

REYES & REYES

A B O G A D O S

Señor

SUPERINTENDENTE DE INDUSTRIA Y C

E.

S.

D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-098747- -00006-0000

Fecha: 2011-10-06 11:46:22 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 46

REF: EXPEDIENTE 10-098-747

TÍTULO SOLICITADO: COMPOSICIÓN FARMACEÚTICA QUE COMPRENDE UNA FORMA DE DOSIS UNITARIA SÓLIDA DE UNO O MÁS INGREDIENTES ACTIVOS Y UN POLÍMERO INSOLUBLE EN AGUA Y/O UN POLÍMERO SOLUBLE EN AGUA.

PUBLICACIÓN: Gaceta 629 de 20/06/2011, número de publicación 635.

PRIORIDAD: IN 89/MUM/2008 DE 11/01/2008; IN489/MUM/2008 DE 10/03/2008; IN619/MUM/2008 DE 24/03/2008.

SOLICITANTE: CIPLA LIMITED.

APODERADO: LUZ CLEMENCIA SUAREZ DE PAEZ.

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 el 16 de septiembre de 2011, en los siguientes términos:

I. COMPLEMENTO DE INFORMACIÓN

Comedidamente me permito presentar los argumentos que demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 16 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario, veamos:

La solicitud colombiana en trámite 10-098-747 que se refiere a una composición farmacéutica caracterizada porque comprende una forma de dosis unitaria sólida la cual comprende uno o más ingredientes activos en combinación con un polímero insoluble en agua y/o un polímero soluble en agua; no reúne los requisitos necesarios para otorgársele el privilegio de patente de invención, como se demuestra a través de los siguientes argumentos:

En primer lugar, y dado que la solicitud en cuestión revela también una dispersión sólida, específicamente en sus reivindicaciones 1 a 3, también se puede afirmar que dicha técnica es una estrategia tecnológica de formulación ampliamente reconocida. Cualquier persona medianamente versada en la producción de formulaciones farmacéuticas debe reconocer que la formación de dichas dispersiones del fármaco en el seno de un portador se puede realizar mediante técnicas de fusión, disolución-dsecación o una mezcla de ambas¹.

Teniendo en cuenta que lo reivindicado por la solicitud colombiana en trámite se refiere específicamente a una composición farmacéutica sólida obtenida por extrusión en masa fundida en caliente del ingrediente activo con el (los) polímero(s), específicamente en sus reivindicaciones 4 a 18, es indispensable aclarar que dicha técnica de formulación es reconocida con anterioridad como granulación por fusión o "melt granulation" si se utiliza el término técnico en el idioma inglés.

La granulación por fusión es un proceso en el cual el granulado se consigue mediante la adición de un agente aglutinante que es sólido a temperatura ambiente y funde a temperaturas relativamente bajas, normalmente se trabaja con sustancias de punto de fusión en torno a 50-80°C, tanto de naturaleza hidrófila

¹ Vila Jato. J.L. Tecnología Farmacéutica. Volumen I. Páginas 201 a 202.

como lipófila, tal y como sucede en el proceso de obtención reivindicado por la solicitud en cuestión.

En este procedimiento generalmente el agente aglutinante puede añadirse ya fundido sobre la mezcla de polvos precalentada o en forma sólida junto con el resto de componentes de la mezcla, de tal forma que la granulación se desarrolla en “un solo paso” al fundir el aglutinante en el seno de la mezcla. Tras la fusión, el agente aglutinante actúa como líquido de unión de las partículas de polvo de forma similar al líquido adicionado en los procesos de vía húmeda. Dependiendo de la cantidad de aglutinante añadido, de los componentes que constituyen la mezcla y de la elección de las condiciones del proceso, es posible obtener gránulos o incluso pellets². Como se puede apreciar, estas mismas son las características técnicas esenciales del procedimiento reivindicado en la solicitud colombiana en trámite.

Esta propiedad permite emplear esta técnica para la formulación de fármacos sensibles a la humedad, evitar el controvertido uso de solventes orgánicos y acortar el proceso de granulación en términos de tiempo y energía al eliminar la fase de secado. Asimismo, una adecuada selección del agente aglutinante y del resto de excipientes permitirá el desarrollo y elaboración de formas farmacéuticas tanto de liberación inmediata como de liberación controlada. Uno de los equipos más empleados en la granulación por fusión es el mezclador granulador de alta velocidad, que permite realizar esta técnica en un solo paso; además, una vez optimizado el proceso, permite su aplicación a escala industrial³.

Seguendo con el razonamiento anterior, cualquier persona medianamente versada en la formulación de productos farmacéuticos también debe reconocer que un mismo principio activo se puede presentar en diferentes formas farmacéuticas, las cuales a su vez se pueden formular utilizando diferentes excipientes farmacéuticamente aceptables; la selección de dicha forma farmacéutica depende de las características fisicoquímicas del fármaco, su vía de administración, entre otros.

² Lourdes OCHOA D.1, Manuela IGARTUA O.1, Rosa Mª HERNÁNDEZ M.1, Alicia R. GASCÓN1 y José L. PEDRAZ M. GRANULACIÓN POR FUSIÓN EN MEZCLADORES GRANULADORES DE ALTA VELOCIDAD. VITAE, REVISTA DE LA FACULTAD DE QUÍMICA FARMACÉUTICA ISSN 0121-4004 Volumen 13 número 1, año 2006. Universidad de Antioquia, Medellín - Colombia. págs. 40-47.

³ Ibid.

En este sentido, y teniendo en cuenta que la solicitud colombiana en cuestión revela una mezcla en polvo de los ingredientes activos y los excipientes para formar un granulado que finalmente se formulara en tabletas y/o capsulas, es importante resaltar que precisamente en el estado de la técnica, la granulación por fusión es un proceso simplificado de aglomeración de partículas primarias de polvo para formar estructuras mayores denominadas gránulos. Generalmente, este granulado se utiliza como producto intermedio en la fabricación de comprimidos y cápsulas, aunque también puede ser empleado como producto final⁴.

Las principales ventajas que conllevaría a cualquier persona medianamente versada en la formulación farmacéutica a escoger la granulación por fusión, son las siguientes: evita la formación de polvo, elimina la fase de secado haciendo el proceso de granulación más corto, y evita el uso de solventes y los posibles problemas que derivan de ello (hidrólisis de principio activo, empleo de equipos ignífugos etc.); así mismo, para dicho formulador, escoger los principios activos que se pueden involucrar en un granulado a través de este proceso, parte del hecho (y mayor inconveniente de la técnica) que no se puede aplicar a sustancias termolábiles a las temperaturas habituales de trabajo⁵.

En cuanto a la selección del aglutinante, y teniendo en cuenta que la solicitud colombiana en trámite no restringe dichos compuestos más que a polímeros hidrófilos y/o lipófilos, es importante indicar que en esta granulación por fusión, la selección adecuada del agente aglutinante es un aspecto de gran importancia, ya que permitirá desarrollar tanto formulaciones de liberación inmediata como de liberación controlada. Como agentes aglutinantes se pueden emplear numerosas sustancias hidrófobas como el monoestearato de glicerilo, ácido esteárico, Compritol 888 Ato (Glyceryl behenate), Gelucire 50/13 (Polyglycolized glyceride) y otros tipos de grasas y alcoholes. Entre las sustancias hidrófilas mas empleadas destacan el polietilenglicol (PEG 6000) (36) y el poloxamer 188 (Lutrol F68)⁶.

En cuanto a la proporción del material aglutinante, en el estado de la técnica se ha reconocido que, en general, la granulación por fusión requiere aproximadamente entre un 10 y un 20 % en peso del agente aglutinante en la mezcla; un exceso de

⁴ Ibid.

⁵ Ibid.

⁶ Ibid.

aglutinante en la mezcla provocaría un sobre amasado, mientras que si no se alcanza la proporción suficiente no tendrá lugar la formación del granulado⁷.

En otras palabras, no se puede sustentar una actividad inventiva de la elaboración de una formulación farmacéutica convencional y reconocida en el estado de la técnica, ni mucho menos en el hecho que una persona con conocimientos en formulaciones de este tipo, seleccione los excipientes y los principios activos adecuados para granularse bajo dicha técnica.

De la misma manera, la selección del equipo para la realización del procedimiento de granulación, tampoco puede sustentar el nivel inventivo de la solicitud en cuestión. Lo anterior, teniendo en cuenta que en las reivindicación 11 se menciona que tanto el (los) ingrediente(s) activo(s), el (los) polímero(s) y demás excipientes de la formulación son procesados para formar una mezcla en polvo la cual se transfiere a través del barril caliente de un extrusor; en este sentido, es relevante indicar que en el estado de la técnica se reconocen como los equipos más empleados en la granulación por fusión, al mezclador granulador de alta velocidad, el lecho fluidizado⁸ y los extrusores de tornillo simple⁹ o de doble tornillo¹⁰.

La versatilidad de dicha técnica de formulación depende, como ya mencionamos, de las características fisicoquímicas del principio activo, en especial lo relacionado con su punto de fusión y su estabilidad a la temperatura del proceso. De esta manera, los fármacos mencionados en las reivindicaciones 1, 13 y 17 de la solicitud colombiana en trámite no pueden sustentar novedad o nivel inventivo alguno, independientemente de que hayan sido incluidos o no en este tipo de formulaciones con anterioridad, dado que como vimos, su selección se reduce a que sus características fisicoquímicas favorezcan su estabilidad durante el proceso de elaboración del granulado por fusión, información que se obtiene durante los ensayos de preformulación y formulación rutinarios en cualquier proceso de formulación farmacéutica.

⁷ Ibid.

⁸ Ibid.

⁹ Liu J, Zhang F, McGinity JW. Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion. Eur J Pharm Biopharm. 2001 Sep;52(2):181-90.

¹⁰ Van Melkebeke B, Vermeulen B, Vervaet C, Remon JP. Melt granulation using a twin-screw extruder: a case study. Int J Pharm. 2006 Dec 1;326(1-2):89-93. Epub 2006 Jul 10.

Sin embargo, podemos hacer evidente dicha versatilidad de la técnica de granulación por fusión, veamos¹¹:

Forma de liberación	Forma farmacéutica	Fármaco	Aglutinante	Referencia
Liberación controlada	Pellets	Fenilefrina	Precirol® + Compritol®	26
Liberación controlada	Pellets	Teofilina	Ácido Estearico	31
Liberación controlada	Gránulos	Ibuprofeno	Poloxamer 188	37
Liberación controlada	Gránulos	Propranolol	Precirol®	56
Liberación inmediata	Gránulos	Diazepam	PEG 3000 o Gelucire 50/13	34
Liberación inmediata	Gránulos	Carbamazepina	PEG 6000	53
Liberación inmediata	Gránulos	Paracetamol	Supernatylate®	55
Liberación inmediata	Gránulos	Diclofenaco	PEG 4000	57
Liberación inmediata	Gránulos	Propranolol	Propranolol oleato	58

Entre otras tras publicaciones que revelan la aplicación de esta técnica de granulación, y que contienen algunos de los mismos principios activos mencionados en la solicitud colombiana, se encuentran la publicación internacional WO2007/084212 publicada el 26 de julio de 2007 (ejemplo 1 y reivindicaciones); la publicación internacional WO/2004/098574 publicada el 18 de noviembre de 2004 (ejemplo 1 y reivindicaciones); la publicación internacional WO/2007/034135 publicada el 29 de marzo de 2007 (tabla 1, ejemplo1 y reivindicaciones); la patente americana US 6,787,157 publicada el 07 de septiembre de 2004 (ejemplo 1) y la publicación internacional WO1993/11749 publicada el 24 de junio de 1993 (ejemplo 1 y reivindicaciones).

Por ejemplo la publicación internacional WO 1993/011749 de 24/06/1993 y titulada "PROCESS FOR THE PREPARATION OF A SOLID DISPERSION" expone lo siguiente:

¹¹ Lourdes OCHOA D.1, Manuela IGARTUA O.1, Rosa Mª HERNÁNDEZ M.1, Alicia R. GASCÓN1 y José L. PEDRAZ M. GRANULACIÓN POR FUSIÓN EN MEZCLADORES GRANULADORES DE ALTA VELOCIDAD. VITAE, REVISTA DE LA FACULTAD DE QUÍMICA FARMACÉUTICA ISSN 0121-4004 Volumen 13 número 1, año 2006. Universidad de Antioquia, Medellín - Colombia. págs. 40-47.

1. A process for the preparation of a poorly water soluble drug in solid dispersion comprising
 - a) blending the drug with a carrier;
 - b) dissolving a surfactant and a plasticizer/solubilizer in water;
 - c) spraying the surfactant-plasticizer/solubilizer solution onto the drug/carrier mixture in a fluid bed granulator;
 - d) extruding the resulting granulation through a twin screw extruder with at least one heating zone; and,
 - e) milling the extrudate to a powdery mass of the solid drug dispersion.

2. The process of claim 1 wherein said drug is selected from the group consisting of acetohexamide, ajamaline, amylobarbitone, bendrofluoside, benzbromarone, benzonatate, benzylbenzoate, betamethazone, chloramphenicol, chlorpropamide, chlorthalidone, clofibrate, corticosteroids, diazepam, dicumerol, digitoxin, dihydroxypropyltheophylline, ergot alkaloids, ethotoin, frusemide, glutethimide, griseofulvin, hydrochlorothiazide, hydrocortisone, hydroflumethiazide, hydroquinone, hydroxyalkylxanthines, indomethacin, isoxsuprine hydrochloride, ketoprofen, khellin, meproamate, nabilone, nicotainamide, nifedipine, nitrofurantoin, novalgin, nystatin, papaverine, paracetamol, phenylbutazone, phenobarbitone, prednisolone, prednisone, primadone, reserpine, romglizone, salicylic acid, spiranolactone, sulphabenzamide, sulphadiazine, sulphamethoxydiazine, sulphamerazine, succinylsulphathiazole, sulphamethizole, sulphamethoxazole, sulphathiazole, sulphisoxazole, testosterone, tolazoline, tolbutamide, trifluoperazine, trimethaprim and mixtures thereof.

Por su parte la publicación internacional WO 2004/098574 de 18/11/2004 y titulada "NANOCOMPOSITE DRUG DELIVERY COMPOSITION" expone:

Polyethylene glycol (PEG) 20000 (Janssen Pharmaceuticals) was the polymer employed and Cloisite 30B (Southern Clay Products, USA) was the clay component. Paracetamol (Sigma, UK) was used as a model active ingredient. Production of the nanocomposites was performed by melt extrusion using a Killon KN-100 (Davis Standard Corporation, USA) single screw extruder with rod shaped die (38 mm screw diameter, speed 20-22 rpm, die temp 54-57 °C, temperature zone 1 50 °C - temperature zone 2 55-60 °C - temperature zone 3 55-60 °C - temperature zone 4 55-60 °C, haul off speed 3-4 m/min, cool to room temperature). The powders were not subjected to any treatments prior to extrusion, other than simple mixing of the three components simultaneously.

(...)

16. A method of manufacturing a drug delivery composition comprising the steps of forming an admixture comprising a polymer, a clay and an active ingredient and extruding the admixture to produce an extrudate.

Finalmente podemos también exponer apartes de la publicación internacional WO 2007/034135 de 29/03/2007 y titulada "COMPOSITION COMPRISING A NSAID AND PARACETAMOL", veamos:

Example 1(a): Preparation of the Granular Component

The process for all illustrative examples involves dry blending the paracetamol and NSAID free acid, optionally with other excipients which may be present in the granular component, and then heating the mixture at a temperature of 100 to 165°C in an extruder to melt the NSAID free acid fully and thereby mix the molten NSAID with the paracetamol and other optional excipients. The molten mass is poured onto cooled stainless steel trays or a cooled moving belt at 10 °C and allowed to cool. The molten mixture typically solidifies within 60 seconds; the mixture may be agitated during cooling. The solid mass thus formed is milled by passing through a cone mill having a screen with a round hole of 1mm. The resulting granules are collected.

Example 1(b): Preparation of a tablet

The respective extra-granular components (shown in normal text in Tables 1, 2 and 4), namely, colloidal silicon dioxide, magnesium stearate, stearic acid, lactose, dicalcium phosphate and microcrystalline cellulose are blended simultaneously with the granular composition formed from Example 1(a) above for approximately 15 minutes in a blender. The dry blended material was fed to a rotary tableting machine (Fette P1200) and compressed into tablets (machine speed of 100,000 tablets per hour and compaction force of from 6 kN to 25 kN) containing a therapeutic dose of NSAID drug and paracetamol.

(...)

1. A process for producing a granular composition comprising a plurality of solidified melt granules including a non-steroidal anti-inflammatory drug (NSAID) and paracetamol, the process comprising the steps of:
 - (a) forming a melt mixture by mixing a molten NSAID free acid and paracetamol, optionally with one or more excipients; and
 - (b) forming the melt mixture into solidified melt granules.

Así mismo existen infinidad de publicaciones que hacen referencia a este proceso de granulación por fusión, y que aunque no involucren los mismos principios activos que la solicitud colombiana en cuestión, son una clara guía para llegar a las formulaciones propuestas por dicha solicitud, veamos:

Las publicaciones científicas:

- ❖ Melt Granulation in A Laboratory Scale High Shear Mixer.
- ❖ Preparation and characterisation of ibuprofen-poloxamer 188 granules obtained by melt granulation.
- ❖ Formulation design of carbamazepine fast-release tablets prepared by melt granulation technique.
- ❖ The Control of Drug Release from Conventional Melt Granulation Matrices.
- ❖ Preparation and evaluation of diltiazem hydrochloride-gelucire 43/01 floating granules prepared by melt granulation.
- ❖ Alternative Granulation Technique: Melt Granulation.

Los documentos de patente de invención:

- ❖ JP59022640A2: METHOD AND APPARATUS FOR MELT GRANULATION.
- ❖ US5,403,593: Melt granulated compositions for preparing sustained release dosage forms.
- ❖ WO9509044A1: MELT GRANULATION WITH DIELECTRIC HEATING.
- ❖ US5,718,923: Melt granulated sucralfate preparations and a process for their production.
- ❖ WO00/69415A2: MELT GRANULATION.

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.

II. ANEXOS

Ruego que se tenga como tal, sin perjuicio de aquellas que el Despacho considere oficiosamente, las siguientes:

- Abstracts de todas las publicaciones científicas mencionadas en el acápite de Fundamentos de la Oposición.
- Portadas y capítulos reivindicatorios de todos los documentos de patente de invención mencionados en el acápite de Fundamentos de la Oposición.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén
T.P.A. 44.655 de C.S.J.



Home

Journals

Books

Resources

Services

Subscribe

Username:

Password:

Login

Register

Athens

Shibboleth

Drug Development and Industrial Pharmacy

Advanced Search

Go

All Books and Journals

Home

All Issues

Current Issue

Early Online

Aims & Scope

Editorial Board

Instructions for Authors

Publish in as little as 5 weeks with

Drug Development & Industrial Pharmacy

Request a Trial



Email Content Alerts



Why publish with us

observation cannot
have ITT-LOCF result
the observed case (O
the LOCF population,

Issue TOC | Next Article

Melt Granulation in A Laboratory Scale High Shear Mixer

1990, Vol. 16, No. 8 , Pages 1249-1277 (doi:10.3109/03639049009115960)

T. Schaefer, P. Holm and H. G. Kristensen
Department of Pharmaceutics, Royal Danish School of Pharmacy
Universitetsparken 2, DK-2100, Copenhagen, Denmark

PDF (1065 KB)

PDF Plus (445 KB)

Reprints

Permissions

Abstract

The applicability of a 10 litre high shear mixer for melt granulation of dicalcium phosphate and lactose is examined. Polyethylene glycol (PEG) 3000 and 6000 were used as melting binders in concentrations of 15-20% w/w. The effects of binder concentration, massing time, impeller speed, and particle size of the PEG 6000 on granule size, granule size distribution and intragranular porosity are investigated.

It is shown that pellets of a narrow size distribution can be produced by the use of a high impeller speed. Granule size and size distribution are markedly influenced by binder concentration and massing time. The particle size of the PEG has only a minor effect on the granule growth. Granule growth mechanisms by melt granulation are discussed on the basis of the liquid saturations and the amounts of binder liquid and are compared with previous results on wet granulation.

PDF (1065 KB) | PDF Plus (445 KB) - What is PDF Plus?

Authors

Submit an Article

Journal Info

Rights

Permissions

Reprints

Custom Publishing



Information for Librarians



Quick Links



Add to Favourites

Download Citations

Email TOC Alert

Related Articles

RSS TOC Alerts

Email Citation Alert

Users Also Read

Reduced and total ascorbate in guinea pig eye tissues in response to dietary intake

Behaviour Completion Mechanisms, Anxiety and Agoraphobia

Metacarpophalangeal Joint Implants: I. Roentgenographic Study on the Silastic® Finger Joint Implant, Swanson Design

More »

Authors

T. Schaefer

P. Holm

H. G. Kristensen

Forward Citations

Lipid-based oral multiparticulate formulations – advantages, technological advances and industrial applications

Formulation of Ketotifen Fumarate Fast-Melt Granulation Sublingual Tablet

Encapsulation and characterization of controlled release flurbiprofen loaded microspheres using beeswax as an encapsulating agent

More

Purchase



Informa Healthcare offers a unique range of publishing formats.

Buy Now

2

Journals

- View All Journals
- Expert Opinion on:
 - Biological Therapy
 - Drug Delivery
 - Drug Discovery
 - Drug Metabolism & Toxicology
 - Drug Safety
 - Emerging Drugs
 - Investigational Drugs
 - Medical Diagnostics
 - Pharmacotherapy
 - Therapeutic Patents
 - Therapeutic Targets
- Current Medical Research and Opinion

Books

- View All Books
- Online Books
- Online Book Collections
- Encyclopedias and Major Reference Works
- Submit Proposal
- Custom Books
- Resource
 - For Authors & Editors
 - For Readers
 - For Librarians
 - For Consortia
 - For Advertisers

Services

- Healthcare Communications
- CME-CPD
- Pre-publication Support
- Reprints and ePrints
- Permissions
- Supplements
- Drug/Clinical Trial Evaluations
- Corporate Books
- Foreign Rights
- Advertising
- Alerting Services
- Manuscript Submission
- Contacts

About Us

- Privacy policy
- Terms & Conditions
- Feedback / Contact Us
- FAQ
- Informa PLC

Jobs

- Advertise
- Subscribe



Copyright © 2010 Informa Plc. All rights reserved.

This site is owned and operated by Informa plc ("Informa") whose registered office is Mortimer House, 37-41 Mortimer Street, London, W1T 3JH. Registered in England and Wales. Number 3099067. UK VAT Group: GB 365 4626 36

PubMed

Display Settings: Abstract

ELSEVIER
FULL-TEXT ARTICLEEur J Pharm Sci. 2002 Feb;15(1):71-8.**Preparation and characterisation of ibuprofen-poloxamer 188 granules obtained by melt granulation.**Passerini N, Albertini B, González-Rodríguez ML, Cavallari C, Rodriguez L.Dipartimento di Scienze Farmaceutiche, Università degli Studi di Bologna, Via S. Donato 19/2, 40127 Bologna, Italy.
passerin@biocfarm.unibo.it**Abstract**

The aim of this study was to prepare, by melt granulation, granules containing ibuprofen as a poorly water soluble model drug in order to improve its dissolution rate and its availability; lactose as a diluent and poloxamer 188 (Lutrol F68), as a new meltable hydrophilic binder, were used. The granules were prepared in a laboratory-scale high-shear mixer, using a jacket temperature of 50 degrees C and an impeller speed of 500 rpm. The particle size analysis shows that the main fraction was between 200 and 500 microm, while the determination of drug content indicated that ibuprofen was quite uniformly distributed in all the fractions. Scanning Electron Microscopy (SEM), image and fractal analysis revealed that the granules did not have a perfect spherical shape and a rugged surface ($D(s)=2.6475$). The in vitro dissolution tests showed an increase in the dissolution rate of granules compared to pure drug and physical mixture. The characterisation of the samples, performed by Differential Scanning Calorimetry (DSC) and X-ray powder diffraction (XRD), suggests that the improvement of dissolution rate could be correlated to the formation of a eutectic mixture between the drug and the binder. Stability studies indicated that the granule properties do not change, at least after 1 year of storage at 25 degrees C. In conclusion, the results of this work suggest that the melt granulation technique is an easy and fast method to improve the dissolution rate of ibuprofen, using poloxamer 188 as a new hydrophilic meltable binder.

PMID: 11803133 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances**LinkOut - more resources**

PubMed

Display Settings: Abstract

ELSEVIER
FULL-TEXT ARTICLEInt J Pharm. 2003 Apr 30;256(1-2):53-63.**Formulation design of carbamazepine fast-release tablets prepared by melt granulation technique.**Perissutti B, Rubessa F, Moneghini M, Voinovich D.Department of Pharmaceutical Sciences, University of Trieste, Piazzale Europa 1, 34127, Trieste, Italy. beatriceperissutti@hotmail.com**Abstract**

This work describes a new approach to prepare a fast-release dosage form for carbamazepine (CBZ), involving the use of melt granulation process in high shear mixer for the production of tablets. In particular, the granules containing CBZ were prepared using polyethylene glycol (PEG) 4000 as a melting binder and lactose monohydrate as a hydrophilic filler. The potential of the intragranular addition of crospovidone as a dissolution enhancer and a disintegrant agent was also evaluated. After the analysis of their solid state performed by means of X-ray powder diffraction (XRD) and differential scanning calorimetry (DSC), the granules were characterised from the technological and dissolution point of view. The subsequent step encompassed the preparation and the evaluation of the tablets, including the effect of the extragranular introduction of crospovidone. Besides the remarkable enhancement of drug dissolution rate of the granulates in comparison to physical mixtures and pure drug, no significant differences were found between the dissolution profiles of the granulates containing lactose or crospovidone. However, the difficult disintegration and bad dissolution performance of the tablets not containing intragranular crospovidone highlight the necessity of this disintegrant in the granulating mixture. Moreover, the extragranular addition of a small amount of crospovidone gave rise to a further amelioration of the disintegration and dissolution performances.

PMID: 12695011 [PubMed - indexed for MEDLINE]

MeSH Terms, Substances**LinkOut - more resources**

15



Home

Journals

Books

Resources

Services

Subscribe

Username:

Password

Login

Register

Athens

Shibboleth

Advanced Search

Go

All Books and Journals

Drug Development and Industrial Pharmacy

Home

All Issues

Current Issue

Early Online

Aims & Scope

Editorial Board

Instructions for Authors

Publish in as little as 5 weeks with



Drug Development & Industrial Pharmacy

Request a Trial



Email Content Alerts



Why publish with us

observation cannot have ITT-LOCF results observed case (O) LOCF population

Issue TOC | Previous Article | Next Article

The Control of Drug Release from Conventional Melt Granulation Matrices

1987, Vol. 13, No. 6 , Pages 1001-1022 (doi:10.3109/03639048709068366)

P. Flanders, G. A. Dyer and D. Jordan

Pharmaceutical Development Department, Hoechst UK Ltd., Walton Manor, Walton, Milton Keynes, Buckinghamshire, MK7 7AJ
Process Development, Roussel Laboratories Ltd., Kingfisher Drive, Covingham, Swindon, Wiltshire

PDF (622 KB)

PDF Plus (319 KB)

Reprints

Permissions

Quick Links



Add to Favourites

Download Citations

Email TOC Alert

Related Articles

RSS TOC Alerts

Email Citation Alert

Users Also Read

Indications for aspirin as a palliative for tinnitus caused by SOAEs: A case study

Methotrexate in the treatment of ankylosing spondylitis

An intra-oral access device

More »

Authors

P. Flanders

G. A. Dyer

D. Jordan

Forward Citations

Preparation of sustained release matrix pellets by melt agglomeration in the fluidized bed: Influence of formulation variables and modelling of agglomerate growth

Application of melt granulation technology to enhance stability of a moisture sensitive immediate-release drug product

Effect of Formulation and Processing Variables on the Granulation Kinetics of Hot Melt Granulation (HMG) Process

More

Purchase



Informa Healthcare offers a unique range of publishing formats.

Buy Now

Authors

Submit an Article

Journal Info

Rights

Permissions

Reprints

Custom Publishing



Information for Librarians



66

Journals

View All Journals

Expert Opinion on:
Biological Therapy
Drug Delivery
Drug Discovery
Drug Metabolism & Toxicology
Drug Safety
Emerging Drugs
Investigational Drugs
Medical Diagnostics
Pharmacotherapy
Therapeutic Patents
Therapeutic Targets

Current Medical Research
and Opinion

Books

View All Books

Online Books
Online Book Collections

Encyclopedias and
Major Reference Works

Submit Proposal

Custom Books

Resource

For Authors & Editors

For Readers

For Librarians

For Consortia

For Advertisers

Services

Healthcare
Communications

CME-CPD

Pre-publication Support

Reprints and ePrints

Permissions

Supplements

Drug/Clinical Trial
Evaluations

Corporate Books

Foreign Rights

Advertising

Alerting Services

Manuscript Submission

Contacts

About Us

Privacy policy

Terms & Conditions

Feedback / Contact Us

FAQ

Informa PLC

Jobs

Advertise

Subscribe



Copyright © 2010 Informa Plc. All rights reserved.

This site is owned and operated by Informa plc ("Informa") whose registered office is Mortimer House, 37-41 Mortimer Street, London, W1T 3JH. Registered in England and Wales. Number 3099067. UK VAT Group: GB 365 4626 36

Preparation and Evaluation of Diltiazem Hydrochloride-Gelucire 43/01 Floating Granules Prepared by Melt Granulation

Submitted: February 3, 2004; Accepted: July 12, 2004.

Shyam Shimpi,¹ Bhaskar Chauhan,¹ K. R. Mahadik,¹ and Anant Paradkar¹

¹Department of Pharmaceutics, Bharati Vidyapeeth Deemed University, Poona College of Pharmacy, Erandawane, Pune-411 038, Maharashtra, India.

ABSTRACT

The basic objective of this study was to explore the application of Gelucire 43/01 for the design of multi-unit floating systems of a highly water-soluble drug diltiazem HCl. Diltiazem HCl-Gelucire 43/01 granules were prepared by melt granulation technique. The granules were evaluated for in vitro and in vivo floating ability, surface topography, and in vitro drug release. Aging effect on storage was evaluated using scanning electron microscopy, hot stage polarizing microscopy (HSPM), differential scanning calorimetry (DSC), and in vitro drug release. Granules were retained in stomach at least for 6 hours. Approximately 65% to 80% drug was released over 6 hours with initial fast release from the surface. Surface topography, HSPM, DSC study of the aged samples showed phase transformation of Gelucire. The phase transformation also caused significant increase in drug release. In conclusion, hydrophobic lipid, Gelucire 43/01, can be considered as an effective carrier for design of a multi-unit floating drug delivery system of highly water-soluble drugs such as diltiazem HCl.

KEYWORDS: multi-unit lipid granules, floating, diltiazem hydrochloride, Gelucire, aging.

INTRODUCTION

Rapid gastrointestinal transit could result in incomplete drug release from the device above the absorption zone leading to diminished efficacy of the administered dose.¹ Therefore different approaches have been proposed to retain the dosage form in the stomach. These include bioadhesive systems,² swelling and expanding systems,^{3,4} and floating systems.^{5,6} Large single-unit dosage forms undergo significant swelling after oral administration, and the swollen matrix inhibits the gastric emptying even at an uncontractile state of the pyloric sphincter. Park and Park reported medicated polymeric sheets and swelling of balloon hydrogels.⁷ But the swelling

and expanding systems may show hazard of permanent retention. Bioadhesive systems may cause problems such as irritation of the mucous layer owing to high localized concentration of the drug.⁸ Hydrodynamically balanced systems, designed using effervescent mixtures, have achieved commercial success but require a high drug:excipient ratio, have unpredictable bioavailability, and are unsuitable for drugs degrading in basic pH due to the alkaline microenvironment. The single-unit systems such as tablet or capsule may exhibit the all-or-none emptying phenomenon, which may be overcome by the design of multi-unit systems.⁹ The multi-unit dosage forms such as pellets and granules may be more suitable because they claim to reduce the intersubject variability in absorption and lower the probability of dose dumping.¹⁰ Many lipid-based sustained release matrix systems are reported in literature.¹¹⁻¹⁴ Recently, Kiran Kumar et al reported floating glycerol monooleate (GMO) single-unit lipid matrix containing high drug:excipient ratio (1:30) to achieve sustained drug release.¹⁵

Gelucires are a family of vehicles derived from mixtures of mono-, di-, and triglycerides with polyethylene glycol (PEG) esters of fatty acids. Gelucires are available with a range of properties depending on their Hydrophilic Lipophilic Balance (HLB 1-18) and melting point (33°C-65°C) range.^{16,17} The Gelucires containing only PEG esters (Gelucire 55/18) are generally used in preparation of fast release formulations, while Gelucires containing only glycerides or a mixture of glycerides and PEG esters (Gelucire 54/02, 50/13, 43/01) are used in preparation of sustained release formulations.^{11,18} Sutananta et al reported sustained release single unit matrices using Gelucire 43/01, where only 1.7% theophylline was released over a period of 20 hours.¹⁹

Thus, the major objective of the present study was to design floating sustained release granules with a low drug:lipid ratio. In order to achieve lower drug to excipient proportion and floating ability, the hydrophobic grade of lipid excipient Gelucire (Gelucire 43/01) was selected. Diltiazem HCl (DTZ), a model drug for this study, is a calcium antagonist used in the treatment of chronic heart diseases such as angina and hypertension. It has elimination half-life of 3.5 hours. Therefore, it is a suitable model candidate for gastro-retentive formulation. High solubility of DTZ is a major challenge in designing its controlled drug delivery system. The extreme

Corresponding Author: Anant Paradkar, Department of Pharmaceutics, Bharati Vidyapeeth Deemed University, Poona College of Pharmacy, Erandawane, Pune-411 038, Maharashtra, India. Tel: +91-20-25437237. Fax: +91-20-25439383. Email: arparadkar@rediffmail.com.

release retarding ability of Gelucire 43/01 may be exploited to overcome this problem. In the present study, DTZ-Gelucire 43/01 floating granules were prepared by melt granulation and were evaluated with respect to in vitro and in vivo floating ability, drug content, surface topography, and in vitro drug release. Effect of aging on the granules was studied using hot stage polarizing microscopy (HSPM), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and in vitro drug release.

MATERIALS AND METHODS

Materials

Gelucire 43/01 (waxy solid, melting point (mp) 43°C, HLB = 01, lot no. 0E4404-2) was a generous gift from Gattefosse (St Priest, Cedex, France). Glyceryl monostearate (GMS, MGS-F 75, white to yellow beads, mp 64°C, HLB = 1.5, lot no. 2054) was kindly supplied by Nikko Chemical Co Ltd (Tokyo, Japan). Methocel K4M (HPMC, lot no. 0G08012N31) and Ethocel 20 FP (EC) were kindly supplied by Colorcon Asia Pvt Ltd (Mumbai, India). Sterotex NF (hydrogenated cotton seed oil, white solid powder, mp 61.4°C, HLB = 1.5, lot no. 065M3NF) was supplied by Abitec Corp (Jenesville, WI). Diltiazem HCl was a kind gift from Sun Pharmaceuticals Ltd (Mumbai, India). All other chemicals were of analytical grade.

Methods

Preparation of Floating Granules

Floating granules containing DTZ were prepared using the melt granulation technique. The drug:lipid ratios used to prepare the different formulations were 1:1, 1:1.3, and 1:1.5. To study the effect of additives of different sustaining agents such as HPMC, EC, Sterotex, and GMS were added separately to the formulations. The proportion of additives was 0.5 parts for HPMC and EC, whereas it was 0.25 parts for Sterotex and GMS. Lipid was melted at 50°C, and the drug or drug and additives mixture was added, mixed well, and cooled to room temperature. The mass was passed through a 510- μ m sieve to obtain uniform-sized granules.

Drug Content and Percentage Yield

Ten milligrams of floating granules were added to 10 mL of distilled water, heated to 60°C to 70°C, and allowed to cool to room temperature. The lipid was solidified and the drug solution was filtered through Whatman No. 1 paper (Whatman plc, Middlesex, UK). The sample was analyzed for drug content by UV spectrophotometry (Jasco V530, Tokyo, Japan) at 236.4 nm after suitable dilutions. Drug stability in the dissolution medium and distilled water was checked for a period of 8 hours. Determinations were per-

formed in triplicate. Percentage yield of each formulation was calculated.

Surface Topography

The surface of the drug and granules were coated with a thin gold-palladium layer by sputter coater unit (VG-Microtech, Uckfield, East Sussex, UK) and the surface topography was analyzed with a Cambridge Stereoscan S120 SEM (Cambridge, UK) operated at an acceleration voltage of 5 kV.

Floating Characteristics

In Vitro Evaluation of Floating Ability

Fifty unit granules were placed in 900 mL of distilled water and United States Pharmacopeia (USP) simulated gastric fluid (pH 1.2) in a vessel maintained at 37°C $\pm$ 0.2°C and stirred at 50 and 100 rpm in a USP 24 type II dissolution test apparatus (Electrolab TDT-06P, Mumbai, India). The percentage of floating granules up to 6 hours was determined, and the floating times were measured by visual observation.¹

γ -Scintigraphy

In vivo floating ability was studied by γ -scintigraphy in 6 healthy human volunteers of aged 25 to 30 years and having 55 to 65 kg total body weight. They were nonalcoholic, non-smokers, and were not taking any other medication. The volunteers were asked to swallow the capsules filled with granules (drug:lipid, 1:1.5) containing radiolabeled technetium (^{99m}Tc) along with 100 mL water after taking a light breakfast in the morning. The dosage form was visualized using a gamma camera (GE Millennium MPR Gamma Camera, Israel). Images were taken at 0 hours, 1 hour, 2 hours, 4 hours, and 6 hours. Volunteers were in supine position during imaging.

In Vitro Release Studies

The release of drug from the granules containing different drug to lipid proportions (1:1, 1:1.3, and 1:1.5) was investigated in triplicate. Studies were performed in USP 24 type II dissolution test apparatus with the agitation speed of 100 rpm in USP simulated gastric fluid (pH 1.2) maintained at 37°C $\pm$ 0.2°C. At appropriate time intervals, samples were withdrawn and assayed spectrophotometrically at 236.4 nm with suitable dilutions. Analysis of data was done using PCP Disso v 2.08 software (Pune, India).²⁰

Effect of Aging

Effect of aging was studied by HSPM, SEM, DSC, and in vitro drug release.

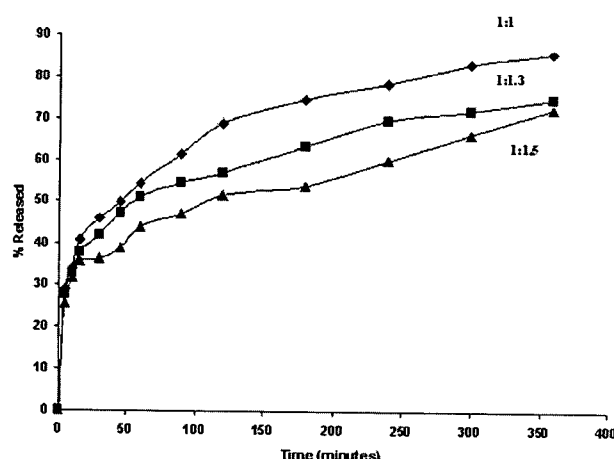


Figure 1. Release profiles of diltiazem hydrochloride from the granules showing the effect of increasing the drug:Gelucire ratios.

Hot Stage Polarizing Microscopy

HSPM was conducted using Mettler Toledo FP82HT hot stage (Greifensee, Switzerland) assembled on Leica DMLP polarizing microscope equipped with Leica MPS-30 camera (Leica, Bensheim, Germany). Untreated, freshly prepared and aged samples were observed under the microscope at scanning speed of 2°C/min. Changes in the samples morphology (melting-crystallization) were noted as a function of temperature. Three types of samples were prepared for the physical evaluation of granules.

1. Freshly solidified samples. Placebo granules were prepared and stored for 6 hours at room temperature in order to avoid effects due to the thermal history.
2. Aged samples. Placebo granules were stored up to 1 month at room temperature (25°C; 60% relative humidity) in order to detect any physical changes (structural or polymorphic) on aging associated with glyceride bases.
3. Untreated samples. Base without any special treatment (as received from supplier).

Differential Scanning Calorimetry

Thermograms of granules were obtained using a Mettler-Toledo DSC 821^e instrument equipped with an intracooler. Indium/zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample of granules were hermetically sealed in an aluminum pan and heated at a constant rate of 10°C/min, over a temperature range of 25°C to 65°C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50 mL/min.



Figure 2. SEM images of (A) diltiazem hydrochloride, original magnification × 199; (B) melt granules, × 73; (C) fresh sample, × 1120; and (D) aged sample, × 1020.

Scanning Electron Microscopy

Surface of the fresh and aged samples were observed by SEM to study the ageing effect.

In Vitro Release

Effect of aging on drug release was studied on samples aged for 10 days and 30 days by the in vitro release method described for fresh samples.

RESULTS AND DISCUSSION

Yield and drug content of the granules were found to be in the range of 95% to 99% and 98% to 102% wt/wt, respectively. In all the formulations (without any additives), 94% to 98% granules were found to float up to 6 hours. No significant difference was observed in the floating ability of granules containing different proportions of Gelucire. But drug release was retarded significantly with increase in the amount of Gelucire (Figure 1). All 3 drug:lipid ratios showed burst release in the initial stage, but increase in lipid ratio above 1:1.5 caused significant retardation, making it unsuitable for gastroretentive release, where complete drug release is expected to occur within the gastric residence period of 6 to 8 hours. The granules containing drug to lipid ratio 1:2 parts by weight showed significant release retardation, as less than 50% drug was released in 6 hours. Hence, the higher level of lipid in this study was restricted to 1.5 parts, and granules containing drug:lipid 1:1.5 were used for further evaluation. The SEM photomicrograph of the granules showed presence of lipid on the surface (Figure 2A-C). There was no effect of agitation speed on floating ability (data not shown). All the formulations floated for more than 6 hours except the formulation containing GMS. The γ -scintigraphy study of the floating granules in

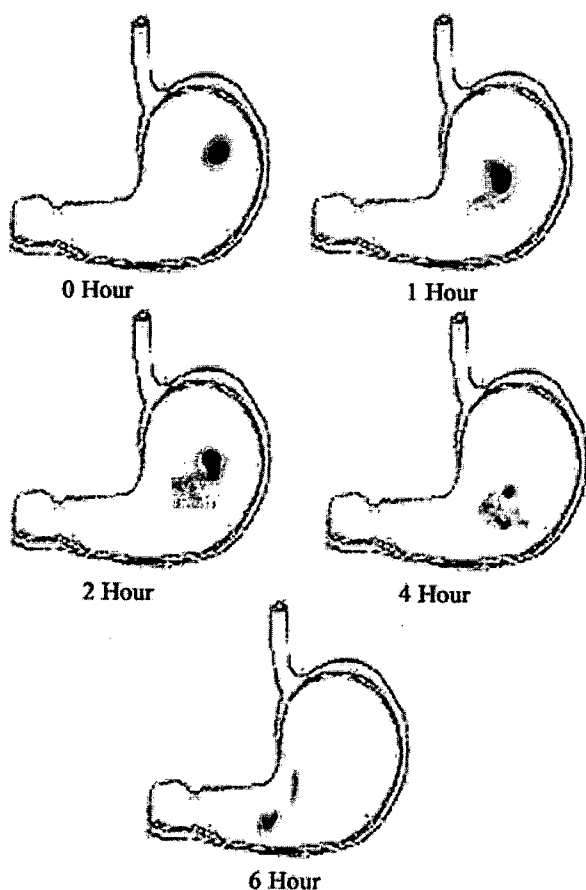


Figure 3. Gamma scintigraphs showing floating ability of diltiazem hydrochloride:lipid granules (1:1.5) in stomach.

human volunteer showed that the formulation remains in the stomach for ~6 hours (Figure 3). Drug release profiles in 0.1 N HCl are shown in Figure 1. It was observed that as the amount of lipid increased, the drug release decreased.

As an attempt to reduce initial drug release GMS, HPMC, EC, and Sterotex were evaluated as release-retardant additives. Surprisingly, the granules containing Gelucire:GMS (1:0.25) did not float despite low HLB of GMS. Whereas, granules containing Sterotex and HPMC floated but showed faster release of drug as compared with plain drug:Gelucire granules. Many workers have reported increased drug release owing to addition of hydrophilic excipient to lipid carriers.²¹⁻²³ Granules containing Gelucire:EC mixture (1:0.5) have shown significant retardation of drug release without hampering the floatability. The surface hydrophobicity imparted to the drug particle by the hydrophobic lipid coat was responsible for floating behavior. But all low HLB excipient did not ensure floating, as similar granules prepared using Compritol and GMS separately did not show floating property. Therefore, apart from hydrophobicity, density also plays an important role in design of floating granules using lipophilic excipient.

The SEM photomicrographs of fresh and aged granules are shown in Figure 2C and D. The SEM photomicrograph of

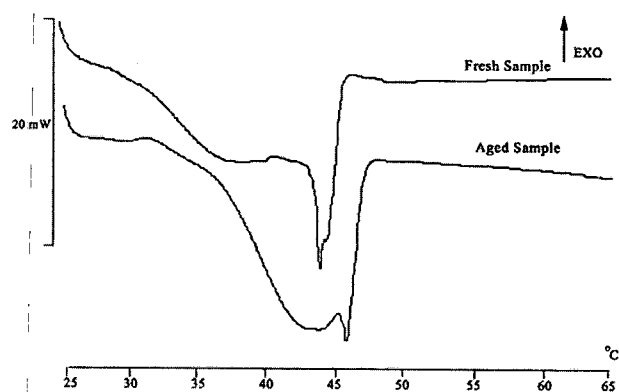


Figure 4. DSC thermograms of granules: fresh sample (0 day) and aged samples (30 days; Room Temperature).

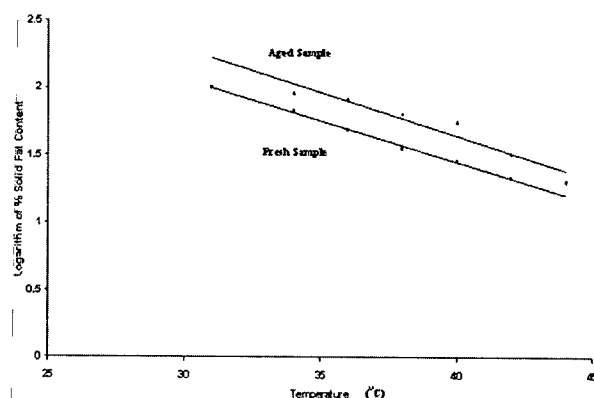


Figure 5. Semi-log solid fat content as a function of temperature of Gelucire 43/01.

surface of the fresh granules did not show any crystalline structure but showed smooth patches of lipid on the surface. After aging, sample showed significant change in the surface, possibly owing to phase transformation.

Thermograms of fresh and aged samples have shown significant difference. Enthalpy of fusion (ΔH_f) increased significantly upon aging (Figure 4). The average ΔH_f of fresh sample was 124.48 J/g, which increased to 130 J/g during aging. The glycerides melted over a narrow temperature range in the aged sample as compared with the fresh one. In the fresh sample, melting onset occurred at a temperature significantly lower than the aged sample, whereas end set temperature was slightly higher in aged sample. Aged sample showed a sharp shoulder at 45.6°C.

As the endotherm area is proportional to the solid content, DSC data was converted in terms of solid fat content. A semi-log plot of solid fat content versus temperature is shown in Figure 5. The data fitted well in following model

$$\% \text{ Solid content} = Me^{-Bt} \quad (1)$$

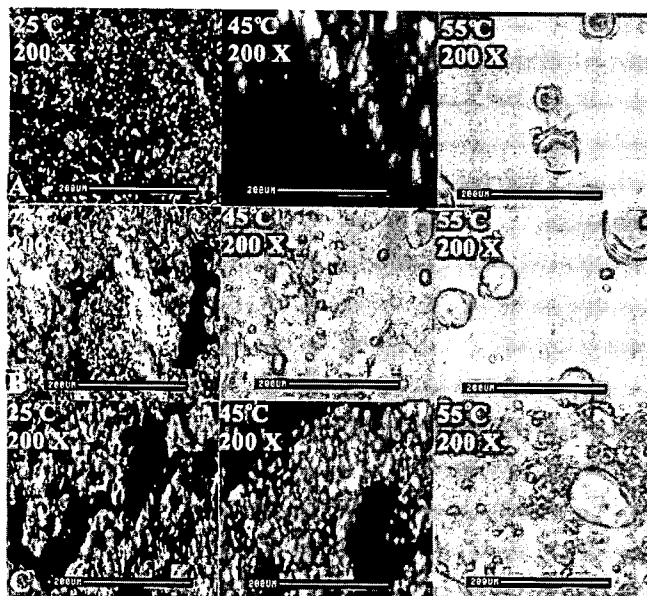


Figure 6. HSPM photomicrographs of Gelucire 43/01: (A) untreated samples; (B) freshly prepared placebo granules; and (C) aged placebo granules.

Where M and B are constant, M and B reflect initial solid content and rate of decrease in solid content respectively. Thus, logarithmic decrease occurred in the solid content in both the samples. Significant differences existed in the slopes of semi-log plots and were found to be 0.061 and 0.052 for fresh and aged samples, respectively. This finding indicated that rate of decrease in solid content was significantly higher in the fresh sample as compared with the aged sample. The similar observation was reported by Sutananta et al.²⁴

HSPM photomicrographs of untreated, fresh and aged placebo samples are shown in Figure 6. It has been observed that complete melting of the Gelucire occurs at 45°C. HSPM photomicrograph showed presence of some unmelted portion even at 45°C in aged sample. Similarly, DSC data analysis showed that 71.5% glycerides melted up to 40°C in fresh samples as compared with 44.6% in aged samples (Figure 5). The energy required for melting increased with aging, which might be attributed to phase transformation due to crystallization of glycerides during aging. This slow crystallization of glycerides may be responsible for phase transformation, showing surface roughness.

Dissolution profiles of granules on aging (after 10 and 30 days) are shown in Figure 7. Drug release increased significantly on aging, which might be attributed to the phase transformation. About 94% to 98% of granules floated up to 6 hours; hence floating ability of the granules was not affected by aging. Initial fast release was owing to the dissolution of drug from the surface, after which release followed zero order kinetics, which may be owing to a noneroding lipid coat on the granule surface. Drug release kinetics were not

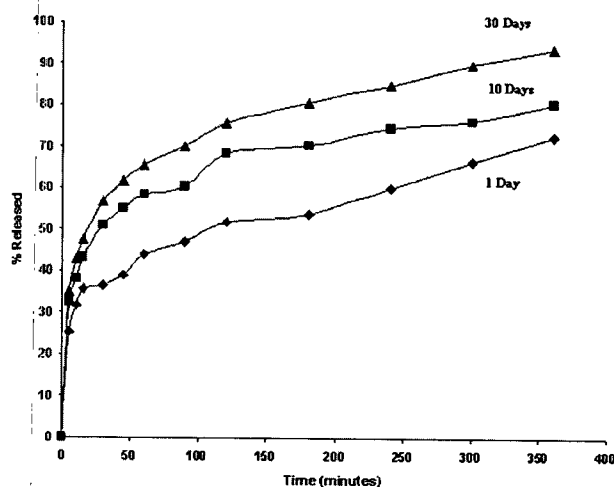


Figure 7. Release profiles of diltiazem hydrochloride from granules (1:1.5) showing effect of aging.

affected by aging. Studies using Gelucires 50/13 and 55/18 have shown similar effects on aging. Sutananta et al studied effect of preparation conditions, drug:Gelucire ratio, and storage on theophylline release from Gelucire 50/13 and 55/18 molded tablets and reported increase in drug release on aging.²⁵ It was attributed to changes in physical structure and chemical composition during aging. Roussin and Duddu attributed the increase in release to the development of surface cracks caused by phase transformation during aging.²⁶ The detailed study about mechanism of changes during aging and its stabilization may further widen the scope of this application.

CONCLUSION

It may be concluded that hydrophobic lipid, Gelucire 43/01, can be considered as an effective carrier for the design of a multi-unit floating drug delivery system of highly water-soluble drugs like diltiazem HCl.

ACKNOWLEDGEMENTS

Anant R. Paradkar and Bhaskar Chauhan are thankful to University Grant Commission (UGC) and Council of Scientific and Industrial Research (CSIR), New Delhi, India, for providing financial support in form of major research project and Senior Research Fellowship respectively. Shyam Shimpi is thankful to Gattefosse, France, and Colorcon, India for the financial support. Authors are thankful to Gattefosse, France, and Colorcon, India for the gift samples. Authors are also grateful to Dr Shrikant Solav, Spect-Lab, Pune, India, and Dr Yuvraj S. Negi, CMET Lab, Pune, for providing the facilities of gamma scintigraphy and hot stage polarizing microscopy facilities, respectively.

REFERENCES

1. Iannuccelli V, Coppi G, Bernabei MT, Camerani R. Air compartment multiple-unit system for prolonged gastric residence. Part I. Formulation study. *Int J Pharm*. 1998;174:47-54.
2. Santus G, Lazzarini G, Bottoni G, et al. An *in vitro-in vivo* investigation of oral bioadhesive controlled release furosemide formulations. *Eur J Pharm Biopharm*. 1997;44:39-52.
3. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled-release drug delivery systems for prolonged gastric residence: an overview. *Drug Dev Ind Pharm*. 1996;22:531-539.
4. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled-release system for gastric retention. *Pharm Res*. 1994;11:815-819.
5. Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. *J Pharm Sci*. 1994;83:239-245.
6. Whitehead L, Fell JT, Collett JH, Sharma HL, Smith AM. Floating dosage forms: an *in vivo* study demonstrating prolonged gastric retention. *J Control Release*. 1998;55:3-12.
7. Park K, Park H. Enzyme digestible balloon hydrogel for long term oral drug delivery: synthesis and characterization. *Int Symp Rel Bioact Mater*. 1987;14:41-42.
8. Ching HS, Park H, Kelly P, Robinson JR. Bioadhesive polymers as platform for oral controlled drug delivery. II. Synthesis and evaluation of some swelling water-insoluble bioadhesive polymers. *J Pharm Sci*. 1985;74:399-405.
9. Kaniwa N, Aoyagi N, Ogata H, Ejima A. Gastric emptying of enteric coated drug preparations. II. Effect of size and density of enteric coated drug preparations and food on the gastric emptying rates in humans. *J Pharmacobiodyn*. 1988;11:571-575.
10. Efentakis M, Koutlis A, Vlachou M. Development and evaluation of oral multiple-unit and single-unit hydrophilic controlled-release systems. *AAPS PharmSciTech*. 2000;1(4):E34.
11. Dennis AB, Farr SJ, Kellaway IW, Taylor G, Davidson R. *In vivo* evaluation of rapid release and sustained release Gelucire capsule formulations. *Int J Pharm*. 1990;65:85-100.
12. Remunan C, Bretal M, Nunez A, Bila Jato JL. Accelerated stability of sustained release tablet prepared with Gelucire. *Int J Pharm*. 1992;80:151-159.
13. Saraiya D, Bolton D. The use of Percirol to prepare sustained release tablets of theophylline and quinidine gluconate. *Drug Dev Ind Pharm*. 1990;16:1963-1969.
14. Li S, Lin S, Chien YW, Daggy BP, Mirchandani HL. Statistical optimization of gastric floating system for oral controlled delivery of calcium. *AAPS PharmSciTech*. 2001;2(1):E1.
15. Kumar K, Shah MH, Ketkar AR, Kadam SS, Paradkar A. Effect of drug solubility and different excipients on floating behavior and release from glyceryl mono-oleate matrices. *Int J Pharm*. 2003.
16. Ainaoui A, Vergnaud JM. Modelling the plasma drug level with oral controlled release forms with lipidic Gelucire. *Int J Pharm*. 1998;169:155-162.
17. Sheu MT, Hsia AHO. Polyglycolized saturated glycerides as carrier and enhancer for drug penetration. *Chin Pharm J*. 2001;33:107-111.
18. Barker SA, Yap SP, Yuen KH, McCoy CP, Murphy JR, Craig DQM. An investigation into the structure and bioavailability of α -tocopherol dispersion in Gelucire 44/14. *J Control Release*. 2003;91:477-488.
19. Sutananta W, Craig DQM, Newton JM. An evaluation of the mechanisms of drug release from glycerides bases. *J Pharm Pharmacol*. 1995;47:182-187.
20. Ketkar AR, Patil VB, Paradkar AR. *Computer Aided Exploratory Data Analysis Model Fitting for Dissolution Kinetics: 4th International Symposium on Advances in Technology and Business Potential of New Drug Delivery System*. Mumbai, India: Controlled Release Society Indian Chapter; 2002:62.
21. Parab PV, Oh CK, Ritschel WA. Sustained release from Precirol(glycerol palmito-stearate) matrix: effect of mannitol and hydroxypropyl methylcellulose on the release of theophylline. *Drug Dev Ind Pharm*. 1986;12:1309-1327.
22. Kaur R, Grant DJW, Eaves T. Comparison of polyethylene glycol and polyoxyethylene stearate as excipients for solid dispersion systems of griseofulvin and tolbutamide. II. Dissolution and solubility studies. *J Pharm Sci*. 1980;69:1321-1326.
23. Savolainen M, Herder J, Khoo C, et al. Evaluation of polar lipid-hydrophilic polymer microparticles. *Int J Pharm*. 2003;262:47-62.
24. Sutananta W, Craig DQM, Newton JM. The effects of ageing on the thermal behaviour and mechanical properties of pharmaceutical glycerides. *Int J Pharm*. 1994;111:51-62.
25. Sutananta W, Craig DQM, Newton JM. An investigation into the effect of preparation condition and storage on the rate of drug release from pharmaceutical glycerides bases. *J Pharm Pharmacol*. 1995;47:355-359.
26. Roussin P, Duddu S. Sustained release theophylline formulations, excipient systems and methods of production. US patent 6 171 615. January 9, 2001.



Home

Journals

Books

Resources

Services

Subscribe

Username:

Password:

Login

Register

Athens

Shibboleth

Advanced Search

Go

All Books and Journals

Drug Development and Industrial Pharmacy

Home

All Issues

Current Issue

Early Online

Aims & Scope

Editorial Board

Instructions for Authors

Publish in as little
as 5 weeks with



Drug Development &
Industrial Pharmacy

Request a Trial



Email Content
Alerts



Why publish
with us

observation cannot
have ITT-LOCF results
have observed case (O
LOCF population.

Authors

Submit an Article

Journal Info

Rights

Permissions

Reprints

Custom
Publishing



Information for
Librarians



Issue TOC | Previous Article | Next Article

Alternative Granulation Technique: Melt
Granulation

1996, Vol. 22, No. 9-10 , Pages 917-924 (doi:10.3109/03639049609065921)

Alan Royce, Jiwaji Suryawanshi, Udayan Shah and Krishna Vishnupad
Drug Delivery Systems, Technical R&D, Sandoz Research Institute,
Sandoz Pharmaceuticals Corp., 59 Route 10, E Hanover, New Jersey,
07936-1080
Warner Lambert Co., 400 W. Lincoln Ave., Litz, Pennsylvania, 17543

PDF (596 KB)

PDF Plus (324 KB)

Reprints

Permissions

Abstract

A melt granulation process has been investigated (1, 2) which efficiently agglomerates pharmaceutical powders for use in both immediate- and sustained-release solid dosage forms. The process utilizes materials that are effective as granulating fluids when they are in the molten state. Cooling of the agglomerated powders and the resultant solidification of the molten materials completes the granulation process. Both the molten agglomeration and cooling solidification were accomplished in a high shear Collette Gral mixer equipped with a jacketed bowl. Hence, the melt granulation process replaces the conventional granulation and drying operations which use water or alcohol solutions. The melt granulation process has been investigated using immediate- and sustained-release TAVIST® (clemastine fumarate USP) tablet formulations. The TAVIST granulations have been characterized by power consumption monitoring, measurement of the granulation particle size distribution, bulk and tapped density determinations, and loss-on-drying measurements. Scale-up of the melt granulation process for the sustained release TAVIST tablet formulation was judged successful based on a comparison of the hardness, friability, weight uniformity during compression, disintegration time, and dissolution rate data obtained at different manufacturing scales.

PDF (596 KB) | PDF Plus (324 KB) - What is PDF Plus?

Quick Links



Add to Favourites

Download Citations

Email TOC Alert

Related Articles

RSS TOC Alerts

Email Citation Alert

Users Also Read

Melt Granulation in A Laboratory Scale High Shear Mixer

Exploration of Melt Granulation Technique for the Development of Coprocessed Directly Compressible Adjuvant Containing Lactose and Microcrystalline Cellulose

Granulation: A Review on Pharmaceutical Wet-Granulation

More »

Authors

Alan Royce

Jiwaji Suryawanshi

Udayan Shah

Krishna Vishnupad

Forward Citations

Novel extended-release formulation of lovastatin by one-step melt granulation: In vitro and in vivo evaluation

In vivo evaluation of two new sustained release formulations elaborated by one-step melt granulation: Level A in vitro-in vivo correlation

Microemulsions as drug delivery systems to improve the solubility and the bioavailability of poorly water-soluble drugs

More

Purchase



Informa Healthcare offers a
unique range of publishing
formats.

Buy Now

25

Journals

[View All Journals](#)

[Expert Opinion on:
Biological Therapy](#)
[Drug Delivery](#)
[Drug Discovery](#)
[Drug Metabolism & Toxicology](#)
[Drug Safety](#)
[Emerging Drugs](#)
[Investigational Drugs](#)
[Medical Diagnostics](#)
[Pharmacotherapy](#)
[Therapeutic Patents](#)
[Therapeutic Targets](#)

[Current Medical Research
and Opinion](#)

Books

[View All Books](#)

[Online Books](#)
[Online Book Collections](#)
[Encyclopedias and
Major Reference Works](#)

[Submit Proposal](#)

[Custom Books](#)

Resource

[For Authors & Editors](#)
[For Readers](#)
[For Librarians](#)
[For Consortia](#)
[For Advertisers](#)

Services

[Healthcare
Communications](#)
[CME-CPD](#)
[Pre-publication Support](#)
[Reprints and ePrints](#)
[Permissions](#)
[Supplements](#)
[Drug/Clinical Trial
Evaluations](#)
[Corporate Books](#)
[Foreign Rights](#)
[Advertising](#)
[Alerting Services](#)
[Manuscript Submission](#)
[Contacts](#)

About Us

[Privacy policy](#)
[Terms & Conditions](#)
[Feedback / Contact Us](#)
[FAQ](#)
[Informa PLC](#)

Jobs

[Advertise](#)
[Subscribe](#)



Copyright © 2010 Informa Plc. All rights reserved.

This site is owned and operated by Informa plc ("Informa") whose registered office is Mortimer House, 37-41 Mortimer Street, London, W1T 3JH. Registered in England and Wales. Number 3099067. UK VAT Group: GB 365 4626 36

PubMed

Display Settings: Abstract

ELSEVIER
FULL-TEXT ARTICLE*Int J Pharm.* 2006 Dec 1;326(1-2):89-93. Epub 2006 Jul 10.**Melt granulation using a twin-screw extruder: a case study.**Van Melkebeke B, Vermeulen B, Vervaet C, Remon JP.

Laboratory of Pharmaceutical Technology, Ghent University, Harelbekestraat 72, B-9000 Ghent, Belgium.

Abstract

The purpose of this study was to use a twin-screw extruder for melt granulation. Polyethylene glycols (PEG 400 and 4000) were used as binders for the development of a drinking water formulation with immediate drug release. The effect of drug content, PEG 400/4000-ratio, surfactant (type and concentration) and granulation temperature on granule properties and dissolution characteristics was determined. The granulation temperature had an important influence on the granule formation. High yield (95% of the granules <1400 microm) was obtained only at a temperature near the melting point of PEG 4000. During granulation the drug of BCS class II was finely dispersed in the PEGs, creating a micro-environment around the drug particles enhancing the dissolution rate. To obtain complete drug release within 10 min for a formulation containing 10% drug, the addition of 2% (w/w) surfactant (polysorbate 80 or Cremophor RH40) was required. At a higher drug content (20%), the PEG 4000 concentration had to be increased to 20% to improve granule properties and 4% polysorbate 80 was required to obtain 100% drug release. X-ray diffractograms showed distinct peaks of crystalline drug, the crystallinity of the drug did not change after 50 days, independent of the storage conditions.

PMID: 16949222 [PubMed - indexed for MEDLINE]

MeSH Terms, Substances**LinkOut - more resources**

PubMed

Display Settings: Abstract

ELSEVIER
FULL-TEXT ARTICLEEur J Pharm Biopharm. 2001 Sep;52(2):181-90.**Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion.**Liu J, Zhang F, McGinity JW.College of Pharmacy, The University of Texas at Austin, Austin, TX, USA. jiping.liu@sanofi-synthelabo.com**Abstract**

The objective of the present study was to investigate the influence of formulation factors on the physical properties of hot-melt extruded granules and compressed tablets containing wax as a thermal binder/retarding agent, and to compare the properties of granules and tablets with those prepared by a high-shear melt granulation (MG) method. Powder blends containing phenylpropanolamine hydrochloride, Precirol and various excipients were extruded in a single-screw extruder at open-end discharge conditions. The extrudates were then passed through a 14-mesh screen to form granules. The extrusion conditions and the optimum amount of wax to function as the thermal binder were dependent on the properties of the filler excipients. At the same wax level, drug release from tablets decreased in the order of using microcrystalline cellulose (MCC), lactose and Emcompress as the filler excipient. The observed differences in the dissolution properties of the tablets were due to the differences in the solubility, swellability and density of the filler excipients. Replacing Precirol with Sterotex K, a higher melting point wax, resulted in slightly increased dissolution rates, when the extrusion was performed at the same temperature conditions. Hot-melt extruded granules were observed to be less spherical than high-shear melt granules and showed lower values of bulk/tap densities. However, tablets containing MCC or lactose granules prepared by hot-melt extrusion (HME) exhibited higher hardness values. Slower drug release rates were found for tablets containing MCC by HME compared with MG. Analysis of the hot-melt extruded granules showed better drug content uniformity among granules of different size ranges compared with high-shear melt granules, resulting in a more reproducible drug release from the corresponding tablets.

PMID: 11522484 [PubMed - indexed for MEDLINE]

MeSH Terms, Substances**LinkOut - more resources**

OCHOA D., Lourdes; IGARTUA O., Manuela; HERNÁNDEZ M., Rosa M^a; R. GASCÓN, Alicia; PEDRAZ M., José L.

GRANULACIÓN POR FUSIÓN EN MEZCLADORES GRANULADORES DE ALTA VELOCIDAD

Vitae, Vol. 13, Núm. 1, marzo, 2006, pp. 40-47
Universidad de Antioquia
Colombia

Disponible en: <http://redalyc.uaemex.mx/src/inicio/ArtPdfRed.jsp?iCve=169813260006>

vitae

Vitae

ISSN (Versión impresa): 0121-4004

vitae@udea.edu.co

Universidad de Antioquia

Colombia

GRANULACIÓN POR FUSIÓN EN MEZCLADORES GRANULADORES DE ALTA VELOCIDAD

MELT GRANULATION IN HIGH SHEAR MIXER

Lourdes OCHOA D.¹, Manuela IGARTUA O.¹, Rosa M^a HERNÁNDEZ M.¹,
Alicia R. GASCÓN¹ y José L. PEDRAZ M.^{1*}

Recibido: Octubre 18 de 2005 Aceptado: Marzo 02 de 2006

RESUMEN

La granulación por fusión en un solo paso es una técnica alternativa basada en la utilización de un agente aglutinante sólido que funde a temperaturas entre 50-80 °C, en lugar de solventes acuosos u orgánicos. Esta propiedad permite emplear esta técnica para la formulación de fármacos sensibles a la humedad, evitar el controvertido uso de solventes orgánicos y acortar el proceso de granulación en términos de tiempo y energía al eliminar la fase de secado. Asimismo, una adecuada selección del agente aglutinante y del resto de excipientes permitirá el desarrollo y elaboración de formas farmacéuticas tanto de liberación inmediata como de liberación controlada. Uno de los equipos más empleados en la granulación por fusión es el mezclador granulador de alta velocidad, que permite realizar esta técnica en un solo paso. Además, una vez optimizado el proceso, permite su aplicación a escala industrial. En este artículo se realiza una descripción de la técnica de granulación por fusión y las variables que influyen en dicho proceso en un mezclador granulador de alta velocidad.

Palabras clave: Granulación por fusión, mezclador granulador de alta velocidad, aglutinante.

ABSTRACT

Melt granulation in a high-shear mixer is an alternative technique that converts fine powders into granules. The powder agglomeration is promoted by the addition of a low melting point binder, which is solid at room temperature and melts at relatively low temperatures (50-80 °C). This technique is a good alternative to the conventional wet granulation process when the use of solvents is not indicated. Moreover, it offers several advantages since the drying phase is eliminated and the process is less consuming in terms of time and energy. By selecting the suitable binder, melt granulation can be used either to prepare immediate or controlled release formulations. One of the equipments most commonly used for melt granulation is the high shear mixer, which allows to development the process in "one-step". Additionally, when the process is optimized, it makes possible the industrial scaling-up. This paper focuses on the description of the melt granulation technique and the parameters that influence the process in high shear mixers.

Key words: Melt granulation, high shear mixer, binder.

¹ Laboratorio de Farmacia y Tecnología Farmacéutica Facultad de Farmacia, Universidad del País Vasco (UPV-EHU), Paseo de la Universidad N° 7, 01006 Vitoria-Gasteiz, España.

* Autor a quien se debe dirigir la correspondencia: knppemuj@vf.ehu.es

INTRODUCCIÓN

La granulación es un proceso de aglomeración de partículas primarias de polvo para formar estructuras mayores denominadas gránulos. Generalmente, este granulado se utiliza como producto intermedio en la fabricación de comprimidos y cápsulas, aunque también puede ser empleado como producto final. Las principales razones por las cuales se recurre a la granulación de una mezcla pulverulenta son las siguientes:

- Prevenir la segregación de sus componentes.
- Mejorar las propiedades de flujo.
- Mejorar las características de compactación.

La preparación de un granulado puede realizarse por vía seca o vía húmeda según se adicione o no un solvente a la mezcla de polvos. La elección del método de granulación dependerá por un lado de la aplicación que se quiera dar al granulado y por otro de las propiedades físico químicas del principio activo y de los excipientes de la formulación, en particular de su sensibilidad a la humedad y al calor (1).

Granulación por vía seca

Conocida como “granulación por doble compresión”, se produce mediante la agregación de los componentes en polvo sometidos a alta presión seguida de una fragmentación o troceado y posterior granulación mediante tamización para conseguir el tamaño de gránulo deseado. Las técnicas más empleadas son el briqueteado (slugging) y la compactación con rodillos. Esta vía se puede utilizar como alternativa a la vía húmeda cuando el fármaco que se va a granular es sensible a la humedad, a los líquidos de granulación, o no es estable a altas temperaturas de secado. Sus principales inconvenientes son que la mezcla debe presentar ciertas propiedades cohesivas, la formación de polvo y la baja reproducibilidad en las propiedades finales del granulado.

Granulación por vía húmeda

Consiste en un proceso de amasado de una mezcla de polvos en presencia de un líquido de granulación, agua o solvente orgánico, que puede llevar disuelto un agente aglutinante o incorporarse con el resto de los componentes de la mezcla para favorecer la adhesión de las partículas una vez secado el granulado.

La figura 1 muestra esquemáticamente las etapas de la granulación por vía húmeda y los equipos necesarios para llevarla a cabo de forma conven-

cional o mediante un proceso desarrollado en “un solo paso”.

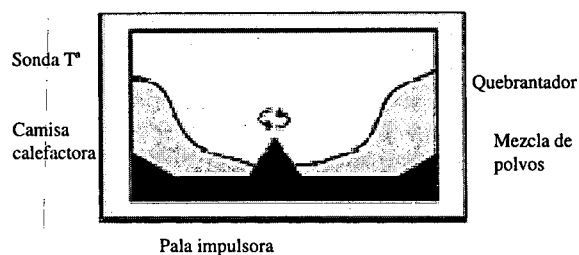


Figura 1. Proceso de granulación por vía húmeda convencional y en “un solo paso”.

Como puede observarse, el empleo del mezclador granulador de alta velocidad (MGAV) o del lecho fluido permite realizar la granulación en “un solo paso” ya que un mismo equipo permite realizar las etapas de mezclado, humectación, granulación y secado. Esto significa una reducción en el número de equipos que se deben utilizar, lo que simplifica considerablemente el proceso y evita posibles problemas en la manipulación o pérdidas que pueden producirse entre un equipo y otro.

La granulación por vía húmeda presenta también algunos inconvenientes, como son la posibilidad de hidrólisis del principio activo en presencia de agua, la necesidad de prolongados tiempos de secado y la pérdida de estabilidad del principio activo por la exposición al calor durante la fase de secado. Los solventes orgánicos se pueden utilizar como alternativa para fármacos sensibles a la humedad o cuando se precisan tiempos de secado cortos; sin embargo, su uso requiere trabajar en locales e instalaciones antideflagrantes, lo que aumenta mucho el coste de la producción.

Otra posibilidad para la elaboración de granulados es la granulación por fusión, que puede ser considerada como una modificación de la granulación por vía húmeda (1, 2 y 3).

Para la realización de este artículo se hizo una revisión bibliográfica durante los últimos 18 meses consultando las bases de datos Scienccedirect y SciFinder Scholar 2006 Edition.

¿Qué es la granulación por fusión?

La granulación por fusión es un proceso en el que la granulación se produce por la adición de un agente aglutinante que es sólido a temperatura ambiente pero funde a temperaturas relativamente bajas. Normalmente se trabaja con sustancias de punto de fusión en torno a 50-80°C, tanto de natu-

raleza hidrófila como lipófila (4). El agente aglutinante puede añadirse ya fundido sobre la mezcla de polvos precalentada (5) o en forma sólida junto con el resto de componentes de la mezcla, de tal forma que la granulación se desarrolla en "un solo paso" al fundir el aglutinante en el seno de la mezcla (6). En este caso, dependiendo del equipo empleado, el agente aglutinante fundirá por el calor generado por una corriente de aire caliente (granulación en lecho fluido), por la acción de una camisa calefactora, por la fricción de los componentes de la mezcla producida por un impulsor durante la fase de mezclado y amasado (7, 8), o por la combinación de estas dos acciones como ocurre en el mezclador granulador de alta velocidad. En cualquier caso, tras la fusión, el agente aglutinante actúa como líquido de unión de las partículas de polvo de forma similar al líquido adicionado en los procesos de vía húmeda (2). Dependiendo de la cantidad de aglutinante añadido, de los componentes que constituyen la mezcla y de la elección de las condiciones del proceso, es posible obtener gránulos o incluso pellets (8, 9). En este sentido, los resultados descritos por Heng *et al.* (10), y Seo *et al.* (11) pusieron de manifiesto que una alta velocidad de mezcla y tiempos prolongados de amasado favorecen la formación de pellets.

Las principales ventajas que presenta la granulación por fusión son las siguientes: evita la formación de polvo, elimina la fase de secado haciendo el proceso de granulación más corto, y evita el uso de solventes y los posibles problemas que derivan de ello (hidrólisis de principio activo, empleo de equipos ignífugos etc.). Su mayor inconveniente es que no se puede aplicar a sustancias termolábiles a las temperaturas habituales de trabajo.

Equipos

Los equipos más empleados en la granulación por fusión son el mezclador granulador de alta velocidad (12) y el lecho fluido (13, 14, 15, 16). Ambos equipos pueden realizar la granulación en un solo paso, lo que permite simplificar considerablemente el tiempo y los costes asociados a los procesos de granulación tradicionales. Además, una vez optimizado el proceso y controlando las variables que pueden influir sobre él, estos equipos permiten la aplicación del proceso a escala industrial (17, 18, 19).

Una cuestión que se debe tener en cuenta a la hora de seleccionar el equipo de granulación más adecuado, es su influencia sobre las características del granulado que se va a realizar. Diversos estudios descritos en la bibliografía ponen de manifiesto que los gránulos obtenidos con el MGAV son más densos que los resultantes del lecho fluido, debido a las altas fuerzas de cizalla y de compactación ejercidas por la pala impulsora del equipo (20, 21). Por consiguiente, una misma formulación puede presentar distinto comportamiento biofarmacéutico dependiendo del equipo utilizado en su elaboración.

A pesar de las numerosas ventajas que presentan ambos equipos, su principal inconveniente es la cantidad de variables (velocidad del impulsor, flujo del aire, carga del equipo, temperatura de trabajo, etc.) que pueden determinar el resultado final y la necesidad de conocer su influencia. El análisis de los parámetros del proceso que pueden condicionar las características del granulado obtenido puede reducirse mediante un diseño factorial, con el objeto de disminuir el número de formulaciones que deben ser elaboradas (22 y 23).

Una vez obtenido el granulado es necesario realizar su correcta caracterización mediante la determinación de distintas propiedades, tales como la distribución del tamaño de partícula, la porosidad, la densidad y voluminosidad, las propiedades de flujo, las características de compresión, la distribución del agente aglutinante y la morfología.

Granulación por fusión en Mezclador Granulador de Alta Velocidad

Como se ha comentado anteriormente, el empleo del MGAV permite realizar el mezclado, granulación y secado/enfriamiento del granulado en un solo paso.

Como puede observarse en la figura 2, el equipo está formado por un recipiente cerrado y termostático mediante una camisa calefactora. Presenta, además, una sonda para el registro continuo de la temperatura del producto y un quebrantador o "chopper" para evitar la formación de grandes aglomerados. En la parte inferior está la pala impulsora que dará lugar al mezclado y permitirá la formación del granulado.

31

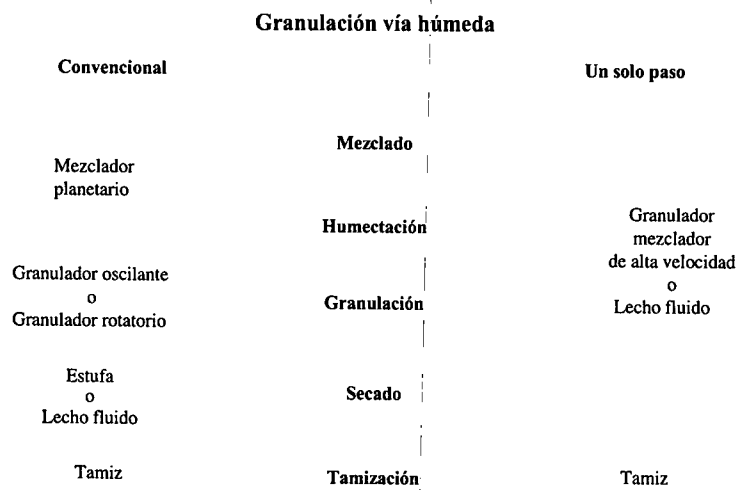


Figura 2. Esquema de un mezclador granulador de alta velocidad.

Para la elaboración de un granulado mediante granulación por fusión en un solo paso, se incorpora al equipo el agente aglutinante en estado sólido junto con el resto de materiales de partida. Los componentes se mezclan durante unos minutos mediante la acción de la pala impulsora a velocidades bajas (150-250 rpm), dependiendo de la cantidad de carga, y durante un corto período de tiempo. Tras la fase de mezclado comienza la de granulación propiamente dicha en la que se aumenta progresivamente la velocidad del impulsor para favorecer una buena distribución del agente aglutinante y alcanzar su temperatura de fusión. Gracias al calor generado por la camisa calefactora y por la fricción de los componentes provocada por el impulsor, el aglutinante funde actuando como líquido de unión entre las partículas y dando lugar a la formación del granulado. En esta etapa del proceso de granulación se puede evitar la formación de grandes aglomerados accionando el quebrantador, cuyo empleo también puede favorecer la obtención de gránulos más densos. Posteriormente se realiza la etapa de enfriamiento, haciendo pasar agua fría a través de la camisa calefactora. Esta etapa se puede acompañar de un movimiento oscilatorio del recipiente (si el equipo lo posee) que evita que la mezcla se adhiera a las paredes y favorece el enfriamiento progresivo del granulado por intercambio de calor con el recipiente. Una vez finalizado el proceso se tamiza el granulado para eliminar los posibles aglomerados obtenidos.

Es importante vigilar el proceso con atención, ya que la granulación progresa con tanta rapidez

que el granulado se puede transformar muy rápidamente en un sistema sobreamasado inutilizable. Por tanto, es conveniente utilizar un sistema de monitorización adecuado para controlar el proceso de granulación (24, 25). En este sentido, se puede emplear la medida de distintos factores para determinar el punto final del proceso de granulación, como son, por ejemplo, el registro del consumo de energía o el esfuerzo de torsión de la pala impulsora (26, 27, 28).

Al igual que el resto de técnicas de granulación, la granulación por fusión en MGAV está condicionada por numerosas variables, como son las características de los materiales de partida y del equipo utilizado. Otras variables que influyen en el proceso aparecen agrupadas en la Tabla 1.

Tabla 1. Principales variables del equipo, proceso y producto que influyen en el proceso de granulación por fusión en MGAV.

Variables del producto	Variables del equipo	Variables del proceso
Viscosidad del aglutinante	Tipo de pala impulsora	Velocidad de la pala impulsora
Cantidad de aglutinante	Acción del quebrantador	Tiempo de amasado
Tamaño de partícula de los materiales		Carga del equipo
		Temperatura del producto
		Temperatura calefactora

Un adecuado conocimiento y control de ellas permitirá la obtención de granulados homogéneos y con buenas propiedades de flujo. A continuación se describe de forma más detallada la influencia de algunas de estas variables sobre las características del granulado obtenido.

Influencia del agente aglutinante

En la granulación por fusión, la selección adecuada del agente aglutinante es un aspecto de gran importancia, ya que permitirá desarrollar tanto formulaciones de liberación inmediata como de liberación controlada (29). Como agentes aglutinantes se pueden emplear numerosas sustancias hidrófobas como el monoestearato de glicerilo (30), ácido esteárico (31), Compritol® 888 Ato (Glyceryl behenate) (32), Gelucire 50/13 (Polyglycolized glyceride) (33, 34) y otros tipos de grasas y alcoholes (7, 35). Entre las sustancias hidrófilas mas empleadas destacan el polietilenglicol (PEG 6000) (36) y el poloxamer 188 (Lutrol® F68) (37).

En la figura 3 se presentan perfiles de disolución de comprimidos de teofilina elaborados mediante granulación por fusión con distintos agentes aglutinantes para conocer su influencia sobre la liberación del fármaco. En dichos perfiles, Ochoa *et al.* (38) observaron que las formulaciones elaboradas con aglutinantes lipófilos presentan una menor velocidad de disolución debido a que su naturaleza lipófila dificulta la penetración de agua en el comprimido, y por consiguiente, la liberación del fármaco.

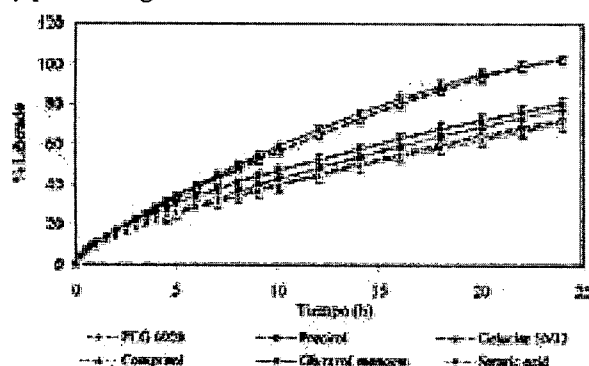


Figura 3. Perfiles de liberación de teofilina a partir de comprimidos elaborados con distintos aglutinante (38).

Los agentes aglutinantes pueden presentarse en forma de escamas o polvo, con una gran diversidad de tamaños de partícula. En principio se considera que el proceso de aglomeración en la granulación por fusión es prácticamente independiente del tamaño de partícula del agente aglutinante, excepto cuando se utilizan sustancias de viscosidad elevada. Esto se debe

a que una vez fundido, el aglutinante pasa a estado líquido humectando el polvo de forma homogénea independientemente de su tamaño de partícula inicial (8, 39, 40). Sin embargo, para evitar problemas de homogenización con el resto de los componentes en las fases de mezclado y granulación, es preferible emplear aglutinantes de tamaño de partícula similar al principio activo y excipientes de la mezcla ya que como observaron Scott *et al.* (41) y Van den Dries *et al.* (42), las diferencias en el tamaño de partícula pueden afectar la composición de los gránulos debido a problemas de segregación de los componentes durante la fase de mezclado.

Otra de las propiedades físico-químicas que condiciona la elección de una sustancia para su empleo como aglutinante es su rango de temperatura de fusión. Tal y como se ha mencionado anteriormente, lo habitual es trabajar con sustancias de punto de fusión en torno a 50-80°C, porque el empleo de aglutinantes con punto de fusión más bajo puede ocasionar problemas ya que se podría alcanzar dicha temperatura durante la manipulación y almacenamiento del granulado y el agente aglutinante fundiría. Por otro lado, temperaturas de fusión mayores implican someter la mezcla a una mayor temperatura, lo que contribuiría a posibles problemas de inestabilidad especialmente con sustancias termolábiles.

La cantidad del aglutinante en la mezcla ha sido estudiada por numerosos autores como una variable importante a la hora de elaborar un granulado (8, 32). Una conclusión a la que llegaron Schaefer (43) y Knight *et al.* (5) es que para granular materiales con tamaños de partícula pequeños es necesaria una cantidad elevada de aglutinante debido a que presentan una mayor área superficial que debe ser adecuadamente humectada para conseguir su aglutinación.

En general, la granulación por fusión requiere aproximadamente entre un 10 y un 20 % en peso del agente aglutinante en la mezcla. Un exceso de aglutinante en la mezcla provocaría un sobreamasado, mientras que si no se alcanza la proporción suficiente no tendrá lugar la formación del granulado.

Influencia de los demás excipientes de la formulación

La elección de los excipientes, junto con la naturaleza del aglutinante condicionará la liberación del principio activo. El tamaño de partícula de los excipientes y del principio activo es otra

de las variables más estudiada y que se debe tener en cuenta ya que su influencia sobre el resultado final es importante. Autores como Thomsen (44) y Mackaplow et al. (45) observaron que materiales con tamaño muy pequeño no se podían granular mediante granulación por fusión, o que en caso de granularse, estos granulados eran muy frágiles. Sin embargo, Farag Badawy *et al.* (46, 47) vieron que los excipientes y fármacos de pequeño tamaño de partícula daban lugar a gránulos mayores y más densos. Así mismo Keningley *et al.* (48) demostraron que existe una importante relación entre el tamaño de partícula y la viscosidad del aglutinante a la hora de controlar el crecimiento y la consistencia del gránulo. En este sentido, Johansen y Schaefer (49) estudiaron esa relación entre tamaño y viscosidad, y sus efectos sobre el mecanismo de crecimiento del granulado en un MGAV observando que aglutinantes de viscosidad baja son suficientes para obtener granulados resistentes con materiales de tamaño pequeño. Por el contrario, con tamaños de partícula mayores se necesitan aglutinantes de alta viscosidad para conseguir un granulado de consistencia suficiente para evitar su ruptura. Estos mismos autores demostraron también que la viscosidad del aglutinante y el tamaño de partícula del resto de componentes afectan la homogeneidad de tamaño de los gránulos de un mismo lote y entre diferentes lotes (50).

Entre los excipientes que se pueden emplear en esta técnica se encuentran los derivados de la celulosa, como la hidroxipropilmetilcelulosa (HPMC) para el desarrollo de matrices hidrófilas con las que

se puede conseguir una liberación sostenida del fármaco debido a la formación de un gel que controlará su liberación. La liberación del principio activo a partir de estas matrices hidrófilas se producirá por difusión a través del gel (si el principio activo es soluble en el medio de disolución), por erosión de la matriz (si es poco soluble) o mediante la combinación de ambos mecanismos (51). También se pueden utilizar otros derivados celulósicos como la etilcelulosa o la hidroximetilcelulosa (HMC). Si se desea incrementar la liberación del principio activo podemos añadir diluyentes hidrófilos como el manitol, o sustancias que mejoren su solubilidad como las ciclodextrinas (52). Por otro lado es posible, mediante la incorporación de sustancias de acción disgregante como la crospovidona, desarrollar formulaciones de liberación inmediata (53, 54). El empleo de un aglutinante hidrófilo como el Superpolystate® (PEG-6-estearato con un punto de fusión de 33-37 °C), junto con un disgregante, permite elaborar formulaciones de disgregación bucal inmediata “flash tablets” (55). Las propiedades de este aglutinante posibilitan incrementar la resistencia física de los comprimidos obtenidos sin afectar el tiempo de disgregación, permitiendo su rápida disgregación al fundir en la cavidad bucal y favoreciendo la rápida solubilización del principio activo.

Como se puede observar en la tabla 2, las aplicaciones de esta técnica son muy numerosas, ya que permite el desarrollo de formulaciones de fármacos de distinta solubilidad y pertenecientes a diferentes grupos terapéuticos.

Tabla 2. Algunos ejemplos de fármacos empleados en el desarrollo de distintas formulaciones mediante granulación por fusión en MGAV.

Forma de liberación	Forma farmacéutica	Fármaco	Aglutinante	Referencia
Liberación controlada	Pellets	Fenilefrina	Precirol® + Compritol®	26
Liberación controlada	Pellets	Teofilina	Ácido Esteárico	31
Liberación controlada	Gránulos	Ibuprofeno	Poloxamer 188	37
Liberación controlada	Gránulos	Propranolol	Precirol®	56
Liberación inmediata	Gránulos	Diazepam	PEG 3000 o Gelucire 50/13	34
Liberación inmediata	Gránulos	Carbamazepina	PEG 6000	53
Liberación inmediata	Gránulos	Paracetamol	Superpolystate®	55
Liberación inmediata	Gránulos	Diclofenaco	PEG 4000	57
Liberación inmediata	Gránulos	Propranolol	Propranolol oleato	58

Influencia de algunas variables del proceso

Además de los componentes de la formulación, también se ha demostrado que el proceso de elaboración del granulado es importante a la hora de controlar la liberación del principio activo ya que cambios en el mismo pueden dar lugar a formulaciones con distintos perfiles de liberación y distinta biodisponibilidad (59).

En cuanto a la velocidad de la pala impulsora, es sabido que altas velocidades de trabajo producen un crecimiento más rápido del granulado haciendo así el proceso más corto. Sin embargo, se corre el riesgo de un crecimiento incontrolado (32). Knight *et al.* (60) recomiendan velocidades bajas de trabajo para conseguir gránulos mayores ya que a velocidad elevada se puede provocar la rotura de los gránulos.

Además, el empleo de la camisa calefactora para la elaboración del granulado puede afectar al comportamiento reológico del agente aglutinante fundido, y por consiguiente, su comportamiento en el mecanismo de granulación, lo cual va a influir sobre las características finales del granulado.

Finalmente, otras variables del proceso que pueden influir en el producto final, y a las que por tanto es importante tener en cuenta, son: el tiempo de amasado y la acción del quebrantador.

En resumen, podemos decir que es de gran importancia conocer y controlar todos los factores y variables que afectan el desarrollo del proceso de granulación por fusión en un MGAV para poder conseguir granulados homogéneos, reproducibles y con buenas propiedades, ya que como Bergman *et al.* (61) demostraron, estas características son imprescindibles para asegurar una buena calidad del producto final.

CONCLUSIONES

La granulación por fusión en MGAV es una técnica adecuada para la formulación de fármacos sensibles a la humedad evitando el uso de solventes orgánicos, y que permite el desarrollo de formas farmacéuticas tanto de liberación inmediata como controlada.

Son muchas las variables a controlar para lograr granulados homogéneos y reproducibles; sin embargo, una vez conocida su influencia, el MGAV permite su aplicación a escala industrial.

El empleo de este equipo permite, además, realizar la granulación por fusión en un solo paso, lo cual simplifica el proceso de elaboración de los granulados.

REFERENCIAS BIBLIOGRÁFICAS

- Summers, M., Aulton, M. (2004) Granulación. La ciencia del diseño de las formas farmacéuticas. Elsevier (Ed). Capítulo 25 pp 368-378.
- Kristensen, H.G., Schaefer, T. (1997) Granulations. Encyclopedia of pharmaceutical technology. Marcel Dekker (Ed) New York Vol. 7. pp 121-160.
- Vila, J.L. (1997) Tecnología farmacéutica. Vol. II: Formas farmacéuticas. Síntesis (Ed). Madrid. Capítulo 2 pp 55-157.
- Heng, P., Wong, T.W. (2003) Melt processes for oral solid dosage forms. Encyclopedia of Pharmaceutical Technology. 1-6.
- Knight, P.C., Instone, T., Pearson, J.M.K., Hounslow, M.J. (1998) An investigation into the kinetics of liquid distribution and growth in high shear mixer agglomeration. Powder Technol. 97: 246-257.
- Zhou, F., Vervact, C., Remon, J.P. (1997) Influence of processing on the characteristics of matrix pellets based on microcrystalline waxes and starch derivatives. Int. J. Pharm. 147: 23-30.
- Mc Taggart, C.M., Ganley, J.A., Sickmueller, A., Walker, S.E. (1984) The evaluation of formulation and processing conditions of a melt granulation process. Int. J. Pharm. 19: 139-148.
- Schaefer, T., Holm, P., Kristensen, H.G. (1990) Melt granulation in a laboratory scale high shear mixer. Drug Dev. Ind. Pharm. 16(8): 1247-1277.
- Vilhemsen, T., Kristensen, J., Schaefer, T. (2004) Melt pelletization with polyethylene glycol in a rotatory processor. Int. J. Pharm. 275: 141-153.
- Heng, P.W.S., Wong, T.W., Chan, L.W. (2000) Influence of production variables on the sphericity of melt pellets. Chem. Pharm. Bull. 48: 420-424.
- Seo, A., Schaefer, T. (2001) Melt agglomeration with polyethylene glycol beads at a low impeller speed in a high shear mixer. Eur. J. Pharm. Biopharm. 52: 315-325.
- Parikh, D.M. (1997) Introduction. Handbook of Pharmaceutical Granulation Technology, Marcel Dekker (Ed.) New York, 1-5.
- Abberger, T., Seo, A., Schaefer, T. (2002) The effect of droplet size and powder particle size on the mechanism of nucleation and growth in fluid bed melt agglomeration. Int. J. Pharm. 249: 185-197.
- Yanze, F.M., Duru, C., Jacob, M. (2000) A process to produce effervescent tablets: fluidized bed dryer melt granulation. Drug Dev. Ind. Pharm. 26: 1167-1176.
- Kidokoro, M., Haramiishi, Y., Sagasaki, S., Shimizu, T., Yamamoto, Y. (2002) Application of fluidized hot-melt granulation (FHMg) for the preparation of granules for tableting: Properties of granules and tablets prepared by FHMg. Drug Dev. Ind. Pharm. 28(1): 67-76.
- Kojima, M., Nakagami, H. (2001) Preparation of the controlled-release matrix tablets of theophylline with micronized low-substituted hydroxypropyl cellulose by a fluidized hot-melt granulation method. S.T.P. Pharma Sci. 11(2): 145-150.
- Sirois, P.J., Craig, G.D. (2000) Scaleup of high-shear granulation process using a normalized impeller work parameter. Pharm. Dev. Technol. 5: 365-374.
- Ameye, D., Keleb, E., Vervact, C., Remon, J.P., Adams, E., Mas-sart, D.L. (2002) Scaling-up of a lactose wet granulation process in Mi-Pro high shear mixers. Eur. J. Pharm. Sci. 17, 247-251.
- Björn, I.N., Jansson, A., Karlsson, M., Folestad, S., Rasmuson, A. (2005) Empirical to mechanistic modelling in high shear granulation. Chem. Engin. Sci. 60: 3795-3803.
- Lin, K., Peck, G.E. (1996) Development of agglomerated talc. III. Comparisons of the physical properties of the agglomerated talc prepared by three different processing methods. Drug Dev. Ind. Pharm. 22: 383-392.
- Tobyn, M.J., Staniforth, J.N., Baichwal, A.R., McCall, T.W. (1996) Prediction of physical properties of a novel polysaccharide controlled release system. Int. J. Pharm. 128: 113-122.

22. Vojnovich, D., Moneghini, M., Rubessa, F. (1995) Experimental design for a granulation process with "a priori" criterias. *Drug Dev. Ind. Pharm.* 1(7) : 823-831.
23. Campisi, B., Vojnovic, D., Chicco, D., Phan-Tan-Luu, R. (1999) Melt granulation in a high shear mixer: optimization of mixture and process variables using a combined experimental design. *Chemom. Intell. Lab. Syst.* 48 : 59-70.
24. Cliff, M.J. (1990) Granulation end point and automated process control of mixer-granulators: Part. I. *Pharm. Tech* 4 : 112-132.
25. Cliff, M.J. (1990) Granulation end point and automated process control of mixer-granulators: Part. II. *Pharm. Tech* 5 : 38-44.
26. Hamdani, J., Moës, A.J., Amighi, K. (2002) Development and evaluation of prolonged release pellets obtained by the melt pelletization process. *Int. J. Pharm.* 245 : 167-177.
27. Betz, G., Bürgin, P.J., Leuenberger, H. (2004) Power consumption measurement and temperature recording during granulation. *Int. J. Pharm.* 272 : 137-149.
28. Bardin, M., Knight, P.C., Seville, J.P.K. (2004) On control of particle size distribution in granulation using high-shear mixers. *Powder Technol.* 140 : 169-175.
29. Flanders, P., Dyer, G.A. Jordan, D. (1987) The control of drug release from conventional melt granulation matrices. *Drug Dev. Ind. Pharm.* 13(6) : 1001-1022.
30. Thies, R., Kleinebudde, P. (1999) Melt pelletization of a hygroscopic drug in a high shear mixer. Part 1. Influence of process variables. *Int. J. Pharm.* 188 : 131-143.
31. Voinovich, D., Moneghini, M., Perissutti, B., Filipovic-Grcic, J., Grabnar, I. (2000) Preparation in high-shear mixer of sustained-release pellets by melt pelletization. *Int. J. Pharm.* 203: 235-244.
32. Faham, A., Prinderre, P., Farah, N., Eichler, K.D., Kalantzis, G., Joachim, J. (2000) Hot-melt coating technology. I. Influence of Compritol® 888 Ato and granule size on theophylline release. *Drug Dev. Ind. Pharm.* 26(2) : 167-176.
33. Gupta, M.K., Goldman, D., Bogner, R.H., Tseng, YC. (2001) Enhanced drug dissolution and bulk properties of solid dispersions granulated with a surface adsorbent. *Pharm. Dev. Technol.* 6(4) : 563-572.
34. Seo, A., Holm, P., Kristensen, H.G., Schaefer, T. (2003) The preparation of agglomerates containing solid dispersions of diazepam by melt agglomeration in a high shear mixer. *Int. J. Pharm.* 259: 161-171.
35. Evrad, B., Amighi, K., Beten, K., Delattre, L., Moës, A.J. (2000) Influence of melting and rheological properties of fatty binders on the melt granulation process in a high-shear mixer. *Drug Dev. Ind. Pharm.* 25(11) : 1177-1184.
36. Hengh, P.W.S., Chan, L.W., Zhu, L. (2000) Effect of process variables and their interaction on melt pelletization in a high shear mixer. *S.T.P. Pharma Sci.* 10(2): 165-172.
37. Passerini, N., Albertini, B., González-Rodríguez, M.L., Cavallari, C., Rodríguez, L. (2002) Preparation and characterisation of ibuprofen-poloxamer 188 granules obtained by melt granulation. *Eur. J. Pharm. Sci.* 15 : 71-78.
38. Ochoa, L., Igartua, M., Hernández, R.M., Gascón, A.R., Pedraz, J.L. (2005) Preparation of sustained release hydrophilic matrices by melt granulation in a high-shear mixer. *J. Pharm. Pharm. Sci.* 8(2) : 132-140.
39. Wong, T.W., Wan, L.S.C., Heng, P.W.S. (1999) Effects of physical properties of PEG 6000 on pellets produced by melt pelletization. *Pharm. Dev. Technol.* 4(3): 449-456.
40. Schaefer, T., Mathiesen, C. (1996) Melt pelletization in a high shear mixer. IX. Effects of binder particle size. *Int. J. Pharm.* 139: 139-148.
41. Scott, A.C., Hounslow, M.J., Instone, T. (2000) Direct evidence of heterogeneity during high-shear granulation. *Powder Technol.* 113 : 205-213.
42. Van de Dries, K., Vromans, H. (2002) Relationship between inhomogeneity phenomena and granule growth mechanisms in a high-shear mixer. *Int. J. Pharm.* 247 : 167-177.
43. Schaefer, T. (1996) Melt pelletization in a high shear mixer. VI. Agglomeration of cohesive powder. *Int. J. Pharm.* 132: 221-230.
44. Thomsen, L.J. (1994) Prolonged release matrix pellets prepared by melt pelletization. Part IV. Drug content, drug particle size, and binder composition. *Pharm. Technol. Eur.* 6(9) : 19-24.
45. Mackaplow, M.B., Rosen, L.A., Michaels, J.N. (2000). Effect of primary particle size on granule growth and end point determination in high shear wet granulation. *Powder Technol.* 108 : 32-45.
46. Farag Badawi, S.I. and Hussain, M.A. (2004) Effect of starting material particle size on its agglomeration behaviour in high shear wet granulation. *AAPS PharmSciTech* 5 (3) : Article 38.
47. Farag Badawi, S.I., Lee, T.J., Menning, M.M. (2000) Effect of drug substance particle size on the characteristics of granulation manufactured in a high-shear mixer. *AAPS PharmSciTech* 1(4) : Article 33.
48. Keningley, S.T., Knight, P.C., Marson, A.D. (1997) An investigation into the effects of binder viscosity on agglomeration behaviour. *Powder Technol.* 91 : 95-103.
49. Johansen, A., Schaefer, T. (2001) Effects of interactions between powder particle size and binder viscosity on agglomerate growth mechanisms in a high shear mixer. *Pharm. Sci.* 12: 297-309.
50. Schaefer, T., Johnsen, D., Johansen, A. (2004) Effects of powder particle size and binder viscosity on intergranular and intragranular particle size heterogeneity during high shear granulation. *Pharm. Sci.* 21 : 525-531.
51. Colombo, P., Santi, P., Bettini, R., Brazel, C.S., Peppas, N.A. (2000). *Handbook of Pharmaceutical Controlled Release Technology*. Marcel Dekker (Ed). New York. Capítulo 9. pp183-210.
52. Pina, M.E., Veiga, F. (2000) The influence of diluent on the release of theophylline from hydrophilic matrix tablets. *Drug Dev. Ind. Pharm.* 26(10) : 1125-1128.
53. Perissutti, B., Rubessa, F., Moneghini, M., Voinovich, D. (2003) Formulation design of carbamazepine fast-release tablets prepared by melt granulation technique. *Int. J. Pharm.* 256 : 53-63.
54. Royce, A., Suryawanshi, J., Shah, U., Vishnupad, H. (1996) Alternative granulation technique: Melt granulation. *Drug Dev. Ind. Pharm.* 22(9 y 10) : 917-924.
55. Abdelbary, G., Prinderre, P., Eouani, C., Joachim, J., Reynier, J.P., Piccerelle, Ph. (2004) The preparation of orally disintegrating tablets using a hydrophilic waxy binder. *Int. J. Pharm.* 278(2) : 423-433.
56. Bertuzzi, G., Cicalini, L., Di Colo, G. (2001) Melt granulation in high shear high speed mixer: preparation of sustained release systems of propranolol hydrochloride. 20th Pharm. Technol. Conference, Liverpool.
57. Rodríguez, L., Cavallari, C., Passerini, N., Albertini, B., González-Rodríguez, M.L., Fini, A. (2002) Preparation and characterization by morphological analysis of diclofenac/PEG 4000 granules obtained using three different techniques. *Int. J. Pharm.* 242 : 285-289.
58. Crowley, K.J., Forbes, R.T., York, P., Nyqvist, H., Camber, O. (2000) Drug-fatty acid salt with wax-like properties employed as binder in melt granulation. *Int. J. Pharm.* 211 : 9-17.
59. Westerhuis, J.A., De Haan, P., Zwinkels, J., Jansen, W.T., Lerk, C.F. (1996) Optimization of the composition and production of mannitol/microcrystalline cellulose tablets. *Int. J. Pharm.* 143: 151-162.
60. Knight, P.C., Johansen, A., Kristensen, H.G., Schaefer, T., Seville, J.P.K. (2000) An investigation of the effects on agglomeration of changing the speed of a mechanical mixer. *Powder Technol.* 110 : 204-209.
61. Bergman, R., Johansson, M.E., Lundstedt, T., Seifert, E., Aberg, J. (1998) Optimization of a granulation and tableting process by sequential design and multivariate analysis. *Chemometr. Intell. Lab.* 44 : 271-286.

- [54] MELT GRANULATED COMPOSITIONS FOR PREPARING SUSTAINED RELEASE DOSAGE FORMS
- [75] Inventor: Alan E. Royce, Effort, Pa.
- [73] Assignee: Sandoz Ltd., Basel, Switzerland
- [21] Appl. No.: 860,920
- [22] Filed: Mar. 31, 1992

Related U.S. Application Data

- [63] Continuation of Ser. No. 664,195, Mar. 4, 1991, abandoned.
- [51] Int. Cl.⁶ A61K 9/14
- [52] U.S. Cl. 424/489; 424/480; 424/498; 424/488
- [58] Field of Search 424/489, 480, 476, 464, 424/469

References Cited

U.S. PATENT DOCUMENTS

3,147,187	9/1964	Playfair	167/82
3,870,790	3/1975	Lowey	424/469
4,140,755	2/1979	Sheth et al.	424/21
4,389,393	6/1983	Schor	424/480
4,774,074	9/1988	Snipes	424/19
4,828,836	5/1989	Elger	424/464
4,849,229	7/1989	Gaylord et al.	424/468
4,882,167	11/1989	Jang	424/468
5,023,108	6/1991	Bagaria	424/476

OTHER PUBLICATIONS

Pharmaceutical Dosage Forms: Tablets, vol. 1 (2nd Ed.) ed. by Lieberman et al., Marcel Dekker Inc. (1989), p. 150.

Flanders, P. et al., The Control of Drug Release from Conventional Melt Granulation Matrices, *Drug Devel. and Ind. Pharm.*, 13 (6), 1001-1022 (1987).

Kopcha, M. et al. Development and In-Vitro Charac-

terization of Sustained -Release Acetaminophen Tablets, *Phar. Res.*, 4, Suppl S27 (1987).

McTaggart et al., "The evaluation of formulation and processing conditions of a melt granulation process," *International Journal of Pharmaceutics*, 19 (1984) 139-148.

Pataki et al., "Rolling Bed Granulation With Local Melt Forming," *Proc. Conf. Appl. Chem. Unit Oper. Processes*, 3(4):258-270 (1983).

Rubinstein et al., Drug Development and Industrial Pharmacy, 6(5), 451-473 (1980).

G Shah, et al., "Polyethylene Glycol as a Binder for Tablets," *Journal of Pharmaceutical Sciences* 66, No. 11, Nov. 1977, 1551-1552.

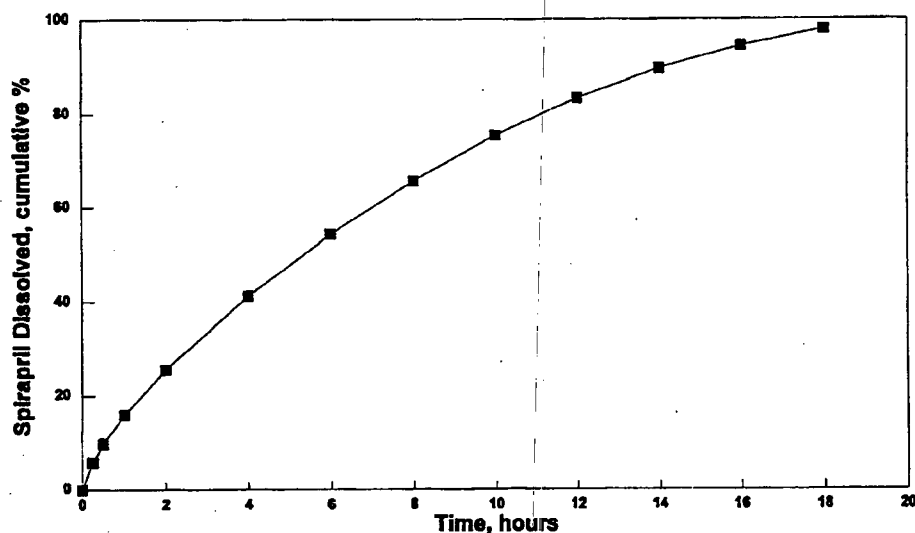
Rubinstein, M., "A New Granulation Method for Compressed Tablets," *Pharm. Pharmac.*, 28, Suppl. 67P (1976).

Primary Examiner—Thurman K. Page
Assistant Examiner—William E. Benston, Jr.
Attorney, Agent, or Firm—Robert S. Honor; Richard E. Vila; Diane E. Furman

[57] ABSTRACT

Therapeutically active sustained release dosage forms are described which are prepared from compositions which comprise (A) a hydrophilic cellulose ether polymer or mixtures thereof as a binder matrix material, (B) a granulating medium selected from the group consisting of a lipid component, polyethylene glycol polymers, and mixtures thereof, said granulating medium having a melting range higher than about 30° C., and (C) a therapeutically active medicament, said components being in melt association. The compositions are prepared by a melt granulation process.

23 Claims, 2 Drawing Sheets



way between the surface of the dissolution medium and the top of the paddle and not less than 1 cm. from each vessel wall.

The amount of medicament present in each of the vessels is calculated by reference to standard solutions using UV spectroscopy.

Accompanying FIGS. 1 and 2 depict the cumulative amount of medicament delivered by each of Tablets 1 and 2, respectively, over an extended period of time.

It will be seen that the tablets of the invention provide a gradual, controlled release of the medicament over an extended period of time.

What is claimed is:

1. A composition for preparing a therapeutically active sustained release dosage form which comprises a melt granulated substantially homogeneous mixture comprising:

(A) 5 to 90 wt. % of a hydrophilic cellulose ether polymer or polymer mixture;

(B) 5 to 50 wt. % of a granulating medium comprising polyethylene glycol and a glyceryl ester of at least one C₁₂₋₂₈ fatty acid, wherein said granulating medium has a melting range above about 30° C.; and

(C) a therapeutically active medicament.

2. A composition according to claim 1 wherein the polyethylene glycol has an average molecular weight of at least about 900.

3. A composition according to claim 2 wherein the polyethylene glycol has an average molecular weight of about 3,000 to about 9,000.

4. A composition according to claim 3 wherein the polyethylene glycol (PEG) is selected from the group consisting of PEG 3350, PEG 4600, PEG 8000, and mixtures thereof.

5. A composition according to claim 3 wherein the hydrophilic cellulose ether polymer is selected from the group consisting of hydroxypropylmethylcellulose, methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, sodiumcarboxymethylcellulose, carboxypolyethylene, carboxymethylhydroxyethylcellulose, and mixtures thereof.

6. A composition according to claim 5 wherein the hydrophilic cellulose ether polymer is selected from hydroxypropylmethylcellulose, methylcellulose, and mixtures thereof.

7. A composition according to claim 6 wherein the hydrophilic cellulose ether polymer comprises methylcellulose.

8. A composition according to claim 6 wherein the lipid component comprises glycerylpalmitostearate.

9. A composition according to claim 7 wherein the methylcellulose has a methoxyl content of about 27.5 to 31.5 wt. %.

10. A composition according to claim 9 wherein the methylcellulose is selected from 4,000 and 15,000 cps viscosity grades.

11. A composition according to claim 6 wherein the hydrophilic cellulose ether polymer comprises hydroxypropylmethylcellulose.

12. A composition according to claim 11 wherein the hydroxypropylmethylcellulose has a methoxyl content of about 16.5 to 30 wt. % and a hydroxypropoxyl content of about 4 to 32 wt. %.

13. A composition according to claim 11 wherein the hydroxypropylmethylcellulose is selected from 100, 4,000, 15,000 and 100,000 cps grades of hydroxypropyl-

methylcellulose having a methoxyl content of 19-24 wt. % and a hydroxypropoxyl content of 7-12 wt. %.

14. A composition according to claim 11 wherein the hydroxypropylmethylcellulose is a 4,000 cps grade having a 28-30 wt. % methoxyl content and a 7-12 wt. % hydroxypropoxyl content.

15. A composition according to claims 1 or 5 comprising:

(A) 30 to 40 wt. % of hydrophilic cellulose ether polymer or polymer mixture;

(B) 15 to 30 wt. % of a granulating medium comprising:

(i) 5 to 20 wt. % polyethylene glycol;

(ii) 5 to 20 wt. % of a glyceryl ester of at least one C₁₂₋₂₈ fatty acid; and

(C) a therapeutically active medicament.

16. A composition for preparing a therapeutically active sustained release solid unit dosage form which comprises a melt granulated substantially homogeneous mixture comprising:

(A) 30 to 40 wt. % of hydroxypropylmethylcellulose polymer;

(B) 15 to 30 wt. % of a granulating medium, which comprises:

(i) 5 to 20 wt. % of glyceryl esters of C₁₂₋₂₈ fatty acids, and

(ii) 5 to 20 wt. % of polyethylene glycol having an average molecular weight of about 3,000 to about 9,000

(weight percents based on total composition), wherein said granulating medium has a melting range of about 30°-100° C.; and

(C) a therapeutically active medicament.

17. A composition according to claim 16 wherein the polyethylene glycol (PEG) is selected from the group consisting of PEG 3350, PEG 4600, PEG 8000, and mixtures thereof.

18. A composition according to claim 17 wherein the hydroxypropylmethylcellulose is selected from 100, 4,000, 15,000 and 100,000 cps grades of hydroxypropylmethylcellulose having a methoxyl content of about 19-24 wt. % and a hydroxypropoxyl content of about 7-12 wt. %.

19. A composition according to claim 18 wherein the glyceryl ester is glycerylpalmitostearate.

20. A composition according to claim 16 wherein the granulating medium has a melting range of 50°-100° C.

21. A process for preparing a therapeutically active composition which comprises:

(a) forming a molten mass by applying heat to a composition comprising:

(A) 5 to 90 wt. % of a hydrophilic cellulose ether polymer or mixtures thereof;

(B) 5 to 50 wt. % of a granulating medium comprising polyethylene glycol and glyceryl esters of C₁₂₋₂₈ fatty acids, wherein the granulating medium has a melting range above about 30° C.; and

(C) a therapeutically active medicament,

(b) mixing the mass to provide a substantially homogeneous mixture; and

(c) cooling the mixture to room temperature.

22. A process according to claim 21 wherein the granulating medium has a melting range of 50°-100° C.

23. A composition according to claims 1, 6 or 16 in tableted form.

* * * * *

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : B01J 2/12, 19/12	A1	(11) International Publication Number: WO 95/09044
		(43) International Publication Date: 6 April 1995 (06.04.95)

(21) International Application Number: PCT/US94/10585
(22) International Filing Date: 28 September 1994 (28.09.94)
(30) Priority Data:
08/128,954 29 September 1993 (29.09.93) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/128,954 (CIP)
Filed on 29 September 1993 (29.09.93)

(71) Applicant (for all designated States except US): E.I. DU PONT DE NEMOURS AND COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): FREEMAN, Roy, Quinn, III [US/US]; 5117 New Kent Road, Wilmington, DE 19808 (US).

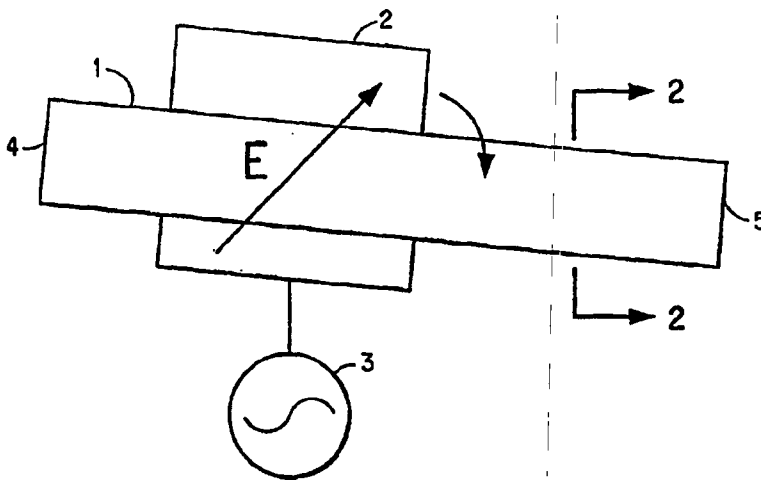
(74) Agents: BLACK, Robert, W. et al.; E.I. du Pont de Nemours and Company, Legal/Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).

(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

Published

With international search report.

(54) Title: MELT GRANULATION WITH DIELECTRIC HEATING



(57) Abstract

A method employing dielectric heating to effect melt granulation and an apparatus therefor, the method employing dielectric heating to melt a meltable component of the composition being granulated.

What is claimed is

1. A process for preparing granular compositions comprising the steps:
 - (i) adding the components of the composition, including at least one component which is meltable, to a chamber;
 - (ii) agitating the mixture of components;
 - (iii) applying dielectric heating to said mixture of components and melting the meltable component; and
 - (iv) collecting melt-formed granules from the chamber, whereby the inside of the chamber walls remains substantially free of caked composition.
2. A process according to Claim 1 wherein one component of the composition is an agriculturally active ingredient.
3. A process according to Claim 1 wherein one component of the composition is a pharmaceutically active ingredient.
4. A process according to Claim 1 comprising operating the granulation steps i to iii and collecting step iv in a continuous manner.
5. A process according to Claim 2 comprising operating the granulation steps i to iii and collecting step iv in continuous manner.
6. A process according to Claim 3 comprising operating the granulation steps i to iii and collecting step iv in a continuous manner.
7. An apparatus for preparing granular compositions comprising:
 - (i) a chamber with agitating means and at least one inlet port; and
 - (ii) an energy source for dielectric heating adjusted to cooperate with (i).
8. An apparatus according to Claim 7 having an outlet port for collecting granular composition made continuously.



US005718923A

United States Patent [19]

Matsuda et al.

[11] **Patent Number:** 5,718,923[45] **Date of Patent:** Feb. 17, 1998**[54] MELT GRANULATED SUCRALFATE PREPARATIONS AND A PROCESS FOR THEIR PRODUCTION****[75] Inventors:** Katsuya Matsuda; Koichi Ozawa, both of Tokyo, Japan**[73] Assignee:** Chugai Seiyaku Kabushiki Kaisha, Tokyo, Japan**[21] Appl. No.:** 727,643**[22] PCT Filed:** Apr. 18, 1995**[86] PCT No.:** PCT/JP95/00753

§ 371 Date: Oct. 15, 1996

§ 102(c) Date: Oct. 15, 1996

[87] PCT Pub. No.: WO95/28938

PCT Pub. Date: Nov. 2, 1995

[30] Foreign Application Priority DataApr. 26, 1994 [JP] Japan 6-088855
Aug. 11, 1994 [JP] Japan 6-189520**[51] Int. CL⁶** A61K 9/50**[52] U.S. Cl.** 424/502; 424/489; 424/472;
424/473; 424/453**[58] Field of Search** 424/502, 489,
424/472, 473, 453; 604/892.1**[56] References Cited****U.S. PATENT DOCUMENTS**4,940,465 7/1990 Theeuwes et al. 604/892.1
5,196,405 3/1993 Packman 514/53
5,417,682 5/1995 Wong et al. 604/892.1**FOREIGN PATENT DOCUMENTS**

WO 89/05645 6/1989 WIPO .

OTHER PUBLICATIONS

Flanders et al, "The Control of Drug Release from Conventional Melt Granulation Matrices," Drug Development and Industrial Pharmacy, vol. 13(6), pp. 1001-1022, 1987.

Kenji Ukita et al, "Preparation of Essential Oils Loaded Granule by Melt Granulation," Drug Development and Industrial Pharmacy, vol. 20(6), pp. 981-992 1994.

Masaharu Miyajima et al, "Design of Sustained-Release Granules prepared by Wax Melting Method," Pharm Tech Japan vol. 8 No. 9 pp. 81-87, 1992.

Yasuo Haramishi et al. "Study on Fluidized Melt-Granulation. I. Examination of the Factors on the Factors on the Granulation¹," Yakugaku Zasshi, vol. 111 (9) pp. 515-523, 1991.*Primary Examiner*—Thurman K. Page*Assistant Examiner*—William E. Benston, Jr.*Attorney, Agent, or Firm*—Browdy and Neimark**[57] ABSTRACT**

Sucralfate preparation produced by melt granulating a mixture of a comminuted sucralfate powder and a water-soluble low-melting point wax, as well as a process for producing a sucralfate preparation comprising the steps of comminuting dry sucralfate into fine particles, mixing the finely divided particles with a water-soluble low-melting point wax and heating the mixture such that the wax is melted to effect melt (adhesion) granulation of the finely divided sucralfate particles are disclosed. Compared to conventional sucralfate preparations, the thus produced sucralfate preparation has a small dispersed particle size, exhibits high capability for binding to plasma proteins and thereby achieves marked improvements in administrability and protein binding capability.

20 Claims, No Drawings

5

30 mg of a dry sucralfate powder and dispersed in water (5 ml). The stock BSA solution (15 ml) was added to the dispersion and mixture was shaken at 37° C. for 30 min. Thereafter, a HCl-KCl buffer solution (20 ml) was added and the mixture was passed through a 0.22 µm membrane filter (Millipore) to separate the sucralfate-bound insoluble BSA. The liquid permanent was used as a sample and subjected to the following assay.

A standard solution (a dilution of the stock BSA solution) and the sample solution were each measured in 20 µl and mixed with a protein measuring reagent (Protein Assay 1→5, Biorad; 5 ml). The quantity of unbound BSA was determined from the absorbance at 595 nm as measured with a spectrophotometer (Shimadzu Corp.); BSA binding capability was calculated as the percentage of the BSA added that bound to sucralfate.

The same measurements were conducted on a commercial sample of subtilized granules (ULCERLMIN, the registered trademark of Chugai Pharmaceutical Co., Ltd.) so that the performance of the subtilized granules prepared in accordance with the invention were compared with the conventional preparation. The results of measurement of dispersed particle size and BSA binding capability are shown in Tables 3 and 4, respectively.

TABLE 3

	Dispersed particle size	
	Average, µm	Percent 50 µm and less
Subtilized granules of invention	5.1	100.0
Conventional subtilized granules	22.0	78.6

TABLE 4

	BSA binding capability, %
Subtilized granules of invention	69.9 (1.5)
Conventional subtilized granules	47.0 (1.0)

* The figures in parentheses are relative values.

Obviously, the subtilized granule preparation of the invention could be dispersed as particles not larger than 50 µm and showed a BSA binding capability 1.5 times as high as the conventional preparation.

EXAMPLE 4

A portion (360 g) of the sucralfate preparation (sucralfate:polyethylene glycol=20:4) obtained in Example 2 was mixed with sucrose (234.6 g), a flavoring agent and other ingredients (in a total of 2.4 g) and a lubricant (3 g) in a V-type mixer (Tsutsui Scientific Instruments Co., Ltd.) to make a powder blend for tableting. The powder was fed into a single-punch machine (Kimura Seisakusho K.K.), where it was compacted into flat, bevel edged tablets each having a diameter of 18 mm and weighing 1 g in a thickness of 3.1 mm.

The thus prepared tablets were measured for the dispersed particle size and BSA binding capability and the results are shown in Tables 5 and 6, which also show the corresponding data on a commercial sample of tablets (ULCERLMIN, the registered trademark of Chugai Pharmaceutical Co., Ltd.)

6

TABLE 5

	Dispersed particle size	
	Average, µm	Percent of 50 µm and less
Invention tablet	10.1	98.8
Conventional tablet	27.2	75.7

TABLE 6

	BSA binding capability, %
Invention tablet	65.1 (2.5)
Conventional Tablet	26.0 (1.0)

* The figures in parentheses are relative values.

Obviously, the tablets prepared in accordance with the invention had very fine dispersed particle sizes as indicated by the presence of at least 98.8% of particles not larger than 50 µm, and they showed a BSA binding capability 2.5 times as high as the conventional tablets.

INDUSTRIAL APPLICABILITY

As described on the foregoing pages, the sucralfate preparations produced by the present invention had small dispersed particle sizes and exhibited high capabilities for binding to plasma proteins as compared with the conventional preparations. Therefore, the invention is expected to make a great contribution in solving the problems associated with the administrability and protein binding capability of the sucralfate preparations produced by conventional methods. The sucralfate preparations produced by the invention have a salient feature in that they can be applied as pharmaceuticals for oral application such as subtilized granules, tablets and capsules or as pharmaceutical for external application.

We claim:

1. A sucralfate preparation produced by melt granulating a mixture of sucralfate with at least 5 wt % of a water-soluble low-melting point wax.
2. A preparation according to claim 1 which comprises sucralfate finely divided into particles at least 90% of which are not larger than 50 µm, and the water-soluble low-melting point wax.
3. A preparation according to claim 2, wherein said finely divided sucralfate has an average particle size of no more than 20 µm and at least 90% of which comprises particles not larger than 50 µm.
4. A preparation according to claim 1, wherein said wax has a melting point not higher than 80° C.
5. A preparation according to claim 4, wherein said wax is polyethylene glycol, polyoxyethylene-polyoxypropylene-glycol or a mixture thereof.
6. A process for producing a sucralfate preparation which comprises the steps of comminuting dry sucralfate into particles at least 90% of which are not larger than 50 µm, mixing the finely divided particles with a water-soluble low-melting point wax and heating the mixture such that said wax is melted thereby enabling the sucralfate particles to be granulated adhesively.
7. A process according to claim 6, wherein said water-soluble low-melting point wax is added in an amount of at least 5 wt % of the sucralfate for mixing with the latter.
8. A process according to claim 6, wherein said dry sucralfate is comminuted into particles having an average

7

size of no more than 20 μm and at least 90% of which are not larger than 50 μm .

9. A process according to claim 6, wherein said wax has a melting point not higher than 80° C.

10. A process according to claim 9, wherein said wax is polyethylene glycol, polyoxyethylene-polyoxypropylene-glycol or a mixture thereof.

11. A process according to claim 6, wherein not only said wax but also an excipient is added.

12. A process according to claim 7, wherein said dry sucralfate is comminuted into particles having an average size of no more than 20 μm and at least 90% of which are not larger than 50 μm .

13. A process according claim 12, wherein said wax has a melting point not higher than 80° C.

14. A process according claim 8, wherein said wax has a melting point not higher than 80° C.

15. A process according to claim 14, wherein said wax is polyethylene glycol, polyoxyethylene-polyoxypropylene-glycol or a mixture thereof.

16. A process according to claim 13, wherein said wax is polyethylene glycol, polyoxyethylene-polyoxypropylene-glycol or a mixture thereof.

8

17. A preparation according to claim 2, wherein said wax has a melting point not higher than 80° C.

18. A preparation according to claim 17, wherein said wax is polyethylene glycol, polyoxyethylene-polyoxypropylene-glycol or a mixture thereof.

19. A sucralfate preparation formed of granules consisting essentially of

finely divided sucralfate particles and an amount sufficient no less than 5% of a water-soluble low-melting point solid wax to agglomerate said finely divided particles into granules.

wherein said finely divided sucralfate particles have an average particle size no greater than about 20 μm with at least 90% of said sucralfate particles having a particle size no greater than 50 μm , and

wherein said water-soluble low-melting point wax has a melting point no greater than 80° C.

20. A sucralfate preparation according to claim 19, in granular form, wherein said solid wax is polyethylene glycol, polyoxyethylene-polyoxypropylene-glycol or a mixture thereof.

* * * * *

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 9/16, 9/52, 31/7048, A61P 31/04		A2	(11) International Publication Number: WO 00/69415
			(43) International Publication Date: 23 November 2000 (23.11.00)
(21) International Application Number: PCT/SI00/00013 (22) International Filing Date: 18 May 2000 (18.05.00) (30) Priority Data: P-9900119 19 May 1999 (19.05.99) SI (71) Applicant (for all designated States except US): LEK, TOVARNA FARMACEVTSKIH IN KEMIČNIH IZDELKOV, D.D. [SI/SI]; Verovškova 57, 1526 Ljubljana (SI). (72) Inventors; and (75) Inventors/Applicants (for US only): FERČEJ TEMELJOTOV, Darja [SI/SI]; Avčinova 10, 1000 Ljubljana (SI). ŠIRCA, Judita [SI/SI]; Polje c. VI/20, 1260 Ljubljana-polje (SI). MOHAR, Milojka [SI/SI]; Gostičeva 9, 1230 Domžale (SI). SALOBIR, Mateja [SI/SI]; Ulica 28. maja 9, 1000 Ljubljana (SI). GOLMAJER, Andrej [SI/SI]; Žigonova 25, 1000 Ljubljana (SI). OPRESNIK, Marko [SI/SI]; Ulica bratov Babnik 42, 1000 Ljubljana (SI). (74) Agent: PATENTNA PISARNA D.O.O.; Copova 14, POB 1725, 1001 Ljubljana (SI).		(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, 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, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(54) Title: MELT GRANULATION			
(57) Abstract The present invention discloses a simple one-step process of coating by means of melt granulation for effective masking of bitterness, and a new, patient-friendly oral pharmaceutical formulation suitable also for diabetics, which at the same time also enables variations in the rate and site of the release of the active component.			

Claims

1. Pharmaceutical formulation in the form of a granulate for oral use, characterized in that it contains clarithromycin or its derivatives coated with a lipid substance.
2. Pharmaceutical formulation according to claim 1, characterized in that clarithromycin or its derivative is admixed with other pharmaceutically acceptable additives.
3. Pharmaceutical formulation according to claim 2, characterized in that the pharmaceutically acceptable additive is a polymer insoluble in stomach.
4. Pharmaceutical formulation according to claim 3, characterized in that the polymer insoluble in stomach is a copolymer of methacrylic acid and methyl methacrylate.
5. Pharmaceutical formulation according to claim 1, characterized in that the lipid substance is a higher fatty alcohol or a suitable acid or a mixture thereof.
6. Pharmaceutical formulation according to claim 1, characterized in that it is, by the addition of other pharmaceutically acceptable substances, prepared in the form of tablets or capsules.
7. Pharmaceutical formulation according to claim 1, characterized in that it is, by the addition of other pharmaceutically acceptable substances, prepared in the form of a suspension.
8. Pharmaceutical formulation according to claim 7, characterized in that it is prepared without sugar (saccharose).

9. Pharmaceutical formulation according to claim 7, characterized in that polyols are added as sweetening agents.
10. Pharmaceutical formulation according to any of claims 1 to 6, characterized in that, additionally, a gastroresistant coating is applied.
11. A process for the preparation of a pharmaceutical formulation according to claim 1, characterized in that it comprises a homogeneous mixing of a coating mixture, melt granulation, cooling and an addition of other excipients for the formation of a granulate.
12. A process for the preparation of a pharmaceutical formulation according to claim 11, characterized in that it is completed by applying a gastroresistant coating.
13. Pharmaceutical formulation in granulate form for oral use, characterized in that it is prepared according to the process of claim 11.
14. Pharmaceutical formulation according to claim 1 useful for the treatment and prophylaxis of bacterial infections.

DELPHION

No active trail

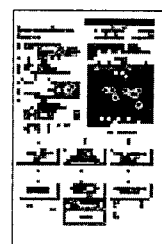
Select CR1**Stop Tracking****RESEARCH****PRODUCTS****INSIDE DELPHION****Log Out****Work Files****Saved Searches****My Account**Search: Quick/Number Boolean Advanced Derwent **Help****The Delphion Integrated View**Buy Now: ☒ PDF | [File History](#) | [Other choices](#)Tools: Add to Work File: [Create new Work File](#) [Add](#)View: [INPADOC](#) | Jump to: [Top](#) Go to: [Derwent](#)☒ [Email this to a friend](#)Title: **JP59022640A2: METHOD AND APPARATUS FOR MELT GRANULATION**Derwent Title: Granulation of molten solns. using dropping tower - where molten soln. is poured through nozzle and meets up-draft of cooling air
[\[Derwent Record\]](#)Country: **JP** JapanKind: **A** DOC. LAID OPEN TO PUBL. INSPEC. [PUBLISHED FROM 1971 ON]Inventor: **NAKANO TOMOTAKA;**
HIDAKI MORIHISA;Assignee: **TOYO ENG CORP**
[News, Profiles, Stocks and More about this company](#)Published /
Filed: **1984-02-04** / 1982-07-28Application
Number: **JP1982000130505**IPC Code: Advanced: **B01J 2/02; B01J 2/04;**
Core: more...
IPC-7: **B01J 2/04;**Priority Number: 1982-07-28 **JP1982000130505**

Abstract: PURPOSE: To lower equipment cost by lowering speed of upward air flow in the lower part of a tower, and raising it nearly to the terminal speed of falling particles as the air rises.

CONSTITUTION: The circular cross section 4 of a granulation tower 4 is continuously larger toward bottom part, and it is linearly decreased as it rises. The tower 4 is erected in a vertical cylinder. The cooling air is blown into the lower end, flows upward at a gradually increasing speed, passes through an upper outlet and a dust collector 6, and drawn out of the tower 4 with a blower 8. A flow rate of the air passing through the tower 4 is controlled with the blower 8 or a damper 7 to be regulated to 0.5W2m/sec at the bottom of the tower 4 and 2W8m/sec at the top.

COPYRIGHT: (C)1984,JPO&Japio

Family: None

Other Abstract
Info: None[Gallery...](#)[Nominate this for the](#)[View Image](#)

1 page



THOMSON REUTERS

[Subscriptions](#) | [Web Seminars](#) | [Privacy](#) | [Terms & Conditions](#) | [Site Map](#) | [Contact Us](#) | [Help](#)

Copyright © 1997-2011 Thomson Reuters