es) and the flow improving additive(s) both melt. In either case, the melt combination of the wax(es) with the additive(s) yields, upon cooling and granulation, a wax-containing particulate diluent having improved and unexpected flow properties over wax diluent particles known in the art. The wax-containing granules can be compressed into matrices containing biologically active agents at relatively low compression pressures, with minimal requirement for added lubricants.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is a particulate (granular) wax-containing composition, suitable for incorporation in oral and other dosage forms including pharmaceutical dosage forms, in which the particles demonstrate unexpectedly good flow properties notwithstanding the presence of wax(es) therein. The granular composition is prepared by the melt addition of one or more waxes and one or more additives, with subsequent cooling and granulation of the admixture. Although the wax(es) always melt during melt admixture, not all the suitable additive(s) necessarily melt, as discussed in greater detail below.

The waxes suitable for inclusion in the granular wax-containing composition are carnauba wax, beeswax, glyceryl esters, hydrogenated vegetable oils, hydrogenated animal fats, stearyl alcohols and their derivatives, polyethylene glycols and their derivatives, microcrystalline wax, and esters of fatty acids including palmitic acid, stearic acid, oleic acid, behenic acid, linoleic acid and linolenic acid. Suitable waxes bearing the trademarks Gelucires®, Precirol® and Compritol® are available from Gattefosse Corporation, Elmsford, N.Y.; these waxes are all esters of fatty acids and are suitable for incorporation in the present granules. Precirol® ATO-5 is glyceryl palmito-stearate; Compritol® 888 is glyceryl behenate; and Gelucires® 64/02 is glyceryl stearate, as examples.

Added to the wax, in the melt, are any of the following: polyethylene glycol (preferably PEG 4000 and/or PEG 8000), polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl acetate, ethylene vinyl acetate copolymer, acrylic polymers such as polymethyl methacrylate,

polyethyl methacrylate, polymethacrylic acid and its esters and acrylic polymers and copolymers such as "Eudragits" and "Eudispers"; cellulose derivatives such as methyl cellulose, ethyl cellulose, cellulose acetate, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose nitrate, hydroxypropyl cellulose, hydroxy propylmethylcellulose, sodium carboxymethylcellulose, micro-crystalline cellulose ("Avicel"), polyethylene oxide, poly(methylvinyl ether/maleic acid), carbomers, poly(methyl vinyl ether/maleic anhydride) ("Gantrez"), and vinyl chloride vinyl acetate polymers. Also suitable are the more common constituents such as finely divided silica, salt (NaCl, NaBr, KCl, KBr) and particulate sugars including sucrose, dextrose, and calcium gluconate, calcium phosphate and calcium carbonate particles, powdered oyster shells and ground bone meal. The ratio of wax(es) to additive(s) can range from 1:9 to 3:1; the constituents are melt combined, cooled and granulated. Ratios of 1:4 to 3:1 are preferred. Additives which do not melt are generally added in particle sizes ranging from submicrometer diameters (on the order of 0.5 micrometers) to 500 micrometer diameters.

Wax granules thus prepared are suitable for incorporation within a wide variety of pharmaceuticals and other matrices. They may be used to prepare oral dosage forms, suppositories or implants. They may be used as directly compressible diluents or may be remelted for any reason, including reformulation or granulation to a different particle size. They may be combined with vitamins, analgesics, antiinflammatory drugs, sedatives or tranquilizers, other neurologically active agents, hormones, diuretics, decongestants, cough and cold formulations and antihistamines, antineoplastic agents, motion sickness and antiemetic drugs, drugs which combat migraine and malaria, antiasthma and antihelmintic drugs, antibacterials, antibiotics, antimicrobials and other antiseptics, anticoagulants, anticonvulsants, antidiabetics and antidiabetic, antifungal and antigout drugs. The modified waxes may also be used to form matrices for the release of household, agricultural and/or marine active agents. Wax encapsulation of the additive results in particles which are inert even to drugs and active agents which would otherwise cause an unwanted reaction, because the active agent and additive are at least predominantly if not completely separated in the final drug formulation by the inert wax.

Under certain circumstances, the wax and additive and active agent may all be combined in the melt, with cooling and granulation of the admixture. The directly compressible, active-agent containing granules have multiple uses because they have good flow properties. They may be compressed directly into dosage forms; they may be stored and shipped for use elsewhere; they can be remelted for reformulation at the same or a different location; they may be dry admixed with other directly compressible diluents; they may be encapsulated/filled in hard gelatin capsules and they may be used in other applications along these lines.

It is believed, although there is no intent to be bound by this theory, that the melt addition of the wax(es) and additive(s) imparts good flow properties in one of two different ways. If the additive does not melt (finely divided silica, for example), it is believed that the silica particles form one or more cores within each wax granule, which core(s) adhesively react with and thus deactivate some (but not all) of the tackifying moieties of the wax molecules freed in the molten state. In addition, the

presence of the one or more cores in the granule imparts a variable density throughout the granule, which variable density promotes flow due to rotational instability (tumbling effect) of the granules. If the additive does melt, it is believed that the admixed additive aligns and binds at the molecular level with some (but again not all) of the tackifying moieties of the wax, reducing tack and improving the flow properties of the granular product. The modified wax granules demonstrate good cohesive strength upon compression, but typically do not adhere to each other under their own weight. An additional benefit afforded by the present wax modification is the improvement, due to the presence of the wax, of the compression cohesion characteristics of the additive in at least some cases. Regardless of theory, of course, the granules of the present invention contain wax(es) and additive(s) combined in adherence patterns characteristic of the melt combination of the wax(es) and additive(s).

When active agents are added to the melt admixture of wax(es) and additive(s), naturally the active agent must be stable to the heat used to melt the wax. However, under the low melting heats (50°-85° C. preferably, or 50°-100° C.) of most waxes, many active agents are suitable. Suitable active agents include but are not limited to heat stable antibiotics, certain heat stable proteins and peptides, and any other pharmaceutical, household (including pesticides), agricultural or marine active agents which retain at least some chemical activity under the melt heat of the selected wax(es). Those skilled in the art appreciate that waxes having lower melting points should be selected for admixture with active agents having lesser heat stability. By contrast, when the active agent is directly compressed with the granules of the present invention after the granules have been cooled and formed, all types and varieties of active agents may be combined with the granules.

The invention will be understood with greater particularity in view of the following examples:

EXAMPLE 1

One hundred parts by weight of Gelucires® glyceryl stearate (product code G64/02) were melted in a beaker contained within an oil bath held between 65°-70° C. Fifty parts by weight of 100-200 mesh size cellulose acetate particles were added to the molten wax with stirring, and the mixture was cooled to room temperature. The cooled mass was triturated to a powder in a glass mortar and pestle and the triturate was sieved into fractions. All fractions demonstrated good flow properties upon observation of mechanical transfer between glass, metal and paper receptacles. One fraction contained Gelucires®/cellulose acetate granules having a mean diameter of 637.5 micrometers.

EXAMPLE 2

Example 1 was repeated, except 33 parts by weight cellulose acetate particles were used and the oil bath temperature was 75°-80° C.

EXAMPLE 3

Examples 1 and 2 were repeated, separately, with a 75°-85° C. oil bath and with addition of 150 parts by weight of procainamide hydrochloride (to the molten Gelucires®/cellulose acetate admixture) adequate to yield a cooled mass containing a standard concentration of procainamide hydrochloride for direct preparation of oral dosage forms.

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EXAMPLE 4

Example 1 was repeated with a 75°-95° C. oil bath and with the following constituents for each of nine formulas:

- (a) 62.5% by wt. carnauba wax
12.5% by wt. Gelucires® 44/14
25.0% by wt. indomethacin
- (b) 65.0% by wt. carnauba wax
10.0% by wt. Gelucires® 44/14
25.0% by wt. indomethacin
- (c) 62.5% by wt. carnauba wax
12.5% by wt. Gelucires® 55/18
25.0% by wt. indomethacin
- (d) 70.0% by wt. carnauba wax
5.0% by wt. Gelucires® 55/18
25.0% by wt. indomethacin
- (e) 62.5% by wt. carnauba wax
12.5% by wt. Gelucires® 53/10
25.0% by wt. indomethacin
- (f) 50.0% by wt. carnauba wax
12.5% by wt. Gelucires® 44/14
12.5% by wt. polyethylene glycol (PEG 4000)
25.0% by wt. indomethacin
- (g) 50.0% by wt. carnauba wax
12.5% by wt. Gelucires® 44/14
12.5% by wt. polyethylene glycol (PEG 8000)
25.0% by wt. indomethacin
- (h) 50.0% by wt. carnauba wax
12.5% by wt. Gelucires® 55/18
2.5% by wt. polyethylene glycol (PEG 4000)
5.0% by wt. indomethacin
- (i) 50.0% by wt. carnauba wax
12.5% by wt. Gelucires® 55/18
12.5% by wt. polyethylene glycol (PEG 8000)
25.0% by wt. indomethacin

Each of the above formulations, when melt-combined, cooled and granulated, exhibited good flow properties under observation. Sieved fractions having a mean particle size of 425 micrometers (40 mesh) and 850 micrometers (20 mesh), separately, were free-flowing and well-suited to capsule-filling applications. Sieved fractions could have been prepared containing granules as small as 38 microns and as large as 1 millimeter.

EXAMPLE 5

Example 1 was repeated with a 75°-95° C. oil bath using the following constituents and amounts:

(a)

- 50.0% by wt. carnauba wax
- 12.5% by wt. Compritol® hydro
- 12.5% by wt. microcrystalline cellulose ("Avicel")
- 25.0% by wt. propranolol hydrochloride

- (b) 50.0% by wt. carnauba wax
12.5% by wt. Gelucires® 64/02
12.5% by wt. microcrystalline cellulose ("Avicel")
25.0% by wt. propranolol hydrochloride

- (c) 50.0% by wt. carnauba wax
12.5% by wt. Gelucires® 62/05
12.5% by wt. microcrystalline cellulose ("Avicel")
25.0% by wt. propranolol hydrochloride

- (d) 50.0% by wt. carnauba wax
12.5% by wt. Gelucires® 48/09
12.5% by wt. microcrystalline cellulose ("Avicel")
25.0% by wt. propranolol hydrochloride

- (e) 55.0% by wt. carnauba wax
7.5% by wt. Gelucires® 48/09
12.5% by wt. microcrystalline cellulose ("Avicel")
25.0% by wt. propranolol hydrochloride

- (f) 48.5% by wt. carnauba wax
14.0% by wt. Gelucires® 64/02
12.5% by wt. microcrystalline cellulose ("Avicel")
25.0% by wt. propranolol hydrochloride

- (g) 45.0% by wt. carnauba wax
17.5% by wt. Compritol® hydro
12.5% by wt. microcrystalline cellulose ("Avicel")
25.0% by wt. propranolol hydrochloride

- (h) 50.0% by wt. carnauba wax
12.5% by wt. Gelucires® 64/02
12.5% by wt. microcrystalline cellulose ("Avicel")
25.0% by wt. propranolol hydrochloride

Each of the above formulations, when melt-combined, cooled and granulated, exhibited good flow properties. Although the invention has been described above with respect to particular constituents and methods, the invention is to be limited only insofar as is set forth in the accompanying claims.

We claim:

1. A modified-wax, directly compressible diluent consisting of:

- 1) at least one wax selected from the group consisting of carnauba wax, beeswax, glyceride esters, fatty acid esters, hydrogenated vegetable oils, hydrogenated animal fats, stearyl alcohols, stearyl alcohol derivatives, polyethylene glycols, and polyethylene glycol derivatives, and

- 2) at least one wax-modifying composition selected from the group consisting of polyethylene glycol, polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl acetate, ethylene vinyl acetate polymer, acrylic polymer, acrylic copolymer cellulose compositions, cellulose derivatives, polyethylene oxide,

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poly(methylvinylether/maleic acid), carbomers, vinyl chloride vinyl acetate polymers, finely divided silica, particulate sodium chloride, particulate sodium bromide, particulate calcium chloride, particulate calcium bromide, particulate sugar, particulate calcium phosphate, particulate calcium carbonate, particulate oyster shells and ground bone meal.

wherein said wax and said wax-modifying composition are present in the ratio of 1:4-4:1 and further wherein said wax and said wax-modifying composition are combined in adherence patterns characteristic of the melt combination of said wax and said wax-modifying composition.

2. A modified-wax, directly compressible diluent consisting of:

1) at least one wax selected from the group consisting of carnauba wax, beeswax, glyceride esters, fatty acid esters, hydrogenated vegetable oils, hydrogenated animal fats, stearyl alcohols, stearyl alcohol

derivatives, polyethylene glycols, and polyethylene glycol derivatives, and

2) at least one wax-modifying composition selected from the group consisting of polyethylene glycol, polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl acetate, ethylene vinyl acetate polymer, acrylic polymer, acrylic copolymer, cellulose compositions, cellulose derivatives, polyethylene oxide, poly(methylvinylether/maleic acid), carbomers, vinyl chloride vinyl acetate polymers, finely divided silica, particulate sodium chloride, particulate sodium bromide, particulate calcium chloride, particulate calcium bromide, particulate sugar, particulate calcium phosphate, particulate calcium carbonate, particulate oyster shells and ground bone meal.

wherein said wax and said wax-modifying composition are present in the ratio of 1:9-9:1 and further wherein said wax and said wax-modifying composition are combined in adherence patterns characteristic of the melt combination of said wax and said wax-modifying composition.

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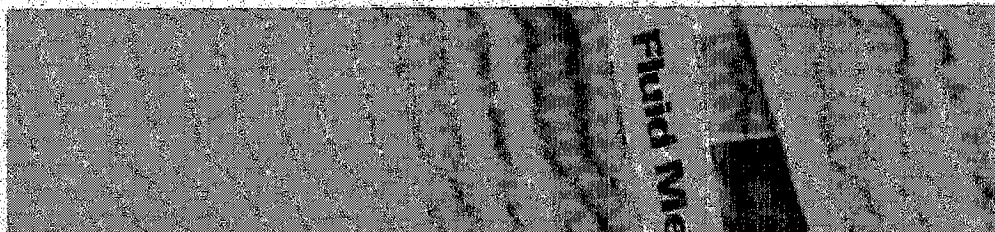
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278**Titre du document / Document title**

Indomethacin sustained release from alginate-gelatin or pectin-gelatin coacervates

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Résumé / Abstract

Gastrointestinal side effects may interrupt essential therapy with indomethacin, a non-steroidal anti-inflammatory drug. Formulation of this drug into sustained release form may reduce some of these side effects by avoiding contact of drug crystals with gastrointestinal mucosa at high concentrations, as may happen with immediate release dosage forms. Indomethacin (IMC) sustained release microparticles (pellets) were prepared from pectin-gelatin or alginate-gelatin hydrocolloid coacervate systems under controlled pH and temperature conditions. Delayed release up to 14 h was obtained with pectin-gelatin or alginate-gelatin systems of varying composition. With the pectin-gelatin systems a low drug to hydrocolloid ratio and low pectin to gelatin ratio was the most optimal composition for sustained release. Incorporation of additives such as carnauba wax was essential for diffusion controlled mechanisms to operate in the alginate-gelatin systems. Additives also showed improvements in particle shape, size distribution and flow properties. The results of this study offer an inexpensive alternative form of sustained release IMC.

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Mots-clés espagnols / Spanish Keywords

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(21) International Application Number: PCT/US99/10186 (22) International Filing Date: 10 May 1999 (10.05.99) (30) Priority Data: 10/133122 15 May 1998 (15.05.98) JP (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US], 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventor; and (73) Inventor/Applicant (for US only): AOMATSU, Akira [JP/JP]; 34-8-302, Matsuka, Hachioji-shi, Tokyo 192-0362 (JP). (74) Agents: RYAN, Andrea, M.; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.	(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: GAMMA-AMINOBUTYRIC ACID DERIVATIVES CONTAINING, SOLID COMPOSITIONS AND PROCESS FOR PREPARING THE SAME (57) Abstract The present invention provides a stabilized solid composition containing a 4-amino-3-substituted-butanolic acid derivative which can be obtained by incorporating a humectant as a stabilizer.		

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GAMMA-AMINOBUTYRIC ACID DERIVATIVES CONTAINING, SOLID COMPOSITIONS AND PROCESS FOR PREPARING THE SAME

FIELD OF THE INVENTION

5 This invention relates to a stabilized solid composition comprising a 4-amino-3-substituted-butanoic acid derivative and a process for the preparation of the same.

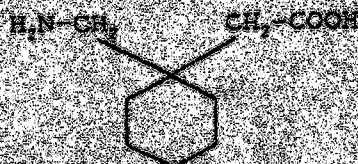
Also, this invention relates to a solid pharmaceutical preparation of the 4-amino-3-substituted-butanoic acid derivative comprising the stabilize solid composition and a process for the preparation of the same.

10 More particularly, the invention is concerned with a stabilized solid pharmaceutical preparation of the 4-amino-3-substituted-butanoic acid derivative, including gabapentin, pregabalin, baclofen, 3-aminomethyl-4-cyclohexyl-butanoic acid, 3-aminomethyl-5-cyclohexyl-pentanoic acid, 3-aminomethyl-4-phenyl-butanoic acid or 3-aminomethyl-5-phenyl-pentanoic acid, in the dosage forms of tablets, powders, granules and capsules, as well as a process
15 for the preparation of the same.

BACKGROUND OF THE INVENTION

1-(Aminomethyl)cyclohexanecarboxylic acid, one of the 4-amino-3-substituted-butanoic acid derivatives, having the

Following structural formula is disclosed in U.S. Patent Nos. 4,024,175 and 4,087,544 and has been called "gabapentin", a generic name, due to its structural relation to γ -aminobutyric acid (GABA).



Gabapentin easily passes across the brain barrier. Owing to this, the compound is used as a medicine for the treatment of certain cerebral diseases such as certain forms of epilepsy, faint and hypokinesia as well as cranial traumas, and also for improving the cerebral functions in senile patients.

Moreover, U.S. Patent No. 5,084,479 discloses that gabapentin is used for the treatment of neurodegenerative disorders such as Alzheimer's disease, Huntington's chorea or Parkinson's disease and amyotrophic lateral sclerosis. U.S. Patent No. 5,023,033 discloses that gabapentin is used for the treatment of depression. U.S. Patent No. 5,510,391 discloses that this compound is used for the treatment of mania and bipolar disorder. Furthermore, this compound, having an analgesic activity, is expected to be used as analgesics. Under these circumstances, there has been a

greatly increased utility of gabapentin as the therapeutic agents for those diseases or disorders or conditions as recited above, in addition to cerebral diseases such as epilepsy and the like.

As stated above, gabapentin is a very effective drug for cerebral diseases such as epilepsy and the like, and it has an extremely low toxicity. However, in order to maintain the effect as expected, it has been administered to adults usually at a single daily dose of 900 - 1800 mg or in some cases a daily dose of up to 2400 mg in three divided doses. Thus, a single dose will be in the range of 300 - 600 mg or in some cases up to 800 mg.

Further, gabapentin has difficulties in that it is a drug having a strongly bitter taste and also a very poor fluidity and that an extremely high dosage should be required for administration in the dosage form of powders. Since gabapentin is very difficult to formulate because of its instability, gabapentin capsules now available in the overseas markets are those manufactured by a simple dry blending of gabapentin with necessary auxiliaries and subsequent encapsulating into hard capsules.

However, a single dose is as high as 300 - 600 mg or in some cases up to 800 mg as stated above, which

neecessitates large-sized capsules, for example, Capsule No. 0 should be applied to capsules having a content of 400 mg per capsule. Consequently, ingesting such capsules is difficult even for adults, much more for children. Although gabapentin capsules have already been marketed, it is still indispensable to attempt any improvement in compliance and easy administration of gabapentin, and a demand for a smaller-sized pharmaceutical preparation of gabapentin exists in the clinical field.

Gabapentin itself is a powdery material having very poor compression-moldability and fluidity. Compression molding or granulation has been usually employed for small-sizing or fluidizing of the drug having such powder properties and the molding properties should be improved with the aid of pharmaceutical auxiliaries. However, many of the auxiliaries to be applied for compression molding tend to react with gabapentin with lapse of time to form 4-cyclohexylpyrrolidone (the corresponding lactam form) by accelerating the dehydration reaction between the amino group and the carboxyl group within the molecule of gabapentin. This dehydration reaction would be far more accelerated as the gabapentin powder is being more tightly compressed. Moreover, the reaction between gabapentin and

such auxiliaries with lapse of time would be further accelerated by the use of water or an organic solvent in manufacturing a pharmaceutical preparation.

It has been standardized in commercially available gabapentin capsules that an allowable content of the lactam up to the beyond-use date should be no more than 1.0% in view of safety. Accordingly, it is necessary in manufacturing a pharmaceutical preparation of gabapentin to prevent the formation of the lactam by retarding the dehydration reaction between the amino group and the carboxyl group within the molecule of gabapentin. On the other hand, there has been a demand for a small-sized dosage form for easier ingesting as discussed above. Under such circumstances, there have been attempted over years various methods. However, none of these attempts has succeeded either because a large-sized dosage form resulted due to a large amount of the auxiliaries used or because an increased amount of the lactam formed or both of them.

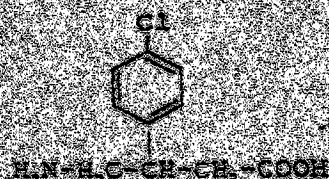
Such instability as encountered in manufacturing a gabapentin preparation has been also observed in other 4-amino-3-substituted-butanoic acid derivatives which are structurally analogous to gabapentin and have a structurally

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bulky substituent at the 3-position thereof similarly to gabapentin.

For example, 4-amino-3-(p-chlorophenyl)butanoic acid, which is represented by the following structural formula and called "Saciufen" in a generic name,



and 3-methyl-3-aminomethyl-hexanoic acid, which is represented by the following structural formula and called "pregabalin" in a generic name,



are also a drug which has very poor compression-moldability and fluidity like gabapentin. Compression molding or granulation used for small-sizing or fluidizing the drug should be improved with the aid of pharmaceutical auxiliaries. However, many of the auxiliaries to be applied to compression molding tend to react with gabapentin with lapse of time to form 4-cyclohexylpyrrolidone (the

corresponding lactam form) by accelerating the dehydration reaction between the amino group and the carboxyl group within the molecule of the compound. This dehydration reaction would be far more accelerated as the compound is being more tightly compressed and would be further accelerated by the use of water or an organic solvent in manufacturing a pharmaceutical preparation, as is the case of gabapentin. It may be said that the mechanism of degradation by the autocondensation is peculiar to the 4-amino-3-substituted-butanoic acid derivatives having a structurally bulky substituent at the 3-position thereof.

To the contrary, in γ -aminobutyric acid derivatives having no or a less bulky substituent at the 3-position thereof, such as γ -aminobutyric acid or 4-amino-3-hydroxy-butanoic acid, the dehydration reaction is not brought about even when maintained in a dried state such as at a temperature of 105°C over 2 - 3 hours, and the formation of 4-cylohexylpyrrolidone (the corresponding lactam form) is not observed. In other words, in the 4-amino-3-substituted-butanoic acid derivative wherein the substituent at the 3-position thereof has a bulky structure, the dehydration reaction could easily be brought about between the amino group and the carboxyl group within the molecule.

In view of the aforesaid background, for drugs which are 4-amino-3-substituted-butanolic acid derivatives, including gabapentin, having a structurally bulky substituent at the 3-position thereof, there have been desired a new pharmaceutical preparation containing said drugs which may be small-sized or fluidized in a dosage form such as tablets or granules and may have a comparable storage stability to commercially available pharmaceutical preparations including commercially available gabapentin capsules, and a process for manufacturing the same.

SUMMARY OF THE INVENTION

We have made earnest studies to solve the prior art problems as stated above and, as a result, have now found that the degradation of 4-amino-3-substituted-butanolic acid derivatives including gabapentin owing to the lactam formation during the formulation and storage can be prevented by blocking the evaporation and movement of a very small amount of residual water in a solid composition containing the 4-amino-3-substituted-butanolic acid derivative manufactured, irrespective of formulation methods employed, that it is effective to add a humectant as a stabilizer against degradation and that a solid composition containing

the 4-amino-3-substituted-butanoic acid derivative stabilized by said humectant and a solid pharmaceutical preparation using said composition such as tablets, granules or the like have an excellent storage stability, on the basis of which this invention has been completed.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative which comprises a 4-amino-3-substituted-butanoic acid derivative having the general formula



wherein,

R_1 is a hydrogen atom, a hydroxyl group, a methyl group or an ethyl group;

R_2 is a monovalent group selected from:

a straight or branched alkyl group of 3 - 8 carbon atoms;

a straight or branched alkylene group of 3-8 carbon atoms;

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The present invention provides an extremely effective stabilizing means in manufacturing a pharmaceutical preparation containing a 4-amino-3-substituted-butanoic acid derivative having a bulky substituent at the 3-position thereof as explained above, and the means of the invention is extremely effective in preparing a pharmaceutical preparation of, for example, gabapentin, pregabalin, baclofen, 3-aminomethyl-4-cyclohexyl-butanoic acid, 3-aminomethyl-5-cyclohexyl-pentanoic acid, 3-aminomethyl-4-phenyl-butanoic acid, 3-aminomethyl-5-phenyl-pentanoic acid, etc.

The humectant which may be employed in the invention in combination with a 4-amino-3-substituted-butanoic acid derivative is selected from ethylene glycol, propylene glycol, butylene glycol, sorbitol and glycerol and an aliphatic acid ester thereof, alone or in any combination of two or more thereof.

Illustrative examples of the glycerol aliphatic acid esters may include glycerol lower aliphatic acid esters such as monoacetylglyceride, diacetylglyceride, triacetylglyceride (triacetin), middle chain aliphatic acid monoglyceride such as monohexanoylglyceride, monooctanoylglyceride, monodecanoylglyceride, and middle

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chain aliphatic acid polyglycerol ester such as monolauric acid polyglyceride or monomyristic acid polyglyceride and the like.

The solid pharmaceutical preparation of the present invention can be obtained in a usual dosage form, typically, in the dosage form of powders, granules, surface-coated granules, capsules, tablets or surface-coated tablets by conducting in turn the granulation step in which a humectant as a stabilizer and, if necessary, an auxiliary agent for manufacturing a pharmaceutical preparation are added to bulk powders of a 4-amino-3-substituted-butanoic acid derivative, such as gabapentin, pregabalin, baclofen and the like and the resulting mixture is granulated by means of a granulator, the encapsulation step in which the resulting granular powders are encapsulated under compression by means of a capsule filler or the tableting step in which the resulting granular powders are compressed by means of a tablet machine and, if necessary, the coating step in which the granular powders, tablets or granules obtained in the preceding steps are surface-coated.

The granulation of the 4-amino-3-substituted-butanoic acid derivative during the process for manufacturing pharmaceutical preparations as stated above

such as gabapentin may be conducted by any granulation method well-known per se, for example, a fluidized granulation method, a high speed stirring granulation method, a melting granulation method and the like. In order to effectively adhere a stabilizer to bulk powders of the 4-amino-3-substituted-butanoic acid derivative, there may be preferably employed a fluidized granulation method in which bulk powders of the said compound are fluidized and then a stabilizer is sprayed onto the fluidized powders. In this fluidized granulation step, a stabilizer is added in the form of its solution dissolved in water or an organic solvent such as alcohols or the like, whereby a small amount of the stabilizer may be sufficient for uniformly adhering to the surface of bulk powders of the 4-amino-3-substituted butanoic acid derivative.

In the granulation step using said fluidized granulation method, granulation may be carried out by adding to bulk powders of the 4-amino-3-substituted-butanoic acid derivative the stabilizer solution as described above and, if necessary, a binder such as corn starch, a cellulose derivative (e.g., hydroxypropylcellulose), polyvinyl alcohol, a polyvinyl pyrrolidone (e.g., Kollidon-K30 or