

Drigard & Castro

Abogados

SUPERINDUSTRIA Y COMERCIO

Radicacion : 00059228 00000004

Folios: 2

Fecha (AMD): 2002-11-12 17:06:11

Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

AS: 82.681

Apartado 3692

Cra. 7 16-56
Bogotá - Colombia S.A.

Tel. Conm. 3802200
Tel./Fax: (57.1) 2827976
(57.1) 3802700

E-Mail:bricas@brigardycastro.com.co

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

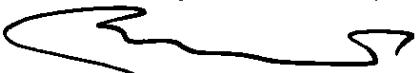
E. S. D.

REF.: Expediente No. 00 059.228 solicitud de Patente a nombre de
BRISTOL MYERS SQUIBB COMPANY

RAMIRO CASTRO DUQUE, vecino de Bogotá, portador de la tarjeta profesional No. 1003 del Consejo Superior de la Judicatura, obrando como apoderado de la Sociedad BRISTOL MYERS SQUIBB COMPANY, según lo acredita el documento de poder presentado en la Secretaría General, de acuerdo con el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito solicitar que se examine si la invención contenida en la solicitud en referencia es patentable.

De acuerdo con lo anterior, me permito anexar el recibo oficial de caja No. 02-71,435 por valor de \$318.000.

Señor Superintendente,


RAMIRO CASTRO DUQUE
C.C. No. 170.322 de Bogotá
Código 340
T.P. No.1003 del C.S.J.
Cra 7 No. 16-56 Piso 9

Noviembre 12, 2002
CPB/hsr

RC 2 177

Industria y Comercio
SUPERINTENDENCIA

18/1

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00059228 00000004 Folios: 2
Fecha (AMD): 2002-11-12 17:06:11
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 02 - 71,435
FECHA : OCTUBRE 24 DE 2002

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	5165316	23/10/2002	8,834,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		85 EXAMEN DE PATENTABILIDAD DE INVEN	318,000.00
		TOTAL :	\$ 318,000.00

SON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

178
182

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor
Ramiro Castro Duque
Apoderado

Oficio N° 000.8834

REFERENCIA	Radicación	00 59228
	Trámite	002
	Evento	001
	Actuación	430
	Folios	034

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 59228, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 6-30
- . Ejemplos: folios 30-49
- . Capítulo reivindicatorio estudiado: folios 167-175
- . Se reivindica prioridad, presentada en Estados Unidos el 12.04.00, bajo el número 09/547948

Objeto de la invención

Según las reivindicaciones 1 a 24 de la presente solicitud, se refiere a una forma de dosificación farmacéutica de rápida disolución que comprende un medicamento y una combinación de cuatro excipientes: un desintegrante, un agente de dispersión, un agente de distribución y un aglutinante.

Clasificación internacional de patentes A 61 K 9/20

179
HS

Claridad de la solicitud

El art. 30 de la decisión 486 establece que *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*

Las reivindicaciones 15-17 contienen todas las características de la reivindicación 1 y deben ser dependientes de ésta.

La frase "una combinación de tres excipientes que consisten de" es inconsistente con la lista de cuatro desintegrantes de la reivindicación 1 y, por lo tanto no es clara.

El término "disolución instantánea" usada en las reivindicaciones 1-9 no tiene sentido bien definido y lleva a dudar de la característica técnica a la cual se refiere, haciendo del sentido de dichas reivindicaciones poco claro. Se recomienda al solicitante caracterizar la composición en términos de tiempo de disolución.

Los términos "agente de dispersión" y "agente de distribución" usados en las reivindicaciones 1-7, 9-12, 22 y 23 no tienen significado definido ya que no es clara la diferencia entre estos dos agentes. Se recomienda hacer la diferencia entre estos agentes dentro de la reivindicación principal.

En las reivindicaciones 5 y 10, el término "sustituida baja" no define ni limita el tipo de celulosa que se utiliza dentro de la composición.

Favor hacer las aclaraciones y correcciones del caso.

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 12.04.00-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
1	WO 9932092	"Proceso para la manufactura de tabletas de dispersión masticables"	01.07.99
2	WO 9846215	"Forma de dosificación robusta rápidamente soluble "	22.10.98
3	EP 0890359	"Tabletas que contienen antibiótico beta lactámico y proceso para producirlas	13.01.99
4	WO 9503785	"Medicaciones para el resfriado/alergia efervescentes de sabor agradable"	09.02.95
5	US 5994348	"Composiciones farmacéuticas que contienen irbesartán"	30.11.99

180
189

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la NOVEDAD

El art. 16 de la decisión 486 contempla *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica"*

WO 9932092 revela tabletas de dispersión rápida de cimetidina, difenhidramina o clorfenhidramina que comprenden un desintegrante y un aglutinante; también contiene un agente de distribución y una agente dispersante.

WO 9846215, EP 0890359, WO 9503785 y US 5994348 revelan tabletas de rápida dispersión que contienen diferentes medicamentos, un desintegrante, un aglutinante, un agente de dispersión y un agente de distribución

Comparando elemento por elemento, las composiciones de las reivindicaciones 1, 5, 9, 10, 13, 15-17 y 22-24 son iguales a las de los documentos citados y puede verse afectada la novedad de dichas reivindicaciones.

Evaluación del NIVEL INVENTIVO

El artículo 18 de la decisión 486 dispone *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"*

WO 9932092 revela tabletas de dispersión rápida de cimetidina, difenhidramina o clorfenhidramina que comprenden un desintegrante y un aglutinante; también contiene un agente de distribución y una agente dispersante.

WO 9846215, EP 0890359, WO 9503785 y US 5994348 revelan tabletas de rápida dispersión que contienen diferentes medicamentos, un desintegrante, un aglutinante, un agente de dispersión y un agente de distribución.

Teniendo en cuenta el objeto de la solicitud, el cual es proporcionar composiciones de rápida disolución que contienen un medicamento y cuatro excipientes, se aprecia que es una derivación evidente del estado de la técnica ya que cualquiera de los documentos citados enseñan composiciones similares que tienen el mismo propósito.

181
185

Un técnico con sus conocimientos y con las enseñanzas de cualquiera de los documentos citados llegaría de manera obvia a las composiciones que se pretenden proteger

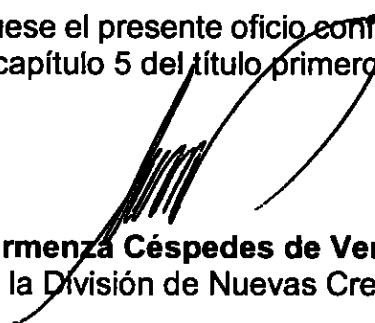
Finalmente, no se muestran pruebas ni resultados en donde se demuestre un efecto sorprendente o mejorado de las composiciones en cuestión

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	WO 9932092	1, 5, 9, 10, 13, 15-17 y 22-24	Novedad
		1-24	Nivel Inventivo
2	WO 9846215	1, 5, 9, 10, 13, 15-17 y 22-24	Novedad
		1-24	Nivel Inventivo
3	EP 0890359	1, 5, 9, 10, 13, 15-17 y 22-24	Novedad
		1-24	Nivel Inventivo
4	WO 9503785	1, 5, 9, 10, 13, 15-17 y 22-14	Novedad
		1-24	Nivel Inventivo
5	US 5994348	1, 5, 9, 10, 13, 15-17 y 22-14	Novedad
		1-24	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001


Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 29 SET. 2005

CONCEPTO TÉCNICO Número 1423	EXAMINADOR TÉCNICO Código 202024
---------------------------------	-------------------------------------

182
H6

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/20	A1	(11) International Publication Number: WO 99/32092 (43) International Publication Date: 1 July 1999 (01.07.99)
(21) International Application Number: PCT/US98/27061 (22) International Filing Date: 17 December 1998 (17.12.98) (30) Priority Data: 61/068,258 19 December 1997 (19.12.97) US (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): VENKATESH, Gopadi, M. [US/US]; 544 General Learned Road, King of Prussia, PA 19406 (US). PALEPU, Nageswara, R. [US/GB]; New Frontiers Science Park (South), Third Avenue, The Pinnacles, Harlow, Essex CM19 5AG (GB). (74) Agents: DINNER, Daru, L. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.
(54) Title: PROCESS FOR MANUFACTURING BITE-DISPERSION TABLETS (57) Abstract This invention relates to a method for the manufacture of Bite-dispersion tablets which disperse easily and quickly in the oral cavity, after a gentle bite, without the aid of water, and if necessary includes masking the bitter taste of medicaments. The process comprises preparing a dry granulation of one or more of medicaments blended with suitable excipients, flavors and a combination of a waxy material and phospholipid (BMI-60) or an intense sweetener derived from fruit flavonoids (Neohesperidine) for taste-masking and compressing into tablets which can be packaged in bottles or blisters using conventional equipment.		

183
184

A need exists for a cost effective, rapid operation process for producing tablets containing medicaments, which provide for ease of oral administration (fast disintegration in the mouth without water) and taste-masking of any bitter ingredients.

5

Summary of the Invention

The present invention is to a fast dispersing tablet, also referred to as a bite-dispersable tablet, containing an active ingredient. The pharmaceutically acceptable fast-dispersing tablet formulation of the present invention has a structure comprising
10 compacted granulates; these granulates comprises a medicament together with a combination of a waxy material and an intense sweetner and/or a taste-masking agent, a pharmaceutically acceptable excipient selected from xylitol, mannitol, maltodextrin, or sorbitol, or a combination thereof; and optionally a flavoring agent and disintegrant; the granulates being compacted together into a tablet form together with extragranular
15 components which are a disintegrant, a sweetner and/or taste-masking agent, and a pharmaceutically acceptable excipient selected from xylitol, mannitol, maltodextrin, or sorbitol, or a combination thereof.

Another aspect of the present invention is a process for the preparation of fast dispersing, or bite-dispersing tablets for oral administration, which process
20 comprises:

A. Manufacturing taste-masked granules:

(i) admixing at least one pharmaceutically active ingredient, with one or more pharmaceutically acceptable excipients selected from the group consisting of a xylitol, directly compressible mannitol, maltodextrin or sorbitol; a waxy material; an
25 intense sweetener or taste-masking agent; and optionally a disintegrant and a flavoring agent; and

(ii) preparing the admixture of step (i) for compression by dry granulation [such as via slugging or roller compacting], milling and sieving; and

30 B. Manufacturing Bite-dispersion tablets

(iii) blending the product of step (ii) with additional pharmaceutically acceptable excipients which comprise xylitol, mannitol, maltodextrin or sorbitol; and optionally includes a flavoring agent, a sweetener/taste-masking agent, and a disintegrant; and

35 (iv) compressing the mixture of step (iii) into tablets.

184

Suitably, the waxy material, in combination with BMI-60 or Neohesperidine DC, is present at a level of from about 1% to about 30%, preferably from about 3% to about 20% by weight of composition. In the intragranular admixture if the first and second component are present it is preferably from about 0.5 to about 2% w/w of the formulation. Alternatively, the waxy material to the taste-masking/sweetener ratio will vary in these formulations from about 20:1 to about 5:1 (total formulation).

The waxy material, taste-masking agents and sweetener agents noted herein for use in the intragranular component mix may also be optionally used in the extragranular admixture.

Suitable active ingredients for incorporation into the bite-dispersion tablets of the present invention include the many bitter, unpleasant tasting, or numbing effects of drugs which include, but are not limited to, histamine H₂-antagonists, such as, cimetidine, ranitidine, famotidine, nizatidine, etinidine; lupitidine, nifenidine, niperotidine, roxatidine, sulfotidine, tuvatidine and zaltidine; antibiotics, such as penicillin, ampicillin, amoxycillin, and erythromycin; acetaminophen; aspirin; caffeine, dextromethorphan, diphenhydramine, bromopheniramine, chloropheniramine, theophylline, spironolactone, NSAIDS's such as ibuprofen, ketoprofen, naprosyn, and nabumetone; 5HT₄ inhibitors, such as granisetron, or ondansetron; serotonin re-uptake inhibitors, such as paroxetine, fluoxetine, and sertraline; vitamins such as ascorbic acid, vitamin A, and vitamin D; dietary minerals and nutrients, such as calcium carbonate, calcium lactate, etc., or combinations thereof.

The above drugs are not limiting but merely exemplary of unpleasant tasting drugs that may be employed in this invention. Additionally, other compounds such as the nonsteroidal anti-inflammatory drugs (NSAIDs), such as naprosyn, i.e. the propionic acid derivatives, are a preferred embodiment of this invention. Suitably, these agents, in particular the anti-inflammatory agents, may also be combined with other active therapeutic agents, such as various steroids, decongestants, antihistamines, etc., as may be appropriate.

The inactive ingredients or excipients, optionally used in the intragranular admixture and the required extragranular admixtures, include the pharmaceutically acceptable excipients such as xylitol [a sweetening agent (2.5 times as sweet as

185

at a level from about 1% to about 10% by weight of composition, preferably from about 2% to about 6% by weight of composition.

5 The formulation may also include coloring agents, or pigments, such as FD&C or D&C approved lakes and dyes, iron oxide and titanium dioxide. The amount of pigment present may be from about 0.1% to about 2.0% by weight of the composition.

10 The formulation may also contain suitable lubricants in the intra and extra-granular mixtures, such as but not limited to, magnesium stearate or stearic acid. Suitably, the lubricant is present in the extra-granular mix.

15 Additional other conventional pharmaceutical diluents or excipients may be also be included, as needed, in either the intragranular or extragranular admixture. Suitable excipients which may be employed include, for example, fillers, binders, lubricants, binders, compression aids, and wetting agents. To further assist patient compliance, the formulation may also contain sweeteners such as aspartame, sodium cyclamate and sodium saccharinate; and flavorants such as those noted above.

20 The present invention provides for a method of manufacturing bite-dispersion tablets which are capable of rapid operation, is cost effective, and suitable particularly to moisture/heat sensitive medicaments.

25 Another aspect of this invention, as compared to other fast-dispersion technologies, is that no specialized manufacturing or packaging equipment is required to manufacture these tablets.

Suitably, the tablets of the present invention include:

- a) 1-60 parts of at least one medicament; and
- 30 b) 10-90 parts, preferably 15-85 parts of xylitol; and
- c) 0.5-20 parts, preferably 1.0-20 parts of a waxy material, such as glyceryl behenate (Compritol®), or glycerol palmitostearate (Precirol®); and
- d) optionally, 0.5-7 parts, more preferably 1.0-4.0 parts of an intense
- 35 sweetener/taste masking agent such as Neohesperidine or BMI-60 (the actual range depending upon the bitterness of the medicament).

190
185

The granulates may further comprises a flavoring agent, or the extragranular component may further comprises a flavoring agent, or a combination thereof.

In the process of making the tablets preferably, the granualtes are optionally subjected to heat treatment prior to being compacted with the extragranular components.

Examples of Bite-Dispersion Tablet Formulations

The examples of typical Bite-dispersion tablet formulations are illustrated in the following sections. These examples are neither exhaustive nor limited in their scope.

Example 1

Blend 80 g of granisetron.HCl with 68 g of xylitol, 4 g of Neohespiridine and 8 g of Compritol (glyceryl behenate) and mill the blend using a micropulverizer.

Prepare the following dry granulation formulation by blending:

Intragranular Admixture

	<u>Ingredient</u>	<u>% W/W</u>
	Milled Granisetron blend	11.2
20	Xylitol	71.0
	Maltodextrin	15.0
	Flavoring agent	1.0
	Aspartame (sweetener)	0.2
	Compritol™ (glyceryl behenate)	1.6

Roller compact, mill and sieve to produce #30-80 mesh granules. Prepare the following compression mix and compress tablets of 1.0 mg (granisetron free base) tablets to weigh 100 mg and of hardness of 1-2 kP:

191
187

	<u>Ingredient</u>	<u>% W/W</u>
	Sieved granules	20.0
	Xylitol	64.6
	Maltodextrin	10.0
5	Sodium starch glycolate	3.0
	Flavoring agent	0.5
	Aspartame	0.3
	Compritol™	<u>1.6</u>
	Total	100.0

10

The tablets thus produced were found to disperse easily in the mouth with a cool feel, after a gentle bite. These tablets conformed to the USP content uniformity requirements and also, exhibited excellent friability (0.3% in 3 min. or 75 revolutions) requiring no special packaging for transportation and distribution.

15

Example 2

Prepare the following roller compactor blend formulation:

	<u>Intragranular Admixture</u>	
20	<u>Ingredient</u>	<u>% W/W</u>
	Paroxetine.HCl	50.0
	Xylitol	21.5
	Flavoring agent	1.0
	BMI-60 (phospho-lipid)	1.5
25	Aspartame	1.0
	Precirol™ (glycerol palmitostearate)	<u>25.0</u>
	Total	100.0

Roller compact the blend, mill and sieve to produce #30-80 mesh granules and heat treat at 45-48°C for 15 min. Prepare the following compression mix and compress into 30 mg strength Bite-Dispersion tablets weighing 200 mg:

30

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau192
188

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/20, 9/26, 9/46		A1	(11) International Publication Number: WO 98/46215 (43) International Publication Date: 22 October 1998 (22.10.98)
(21) International Application Number: PCT/US98/07216 (22) International Filing Date: 13 April 1998 (13.04.98) (30) Priority Data: 60/043,242 16 April 1997 (16.04.97) US Not furnished 9 April 1998 (09.04.98) US (71) Applicant: CIMA LABS INC. [US/US]; 10000 Valley View Road, Eden Prairie, MN 55344-9361 (US). (72) Inventors: KHANKARI, Rajendra, K.; 18065 87th Place North, Maple Grove, MN 55311 (US). HONTZ, John; 12800 54th Avenue North, Plymouth, MN 55442 (US). CHASTAIN, Sara, J.; 10550 Nathan Lane North, Maple Grove, MN 55369 (US). KATZNER, Leo; 2460 Emerald Lane, Eden Prairie, MN 55346 (US). (74) Agents: TESCHNER, Michael, H. et al.; Lerner, David, Littenberg, Krumholz & Mentlik, 600 South Avenue West, Westfield, NJ 07090 (US).			(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.
(54) Title: RAPIDLY DISSOLVING ROBUST DOSAGE FORM			
(57) Abstract The invention is directed to a hard tablet that can be stored, packaged and processed in bulk. Yet the tablet dissolves rapidly in the mouth of the patient with a minimum of grit. The tablet is created from an active ingredient mixed into a matrix of a non-direct compression filler and a relatively high lubricant content.			

terms of production, storage, transport and during consumer usage. They are also significantly more costly to produce.

According to U.S. Pharmacopoeia No. 23, 1995, Chap. 1216 entitled "Tablet Friability," the text of which is hereby incorporated by reference, effervescent tablets and chewable tablets often have different specifications as far as friability, when compared to normal tablets. These tablets normally require special packaging. That, however, is a great understatement.

The Zydis tablets, for example, are so fragile that the matrix material must be formed by freeze-drying in an individual tablet-sized container. While the use of an effervescent couple in combination with microparticles as disclosed in *Wheling et al.* does overcome the need for such extreme measures, the need to minimize in-mouth disintegration times still require the use of non-traditional packaging and processing methodology. For example, normal conveyors such as vibratory conveyors or bulk hoppers common in the pharmaceutical industry could not be used, as these high-speed, high-volume devices tend to cause damage to the resulting tablets. Similarly, the resulting tablets cannot be stored on a hopper after tableting but before packaging. This can seriously interfere with the processing efficiencies of high-volume presses.

Moreover, the resulting tablets have to be packaged in individual, blister-type packages that are robust enough to avoid tablet breakage. They could not be packaged in a conventional, multi-tablet bottle, individual foil pouches or traditional blister packaging.

SUMMARY OF THE INVENTION

The present invention relates to a hard, compressed, rapidly dissolvable dosage form adapted for direct oral dosing. The dosage form includes an active ingredient and a matrix. The matrix is composed of at least a non-direct compression filler and a lubricant. The dosage form is

199
190

adapted to rapidly dissolve in the mouth of a patient and thereby liberate the active ingredient. Preferably, the dosage form has a friability of about 2% or less when tested according to the U.S.P. The dosage form also preferably has a hardness of 15-50 Newtons ("N").

5 It is desirable that the dosage form dissolve in about 90 seconds or less in the patient's mouth. It is also often desirable that the dosage form include at least one particle. The particle would the active ingredient and a protective material. These particles can include rapid release particles and or sustained release particles.

10 In a particularly preferred formulation in accordance with the present invention there is provided a hard, compressed, rapidly dissolving tablet adapted for direct oral dosing. The tablet includes particles made of an active ingredient and a protective material. These particles are provided in an amount of between about 0.01 and about 75 % by weight based on
15 the weight of the tablet. The tablet also includes a matrix made from a non-direct compression filler, a wicking agent, and a hydrophobic lubricant. The tablet matrix comprises at least about 60% rapidly water soluble ingredients based on the total weight of the matrix material. The tablet has a hardness of between about 15 and about 50 Newtons, a
20 friability of less than 2% when measured by U.S.P. and is adapted to dissolve spontaneously in the mouth of a patient in less than about 60 seconds and thereby liberate said particles and be capable of being stored in bulk.

 The dosage forms described above are able to dissolve
25 rapidly in the mouth of the patient, with a minimum of grit or other organoleptically unpleasant species. Moreover, because the dosage forms are hard and have low friability they can be handled and packaged like other, non-rapidly dissolving dosage forms.

Therefore, it was surprising to discover that non-direct compression fillers may in fact be used in the production of a hard, non-friable, directly compressible, yet rapidly dissolvable, in-mouth dosage form, particularly in an automated, commercial production setting.

5 Any conventional material can be used as a filler in accordance with the present invention, so long as it meets the overall objectives hereof. The filler must be rapidly dissolvable when a tablet produced from same is placed in the mouth. This means that the material must be significantly rapidly water soluble. In addition, generally, the
10 particle size of the filler will be relatively small, particularly compared to direct compression fillers.

Generally, direct compression excipients, particularly fillers and binders, are specialty excipients. In most cases, they are common materials that have been physically modified to impart greater fluidity and
15 compressibility. In the case of sugars, such as, for example, dextrose, this generally means granulation to increase particle size. Direct compression mannitol, for example, generally has a minimum of at least about 80% average particle size over 100 microns. Other commercially available direct compression mannitols have a minimum particle size standard of
20 greater than 90% over 200 microns. The opposite is true of the fillers in accordance with the present invention. While direct compression fillers may have at least 85% of the particles over 100 microns in size, often 85% of the particles of filler used in the present invention are significantly under 100 microns. In accordance with the present invention, average
25 particle size generally ranges from between about 10 and about 80 microns, and most preferably, between about 20 to about 65 microns.

Particularly preferred fillers, in accordance with the present invention are non-direct compression sugars and sugar alcohols which meet the specifications discussed above. Such sugars and sugar alcohols include,

192 196
without limitation, dextrose, mannitol, sorbitol, lactose and sucrose. Of course, dextrose, for example, can exist as either a direct compression sugar, *i.e.*, a sugar which has been modified to increase its compressibility, or a non-direct compression sugar.

- 5 Generally, the balance of the formulation can be matrix. Thus the percentage of filler can approach 100%. However, generally, the amount of non-direct compression filler useful in accordance with the present invention ranges from about 25 to about 95%, preferably between about 50 and about 95% and more preferably from about 60 to about 95%.
- 10 In contrast, the prior art, as represented by *Cousins et al.* uses only up to about 42% of a filler and it is a direct compression sugar as well.

- It has also been surprisingly found that when formulating dosage forms in accordance with the present invention, a relatively high proportion of lubricant should be used when compared to the prior art.
- 15 Lubricants, and in particular, hydrophobic lubricants such as magnesium stearate, are generally used in an amount of between about 0.25 to about 5%, according to the Handbook of Pharmaceutical Excipients. However, as *Cousins et al.* amply demonstrate, when making a rapidly disintegrable tablet for direct in-mouth administration, one would seek to minimize the
- 20 amount of magnesium stearate or other lubricant used. These hydrophobic lubricants generally interfere with disintegration and dissolution. They can also interfere with the compressibility of the material hindering the ability to make hard, non-friable tablets and the like. Not surprisingly, *Cousins et al.*, who were seeking to make hard tablets that will rapidly disintegrate,
- 25 teach the use of an amount of magnesium stearate which ranges from between about 0.4 to about 0.5% by weight, *i.e.*, at the lower portion of the conventional range.

Moreover, the generally high level of non-direct compressible filler and the relatively low proportions of disintegrants used

193 HJ
fillers, can be formulated using direct compression. Direct compression involves mixing the various ingredients in a mixing vessel and then metering them directly into a tablet press whereupon they are pressed into tablets.

5 It is also surprising that, in accordance with the present invention, rapidly dissolving tablets can be manufactured with not only high levels of lubricant, but also that lubricant blend times of 10 to 25 minutes and greater can be used. However, according to the present invention, blend times of ten minutes and greater can be used without
10 compromising compressibility, disintegration and dissolution of the tablets. In fact, this even improves the flow characteristics of this material.

In summary, it has been found that non-direct compression fillers, namely powdered mannitol, can be directly compressed, using lower than expected compression forces, at fairly high levels of lubricant
15 and long lubricant blending. The result is a hard, yet rapidly orally dissolvable tablet.

In accordance with the present invention, the dosage forms can have any size conventional in the industry. However, dosage forms of up to about 2.54 centimeters or 1 inch, are generally preferable. It is also
20 preferred that tablets produced have generally convex surfaces. Applicants have found that, by insuring that the tablet in question has as few sharp edges as possible, it is also possible to help retard the dusting or break-up of the tablets in accordance with the present invention, particularly during handling and shipping. Other shapes which retard the formation of sharp
25 edges are also specifically contemplated hereby.

In addition to the ingredients previously discussed, the matrix may also include wicking agents, non-effervescent disintegrants and effervescent disintegrants. Wicking agents are compositions which are capable of drawing water up into the dosage form. They help transport

194 ~~108~~

-25-

moisture into the interior of the dosage form. In that way the dosage form can dissolve from the inside, as well as from the outside.

Any chemical which can function to transport moisture as discussed above can be considered a wicking agent. Wicking agents include a number of traditional non-effervescent disintegration agents. These include, for example, microcrystalline cellulose (AVICEL PH 200, AVICEL PH 101), Ac-Di-Sol (Croscarmellose Sodium) and PVP-XL (a crosslinked polyvinylpyrrolidone); starches and modified starches, polymers, and gum such as arabic and xanthan. Hydroxyalkyl cellulose such as hydroxymethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose, as well as compounds such as carbopol may be used as well.

The conventional range of non-effervescent disintegrant agents used in conventional tablets can be as high as 20%. However, generally, the amount of disintegration agent used ranges from between about 2 and about 5%, according to the Handbook of Pharmaceutical Excipients. Understandably, however, when a rapidly disintegrating dosage form is envisioned, the relative proportion of disintegration agent used will be increased. *Cousins et al.*, for example, requires from about 6.1 to about 13.3% reticulated PVP, as described in its various examples.

In accordance with the preferred embodiments of the present invention, the amount of wicking agents used ranges from between 2 to about 12% and preferably from between 2 to about 5%. This is surprising as tablets containing the same amount of the same materials used as disintegration agents normally exhibit disintegration times on the order of tens of minutes. In accordance with the preferred embodiments of the present invention, dissolution occurs in under 90 seconds and most preferably under 45 seconds. This also underscores the fact that while there may be some incidental disintegration due to the inclusion of these

195 199

-34-

Formula:	Coated Acetaminophen	944mg
	(10% coating factor)	
	Aspartame	50mg
	Disintegrant	89mg
	Lubricant	5mg
	Flavor	<u>12mg</u>
	Total	1100mg total tablet weight

Tablets were compressed using an average compression force of 23.28kN (109N Hardness) and had an average ejection force of 802.8N. Disintegration time in vitro was 43.90 seconds in vivo was greater than 40
5 seconds. Friability was not measured. Tablets tasted terrible and were extremely gritty.

Example 10.

Coated APAP (7% coated with ethylcellulose)	530mg
Compressible Sugar	160mg
Microcrystalline Cellulose	90mg
Crospovidone	60mg
Sodic Carbocymethylcellulose	50mg
Silicon Dioxide	6mg
Lubricant	4mg
Sweetener	25mg
Flavor	15mg
Magnesium Trisilicate	<u>50mg</u>
Total	990mg total tablet weight

Tablets were compressed using an average compression force of 35.68kN (101N Hardness) and had an average ejection force of 362.8N.
10 Disintegration time in vitro was 65.59 seconds.

Examples 9 and 10 are very similar to the formulations described in the *Cousins et al.* patent discussed herein. These examples illustrate many of the advantages of the present invention. First, it should be noted that in both cases, the relative proportion of rapidly water soluble
15 materials was minimal. Thus, when these tablets disintegrate, the patient is left with a mouth full of particulate materials which must be swallowed,

700
196

(19)  **Europäisches Patentamt**
European Patent Office
Office européen des brevets



(11) **EP 0 890 359 A1**

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

(43) Date of publication:
13.01.1999 Bulletin 1999/02

(51) Int. Cl.⁶: **A61K 31/545**, **A61K 9/20**,
A61K 47/30, **A61K 47/38**

(21) Application number: **97904616.6**

(86) International application number:
PCT/JP97/00509

(22) Date of filing: **21.02.1997**

(87) International publication number:
WO 97/31639 (04.09.1997 Gazette 1997/38)

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL
PT SE

(72) Inventor: **YAMAGUCHI, Hisami**
Toyono-gun, Osaka 563-01 (JP)

(30) Priority: **29.02.1996 JP 42743/96**
29.11.1996 JP 320264/96

(74) Representative:
Türk, Gille, Hrabal
Brucknerstrasse 20
40593 Düsseldorf (DE)

(71) Applicant:
FUJISAWA PHARMACEUTICAL CO., LTD.
Osaka-shi Osaka 541-8514 (JP)

(54) **TABLETS CONTAINING BETA-LACTAM ANTIBIOTIC AND PROCESS FOR PRODUCING THE SAME**

(57) Tablets containing a β -lactam antibiotic which can be easily taken as such because they are small and which, for administration to a dysphagic person, e.g. one of an advanced age, can be taken as a dispersion because they readily disintegrate by themselves when dropped into water in a glass. Each tablet comprises 60 to 85 wt.% β -lactam antibiotic, 1 to 10 wt.% lowly substituted hydroxypropylcellulose and/or crosslinked polyvinylpyrrolidone as a disintegrator, and 0.5 to 2 wt.% binder. For producing the tablets, these ingredients are tableted using water or an aqueous solution of ethanol, etc.

EP 0 890 359 A1

Description

TECHNICAL FIELD

5 This invention relates to β -lactam antibiotic-containing tablets and a method of producing the same. More particularly, it relates to tablets of the above variety which can be orally taken either as such or, for taking by, for example, the aged who have difficulties in swallowing, as a dispersion available upon dropping the same into water in a glass for self-disintegration, and to a method of producing the same.

10 BACKGROUND TECHNOLOGY

Particularly in Europe and America, where β -lactam antibiotics such as cefixime and cefdinir are administered generally in single doses of as great as 200 mg to 400 mg potency, unit dosage forms, whether they are capsules or tablets, have to be considerably large in size. When 400 mg potency capsules are prepared, for instance, the capsule size reaches approximately No. 0, so that not only patients having difficulties in swallowing but also ordinary adult patients become reluctant to take them or get a repulsive sensation in taking them. Such capsules are indeed difficult to take. In the case of tablets, too, 400 mg potency tablets generally weigh 700 to 1,000 mg per tablet and accordingly are large-sized.

20 The problems encountered in taking such large dosage forms give an unnecessary sensation of oppression to patients on the occasion of taking them. Improvements in their administrability have thus been required.

Therefore, the present inventor attempted to provide a dosage form with improved administrability by reducing the tablet size as much as possible to thereby facilitate the taking of tablets by the recipient and at the same time to provide a dosage form capable of being taken in the form of a dispersion resulting from rapid self-disintegration upon its being simply dropped into water or the like in a glass, for instance, to thereby make said dosage form administrable to persons of advanced age or children having difficulties in swallowing the dosage form as such. The expression "rapid self-disintegration" as used herein means that when the preparation is dropped into a glass containing a liquid such as water, the tablet form spontaneously collapses generally within 3 minutes, preferably within 1 minute, so that said preparation can be orally taken in dispersion form without awaiting long before taking.

It is indeed easy to produce tablets capable of self-disintegrating very rapidly by incorporating an effervescent agent comprising a combination of sodium hydrogen carbonate and tartaric acid, for instance. However, when such tablets are orally taken, they give off bubbles in the oral cavity, so that patients feel a discomfort or an unnecessary sensation of anxiety. For securing a good shelf-life in a humid environment, it is necessary to use a moisture-proof packaging material, which increases the production cost. Therefore, in developing the dosage form which the present invention is intended to provide, it has been a tough problem to find out a formulation enabling very rapid self-disintegration without the aid of any effervescent component.

35 For producing β -lactam antibiotic-containing tablets which can be easily ingested as they are and be also ingested in the form of a dispersion resulting from self-disintegration thereof, a technology is described in European Patent EP 0281200 B (corresponding Japanese patent application: Kokai Tokkyo Koho S63-301820), which comprises adding 24 to 70% by weight, based on the weight of the β -lactam antibiotic, of microcrystalline cellulose or microfibrillated cellulose as a first disintegrator and 2 to 20% by weight, on the same basis, of low-substituted hydroxypropylcellulose or the like as a second disintegrator.

However, said first disintegrator, which is used in a large amount, increases the tablet size. In addition, the proportion of a binder component for wet granulation is as low as 0 to 0.1% by weight based on the antibiotic, hence is substantially nil. This is because the use of a binder renders tablets extremely poor in self-disintegrating properties. In the process for producing these tablets, in which no binder is used, a special method of insuring an integrity of the artefact is employed which comprises mixing the antibiotic bulk substance with microcrystalline cellulose and kneading the mixture with the aid of water under application of a great deal of force, without using any alcohol. As a result, large lumps are formed inevitably and they are milled in the wet state and then dried, followed by further milling to provide granules for tableting. It is a problem that these steps are very inefficient.

45 Meanwhile, tablets containing amoxicillin, which is a β -lactam antibiotic, are commercially available under the trade name of Flemoxin Solutab 500 from Brocades Pharma (Netherlands), the patentee to whom said European patent has been granted. Said tablets each contains 500 mg potency (about 570 mg) of amoxicillin and weighs about 970 mg, hence is very large and not entirely suited for oral administration.

Most β -lactam antibiotics are bitter. Therefore, aqueous dispersions prepared from tablets containing them, when orally taken, give a bitter taste, although the tablets, when taken as such, taste not so bitter. For masking the bitter taste, it thus becomes necessary to incorporate a sweetener, preferably a synthetic sweetener which is effective at low addition levels and thus suited for tablet miniaturization. However, when a commercial synthetic sweetener is incorporated, a problem arises, namely the self-disintegrating properties of tablets become poor, since synthetic sweeteners are sol-

201
198

uble in water and become viscous and sticky.

DISCLOSURE OF THE INVENTION

5 In an attempt to develop a method of improving the rate of self-disintegration of tablets and at the same time miniaturizing the same, the present inventor made investigations concerning the disintegrator species to be used, the level of addition thereof, the binder addition level, the synthetic sweetener particle size and the method of incorporating the same, among others and, as a result, the inventor invented β -lactam antibiotic-containing tablets which are small-sized, show good self-disintegrating properties and can be produced by a conventional method.

10 Furthermore, the inventor found that when granulation is performed using ethanol, isopropyl alcohol or an aqueous solution of ethanol or isopropyl alcohol, tablets showing better dispersibility upon self-disintegration can be obtained.

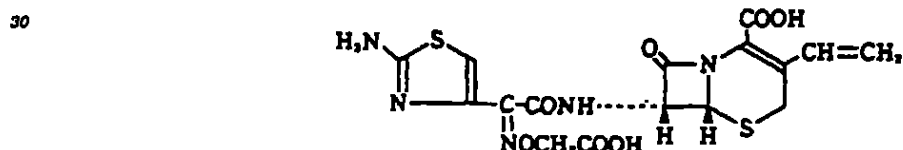
The β -lactam antibiotic-containing tablets of this invention contain, per tablet, 60 to 85% by weight of an β -lactam antibiotic, 1 to 10% by weight of low-substituted hydroxypropylcellulose and/or crosslinked polyvinylpyrrolidone as a disintegrator, and 0.5 to 2% by weight of a binder.

15 Preferably, the β -lactam antibiotic-containing tablets of this invention further contain, per tablet, 0.5 to 15% by weight of a synthetic sweetener and/or a granulated synthetic sweetener.

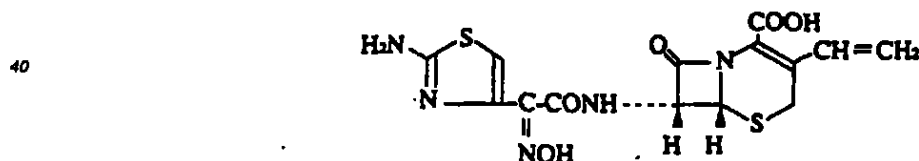
The β -lactam antibiotic-containing tablet production method of this invention is characterized in that the above-specified respective proportions of a β -lactam antibiotic, the disintegrator and a binder, optionally together with one or more excipients, are granulated using ethanol, isopropyl alcohol or an aqueous solution of ethanol or isopropyl alcohol, the granulation product is mixed with the above-specified proportion of a synthetic sweetener and/or a granulated synthetic sweetener, optionally together with one or more other additives, and the resulting mixture is compressed.

20 The β -lactam antibiotic to be used in the practice of this invention is one capable of producing a beneficial effect upon oral administration and includes, for example, cefixime and cefdinir respectively represented by the structural formulas shown below as well as cefaclor, cefroxadine, cefadroxil, cefaloglycin, cefalexin, cefradine, amoxicillin, ampicillin and the like.

Cefixime



Cefdinir



Each tablet contains such β -lactam antibiotic in a proportion of 60 to 85% by weight, preferably 65 to 80% by weight.

50 As a result of investigations concerning the disintegrator species to be used in the practice of this invention and the level of addition thereof, it was found that, as compared with such salt type disintegrators as ECG 505 (trademark; carboxymethylcellulose calcium), Ac-Di-Sol (trademark; crosslinked carboxymethylcellulose sodium) and Primojel (trademark; starch glycolic acid sodium), nonion type disintegrators, such as low-substituted hydroxypropylcellulose (L-HPC) and crosslinked polyvinylpyrrolidone, can produce a very good disintegrating effect even when they are added in small proportions. Low-substituted hydroxypropylcellulose is a product derived from cellulose by partial substitution with the 2-hydroxypropoxy group, the degree of substitution being not higher than 25%, preferably 7 to 16%.

Generally, low-substituted hydroxypropylcellulose and crosslinked polyvinylpyrrolidone are incorporated in tablets independently, although both may be used combinedly.

Such disintegrator is used in a proportion of 1 to 10% by weight, preferably 3 to 8% by weight, on a per-tablet basis.

203
199

EP 0 890 359 A1

followed by observation of the appearance.

Table 7

	Disintegration time (sec.)	Dispersibility after standing
Granulation using 50% ethanol	39	a
Granulation using 10% ethanol	84	a
Granulation using water	62	b
Flemoxin Solutab 500 (commercial product)	46	b

a : Wholly uniform in color, substantially without any precipitate.
b : A supernatant and a slight amount of a precipitate.

The tablets derived from the granules prepared using ethanol are still better in dispersibility after standing as compared with those derived from the granules prepared using water.

Test Example 5 (Disintegration test)

Test preparations A: Tablets produced in Example 1 to be mentioned later. B: Tablets produced in Example 7 to be mentioned later. C: Tablets produced in Example 8 to be mentioned later.

Test method

The disintegration time evaluation was performed in distilled water at $20 \pm 1^\circ\text{C}$ with 4 cycles per minute of basket ascending and descending, using an apparatus prescribed in the Japanese Pharmacopeia (12th edition) under

Disintegration Test.

Test results

A: 1.13 minutes
B: 1.30 minutes
C: 1.02 minutes

The disintegration test results indicate that the test preparations A to C of this invention each shows good disintegrability.

EXAMPLE

Example 1

Water was added to saccharin calcium and the mixture was granulated by a conventional method, followed by drying, sieving and sizing to give saccharin calcium granules not less than $150\ \mu\text{m}$ in particle size.

According to the formulation shown below, micronized cefixime bulk substance, microcrystalline cellulose, low-substituted hydroxypropylcellulose (L-HPC) and polyvinylpyrrolidone were weighed and mixed together, water was then added, and the mixture was granulated. The granulation product was dried under flowing air at 40°C for 17 hours and then sized using a $500\text{-}\mu\text{m}$ sieve. The granules sieved out were mixed with magnesium stearate, light anhydrous silicic acid, strawberry flavor and the above-mentioned granulated saccharin calcium according to the formulation shown below, followed by compressing on a single-punch tablet machine to give tablets each having the specified weight.

Table 8

Micronized cefixime bulk substance	448.9 mg (400 mg potency)
Microcrystalline cellulose (Avicel™ PH101; Asahi Chemical Industry)	38.9 mg

Table 8 (continued)

L-HPC (LH-21; Shin-Etsu Chemical)	38.9 mg
Polyvinylpyrrolidone (Kollidon™ 30; BASF)	4.9 mg
Light anhydrous silicic acid (Aerosil™; Tomita Seiyaku)	1.2 mg
Magnesium stearate	5.9 mg
Saccharin calcium (not less than 150 µm in particle size)	20.0 mg
Strawberry flavor	7.5 mg
Total	566.2 mg

Example 2

Saccharin calcium and light anhydrous silicic acid were mixed together in a ratio of 20:1 and then water was added. The resultant mixture was granulated by a conventional method, followed by drying and sizing to give a granulated mixture of saccharin calcium and light anhydrous silicic acid (75-500 µm in particle size).

Then, tablets were produced following the procedure of Example 1 except that 21 mg of the above granulated mixture was used in lieu of 20 mg of saccharin calcium (Example 1, Table 8).

Example 3

Saccharin calcium and hydrated silicon dioxide were mixed together in a ratio of 20:1 and then water was added. The resultant mixture was granulated by a conventional method, followed by drying and sizing to give a granulated mixture of saccharin calcium and hydrated silicon dioxide (75-500 µm in particle size).

Then, tablets were produced following the procedure of Example 1 except that 21 mg of the above granulated mixture was used in lieu of 20 mg of saccharin calcium (Example 1, Table 8).

Example 4

Tablets each containing 400 mg (potency) of cefixime were produced in the same manner as in Example 1 except that L-HPC of Example 1 (Table 8) was replaced by the same amount of crosslinked polyvinylpyrrolidone (Kollidon™ CL; BASF).

Example 5

Tablets each containing 400 mg (potency) of cefixime were produced in the same manner as in Example 1 except that polyvinylpyrrolidone of Example 1 (Table 8) was replaced by the same amount of hydroxypropylcellulose (HPC-L; Nippon Soda).

Example 6

Tablets each containing 400 mg (potency) of cefixime were produced in the same manner as in Example 1 except that polyvinylpyrrolidone of Example 1 (Table 8) was replaced by the same amount of hydroxypropylmethylcellulose (TC-5R™; Shin-Etsu Chemical).

Example 7

According to the same formulation as that shown in Example 1 (Table 8), micronized cefixime bulk substance, microcrystalline cellulose, L-HPC and polyvinylpyrrolidone were weighed and mixed together, 50% aqueous ethanol was added, and the mixture was granulated. The granulation product was dried under flowing air at 40°C for 17 hours and then sized using a 500-µm sieve. The granules sieved out were mixed with magnesium stearate, light anhydrous silicic acid, strawberry flavor and the granulated saccharin calcium prepared in Example 1 (not less than 150 µm in particle size) and the resultant mixture was compressed on a single-punch tablet machine to give tablets having the same composition as that in Example 1 (Table 8).

201 705

Example 8

According to the formulation shown below, cefdinir-containing tablets were produced in the same manner as in

5 Example 7.

Table 9

10	Micronized cefdinir bulk substance	306.8 mg (300 mg potency)
	Microcrystalline cellulose (Avicel PH101)	29.2 mg
	L-HPC (LH-21)	29.2 mg
	Polyvinylpyrrolidone (Kollidon 30)	3.7 mg
15	Light anhydrous silicic acid (Aerosil)	0.9 mg
	Magnesium stearate	4.4 mg
	Saccharin calcium (not less than 150 µm in particle size)	15.0 mg
20	Strawberry flavor	5.6 mg
	Total	394.8 mg

Claims

- 25 1. A β -lactam antibiotic-containing tablet which comprises 60 to 85% by weight of a β -lactam antibiotic, 1 to 10% by weight of low-substituted hydroxypropylcellulose and/or crosslinked polyvinylpyrrolidone as a disintegrator and 0.5 to 2% by weight of a binder per tablet.
- 30 2. A tablet as claimed in Claim 1, wherein the binder is polyvinylpyrrolidone, hydroxypropylcellulose or hydroxypropyl-methylcellulose.
3. A tablet as claimed in Claim 1 or 2 which further comprises 0.5 to 15% by weight of a synthetic sweetener and/or a granulated synthetic sweetener.
- 35 4. A tablet as claimed in Claim 3, wherein the synthetic sweetener or the granulated synthetic sweetener has an mean particle size of not less than 150 µm.
5. A tablet as claimed in Claim 4, wherein the synthetic sweetener or the granulated synthetic sweetener is not less than 150 µm in particle size.
- 40 6. A tablet as claimed in Claim 3, wherein the granulated synthetic sweetener comprises a synthetic sweetener, and light anhydrous silicic acid and/or hydrated silicon dioxide.
- 45 7. A tablet as claimed in any of Claims 1 to 6, wherein the β -lactam antibiotic is cefixime or cefdinir.
8. A tablet as claimed in Claim 7 which contains 400 mg potency of cefixime, the tablet weight being not greater than 650 mg.
- 50 9. A tablet as claimed in Claim 7 which contains 300 mg potency of cefdinir, the tablet weight being not greater than 450 mg.
10. A method of producing β -lactam antibiotic-containing tablets which comprises admixing a synthetic sweetener and/or a granulated synthetic sweetener, optionally together with one or more other additives, with a granulation product prepared from the β -lactam antibiotic, disintegrator and binder specified in Claim 1, optionally together with one or more excipients, by using ethanol, isopropyl alcohol or an aqueous solution of ethanol or isopropyl alcohol, and then tableting the resulting mixture.
- 55

202 706



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/00, 9/14	A1	(11) International Publication Number: WO 95/03785 (43) International Publication Date: 9 February 1995 (09.02.95)
(21) International Application Number: PCT/US94/08551 (22) International Filing Date: 27 July 1994 (27.07.94) (30) Priority Data: 08/100,956 3 August 1993 (03.08.93) US (71) Applicant: WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors: LECH, Stanley; 46 Cherokee Avenue, Rockaway, NJ 07866 (US). DENICK, John, Jr.; 413 Springdale-Greendell Road, Newton, NJ 07860 (US). SCHOBEL, A., Mark; 307 Van Nest Road, Flemington, NJ 08822 (US). (74) Agents: ALMER, Charles, W., III; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.		(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.
(54) Title: PLEASANT TASTING EFFERVESCENT COLD/ALLERGY MEDICATIONS (57) Abstract A pleasant tasting, effervescent cold/allergy medication is provided in a solid tablet form. Bitter tasting decongestants, antihistamines, antitussive and expectorants are effectively taste masked using a magnesium trisilicate/fumed silica adsorbate which is undetectable during dissolution in the mouth yet provides a high degree of drug bioavailability when it reaches the acidic conditions of the stomach.		

203
204

et. al. teaches and discloses an effervescent tablet for the oral administration of a wide variety of drugs and other active pharmaceutical agents. The tablets are dissolved in the mouth and the active agent of choice is microencapsulated for dissolution and absorption in the stomach. The microcapsules allegedly provide a taste-masking function for bitter-tasting drugs. However, the tablet must not be chewed or crushed within the mouth since this would cause a rupture of the microcapsules and a release of the actives therein which would result in a bitter, unpleasant taste and a drawback to patient compliance. Moreover, microencapsulated drugs tend to have slow and unpredictable release profiles.

It is an object of the present invention to provide an orally administered effervescent medication for the relief of cold, sinus and allergy symptoms that is both pleasant tasting and rapidly disintegratable for enhanced drug bioavailability. It is a further object of the present invention to provide a solid dosage form of medication that provides a pleasant organoleptic mouthfeel through the effervescent disintegration thereof and also taste masks otherwise bitter tasting drugs which are readily available for absorption into the system.

Summary of the Invention

The present invention provides a pleasant tasting, organoleptically pleasing medication for the relief of colds, sinus and allergy by taste-masking a bitter-tasting pharmaceutical such as a decongestant, antihistamine and/or expectorant by

204
701

adsorption of the drug(s) onto a complex silica adsorbate and combining the resultant mixture with a carbonate-acid effervescent system.

Detailed Description of the Invention

Decongestants, antihistamines and expectorants are generally bitter tasting chemical compositions that must be encapsulated or taste-masked in some fashion when orally administered in order to allow them to pass through the mouth undetected for dissolution and absorption in the stomach. The problem with most attempts by the prior art to do this is that they also hamper the release of the drug and hence its bioavailability to the system which delays any relief provided thereby. The present invention comprises adsorbing any or all of the bitter tasting drugs onto a complex magnesium trisilicate and then mixing the drug carrier system thus formed with an effervescent component comprised of a carbonate-acid reaction system which is then dried and tableted for oral administration.

Complex magnesium trisilicate adsorbates are well known in the art and both their composition and method of preparation are clearly set forth and described in United States Patent No. 4,581,232 to Peters et. al. and U.S. Patent No. 4,711,774 to Denick et. al., both of which are hereby incorporated by reference. The trisilicate powder is comprised of many flake-like masses which hold the active drug within interstitial crevices. By containing the drug in this manner, the adsorbate acts to render bitter tasting drugs tasteless in liquid, tablet and chewable dosage forms which then become readily bioavailable when

205
208

the adsorbate reaches the lower acid pH of the stomach. The drug adsorbate by itself however, does not possess a particularly pleasant taste or mouthfeel that would appeal to children or adults for that matter.

It has been unexpectedly and surprisingly found that by combining the complex magnesium trisilicate with a fumed silica such as Cab-o-sil®, Cabot Co., Boston, Massachusetts the bitter, bad tasting drugs such as antihistamines and decongestants can be placed within a readily disintegratable vehicle such as an effervescent tablet. As the tablet effervesces in the mouth, the drug is released for swallowing in a form that is highly bioavailable for later absorption in the stomach but taste-masked so as to inhibit the perception of the bad tasting actives prior to the drug being swallowed. It is readily absorbed in the stomach as the lower pH environment breaks the complex down.

The drugs of interest are first adsorbed onto the flake-like structures of the magnesium trisilicate by methods known in the art (see Peters et. al. '232). Prior to drying however, fumed silica that is commercially available as Cab-o-Sil® EH5 is added and mixed until granules are formed. The adsorbate, comprised of the flaked magnesium trisilicate, the drug disposed therein and the fumed silica disposed thereon is dried to a LOD of not more than 2.0%. This adsorbate serves as the active component about which the effervescent tablet is made.

The drug adsorbate is then combined with an effervescent disintegration agent which dissolves rapidly and completely once the tablet is placed

206
200

within the patients mouth without the need for any chewing or voluntary muscular contraction such as sucking. The effervescence is generated by a combination of an alkali metal salt of bicarbonate or carbonate with an edible food grade carboxylic acid that produces a chemical reaction when the composition contacts the water component of saliva in the mouth. This reaction generally results in the release of carbon dioxide gas which produces the fizzy or bubbly sensation of effervescence. Suitable alkaline earth metal salts of bicarbonate include sodium bicarbonate, sodium carbonate, potassium carbonate and bicarbonate, calcium carbonate and bicarbonate and the like. Suitable food grade acids include citric acid, tartaric acid, malic acid, adipic acid, fumaric acid, succinic acid and mixtures thereof. Preferably, the effervescent composition of the present invention will be comprised of a mixture of sodium bicarbonate and citric acid.

The combination of the drug adsorbate and effervescent composition provides for an oral delivery system for otherwise bitter tasting medicaments that is both pleasant tasting and organoleptically pleasing due to the release of gas by the chemical reaction. Generally, the carbonate and acid are mixed and employed in amounts that will release about 20 ccs. to about 120 ccs. of gas per tablet. Additional sweeteners, flavors and the like may also be added in order to make the tablet even more pleasing to the taste and as additional aids in the taste masking of the bitter tasting drugs.

Whereas, the delivery system of the present invention may be used to taste mask and deliver

207 74

tablet and from about 50 mg. to about 200 mg. per tablet, respectively.

The magnesium trisilicate composition is comprised as set forth in the Peters et. al. '232 patent and is combined with the fumed silica in approximately a 1:1 ratio of trisilicate/silica on a weight basis, respectively. The bicarbonate or carbonate salt and acid are also combined in approximately a 1:1 to approximately a 4:1 weight ratio to ensure a complete effervescent reaction during administration.

In general, the amount of carbonate salt/carboxylic acid composition used in the formation of the tablets of the present invention will comprise from about 5% to about 90% by weight of the entire tablet composition. Preferably, the effervescent reactants will comprise from about 15% to about 30% by weight of the total weight of the tablet and most preferably in an amount of from about 20% to about 25% by weight of the composition.

The amounts of effervescent composition employed should be enough to create a distinct fizzing or bubbling sensation within the mouth as the tablet disintegrates. To provide an adequate sensation in this manner, the amount of effervescent material should provide from about 10 ccs. to about 100 ccs. of carbon dioxide gas per tablet, and preferably, from about 20 ccs. to about 40 ccs. of gas per tablet.

The adsorbate/effervescent cold/sinus tablets of the present invention will preferably also include sweeteners, flavors, colorants, binders, fillers, lubricants, tableting agents and the like to aid in the taste masking and the tablet

28
24

formation process.

Suitable sweeteners include those sweeteners both natural and artificial well known in the art such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolyzed starch or corn syrup solids and sugar alcohols such as sorbitol, xylitol, mannitol and mixtures thereof. These may be utilized in amounts from about 5% to about 30% and preferably from about 5% to about 20% by weight of the tablet composition. Water soluble artificial sweeteners such as saccharin and saccharin salts such as sodium or calcium, cyclamate salts, acesulfame-K, aspartame and the like and mixtures thereof may be utilized in amounts from about 0.001% to about 5% by weight of the tablet composition.

Flavorants may also be added to enhance the overall taste perception and these include both natural and artificial flavors, mints such as spearmint, peppermint and menthol, vanilla, artificial vanilla, chocolate, artificial chocolate, cinnamon, various fruit flavors, both individual and mixtures thereof may be utilized in amounts of from about 0.5% to about 5.0% by weight of the total weight of the final tablet composition.

Colorants useful in the present invention include pigments which may be incorporated in amount up to about 6% by weight of the composition. A preferred pigment, titanium dioxide, may be incorporated in amounts up to about 1%. Also, the colorants may include other dyes suitable for food, drug and cosmetic



US005994348A

United States Patent [19]

Ku et al.

[11] Patent Number: 5,994,348

[45] Date of Patent: Nov. 30, 1999

[54] PHARMACEUTICAL COMPOSITIONS
CONTAINING IRBESARTAN5,541,209 7/1996 Spinale 514/381
5,753,651 5/1998 dePadova .[75] Inventors: Cathy C. Ku, Martinsville; Omar L.
Spruckel, Bridgewater; Beth A. Lang,
Bedminster; Divyakant S. Desai,
Robbinsville, all of N.J.

[73] Assignee: Sanofi, Paris, France

[21] Appl. No.: 09/081,685

[22] Filed: May 20, 1998

Related U.S. Application Data

[63] Continuation of application No. 08/642,978, May 6, 1996,
abandoned, which is a continuation-in-part of application
No. 08/472,618, Jun. 7, 1995.[51] Int. Cl.⁶ A61K 31/41; A61K 31/415;
A61K 31/44; A61K 9/20[52] U.S. Cl. 514/223.5; 514/223.2;
514/222.8; 424/465[58] Field of Search 514/222.8, 223.2,
514/223.5; 424/465

[56] References Cited

U.S. PATENT DOCUMENTS

4,414,198	11/1983	Michaelson	424/44
4,769,236	9/1988	Panoz et al.	424/80
4,793,999	12/1988	Sheth	424/451
4,894,540	2/1989	Nugent et al.	424/457
4,898,413	2/1989	Joshi et al.	424/458
4,898,729	2/1990	Miller et al.	424/80
4,904,699	2/1990	Bauer	514/972
4,910,022	3/1990	Bavitz et al.	424/465
4,952,410	8/1990	Armah et al.	424/465
5,006,344	4/1991	Jerzewski et al.	424/465
5,037,823	8/1991	Jones et al.	514/222.8
5,047,246	9/1991	Gallian et al.	424/464
5,049,394	9/1991	Howard et al.	424/490
5,073,374	12/1991	McCarthy	424/435
5,087,454	2/1992	Duerholz et al.	424/464
5,112,616	5/1992	McCarthy	424/435
5,155,105	10/1992	Jones et al.	514/223.5
5,270,317	12/1993	Bernhart et al.	514/269
5,288,501	2/1994	Nurnberg et al.	424/465
5,298,261	3/1994	Pebbley et al.	424/488
5,370,870	12/1994	Shah	424/469
5,370,878	12/1994	Shah	424/469
5,393,531	2/1995	Gerhard et al.	424/466
5,424,075	6/1995	Daher et al.	424/465
5,464,632	11/1995	Cousin et al.	424/465
5,464,854	11/1995	dePadova .	
5,501,861	3/1996	Makino et al.	424/464
5,503,845	4/1996	Goede et al.	424/464

FOREIGN PATENT DOCUMENTS

475898	3/1992	European Pat. Off. .
629408	12/1994	European Pat. Off. .
708103	4/1996	European Pat. Off. .
2270841	3/1994	United Kingdom .
91/14679	10/1991	WIPO .

OTHER PUBLICATIONS

Abstract of Desai et al Int. J. Pharmaceutics 142 (11:61-66
"Povidone, and Poloxamer-Mediated Degradation of
Hydrochlorothiazide in an Anti Hypertensive Combination
Tablet Product", 1996.

Desai et al., "Effect of formaldehyde formation on dissolution
stability on hydrochlorothiazide bead formulations",
International Journal of Pharmaceutics, 107(2) 141-147
(1994).

Desai et al., "Effects of different types of lactose and
disintegrant on dissolution stability of hydrochlorothiazide
capsule formulations", *International Journal of Pharmaceu-
tics*, 110, 257-265 (1994).

BASF, "Pluronic® & Tetronic® Surfactants." pp. 1-29
(1989).

I.R. Schmolka, "Poloxamers in the Pharmaceutical Indus-
try", "Polymers For Controlled Drug Delivery", (ed. P. J.
Tarcha) (1991) pp. 189, 193, 197, 201, 205, 209 and 213.
Poloxamer, *Handbook of Pharmaceutical Excipients*, pp.
207-208 (1986).

Official Monographs, Poloxamer, USP23/NF18, pp.
2279-2281 (1995).

Physicians' Desk Reference, World Search Report, Jan. 31,
1994, "poloxamer", with attachments (the latter: formula-
tions of Benlylin DM, Cleocin Pediatric, Colace, Lariam,
Peri-colace, Pediazole, Almay Eyelid, Baby Orajel and
Geriplex-ES).

Lachman, L. et al., "The Theory and Practice of Industrial
Pharmacy", Third Edition, (1986), cover page and p. 321.
Poloxamer, *Handbook of Pharmaceutical Excipients*, 2nd
Edition, pp. 352-354 (1995).

Povidone, *Handbook of Pharmaceutical Excipients*, 2nd
Edition, pp. 392, 396 and 399 (1995).

Primary Examiner—Shep K. Rose

Attorney, Agent, or Firm—Michael D. Alexander

[57] ABSTRACT

Pharmaceutical compositions containing irbesartan, alone or
in combination with a diuretic, providing tablets with a high
relative amount of active agent and excellent wetting and
disintegration properties.

26 Claims, No Drawings

The "dissolution performance" of a tablet, as used herein with respect to irbesartan, refers to the weight % of irbesartan, based on the total weight of irbesartan contained in the tablet, which dissolves within 30 minutes under the following conditions: using a tablet having a total weight of from 150 to 600 mg and a USP Apparatus 2, placing the tablet in 1000 mL of 0.1 N hydrochloric acid at 37° C., with a paddle speed of 50 rpm, and measuring the amount of irbesartan dissolved (especially, using UV at 244 nm or, when hydrochlorothiazide is also present, using HPLC, wavelength 272 nm) at 30 minutes. (If desired, the progress of dissolution may also be monitored at various time points.)

The "dissolution performance" of a tablet, as used herein with respect to a diuretic (preferably, hydrochlorothiazide), refers to the weight % of diuretic, based on the total weight of diuretic contained in the tablet, which dissolves within 30 minutes under the conditions described above for irbesartan dissolution. The dissolution performance for the diuretic preferably meets the USP dissolution specification for the diuretic (for hydrochlorothiazide, greater than 60% dissolution at 30 minutes). The dissolution performance of a tablet containing hydrochlorothiazide is most preferably such that about 90% or greater of the hydrochlorothiazide is dissolved at 30 minutes.

The "diuretic" employed in a composition of the present invention may be any suitable diuretic, or combination of two or more diuretics, such as hydrochlorothiazide, bendroflumethiazide, benzthiazide, chlorothiazide, chlorthalidone, cyclothiazide, hydroflumethiazide, methyclothiazide, metolazone, polythiazide, quinethazone, and trichlormethiazide. Preferably, the diuretic is hydrochlorothiazide.

The "diluent" employed in a composition of the present invention may be one or more compounds which are capable of providing bulk to obtain a desired tablet mass. It is desirable to employ the diluent in an amount at the lower end of the weight range for the diluent. Preferred diluents are inorganic phosphates such as dibasic calcium phosphate; sugars such as lactose hydrous or lactose anhydrous; and cellulose or cellulose derivatives such as microcrystalline cellulose.

The "binder" employed in a composition of the present invention may be one or more compounds which are capable of facilitating granulation of the irbesartan and/or diuretic into larger, denser, and/or more free-flowing particles. Preferred binders are alginic acid (most preferably employed in the range of 2–5% by weight) or sodium alginate (most preferably employed in the range of 2–3% by weight); cellulose or cellulose derivatives such as carboxymethylcellulose sodium (most preferably employed in the range of 2–6% by weight), ethylcellulose (most preferably employed in the range of 2–3% by weight), hydroxyethyl cellulose (most preferably employed in the range of 2–5% by weight), hydroxypropyl cellulose (most preferably employed in the range of 2–6% by weight), hydroxypropyl methylcellulose (most preferably employed in the range of 2–5% by weight), or methylcellulose (most preferably employed in the range of 2–6% by weight); gelatin (most preferably employed in the range of 2–10% by weight); povidone (polyvinylpyrrolidone, i.e., 1-ethenyl-2-pyrrolidinone homopolymer) (e.g., povidone K-30) (most preferably employed in the range of 2–20% by weight); or starch (most preferably employed in the range of 5–20% by weight) or pregelatinized starch (most preferably employed in the range of 2–20, such as 5–20% by weight).

The "disintegrant" employed in a composition of the present invention may be one or more compounds which are

capable of facilitating the break up of a tablet prepared from the composition when placed in contact with an aqueous medium. Preferred disintegrants are alginic acid (most preferably employed in the range of 2–5% by weight) or sodium alginate (most preferably employed in the range of 2.5–10% by weight); cellulose or cellulose derivatives such as carboxymethylcellulose sodium (most preferably employed in the range of 2–6% by weight), microcrystalline cellulose (most preferably employed in the range of 5–15% by weight), powdered cellulose (most preferably employed in the range of 5–15% by weight), or croscarmellose sodium (cross-linked polymer of carboxymethylcellulose sodium) (most preferably employed in the range of 2–5% by weight); crospovidone (cross-linked homopolymer of N-vinyl-2-pyrrolidinone, i.e., cross-linked 1-ethenyl-2-pyrrolidinone) (most preferably employed in the range of 2–5% by weight); pregelatinized starch (most preferably employed in the range of 5–10% by weight), sodium starch glycolate (most preferably employed in the range of 2–8% by weight), or starch (most preferably employed in the range of 3–15% by weight).

The "antiadherent" employed in a composition of the present invention may be one or more compounds which are capable of reducing the stickiness of the formulation, for example, preventing adherence to metal surfaces. Preferred antiadherents are silicon-containing compounds such as silicon dioxide (most preferably employed in the range of 0.25–5% (such as 0.5–2 or 2.5 to 3.0%) by weight), magnesium trisilicate (most preferably employed in the range of 0.5–2% by weight), or talc (most preferably employed in the range of 1–5% by weight).

The "lubricant" employed in a composition of the present invention may be one or more compounds which are capable of preventing tableting problems, such as those relating to the release of a tablet prepared from the composition from the apparatus on which it is formed, for example, preventing adherence to the face of the upper punch (picking) or lower punch (sticking) of a tableting apparatus. Preferred lubricants are fatty acids or fatty acid derivatives such as calcium stearate (most preferably employed in the range of 0.5–2% by weight), glyceryl monostearate (most preferably employed in the range of 0.5–2% by weight), glyceryl palmitostearate (most preferably employed in the range of 0.5–2% by weight), magnesium stearate (most preferably employed in the range of 0.2–2% by weight), sodium lauryl sulfate (most preferably employed in the range of 1–2% by weight), sodium stearyl fumarate (most preferably employed in the range of 0.5–2% by weight), zinc stearate (most preferably employed in the range of 0.5–1.5% by weight) or stearic acid (most preferably employed in the range of 1–3% by weight); hydrogenated vegetable oil (most preferably employed in the range of 1–5% by weight); polyalkylene glycols such as polyethylene glycol (most preferably employed in the range of 1–5% by weight); sodium benzoate (most preferably employed in the range of 2–5% by weight); or talc (most preferably employed in the range of 1–5% by weight).

The "surfactant" employed in a composition of the present invention may be one or more compounds which are capable of improving the wetting of the tablets and/or enhancing dissolution. Preferred surfactants are sodium lauryl sulfate (most preferably employed in the range of 0.2–6% by weight), and poly(oxyethylene).poly(oxypropylene) block co-polymers such as poloxamers, especially poloxamer 188 (most preferably employed in the range of 1–6% by weight).

The "coloring agent" (or "colorant") employed in a composition of the present invention may be one or more

compounds which impart a desired color to a tablet prepared from the composition. Addition of a coloring agent may be used, for example, so that tablets of different potencies may be easily distinguished. Preferred coloring agents are ferric oxides, which are universally accepted.

As can be seen from the above, a single compound may perform two or more functions. Calculation of weight percent is preferably on the basis of the primary function of a compound in a given composition. The present compositions preferably consist essentially of, most preferably, consist of the above-described components.

Preferred Compositions

Preferred compositions of the present invention contain one or more of the following components in the indicated concentration range (% by weight): irbesartan, 20 to 60 (e.g., 25 to 60), such as 30 to 60, most preferably, 30 to 50, especially about 50%; diuretic, 2 to 20, most preferably 2 to 17, especially 4 to 9%; diluent, 1 to 70, most preferably 1 to 60, especially 1 to 40%; binder, 5 to 20, most preferably 5 to 15%; disintegrant, 4 to 8, most preferably about 5%; antiadherent, 0.25 to 5.0% (such as 0.25 to 1.5, most preferably 0.7 to 0.8%, for example, when a diuretic is present or 2.5 to 3.0%, for example, when a diuretic is not present); lubricant, 0.5 to 1.5, most preferably about 1%; and surfactant, 1 to 3, most preferably, about 3%.

The following tables recite preferred compositions of the present invention which produce tablets of especially high quality and superior performance. Table A recites preferred compositions containing irbesartan; Table B recites preferred compositions containing irbesartan in combination with a diuretic.

TABLE A

IRBESARTAN		
Preferred Ingredient	Component	Concentration Range (% w/w)
irbesartan	active drug	20-50
lactose hydrous	diluent	1-70
microcrystalline cellulose (e.g., Avicel® PH 102)	diluent	5-20
pregelatinized starch (e.g., Starch® 1500)	binder	10-20
croscarmellose sodium (e.g., Ac-Di-Sol®)	disintegrant	4-8
poloxamer, especially poloxamer 188 (e.g., Pluronic® F68)	surfactant	1-6
silicon dioxide (e.g., Syloid® 244)	antiadherent	0.25-5.0 (0.25 to 1.5 or, especially, 2.5 to 3.0)
magnesium stearate	lubricant	0.5-1.5
TOTAL		100

*Optional, but preferred, component.

"These exemplary compounds may be used as desired throughout this specification as appropriate. For example, Starch® 1500 may be used as desired wherever pregelatinized starch appears in this specification.

In the above compositions of Table A, the combination of magnesium stearate and silicon dioxide provides a superior lubrication effect while minimizing any decline in tablet dissolution performance; the intragranular:extragranular placement ratio of the disintegrant croscarmellose sodium is superior (e.g., 1:1); and the poloxamer surfactant improves the aqueous granulation of irbesartan (which is hydrophobic), eases the ejection of tablets after compression and accelerates the dissolution of the irbesartan active agent.

TABLE B

IRBESARTAN IN COMBINATION WITH DIURETIC		
Preferred Ingredient	Component	Concentration Range (% w/w)
irbesartan	active drug	20-50
hydrochlorothiazide	diuretic, active drug	2-20*
lactose hydrous	diluent	1-70
microcrystalline cellulose (e.g., Avicel® PH 102)	diluent	10-20
croscarmellose sodium (e.g., Ac-Di-Sol®)	disintegrant	4-6
pregelatinized starch (e.g., Starch® 1500)	binder	10-20
silicon dioxide (e.g., Syloid® 244)	antiadherent	0.5-1.0
magnesium stearate	lubricant	0.5-1.5
TOTAL		100

*The concentration of hydrochlorothiazide can vary according to the hydrochlorothiazide potency sought in the combination tablet, which preferably ranges from 6.25 mg to 25 mg per tablet.

The compositions of Tables A and B preferably also contain 0.08 to 0.12% by weight ferric oxide, red and 0.08 to 0.12% by weight ferric oxide, yellow as a colorant.

Methods of Manufacture

Tablets may be prepared from the present compositions by any suitable method for forming tablets. Preferably, tablets are prepared from the present compositions by a wet granulation process. An exemplary such method comprises the following steps:

(a) preparing an intragranular composition by:

(i) mixing the irbesartan, diuretic (for combined tablets), a portion of the diluent (preferably, from about 5 to about 80% by weight of the total diluent), a portion of the disintegrant (preferably, from about 50 to about 80% by weight of the total disintegrant), the binder, and, optionally, a portion of the antiadherent (preferably, from about 50 to about 80% by weight of the total antiadherent), to form a powder blend and, optionally, sizing the blend (e.g., milling the blend to break up aggregates);

(ii) re-mixing the blend;

(iii) granulating the blend with a granulating fluid, preferably water and/or an aqueous solution of the surfactant, to form granules (e.g., using a high shear mixer/granulator);

(iv) drying the granules (e.g., in an oven or, preferably, in a fluid bed dryer); and

(v) sizing the dried granules (e.g., by milling or screening);

(b) preparing a mixture of the sized granules of step (a)(v) with an extragranular composition by:

(i) mixing the remainder of the diluent, the remainder of the disintegrant, the antiadherent or the remainder of the antiadherent, and, optionally, the coloring agent, where one or more of these may be pre-blended, sized (e.g., milled to break up aggregates) and re-mixed prior to this step, with the sized granules from step (a)(v) to form a granule blend; and

(ii) mixing the lubricant with the granule blend; and

(c) compressing the mixture from step (b)(ii) to form tablets (for example, employing a tablet press).

The solid starting materials of the present compositions are preferably screened prior to use. The weight ratio of water (preferably, purified water, USP or water for injection,