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1

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☐ Patente de Modelo de Utilidad.

☐ Capítulo I.

☒ Capítulo II.

2

SOLICITANTE
(71)

Nombre: **BRISTOL - MYERS SQUIBB COMPANY**

Dirección: Lawrenceville-Princeton Road, P.O. Box 4000, Princeton, NJ 08543-4000, Estados Unidos de América

Nacionalidad o Domicilio: Estados Unidos

Lugar de Constitución: Estados Unidos

Teléfono:

Fax:

E-mail:

IDENTIFICACION

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

3

**REPRESENTANTE
O APODERADO**

Nombre: **RAMIRO CASTRO DUQUE**

Dirección: Cra. 7 No. 16-56 Piso 9

Teléfono: 380-2200

Fax: 380-2700

E-mail:

IDENTIFICACION

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 170.322 TP 1003

4

INVENTOR (ES)
(72)

Nombre: Sanjeev Kothari, Divyakant Desai

Dirección: 99 Harvard Circle, Princeton, NJ 08540, US; 19 Greenfield Drive, North, West Windsor, NJ 08550, Estados Unidos de América (Respectivamente)

Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)

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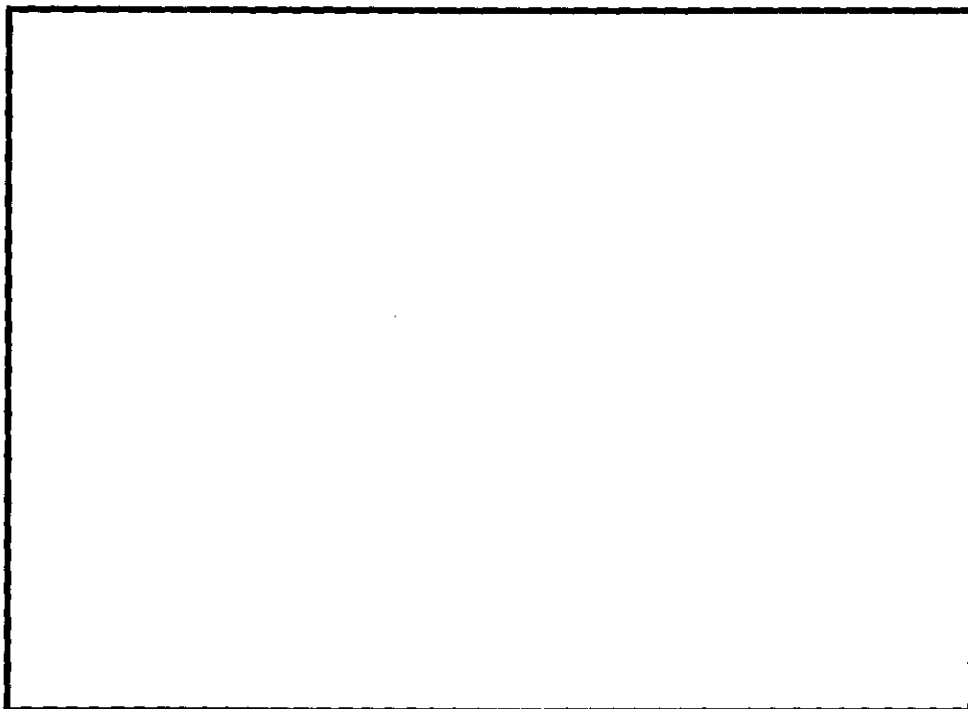
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$422.000
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. **Protocolo No. 19358**
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros - Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente,

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170.322 de Bogotá T.P. 1003 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

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(71) Applicant: BRISTOL-MYERS SQUIBB COMPANY
[US/US]; Lawrenceville-Princeton Road, P.O. Box 4000,
Princeton, NJ 08543-4000 (US).(72) Inventors: KOTHARI, Sanjeev, 99 Harvard Circle,
Princeton, NJ 08540 (US). DESAI, Divyakant, 19 Green-
field Drive, North, West Windsor, NJ 08550 (US).(74) Agent: MAKUJINA, Shah, R.; Bristol-Myers Squibb
Company, Laurenceville-Princeton Road, P.O. Box 4000,
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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: FLASHMELT ORAL DOSAGE FORMULATION

(57) Abstract: There is provided granules for the production of improved flash-melt pharmaceutical oral dosage forms. In addition to one or more medicaments, the granules are composed of an excipient combination consisting of a superdisintegrant (of two or more agents selected from the group consisting of croscopovidone, croscarmellose sodium, sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose or pregelatinized starch), a dispersing agent, a distributing agent, and a binder and may also include other conventional ingredients such as sweetening and flavoring agents. The subject granules are advantageous in that they are stable and can be prepared without the aid of solvents and without the need for special environments or handling. Dosage forms, especially tablets, prepared therefrom on conventional equipment disintegrate in the mouth in under about twenty five seconds.

WO 03/030868 A1

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FLASHMELT ORAL DOSAGE FORMULATION

The present invention relates to a formulation for solid pharmaceutical oral dosage forms that rapidly disperses in the mouth.

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There are a variety of solid pharmaceutical dosage forms that rapidly dissolve or disintegrate in a glass of water or in the gastrointestinal tract. Such dosage forms have been known in the art for many years. The obvious advantages of the convenience of carrying dosage forms that will dissolve or effervesce in water to release medicaments are well known. The therapeutic need of having an oral dosage form that will rapidly dissolve or disintegrate in the mouth for situations where immediate medication is necessary and water is not available has long been recognized.

Initially, a distinction must be drawn between flash-melt dosage forms and rapidly disintegrating dosage forms. The former are intended to dissolve or disintegrate in the mouth of the patient in less than one minute whereas the latter are intended for primary dissolution or disintegration within 3 to 20 minutes in the acidic medium of the stomach or a container of water. The recognized test for rapidly disintegrating dosage forms is disintegration time in 0.1 N hydrochloric acid. Those of ordinary skill in the art will appreciate that the requirements for formulating dosage forms to meet these criteria must necessarily be different since the conditions, particularly pH, in the mouth and the stomach are quite different. More importantly, the time in which a dosage form must dissolve or disintegrate in the mouth is necessarily much shorter than in the stomach with the obvious exception of dosage forms, e.g. lozenges, that are specifically formulated to slowly dissolve in the mouth.

Another consideration common to most if not all dosage form formulations intended for flash-melt or rapid disintegration is the need to take precautions in the preparation, packaging, handling and storing of the finished dosage forms since they tend to be both hygroscopic and friable. Dosage forms dependent on effervescence to

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promote their disintegration are particularly susceptible to moisture and must be packaged with special wrapping, stoppers, packets of drying agent and the like.

Regardless of such potential problems, there is still an acute need for dosage forms that can rapidly dissolve or disintegrate for the obvious benefits of having a therapeutic dosage of the medicament contained therein available for absorption in a very short time. In addition to the benefits of rapid availability, flash-melt dosage forms are advantageous for administration of medicaments to patients such as the very young, the elderly, the non-compliant and those with a physical impairment that makes it difficult if not impossible to swallow an intact dosage form. Flash-melt dosage forms are further a convenience for situations where potable water may not be readily available or desirable. Medicaments amenable to such dosage forms would include sedatives, hypnotics, antipsychotics, motion sickness medication, mild stimulants such as caffeine and the like.

15

Those of ordinary skill in the art are aware that there are two basic compounding concepts recognized for the preparation of rapidly dissolving/disintegrating dosage forms. The first of these, particularly suited for the preparation of flash-melt dosage forms, is freeze drying wherein a cake or wafer is prepared from a freeze-dried solution or suspension of medicament and suitable excipients in water or other solvents. Such wafers dissolve very rapidly on the tongue, i.e. within about ten seconds, due to a combination of a high affinity for moisture resulting from the freeze drying process and a very high porosity, which promotes rapid ingress of saliva. While such dosage forms are capable of rapid disintegration/dissolution in the mouth, the freeze drying process suffers from several disadvantages, primary among which is the fact that a solution or a stable suspension of the medicament must be formed before it can be freeze dried. While not always the case, typically such solutions are aqueous and, therefore, not suited to formulating medicaments sensitive to water. The process itself is typically laborious and time-consuming. Finally, the resultant dosage forms, in addition to being hygroscopic, tend to be very soft and, therefore, require special moisture-and impact-resistant packaging and require careful handling prior to administration.

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The second major technology utilized in the manufacture of rapidly disintegrating dosage forms is based on special grades of sugars such as mannitol, sorbitol and the like in combination with superdisintegrants. The latter are excipients that are characterized by a special wicking capacity to channel water into the interior of the dosage form, or by rapid swelling in water, both of which act to hasten disintegration. It is also known to enhance dissolution of dosage forms by the inclusion of effervescent combinations, typically sodium bicarbonate and a weak acid, such as citric acid. As noted above, effervescent formulations require special moisture resistant packaging as even very small levels of moisture may be sufficient to initiate the effervescent reaction. Techniques, such as fluidized bed granulation, are recognized as being useful in the preparation of such formulations. Too often, however, such technologies require a specific, very costly plant including special handling equipment, controlled-humidity environments and the like. In spite of such measures, dosage forms produced by such techniques typically require moisture resistant packaging, the need to include in the packaging packets or capsules of moisture absorbing agents and the like.

An example of a teaching of the incorporation of super disintegrants in dosage form formulations to enhance dissolution is WO 98/030640, FMC Corporation. It is disclosed therein that, for cost considerations, up to 90% of a group of super disintegrants including cross-linked cellulose, cross-linked carboxymethyl cellulose, cross-linked starch, croscarmellose alkali metal salt, crospovidone, alkali metal starch glycolate and the like can be replaced by a co-disintegrant. Included among the latter group are natural diatomaceous silica, a synthetic hydrous alkaline earth metal calcium silicate and a porous hydrophilic zeolite. The weight ratio of super disintegrant to co-disintegrant is stated as from 4:1 to 1:10, preferably 2-1:1. There is no indication of any recognition of benefits to be derived from the formulation other than the obvious consideration of cost savings since the co-disintegrants are less expensive and the combination is stated to accomplish the desired results.

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In contrast, Japanese patent 10114655, Kyowa Hakko Kogyo KK discloses a formulation intended for rapid dissolution in the stomach that can contain up to 30% by weight of a superdisintegrant, such as crospovidone or hydroxypropylcellulose, croscarmellose and the like and up to 30 % of a neutral or basic ingredient including
5 magnesium aluminum metasilicate, calcium silicate, a phosphoric acid salt or a metal hydroxide. The dosage form is intended for medicaments that produce a gel at acidic pH.

There are numerous other examples of specific formulations that utilize one or
10 more of the techniques or mechanisms discussed above. For the most part, however, they also possess one or more of the enumerated disadvantages to some degree, e.g. it is difficult or expensive to produce dosage forms by such techniques, the resulting dosage forms are friable or are sensitive to environmental factors such as moisture. There continues to be the need for a formulation that mitigates or eliminates these
15 disadvantages, yet yields a flash-melt dosage form that will disintegrate in the mouth within about 25 seconds. Such formulations are provided in accordance with the present invention.

The present invention is directed to a particular aspect and improvement of the
20 flashmelt formulations described in U.S. application Serial Number 09/547,948 filed April 12, 2000. The present invention is directed to a particular aspect of USSN 09/547,948 which improves upon the flashmelt formulation described in said application by enhancing the bioequivalency and stability of particular flashmelt preparations described herein. In particular, "Prototype II" described herein is one
25 example of the improved flashmelt formulation claimed herein wherein a combination of superdisintegrants is utilized to enhance bioequivalency and stability.

Thus according to a first embodiment of the present invention is provided a flash-melt pharmaceutical dosage form comprising a medicament, a superdisintegrant, a
30 dispersing agent and a binder wherein said medicament is aripiprazole, entecavir, cefprozil, pravastatin, captopril, gatifloxacin, desquinolone, omapatrilat or irbesartan and wherein said dispersing agent is calcium silicate and wherein said

superdisintegrant is comprised of two or more agents selected from the group consisting of crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose or pregelatinized starch.

5 According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein greater than 50% of said dispersing agent by weight is comprised of calcium silicate.

10 According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein greater than 80% of said dispersing agent by weight is comprised of calcium silicate.

15 According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said calcium silicate is crystalline.

20 According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said calcium silicate is amorphous.

25 According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said calcium silicate is ortho-, meta- or alpha triclinic-calcium silicate.

30 According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said calcium silicate is alpha triclinic-calcium silicate.

35 According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said calcium silicate is comprised of a combination of alpha triclinic-calcium silicate and at least one other

pharmaceutical grade of calcium silicate wherein said alpha triclinic-calcium silicate comprises from about 10% to about 90% by weight of said combination.

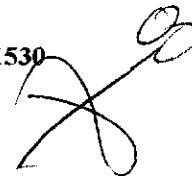
According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said calcium silicate
5 has a surface area of $1.0 \text{ m}^2/\text{gm}$ to $210 \text{ m}^2/\text{gm}$, bulk density of 0.075 g/cc to 0.90 g/cc , true density of 1.70 g/cc to 2.90 g/cc and volatile content of less than 1% to 14% w/w.

According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said calcium silicate is
10 alpha triclinic calcium silicate that has a surface area of about $1.3 \text{ m}^2/\text{gm}$, bulk density of about 0.63 g/cc , true density of about 2.90 g/cc and volatile content of less than 1% w/w.

According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said calcium silicate is
15 ortho crystalline calcium silicate that has a surface area of about $0.98 \text{ m}^2/\text{gm}$, bulk density of about 0.492 g/cc , true density of about 3.252 g/cc and volatile content of less than 1% w/w.

According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said calcium silicate is
20 meta crystalline calcium silicate that has a surface area of about $2.5 \text{ m}^2/\text{gm}$, bulk density of about 0.867 g/cc , true density of about 2.940 g/cc and volatile content of less than 1% w/w.
25

According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said calcium silicate is
30 crystalline calcium silicate that has a surface area of about $90.4 \text{ m}^2/\text{gm}$, bulk density of about 0.094 g/cc , true density of about 2.596 g/cc and volatile content of less than 1% w/w.



According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said calcium silicate is amorphous calcium silicate that has a surface area of about $191.3 \text{ m}^2/\text{gm}$, bulk density of about 0.120 g/cc , true density of about 2.314 g/cc and volatile content of about less than 14% w/w.

According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said calcium silicate is amorphous calcium silicate that has a surface area of about $103.0 \text{ m}^2/\text{gm}$, bulk density of about 0.130 g/cc , true density of about 1.702 g/cc and volatile content of about less than 14% w/w.

According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said calcium silicate is amorphous calcium silicate that has a surface area of about $209 \text{ m}^2/\text{gm}$, bulk density of about 0.075 g/cc , true density of about 2.035 g/cc and volatile content of about less than 14% w/w.

According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said medicament comprises not more than about 30 percent by weight of said medicament based on the total weight of said dosage form.

According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said medicament comprises not more than about 15 percent by weight of said medicament based on the total weight of said dosage form.

According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said medicament is aripiprazole.

According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said superdisintegrant agent comprises from about 3 to about 15 percent by weight of said superdisintegrant agent based on the total weight of said dosage form.

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According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said superdisintegrant agent comprises from about 4 to about 10 percent by weight of said superdisintegrant agent based on the total weight of said dosage form.

10

According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said superdisintegrant agent comprises from about 4 to about 8 percent by weight of said superdisintegrant agent based on the total weight of said dosage form.

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According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said superdisintegrant agent comprises from about 5 to about 7 percent by weight of said superdisintegrant agent based on the total weight of said dosage form.

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According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said superdisintegrant agent comprises from about 8 to about 12 percent by weight of said superdisintegrant agent based on the total weight of said dosage form.

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According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein **wherein** said superdisintegrant agent comprises from about 9 to about 10 percent by weight of said superdisintegrant agent based on the total weight of said dosage form.

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According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said superdisintegrant agent is comprised of crospovidone and croscarmellose sodium.

5 According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein, wherein based on the total weight of said dosage form, said crospovidone comprises from about 6 to about 8 percent by weight of said crospovidone and said croscarmellose sodium comprises from about 2 to about 4 percent by weight of said croscarmellose sodium.

10

According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said distributing agent comprises from about 1 to about 10 percent by weight of said distributing agent based on the total weight of said dosage form.

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According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said distributing agent comprises from about 1.5 to about 3 percent by weight of said distributing agent based on the total weight of said dosage form.

20

According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said distributing agent is amorphous silica, fumed silica, diatomaceous earth, talc, kaolin or magnesium aluminum trisilicate.

25

According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said distributing agent comprises from about 10 to about 50 percent by weight of said binder based on the total weight of said dosage form.

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According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said distributing agent

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comprises from about 12 to about 20 percent by weight of said binder based on the total weight of said dosage form.

According to other embodiments of the present invention are provided flash-melt pharmaceutical dosage forms as described herein wherein said binder is
5 microcrystalline cellulose, hydroxypropyl cellulose, ethyl cellulose, lactose, mannitol or calcium phosphate.

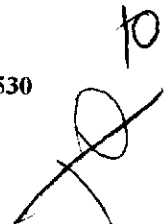
Yet other embodiments or aspects of the present invention reside in the
10 combination of one or more of the embodiments or aspects described herein.

Yet other embodiments or aspects of the present invention are described below.

The flash-melt pharmaceutical dosage forms the present invention may be
15 prepared by dry granulation of the excipients with the medicament and suitable conventional ingredients, such as flavoring and sweetening agents, without the use of any solvent, to form stable granules that can be readily compressed into dosage forms on conventional equipment without the need for special handling techniques.

20 The active medicament may comprise up to about 30% by weight, particularly up to about 15% by weight, of the formulation, depending on the amount required for a therapeutically effective dosage and factors such as its capacity to be directly granulated, the amount of flavoring/sweetening agents required to mask the taste or bitterness thereof and the like. It is within the scope of the present invention to utilize
25 medicaments that are coated for taste or other reason in the subject formulations provided that the coatings do not interfere with either the compounding or the disintegration of the tablets.

Suitable superdisintegrants include crospovidone, croscarmellose sodium,
30 sodium starch glycolate, low-substituted hydroxypropylcellulose, pregelatinized starch and the like. Crospovidone can be utilized in large amounts without causing a formulation containing it to have a propensity to gel.

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Suitable dispersing agents, also sometimes referred to in the art as anticaking agents, include calcium silicate-ortho, meta and alpha triclinic forms thereof, magnesium trisilicate-ortho and meta forms thereof and silicic acid. Calcium silicate is the preferred dispersing agent. Particularly preferred is a crystalline alpha triclinic calcium silicate, commercially available from Aldrich Chemical Company which meets the following specifications: 1.3 m²/gm surface area; 0.63 g/cc bulk density; 2.90 g/cc true density; and < 1% w/w volatiles. Also particularly preferred is a crystalline alpha triclinic calcium silicate, commercially available from J.M. Huber Inc., Tomita Pharmaceutical Co., Aldrich Chemical Company which meets the following specifications: 1.0 to 15 m²/gm surface area; 0.50 to .63 g/cc bulk density; 2.40 to 2.90 g/cc true density; and < 1% w/w volatiles. A variety of pharmaceutical grades of calcium silicate available from other vendors, as shown in Table 1, have also been found to produce satisfactory flash-melt dosage forms as well. These include ortho and meta forms of calcium silicate available from Alfa-Aesar, synthetic calcium silicates Micro-cel C and Micro-cel E, available from Celite Corp, Hubersorb 600 NF and Hubersorb 250 NF available from J. M. Huber Corp, and combinations of various grades thereof. These products have been found to cover the following range of specifications for calcium silicate: 1.0 m²/gm to 210 m²/gm surface area; 0.075 g/cc to 0.90 g/cc bulk density; 1.70 g/cc to 2.90 g/cc true density; and < 1% to 14% w/w volatiles. Table 1 lists the individual specifications for each of the materials obtained from the vendors listed above.

Table 1.

Source	Description	Surface area m ² /gm	Bulk Density g/cc (± s.d.)	True Density g/cc	Volatiles (% w/w)
Aldrich	CaSiO ₃ < 200mesh (crystalline, alpha triclinic)	1.3	0.627 (0.020)	2.934	0.50
Alfa Aesar	2CaO.SiO ₂ (crystalline, ortho)	0.98	0.492 (0.003)	3.252	0.02
Alfa Aesar	CaSiO ₃	2.5	0.867 (0.009)	2.940	0.50

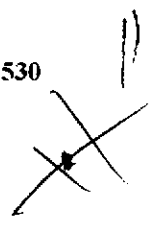
- 12 -

Source	Description	Surface area m ² /gm	Bulk Density g/cc ($\pm$ s.d.)	True Density g/cc	Volatiles (% w/w)
	(crystalline, meta)				
Celcite	Micro-cel E (crystalline)	90.4	0.094 (0.006)	2.596	0.94
Celcite	Micro-cel C (amorphous)	191.3	0.120 (0.006)	2.314	5.11
JM Huber	Hubersorb 250NF (amorphous)	103.0	0.130 (0.008)	1.702	9.90
JM Huber	Hubersorb 600NF (amorphous)	209	0.075 (<0.001)	2.035	13.8

Alpha triclinic calcium silicate is advantageously combined in the subject formulations with at least one other pharmaceutical grade of calcium silicate wherein the alpha triclinic form would comprise from about 10% to about 90% by weight of the combination. In contrast to its use in conventional tableting formulations, it is considered unexpected that the dispersing agent, i.e. calcium silicate, is the primary constituent of the excipient combination of the subject formulations since it is generally recognized by those of ordinary skill in the art as being poorly compressible.

Examples of suitable distributing agents for the excipient combination of the subject formulations include amorphous silica, fumed silica, diatomaceous earth, talc, kaolin, magnesium aluminum trisilicate and the like.

Suitable binders are those that also function as a wicking or distributing agent in that they act to promote water intake into dosage forms made therefrom. Suitable binders include carbohydrates such as, microcrystalline cellulose, hydroxypropyl cellulose, ethyl cellulose, starch, lactose, and also, mannitol and calcium phosphate. Microcrystalline cellulose is commercially available as Avicel® PH (pharmaceutical grade) from FMC Corporation, Philadelphia, Pa., particularly Avicel® PH 101, PH 102, PH 103, PH 112, PH 200, PH 301, PH 302 and Ceolus. Microcrystalline cellulose is also available from Mendell, Penwest Company, Patterson, N.Y., as Emcocel® 90M and Emcocel® 50M, which could be used satisfactorily.



The formulations of the present invention may contain other conventional ingredients found in similar preparations known in the art and recognized as approved for use in preparations to be taken into the body. These would include, for example, natural and artificial flavors, polyols such as mannitol, sorbitol, maltitol and xylitol, artificial sweetening agents such as, N- α -L-Aspartyl-L-phenylalanine 1- methyl ester (aspartame) and 6-methyl-3,4-dihydro-1,2,3-oxathiazin-4(3H)-one-2,2-dioxide, particularly the potassium salt thereof (acesulfame K), flavor adjuncts such as tartaric acid, tableting lubricants, such as magnesium stearate, and the like. Those skilled in the art of pharmaceutical compounding will appreciate that the amount of flavoring and sweetening agents, if any, present in the formulations of the present invention will be directly proportional to the taste or bitterness of the medicament. The flavoring and sweetening agents do not serve to coat the medicament, but are adequate to mask the objectionable taste of the medicaments in homogeneous admixture therewith. In general, the total of such conventional ingredients will not exceed about 32 percent, preferably from about 25 to about 30 percent by weight based on the total weight of the formulation.

The medicament in the formulations of the present invention typically will not exceed about 30 percent by weight, preferably from about 1 to about 15 percent by weight of the formulation. Those of ordinary skill in the art will appreciate that the physical characteristics of the medicament itself, i.e. its particle size and morphology, will directly influence its limiting content in the subject formulations. Clearly, there has to be sufficient medicament in the dosage form produced from the subject formulations to provide a therapeutically effective dosage. While solid dosage forms can be prepared from the formulations of the present invention by any recognized technique, including wet granulation, it is a particular advantage that the formulations can be dry granulated without the use of specialized equipment and conditions, thereby making them suitable for the formulation of medicaments that are sensitive to moisture and high temperatures.

Examples of medicaments that can be formulated into flash-melt tablets in accordance with the present invention include, without intended limitation, antihistamines, anti-motion sickness agents, analgesics, anti-inflammatory agents, antibiotics, cholesterol lowering agents, anti-anxiety agents, anti-hypertensives, anti-
5 cancer agents, hypnotics, anti-ulcer agents, coronary dilators, antivirals, anti-psychotics, anti-depressants, neuromuscular agents, anti-diarrheals, hypoglycemic agents, thyroid suppressors, anabolic agents, antispasmodics, antimigraine agents, diuretics, stimulants, decongestants, uterine relaxants, anti-arrhythmics, male erectile dysfunction compounds, Maxi-K channel openers or neuroprotective agents for the
10 treatment of stroke or Alzheimer's disease and therapeutically appropriate combinations thereof. Specific therapeutic agents falling into the foregoing categories include, again without intended limitation, aripiprazole, ibuprofen, aspirin, acetaminophen, chlorpheniramine maleate, pseudoephedrine, diphenhydramine HCl, ranitidine, phenylpropanolamine, cimetidine, loperamide, meclizine, caffeine,
15 entecavir, cefprozil, melatonergic agonists, pravastatin, captopril, fosinopril, irbesartan, omapatrilat, gatifloxacin and desquinolone and therapeutically appropriate combinations thereof.

As stated above, a decided advantage of the formulation of the present
20 invention is that it can be dry-granulated into stable, fine granules that can be directly compressed into pharmaceutically elegant flash-melt oral dosage forms, e.g. tablets, caplets, wafers and the like. Preferably, the granules for flash-melt dosage forms in accordance with the present invention are formed in two steps. The process comprises initially forming granules, referred to herein as the intragranulation, by blending all of
25 the medicament, the dispersing agent, (distributing agent), other conventional ingredients as described above and a portion of each of the superdisintegrant, binder and tableting lubricant together in a suitable mixer to assure uniform distribution throughout. A conventional V-blender is a preferred apparatus for this step. While a minor portion of the dispersing agent may be omitted from the intragranulation, it is
30 preferred that all be incorporated therein. The blended mixture is then compacted in a conventional roller compactor having an orifice such that the compacts thereof are in the form of ribbons. Alternately, a slugging process can be used. The compacts from

the roller compactor or the slugs from the slugger are passed through a fine screen, e.g. a 30 mesh (600 microns) screen, thereby breaking them into granules between about 150 and 400 microns in size. The intragranulation granules thus-prepared are thereafter blended in a suitable mixer with the remaining ingredients, i.e.,

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5 superdisintegrant, binder and lubricant, referred to herein as the extragranulation ingredients, to form a final blend that can be directly compressed into pharmaceutical dosage forms utilizing conventional equipment such as a tablet press. Rather than directly compress the final blend upon formation, since it is stable, it can be stored and subsequently pressed into dosage forms at a later time. It is a decided advantage of
10 particular aspects of the subject invention that these operations are carried out without the need to resort to special handling such as taking precautions against any moisture coming in contact with the ingredients or the granules, and without the use of specially controlled temperature and humidity conditions.

15 The intragranulation comprises from about 80 to 99, preferably from about 85 to 95, most preferably about 90, percent by weight of the final blend. Based on the weight of the final blend, the intragranulation preferably comprises up to about 30 percent by weight, preferably from about 6 to 20 percent by weight, of the binder, up to about 5 percent by weight, preferably from about 2 to 4 percent by weight, of the
20 superdisintegrant, and all of the dispersing agent and the distributing agent. The binder and superdisintegrant are divided between the intragranulation and the extragranulation ingredients in weight ratios of approximately 2:1 to 4:1 for the binder and 0.5:2.0 to 2.0:0.5 for the superdisintegrant. The conventional tableting lubricant is divided approximately equally between the intragranulation and the
25 extragranulation ingredients.

The final blend is formed by mixing the intragranulation and the extragranulation components of the excipient combination, adding the remaining tableting lubricant thereto and blending until uniform. Alternatively, a direct
30 compression approach can be utilized in which all of the ingredients with the exception of the tableting lubricant are mixed in a suitable blender, such as a conventional V-blender, by geometrically building the entire mass of the formulation

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via sequential blending for three minutes after each addition, and finally adding the lubricant to the mixture after all other ingredients have been blended.

Tablets compressed on a conventional tablet press from the final blend
5 obtained from either a one-step granulation or a direct compression blend, were pharmaceutically elegant and disintegrated in water within ten seconds. A tablet is considered as disintegrated when it has totally broken down to granules and there are no discernible lumps remaining. Since the medicament is not intimately bound to any of the ingredients of the formulation, it is released within the same time period.
10 Another advantage of particular aspects of the subject formulations is that dosage forms can be manufactured therefrom which are robust and, hence, avoid the need for specialized unit dose packaging and careful handling during manufacture or use as is often the case with present dosage forms. The dosage forms prepared from formulations of particular aspects of the present invention can be packaged in
15 conventional blister packs or in HDPE bottles.

It is understood that various other embodiments and modifications in the practice of the invention will be apparent to, and can be readily made by, those of ordinary skill in the art without departing from the scope and spirit of the invention as
20 described above. Accordingly, it is not intended that the scope of the claims appended hereto be limited to the exact description set forth above, but rather that the claims be construed as encompassing all of the features of patentable novelty that reside in the present invention, including all the features and embodiments that would be treated as equivalents thereof by those skilled in the art to which the invention pertains. The
25 invention is further described with reference to the following experimental work.

Means of manufacturing aripiprazole drug substance for formulating according to the present flashmelt invention may be performed as follows.

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Aripiprazole Hydrate

The aripiprazole hydrate (grains) of the present invention have the physicochemical properties given in (1)-(5) below. This aripiprazole hydrate is described hereinafter as "Aripiprazole Hydrate A".

(1) It has an endothermic curve which is substantially the same as the thermogravimetric/differential thermal analysis (heating rate 5°C/min) endothermic curve shown in Figure 1. Specifically, it is characterized by the appearance of a small peak at about 71°C and a gradual endothermic peak around 60°C to 120°C.

(2) It has an ¹H-NMR spectrum which is substantially the same as the ¹H-NMR spectrum (DMSO-d₆, TMS) shown in Figure 2. Specifically, it has characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J = 7.4 Hz, 2H), 2.97 ppm (brt, J = 4.6 Hz, 4H), 3.92 ppm (t, J = 6.3 Hz, 2H), 6.43 ppm (d, J = 2.4 Hz, 1H), 6.49 ppm (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.04 ppm (d, J = 8.1 Hz, 1H), 7.11-7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).

(3) It has a powder x-ray diffraction spectrum which is substantially the same as the powder x-ray diffraction spectrum shown in Figure 3. Specifically, it has characteristic peaks at 2θ = 12.6°, 15.4°, 17.3°, 18.0°, 18.6°, 22.5° and 24.8°.

(4) It has clear infrared absorption bands at 2951, 2822, 1692, 1577, 1447, 1378, 1187, 963 and 784 cm⁻¹ on the IR (KBr) spectrum.

(5) It has a mean grain size of 50 μm or less.

Method of Manufacturing Aripiprazole Hydrate A

Aripiprazole Hydrate A is manufactured by milling conventional aripiprazole hydrate.

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Conventional milling methods can be used to mill the aripiprazole hydrate. For example, the aripiprazole hydrate can be milled in a milling machine. A widely used milling machine can be used, such as an atomizer, pin mill, jet mill or ball mill. Of these, the atomizer is preferred.

5

Regarding the specific milling conditions when using an atomizer, a rotational speed of 5000-15000 rpm could be used for the main axis, for example, with a feed rotation of 10-30 rpm and a screen hole size of 1-5 mm.

10 The mean grain size of the Aripiprazole Hydrate A obtained by milling should normally be 50 μm or less, preferably 30 μm or less. Mean grain size can be ascertained by the grain size measurement method described hereinafter.

Grain Size Measurement: 0.1 g of the grains to be measured were suspended in
15 a 20 ml n-hexane solution of 0.5 g soy lecithin, and grain size was measured using a size distribution meter (Microtrack HRA, Microtrack Co.).

Aripiprazole Anhydride Crystals

20 The aripiprazole anhydride crystals of the present invention have the physicochemical properties given in (6)-(10) below. These aripiprazole anhydride crystals are referred to hereinafter as "Aripiprazole Anhydride Crystals B".

(6) They have an ^1H -NMR spectrum which is substantially the same as the
25 ^1H -NMR spectrum (DMSO- d_6 , TMS) shown in Figure 4. Specifically, they have characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, $J = 7.4$ Hz, 2H), 2.97 ppm (brt, $J = 4.6$ Hz, 4H), 3.92 ppm (t, $J = 6.3$ Hz, 2H), 6.43 ppm (d, $J = 2.4$ Hz, 1H), 6.49 ppm (dd, $J = 8.4$ Hz, $J = 2.4$ Hz, 1H), 7.04 ppm (d, $J = 8.1$ Hz, 1H), 7.11-7.17 ppm
30 (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).

(7) They have a powder x-ray diffraction spectrum which is substantially the same as the powder x-ray diffraction spectrum shown in Figure 5. Specifically, they have characteristic peaks at $2\theta = 11.0^\circ$, 16.6° , 19.3° , 20.3° and 22.1° .

5 (8) They have clear infrared absorption bands at 2945, 2812, 1678, 1627, 1448, 1377, 1173, 960 and 779 cm^{-1} on the IR (KBr) spectrum.

(9) They exhibit an endothermic peak near about 141.5°C in thermogravimetric/differential thermal analysis (heating rate $5^\circ\text{C}/\text{min}$).

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(10) They exhibit an endothermic peak near about 140.7°C in differential scanning calorimetry (heating rate $5^\circ\text{C}/\text{min}$).

Aripiprazole Anhydride Crystals B of the present invention have low
15 hygroscopicity. For example, Aripiprazole Anhydride Crystals B of the present invention maintain a water content of 0.4% or less after 24 hours inside a dessicator set at a temperature of 60°C and a humidity of 100%.

Well-known methods of measuring water content can be used as long as they
20 are methods commonly used for measuring the water content of crystals. For example, a method such as the Karl Fischer method can be used.

Method of Manufacturing Aripiprazole Anhydride Crystals B

25 The Aripiprazole Anhydride Crystals B of the present invention are prepared for example by heating the aforementioned Aripiprazole Hydrate A at $90\text{--}125^\circ\text{C}$. The heating time is generally about 3-50 hours, but cannot be stated unconditionally since it differs depending on heating temperature. The heating time and heating temperature are inversely related, so that for example the heating time will be longer the lower the
30 heating temperature, and shorter the higher the heating temperature. Specifically, if the heating temperature of Aripiprazole Hydrate A is 100°C , the heating time should normally be 18 hours or more or preferably about 24 hours. If the heating temperature

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of Aripiprazole Hydrate A is 120°C, on the other hand, the heating time can be about 3 hours. The Aripiprazole Anhydride Crystals B of the present invention can be prepared with certainty by heating Aripiprazole Hydrate A for about 18 hours at 100°C, and then heating it for about 3 hours at 120°C. The Aripiprazole Anhydride
5 Crystals B of the present invention can also be obtained if the heating time is extended still further, but this is not economical.

Furthermore, the Aripiprazole Anhydride Crystals B of the present invention are prepared for example by heating conventional aripiprazole anhydride crystals at
10 90-125°C. The heating time is generally about 3-50 hours, but cannot be stated unconditionally since it differs depending on heating temperature. The heating time and heating temperature are inversely related, so that for example the heating time will be longer the lower the heating temperature, and shorter the higher the heating temperature. Specifically, if the heating temperature of the aripiprazole anhydride
15 crystals is 100°C, the heating time can be about 4 hours, and if the heating temperature is 120°C the heating time can be about 3 hours.

The aripiprazole anhydride crystals which are the raw material for preparing the Aripiprazole Anhydride Crystals B of the present invention are prepared for
20 example by Method a or b below.

Method a:

Aripiprazole anhydride crystals are prepared by well-known methods, as by
25 reacting 7-(4-bromobutoxy)-3,4-dihydrocarbostyrl with 1-(2,3-dichlorophenyl) piperadine and recrystallizing the resulting raw aripiprazole crystals with ethanol as described in Example 1 of Japanese Unexamined Patent Publication No. 191256/1990.

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Method b:

Aripirazole anhydride crystals are prepared by heating conventional aripirazole hydrate at a temperature of at least 60°C and less than 90°C. The heating
5 time is generally about 1-30 hours, but cannot be stated unconditionally since it differs depending on heating temperature. The heating time and heating temperature are inversely related, so that for example the heating time will be longer the lower the heating temperature, and shorter the higher the heating temperature. Specifically, if the heating temperature of the aripirazole hydrate is about 60°C, the heating time
10 can be about 8 hours, while if the heating temperature is 80°C, the heating time can be about 4 hours.

The Method b is described in the Proceedings of the 4th Japanese-Korean Symposium on Separation Technology (October 6-8, 1996).

15

Furthermore, the Aripirazole Anhydride Crystals B of the present invention are prepared for example by heating conventional aripirazole hydrate at 90-125°C. The heating time is generally about 3-50 hours, but cannot be stated unconditionally since it differs depending on heating temperature. The heating time and heating
20 temperature are inversely related, so that for example the heating time will be longer the lower the heating temperature, and shorter the higher the heating temperature. Specifically, if the heating temperature of the aripirazole hydrate is 100°C, the heating time can be about 24 hours, while if the heating temperature is 120°C, the heating time can be about 3 hours.

25

The aripirazole hydrate which is the raw material for preparing the Aripirazole Anhydride Crystals B of the present invention is prepared for example by Method c below.

Method c:

Aripiprazole hydrate is easily obtained by dissolving the aripiprazole anhydride crystals obtained by Method a above in a hydrous solvent, and heating and
5 then cooling the resulting solution. Using this method, aripiprazole hydrate is precipitated as crystals in the hydrous solvent.

An organic solvent containing water is usually used as the hydrous solvent. The organic solvent should be one which is miscible with water, such as for example
10 an alcohol such as methanol, ethanol, propanol or isopropanol, a ketone such as acetone, an ether such as tetrahydrofuran, dimethylformamide, or a mixture thereof, with ethanol being particularly desirable. The amount of water in the hydrous solvent can be 10-25% by weight of the solvent, or preferably close to 20% by weight.

15 As mentioned above, the Aripiprazole Anhydride Crystals B of the present invention are prepared by heating at 90-125°C of said Aripiprazole Hydrate A, conventional aripiprazole anhydride crystals or conventional aripiprazole hydrate, and said Aripiprazole Hydrate A, conventional aripiprazole anhydride crystals or conventional aripiprazole hydrate may be used either individually or in combination.

20 The following examples used aripiprazole drug substance made by first milling the conventional hydrate of aripiprazole and then heating it to form the anhydrous form (anhydride B).

EXAMPLE 1

Flash-melt tablets were prepared as follows:

5 Intragranulation:

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Xylitol (300) Xylisorb	26	52
Avicel® PH 102	12	24
Calcium Silicate	43.35	86.7
Crospovidone	3	6
Amorphous silica	2	4
Aspartame	2	4
Wild cherry flavor	0.15	0.3
Tartaric acid	2	4
Acesulfame K	2	4
Magnesium stearate	0.25	0.5
Total weight	92.75	185.5

10 The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was then added and the mixture blended for an additional three minutes. The blended formulation was compacted at a pressure of 30-35 kgF/cm² in a commercial compactor equipped with an orifice such that the compacts therefrom are in the form of ribbons. The ribbons were passed through a 30 mesh (600 microns) screen to form stable granules of about 150 to 400 microns.

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Extragranulation Ingredients:

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Intragranulation	92.75	185.5

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Avicel® PH 200	3	6
Crospovidone	4	8
Magnesium stearate	0.25	0.5
Total weight	100	200

The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to form the final blend. Tablets compressed therefrom had a breaking force of 2.3 kP (3.5 SCU) and disintegrated in 10 seconds in 5 ml of water. The final blend formulation demonstrated excellent flow and was free of other problems such as chipping, capping and sticking. It has been found that utilizing Avicel® PH 102 for the intragranulation and Avicel® PH 200 for the extragranulation ingredient enhanced the quality of the resultant tablets.

EXAMPLE 2

Flash-melt tablets containing a combination of two grades of calcium silicate were prepared as follows:

Intragranulation:

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Xylitol (300) Xylisorb	26	52
Avicel® PH 102	12	24
Calcium Silicate (crystalline, alpha triclinic)	33.35	66.7
Hubersorb 600 NF (amorphous calcium silicate)	10	20
Crospovidone	3	6
Amorphous silica	2	4

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Aspartame	2	4
Wild cherry flavor	0.15	0.3
Tartaric acid	2	4
Acesulfame K	2	4
Magnesium stearate	0.25	0.5
Total weight	92.75	185.5

The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was added and the mixture blended for an additional 5 three minutes. The blended formulation was compacted, and screened to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Intragranulation	92.75	185.5
Avicel® PH 200	3	6
Crospovidone	4	8
Magnesium stearate	0.25	0.5
Total weight	100	200

10

The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to form the final blend. Tablets compressed therefrom had a breaking force of 2.0 kP (3.1 SCU) 15 and disintegrated in 10 seconds in 5 ml of water.

EXAMPLE 3

Flash-melt tablets containing aripiprazole, an antischizophrenic drug, were prepared as follows:

5

Intragranulation

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Aripiprazole	15	30
Xylitol (300) Xylisorb	25	50
Avicel® PH 102	6	12
Calcium Silicate	37	74
Crospovidone	3	6
Amorphous silica	2	4
Aspartame	2	4
Wild cherry flavor	0.15	0.3
Tartaric acid	2	4
Acesulfame K	2	4
Magnesium stearate	0.25	0.5
Total weight	94.4	188.8

10 The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was added and the mixture blended for an additional three minutes. The blended formulation was compacted, and screened to form stable granules in accordance with the procedure of Example 1.

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Extragranulation Ingredients:

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Intragranulation	94.4	188.8
Avicel® PH 200	1.1	2.2
Crospovidone	4	8
Magnesium stearate	0.5	1
Total weight	100	200

The intragranulation was placed in the blender and the Avicel® PH 200 and
5 crospovidone added thereto and blended for five minutes. The magnesium stearate
was then added and the mixture blended for an additional three minutes to form the
final blend. Tablets compressed therefrom had a breaking force of 2.0 kP (3.1 SCU)
and disintegrated in 10 seconds in 5 ml of water.

EXAMPLE 4

Flash-melt tablets containing aripiprazole were prepared as follows:

Intragranulation:

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Aripiprazole	0.5	1
Xylitol (300) Xylisorb	27	54
Avicel® PH 102	12	24
Calcium Silicate	42	84
Crospovidone	3	6
Amorphous silica	2	4
Aspartame	2	4
Wild cherry flavor	0.15	0.3
Tartaric acid	2	4

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<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Acesulfame K	2	4
Magnesium stearate	0.25	0.5
Total weight	92.9	185.8

The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was added and the mixture blended for an additional
5 three minutes. The blended formulation was compacted, and screened to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Intragranulation	92.9	185.8
Avicel® PH 200	2.6	5.2
Crospovidone	4	8
Magnesium stearate	0.5	1
Total weight	100	200

10

The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to form the final blend. Tablets compressed therefrom had a breaking force of 2.3 kP (3.5 SCU)
15 and disintegrated in 10 seconds in 5 ml of water.

EXAMPLE 5

Flash-melt tablets can be prepared containing the antiviral medicament
20 entecavir as follows:

Intragranulation:

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Entecavir	1	2
Xylitol (300) Xylisorb	26	52
Avicel® PH 102	10	20
Calcium Silicate	45	90
Crospovidone	4	8
Amorphous silica	2.	4
Aspartame	2	4
Wild cherry flavor	0.25	0.5
Tartaric acid	2	4
Acesulfame K	2.	4
Magnesium stearate	0.25	0.5
Total weight	94.5	189

The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was added and the mixture blended for an additional three minutes. The blended formulation was compacted, and screened to form stable granules in accordance with the procedure of Example 1.

10 Extragranulation Ingredients:

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Intragranulation	94.5	189
Avicel® PH 200	2	4
Crospovidone	3	6
Magnesium stearate	0.5	1
Total weight	100	200

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The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to form the final blend. Tablets compressed therefrom had a breaking force of 2.3 kP (3.5 SCU) and disintegrated in 10 seconds in 5 ml of water. The percent w/w/ ratios taught in this example can also be used to formulate a suitable formulation of the present invention comprising 0.1 mg of entecavir per unit dose.

EXAMPLE 6

Flash-melt tablets can be prepared containing the antibiotic medicament cefprozil as follows:

Intragranulation:

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Cefzil	25	125
Xylitol (300) Xylisorb	17	85
Avicel® PH 102	6	30
Calcium Silicate	35	175
Crospovidone	3	15
Amorphous silica	2	10
Aspartame	2	10
Wild cherry flavor	0.25	1.25
Tartaric acid	2	10
Acesulfame K	2	10
Magnesium stearate	0.25	1.25
Total weight	94.5	472.5

Blend the ingredients except for the magnesium stearate in a commercial V-blender in geometric proportions for 5 minutes each until all are added. Then add the

magnesium stearate to the mixture prepared and mix for an additional three minutes. Then compact the blended formulation, and screen to form stable granules in accordance with the procedure of Example 1.

5 Extragranulation Ingredients:

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Intragranulation	94.5	472.5
Avicel® PH 200	2	10
Crospovidone	3	15
Magnesium stearate	0.5	2.5
Total weight	100	500

10 Place the intragranulation in the blender and add the Avicel® PH 200 and crospovidone thereto and blend for five minutes. Then add magnesium stearate to the mixture and blend for an additional three minutes to form the final blend. Compress tablets therefrom to have a breaking force of 2.5 kP (3.8 SCU) and a disintegration time of 10 seconds or less in 5 ml of water.

EXAMPLE 7

15

Flash-melt tablets can be prepared containing the antihypertensive medicament irbesartan as follows:

Intragranulation:

20

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Irbesartan	25	125
Xylitol (300) Xylisorb	17	85
Avicel® PH 102	6	30
Calcium Silicate	35	175

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<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Crospovidone	3	15
Amorphous silica	2	10
Aspartame	2	10
Wild cherry flavor	0.25	1.25
Tartaric acid	2	10
Acesulfame K	2	10
Magnesium stearate	0.25	1.25
Total weight	94.5	472.5

Blend the ingredients except for the magnesium stearate in a commercial V-blender in geometric proportions for 5 minutes each until all are added. Then add the magnesium stearate to the mixture prepared and mix for an additional three minutes.

- 5 Then compact the blended formulation, and screen to form stable granules in accordance with the procedure of Example 1.

Extrgranulation Ingredients:

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Intrgranulation	94.5	472.5
Avicel® PH 20	2	10
Crospovidone	3	15
Magnesium stearate	0.5	2.5
Total weight	100	500

10

Place the intrgranulation in the blender and add the Avicel® PH 200 and crospovidone thereto and blend for five minutes. Then add magnesium stearate to the mixture and blend for an additional three minutes to form the final blend. Compress tablets therefrom to have a breaking force of 2.5 kP (3.8 SCU) and a disintegration

15 time of 10 seconds or less in 5 ml of water.

EXAMPLE 8

Flash-melt tablets can be prepared containing the quinolone antibiotic, des-Quinolone as follows:

5

Intragranulation:

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
des-Quinolone	20.0	100
Xylitol (300) Xylisorb	22.0	110
Avicel® PH 102	6.0	30
Calcium Silicate	35.0	175
Crospovidone	3.0	15
Amorphous silica	2.0	10
Aspartame	2.0	10
Wild cherry flavor	0.25	1.25
Tartaric acid	2.0	10
Acesulfame K	2.0	10
Magnesium stearate	0.25	1.25
Total weight	94.5	472.5

10 Blend the ingredients except for the magnesium stearate in a commercial V-blender in geometric proportions for 5 minutes each until all are added. Then add the magnesium stearate to the mixture prepared and mix for an additional three minutes. Then compact the blended formulation, and screen to form stable granules in accordance with the procedure of Example 1.

15 Extragranulation Ingredients:

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Intragranulation	94.5	472.5

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Avicel® PH 200	2.0	10.0
Crospovidone	3.0	15.0
Magnesium stearate	0.5	2.5
Total weight	100	500

- Place the intragranulation in the blender and add the Avicel® PH 200 and crospovidone thereto and blend for five minutes. Then add magnesium stearate to the mixture and blend for an additional three minutes to form the final blend. Compress
- 5 tablets therefrom to have a breaking force of 2.5 kP (3.8 SCU) and a disintegration time of 10 seconds or less in 5 ml of water.

EXAMPLE 9

- 10 Flash-melt tablets can be prepared containing the antibiotic gatifloxacin (Tequin®), as a taste masked co-precipitate (30% w/w active) to deliver 50 mg dose:

Intragranulation:

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Gatifloxacin:stearic acid co-precipitate	33.3	166.7
Xylitol (300) Xylisorb	11.7	58.5
Avicel® PH 102	6.0	30
Calcium Silicate	32.0	160
Crospovidone	3.0	15
Amorphous silica	2.0	10
Aspartame	2.0	10
Wild cherry flavor	0.25	1.23
Tartaric acid	2.0	10
Acesulfame K	2.0	10
Magnesium stearate	0.25	1.25
Total weight	94.5	472.5

Blend the ingredients except for the magnesium stearate in a commercial V-blender in geometric proportions for 5 minutes each until all are added. Then add the magnesium stearate to the mixture prepared and mix for an additional three minutes. Then compact the blended formulation, and screen to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:

<u>Ingredient</u>	<u>Percent w/w</u>	<u>Mg. per tablet</u>
Intragranulation	94.5	472.5
Avicel® PH 200	2.0	10.0
Crospovidone	3.0	15.0
Magnesium stearate	0.5	2.5
Total weight	100	500

Place the intragranulation in the blender and add the Avicel® PH 200 and crospovidone thereto and blend for five minutes. Then add magnesium stearate to the mixture and blend for an additional three minutes to form the final blend. Compress tablets therefrom to have a breaking force of 2.5 kP (3.8 SCU) and a disintegration time of 10 seconds or less in 5 ml of water.

EXAMPLE 10

PREPARATION OF 2.5 % W/W ARIPIRAZOLE GRANULATION FOR
AND 2 MG AND 5 MG TABLETS- PROTOTYPE II

Intragranular formulation:

<u>Ingredient</u>	<u>% w/w</u>
Aripiprazole	2.50
Xylitol, NF (Xylisorb 300)	21.15

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Microcrystalline Cellulose, NF (Avicel PH 102)	12.0
Calcium Silicate, NF	42.0
Crospovidone, NF (XL-10)	3.0
Silicon Dioxide, NF (previously referred to as Amorphous Silica)	2.0
Croscarmellose Sodium, NF	3.0
Aspartame, NF	2.0
Flavor Crème de Vanilla	0.5
Tartaric Acid, NF	2
Acesulfame K (E.P)	2.0
Magnesium stearate NF	0.25
Total	92.40

Intragranular Blend preparation:

1. V-blender is chosen (that operates at 50 rpm speed) for the mixing operation. In
5 the first mixing step, aripiprazole is placed in between Xylitol and Avicel PH 102
mixed in the V-blender for 10 minutes.
2. In step 2, all other excipients are weighed out and placed in the V-blender from
step 1. Deaggregation was performed where necessary. Mixing was done for 5
minutes.
- 10 3. Finally, 0.25% magnesium stearate was added and blended for 3 minutes.
4. For roller compaction Alexanderwerk WP 120X40 (roller compactor) or other
similar equipment can be used with the following parameters:
Screw speed: 25 rpm Rolls speed: 5 rpm; Vacuum pressure: -105 mbar
Granulator: 75 rpm (fixed with top 4mm screen and bottom 0.8 mm or 20#
15 screen)
Hydraulic pressure: 50 bar

Post Dry granulation Blend Preparation:

223

<u>Ingredient</u>	<u>% w/w</u>
Granulation from step 4	92.40
Crospovidone, NF (XL-10)	4.00
Microcrystalline Cellulose, NF (Avicel® PH 200)	3.10
Magnesium stearate, NF	0.5
Total	100.00

1. Based on the yield from step 4 calculate the new batch size and place the intragranulation in the blender with the calculated amounts of Avicel® PH 200 and crospovidone and blend for 5 minutes.

- 5 2. Finally add the remaining amount of magnesium stearate and mix for 3 minutes.

2 mg tablets may have a green pigment blend incorporated in the extragranular portion above in a concentration of 0.3% w/w adjusted by replacing the same amount of Avicel PH 200, i.e. the amount of Avicel PH 200 will be 2.8% w/w.

10

5 mg tablets may have a blue aluminum lake incorporated in the extragranular portion above in a concentration of 0.3% w/w adjusted by replacing the same amount of Avicel PH 200, i.e. the amount of Avicel PH 200 will be 2.8% w/w.

15 **Tablet Compression:**

1. Using the granulation prepared above, 2 mg potency aripiprazole tablets can be prepared by compressing 80 mg weight tablets on any conventional tablet press that can produce tablets having a breaking force of 3.0 kP or 4.5 SCU.
2. Using the granulation prepared above, 5 mg potency aripiprazole tablets can be prepared by compressing 200 mg weight tablets on any conventional tablet press that can produce tablets having a breaking force of 3.0 kP or 4.5 SCU.

20

EXAMPLE 11PREPARATION OF 10 % W/W ARIPIRAZOLE GRANULATION FOR AND 10 MG, 15 MG, 20 MG AND 30 MG TABLETS- PROTOTYPE II

5 Intragranular formulation:

<u>Ingredient</u>	<u>% w/w</u>
Aripiprazole	10.00
Xylitol, NF (Xylisorb 300)	21.15
Microcrystalline Cellulose, NF (Avicel PH 102)	10.0
Calcium Silicate, NF	36.5
Crospovidone, NF (XL-10)	3.0
Silicon Dioxide, NF (previously referred to as Amorphous Silica)	3.0
Croscarmellose Sodium, NF	2.0
Aspartame, NF	2.0
Flavor Crème de Vanilla	0.5
Tartaric Acid, NF	2
Acesulfame K (E.P)	2.0
Magnesium stearate NF	0.25
Total	92.40

Intragranular Blend preparation:

- 10 1. V-blender is chosen (that operates at 50 rpm speed) for the mixing operation. In the first mixing step, aripiprazole is placed in between Xylitol and Avicel PH 102 mixed in the V-blender for 10 minutes.
- 15 2. In step 2, all other excipients are weighed out and placed in the V-blender from step 1. Deaggregation was performed where necessary. Mixing was done for 5 minutes.
3. Finally, 0.25% magnesium stearate was added and blended for 3 minutes.

4. For roller compaction Alexanderwerk WP 120X40 (roller compactor) or other similar equipment can be used with the following parameters:

Screw speed: 25 rpm Rolls speed: 5 rpm; Vacuum pressure: -105 mbar

Granulator: 75 rpm (fixed with top 4mm screen and bottom 0.8 mm or 20# screen)

- 5 Hydraulic pressure: 50 bar

Post Dry granulation Blend Preparation:

<u>Ingredient</u>	<u>% w/w</u>
Granulation from step 4	92.40
Crospovidone, NF (XL-10)	4.00
Microcrystalline Cellulose, NF (Avicel® PH 200)	3.10
Magnesium stearate, NF	0.5
Total	100.00

- 10 5. Based on the yield from step 4 calculate the new batch size and place the intragranulation in the blender with the calculated amounts of Avicel® PH 200 and crospovidone and blend for 5 minutes.

6. Finally add the remaining amount of magnesium stearate and mix for 3 minutes.

- 15 • 10 mg tablets may have red iron oxide incorporated in the extragranular portion above in a concentration of 0.04% w/w adjusted by replacing the same amount of Avicel PH 200, i.e. the amount of Avicel PH 200 will be 3.06 % w/w.

- 20 • 15 mg tablets may have yellow iron oxide incorporated in the extragranular portion above in a concentration of 0.3% w/w adjusted by replacing the same amount of Avicel PH 200, i.e. the amount of Avicel PH 200 will be 2.8% w/w.

- 20 mg tablets may be white in color and directly made from the formulation shown above.

- 25 • 30 mg tablets may have red iron oxide incorporated in the extragranular portion above in a concentration of 0.04% w/w adjusted by replacing the same amount of Avicel PH 200, i.e. the amount of Avicel PH 200 will be 3.06 % w/w.

Tablet Compression:

1. Using the granulation prepared above, 10 mg potency aripiprazole tablets can be prepared by compressing 100 mg weight tablets on any conventional tablet press that can produce tablets having a breaking force of 3.0 kP or 4.5 SCU.
2. Using the granulation prepared above, 15 mg potency aripiprazole tablets can be prepared by compressing 150 mg weight tablets on any conventional tablet press that can produce tablets having a breaking force of 3.0 kP or 4.5 SCU.
3. Using the granulation prepared above, 20 mg potency aripiprazole tablets can be prepared by compressing 200 mg weight tablets on any conventional tablet press that can produce tablets having a breaking force of 3.0 kP or 4.5 SCU.
4. Using the granulation prepared above, 30 mg potency aripiprazole tablets can be prepared by compressing 300 mg weight tablets on any conventional tablet press that can produce tablets having a breaking force of 3.0 kP or 4.5 SCU.

Pharmacokinetic Evaluation of 5 mg Flash-melt tablets- Prototypes I and II in healthy human subjects

Open label, randomized, 2-period, 3 treatment control balanced crossover study involving 33 healthy volunteers was conducted. Each subject received one single 5 mg aripiprazole commercial tablet and a 5 mg dose of aripiprazole as either flash-melt Prototype I or flash-melt Prototype II (both from a 2.5% w/w granulation).

COMPOSITION (mg/tablet)				
INGREDIENT	Prototype I		Prototype II	
	5 mg ^a	%	5 mg ^b	%
Aripiprazole	5.0	2.50	5.0	2.50
Calcium Silicate, NF	84.0	42.00	84.0	42.00
Crospovidone NF (XL-10)	14.0	7.00	14.0	7.00
Croscarmellose Sodium, NF	—	—	6.0	3.00
Silicon Dioxide, NF (Syloid)	4.0	2.00	4.0	2.00
Xylitol NF (Xylisorb [®] 300)	48.3	24.15	42.3	21.15

Microcrystalline Cellulose NF (Avicel® PH 102)	24	12.00	24	12.00
Microcrystalline Cellulose NF (Avicel® PH 200)	6.2	3.10	6.2	3.10
Aspartame NF	4.0	2.00	4.0	2.00
Acesulfame Potassium	4.0	2.00	4.0	2.00
Crème de Vanilla (Natural & Artificial Flavors)	1.0	0.50	1.0	0.50
Tartaric Acid NF	4.0	2.00	4.0	2.00
Magnesium Stearate NF	1.5	0.75	1.5	0.75
Total	200 mg	100.00	200 mg	100.0

^a Product Identification Number: 337039-A005-050; ^b Product Identification Number: 337039-A005-051

- 5 The disintegration time for both prototypes in the mouth was less than 30 seconds. However, the two prototypes show different dissolution rates in in-vitro dissolution tests using USP dissolution testing methods. Hence, the goal of this study was to evaluate if these differences would affect in-vivo performance of the two prototypes.
- 10 The pharmacokinetic parameters from the clinical study are shown below:

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Formulation	Dose (mg)	N	C _{max} (ng/mL)	T _{max} * (h)	AUC(INF) [ng.h/mL]	F*** (%)
Commercial Tablet	5	33	21.4 (5.85)	3 (1, 8)	1393 (504)	-
Flashmelt Prototype I	5	16	17.8 (3.85)	4 (2, 12)	1260 (474)	99.7 (21.8)
Flashmelt Prototype II	5	17	21.0 (4.40)	4 (1.5, 8)	1567 (677)	105 (18.4)

Based on statistical analysis for C_{max} and AUC for the two prototypes (shown below) it was concluded that Prototype II is bioequivalent to the regular commercial aripiprazole tablets.

<u>Parameter</u>	<u>Ratio</u>	<u>N</u>	<u>Point Estimate</u>	<u>90% CI</u>
C _{max}	B/A	16	0.8809	(0.7534, 1.0300)
	C/A	17	0.9741	(0.8767, 1.0823)
AUC (INF)	B/A	16	0.9744	(0.9107, 1.0491)
	C/A	17	1.0141	(0.9688, 1.0616)
AUC (0-T)	B/A	16	0.9647	(0.8941, 1.0408)
	C/A	17	0.9979	(0.9438, 1.0551)

5

A = Aripiprazole 5 mg commercial tablet

B = Aripiprazole 5 mg flash-melt prototype I

C = Aripiprazole 5 mg flash-melt prototype II

10 One Year Chemical Stability of 2 mg and 30 mg potency aripiprazole flash-melt tablets:

Shown below are the stability results for the 2 mg and 30 mg potency tablets placed on official IND stability testing. As seen from the results, only one degradant is seen
15 that shows growth under accelerated conditions as well as at room temperature. This

Table 1: Aripiprazole Flash-Melt Tablets; IND Stability Study -- 2-mg Prototype

I

Time Point and Storage Condition	(%) calculated from the area under the chromatogram peak normalized for the area under the entire chromatogram							
	Metabolite of aripiprazole / oxidation product	aripiprazole	N-oxide of aripiprazole	Unknown Impurities	Total Impurities	Potency (Result #1)	Potency (Result #2)	Potency (Reported Result)
	%	%	%	%	%	mg/tab	mg/tab	mg/tab
	RRT 0.91	RRT 1.00	RRT 1.08	RRT in ()				
Initial	0.06	99.94	--	--	0.06	2.01	1.97	1.99
1 day @ 25C/75%RH (open)	0.07	99.86	0.07	--	0.14	1.98	NP	1.98
4 days @ 25C/HIL/UVA (exposed)	0.06	99.81	0.13	--	0.19	1.97	NP	1.97
4 days @ 25C/HIL/UVA (wrapped)	--	99.95	0.05	--	0.05	2.02	NP	2.02
1 week @ 25C/75%RH (open)	0.09	99.73	0.18	--	0.27	1.96	NP	1.96
2 wks @ 25C/HIL/UVA (exposed)	0.08	99.71	0.15	0.06 (0.87)	0.29	2.02	NP	2.02
2 wks @ 25C/HIL/UVA (wrapped)	0.05	99.90	0.05	--	0.10	1.98	NP	1.98
2 wks @ 25C/60%RH (closed)	0.05	99.95	--	--	0.05	2.03	NP	2.03
2 wks @ 25C/75%RH (open)	0.11	99.63	0.26	--	0.37	1.98	NP	1.98
4 wks @ 25C/60%RH (closed)	0.05	99.95	--	--	0.05	2.01	NP	2.01
4 wks @ 40C/75%RH (closed)	0.05	99.82	0.13	--	0.18	2.01	NP	2.01
4 wks @ 50C (closed)	0.06	99.62	0.32	--	0.38	1.97	NP	1.97
13 wks @ 25C/60%RH (closed)	0.06	99.85	0.09	--	0.15	1.97	NP	1.97
13 wks @ 40C/75%RH (closed)	0.09	99.46	0.45	--	0.54	1.95	NP	1.95
13 wks @ 50C (closed)	0.13	98.70	0.92	0.19 (0.38)	1.30	1.95	NP	1.95
26 wks @ 25C/60%RH (closed)	0.05	99.81	0.14	--	0.19	2.05	NP	2.05
26 wks @ 40C/75%RH (closed)	0.11	99.18	0.71	--	0.82	2.03	NP	2.03
52 wks @ -15C (closed)	--	100.00	--	--	0.00	2.05	NP	2.05
52 wks @ 25C/60%RH (closed)	--	99.77	0.23	--	0.23	1.97	NP	1.97

RRT = relative retention time (relative to the active compound, aripiprazole) during the chromatography analysis

Comments:

"--" indicates that no peak was detected or that the peak measured less than the reporting limit (<0.05 I.L.)

"NP" indicates, "Not Performed"

Table 2: Aripiprazole Flash-Melt Tablets; IND Stability Study -- 2-mg Prototype

II

Time Point and Storage Condition	(%) calculated from the area under the chromatogram peak normalized for the area under the entire chromatogram							
	Metabolite of aripiprazole / oxidation product	aripiprazole	N-oxide of aripiprazole	Unknown Impurities	Total Impurities	Potency (Result #1)	Potency (Result #2)	Potency (Reported Result)
	%	%	%	%	%	mg/tab	mg/tab	mg/tab
	RRT 0.91	RRT 1.00	RRT 1.08	RRT in ()				
Initial	0.05	99.95	--	--	0.05	2.05	2.04	2.05
1 day @ 25C/75%RH (open)	0.07	99.86	0.07	--	0.14	2.01	NP	2.01
4 days @ 25C/HIL/UVA (exposed)	0.06	99.86	0.08	--	0.14	2.00	NP	2.00
4 days @ 25C/HIL/UVA (wrapped)	0.06	99.89	0.06	--	0.11	2.00	NP	2.00
1 week @ 25C/75%RH (open)	0.08	99.80	0.12	--	0.20	2.00	NP	2.00
2 wks @ 25C/HIL/UVA (exposed)	0.09	99.74	0.12	0.06 (0.87)	0.26	2.00	NP	2.00
2 wks @ 25C/HIL/UVA (wrapped)	0.05	99.95	--	--	0.05	2.02	NP	2.02
2 wks @ 25C/60%RH (closed)	0.06	99.89	0.05	--	0.11	2.00	NP	2.00
2 wks @ 25C/75%RH (open)	0.10	99.72	0.18	--	0.28	1.99	NP	1.99
4 wks @ 25C/60%RH (closed)	0.05	99.95	--	--	0.05	2.01	NP	2.01
4 wks @ 40C/75%RH (closed)	0.05	99.90	0.05	--	0.10	2.04	NP	2.04
4 wks @ 50C (closed)	0.07	99.68	0.25	--	0.32	2.02	NP	2.02
13 wks @ 25C/60%RH (closed)	0.06	99.88	0.06	--	0.12	2.00	NP	2.00
13 wks @ 40C/75%RH (closed)	0.08	99.63	0.29	--	0.37	1.98	NP	1.98
13 wks @ 50C (closed)	0.12	98.89	0.74	0.20 (0.38)	1.11	1.98	NP	1.98
26 wks @ 25C/60%RH (closed)	0.06	99.86	0.08	--	0.14	2.06	NP	2.06
26 wks @ 40C/75%RH (closed)	0.16	99.29	0.55	--	0.71	2.02	NP	2.02
52 wks @ -15C (closed)	--	100.00	--	--	0.00	2.01	NP	2.01
52 wks @ 25C/60%RH (closed)	--	99.89	0.11	--	0.11	2.02	NP	2.02

RRT = relative retention time (relative to the active compound, aripiprazole) during the chromatography analysis

Comments:

"--" indicates that no peak was detected or that the peak measured less than the reporting limit (<0.05 I.U.)

"NP" indicates, "Not Performed"

Table 3: Aripiprazole Flash-Melt Tablets; IND Stability Study -- 30-mg Prototype I

Time Point and Storage Condition	(%) calculated from the area under the chromatogram peak normalized for the area under the entire chromatogram							
	Metabolite of aripiprazole / oxidation product	aripiprazole	N-oxide of aripiprazole	Unknown Impurities	Total Impurities	Potency (Result #1)	Potency (Result #2)	Potency (Reported Result)
	%	%	%	%	%	mg/tab	mg/tab	mg/tab
	RRT 0.91	RRT 1.00	RRT 1.08	RRT in ()				
Initial	0.06	99.94	--	--	0.06	29.54	29.90	29.7
1 day @ 25C/75%RH (open)	0.07	99.88	0.05	--	0.12	28.98	NP	29.0
4 days @ 25C/HIL/UVA (exposed)	0.05	99.89	0.06	--	0.11	29.39	NP	29.4
4 days @ 25C/HIL/UVA (wrapped)	0.06	99.89	0.05	--	0.11	29.41	NP	29.4
1 week @ 25C/75%RH (open)	0.10	99.82	0.08	--	0.18	28.24	29.30	29.3*
2 wks @ 25C/HIL/UVA (exposed)	0.05	99.85	0.10	--	0.15	29.52	NP	29.5
2 wks @ 25C/HIL/UVA (wrapped)	0.05	99.89	0.06	--	0.11	29.98	NP	30.0
2 wks @ 25C/60%RH (closed)	0.06	99.87	0.07	--	0.13	29.77	NP	29.8
2 wks @ 25C/75%RH (open)	0.08	99.81	0.11	--	0.19	29.74	NP	29.7
4 wks @ 25C/60%RH (closed)	0.05	99.95	--	--	0.05	29.08	NP	29.1
4 wks @ 40C/75%RH (closed)	--	99.95	0.05	--	0.05	29.37	NP	29.4
4 wks @ 50C (closed)	0.06	99.87	0.07	--	0.13	29.70	NP	29.7
13 wks @ 25C/60%RH (closed)	0.06	99.90	0.05	--	0.10	29.73	NP	29.7
13 wks @ 40C/75%RH (closed)	0.06	99.85	0.09	--	0.15	29.89	NP	29.9
13 wks @ 50C (closed)	0.06	99.77	0.17	--	0.23	29.74	NP	29.7
26 wks @ 25C/60%RH (closed)	0.05	99.91	0.04	--	0.09	29.26	NP	29.3
26 wks @ 40C/75%RH (closed)	0.06	99.81	0.13	--	0.19	29.41	NP	29.4
52 wks @ -15C (closed)	0.05	99.95	--	--	0.05	29.70	NP	29.7
52 wks @ 25C/60%RH (closed)	0.06	99.88	0.06	--	0.12	29.90	NP	29.9

RRT = relative retention time (relative to the active compound, aripiprazole) during the chromatography analysis

Comments:

"--" indicates that no peak was detected or that the peak measured less than the reporting limit (<0.05 I.I.)

"NP" indicates, "Not Performed"

* Only Result 2 is reported (29.3); Result 1 (28.2) is believed to be low because of incomplete extraction.

Table 4: Aripiprazole Flash-Melt Tablets; IND Stability Study - 30-mg
 Prototype II

Time Point and Storage Condition	(%) calculated from the area under the chromatogram peak normalized for the area under the entire chromatogram							
	Metabolite of aripiprazole / oxidation product	aripiprazole	N-oxide of aripiprazole	Unknown Impurities	Total Impurities	Potency (Result #1)	Potency (Result #2)	Potency (Reported Result)
	%	%	%	%	%	mg/tab	mg/tab	mg/tab
	RRT 0.91	RRT 1.00	RRT 1.08	RRT in ()				
Initial	0.05	99.95	--		0.05	28.86	29.78	29.3
1 day @ 25C/75%RH (open)	0.07	99.88	0.05	--	0.12	29.01	NP	29.0
4 days @ 25C/HIL/UVA (exposed)	0.05	99.91	0.05	--	0.09	29.20	NP	29.2
4 days @ 25C/HIL/UVA (wrapped)	0.06	99.94	--	--	0.06	29.54	NP	29.5
1 week @ 25C/75%RH (open)	0.08	99.86	0.06	--	0.14	28.94	NP	28.9
2 wks @ 25C/HIL/UVA (exposed)	0.05	99.87	0.07	--	0.13	29.23	NP	29.2
2 wks @ 25C/HIL/UVA (wrapped)	0.05	99.95	--	--	0.05	29.45	NP	29.5
2 wks @ 25C/60%RH (closed)	0.05	99.95	--	--	0.05	29.02	NP	29.0
2 wks @ 25C/75%RH (open)	0.07	99.86	0.07	--	0.14	29.79	NP	29.8
4 wks @ 25C/60%RH (closed)	0.05	99.95	--	--	0.05	29.53	NP	29.5
4 wks @ 40C/75%RH (closed)	0.05	99.95	--	--	0.05	29.14	NP	29.1
4 wks @ 50C (closed)	0.05	99.90	0.05	--	0.10	29.68	NP	29.7
13 wks @ 25C/60%RH (closed)	0.05	99.95	--	--	0.05	30.145	NP	30.1
13 wks @ 40C/75%RH (closed)	0.06	99.88	0.06	--	0.12	29.80	NP	29.8
13 wks @ 50C (closed)	0.07	99.83	0.10	--	0.17	30.14	NP	30.1
26 wks @ 25C/60%RH (closed)	0.05	99.95	--	--	0.05	29.76	NP	29.8
26 wks @ 40C/75%RH (closed)	0.05	99.87	0.07	--	0.13	28.98	NP	29.0
52 wks @ -15C (closed)	0.05	99.95	--	--	0.05	29.14	NP	29.1
52 wks @ 25C/60%RH (closed)	0.07	99.93	--	--	0.07	30.17	NP	30.2

RRT = relative retention time (relative to the active compound, aripiprazole) during the chromatography analysis

Comments:

"--" indicates that no peak was detected or that the peak measured less than the reporting limit (<0.05 I.I.)

"NP" indicates, "Not Performed"

We claim:

1. A flash-melt pharmaceutical dosage form comprising a medicament, a
superdisintegrant, a dispersing agent and a binder wherein said medicament is
5 aripiprazole, entecavir, cefprozil, pravastatin, captopril, gatifloxacin,
desquinalone, omapatrilat or irbesartan and wherein said dispersing agent is
calcium silicate and wherein said superdisintegrant is comprised of two or more
agents selected from the group consisting of crospovidone, croscarmellose
sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose or
10 pregelatinized starch.
2. A flash-melt pharmaceutical dosage form according to claim 1 wherein said
dispersing agent comprises from about 20 to about 70 percent by weight of said
dispersing agent based on the total weight of said dosage form.
15
3. A flash-melt pharmaceutical dosage form according to claim 1 wherein said
dispersing agent comprises from about 35 to about 45 percent by weight of said
dispersing agent based on the total weight of said dosage form.
- 20 4. A flash-melt pharmaceutical dosage form according to claim 1 wherein greater
than 50% of said dispersing agent by weight is comprised of calcium silicate.
5. A flash-melt pharmaceutical dosage form according to claim 1 wherein greater
than 80% of said dispersing agent by weight is comprised of calcium silicate.
25
6. A flash-melt pharmaceutical dosage form according to claim 1 wherein said
calcium silicate is crystalline.
7. A flash-melt pharmaceutical dosage form according to claim 1 wherein said
30 calcium silicate is amorphous.

8. A flash-melt pharmaceutical dosage form according to claim 1 wherein said calcium silicate is ortho-, meta- or alpha triclinic-calcium silicate.
- 5 9. A flash-melt pharmaceutical dosage form according to claim 1 wherein said calcium silicate is alpha triclinic-calcium silicate.
- 10 10. A flash-melt pharmaceutical dosage form according to claim 1 wherein said calcium silicate is comprised of a combination of alpha triclinic-calcium silicate and at least one other pharmaceutical grade of calcium silicate wherein said alpha triclinic-calcium silicate comprises from about 10% to about 90% by weight of said combination.
- 15 11. A flash-melt pharmaceutical dosage form according to claim 1 wherein said calcium silicate has a surface area of $1.0 \text{ m}^2/\text{gm}$ to $210 \text{ m}^2/\text{gm}$, bulk density of 0.075 g/cc to 0.90 g/cc , true density of 1.70 g/cc to 2.90 g/cc and volatile content of less than 1% to 14% w/w.
- 20 12. A flash-melt pharmaceutical dosage form according to claim 1 wherein said calcium silicate is alpha triclinic calcium silicate that has a surface area of about $1.3 \text{ m}^2/\text{gm}$, bulk density of about 0.63 g/cc , true density of about 2.90 g/cc and volatile content of less than 1% w/w.
- 25 13. A flash-melt pharmaceutical dosage form according to claim 1 wherein said calcium silicate is ortho crystalline calcium silicate that has a surface area of about $0.98 \text{ m}^2/\text{gm}$, bulk density of about 0.492 g/cc , true density of about 3.252 g/cc and volatile content of less than 1% w/w.
- 30 14. A flash-melt pharmaceutical dosage form according to claim 1 wherein said calcium silicate is meta crystalline calcium silicate that has a surface area of about $2.5 \text{ m}^2/\text{gm}$, bulk density of about 0.867 g/cc , true density of about 2.940 g/cc and volatile content of less than 1% w/w.

15. A flash-melt pharmaceutical dosage form according to claim 1 wherein said calcium silicate is crystalline calcium silicate that has a surface area of about 90.4 m²/gm, bulk density of about 0.094 g/cc, true density of about 2.596 g/cc and volatile content of less than 1% w/w.

5

16. A flash-melt pharmaceutical dosage form according to claim 1 wherein said calcium silicate is amorphous calcium silicate that has a surface area of about 191.3 m²/gm, bulk density of about 0.120 g/cc, true density of about 2.314 g/cc and volatile content of about less than 14% w/w.

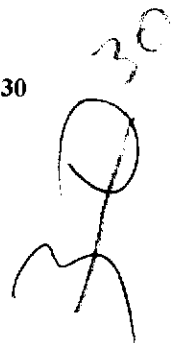
10 17. A flash-melt pharmaceutical dosage form according to claim 1 wherein said calcium silicate is amorphous calcium silicate that has a surface area of about 103.0 m²/gm, bulk density of about 0.130 g/cc, true density of about 1.702 g/cc and volatile content of about less than 14% w/w.

15 18. A flash-melt pharmaceutical dosage form according to claim 1 wherein said calcium silicate is amorphous calcium silicate that has a surface area of about 209 m²/gm, bulk density of about 0.075 g/cc, true density of about 2.035 g/cc and volatile content of about less than 14% w/w.

20 19. A flash-melt pharmaceutical dosage form according to claim 1 wherein said medicament comprises not more than about 30 percent by weight of said medicament based on the total weight of said dosage form.

20. A flash-melt pharmaceutical dosage form according to claim 1 wherein said
25 medicament comprises not more than about 15 percent by weight of said medicament based on the total weight of said dosage form.

21. A flash-melt pharmaceutical dosage form according to claim 1 wherein said
30 superdisintegrant comprises from about 3 to about 15 percent by weight of said superdisintegrant based on the total weight of said dosage form.



22. A flash-melt pharmaceutical dosage form according to claim 1 wherein said superdisintegrant comprises from about 4 to about 10 percent by weight of said superdisintegrant based on the total weight of said dosage form.
- 5 23. A flash-melt pharmaceutical dosage form according to claim 1 wherein said superdisintegrant comprises from about 4 to about 8 percent by weight of said superdisintegrant based on the total weight of said dosage form.
- 10 24. A flash-melt pharmaceutical dosage form according to claim 1 wherein said superdisintegrant comprises from about 5 to about 7 percent by weight of said superdisintegrant based on the total weight of said dosage form.
- 15 25. A flash-melt pharmaceutical dosage form according to claim 1 wherein said superdisintegrant comprises from about 8 to about 12 percent by weight of said superdisintegrant based on the total weight of said dosage form.
- 20 26. A flash-melt pharmaceutical dosage form according to claim 1 wherein said superdisintegrant comprises from about 9 to about 10 percent by weight of said superdisintegrant based on the total weight of said dosage form.
- 25 27. A flash-melt pharmaceutical dosage form according to claim 1 wherein said superdisintegrant agent is crospovidone and croscarmellose sodium.
- 30 28. A flash-melt pharmaceutical dosage form according to claim 27 wherein based on the total weight of said dosage form, said crospovidone comprises from about 6 to about 8 percent by weight of said crospovidone and said croscarmellose sodium comprises from about 2 to about 4 percent by weight of said croscarmellose sodium.
- 30 29. A flash-melt pharmaceutical dosage form according to claim 1 further comprising a distributing agent.

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30. A flash-melt pharmaceutical dosage form according to claim 29 wherein said distributing agent comprises from about 1 to about 10 percent by weight of said distributing agent based on the total weight of said dosage form.
- 5 31. A flash-melt pharmaceutical dosage form according to claim 29 wherein said distributing agent comprises from about 1.5 to about 3 percent by weight of said distributing agent based on the total weight of said dosage form.
- 10 32. A flash-melt pharmaceutical dosage form according to claim 29 wherein said distributing agent is amorphous silica, fumed silica, diatomaceous earth, talc, kaolin or magnesium aluminum trisilicate.
- 15 33. A flash-melt pharmaceutical dosage form according to claim 1 wherein said distributing agent comprises from about 10 to about 50 percent by weight of said binder based on the total weight of said dosage form.
- 20 34. A flash-melt pharmaceutical dosage form according to claim 1 wherein said distributing agent comprises from about 12 to about 20 percent by weight of said binder based on the total weight of said dosage form.
35. A flash-melt pharmaceutical dosage form according to claim 1 wherein said binder is microcrystalline cellulose, hydroxypropyl cellulose, ethyl cellulose, lactose, mannitol or calcium phosphate.
- 25 36. A flash-melt pharmaceutical dosage form comprising a medicament, a superdisintegrant, a dispersing agent and a binder wherein said medicament is aripiprazole and comprises not more than about 30 percent by weight of said medicament based on the total weight of said dosage form, said dispersing agent is calcium silicate having a surface area of $1.0 \text{ m}^2/\text{gm}$ to $210 \text{ m}^2/\text{gm}$, bulk density of 0.075 g/cc to 0.90 g/cc , true density of 1.70 g/cc to 2.90 g/cc and volatile content of less than 1% to 14% w/w and which comprises from about 20 to about 70 percent by weight of said dispersing agent based on the total weight of said
- 30

dosage form, said superdisintegrants are two or more agents selected from the group consisting of crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose or pregelatinized starch and which comprise 3 to 15 percent by weight of combination of said
5 superdisintegrant agents based on the total weight of said dosage form.

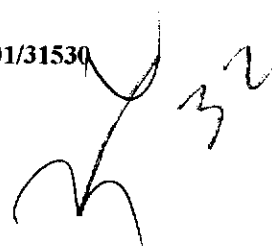
37. A flash-melt pharmaceutical dosage form comprising a medicament, a superdisintegrant, a dispersing agent and a binder wherein said medicament is aripiprazole and comprises not more than about 30 percent by weight of said
10 medicament based on the total weight of said dosage form, said dispersing agent is calcium silicate having a surface area of $1.0 \text{ m}^2/\text{gm}$ to $210 \text{ m}^2/\text{gm}$, bulk density of 0.075 g/cc to 0.90 g/cc , true density of 1.70 g/cc to 2.90 g/cc and volatile content of less than 1% to 14% w/w and which comprises from about 35 to about
15 45 percent by weight of said dispersing agent based on the total weight of said dosage form, said superdisintegrant is crospovidone and croscarmellose sodium, said crospovidone comprises from about 6 to about 8 percent by weight of said crospovidone based on the total weight of said dosage form and said croscarmellose sodium comprises from about 2 to about 4 percent by weight of said croscarmellose sodium based on the total weight of said dosage form.

38. A flash-melt pharmaceutical dosage form comprising a medicament, a superdisintegrant, a dispersing agent and a binder wherein said medicament is aripiprazole and comprises not more than about 30 percent by weight of said
25 medicament based on the total weight of said dosage form, said dispersing agent is calcium silicate having a surface area of $1.0 \text{ m}^2/\text{gm}$ to $210 \text{ m}^2/\text{gm}$, bulk density of 0.075 g/cc to 0.90 g/cc , true density of 1.70 g/cc to 2.90 g/cc and volatile content of less than 1% to 14% w/w and which comprises from about 35 to about
30 45 percent by weight of said dispersing agent based on the total weight of said dosage form, said superdisintegrant is crospovidone and croscarmellose sodium, said crospovidone comprises from about 6 to about 8 percent by weight of said crospovidone based on the total weight of said dosage form and said croscarmellose sodium comprises from about 2 to about 4 percent by weight of

said croscarmellose sodium based on the total weight of said dosage form and wherein said distributing agent is is amorphous silica, fumed silica, diatomaceous earth, talc, kaolin or magnesium aluminum trisilicate and comprises from about 1 to about 10 percent by weight of said distributing agent based on the total weight of said dosage form.

39. A flash-melt pharmaceutical dosage form according to claim 38 prepared by dry blending into a mixture, said medicament and said superdisintegrant, said dispersing agent and said binder, compressing said mixture through a suitable compactor or slugger to form compacts or slugs, passing said compacts or slugs through a screen to form granules and compressing said granules to form said flash-melt pharmaceutical dosage form.

40. A flash-melt pharmaceutical dosage form comprising a medicament, a superdisintegrant, a dispersing agent, a distributing agent and a binder wherein said medicament is aripiprazole and comprises not more than about 30 percent by weight of said medicament based on the total weight of said dosage form, said dispersing agent is calcium silicate having a surface area of $1.0 \text{ m}^2/\text{gm}$ to $210 \text{ m}^2/\text{gm}$, bulk density of 0.075 g/cc to 0.90 g/cc , true density of 1.70 g/cc to 2.90 g/cc and volatile content of less than 1% to 14% w/w and which comprises from about 20 to about 70 percent by weight of said dispersing agent based on the total weight of said dosage form, said superdisintegrant is crospovidone and croscarmellose sodium and wherein said crospovidone comprises 5 to 8 percent by weight of said crospovidone based on the total weight of said dosage form and wherein said croscarmellose comprises 1 to 4 percent by weight of said crospovidone based on the total weight of said dosage form, and wherein said distributing agent is is amorphous silica, fumed silica, diatomaceous earth, talc, kaolin or magnesium aluminum trisilicate and comprises from about 10 to about 50 percent by weight of said distributing agent based on the total weight of said dosage form.



41. A flash-melt pharmaceutical dosage form comprising a medicament, a superdisintegrant, a dispersing agent, a distributing agent and a binder wherein said medicament is aripiprazole and comprises not more than about 30 percent by weight of said medicament based on the total weight of said dosage form, said
5 dispersing agent is calcium silicate having a surface area of $1.0 \text{ m}^2/\text{gm}$ to $210 \text{ m}^2/\text{gm}$, bulk density of 0.075 g/cc to 0.90 g/cc , true density of 1.70 g/cc to 2.90 g/cc and volatile content of less than 1% to 14% w/w and which comprises from about 20 to about 70 percent by weight of said dispersing agent based on the total weight of said dosage form, said superdisintegrant is crospovidone and
10 croscarmellose sodium and wherein said crospovidone comprises about 7 percent by weight of said crospovidone based on the total weight of said dosage form and wherein said croscarmellose comprises about 3 percent by weight of said crospovidone based on the total weight of said dosage form, and wherein said distributing agent is is amorphous silica, fumed silica, diatomaceous earth, talc,
15 kaolin or magnesium aluminum trisilicate and comprises from about 10 to about 50 percent by weight of said distributing agent based on the total weight of said dosage form.

42. A flash-melt pharmaceutical dosage form comprising a medicament, a
20 superdisintegrant, a dispersing agent, a distributing agent and a binder wherein said medicament is aripiprazole and comprises not more than about 30 percent by weight of said medicament based on the total weight of said dosage form, said dispersing agent is calcium silicate having a surface area of $1.0 \text{ m}^2/\text{gm}$ to $210 \text{ m}^2/\text{gm}$, bulk density of 0.075 g/cc to 0.90 g/cc , true density of 1.70 g/cc to 2.90 g/cc and volatile content of less than 1% to 14% w/w and which comprises from
25 about 35 to about 45 percent by weight of said dispersing agent based on the total weight of said dosage form, said superdisintegrant is crospovidone and croscarmellose sodium and wherein said crospovidone comprises about 7 percent by weight of said crospovidone based on the total weight of said dosage form and
30 wherein said croscarmellose comprises about 3 percent by weight of said crospovidone based on the total weight of said dosage form, and wherein said distributing agent is is amorphous silica, fumed silica, diatomaceous earth, talc,

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kaolin or magnesium aluminum trisilicate and comprises from about 10 to about 50 percent by weight of said distributing agent based on the total weight of said dosage form.

- 5 43. A flash-melt pharmaceutical dosage form comprising a medicament, a
superdisintegrant, a dispersing agent, a distributing agent and a binder wherein
said medicament is aripiprazole and comprises not more than about 20 percent by
weight of said medicament based on the total weight of said dosage form, said
dispersing agent is calcium silicate having a surface area of 1.0 m²/gm to 210
10 m²/gm, bulk density of 0.075 g/cc to 0.90 g/cc, true density of 1.70 g/cc to 2.90
g/cc and volatile content of less than 1% to 14% w/w and which comprises from
about 35 to about 45 percent by weight of said dispersing agent based on the total
weight of said dosage form, said superdisintegrant is crospovidone and
croscarmellose sodium and wherein said crospovidone comprises about 7 percent
15 by weight of said crospovidone based on the total weight of said dosage form and
wherein said croscarmellose comprises about 3 percent by weight of said
crospovidone based on the total weight of said dosage form, and wherein said
distributing agent is is amorphous silica, fumed silica, diatomaceous earth, talc,
kaolin or magnesium aluminum trisilicate and comprises from about 10 to about
20 50 percent by weight of said distributing agent based on the total weight of said
dosage form.
44. A flash-melt pharmaceutical dosage form comprising a medicament, a
superdisintegrant, a dispersing agent, a distributing agent and a binder wherein
25 said medicament is aripiprazole and comprises not more than about 10 percent by
weight of said medicament based on the total weight of said dosage form, said
dispersing agent is calcium silicate having a surface area of 1.0 m²/gm to 210
m²/gm, bulk density of 0.075 g/cc to 0.90 g/cc, true density of 1.70 g/cc to 2.90
g/cc and volatile content of less than 1% to 14% w/w and which comprises from
30 about 35 to about 45 percent by weight of said dispersing agent based on the total
weight of said dosage form, said superdisintegrant is crospovidone and
croscarmellose sodium and wherein said crospovidone comprises about 7 percent

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by weight of said crospovidone based on the total weight of said dosage form and wherein said croscaremellose comprises about 3 percent by weight of said crospovidone based on the total weight of said dosage form.

- 5 45. A flash-melt pharmaceutical dosage form comprising a medicament, a superdisintegrant, a dispersing agent, a distributing agent and a binder wherein said medicament is aripiprazole and comprises not more than about 5 percent by weight of said medicament based on the total weight of said dosage form, said dispersing agent is calcium silicate having a surface area of 1.0 m²/gm to 210
- 10 m²/gm, bulk density of 0.075 g/cc to 0.90 g/cc, true density of 1.70 g/cc to 2.90 g/cc and volatile content of less than 1% to 14% w/w and which comprises from about 35 to about 45 percent by weight of said dispersing agent based on the total weight of said dosage form, said superdisintegrant is crospovidone and
- 15 croscarmellose sodium and wherein said crospovidone comprises about 7 percent by weight of said crospovidone based on the total weight of said dosage form and wherein said croscaremellose comprises about 3 percent by weight of said crospovidone based on the total weight of said dosage form.

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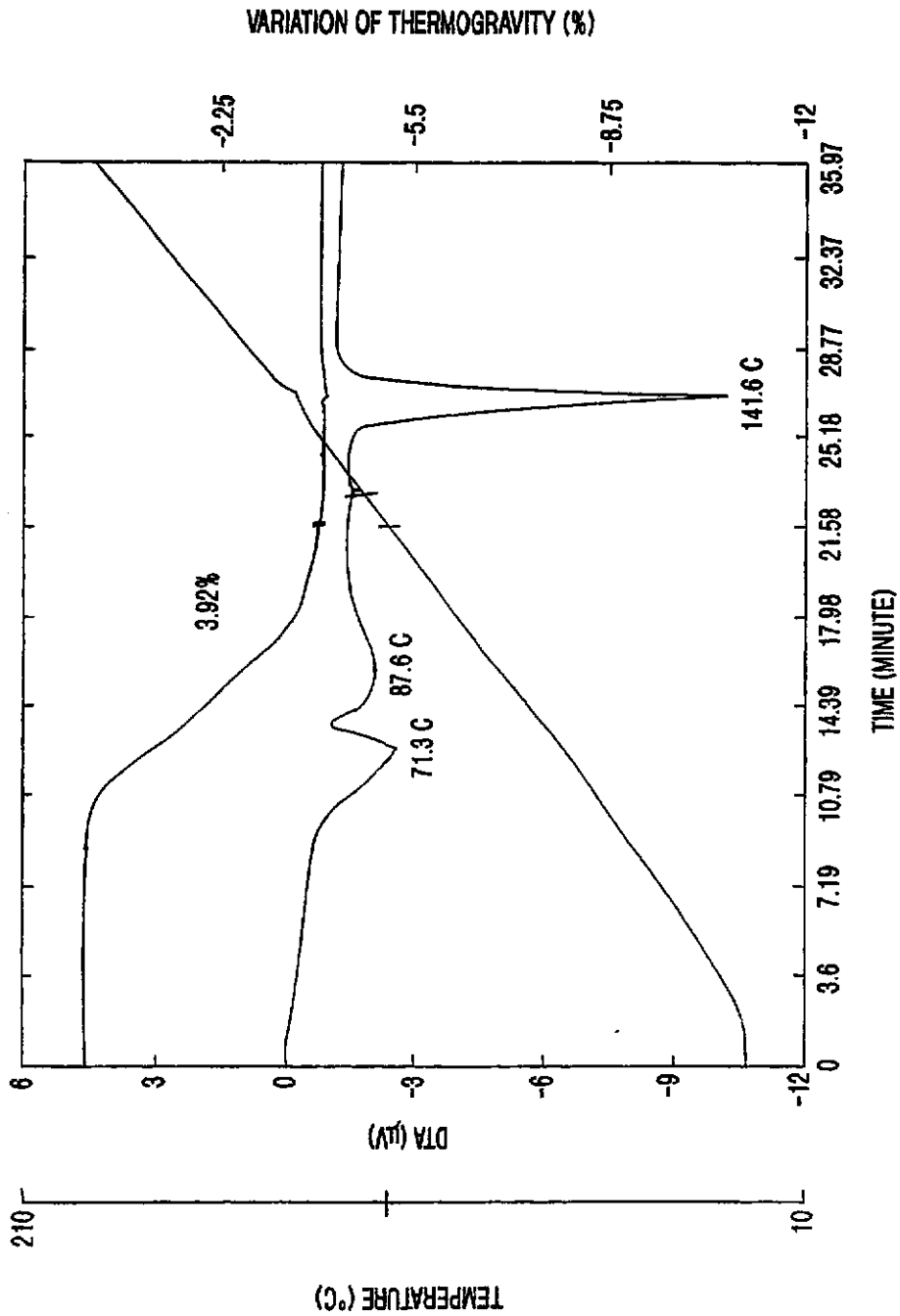


FIG. 1

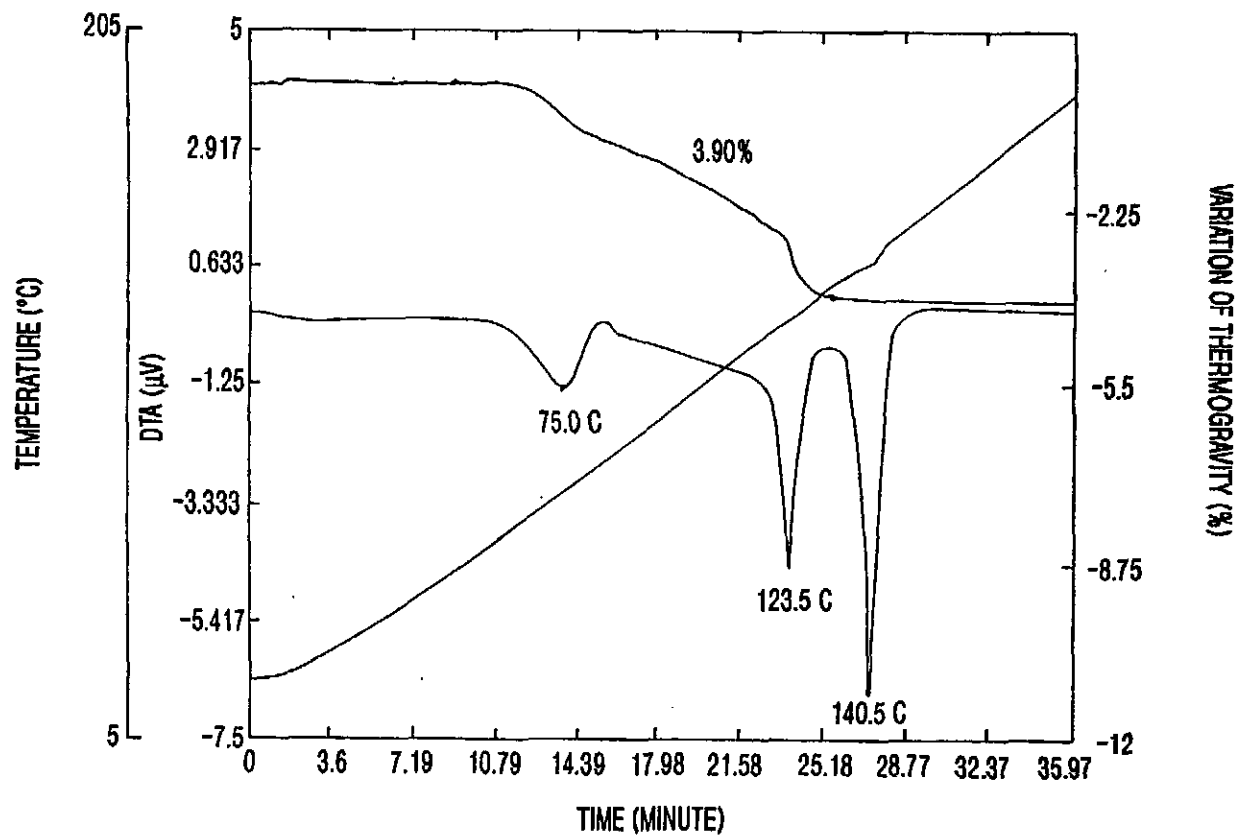


FIG. 6

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(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACIÓN PARA PATENTES (PCT)

I N T E R N A T I O N A L P A T E N T C O O P E R A T I O N T R A T A D O D E C O O P E R A C I O N P A R A P A T E N T E S

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(75) Inventores: KOTHARI, Sanjeev; 99 Harvard Circle, Princeton, NJ 08540 (US). DESAI, Divyakant; 19 Greenfield Drive, North West Windsor, NJ 08550 (US)	
(74) Agente: MAKUJINA, Shah, R.; Bristol-Meyers Squibb Company,]; Lawrenceville-Princeton Road, P.O. Box 4000, Princeton, NJ 08543-4000 (US)	

(54) Título: FORMULACIÓN FARMACÉUTICA DE FUSIÓN INSTANTÁNEA

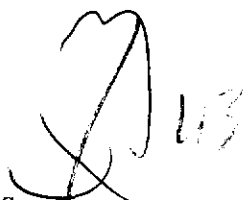
(57) Extracto: Se disponen unos gránulos para la producción de formulaciones farmacéuticas de fusión instantánea mejoradas. Además de uno o varios medicamentos, los gránulos se componen de una combinación de excipientes consistentes de un disgregante de acción superior (de dos o más agentes seleccionados entre el grupo conformado por crospovidonas, croscarmelosa sódica, sodio, glicolato sódico de almidón, hidroxipropilcelulosa de sustitución baja o un almidón pregelatinizado), un agente dispersante, un agente redistribuidor y un aglutinante e igualmente puede incluir otros ingredientes convencionales como edulcorantes y agentes saborizantes. Los citados gránulos son ventajosos en cuanto que son estables y se pueden preparar sin la ayuda de solventes y sin requerir unos medios o manejos especiales. Las formas de dosis, especialmente las tabletas, se preparan con los mismos por medio de un equipo convencional y se desintegran en la boca aproximadamente en veinticinco segundos.

FORMULACIÓN FARMACÉUTICA DE FUSIÓN INSTANTÁNEA

La presente invención hace referencia a unas formas farmacéuticas orales sólidas que se dispersan rápidamente en la boca.

Existe una gran variedad de formas farmacéuticas sólidas que se desintegran o disuelven rápidamente en un vaso de agua o en el tracto gastrointestinal. Estas formas farmacéuticas se han conocido en el arte durante muchos años. Las ventajas evidentes derivadas de la conveniencia de las formas farmacéuticas de transporte que se disolverán o que se volverán efervescentes cuando se disuelven en agua para liberar el medicamento se conocen ampliamente. La necesidad terapéutica de contar con una forma farmacéutica oral que se disolverá o desintegrará rápidamente en la boca cuando se presenten situaciones que requieren una medicación instantánea y cuando no hay agua disponible se ha reconocido desde tiempo atrás.

Inicialmente se debe hacer una distinción entre las formas farmacéuticas de fusión instantánea y las formas farmacéuticas de desintegración rápida. Las primeras se deben disolver o desintegrar en la boca del paciente en menos de un minuto, mientras que las últimas se deben disolver o desintegrar en un periodo comprendido entre 3 y 20 minutos en el medio ácido del estómago o en un recipiente con agua. La prueba reconocida para las formas farmacéuticas de desintegración rápida es un tiempo de desintegración en 0.1 ácido clorhídrico N. Aquellos con destreza en el arte reconocerán que los requerimientos para que las formulaciones de formas farmacéuticas cumplan estos criterios necesariamente deben ser diferentes puesto que las condiciones, particularmente el pH, en la boca y el estómago difieren significativamente. Más importante, el tiempo en el cual una forma farmacéutica se debe disolver o desintegrar en la boca es necesariamente mucho más corto que en el estómago con la obvia excepción



de las formas farmacéuticas como por ejemplo las pastillas formuladas específicamente para que se disuelvan lentamente en la boca.

Otra consideración común para la mayoría, por no decir todas las formulaciones de formas farmacéuticas destinadas a una fusión instantánea o a una desintegración rápida es la necesidad de tomar unas precauciones en el momento de la preparación, el empaque, manejo y almacenamiento de las formas farmacéuticas terminadas puesto que tienden a ser tanto higroscópicas como deleznales. Las formas farmacéuticas que dependen de una efervescencia para originar su desintegración son particularmente susceptibles a la humedad y se deben empacar con envolturas especiales, con tapones, con paquetes de agentes secantes y similares.

Independientemente de estos problemas potenciales, aún persiste la urgente necesidad de formas farmacéuticas que se puedan disolver o desintegrar rápidamente para obtener los beneficios obvios de una dosis terapéutica del medicamento allí contenido disponible para una absorción en un periodo de tiempo muy corto. Además de los beneficios de una rápida disponibilidad, las formas farmacéuticas de fusión instantánea son ventajosas para la administración de medicamentos a pacientes como los que son muy pequeños, ancianos, los que no colaboran y aquellos con impedimentos físicos que les ocasionan dificultades o que les es imposible deglutir una forma farmacéutica intacta. Además las formas farmacéuticas de fusión instantánea son muy convenientes cuando no hay agua potable disponible o cuando esta no sea deseable. Los medicamentos receptivos a estas formas farmacéuticas pueden incluir los sedantes, hipnóticos, antipsicóticos, medicamentos antieméticos y estimulantes suaves como la cafeína y similares.

Aquellos con destrezas ordinarias en el arte sabían que hay dos conceptos básicos para la preparación de compuestos reconocidos para la preparación de formas farmacéuticas de disolución / desintegración rápida.

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El primero, particularmente apto para la preparación de formas farmacéuticas de fusión instantánea, es el secado por congelamiento donde se prepara una torta u oblea a partir de una solución secada por congelamiento o de la suspensión del medicamento y los excipientes apropiados en agua u otros solventes. Estas obleas se disuelven muy rápidamente sobre la lengua, es decir en unos 10 segundos, debido a una combinación de una alta afinidad con la humedad que resulta de un proceso de secado por congelamiento y una muy alta porosidad, que fomenta el rápido ingreso de la saliva. Aunque estas formas farmacéuticas permiten una rápida desintegración / disolución en la boca, el proceso de secado por congelamiento tiene varias desventajas, que incluyen principalmente que se debe formar una solución o una suspensión estable del medicamento antes de que se pueda secar por congelamiento. Aunque no siempre es el caso, típicamente estas soluciones son acuosas y por lo tanto no son aptas para formular medicamentos sensibles al agua. El proceso en sí es típicamente laborioso y requiere mucho tiempo. Finalmente las formas farmacéuticas resultantes, además de ser higroscópicas, tienden a ser muy suaves y por lo tanto requieren un empaque especial resistente a la humedad y a los impactos, y se debe manejar con sumo cuidado antes de su administración.

La segunda tecnología importante empleada en la manufactura de formas farmacéuticas de desintegración rápida se basa en unos grados especiales de azúcares tales como el manitol, sorbitol y similares en combinación con disgregantes de acción superior. Estos últimos son excipientes que se caracterizan por una capacidad de impregnado especial que canaliza el agua hacia el interior de la forma farmacéutica, o por un rápido esponjamiento en el agua y ambos actúan para acelerar la desintegración. También se sabe que se mejora la disolución de las formas farmacéuticas si se incluyen combinaciones efervescentes, típicamente bicarbonato de sodio y un ácido débil como el ácido cítrico. Como se anotó más arriba, las formulaciones efervescentes requieren un empaque especial resistente a la humedad, puesto que incluso cantidades muy pequeñas de

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humedad pueden ser suficientes para iniciar la reacción efervescente. Técnicas como la granulación de lecho fluidificado se reconocen como útiles en la preparación de estas formulaciones. Sin embargo, con demasiada frecuencia estas tecnologías requieren una planta específica y extremadamente costosa incluyendo el equipo especial para su manejo, medios de humedad controlada y similares. A pesar de estas medidas, las formas farmacéuticas producidas por medio de estas técnicas típicamente requieren un empaque resistente a la humedad, y en el empaque se deben incluir paquetes o cápsulas con agentes que absorben la humedad y similares.

Un ejemplo de una enseñanza sobre la incorporación de disgregantes de acción superior en formulaciones de formas farmacéuticas para mejorar la disolución es WO 98/030640, FMC Corporation. En la misma se revela que, por motivos de costos, hasta el 90% de un grupo de disgregantes incluyendo celulosas enlazadas en forma cruzada, carboximetilcelulosa enlazada en forma cruzada, almidón enlazado en forma cruzada, sal de metal alcalino de croscarmelosa, crospovidona, glicolato de almidón de metal alcalino y similares se pueden reemplazar por un co-disgregante. Entre el último grupo se incluyen las sílices naturales diatomáceas, un silicato de calcio de metal terroso alcalinotérreo hidratado sintético y una zeolita hidrófila porosa. La proporción de peso del disgregante de acción superior en relación con el co-disgregante se describe desde 4:1 hasta 1:10, preferiblemente 2-1:1. No hay ninguna indicación de un reconocimiento de beneficios que se derivarán de la formulación salvo la consideración obvia del ahorro de costos puesto que los co-disgregantes son menos costosos y se afirma que la combinación permite obtener los resultados deseados.

En contraste, la patente japonesa 10114655, Kyowa Hakko Kogyo KK revela una formulación para obtener una rápida disolución en el estómago que puede contener hasta 30% por peso de un disgregante de acción superior, como una crospovidona o una hidroxipropilcelulosa,

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croscarmelosa y similares y hasta un 30 % de un ingrediente neutro o alcalino incluyendo metasilicato de aluminio y magnesio, silicato de calcio, una sal fosfórica ácida o un metal hidróxido. La forma farmacéutica está destinada a medicamentos de producen un gel con un pH acidógeno.

Existen muchos otros ejemplos de formulaciones específicas que utilizan una o varias de las técnicas o mecanismos descritos arriba. Sin embargo, por lo general también poseen una o varias desventajas ya enumeradas hasta cierto grado, es decir que es difícil o costoso producir formas farmacéuticas por medio de estas técnicas. Las formas farmacéuticas son deleznales o sensibles a los factores del medio ambiente como la humedad. Sigue existiendo la necesidad de una formulación que mitigue o elimine estas ventajas, generando al mismo tiempo una forma farmacéutica de fusión instantánea que se desintegrará en la boca en aproximadamente 25 segundos. Estas formulaciones se describen de conformidad con la presente invención.

La presente invención se refiere a un aspecto particular y al mejoramiento de las formulaciones de fusión instantánea descritos en la solicitud con numero serial 09/547,948 de Estados Unidos presentada el 12 de abril de 2000. La presente invención se refiere a un aspecto particular de USSN 09/547,948 que mejora la formulación de fusión instantánea descrita en la citada solicitud al mejorar la bioequivalencia y la estabilidad de una preparación de fusión instantánea en particular descrita en la misma. En particular, el "Prototipo II" descrito en la misma es un ejemplo de la formulación de fusión instantánea mejorada reivindicado en la presente, donde se utiliza una combinación de un disgregante de acción superior para mejorar la bioequivalencia y la estabilidad.

Así, de conformidad con una primera incorporación de la presente invención, se describe una forma farmacéutica de fusión instantánea comprendiendo un medicamento, un disgregante de acción superior, un

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agente dispersante y un aglutinante donde el citado medicamento es aripiprazole, entecavir, cefprozil, pravastatin, captopril, gatifloxacina, desquinalona, omapatrilato o irbesartan, y donde el citado agente dispersante es silicato de calcio, y donde el referido disgregante de acción superior está conformado por dos o más agentes seleccionados entre el grupo conformado por crospovidona, croscarmelosa sódica, glicolato sódico de almidón, hidroxipropilcelulosa de baja sustitución o almidón pregelatinizado.

De conformidad con otras incorporaciones de la presente invención, se disponen formas farmacéuticas de fusión instantánea como se describe en la presente, donde más del 50% por peso del referido agente dispersante está compuesto por silicato de calcio.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde más del 80% por peso del referido agente dispersante está compuesto por silicato de calcio.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el referido silicato de calcio es cristalino.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el referido silicato de calcio es amorfo.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el referido silicato de calcio es un silicato de calcio orto – meta o alfa triclinico.

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De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el referido silicato de calcio es un silicato de calcio alfa triclinico.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el referido silicato de calcio está conformado por una combinación de silicato de calcio alfa triclinico y por lo menos otro grado farmacéutico de silicato de calcio donde el referido silicato de calcio alfa triclinico comprende entre 10% hasta alrededor de 90% por peso de la referida combinación.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el área de superficie del referido silicato de calcio es entre $1.0 \text{ m}^2/\text{gm}$ y $210 \text{ m}^2/\text{gm}$, con una densidad aparente de 0.075 g/cc a 0.90 g/cc , una densidad cierta de 1.70 g/cc a 2.90 g/cc y un contenido volátil de menos de 1% a 14% peso / peso.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el referido silicato de calcio es un silicato de calcio alfa triclinico cuya área de superficie es de alrededor $1.3 \text{ m}^2/\text{gm}$, con una densidad aparente de alrededor de 0.63 g/cc , una densidad cierta aproximadamente de 2.90 g/cc y un contenido volátil inferior a 1% peso / peso.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el referido silicato de calcio es un silicato de calcio orto cristalino cuya área de superficie es de alrededor de $0.98 \text{ m}^2/\text{gm}$, con una

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densidad aparente de 0.492 g/cc, una densidad cierta aproximadamente de 3.252 g/cc y un contenido volátil inferior a 1% peso / peso.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el referido silicato de calcio es un silicato de calcio cristalino cuya área de superficie es alrededor de 2.5 m²/gm, con una densidad aparente de alrededor de 0.867 g/cc, una densidad cierta aproximadamente de 2.940 g/cc y un contenido volátil inferior a 1% peso / peso.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el referido silicato de calcio es un silicato de calcio cristalino cuya área de superficie es alrededor de 90.4 m²/gm, con una densidad aparente de alrededor de 0.094 g/cc, una densidad cierta aproximadamente de 2.596 g/cc y un contenido volátil inferior a 1% peso / peso.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el referido silicato de calcio es un silicato de calcio amorfo cuya área de superficie es alrededor de 191.3 m²/gm, con una densidad aparente de alrededor de 0.120 g/cc, una densidad cierta aproximadamente de 2.314 g/cc y un contenido volátil de alrededor de menos de 14% peso / peso.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el referido silicato de calcio es un silicato de calcio amorfo cuya área de superficie es alrededor de 103.0 m²/gm, con una densidad aparente de alrededor de 0.130 g/cc, una densidad cierta aproximadamente de 1.702 g/cc y un contenido volátil de alrededor de menos de 14% peso / peso.

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De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el referido silicato de calcio es un silicato de calcio amorfo cuya área de superficie es alrededor de $209 \text{ m}^2/\text{gm}$, con una densidad aparente de alrededor de 0.075 g/cc , una densidad cierta aproximadamente de 2.035 g/cc y un contenido volátil de alrededor de menos de 14% peso / peso.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el citado medicamento comprende no más de alrededor de 30 por ciento por peso del referido medicamento con base en el peso total de la citada forma farmacéutica.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el citado medicamento comprende no más de alrededor 15 por ciento por peso del citado medicamento con base en el peso total de la citada forma farmacéutica.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el citado medicamento es aripiprazole.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el referido agente disgregante de acción superior comprende entre alrededor de 3 hasta alrededor de 15 por ciento por peso del citado agente disgregante de acción superior con base en el peso total de la referida forma farmacéutica.



De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el citado agente disgregante de acción superior comprende entre alrededor de 4 hasta alrededor de 10 por ciento por peso del citado agente disgregante de acción superior con base en el peso total de la citada forma farmacéutica.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el citado agente disgregante de acción superior comprende entre alrededor de 4 hasta alrededor de 8 por ciento por peso del citado agente disgregante de acción superior con base en el peso total de la citada forma farmacéutica.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el citado agente disgregante de acción superior comprende entre alrededor de 5 hasta alrededor de 7 por ciento por peso del citado agente disgregante de acción superior con base en el peso total de la citada forma farmacéutica.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el citado agente disgregante de acción superior comprende entre alrededor de 8 hasta alrededor de 12 por ciento por peso del citado agente disgregante de acción superior con base en el peso total de la citada forma farmacéutica.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el citado agente disgregante de acción superior comprende entre alrededor de 9 hasta alrededor de 10 por ciento por peso del citado

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agente disgregante de acción superior con base en el peso total de la citada forma farmacéutica.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el citado agente disgregante de acción superior está compuesto por crospovidona y croscarmelosa sódica.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente, donde con base en el peso total de la citada forma farmacéutica, la citada crospovidona comprende entre alrededor de 6 hasta alrededor de 8 por ciento por peso de la citada crospovidona y la referida croscarmelosa sódica comprende entre alrededor de 2 hasta alrededor de 4 por ciento por peso de la citada croscarmelosa sódica.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el citado agente distribuidor comprende entre alrededor de 1 hasta alrededor de 10 por ciento por peso del citado agente distribuidor con base en el peso total de la citada forma farmacéutica.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el citado agente distribuidor comprende entre alrededor de 1.5 hasta alrededor de 3 por ciento por peso del citado agente distribuidor con base en el peso total de la citada forma farmacéutica.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el citado agente distribuidor es una sílice amorfa, una sílice

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de combustión, tierra diatomita, talco, caolín o trisilicato de magnesio y aluminio.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el referido agente distribuidor comprende entre alrededor de 10 hasta alrededor de 50 por ciento por peso del citado aglutinante con base en el peso total de la citada forma farmacéutica.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el referido agente distribuidor comprende entre alrededor de 12 hasta alrededor de 20 por ciento por peso del citado aglutinante con base en el peso total de la citada forma farmacéutica.

De conformidad con otras incorporaciones de la presente invención se disponen formas farmacéuticas de fusión instantánea como se describe en la presente donde el referido aglutinante es celulosa microcristalina, hidroxipropilcelulosa, etilcelulosa, lactosa, manitol o fosfato de calcio.

Sin embargo, otras incorporaciones o aspectos de la presente invención residen en la combinación de una o varias de las incorporaciones o aspectos aquí descritos

Aún otras incorporaciones o aspectos de la presente invención se describen a continuación.

Las formas farmacéuticas de fusión instantánea de la presente invención se pueden preparar mediante la granulación seca de los ingredientes con el medicamento y los ingredientes convencionales aditivos, tales como agentes saborizantes y edulcorantes, sin utilizar solvente, para formar unos gránulos estables que se pueden

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comprimir rápidamente en formas farmacéuticas con equipos convencionales, sin requerir unas técnicas de manejo especiales.

El medicamento activo puede comprender hasta alrededor de 30% por peso, particularmente hasta alrededor de 15% por peso de la formulación, dependiendo de la cantidad requerida para una dosis terapéuticamente efectiva y de factores tales como la capacidad de poderse granular directamente, la cantidad de agentes saborizantes / edulcorantes requerida para disimular el sabor o la acritud de los mismos y similares. Dentro del alcance de la presente invención se comprende la utilización de medicamentos recubiertos a causa del sabor o por otro motivo en las formulaciones siempre que las recubiertas no interfieran ni con la preparación de los compuestos ni con la desintegración de las tabletas.

Los disgregantes de acción superior apropiados incluyen crospovidona, croscarmelosa sódica, glicolato sódico de almidón, hidroxipropilcelulosa de baja sustitución, almidón pregelatinizado y similares. La crospovidona se puede utilizar en grandes cantidades sin que la formulación que la contenga sea propensa a gelatinizarse.

Unos agentes dispersantes adecuados, a los cuales también se hace referencia en el arte como agentes antiapelmazantes, incluyen formas orto, meta y alfa triclinicos de silicato de calcio de los mismos, y formas orto meta trisilicatos de magnesio de los mismos y ácido silícico. El silicato de calcio es el agente dispersante preferido. Particularmente se prefiere un silicato de calcio cristalino alfa triclinico que se puede obtener comercialmente en Aldrich Chemical Company el cual cumple con las siguientes especificaciones: área de superficie $1.3 \text{ m}^2/\text{gm}$; densidad aparente de 0.63 g/cc ; densidad real de 2.90 g/cc ; y $< 1\%$ peso / peso volátiles. Además particularmente se prefiere un silicato de calcio cristalino alfa triclinico, comercialmente disponible J.M. Huber Inc., Tomita Pharmaceutical Co., Aldrich Chemical Company que cumple con las

siguientes especificaciones: área de superficie de 1.0 a 15 m²/gm; densidad aparente de 0.50 a .63 g/cc; densidad real de 2.40 a 2.90 g/cc; y < 1% peso / peso volátiles. También se ha encontrado que una variedad de grados farmacéuticos de silicato de calcio disponible donde otros proveedores, como aparece en la Tabla 1, produce formas farmacéuticas de fusión instantánea satisfactorias. Estos incluyen formas orto y meta de silicato de calcio disponibles en Alfa-Aesar, silicatos de calcio sintéticos Micro-cel C y Micro-cel E, disponibles en Celite Corp, Hubersorb 600 NF y Hubersorb 250 NF disponibles en J. M. Huber Corp, y combinaciones de varios grados de los mismos. Se ha descubierto que estos productos cubren el siguiente rango de especificaciones para el silicato de calcio: área de superficie de 1.0 m²/gm a 210 m²/gm; densidad aparente de 0.075 g/cc a 0.90 g/cc; densidad real de 1.70 g/cc a 2.90 g/cc; y < 1% a 14% peso / peso volátiles. La Tabla 1 enumera las especificaciones individuales para cada uno de los materiales obtenidos de los proveedores enumerados arriba.

Tabla 1.

Fuente	Descripción	Área de superficie m ² /gm	Densidad aparente g/cc(±s.d.)	Densidad real g/cc	Volátiles (% peso / peso)
Aldrich	CaSiO ₃ < malla de 200 (cristalino, alfa triclinico)	1.3	0.627 (0.020)	2.934	0.50
Alfa Aesar	2CaO.SiO ₂ (cristalino, orto)	0.98	0.492 (0.003)	3.252	0.02
Alfa Aesar	CaSiO ₃ (cristalino, meta)	2.5	0.867 (0.009)	2.940	0.50
Celite	Micro-cel E (cristalino)	90.4	0.094 (0.006)	2.596	0.94
Celite	Micro-cel C (amorfo)	191.3	0.120 (0.006)	2.314	5.11
JM Huber	Hubersorb 250NF (amorfo)	103.0	0.130 (0.008)	1.702	9.90
JM Huber	Hubersorb 600NF (amorfo)	209	0.075 (<0.001)	2.035	13.8

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En las formulaciones en cuestión, el silicato de calcio alfa triclinico se combina en forma ventajosa por lo menos con otro grado farmacéutico de silicato de calcio, donde la forma alfa triclinica comprendería entre alrededor de 10% hasta alrededor de 90% por peso de la combinación. En contraste con su uso en las formulaciones convencionales en tabletas, se considera inesperado que el agente dispersante, es decir el silicato de calcio, sea el constituyente primario de la combinación de excipientes de las formulaciones en cuestión, pero las personas con destrezas ordinarias en el arte reconocen en forma general que su capacidad de compresión es baja.

Ejemplos de agentes distribuidores adecuados para la combinación de excipientes en las formulaciones en cuestión incluyen sílice amorfa, sílice de combustión, tierra diatomita, talco, caolín, trisilicato de magnesio y aluminio y sílice, tierra diatomita, talco, caolín, trisilicato de magnesio y aluminio y similares.

Los aglutinantes aptos son aquellos que también funcionan como un agente de impregnado o un agente distribuidor en cuanto que actúan para promover la absorción de agua en las formas farmacéuticas manufacturadas a partir de ellos. Los aglutinantes aptos incluyen carbohidratos tales como, celulosa microcristalina, hidroxipropilcelulosa, etilcelulosa, almidón, lactosa, y también manitol y fosfato de calcio. La celulosa microcristalina está comercialmente disponible como Avicel® PH (grado farmacéutico) en PMC Corporation, Philadelphia, Pa., particularmente Avicel® PH 101, PH 102, PH 103, PH 112, PH 200, PH 301, PH 302 y Ceolus. La celulosa microcristalina también está disponible en Mendell, Penwest Company, Patterson, N.Y., como Emcocel® 90M y Emcocel® 50M, que se podrían utilizar en forma satisfactoria.

Las formulaciones de la presente invención pueden contener otros ingredientes convencionales que se encuentran en preparaciones similares conocidas en el arte y cuyo uso está aprobado en las preparaciones que van a

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ingresar al organismo. Estos incluirían por ejemplo, sabores naturales y artificiales, polioles tales como manitol, sorbitol, maltitol y xilitol, agentes edulcorantes artificiales tales como, N- α -L-Aspartil-L-fenilalanina 1- metil éster (aspartame) y dióxido 6-metil-3,4-dihidro-1,2,3-oxatiazina-4(3H)-uno-2,2-, particularmente la sal potásica del mismo (acesulfame K), adjuntos saborizantes como el ácido tartárico, lubricantes para compresión como el estearato de magnesio y similares. Aquellos con destreza en el arte de la preparación de compuestos apreciarán que la cantidad de agentes saborizantes y edulcorantes, de existir, presente en las formulaciones de la presente invención será directamente proporcional al sabor o la acritud del medicamento. Los agentes saborizantes y edulcorantes no sirven para recubrir el medicamento, pero son aptos para enmascarar el sabor objetable de los medicamentos en una mezcla homogénea de los mismos. En general, el total de estos ingredientes convencionales no sobrepasará alrededor del 32 por ciento, preferiblemente entre alrededor de 25 hasta alrededor de 30 por ciento por peso con base en el peso total de la formulación.

El medicamento en las formulaciones de la presente invención típicamente no sobrepasará alrededor del 30 por ciento por peso, preferiblemente entre alrededor de 1 hasta alrededor de 15 por ciento por peso de la formulación. Aquellos con destrezas ordinarias en el arte apreciarán que las características físicas del medicamento en sí, es decir el tamaño de sus partículas y su morfología tendrán una influencia directa sobre su contenido limitante en las formulaciones en cuestión. Claramente debe haber suficiente medicamento en la forma farmacéutica producida en las formulaciones en cuestión para obtener una dosis terapéuticamente efectiva. Aunque se pueden preparar formas farmacéuticas sólidas a partir de las formulaciones de la presente invención por medio de cualquier técnica reconocida, incluyendo una granulación húmeda, es una ventaja particular que las formulaciones se pueden granular en seco sin el uso de equipos y condiciones especializados, puesto que de esta manera son aptos



para la formulación de medicamentos sensibles a la humedad y a altas temperaturas.

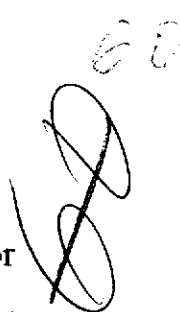
Los ejemplos de medicamentos que se pueden formular en tabletas de fusión instantánea de conformidad con la presente invención incluyen, sin ánimo de limitación, antihistamínicos, antieméticos, analgésicos, agentes antiinflamatorios, antibióticos, agentes para reducir los niveles de colesterol, ansiolíticos, antihipertensores, antineoplásicos, hipnóticos, antiulcerosos, dilatores coronarios, antivirales, antisicóticos, antidepresivos, neuromusculares, antidiarreicos, hipoglicémicos, supresores de tiroides, agentes anabólicos, antiespasmódicos, antijaquecosos, diuréticos, estimulantes, decongestionantes, relajantes uterinos, antiarrítmicos, compuestos para la disfunción eréctil masculina, agentes para la dilatación de conductos Maxi-K o agentes neuroprotectores para tratar las apoplejías o la enfermedad de Alzheimer y las combinaciones terapéuticamente adecuadas de los mismos. Los agentes terapéuticos específicos incluidos en las anteriores categorías comprenden, una vez más sin ánimo de limitación, aripiprazole, ibuprofen, aspirina, acetaminofen, maleato de clorfeniramina, pseudoefedrina, difenhidramina HCl, ranitidina, fenilpropanolamina, cimetidina, loperamide, meclizina, cafeína, entecavir, cefprozil, agonistas melatonérgicos, pravastatin, captopril, fosinopril, irbesartan, omapatrilato, gatifloxacina y desquinolona, y combinaciones terapéuticamente aceptables de los mismos.

Como se manifestó arriba, una ventaja cierta de la formulación de la presente invención es que se puede granular en seco, para formar gránulos estables y finos los cuales se pueden comprimir directamente y formar formas farmacéuticas de fusión instantánea farmacéuticamente elegantes, por ejemplo tabletas, comprimidos oblongos, obleas y similares. Preferiblemente, de conformidad con la presente invención los gránulos para las formas farmacéuticas de fusión instantánea se forman en dos pasos. El proceso comprende inicialmente la formación de gránulos, en la presente se

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denomina el intragranulado mezclando todo el medicamento, el agente dispersante, (agente distribuidor), otros ingredientes convencionales como se describieron arriba y una porción de cada uno de los disgregantes de acción superior, un aglutinante y un lubricante de tabletas juntos en una mezcladora adecuada para garantizar una distribución totalmente homogénea. Para este paso, el aparato preferido es una mezcladora convencional V. Aunque se puede omitir una porción del agente dispersante en el intragranulado, se prefiere incorporar todo en la misma. Luego la mezcla combinada se compacta en un rodillo compactador convencional con un orificio de manera que el producto compactado tenga la forma de cintas. Como alternativa, se puede emplear un proceso de balines. El producto comprimido del rodillo compactador o de los balines del disco se pasa por una zaranda muy fina, por ejemplo con una malla 30 (600 micrones), fraccionándolos en gránulos cuyo tamaño está entre alrededor de 150 y 400 micrones. Posteriormente, los gránulos intragranulados preparados en esta forma se mezclan en una mezcladora apropiada con el resto de los ingredientes, es decir el disgregante de acción superior, el aglutinante y el lubricante, a los cuales se hace referencia en la presente como los ingredientes de extragranulado, para formar una mezcla final que se puede comprimir directamente en formas farmacéuticas utilizando un equipo convencional como una prensa para tabletas. En vez de comprimir la mezcla final directamente en el momento de su formación, puesto que es estable, se puede almacenar y posteriormente prensar en las formas farmacéuticas. Una ventaja cierta de los aspectos particulares de la invención en cuestión es que estas operaciones se llevan a cabo sin tener que recurrir a unos manejos especiales como tomar medidas contra el contacto de la humedad con los ingredientes o los gránulos, y sin tener que emplear unas condiciones de control de temperatura y de humedad.

El intragranulado comprende entre alrededor de 80 a 99, preferiblemente entre alrededor de 85 a 95, más preferiblemente alrededor de 90 por ciento por peso de la mezcla final. Con base en el peso de la

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mezcla final, el intragranulado preferiblemente comprende hasta alrededor de 30 por ciento por peso, preferiblemente entre alrededor de 6 a 20 por ciento por peso, del aglutinante, hasta alrededor de 5 por ciento por peso, preferiblemente entre alrededor de 2 a 4 por ciento por peso del disgregante de acción superior, y la totalidad del agente dispersante y del agente distribuidor. El aglutinante y el disgregante de acción superior se dividen entre los ingredientes de intragranulado y los ingredientes de extragranulado en una relación de peso de aproximadamente 2:1 a 4:1 para el aglutinante y de 0.5:2.0 a 2.0:0.5 para el disgregante de acción superior. El lubricante convencional para las tabletas se divide aproximadamente en forma equitativa entre los ingredientes de intragranulado y de extragranulado.

La mezcla final se forma combinando los componentes del intragranulado y del extragranulado de la mezcla de excipientes, agregándoles el resto del lubricante para las tabletas y luego mezclando hasta obtener una mezcla uniforme. Como alternativa, se puede emplear un enfoque de compresión directa en el cual todos los ingredientes, a excepción del lubricante de tabletas, se mezclan en una mezcladora adecuada, como una mezcladora convencional V, formando geométricamente la totalidad de la masa de la formulación por medio de un mezclado secuencial durante 3 minutos después de agregar cada producto, y finalmente añadiendo el lubricante a la mezcla una vez se hayan mezclado todos los demás ingredientes.

Las tabletas comprimidas en una prensa convencional de tabletas a partir de la mezcla final obtenida bien sea por el granulado de un paso o por una mezcla de compresión directa eran farmacéuticamente elegantes y se desintegraron en el agua en diez segundos. Se considera que una tableta se desintegró cuando se fracciona en gránulos y no queda ningún trozo discernible. Puesto que el medicamento no está ligado íntimamente con ninguno de los ingredientes de la formulación, este se libera durante el mismo periodo de tiempo. Otra ventaja de los aspectos particulares de las

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formulaciones en cuestión es que a partir de estas se pueden manufacturar formas farmacéuticas robustas y por lo tanto evitar la necesidad de unos empaques especializados para las dosis unitarias y un manejo cuidadoso durante su manufactura o uso, como es frecuente con las formas farmacéuticas actuales. Las formas farmacéuticas preparadas a partir de las formulaciones de los aspectos particulares de la presente invención se pueden empacar en paquetes blíster convencionales o en frascos HDPE.

Se entiende que varias otras incorporaciones y modificaciones en la práctica de la invención serán aparentes también, y se pueden preparar fácilmente por parte de aquellos con destrezas ordinarias en el arte sin partir del alcance y del sentido de la invención como se describe arriba. Por lo tanto, no se espera que el alcance de las reivindicaciones adjuntas a la presente se limite a la descripción exacta descrita arriba, sino más bien las reivindicaciones se deben interpretar de forma que abarcan todas las características de novedad patentable que residen en la presente invención, incluyendo todas las características e incorporaciones que se podrían tratar como equivalentes de las mismas por parte de aquellos con destrezas en el arte al cual pertenece la invención. La invención también se describe con referencia a los siguientes trabajos experimentales.

Se puede manufacturar la sustancia del fármaco aripiprazole de conformidad con la presente invención de fusión instantánea como sigue:

Hidrato de Aripiprazole

El hidrato de aripiprazole (granos) de la presente invención tiene las propiedades físico – químicas descritas en (1)-(5) a continuación. Este hidrato de aripiprazole se describe en adelante como "Hidrato de Aripiprazole A".

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(1) Tiene una curva endotérmica sustancialmente igual a la curva endotérmica del análisis térmico termogravimétrico / diferencial (índice de calentamiento de 5°C/min) que aparece en la Figura 1. Específicamente se caracteriza por la aparición de pequeños picos en alrededor de 71° C y un pico endotérmico gradual entre alrededor de 60°C a 120 °C.

(2) Tiene un espectro ¹H-NMR que es sustancialmente igual al espectro ¹H-NMR (DMSO-d₆, TMS) que aparece en la Figura 2. Específicamente tiene picos característicos a 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J = 7.4 Hz, 2H), 2.97 ppm (brt, J = 4.6 Hz, 4H), 3.92 ppm (t, J = 6.3 Hz, 2H), 6.43 ppm (d, J = 2.4 Hz, 1H), 6.49 ppm (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.04 ppm (d, J = 8.1 Hz, 1H), 7.11-7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) y 10.00 ppm (s, 1H).

(3) Tiene un espectro de difracción de rayos X de polvos que es sustancialmente igual al espectro de difracción de rayos X de polvos que aparece en la Figura 3. Específicamente tiene picos característicos a 2θ = 12.6°, 15.4°, 17.3°, 18.0°, 18.6°, 22.5° y 24.8°.

(4) Tiene unas bandas de absorción infrarrojas transparentes en 2951, 2822, 1692, 1577, 1447, 1378, 1187, 963 y 784 cm⁻¹ en el espectro IR (KBr).

(5) El tamaño medio del grano es de 50 μm o menos.

Método para manufacturar el Hidrato de Aripiprazole A

El Hidrato de Aripiprazole A se manufactura moliendo el hidrato de aripiprazole convencional.

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Se pueden emplear los métodos convencionales de molido para moler el hidrato de aripiprazole. Por ejemplo, se puede moler el hidrato de aripiprazole en un molino. Se puede emplear una máquina de moler ampliamente utilizada, como un atomizador, un molino de dientes, un molino de inyección o un molino de válvulas esféricas. Entre los anteriores, se prefiere el atomizador.

Con relación a las condiciones especiales de molido cuando se emplea un atomizador, se podría utilizar una velocidad rotacional de 5000-15000 rpm para el eje principal, por ejemplo, con una rotación de alimentación de 10-30 rpm y un tamaño de orificio en la zaranda de 1-5 mm.

El tamaño medio del grano de Hidrato de Aripiprazole A obtenido por molido normalmente debe ser de 50 μm o menos, preferiblemente 30 μm o menos. Se puede verificar el tamaño medio del grano por medio del método para medir el tamaño del grano descrito a continuación.

Medición del Tamaño del Grano: 0.1 g de los granos que se van a medir se suspendieron en una solución de 0.5 g de lecitina de soya en 20 ml de n-hexano y se midió el tamaño del grano por medio de un medidor de distribución de tamaño (Microtrack HRA, Microtrack Co.).

Cristales de Anhídrido de Aripiprazole

Los cristales de anhídrido de aripiprazole de la presente invención tienen las propiedades físico-químicas descritas abajo en (6)-(10). En adelante se hace referencia a estos cristales de anhídrido de aripiprazole como "Cristales de Anhídrido de Aripiprazole B".

(6) Tienen un espectro $^1\text{H-NMR}$ que es sustancialmente igual al espectro $^1\text{H-NMR}$ (DMSO-d_6 , TMS) que aparece en la Figura 4. Específicamente tienen picos característicos a 1.55-1.63 ppm (m, 2H), 1.68-

1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J = 7.4 Hz, 2H), 2.97 ppm (brt, J = 4.6 Hz, 4H), 3.92 ppm (t, J = 6.3 Hz, 2H), 6.43 ppm (d, J = 2.4 Hz, 1H), 6.49 ppm (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.04 ppm (d, J = 8.1 Hz, 1H), 7.11-7.17 ppm (m, 1H). 7.28-7.32 ppm (m, 2H) y 10.00 ppm (s, 1H).

(7) Tienen un espectro de difracción de rayos X de polvos que es sustancialmente igual al espectro de difracción de rayos X de polvos que aparece en la Figura 5. Específicamente, tienen picos característicos en $2\theta = 11.0^\circ, 16.6^\circ, 19.3^\circ, 20.3^\circ$ y 22.1° .

(8) Tienen unas bandas de absorción infrarrojas transparentes en 2945, 2812, 1678, 1627, 1448, 1377, 1173, 960 y 779 cm^{-1} en el espectro IR (KBr).

(9) Presentan un pico endotérmico cerca de alrededor de 141.5°C en el análisis térmico termogravimétrico / diferencial (índice de calentamiento de $5^\circ\text{C}/\text{min}$).

(10) Presentan un pico endotérmico cerca de alrededor de 140.7°C en una calorimetría diferencial de barrido (índice de calentamiento de $5^\circ\text{C}/\text{min}$).

Los Cristales de Anhídrido de Aripiprazole B de la presente invención tienen una baja higroscopicidad. Por ejemplo los Cristales de Anhídrido de Aripiprazole B de la presente invención mantienen un contenido de agua de 0.4% o menos después de llevar 24 horas en un desecador a una temperatura de 60°C y a una humedad del 100%.

Se pueden emplear métodos bien conocidos para medir el contenido de agua, siempre que sean métodos utilizados comúnmente para medir el

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contenido de agua de cristales. Por ejemplo se puede utilizar un método como el de Karl Fischer.

Método para Manufacturar Cristales de Anhídrido de Aripiprazole B

Los Cristales de Anhídrido de Aripiprazole B de la presente invención se preparan por ejemplo calentando el ya citado Hidrato de Aripiprazole A a 90-125°C. Por lo general el tiempo de calentamiento es de alrededor de 3-50 horas, pero no se puede afirmar en forma incondicional puesto que difiere según la temperatura de calentamiento. El tiempo de calentamiento y la temperatura de calentamiento tienen una relación inversa, de manera que por ejemplo el tiempo de calentamiento será más largo mientras más baja sea la temperatura de calentamiento, y más corto si la temperatura es más alta. Específicamente, si la temperatura de calentamiento del Hidrato de Aripiprazole A es de 100°C, normalmente el tiempo de calentamiento será de 18 horas o más, o preferiblemente alrededor de 24 horas. Por otro lado, si la temperatura de calentamiento del Hidrato de Aripiprazole A es de 120°C, el tiempo de calentamiento puede ser de unas 3 horas. Con certeza se pueden preparar los Cristales de Anhídrido de Aripiprazole B de la presente invención calentando el Hidrato de Aripiprazole A durante unas 18 horas a 100°C, y luego calentándolos durante unas 3 horas a 120°C. También se pueden obtener los Cristales de Anhídrido de Aripiprazole B de la presente invención si el tiempo de calentamiento se extiende aún más, pero esto no es económico.

Adicionalmente, los Cristales de Anhídrido de Aripiprazole B de la presente invención se preparan por ejemplo calentando los cristales de Anhídrido de Aripiprazole B a 90-125 °C. Por lo general el tiempo de calentamiento es de alrededor de 3-50 horas, pero no se puede afirmar en forma incondicional puesto que difiere según la temperatura de calentamiento. El tiempo de calentamiento y la temperatura de calentamiento tienen una relación inversa, de manera que por ejemplo el

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tiempo de calentamiento será más largo mientras más baja sea la temperatura de calentamiento, y más corto si la temperatura es más alta. Específicamente, si la temperatura de calentamiento de los cristales de hidrato de aripiprazole es de 100°C, el tiempo de calentamiento puede ser de 4 horas y si la temperatura de calentamiento es de 120 °C, el tiempo de calentamiento puede ser de unas 3 horas.

Los cristales de anhídrido de aripiprazole, que son la materia prima para preparar los Cristales de Anhídrido de Aripiprazole B de la presente invención se preparan por medio del Método a o b a continuación.

Método a:

Los cristales de anhídrido de aripiprazole se preparan mediante métodos bien conocidos, como por medio de la reacción de 7-(4-bromobutoxi)-3,4-dihidrocarbostirilo con 1-(2,3-diclorofenilo) piperadina y recrystalizando los cristales primarios de aripiprazole en etanol como se describe en el Ejemplo 1 de la Publicación de Patente Japonesa Pendiente de Examen No. 191256/1990.

Método b:

Los cristales de anhídrido de aripiprazole se preparan calentando el hidrato de aripiprazole convencional a una temperatura de por lo menos 60°C y menos de 90°C. Por lo general el tiempo de calentamiento es alrededor de 1-30 horas, pero no se puede afirmar en forma incondicional puesto que difiere según la temperatura de calentamiento. El tiempo de calentamiento y la temperatura de calentamiento tienen una relación inversa, de manera que por ejemplo el tiempo de calentamiento será más largo mientras más baja sea la temperatura de calentamiento, y más corto si la temperatura es más alta. Específicamente, si la temperatura de calentamiento del hidrato de aripiprazole es alrededor de 60°C, el tiempo de

calentamiento puede ser de 8 horas mientras que si la temperatura de calentamiento es de 80 °C, el tiempo de calentamiento puede ser de unas 4 horas.

El Método b se describe en los Procesos del Cuarto Simposio Japonés – Coreano sobre Tecnología de Separación (Octubre 6-8, 1996).

Adicionalmente, los Cristales de Anhídrido de Aripiprazole B de la presente invención se preparan por ejemplo calentando el hidrato de aripiprazole convencional a 90-125°C. Por lo general el tiempo de calentamiento es de alrededor de 3-50 horas, pero no se puede afirmar en forma incondicional puesto que difiere según la temperatura de calentamiento. El tiempo de calentamiento y la temperatura de calentamiento tienen una relación inversa, de manera que por ejemplo el tiempo de calentamiento será más largo mientras más baja sea la temperatura de calentamiento, y más corto si la temperatura es más alta. Específicamente, si la temperatura de calentamiento del hidrato de aripiprazole es de 100°C, el tiempo de calentamiento puede ser de 24 horas mientras que si la temperatura de calentamiento es de 120 °C, el tiempo de calentamiento puede ser de unas 3 horas.

El hidrato de aripiprazole que es la materia prima para preparar los Cristales de Anhídrido de Aripiprazole B de la presente invención se prepara por ejemplo por medio del Método c abajo.

Método c

Es fácil obtener hidrato de aripiprazole disolviendo los cristales de anhídrido de aripiprazole obtenidos por medio del Método a arriba en un solvente hidratado y luego calentando y posteriormente enfriando la solución resultante. Utilizando este método, el hidrato de aripiprazole se precipita como cristales en el solvente hidratado.

Por lo general se emplea un solvente orgánico conteniendo agua como el agente hidratado. El solvente orgánico debe ser miscible con el agua, por ejemplo un alcohol como el metanol, etanol, propanol o isopropanol, una cetona como una acetona, un éter como tetrahidrofurano, dimetilformamida, o una mezcla de estos y el etanol es particularmente deseable. La cantidad de agua en el solvente hidratado puede ser de 10-25% por peso del solvente o preferiblemente cerca a 20% por peso.

Como se mencionó arriba, los Cristales de Anhídrido de Aripiprazole B de la presente invención se preparan calentando el citado Hidrato de Aripiprazole A, los cristales convencionales de anhídrido de aripiprazole o el hidrato convencional de aripiprazole y el citado Hidrato de Aripiprazole A a 90-125 °C. Se pueden emplear cristales anhídridos convencionales de aripiprazole o hidrato de aripiprazole convencional en forma individual o combinada.

Los siguientes ejemplos utilizaron una sustancia de fármaco de aripiprazole moliendo primero el hidrato convencional de aripiprazole y luego calentándolo para formar la forma anhidra (anhídrido B).

EJEMPLO 1

Se prepararon tabletas de fusión instantánea como sigue:

Intragranulado:

<u>Ingrediente</u>	<u>Por ciento peso</u>	<u>Mg. por tableta</u>
Xilitol (300) Xilisorb	26	52
Avicel® PH 102	12	24
Silicato de calcio	43.35	86.7
Crospovidona	3	6

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Sílice amorfa	2	4
Aspartame	2	4
Sabor de cereza salvaje	0.15	0.3
Ácido tartárico	2	4
Acesulfame K	2	4
Estearato de magnesio	0.25	0.5
Peso total	92.75	185.5

Los ingredientes a excepción del estearato de magnesio, se mezclaron en una mezcladora V comercial en proporciones geométricas durante 5 minutos hasta que se agregaron todos. Luego se añadió el estearato de magnesio a la mezcla mezclada durante 3 minutos más. La formulación mezclada se compactó a una presión de 30-35 kgF/cm² en un compactador comercial equipado con un orificio de manera que los compactos tuvieran forma de cintas. Las cintas se pasaron por una zaranda con una malla 30 (600 micrones) para formar gránulos estables de alrededor de 150 hasta 400 micrones.

Ingredientes de Extragranulado:

<u>Ingrediente</u>	<u>Por ciento peso /</u>	<u>Mg. por tableta</u>
Intragranulado	92.75	185.5
Avicel® PH 200	3	6
Crospovidona	4	8
Estearato de magnesio	0.25	0.5
Peso total	100	200

Se colocó el intragranulado en el mezclador y se le agregó el Avicel® PH 200 y la crospovidona y se mezclaron durante 5 minutos. Luego se añadió el estearato de magnesio y se revolvió la mezcla durante 3 minutos más para formar la mezcla final. Las tabletas comprimidas tuvieron una fuerza de ruptura de 2.3 kP (3.5 SCU) y se desintegraron en 10 segundos en 5 ml de agua. La formulación de la mezcla final exhibió

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un flujo excelente y no tenía otros problemas como desportilladuras, y problemas de recubrimiento y de adhesión. Se ha visto que si se utiliza el Avicel® PH 102 para el intragranulado y el Avicel® PH 200 para el ingrediente extragranulado se mejoraba la calidad de las tabletas resultantes.

EJEMPLO 2

Se prepararon tabletas de fusión instantánea conteniendo una combinación de dos grados de silicato de calcio como sigue:

Intragranulado:

<u>Ingrediente</u>	<u>Por ciento peso /</u>	<u>Mg. por tableta</u>
Xilitol (300) Xilisorb	26	52
Avicel® PH 102	12	24
Silicato de calcio (cristalino, alfa triclinico)	33.35	66.7
Hubersorb 600 NF (Silicato de calcio amorfo)	10	20
Crospovidona	3	6
Sílice amorfa	2	4
Aspartame	2	4
Sabor de cereza salvaje	0.15	0.3
Ácido tartárico	2	4
Acesulfame K	2	4
Estearato de magnesio	0.25	0.5
Peso total	92.75	185.5

Los ingredientes a excepción del estearato de magnesio, se mezclaron en una mezcladora V comercial en proporciones geométricas durante 5 minutos hasta que se agregaron todos. Luego se añadió el estearato de magnesio a la mezcla mezclada durante 3 minutos más. La formulación

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mezclada se compactó y se pasó por una zaranda para formar unos gránulos estables de conformidad con el procedimiento del Ejemplo 1.

Ingredientes de Extragranulado:

<u>Ingrediente</u>	<u>Por ciento peso / peso</u>	<u>Mg. por tableta</u>
Intragranulado	92.75	185.5
Avicel® PH 200	3	6
Crospovidona	4	8
Estearato de magnesio	0.25	0.5
Peso total	100	200

Se colocó el intragranulado en el mezclador y se le agregó el Avicel® PH 200 y la crospovidona y se mezclaron durante 5 minutos. Luego se añadió el estearato de magnesio y se revolvió la mezcla durante 3 minutos más para formar la mezcla final. Las tabletas comprimidas tuvieron una fuerza de ruptura de 2.0 kP (3.1 SCU) y se desintegraron en 10 segundos en 5 ml de agua.

EJEMPLO 3

Se prepararon tabletas de fusión instantánea conteniendo aripiprazole, un fármaco antiesquizofrénico como se indica a continuación:

Intragranulado:

<u>Ingrediente</u>	<u>Por ciento peso / peso</u>	<u>Mg. por tableta</u>
Aripiprazole	15	30
Xilitol (300) Xilisorb	25	50
Avicel® PH 102	6	12
Silicato de calcio	37	74

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Crospovidona	3	6
Sílice Amorfa	2	4
Aspartame	2	4
Sabor de cereza salvaje	0.15	0.3
Ácido Tartárico	2	4
Acesulfame K	2	4
Estearato de magnesio	0.25	0.5
Peso total	94.4	188.8

Los ingredientes a excepción del estearato de magnesio, se mezclaron en una mezcladora V comercial en proporciones geométricas durante 5 minutos hasta que se agregaron todos. Luego se añadió el estearato de magnesio a la mezcla mezclada durante 3 minutos más. La formulación mezclada se compactó y se pasó por una zaranda para formar unos gránulos estables de conformidad con el procedimiento del Ejemplo 1.

Ingredientes de Extragranulado:

<u>Ingrediente</u>	<u>Por ciento peso</u>	<u>Mg. por tableta</u>
Intragranulado	94.4	188.8
Avicel® PH 200	1.1	2.2
Crospovidona	4	8
Estearato de magnesio	0.5	1
Peso total	100	200

Se colocó el intragranulado en el mezclador y se le agregó el Avicel® PH 200 y la crospovidona y se mezclaron durante 5 minutos. Luego se añadió el estearato de magnesio y se revolvió la mezcla durante 3 minutos más para formar la mezcla final. Las tabletas comprimidas tuvieron una fuerza de ruptura de 2.0 kP (3.1 SCU) y se desintegraron en 10 segundos en 5 ml de agua.

EJEMPLO 4

2.3



Se prepararon tabletas de fusión instantánea conteniendo aripiprazole como sigue:

Intragranulado:

<u>Ingrediente</u>	<u>Por ciento peso</u> <u>/ peso</u>	<u>Mg. por tableta</u>
Aripiprazole	0-5	1
Xilitol (300) Xilisorb	27	54
Avicel® PH 102	12	24
Silicato de calcio	42	84
Crospovidona	3	6
Sílice amorfa	2	4
Aspartame	2	4
Sabor de cereza salvaje	0.15	0.3
Ácido tartárico	2	4
Acesulfame K	2	4
Estearato de magnesio	0.25	0.5
Peso total	92.9	185.8

Los ingredientes a excepción del estearato de magnesio, se mezclaron en una mezcladora V comercial en proporciones geométricas durante 5 minutos hasta que se agregaron todos. Luego se añadió el estearato de magnesio a la mezcla mezclada durante 3 minutos más. La formulación mezclada se compactó y se pasó por una zaranda para formar unos gránulos estables de conformidad con el procedimiento del Ejemplo 1.

Ingredientes de Extragranulado:

<u>Ingrediente</u>	<u>Por ciento peso</u>	<u>Mg. por tableta</u>
Intragranulado	92.9	185.8
Avicel® H 200	2.6	5.2
Crospovidona	4	8

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Estearato de magnesio	0.5	1
Peso total	100	200

Se colocó el intragranulado en el mezclador y se le agregó el Avicel® PH 200 y la crospovidona y se mezclaron durante 5 minutos. Luego se añadió el estearato de magnesio y se revolvió la mezcla durante 3 minutos más para formar la mezcla final. Las tabletas comprimidas tuvieron una fuerza de ruptura de 2.3 kP (3.5 SCU) y se desintegraron en 10 segundos en 5 ml de agua.

EJEMPLO 5

Se pueden preparar las tabletas de fusión instantánea conteniendo el medicamento antiviral entecavir como sigue:

Intragranulado:

<u>Ingrediente</u>	<u>Por ciento peso</u>	<u>Mg. por tableta</u>
	<u>/ peso</u>	
Entecavir	1	2
Xilitol (300) Xilisorb	26	52
Avicel® PH 102	10	20
Silicato de calcio	45	90
Crospovidona	4	8
Sílice amorfa	2.	4
Aspartame	2	4
Sabor de cereza salvaje	0.25	0.5
Ácido tartárico	2	4
Acesulfame K	2.	4
Estearato de magnesio	0.25	0.5
Peso total	94.5	189

Los ingredientes a excepción del estearato de magnesio, se mezclaron en una mezcladora V comercial en proporciones geométricas durante 5

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minutos hasta que se agregaron todos. Luego se añadió el estearato de magnesio a la mezcla mezclada durante 3 minutos más. La formulación mezclada se compactó y se pasó por una zaranda para formar unos gránulos estables de conformidad con el procedimiento del Ejemplo 1.

Ingredientes de Extragranulado:

<u>Ingrediente</u>	<u>Por ciento peso</u> <u>/ peso</u>	<u>Mg. por tableta</u>
Intragranulado	94.5	189
Avicel® PH 200	2	4
Crospovidona	3	6
Estearato de magnesio	0.5	1
Peso total	100	200

Se colocó el intragranulado en el mezclador y se le agregó el Avicel® PH 200 y la crospovidona y se mezclaron durante 5 minutos. Luego se añadió el estearato de magnesio y se revolvió la mezcla durante 3 minutos más para formar la mezcla final. Las tabletas comprimidas tuvieron una fuerza de ruptura de 2.3 kP (3.5 SCU) y se desintegraron en 10 segundos en 5 ml de agua. Las proporciones en porcentajes peso / peso/ enseñadas en este ejemplo también se pueden utilizar para formular una formulación apropiada de la presente invención comprendiendo 0.1 mg de entecavir por dosis unitaria.

EJEMPLO 6

Se pueden preparar tabletas de fusión instantánea conteniendo el medicamento antibiótico cefprozil como sigue:

Intragranulado:

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<u>Ingrediente</u>	<u>Por ciento peso</u>	<u>Mg. por tableta</u>
Cefzil	25	125
Xilitol (300) Xilisorb	17	85
Avicel® PH 102	6	30
Silicato de calcio	35	175
Crospovidona	3	15
Sílice amorfa	2	10
Aspartame	2	10
Sabor de cereza salvaje	0.25	1.25
Ácido tartárico	2	10
Acesulfame K	2	10
Estearato de magnesio	0.25	1.25
Peso total	94.5	472.5

Mezcle los ingredientes a excepción del estearato de magnesio en una mezcladora V comercial en proporciones geométricas durante 5 minutos hasta que se agreguen todos. Luego añada el estearato de magnesio a la mezcla preparada durante 3 minutos más. Después compacte la formulación mezclada y pásela por una zaranda para formar gránulos estables de conformidad con el procedimiento del Ejemplo 1.

Ingredientes de Extragranulado:

<u>Ingrediente</u>	<u>Por ciento</u>	<u>Mg. por tableta</u>
Intragranulado	94.5	472.5
Avicel® PH 200	2	10
Crospovidona	3	15
Estearato de magnesio	0.5	2.5
Peso total	100	500

Coloque el intragranulado en el mezclador y agréguele el Avicel® PH 200 y la crospovidona y mezcle durante 5 minutos. Luego añada el estearato de magnesio y revuelva la mezcla durante 3 minutos más para formar la mezcla final. Comprima las tabletas resultantes para obtener una

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fuerza de ruptura de 2.5 kP (3.8 SCU) y un tiempo de desintegración de 10 segundos en 5 ml de agua.

EJEMPLO 7

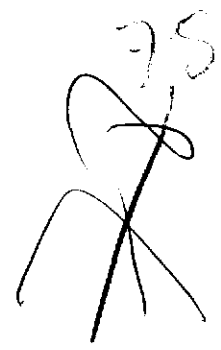
Se pueden preparar tabletas de fusión instantánea conteniendo el medicamento antihipertensor irbesartan como sigue:

Intragranulado:

<u>Ingrediente</u>	<u>Por ciento peso</u>	<u>Mg. por tableta</u>
Irbesartan	25	125
Xilitol (300) Xilisorb	17	85
Avicel® PH 102	6.	30
Silicato de calcio	35	175
Crospovidona	3	15
Sílice amorfa	2	10
Aspartame	2	10
Sabor de cereza salvaje	0.25	1.25
Ácido tartárico	2	10
Acesulfame K	2	10
Estearato de magnesio	0.25	1.25
Peso total	94.5	472.5

Mezcle los ingredientes a excepción del estearato de magnesio en una mezcladora V comercial en proporciones geométricas durante 5 minutos hasta que se agreguen todos. Luego se añada el estearato de magnesio a la mezcla preparada durante 3 minutos más. Después compacte la formulación mezclada y pásela por una zaranda para formar gránulos estables de conformidad con el procedimiento del Ejemplo 1.

Ingredientes de Extragranulado:

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Ingredientes	Por ciento	Mg. por tableta
Intragranulado	94.5	472.5
Avicel® PH 20	2	10
Crospovidona	3	15
Estearato de magnesio	0.5	2.5
Peso total	100	500

Coloque el intragranulado en el mezclador y agréguele el Avicel® PH 200 y la crospovidona y mezcle durante 5 minutos. Luego añada el estearato de magnesio y revuelva la mezcla durante 3 minutos más para formar la mezcla final. Comprima las tabletas resultantes para obtener una fuerza de ruptura de 2.5 kP (3.8 SCU) y un tiempo de desintegración de 10 segundos en 5 ml de agua.

EJEMPLO 8

Se pueden preparar tabletas de fusión instantánea conteniendo el antibiótico quinolona, Des-Quinolona como sigue:

Intragranulado:

<u>Ingrediente</u>	<u>Por ciento</u>	<u>Mg. por tableta</u>
Des-Quinolona	20.0	100
Xilitol (300) Xilisorb	22.0	110
Avicel® PH 102	6.0	30
Silicato de calcio	35.0	175
Crospovidona	3.0	15
Sílice amorfa	2.0	10
Aspartame	2.0	10
Sabor de cereza salvaje	0.25	1.25
Ácido tartárico	2.0	10
Acesulfame K	2.0	10
Estearato de magnesio	0.25	1.25
Peso total	94.5	472.5

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Mezcle los ingredientes a excepción del estearato de magnesio en una mezcladora V comercial en proporciones geométricas durante 5 minutos hasta que se agreguen todos. Luego se añada el estearato de magnesio a la mezcla preparada durante 3 minutos más. Después compacte la formulación mezclada y pásela por una zaranda para formar gránulos estables de conformidad con el procedimiento del Ejemplo 1.

Ingredientes de Extragranulado:

<u>Ingrediente</u>	<u>Por ciento</u>	<u>Mg. por tableta</u>
Intragranulado	94.5	472.5
Avicel® PH 200	2.0	10.0
Crospovidona	3.0	15.0
Estearato de magnesio	0.5	2.5
Peso total	100	500

Coloque el intragranulado en el mezclador y agréguele el Avicel® PH 200 y la crospovidona y mezcle durante 5 minutos. Luego añada el estearato de magnesio y revuelva la mezcla durante 3 minutos más para formar la mezcla final. Comprima las tabletas resultantes para obtener una fuerza de ruptura de 2.5 kP (3.8 SCU) y un tiempo de desintegración de 10 segundos en 5 ml de agua.

EJEMPLO 9

Se pueden preparar tabletas de fusión instantánea conteniendo el antibiótico gatifloxacina (Tequin®), como un co-precipitado para enmascarar el sabor (30% peso / peso activo) para administrar una dosis de 50 mg:

Intragranulado:

<u>Ingrediente</u>	<u>Por ciento peso / peso</u>	<u>Mg. por tableta</u>
Gatifloxacina: ácido esteárico co-precipitado	33.3	166.7
Xilitol (300) Xilisorb	11.7	58.5
Avicel® PH 102	6.0	30
Silicato de calcio	32.0	160
Crospovidona	3.0	15
Sílice amorfa	2.0	10
Aspartame	2.0	10
Sabor de cereza salvaje	0.25	1.23
Ácido tartárico	2.0	10
Acesulfame K	2.0	10
Estearato de magnesio	0.25	1.25
Peso total	94.5	472.5

Mezcle los ingredientes a excepción del estearato de magnesio en una mezcladora V comercial en proporciones geométricas durante 5 minutos hasta que se agreguen todos. Luego se añada el estearato de magnesio a la mezcla preparada durante 3 minutos más. Después compacte la formulación mezclada y pásela por una zaranda para formar gránulos estables de conformidad con el procedimiento del Ejemplo 1.

Ingredientes de Extragranulado:

<u>Ingrediente</u>	<u>Por ciento peso</u>	<u>Mg. por tableta</u>
Intragranulado	94.5	472.5
Avicel® PH 200	2.0	10.0
Crospovidona	3.0	15.0
Estearato de magnesio	0.5	2.5
Peso total	100	500

Coloque el intragranulado en el mezclador y agréguele el Avicel® PH 200 y la crospovidona y mezcle durante 5 minutos. Luego añada el

estearato de magnesio y revuelva la mezcla durante 3 minutos más para formar la mezcla final. Comprima las tabletas resultantes para obtener una fuerza de ruptura de 2.5 kP (3.8 SCU) y un tiempo de desintegración de 10 segundos en 5 ml de agua.

EJEMPLO 10

PREPARACIÓN DE GRANULACIÓN DE ARIPIRAZOLE PARA TABLETAS DE 2 MG Y DE 5 MG AL 2.5 % PESO / PESO - PROTOTIPO II

Formulación intragranular:

<u>Ingrediente</u>	<u>% peso /</u>
Aripiprazole	2.50
Xilitol, NF (Xilisorb 300)	21.15
Celulosa Microcristalina, NF (Avicel PH 102)	12.0
Silicato de Calcio, NF	42.0
Crospovidona, NF (XL-10)	3.0
Dióxido de Silicio, NF (previamente citado como Sílice amorfa)	2.0
Croscarmelosa Sódica, NF	3.0
Aspartame, NF	2.0
Sabor Crema de Vainilla	0.5
Ácido Tartárico, NF	2
Acesulfame K (E.P)	2.0
Estearato de Magnesio NF	0.25
Total	92.40

Preparación de la Mezcla Intragranular:

1. Se escoge la mezcladora V (que opera a una velocidad de 50 rpm) para la operación de mezclado. En el primer paso de mezclado, se coloca el

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aripiprazole entre el Xilitol y el Avicel PH 102 mezclado en la mezcladora V durante 10 minutos.

2. En el paso 2, se pesan todos los otros excipientes y se colocan en la mezcladora V del paso 1. Se efectuó la disgregación cuando fue necesario. Se mezcló durante 5 minutos.
3. Finalmente se agregó 0.25% de estearato de magnesio y se mezcló durante tres minutos.
4. Para la compactación con rodillo, se puede emplear el equipo Alexanderwerk WP 120X40 (compactador de rodillo) u otro equipo similar con los siguientes parámetros:

Velocidad tornillo: 25 rpm Velocidad rodillo: 5 rpm; Presión en vacío: -105 mbar

Granulador: 75 rpm (adaptado con una zaranda superior de 4mm e inferior de 0.8 mm o una zaranda 20#)

Presión hidráulica: 50 bar

Preparación de Mezcla de Granulación Post Secado:

<u>Ingrediente</u>	<u>%peso /</u>
Granulación del paso 4	92.40
Crospovidona, NF (XL-10)	4.00
Celulosa Microcristalina, NF (Avicel® PH 200)	3.10
Estearato de Magnesio, NF	0.5
Total	100.00

1. Con base en el rendimiento del paso 4, calcule el nuevo tamaño del lote y coloque el intragranulado en la mezcladora con las cantidades calculadas de Avicel® PH 200 y de crospovidona y mezcle durante 5 minutos.
2. Finalmente agregue la cantidad restante del estearato de magnesio y mezcle durante 3 minutos.

Las tabletas de 2 mg pueden tener incorporada una mezcla de pigmento verde en la porción extragranular anterior a una concentración de 0.3% peso / peso que se ajusta al reemplazar la misma cantidad de Avicel PH 200, es decir que la cantidad de Avicel PH 200 será de 2.8% peso / peso.

Las tabletas de 5 mg pueden tener incorporado una mezcla de pigmento de color aluminio azulado en la porción extragranular anterior a una concentración de 0.3% peso / peso que se ajusta al reemplazar la misma cantidad de Avicel PH 200, es decir que la cantidad de Avicel PH 200 será de 2.8% peso / peso.

Compresión de tabletas:

1. Utilizando la granulación preparada arriba, se pueden preparar tabletas de aripiprazole de 2mg de potencia comprimiendo tabletas cuyo peso es de 80 mg en cualquier prensa convencional para tabletas que pueda producir tabletas cuya fuerza de ruptura es de 3.0 kP o 4.5 SCU.
2. Utilizando la granulación preparada arriba, se pueden preparar tabletas de aripiprazole de 5 mg de potencia comprimiendo tabletas cuyo peso es de 200 mg en cualquier prensa convencional para tabletas que pueda producir tabletas cuya fuerza de ruptura es de 3.0 kP o 4.5 SCU.

EJEMPLO 11

**PREPARACIÓN DE GRANULACIÓN DE ARIPIPAZOLE PARA
TABLETAS DE 10 MG, 15 MG, 20 MG Y 30 MG AL 10 % PESO / PESO
- PROTOTIPO II**

Formulación Intragranular:

<u>Ingrediente</u>	<u>% peso / peso</u>
Aripiprazole	10.00
Xilitol, NF (Xilisorb 300)	21.15

Celulosa Microcristalina, NP (Avicel PH 102)	10.0
Silicato de Calcio, NF	36.5
Crospovidona, NF (XL-10)	3.0
Dióxido de Silicio, NF (previamente citado como Sílice Amorfa)	3.0
Croscarmelosa Sódica, NF	2.0
Aspartame, NF	2.0
Sabor Crema de Vainilla	0.5
Ácido Tartárico, NF	2
Acesulfame K (E.P)	2.0
Estearato de Magnesio NF	0.25
Total	92.40

Preparación de la Mezcla Intragranular:

1. Se escoge la mezcladora V (que opera a una velocidad de 50 rpm) para la operación de mezclado. En el primer paso de mezclado, se coloca el aripiprazole entre el Xilitol y el Avicel PH 102 mezclado en la mezcladora V durante 10 minutos.
2. En el paso 2, se pesan todos los otros excipientes y se colocan en la mezcladora V del paso 1. Se efectuó la disgregación cuando fue necesario. Se mezcló durante 5 minutos.
3. Finalmente se agregó 0.25% de estearato de magnesio y se mezcló durante tres minutos.
4. Para la compactación con rodillo, se puede emplear el equipo Alexanderwerk WP 120X40 (compactador de rodillo) u otro equipo similar con los siguientes parámetros:

Velocidad tornillo: 25 rpm Velocidad rodillo: 5 rpm; Presión en vacío: -105 mbar

Granulador: 75 rpm (adaptado con una zaranda superior de 4mm e inferior de 0.8 mm o una zaranda 20#)

Presión hidráulica: 50 bar

Preparación de Mezcla de Granulación Post Secado:

<u>Ingrediente</u>	<u>% peso /</u> <u>peso</u>
Granulación del paso 4	92.40
Crospovidona, NF (XL- 10)	4.00
Celulosa Microcristalina, NF (Avicel® PH 200)	3.10
Estearato de Magnesio, NF	0.5
Total	100.00

5. Con base en el rendimiento del paso 4, calcule el nuevo tamaño del lote y coloque el intragranulado en la mezcladora con las cantidades calculadas de Avicel® PH 200 y de crospovidona y mezcle durante 5 minutos.
6. Finalmente agregue la cantidad restante de estearato de magnesio y mezcle durante 3 minutos.
- Las tabletas de 10 mg pueden tener incorporado un óxido de hierro rojo en la porción extragranular de 0.04% peso / peso que se ajusta al reemplazar la misma cantidad de Avicel PH 200, es decir que la cantidad de Avicel PH 200 será de 3.06% peso / peso.
 - Las tabletas de 15 mg pueden tener incorporado un óxido de hierro amarillo en la porción extragranular arriba de 0.3 % peso / peso que se ajusta al reemplazar la misma cantidad de Avicel PH 200, es decir que la cantidad de Avicel PH 200 será de 2.8% peso / peso.
 - Las tabletas de 20 mg pueden ser de color blanco y se pueden fabricar directamente a partir de la formulación descrita arriba.
 - Las tabletas de 30 mg pueden tener incorporado un óxido de hierro rojo en la porción extragranular con una concentración superior a 0.04% peso / peso que se ajusta al reemplazar la misma cantidad de Avicel PH 200, es decir que la cantidad de Avicel PH 200 será de 3.06% peso / peso.

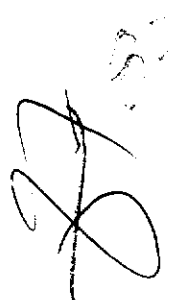
Compresión de Tableta:

1. Utilizando la granulación preparada arriba, se pueden preparar tabletas de aripiprazole de 10mg de potencia comprimiendo tabletas cuyo peso es de 100 mg en cualquier prensa convencional para tabletas que pueda producir tabletas cuya fuerza de ruptura es de 3.0 kP o 4.5 SCU.
2. Utilizando la granulación preparada arriba, se pueden preparar tabletas de aripiprazole de 15mg de potencia comprimiendo tabletas cuyo peso es de 150 mg en cualquier prensa convencional para tabletas que pueda producir tabletas cuya fuerza de ruptura es de 3.0 kP o 4.5 SCU.
3. Utilizando la granulación preparada arriba, se pueden preparar tabletas de aripiprazole de 20 mg de potencia comprimiendo tabletas cuyo peso es de 200 mg en cualquier prensa convencional para tabletas que pueda producir tabletas cuya fuerza de ruptura es de 3.0 kP o 4.5 SCU.
4. Utilizando la granulación preparada arriba, se pueden preparar tabletas de aripiprazole de 30 mg de potencia comprimiendo tabletas cuyo peso es de 300 mg en cualquier prensa convencional para tabletas que pueda producir tabletas cuya fuerza de ruptura es de 3.0 kP o 4.5 SCU.

Evaluación Farmacocinética de Tablet de 5 mg de Fusión Instantánea **- Prototipos I y II en Humanos Sanos**

Se efectuaron 3 estudios cruzados con tratamientos de control balanceado de rótulo abierto, aleatorios, de 2 periodos, con la participación de 33 voluntarios sanos. Cada persona recibió una sola tableta comercial de 5 mg de aripiprazole y una dosis de 5 mg de aripiprazole bien sea como el Prototipo I de Fusión Instantánea o el Prototipo II de Fusión Instantánea (ambas con una granulación de 2.5% peso / peso).

COMPOSICIÓN (mg/tableta)				
INGREDIENTE	Prototipo I		Prototipo II	
	5 mg ^a	%	5 mg ^b	%
Aripiprazole	5.0	2.50	5.0	2.50



Silicato de Calcio, NF	84.0	42.00	84.0	42.00
Crospovidona NP (XL-10)	14.0	7.00	14.0	7.00
Croscarmelosa Sódica, NF	—	—	6.0	3.00
Dióxido de Silicio, NF (Syloid)	4.0	2.00	4.0	2.00
Xilitol NF (Xilisorb® 300)	48.3	24.15	42.3	21.15
Celulosa Microcristalina NP (Avicel® PH 102)	24	12.00	24	12.00
Celulosa Microcristalina NF (Avicel® PH 200)	6.2	3.10	6.2	3.10
Aspartame NF	4.0	2.00	4.0	2.00
Acesulfame Potásico	4.0	2.00	4.0	2.00
Crema de Vainilla (Sabores Natural y Artificiales)	1.0	0.50	1.0	0.50
Ácido Tartárico NF	4.0	2.00	4.0	2.00
Estearato de Magnesio NF	1.5	0.75	1.5	0.75
Total	200 mg	100.00	200 mg	100.0

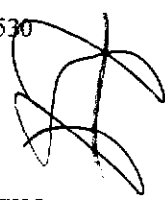
^aNúmero de Identificación de Producto 337039-A005-050; ^bNúmero de Identificación de Producto 337039-A005-051

El tiempo de desintegración de ambos prototipos en la boca fue inferior a 30 segundos. Sin embargo, los dos prototipos exhiben unas tasas de disolución diferentes en las pruebas de disolución in-vitro empleando métodos de prueba USP. Por lo tanto, la meta de este estudio fue evaluar si estas diferencias afectarían el desempeño de los dos prototipos en vivo.

Los parámetros farmacocinéticos del estudio clínico aparecen a continuación:

Formulación	Dosis (mg)	N	Cmax (ng/mL)	Tmax* (ni)	AUC(INF) [ng.h/mL]	F** (%)
Tableta Comercial	5	33	21.4 (5.85)	3 (1.8)	1393 (504)	-
Prototipo I	5	16	17.8 (3.85)	4 (2.12)	1260 (474)	99.7 (21.8)
Fusión Instantánea	5	17	21.0 (4.40)	4 (1.5,8)	1567 (677)	105 (18.4)
Prototipo II						
Fusión Instantánea						

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Con base en el análisis estadístico para la C_{max} y el AUC de prototipos (que aparecen abajo) se concluyó que el Prototipo II es bioequivalente a las tabletas comerciales habituales de aripiprazole.

Parámetro	Proporción	N	Punto Estimado	90% CI
C_{max}	B/A	16	0.8809	(0.7534,1.0300)
	C/A	17	0.9741	(0.8767,1.0823)
AUC (INF)	B/A	16	0.9744	(0.9107,1.0491)
	C/A	17	1.0141	(0.9688,1.0616)
AUC (0-T)	B/A	16	0.9647	(0.8941,1.0408)
	C/A	17	0.9979	(0.9438,1.0551)

- A = Aripiprazole 5 mg tableta comercial
B = Aripiprazole 5 mg fusión instantánea prototipo I
C = Aripiprazole 5 mg fusión instantánea prototipo II

Estabilidad química de un año de las tabletas de fusión instantánea de aripiprazole de 2 mg y de 30 mg de potencia:

A continuación aparecen los resultados de estabilidad de las tabletas de 2 mg y de 30 mg de potencia sometidas a pruebas oficiales de estabilidad IND. Como se aprecia a partir de los resultados, únicamente se ve que un degradante muestra un crecimiento bajo unas condiciones aceleradas al igual que a temperatura ambiente. Este degradante se identificó como el N-óxido aripiprazole (SFO-14094). Los niveles apreciados en las tabletas de 2 mg son significativamente superiores a aquellos de las tabletas de 30 mg. Igualmente, los niveles de N-óxido en la formulación del Prototipo II son significativamente inferiores a aquellos de la formulación del Prototipo I.

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Tabla 1: Tabletas de Fusión Instantánea de Aripiprazole -2 mg; Estudio de Estabilidad IND - Prototipo I

Tiempo y Condición de Almacenamiento	(%) calculado en el área debajo del pico del cromatograma normalizado para el área bajo todo el cromatograma							
	Metabolito de aripiprazole / producto de oxidación	aripiprazole	N-óxido de aripiprazole	Impurezas desconocidas	Total Impurezas	Potencia (Resultado #1)	Potencia Resultado #2)	Potencia (Resultado Reportado)
	%	%	%	%	%	mg/tab	mg/tab	mg/tab
	RRT 0.91	RRT 1.00	RRT 1.08	RRT in()				
Inicial	0.06	99.34	--		0.06	2.01	1.97	1.99
1 día @ 25C/75%RH (abierto)	0.07	99.86	0.07	--	0.14	1.98	NP	1.98
4 días @ 25C/HIL/UVA (expuesto)	0.06	99.81	0.13	--	0.19	1.97	NP	1.97
4 días @ 25C/HIL/UVA (envuelto)	--	99.95	0.05	--	0.05	2.02	NP	2.02
1 week @ 25C/75%RH (abierto)	0.09	99.73	0.18	--	0.27	1.96	NP	1.96
2 sem @ 25C/HIL/UVA (expuesto)	0.08	99.71	0.15	6 (0.87)	0.29	2.02	NP	2.02
2 sem @ 25C/HIL/UVA (envuelto)	0.05	99.90	0.05	--	0.10	1.98	NP	1.98
2 sem @ 25C/60%RH (cerrado)	0.05	99.95	--	--	0.05	2.03	NP	2.03
2 sem @ 25C/75%RH (abierto)	0.11	99.63	0.26	--	0.37	1.98	NP	1.98
4 sem @ 25C/60%RH (cerrado)	0.05	99.95		--	0.05	2.01	NP	2.01
4 sem @ 40C/75%RH (cerrado)	0.05	99.82	0.13	--	0.18	2.01	NP	2.01
4 sem @ 50C (cerrado)	0.06	99.62	0.32	--	0.38	1.97	NP	1.97
13 sem @ 25C/60%RH (cerrado)	0.06	99.85	0.09	--	0.15	1.97	NP	1.97
13 sem @ 40C/75%RH (cerrado)	0.09	99.46	0.45	--	0.54	1.95	NP	1.95
13 sem @ 50C (cerrado)	0.13	98.70	0.92	0.19 (0.38)	1.30	1.95	NP	1.95
26 sem @ 25C/60%RH (cerrado)	0.05	99.81	0.14	--	0.19	2.05	NP	2.05
26 sem @ 40C/75%RH (cerrado)	0.11	99.18	0.71	--	0.82	2.03	NP	2.03
52sem@-15C (cerrado)	--	100.00	--	--	0.00	2.05	NP	2.05
52 sem @ 25C/60%RH (cerrado)	--	99.77	0.23	--	0.23	1.97	NP	1.97

RRT = Periodo Relativo de Retención (relativo al compuesto aripiprazole) durante la cromatografía de análisis

Comentarios:

"—" indica que no se detectó ningún pico o que el pico medido midió menos que el limite de reporte (<0.05 I.I.)

"NP" indica, "No Practicado"

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Tabla 2: Tabletas de Fusión Instantánea de Aripiprazole -2 mg; Estudio de Estabilidad IND - Prototipo II

Tiempo y Condición de Almacenamiento	(%) calculado en el área debajo del pico del cromatograma normalizado para el área bajo todo el cromatograma							
	aripiprazole / producto de oxidación de aripiprazole	aripiprazole	N-óxido de aripiprazole	Impurezas desconocidas	Total Impurezas	Potencia (Resultado #1)	Potencia Resultado #2)	Potencia (Resultado Reportado)
	%	%	%	%	%	mg/tab	mg/tab	mg/tab
	RRT 0.91	RRT 1.00	RRT 1.08					
Inicial	0.05	99.95	-	-	0.05	2.05	2.04	2.05
1 día @ 25C/75%RH (abierto)	0.07	99.86	0.07	-	0.14	2.01	NP	2.01
4 días @25C/HIL/UVA (expuesto)	0.06	99.86	0.08	-	0.14	2.00	NP	2.00
4 días @ 25C/HIL/UVA (envuelto)	0.06	99.89	0.06	-	0.11	2.00	NP	2.00
1 week @ 25C/75%RH (abierto)	0.08	99.80	0.12	-	0.20	2.00	NP	2.00
2 sem @ 25C/HIL/UVA (expuesto)	0.09	99.74	0.12	0.06 (0.87)	0.26	2.00	NP	2.00
2 sem @ 25C/HIL/UVA (envuelto)	0.05	99.95	-	-	0.05	2.02	NP	2.02
2 sem @ 25C/60%RH (cerrado)	0.06	99.89	0.05	-	0.11	2.00	NP	2.00
2 sem @ 25C/75%RH (abierto)	0.10	99.72	0.18	-	0.28	1.99	NP	1.99
4 sem @ 25C/60%RH (cerrado)	0.05	99.95	-	-	0.05	2.01	NP	2.01
4 sem @ 40C/75%RH (cerrado)	0.05	99.90	0.05	-	0.10	2.04	NP	2.04
4 sem @ 50C (cerrado)	0.07	99.68	0.25	-	0.32	2.02	NP	2.02
13 sem @ 25C/60%RH (cerrado)	0.06	99.88	0.06	-	0.12	2.00	NP	2.00
13 sem @ 40C/75%RH (cerrado)	0.08	99.63	0.29	-	0.37	1.98	NP	1.98
13 sem @ 50C (cerrado)	0.12	98.89	0.74	0.20 (0.38)	1.11	1.98	NP	1.98
26 sem @ 25C/60%RH (cerrado)	0.06	99.86	0.08	-	0.14	2.06	NP	2.06
26 sem @ 40C/75%RH (cerrado)	0.16	99.29	0.55	-	0.71	2.02	NP	2.02
52sem@-15C (cerrado)	-	100.00	-	-	0.00	2.01	NP	2.01
52 sem @ 25C/60%RH (cerrado)	-	99.89	0.11	-	0.11	2.02	NP	2.02

RRT = Periodo Relativo de Retención (relativo al compuesto aripiprazole) durante la cromatografía de análisis

Comentarios:

"—" indica que no se detectó ningún pico o que el pico medido midió menos que el limite de reporte (<0.05 I.I.)
"NP" indica, "No Practicado"

Tabla 3: Tabletas de Fusión Instantánea de Aripiprazole -30 mg;
Estudio de Estabilidad IND - Prototipo I

Tiempo y Condición de Almacenamiento	(%) calculado en el área debajo del pico del cromatograma normalizado para el área bajo todo el cromatograma							
	Metabolito de aripiprazole / producto de oxidación	aripiprazole	N-óxido de aripiprazole	Impurezas desconocidas	Total Impurezas	Potencia (Resultado #1)	Potencia Resultado #2)	Potencia (Resultado Reportado)
	%	%	%	%	%	mg/tab	mg/tab	mg/tab
	RRT 0.91	RRT 1.00	RRT 1.08	RRT in()				
Inicial	0.06	99.94	-	-	0.06	29.54	29.90	29.7
1 día @ 25C/75%RH (abierto)	0.07	99.88	0.05	-	0.12	28.98	NP	29.0
4 días @25C/HIL/UVA (expuesto)	0.05	99.89	0.06	-	0.11	29.39	NP	29.4
4 días @ 25C/HIL/UVA (envuelto)	0.06	99.89	0.05	-	0.11	29.41	NP	29.4
1 week @ 25C/75%RH (abierto)	0.10	99.82	0.08	-	0.18	29.24	29.30	29.3*
2 sem @ 25C/HIL/UVA (expuesto)	0.05	99.85	0.10	-	0.15	29.52	NP	29.5
2 sem @ 25C/HIL/UVA (envuelto)	0.05	99.89	0.06	-	0.11	29.98	NP	30.0
2 sem @ 25C/60%RH (cerrado)	0.06	99.87	0.07	-	0.13	29.77	NP	29.8
2 sem @ 25C/75%RH (abierto)	0.08	99.81	0.11	-	0.19	29.74	NP	29.7
4 sem @ 25C/60%RH (cerrado)	0.05	99.95	-	-	0.05	29.08	NP	29.1
4 sem @ 40C/75%RH (cerrado)	-	99.95	0.05	-	0.05	29.37	NP	29.4
4 sem @ 50C (cerrado)	0.06	99.87	0.07	-	0.13	29.70	NP	29.7
13 sem @ 25C/60%RH (cerrado)	0.06	99.90	0.05	-	0.10	29.73	NP	29.7
13 sem @ 40C/75%RH (cerrado)	0.06	99.85	0.09	-	0.15	29.89	NP	29.9
13 sem @ 50C (cerrado)	0.06	99.77	0.17	-	0.23	29.74	NP	29.7
26 sem @ 25C/60%RH (cerrado)	0.05	99.91	0.04	-	0.09	29.26	NP	29.3
26 sem @ 40C/75%RH (cerrado)	0.06	99.81	0.13	-	0.19	29.41	NP	29.4
52sem@-15C (cerrado)	0.05	99.95	-	-	0.05	29.70	NP	29.7
52 sem @ 25C/60%RH (cerrado)	0.06	99.88	0.06	-	0.12	29.90	NP	29.9

RRT = Periodo Relativo de Retención (relativo al compuesto aripiprazole) durante la cromatografía de análisis

Comentarios

"—" indica que no se detectó ningún pico o que el pico medido midió menos que el limite de reporte (<0.05 I.I.)

"NP" indica, "No Practicado"

* Únicamente se reporta el Resultado 2 (29.3); Se cree que el Resultado 1 (28.2) es bajo debido a una extracción incompleta

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Tabla 4: Tabletas de Fusión Instantánea de Aripiprazole -30 mg;
Estudio de Estabilidad IND - Prototipo II

Tiempo y Condición de Almacenamiento	(%) calculado en el área debajo del pico del cromatograma normalizado para el área bajo todo el cromatograma							
	metabolito de aripiprazole / producto de oxidación de aripiprazole	aripiprazole	N-óxido de aripiprazole	Impurezas desconocidas	Total Impurezas	Potencia (Resultado #1)	Potencia (Resultado #2)	Potencia (Resultado Reportado)
	%	%	%	%	%	mg/tab	mg/tab	mg/tab
	RRT 0.91	RRT 1.00	RRT 1.08	RRT in()				
Inicial	0.05	99.95	-		0.05	28.86	29.78	293
1 día @ 25C/75%RH (abierto)	0.07	99.88	0.05	-	0.12	29.01	NP	29.0
4 días @25C/HIL/UVA (expuesto)	0.05	99.91	0.05	-	0.09	29.20	NP	29.2
4 días @ 25C/HIL/UVA (envuelto)	0.06	99.94	-	-	0.06	29.54	NP	29.5
1 week @ 25C/75%RH (abierto)	0.08	99.86	0.06	-	0.14	28.94	NP	28.9
2 sem @ 25C/HIL/UVA (expuesto)	0.05	99.87	0.07	-	0.13	29.23	NP	29.2
2 sem @ 25C/HIL/UVA (envuelto)	0.05	99.95	-	-	0.05	29.45	NP	29.5
2 sem @ 25C/60%RH (cerrado)	0.05	99.95	-	-	0.05	29.02	NP	29.0
2 sem @ 25C/75%RH (abierto)	0.07	99.86	0.07	-	0.14	29.79	NP	29.8
4 sem @ 25C/60%RH (cerrado)	0.05	99.95	-	-	0.05	29.53	NP	29.5
4 sem @ 40C/75%RH (cerrado)	0.05	99.95	-	-	0.05	29.14	NP	29.1
4 sem @ 50C (cerrado)	0.05	99.90	0.05	-	0.10	29.68	NP	29.7
13 sem @ 25C/60%RH (cerrado)	0.05	99.95	-	-	0.05	30.145	NP	30.1
13 sem @ 40C/75%RH (cerrado)	0.06	99.88	0.06	-	0.12	29.80	NP	29.8
13 sem @ 50C (cerrado)	0.07	99.83	0.10	-	0.17	30.14	NP	30.1
26 sem @ 25C/60%RH (cerrado)	0.05	99.95	-	-	0.05	29.76	NP	29.8
26 sem @ 40C/75%RH (cerrado)	0.05	99.87	0.07	-	0.13	28.98	NP	29.0
52sem@-15C (cerrado)	0.05	99.95	-	-	0.05	29.14	NP	29.1
52 sem @ 25C/60%RH (cerrado)	0.07	99.93	-	-	0.07	30.17	NP	30.2

RRT = Periodo Relativo de Retención (relativo al compuesto aripiprazole) durante la cromatografía de análisis

Comentarios

"—" indica que no se detectó ningún pico o que el pico medido midió menos que el limite de reporte (<0.05 I.I.)

"NP" indica, "No Practicado"

**Nosotros reivindicamos:**

1. Una forma farmacéutica de fusión instantánea comprendiendo un medicamento, un disgregante de acción superior, un agente dispersante y un aglutinante donde el citado medicamento es aripiprazole, entecavir, cefprozil, pravastatin, captopril, gatifloxacina, desquinalona, omapatrilato o irbesartan, y donde el citado agente dispersante es silicato de calcio y donde el citado disgregante de acción superior está compuesto por dos o más agentes seleccionados entre el grupo conformado por crospovidona, croscarmelosa sódica, glicolato sódico de almidón, hidroxipropilcelulosa de baja sustitución o almidón pregelatinizado.
2. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el citado agente dispersante comprende entre alrededor de 20 hasta alrededor de 70 por ciento por peso del citado agente dispersante con base en el peso total de la citada forma farmacéutica.
3. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el citado agente dispersante comprende entre alrededor de 35 hasta alrededor de 45 por ciento por peso del citado agente dispersante con base en el peso total de la citada forma farmacéutica.
4. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde más del 50% del citado agente dispersante por peso está compuesto por silicato de calcio.
5. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde más del 80% del citado agente dispersante por peso está compuesto por silicato de calcio.

6. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el referido silicato de calcio es cristalino.

7. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el referido silicato de calcio es amorfo.

8. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el referido silicato de calcio es silicato de calcio orto-, meta- o alfa triclinico.

9. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el referido silicato de calcio es silicato de calcio alfa triclinico.

10. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el referido silicato de calcio está conformado por una combinación de silicato de calcio alfa triclinico y por lo menos otro grado farmacéutico de silicato de calcio donde el citado silicato de calcio alfa triclinico comprende entre alrededor de 10% hasta alrededor de 90% por peso de la citada combinación.

11. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el referido silicato de calcio tiene un área de superficie de $1.0 \text{ m}^2/\text{gm}$ a $210 \text{ m}^2/\text{gm}$, una densidad aparente de 0.075 g/cc a 0.90 g/cc , una densidad real de 1.70 g/cc a 2.90 g/cc y un contenido volátil inferior de 1 % a 14% peso / peso.

12. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el referido silicato de calcio es un silicato de calcio alfa triclinico cuya área de superficie es alrededor de $1.3 \text{ m}^2/\text{gm}$, con una densidad aparente de alrededor de 0.63 g/cc , una densidad cierta

95
X
X

aproximadamente de 2.90 g/cc y un contenido volátil inferior a 1% peso / peso.

13. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el referido silicato de calcio es silicato de calcio orto cristalino cuya área de superficie es alrededor de $0.98 \text{ m}^2/\text{gm}$, con una densidad aparente de alrededor de 0.492 g/cc, una densidad cierta aproximadamente de 3.252 g/cc y un contenido volátil inferior a 1% peso / peso.

14. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el referido silicato de calcio es silicato de calcio meta cristalino cuya área de superficie es alrededor de $2.5 \text{ m}^2/\text{gm}$, con una densidad aparente de alrededor de 0.867 g/cc, una densidad cierta aproximadamente de 2.940 g/cc y un contenido volátil inferior a 1% peso / peso.

15. A Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el referido silicato de calcio es silicato de calcio cristalino cuya área de superficie es alrededor de $90.4 \text{ m}^2/\text{gm}$, con una densidad aparente de alrededor de 0.094 g/cc, una densidad cierta aproximadamente de 2.596 g/cc y un contenido volátil inferior a 1% peso / peso.

16. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el referido silicato de calcio es silicato de calcio amorfo cuya área de superficie es alrededor de $191.3 \text{ m}^2/\text{gm}$, con una densidad aparente de alrededor de 0.120 g/cc, una densidad cierta aproximadamente de 2.314 g/cc y un contenido volátil de alrededor de menos de 14% peso / peso.

17. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el referido silicato de calcio es silicato de calcio amorfo cuya área de superficie es alrededor de $103.0 \text{ m}^2/\text{gm}$, con una densidad aparente de alrededor de 0.130 g/cc , una densidad cierta aproximadamente de 1.702 g/cc y un contenido volátil de alrededor de menos de 14% peso / peso.

18. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el referido silicato de calcio es silicato de calcio amorfo, cuya área de superficie es alrededor de $209 \text{ m}^2/\text{gm}$, con una densidad aparente de alrededor de 0.075 g/cc , una densidad cierta aproximadamente de 2.035 g/cc y un contenido volátil de alrededor de menos de 14% peso / peso.

19. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el citado medicamento comprende no más de alrededor de 30 por ciento por peso del citado medicamento con base en el peso total de la citada forma farmacéutica.

20. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el citado medicamento comprende no más de alrededor de 15 por ciento por peso del citado medicamento con base en el peso total de la citada forma farmacéutica.

21. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el citado disgregante de acción superior comprende entre alrededor de 3 hasta alrededor de 15 por ciento por peso del citado disgregante de acción superior con base en el peso total de la citada forma farmacéutica.

22. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el citado disgregante de acción superior comprende

entre alrededor de 4 hasta alrededor de 10 por ciento por peso del citado disgregante de acción superior con base en el peso total de la citada forma farmacéutica.

23. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el citado disgregante de acción superior comprende entre alrededor de 4 hasta alrededor de 8 por ciento por peso del citado disgregante de acción superior con base en el peso total de la citada forma farmacéutica.

24. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el citado disgregante de acción superior comprende entre alrededor de 5 hasta alrededor de 7 por ciento por peso del citado disgregante de acción superior con base en el peso total de la citada forma farmacéutica.

25. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el citado disgregante de acción superior comprende entre alrededor de 8 hasta alrededor de 12 por ciento por peso del citado disgregante de acción superior con base en el peso total de la citada forma farmacéutica.

26. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el citado disgregante de acción superior comprende entre alrededor de 9 hasta alrededor de 10 por ciento por peso del citado disgregante de acción superior con base en el peso total de la citada forma farmacéutica.

27. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el citado agente disgregante de acción superior es crospovidona y croscarmelosa sódica.

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28. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 27 donde con base en el peso total de la citada forma farmacéutica, la citada crospovidona comprende entre alrededor de 6 hasta alrededor de 8 por ciento por peso de la citada crospovidona y la citada croscarmelosa sódica comprende entre alrededor de 2 hasta alrededor de 4 por ciento por peso de la citada croscarmelosa sódica.

29. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 comprendiendo además un agente distribuidor.

30. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 29 donde el citado agente distribuidor comprende entre alrededor de 1 hasta alrededor de 10 por ciento por peso del citado agente distribuidor con base en el peso total de la citada forma farmacéutica.

31. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 29 donde el citado agente distribuidor comprende entre alrededor de 1.5 hasta alrededor de 3 por ciento por peso del citado agente distribuidor con base en el peso total de la citada forma farmacéutica.

32. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 29 donde el citado agente distribuidor es sílice amorfa, sílice de combustión, tierra diatomita, talco, caolín o trisilicato de magnesio y aluminio.

33. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el citado agente distribuidor comprende entre alrededor de 10 hasta alrededor de 50 por ciento por peso del citado aglutinante con base en el peso total de la citada forma farmacéutica.

34. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el citado agente distribuidor comprende entre

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alrededor de 12 hasta alrededor de 20 por ciento por peso del citado aglutinante con base en el peso total de la citada forma farmacéutica.

35. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 1 donde el citado aglutinante es celulosa microcristalina, hidroxipropilcelulosa, etilcelulosa, lactosa, manitol o fosfato de calcio.

36. Una forma farmacéutica de fusión instantánea comprendiendo un medicamento, un disgregante de acción superior, un agente dispersante y un aglutinante donde el citado medicamento es aripiprazole y comprende no más de alrededor de 30 por ciento por peso del citado medicamento con base en el peso total de la citada forma farmacéutica, el citado agente dispersante es silicato de calcio con un área de superficie de $1.0 \text{ m}^2/\text{gm}$ a $210 \text{ m}^2/\text{gm}$, una densidad aparente de 0.075 g/cc a 0.90 g/cc , una densidad real de 1.70 g/cc a 2.90 g/cc y un contenido volátil de menos de 1% a 14% peso / peso y el cual comprende entre alrededor de 20 hasta alrededor de 70 por ciento por peso del citado agente dispersante con base en el peso total de la citada forma farmacéutica. Los citados disgregantes de acción superior son dos o más agentes seleccionados entre el grupo conformado por crospovidona, croscarmelosa sódica, glicolato sódico de almidón, hidroxipropilcelulosa de baja sustitución o almidón pregelatinizado y que comprenden entre 3 a 15 por ciento por peso de la combinación de los citados disgregantes de acción con base en el peso total de la citada forma farmacéutica.

37. Una forma farmacéutica de fusión instantánea comprendiendo un medicamento, un disgregante de acción superior, un agente dispersante y un aglutinante donde el citado medicamento es aripiprazole y comprende no más de alrededor de 30 por ciento por peso del citado medicamento con base en el peso total de la citada forma farmacéutica. El citado agente dispersante es silicato de calcio con un área de superficie de $1.0 \text{ m}^2/\text{gm}$ a $210 \text{ m}^2/\text{gm}$, una densidad aparente de 0.075 g/cc a 0.90 g/cc , una densidad real de 1.70 g/cc a 2.90 g/cc y un contenido volátil de menos de 1% a 14%

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peso / peso y que comprende entre alrededor de 35 hasta alrededor de 45 por ciento por peso del citado agente dispersante con base en el peso total de la citada forma farmacéutica. El citado disgregante de acción superior es crospovidona y croscarmelosa sódica, la citada crospovidona comprende entre alrededor de 6 hasta alrededor de 8 por ciento por peso de la citada crospovidona con base en el peso total de la citada forma farmacéutica y la citada croscarmelosa sódica comprende entre alrededor de 2 hasta alrededor de 4 por ciento por peso de la citada croscarmelosa sódica con base en el peso total de la citada forma farmacéutica.

38. Una forma farmacéutica de fusión instantánea comprendiendo un medicamento, un disgregante de acción superior, un agente dispersante y un aglutinante donde el citado medicamento es aripiprazole y comprende no más de alrededor de 30 por ciento por peso del citado medicamento con base en el peso total de la citada forma farmacéutica. El citado agente dispersante es silicato de calcio con un área de superficie de 1.0 m²/gm a 210 m²/gm, una densidad aparente de 0.075 g/cc a 0.90 g/cc, una densidad real de 1.70 g/cc a 2.90 g/cc y un contenido volátil de menos de 1% a 14% peso / peso y que comprende entre alrededor de 35 hasta alrededor de 45 por ciento por peso del citado agente dispersante con base en el peso total de la citada forma farmacéutica. El citado disgregante de acción superior es crospovidona y croscarmelosa sódica, la citada crospovidona comprende entre alrededor de 6 hasta alrededor de 8 por ciento por peso de la citada crospovidona con base en el peso total de la citada forma farmacéutica y la citada croscarmelosa sódica comprende entre alrededor de 2 hasta alrededor de 4 por ciento por peso de la citada croscarmelosa sódica con base en el peso total de la citada forma farmacéutica y donde el citado agente distribuidor es sílice amorfa, sílice de combustión, tierra diatomita, talco, caolín o trisilicato de magnesio y aluminio y comprende entre alrededor de 1 hasta alrededor de 10 por ciento por peso del citado agente distribuidor con base en el peso total de la citada forma farmacéutica.

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39. Una forma farmacéutica de fusión instantánea de conformidad con la reivindicación 38 preparada mediante el mezclado en seco del citado medicamento y del citado disgregante de acción superior. El citado agente dispersante y el citado aglutinante, comprimiendo la mezcla citada en un compactador o una llanta del cilindro triturador adecuado para formar compactos o balines, pasando los citados compactos o balines por una zaranda para formar gránulos y comprimir los citados gránulos para formar la citada forma farmacéutica de fusión instantánea.

40. Una forma farmacéutica de fusión instantánea comprendiendo un medicamento, un disgregante de acción superior, un agente dispersante, un agente distribuidor y un aglutinante donde el citado medicamento es aripiprazole y comprende no más de alrededor de 30 por ciento por peso del citado medicamento con base en el peso total de la citada forma farmacéutica. El citado agente dispersante es silicato de calcio con un área de superficie de $1.0 \text{ m}^2/\text{gm}$ a $210 \text{ m}^2/\text{gm}$, una densidad aparente de 0.075 g/cc a 0.90 g/cc , una densidad real de 1.70 g/cc a 2.90 g/cc y un contenido volátil de menos de 1% a 14% peso / peso y que comprende entre alrededor de 20 hasta alrededor de 70 por ciento por peso del citado agente dispersante con base en el peso total de la citada forma farmacéutica. El citado disgregante de acción superior es crospovidona y croscarmelosa sódica y donde la citada crospovidona comprende de 5 a 8 por ciento por peso de la citada crospovidona con base en el peso total de la citada forma farmacéutica y donde la citada croscarmelosa comprende de 1 a 4 por ciento por peso de la citada crospovidona con base en el peso total de la citada forma farmacéutica, y donde el citado agente distribuidor es sílice amorfa, sílice de combustión, tierra diatomita, talco, caolín o trisilicato de magnesio y aluminio y comprende entre alrededor de 10 hasta alrededor de 50 por ciento por peso del citado agente distribuidor con base en el peso total de la citada forma farmacéutica.

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41. Una forma farmacéutica de fusión instantánea comprendiendo un medicamento, un disgregante de acción superior, un agente dispersante, un agente distribuidor y un aglutinante donde el citado medicamento es aripiprazole y comprende no más de alrededor de 30 por ciento por peso del citado medicamento con base en el peso total de la citada forma farmacéutica. El citado agente dispersante es silicato de calcio con un área de superficie de $1.0 \text{ m}^2/\text{gm}$ a $210 \text{ m}^2/\text{gm}$, una densidad aparente de 0.075 g/cc a 0.90 g/cc , una densidad real de 1.70 g/cc a 2.90 g/cc y un contenido volátil de menos de 1 a 14% peso / peso y que comprende entre alrededor de 20 hasta alrededor de 70 por ciento por peso del citado agente dispersante con base en el peso total de la citada forma farmacéutica. El citado disgregante de acción superior es crospovidona y croscarmelosa sódica y donde la citada crospovidona comprende alrededor de 7 por ciento por peso de la citada crospovidona con base en el peso total de la citada forma farmacéutica y donde la citada croscarmelosa comprende alrededor de 3 por ciento por peso de la citada crospovidona con base en el peso total de la citada forma farmacéutica, y donde el citado agente distribuidor es sílice amorfa, sílice de combustión, tierra diatomita, talco, caolín o trisilicato de magnesio y aluminio y comprende entre alrededor de 10 hasta alrededor de 50 por ciento por peso del citado agente distribuidor con base en el peso total de la citada forma farmacéutica.

42. Una forma farmacéutica de fusión instantánea comprendiendo un medicamento, un disgregante de acción superior, un agente dispersante, un agente distribuidor y un aglutinante donde el citado medicamento es aripiprazole y comprende no más de alrededor de 30 por ciento por peso del citado medicamento con base en el peso total de la citada forma farmacéutica. El citado agente dispersante es silicato de calcio con un área de superficie de $1.0 \text{ m}^2/\text{gm}$ a $210 \text{ m}^2/\text{gm}$, una densidad aparente de 0.075 g/cc a 0.90 g/cc , una densidad real de 1.70 g/cc a 2.90 g/cc y un contenido volátil de menos de 1% a 14% peso / peso y que comprende entre alrededor de 35 hasta alrededor de 45 por ciento por peso del citado agente dispersante

con base en el peso total de la citada forma farmacéutica. El citado disgregante de acción superior es crospovidona y croscarmelosa sódica y donde la citada crospovidona comprende alrededor de 7 por ciento por peso de la citada crospovidona con base en el peso total de la citada forma farmacéutica y donde la citada croscarmelosa comprende alrededor de 3 por ciento por peso de la citada crospovidona con base en el peso total de la citada forma farmacéutica, y donde el citado agente distribuidor es sílice amorfa, sílice de combustión, tierra diatomita, talco, caolín o trisilicato de magnesio y aluminio y comprende entre alrededor de 10 hasta alrededor de 50 por ciento por peso del citado agente distribuidor con base en el peso total de la citada forma farmacéutica.

43. Una forma farmacéutica de fusión instantánea comprendiendo un medicamento, un disgregante de acción superior, un agente dispersante, un agente distribuidor y un aglutinante donde el citado medicamento es aripiprazole y comprende no más de alrededor de 20 por ciento por peso del citado medicamento con base en el peso total de la citada forma farmacéutica. El citado agente dispersante es silicato de calcio con un área de superficie de $1.0 \text{ m}^2/\text{gm}$ a $210 \text{ m}^2/\text{gm}$, una densidad aparente de 0.075 g/cc a 0.90 g/cc , una densidad real de 1.70 g/cc a 2.90 g/cc y un contenido volátil de menos de 1% a 14% peso / peso y que comprende entre alrededor de 35 hasta alrededor de 45 por ciento por peso del citado agente dispersante con base en el peso total de la citada forma farmacéutica. El citado disgregante de acción superior es crospovidona y croscarmelosa sódica y donde la citada crospovidona comprende alrededor de 7 por ciento por peso de la citada crospovidona con base en el peso total de la citada forma farmacéutica y donde la citada croscarmelosa comprende alrededor de 3 por ciento por peso de la citada crospovidona con base en el peso total de la citada forma farmacéutica, y donde el citado agente distribuidor es sílice amorfa, sílice de combustión, tierra diatomita, talco, caolín o trisilicato de magnesio y aluminio y comprende entre alrededor de 10 hasta alrededor de

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50 por ciento por peso del citado agente distribuidor con base en el peso total de la citada forma farmacéutica.

44. Una forma farmacéutica de fusión instantánea comprendiendo un medicamento, un disgregante de acción superior, un agente dispersante, un agente distribuidor y un aglutinante donde el citado medicamento es aripiprazole y comprende no más de alrededor de 10 por ciento por peso del citado medicamento con base en el peso total de la citada forma farmacéutica. El citado agente dispersante es silicato de calcio con un área de superficie de $1.0 \text{ m}^2/\text{gm}$ a $210 \text{ m}^2/\text{gm}$, una densidad aparente de 0.075 g/cc a 0.90 g/cc , una densidad real de 1.70 g/cc a 2.90 g/cc y un contenido volátil de menos de 1% a 14% peso / peso y que comprende entre alrededor de 35 hasta alrededor de 45 por ciento por peso del citado agente dispersante con base en el peso total de la citada forma farmacéutica. El citado disgregante de acción superior es crospovidona y croscarmelosa sódica y donde la citada crospovidona comprende alrededor de 7 por ciento por peso de la citada crospovidona con base en el peso total de la citada forma farmacéutica y donde la citada croscarmelosa comprende alrededor de 3 por ciento por peso de la citada crospovidona con base en el peso total de la citada forma farmacéutica.

45. Una forma farmacéutica de fusión instantánea comprendiendo un medicamento, un disgregante de acción superior, un agente dispersante, un agente distribuidor y un aglutinante donde el citado medicamento es aripiprazole y comprende no más de alrededor de 5 por ciento por peso del citado medicamento con base en el peso total de la citada forma farmacéutica. El citado agente dispersante es silicato de calcio con un área de superficie de $1.0 \text{ m}^2/\text{gm}$ a $210 \text{ m}^2/\text{gm}$, una densidad aparente de 0.075 g/cc a 0.90 g/cc , una densidad real de 1.70 g/cc a 2.90 g/cc y un contenido volátil de menos de 1% a 14% peso / peso y que comprende entre alrededor de 35 hasta alrededor de 45 por ciento por peso del citado agente dispersante con base en el peso total de la citada forma farmacéutica. El citado

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disgregante de acción superior es crospovidona y croscarmelosa sódica y donde la citada crospovidona comprende alrededor de 7 por ciento por peso de la citada crospovidona con base en el peso total de la citada forma farmacéutica y donde la citada croscarmelosa comprende alrededor de 3 por ciento por peso de la citada crospovidona con base en el peso total de la citada forma farmacéutica.

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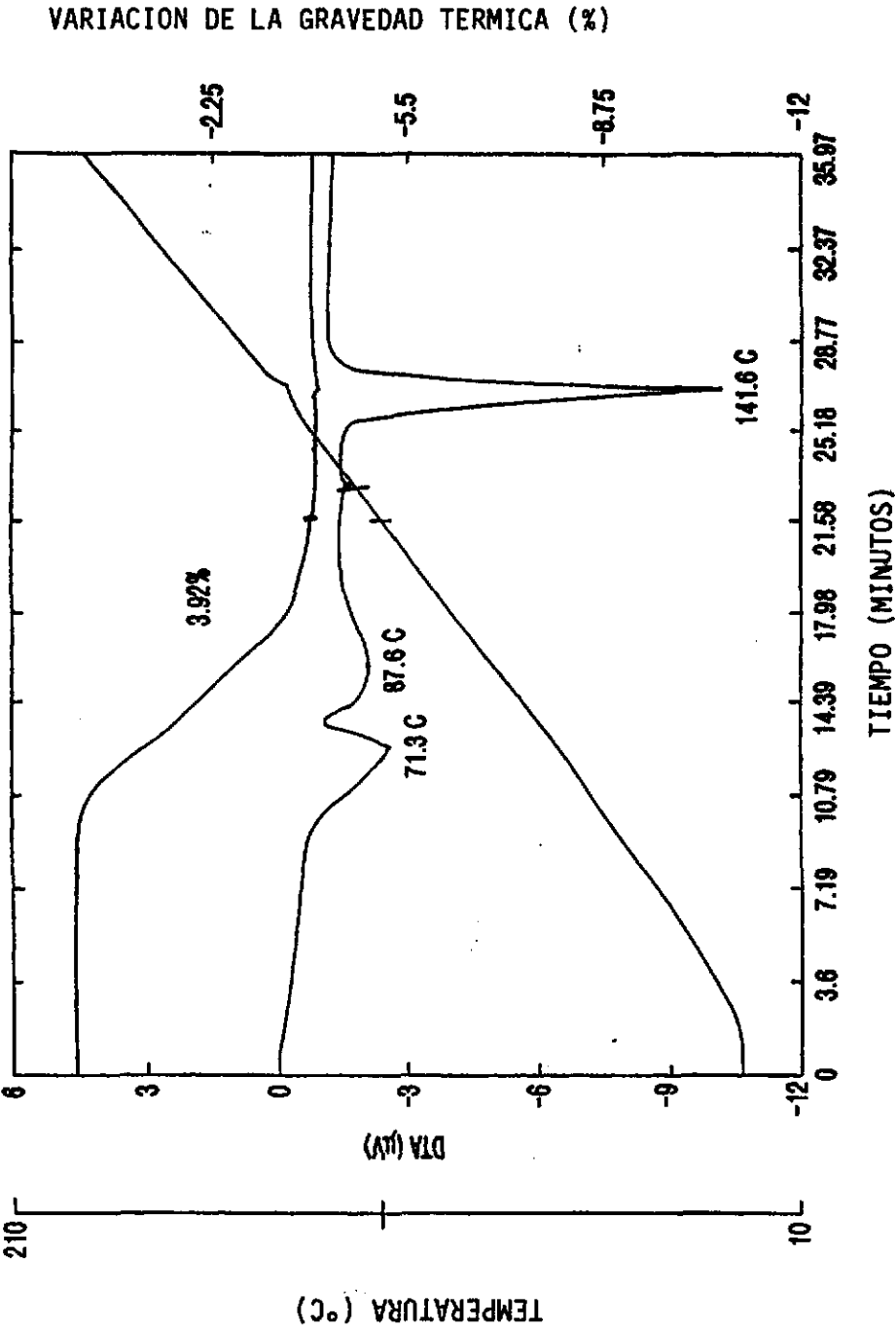


FIG. 1

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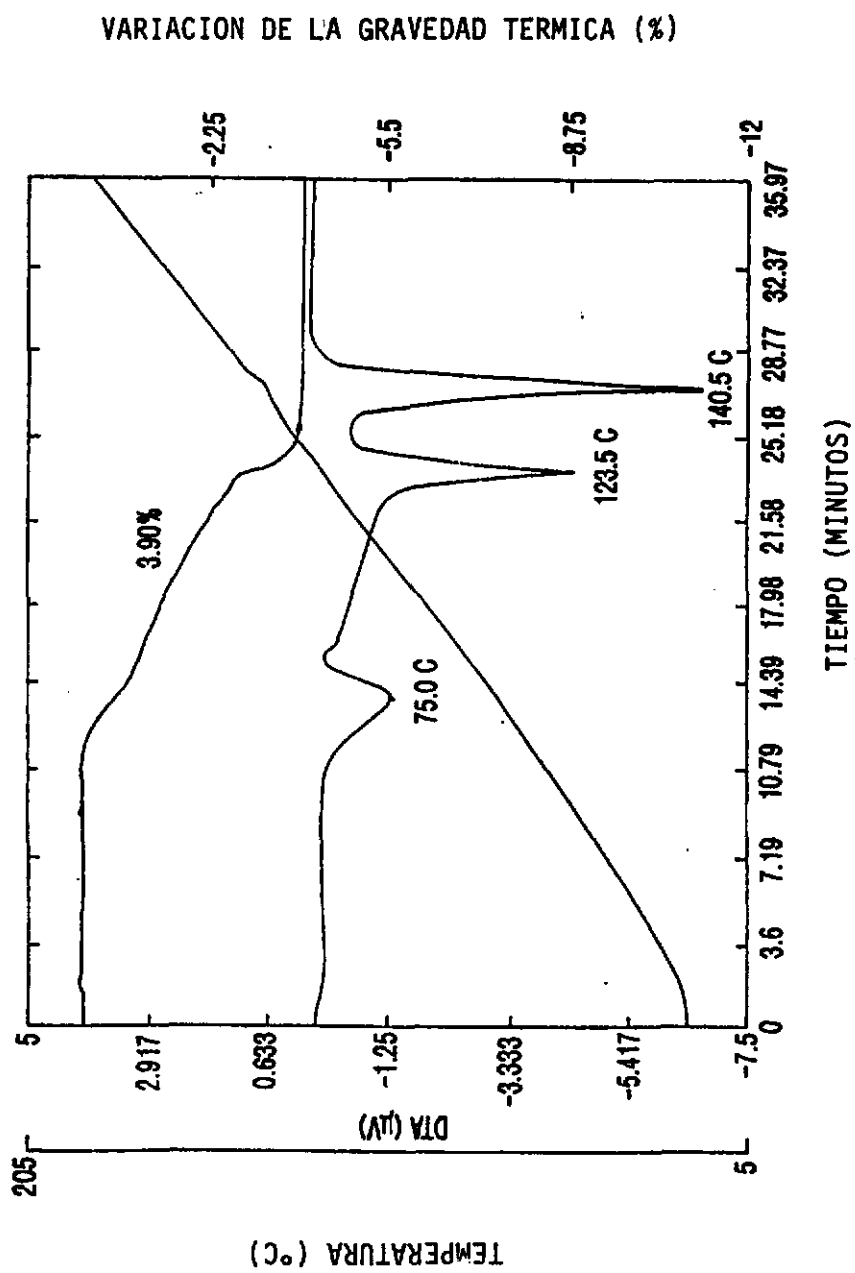


FIG. 6

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The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ US

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION	
Applicant's or agent's file reference CT2545ACIP	
International application No. PCT/US01/31530	International filing date (day/month/year) 09 October 2001 (09.10.01)
(Earliest) Priority date (day/month/year)	
Title of invention Flashmelt Oral Dosage Formulation	
Box No. II APPLICANT(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) BRISTOL-MYERS SQUIBB COMPANY P. O. Box 4000 Lawrenceville-Princeton Road Princeton, NJ 08543-4000 United States of America	
Telephone No. 609-252-3950	
Facsimile No. 609-252-4526	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: US	State (that is, country) of residence: US
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
State (that is, country) of nationality:	
State (that is, country) of residence:	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
State (that is, country) of nationality:	
State (that is, country) of residence:	
☐ Further applicants are indicated on a continuation sheet.	

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative
 and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: (Family name followed by given name; for a legal entity, full official designation.
 The address must include postal code and name of country.)

MAKUJINA, Shah
 BRISTOL-MYERS SQUIBB COMPANY
 P. O. Box 4000
 Lawrenceville-Princeton Road
 Princeton, NJ 08543-4000
 United States of America

Telephone No.

203-677-7268

Facsimile No.

203-677-6900

Teleprinter No.

Agent's registration No. with the Office

41,174

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION**Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☐ as originally filed
☐ as amended under Article 34

the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ...English.....

☒ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☐ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary Examining Authority use only

received

not received

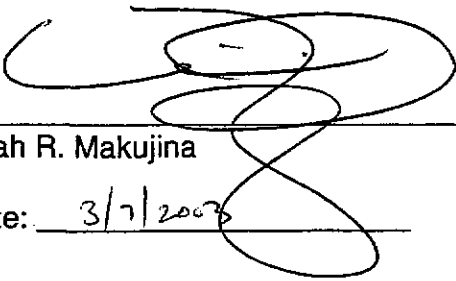
☐☐☐☐☐☐☐☐☐☐☐☐

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ other (specify): |
| 4. ☐ copy of general power of attorney; reference number, if any: | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).


_____, Agent

Shah R. Makujina

Date:

3/7/2003

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

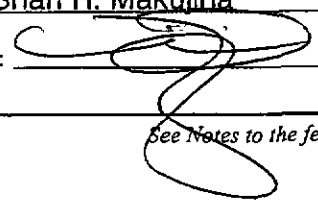
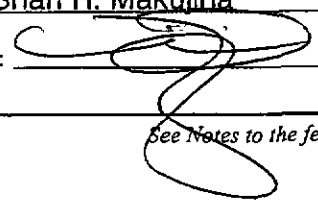
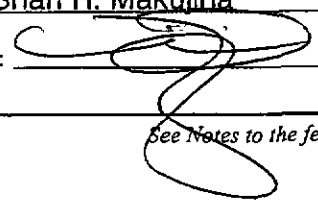
For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US01/31530 Applicant's or agent's file reference CT2545ACIP Applicant BRISTOL-MYERS SQUIBB, ET AL.	For International Preliminary Examining Authority use only Date stamp of the IPEA												
CALCULATION OF PRESCRIBED FEES <table style="width: 100%;"><tr><td style="width: 60%;">1. Preliminary examination fee</td><td style="width: 20%; text-align: right;">490.00</td><td style="width: 20%; text-align: center;">P</td></tr><tr><td>2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>)</td><td style="text-align: right;">146.00</td><td style="text-align: center;">H</td></tr><tr><td>3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box</td><td style="text-align: right;">636.00</td><td></td></tr><tr><td></td><td style="text-align: right;">TOTAL</td><td></td></tr></table>		1. Preliminary examination fee	490.00	P	2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>)	146.00	H	3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	636.00			TOTAL	
1. Preliminary examination fee	490.00	P											
2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>)	146.00	H											
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	636.00												
	TOTAL												
MODE OF PAYMENT <table style="width: 100%;"><tr><td>☒ authorization to charge deposit account with the IPEA (see below)</td><td>☐ cash</td></tr><tr><td>☐ cheque</td><td>☐ revenue stamps</td></tr><tr><td>☐ postal money order</td><td>☐ coupons</td></tr><tr><td>☐ bank draft</td><td>☐ other (specify):</td></tr></table>		☒ authorization to charge deposit account with the IPEA (see below)	☐ cash	☐ cheque	☐ revenue stamps	☐ postal money order	☐ coupons	☐ bank draft	☐ other (specify):				
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash												
☐ cheque	☐ revenue stamps												
☐ postal money order	☐ coupons												
☐ bank draft	☐ other (specify):												
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all IPEAs) <table style="width: 100%;"><tr><td style="width: 50%; vertical-align: top;"> ☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. </td><td style="width: 50%; vertical-align: top;"> IPEA/ <u>US</u> Deposit Account No.: <u>19-3880</u> Date: <u>3/7/2003</u> Name: <u>Shah R. Makujina</u> Signature:  </td></tr></table>		☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPEA/ <u>US</u> Deposit Account No.: <u>19-3880</u> Date: <u>3/7/2003</u> Name: <u>Shah R. Makujina</u> Signature: 										
☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPEA/ <u>US</u> Deposit Account No.: <u>19-3880</u> Date: <u>3/7/2003</u> Name: <u>Shah R. Makujina</u> Signature: 												

PATENT COOPERATION TREATY

RECEIVED

From the INTERNATIONAL SEARCHING AUTHORITY

To:

SHAH R. MAKUJINA
BRISTOL-MYERS SQUIBB COMPANY
LAWRENCEVILLE-PRINCETON ROAD
P.O. BOX 4000
PRINCETON, NJ 08543-4000

IMS PATENT LAW**PCT**

Docketed Item

Due Date

Attorney

FEB 25 2002

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing
(day/month/year)

12 FEB 2002

Applicant's or agent's file reference
CT2545ACIP

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US01/31530

International filing date
(day/month/year)

09 October 2001 (09.10.2001)

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompany sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703)305-3230

Authorized officer

Felicia D. Roberts for
Amy Pulliam

Telephone No. 703-308-1235

Form PCT/ISA/220 (July 1998)

RECEIVED

FEB 26 2002

BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
WALLINGFORD, CT

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference CT2545ACIP	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US01/31530	International filing date (day/month/year) 09 October 2001 (09.10.2001)	(Earliest) Priority Date (day/month/year) NONE
Applicant BRISTOL-MYERS SQUIBB COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (See Box II).

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/31530

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/14, 9/20
US CL : 424/489, 464, 465

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/489, 464, 465

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST/ WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98/03064 A1 (FMC CORPORATION) 29 January 1998 (28.01.1998), page 4, lines 25-30, page 7, lines 4-36, page 9, lines 15, 30, 31, page 6, line 29 - page 7, line 2, page 4, lines 1-15.	1-41

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

14 December 2001 (14.12.2001)

Date of mailing of the international search report

12 FEB 2002

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Amy Pulliam *Felicia D. Roberts for*

Telephone No. 703-308-1235

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

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CT 2545ACIP

IN THE UNITED STATES RECEIVING OFFICE

International Application No.: PCT/US01/31530
International Filing date: 09 October 2001
Priority Date: ---
Applicants: Bristol-Myers Squibb Company
For: Flashmelt Oral Dosage Formulation

Mail Stop PCT, Attn: IPEA/US
Attention: Amy Pulliam
Commissioner for Patents
P. O. Box 1450
Arlington, VA 22313-1450

Dear Sir:

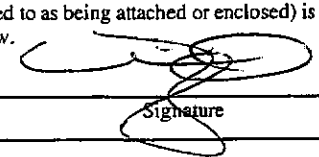
REPLY TO FIRST WRITTEN OPINION
PURSUANT TO PCT RULE 66.3

This communication is Applicants' Reply in response to the International Preliminary Examining Authority's First Written Opinion providing a reasoned statement under Rule 66.2(a)(ii) regarding the novelty, inventive step or industrial applicability of Applicants' invention. The First Written Opinion was mailed 05 September 2003 and has a reply deadline of two months ending 05 November 2003.

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being facsimile transmitted to 703-305-3230 at the Patent and Trademark Office on the date shown below.

Shah R. Makujina
Type or print name


Signature

11/3/2003
Date

Remarks

Claims 1-45 were said to have lacked inventive step under PCT Article 33(3) over WO 98/03064 to FMC Corporation (hereinafter "Sullivan"). Applicants respectfully traverse. Provided hereinbelow are some but not necessarily all of the examples which typify why Applicants' invention possesses the necessary inventive step for patentability over Sullivan.

First, Sullivan is a non-analogous art reference because it is not directed to flashmelt pharmaceutical formulations as is Applicants' invention, but is simply directed to immediate release tablet formulations that are meant to be swallowed. The two are in entirely different classes and the technology suitable for one class would not suggest to anyone skilled in the art that it would be useful in the other. A thorough reading of Sullivan will reveal that it simply does not teach or suggest that its methods can be used to make a *flashmelt* (orally disintegrating tablets) pharmaceutical preparation as do Applicants. Applicants' invention is directed to a pharmaceutical formulation that allows for rapid disintegration of the dosage form on a patient's *tongue*. The only "rapid disintegration" Sullivan discloses is that which occurs in a *beaker*. No where in Sullivan is it taught or suggested that the formulations disclosed therein will rapidly dissolve on the tongue of a patient. Instead, Sullivan's tablets are intended to be swallowed. This is supported by the fact that Sullivan is only able to assert that their formulations will disintegrate when *repeatedly agitated* after being placed in nearly a liter of water heated to 37 °C. (10:16-17) *See* USP 701 XXII Disintegration Test. Even under these conditions, many of Sullivan's examples take several minutes to disintegrate. Applicants' invention falls in an altogether different class because it allows for rapid disintegration (less than one minute) on the tongue of the patient. Thus, Applicants show inventive step over Sullivan.

Second, Sullivan is primarily directed to substituting costly superdisintegrants with less expensive "co-disintegrants" in an effort to cut costs in agricultural preparations. Sullivan explains,

[i]t will be understood, however, that in many applications, particularly those used in relatively low unit cost formulations such as in the agricultural field, a *less-than-optimum* disintegration rate may be justified if there is a sufficient cost saving. (2:27-29). (emphasis added)

Thus, Sullivan plainly admits that its method, may result in suboptimal disintegration times which would not be desirable in Applicants' strict pharmaceutical context. Thus, Applicants again show inventive step over Sullivan.

Third, Sullivan speculates that any number of ingredients can be added to the composition including

lubricants, glidants, *dispersants*, suspending agents, surfactants, and fillers or auxillary binders, which are preferably employed in relatively small amounts, *if any*, i.e., zero up to about 20% by weight of the total solid dosage form more often less than about 10% by weight. However, this amount is *not* critical and may comprise as much as a major proportion by weight . . . (6:23-31) (emphasis added)

Again, this does not suggest let alone teach Applicants' specifically claimed combination of excipients. Instead, Sullivan merely conjectures about a myriad of excipients that a pharmaceutical development scientist could experiment with. Such a disclosure cannot form the basis for a proper inventive step rejection and therefore, Applicants show inventive step over Sullivan.

Fourth, Sullivan mentions "dry granulation" in a laundry-list of suitable tableting methods, but qualifies this in such a manner that one skilled in the art would not be led to believe that this art-preferred low-maintenance tableting method is achievable by the teachings therein. Sullivan states,

[t]he selection of the method depends primarily on the active agent, the ability of the mixture of the disintegrants and active agent to flow freely in the tableting machine or extruder, and the cohesiveness of the ingredients. If the active agent can be admixed with the disintegrants to produce a free flowing, dense powder, the mixture can be directly compressed. (4:7-10)

Sullivan does nothing more than pose questions using conditional "if then" statements. It does not teach or suggest that his method will *with any reasonable certainty* allow one skilled in the art to successfully use the preferred method of direct compression and dry granulation. Contrary to Sullivan's lack of teaching in this regard, Applicants explicitly state that "a decided advantage of the formulation of the present invention is that it can be dry-granulated into stable, fine granules that can be directly compressed into pharmaceutically elegant flash-melt oral

Reply to Written Opinion
PCT/US01/31530
Page 4

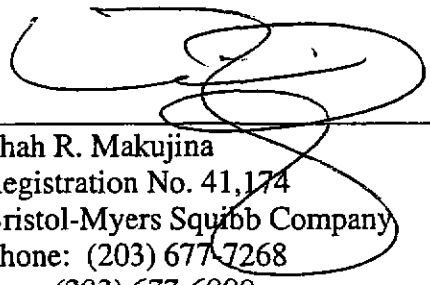
125
CT 2545A CH

dosage forms, e.g. tablets, caplets, wafers and the like." (16:1-4) Thus, Applicants show inventive step over Sullivan.

In light of the above, Applicants submit that Sullivan does not render the claimed invention unpatentable for lack of inventive step over Sullivan. Instead, Applicants submit that the claims plainly show inventive step over Sullivan and therefore are patentable. Applicants therefore respectfully request that the arguments contained herein be considered by the International Preliminary Examining Authority in rendering any Second Written Opinion in accordance with Applicants' position.

Respectfully submitted,

Dated: 11/3/2003



Shah R. Makujina
Registration No. 41,174
Bristol-Myers Squibb Company
Phone: (203) 677-7268
Fax: (203) 677-6900

PATENT COOPERATION TREATY

126
4
X

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24.2(a))

RECEIVED
Int'l Patent Law

DEC 04 2001 (SRM)

To:

MAKUJINA, Shah, R.
Bristol-Myers Squibb Company
Laurenceville-Princeton Road
P.O. Box 4000
Princeton, NJ 08543-4000
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 22 November 2001 (22.11.01)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference CT2545ACIP	International application No. PCT/US01/31530

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

BRISTOL-MYERS SQUIBB COMPANY (all designated States)

International filing date : 09 October 2001 (09.10.01)
 Priority date(s) claimed :
 Date of receipt of the record copy by the International Bureau : 08 November 2001 (08.11.01)
 List of designated Offices :

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW
 EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR
 OA : BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
 National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, 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, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW

RECEIVED**ATTENTION**

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Applicant's Information Sheet.

- ☒ time limits for entry into the national phase
☒ confirmation of precautionary designations
☐ requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

David LOPEZ-RAMIREZ

Telephone No. (41-22) 338.83.38

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. **It is the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

TRANSMITTAL LETTER TO THE UNITED STATES RECEIVING OFFICE

PTO-1382 (Rev. 4-1995) (Modified)

PCTUS2.FRP /REV03

Date	09 Oct 2001
International Application No.	
Attorney Docket No.	CT2545ACIP

I. Certification under 37 CFR 1.10 (if applicable)

EL750821095US
Express Mail mailing number

09 October 2001
Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Assistant Commissioner for Patents, Washington, D.C. 20231.

Signature of person mailing correspondence

Shah R. Makujina
Typed or printed name of person mailing correspondence

II. ☒ New International Application

TITLE	Flashmelt Oral Dosage Formulation
-------	-----------------------------------

Earliest priority date (Day/Month/Year)
--

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

- A. ☐ The invention disclosed was not made in the United States.
- B. ☐ There is no prior U.S. application relating to this invention.
- C. ☐ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. (NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority).

application no.		filed on	
application no.		filed on	

- D. ☐ The present international application ☐ is identical ☐ contains less subject matter than that found in the prior U.S. application(s) identified in paragraph C.
- E. ☐ The present international application ☐ contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages and ☐ DOES NOT ALTER ☐ MIGHT BE CONSIDERED TO ALTER the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15

III. ☐ A Response to an Invitation from the RO/US. The following document(s) is (are) enclosed:

- A. ☐ A Request for An Extension of Time to File a Response
- B. ☐ A Power of Attorney (General or Regular)
- C. ☐ Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

- D. ☐ Submission of Priority Documents

Priority document		Priority document	
-------------------	--	-------------------	--

- E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☐ A Request for Rectification under PCT 91 ☐ A Petition ☐ A Sequence Listing Diskette

V. ☐ Other (please specify):

The person signing this form is the:

☐ Applicant
☒ Attorney/Agent (Reg. No.) 41,174
☐ Common Representative

Shah R. Makujina

Typed name of signer

Signature

U.S. Department of Commerce: Patent and Trademark Office

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) CT2545ACIP

Box No. I TITLE OF INVENTION Flashmelt Oral Dosage Formulation	
Box No. II APPLICANT ☐ This person is also inventor	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) BRISTOL-MYERS SQUIBB COMPANY Lawrenceville-Princeton Road P. O. Box 4000 Princeton, New Jersey 08543-4000 United States of America	
Telephone No. 609-252-3745	
Facsimile No. 609-252-4526	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: US	State (that is, country) of residence: US
This person is applicant for the purposes of: ☒ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) KOTHARI, Sanjeev 99 Harvard Circle Princeton, New Jersey 08540 United States of America	
This person is: ☐ applicant only ☐ applicant and inventor ☒ inventor only (If this check-box is marked, do not fill in below.)	
Applicant's registration No. with the Office	
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) MAKUJINA, Shah R. Bristol-Myers Squibb Company Lawrenceville-Princeton Road P. O. Box 4000 Princeton, New Jersey 08543-4000 United States of America	
Telephone No. 203-677-7268	
Facsimile No. 203-677-6877	
Teleprinter No.	
Agent's registration No. with the Office 41,174	
☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTOR(S)*If none of the following sub-boxes is used, this sheet should not to be included in the request.*

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

DESAI, Divyakant
19 Greenfield Drive, North
West Windsor, New Jersey 08550
United States of America

This person is:

- ☐ applicant only
☐ applicant and inventor
☒ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|---|--|--|
| ☒ AE United Arab Emirates | ☒ GH Ghana | ☒ MX Mexico |
| ☒ AG Antigua and Barbuda | ☒ GM Gambia | ☒ MZ Mozambique |
| ☒ AL Albania | ☒ HR Croatia | ☒ NO Norway |
| ☒ AM Armenia | ☒ HU Hungary | ☒ NZ New Zealand |
| ☒ AT Austria | ☒ ID Indonesia | ☒ PL Poland |
| ☒ AU Australia | ☒ IL Israel | ☒ PT Portugal |
| ☒ AZ Azerbaijan | ☒ IN India | ☒ RO Romania |
| ☒ BA Bosnia and Herzegovina | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BB Barbados | ☒ JP Japan | |
| ☒ BG Bulgaria | ☒ KE Kenya | ☒ SD Sudan |
| ☒ BR Brazil | ☒ KG Kyrgyzstan | ☒ SE Sweden |
| ☒ BY Belarus | ☒ KP Democratic People's Republic of Korea | ☒ SG Singapore |
| ☒ BZ Belize | ☒ KR Republic of Korea | ☒ SI Slovenia |
| ☒ CA Canada | ☒ KZ Kazakhstan | ☒ SK Slovakia |
| ☒ CH & LI Switzerland and Liechtenstein | ☒ LC Saint Lucia | ☒ SL Sierra Leone |
| ☒ CN China | ☒ LK Sri Lanka | ☒ TJ Tajikistan |
| ☒ CO Colombia | ☒ LR Liberia | ☒ TM Turkmenistan |
| ☒ CR Costa Rica | ☒ LS Lesotho | ☒ TR Turkey |
| ☒ CU Cuba | ☒ LT Lithuania | ☒ TT Trinidad and Tobago |
| ☒ CZ Czech Republic | ☒ LU Luxembourg | ☒ TZ United Republic of Tanzania |
| ☒ DE Germany | ☒ LV Latvia | ☒ UA Ukraine |
| ☒ DK Denmark | ☒ MA Morocco | ☒ UG Uganda |
| ☒ DM Dominica | ☒ MD Republic of Moldova | ☐ US United States of America |
| ☒ DZ Algeria | ☒ MG Madagascar | ☒ UZ Uzbekistan |
| ☒ EC Ecuador | ☒ MK The former Yugoslav Republic of Macedonia | ☒ VN Viet Nam |
| ☒ EE Estonia | ☒ MN Mongolia | ☒ YU Yugoslavia |
| ☒ ES Spain | ☒ MW Malawi | ☒ ZA South Africa |
| ☒ FI Finland | | ☒ ZW Zimbabwe |
| ☒ GB United Kingdom | | |
| ☒ GD Grenada | | |
| ☒ GE Georgia | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☒ GQ Equatorial Guinea ☐
- ☒ PH Philippines ☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1)				
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA/ US

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

Number of
declarations

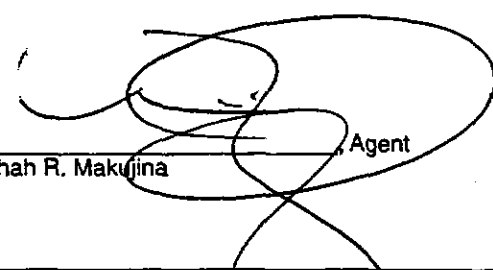
- ☐ Box No. VIII (i) Declaration as to the identity of the inventor :
- ☐ Box No. VIII (ii) Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent :
- ☐ Box No. VIII (iii) Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application :
- ☐ Box No. VIII (iv) Declaration of inventorship (only for the purposes of the designation of the United States of America) :
- ☐ Box No. VIII (v) Declaration as to non-prejudicial disclosures or exceptions to lack of novelty :

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:		This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):	Number of items
(a) the following number of sheets in paper form:		1. ☒ fee calculation sheet	M
request (including declaration sheets)	: 5	2. ☒ original separate power of attorney	
description (excluding sequence listing part)	: 47	3. ☐ original general power of attorney	
claims	: 10	4. ☐ copy of general power of attorney; reference number, if any:	
abstract	: 1	5. ☐ statement explaining lack of signature	
drawings	: 7	6. ☐ priority document(s) identified in Box No. VI as item(s):	
Sub-total number of sheets	: 70	7. ☐ translation of international application into (language):	
sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)	:	8. ☐ separate indications concerning deposited microorganism or other biological material	
Total number of sheets	: 70	9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))	
(b) sequence listing part of description filed in computer readable form		(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)	
(i) ☐ only (under Section 801 (a)(i))		(ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter	
(ii) ☐ in addition to being filed in paper form (under Section 801 (a)(ii))		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	
Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(ii), in right column):		10. ☐ other (specify):	
Figure of the drawings which should accompany the abstract:		Language of filing of the international application: English	

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).


 Shah R. Makujina, Agent

For receiving Office use only		2. Drawings: ☐ received: ☐ not received:
1. Date of actual receipt of the purported international application:		
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA/	6. ☐ Transmittal of search copy delayed until search fee is paid	

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International Application No.

Date stamp of the receiving Office

Applicant's or agent's
file reference

CT2545ACIP

Applicant

Bristol-Myers Squibb Company

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE

240.00

T

2. SEARCH FEE

700.00

S

International search to be carried out by ISA/US

(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

Where item (b) of Box No. IX applies, enter Sub-total number of sheets }
Where item (b) of Box No. IX does not apply, enter Total number of sheets }

b1 first 30 sheets 382.00 b1

b2 28 x 9.00 = 252.00 b2
number of sheets fee per sheet

b3 additional component (only if sequence listing part of description
is filed in computer readable form under Section 801(a)(i), or both
in that form and on paper, under Section 801(a)(ii)):

400 x = b3
fee per sheet

Add amounts entered at b1, b2 and b3 and enter total at B 634.00 B

Designation Fees

The international application contains 111 designations.
6 x 82.00 =
number of designation fees amount of designation fee

payable (maximum 6)

492.00 D

Add amounts entered at B and D and enter total at I 1,126.00 I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT (if applicable) P

5. TOTAL FEES PAYABLE

2,066.00

TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☒ authorization to charge

☐ postal money order

☐ cash

☐ coupons

☐ cheque

☐ bank draft

☐ revenue stamps

☐ other (specify):

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all receiving Offices)

☒ Authorization to charge the total fees indicated above.

☒ (This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

☐ Authorization to charge the fee for priority document.

Receiving Office: RO/

Deposit Account No.: 19-3880

Date: 09 Oct 2001

Name: Shah R. Mokujina

Signature: [Signature]

PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) (Names should be indicated as they appear in the request):

Bristol-Myers Squibb Company

hereby appoints (appoint) the following person as:



agent



common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ALGIERI, Aldo A.; BABAJKO, Suzanne; BABCOCK, Timothy; D'AMICO, Stephen; DAVIS, Stephen; BUCHHOLZ, Briana; DUBOFF, Samuel J.; FURMAN, Theodore; GIBBONS, Maureen; HERMENA, Ronald S.; KILCOYNE, John; KLEIN, Christopher; KRIEGER, Stuart; LANGE, Keith; LOPEZ, Gabriel; MAKUJINA, Shah; MATHIAS, Maria; MORSE, David M.; MCNEIL, Scott A.; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; RYAN, Richard P.; SHER, Audrey; SWITZER, Joan; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia; all of Bristol-Myers Squibb Company, P.O. Box 4000, Lawrenceville and Princeton Road, Princeton, New Jersey 08543-4000, United States of America

to represent the undersigned before



all the competent International Authorities



the International Searching Authority only



the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention: Flashmelt Oral Dosage Formulation

Applicant's or agent's file reference: CT2545ACIP

International application number (if already available):

filed with the following Office United States Patent and Trademark Office as receiving Office and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) (where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power):

David M. Morse
David M. Morse, Patent Counsel

Date: October 5, 2001

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30

CERTIFICATION

The undersigned, being the Executive Vice President and General Counsel of Bristol-Myers Squibb Company, hereby designates:

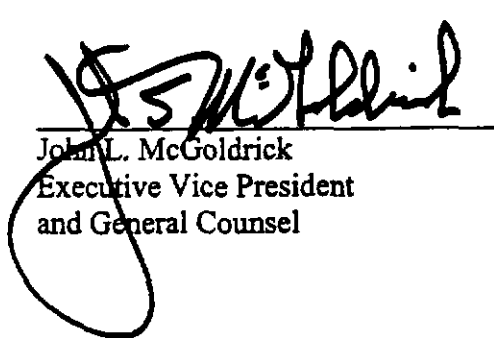
Marla J. Mathias

Stephen B. Davis

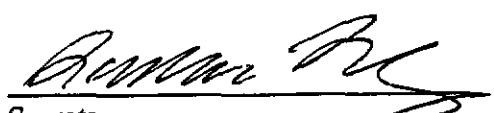
David M. Morse

(a) to present to the Patent, Trademark, Copyright and similar Government Offices of all countries or to any competent authority, all original, divisional, continuation and reissue applications, petitions and requests in the name of Bristol-Myers Squibb Company and its subsidiary companies, for letters patent for inventions, utility models, industrial models and designs and improvements or additions thereof, trademarks and copyrights: (b) to initiate and prosecute oppositions and appeals: (c) to appear before all officers duly authorized, all Ministers, Bureaus, Clerks' Offices and Commissions or Commissioners that may be necessary: (d) to sign and approve on behalf of this corporation all documents and powers of attorney which in the judgment of the authorized individuals may be necessary or desirable to carry out the powers hereby conferred: (e) to request all proceedings: (f) to pay over or withdraw all taxes, obtain receipts therefor and give discharge: (g) to withdraw applications and all documents relating thereto: (h) to commence proceedings against infringers and assure the defense in infringement actions: and (i) generally to do all that in the judgment of the authorized individual may be necessary to secure the granting of the privileges above-mentioned.

IN WITNESS WHEREOF, I have placed my hand and caused the seal of the Company to be affixed hereto on this 3rd day of Dec. 2000.



John L. McGoldrick
Executive Vice President
and General Counsel



Secretary

137
CT 2545A CIP

IN THE UNITED STATES RECEIVING OFFICE

International Application No.: PCT/US01/31530
International Filing date: 09 October 2001
Priority Date: ---
Applicants: Bristol-Myers Squibb Company
For: Flashmelt Oral Dosage Formulation

Box PCT
Attention: RO/US, D. Procter
Assistant Commissioner for Patents
P. O. Box 2327
Arlington, VA 22202

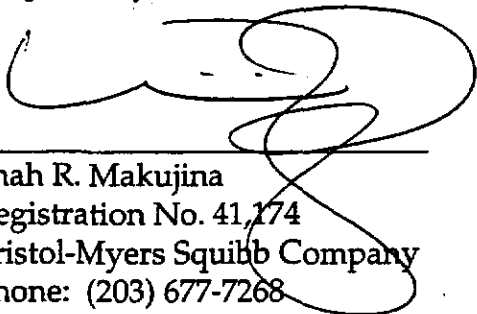
Dear Sir:

**RESPONSE TO INVITATION TO CORRECT DEFECTS
IN THE INTERNATIONAL APPLICATION**

In response to the invitation to correct defects mailed November 6, 2001, which has a one-month deadline for reply, regarding the international application noted above, enclosed herewith are seven replacement formal drawings for the international application. It is believed that these replacement formal drawings correct the indicated defect.

Respectfully submitted,

Dated: 30 NOV 2001


Shah R. Makujina
Registration No. 41,174
Bristol-Myers Squibb Company
Phone: (203) 677-7268
Fax: (203) 677-6900

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EL442237295415
Express Mail Label Number

30 NOV 2001
Date of Deposit

I TENT COOPERATION TREA'

From the RECEIVING OFFICE

To: SHAH R. MAKUJINA BRISTOL-MYERS SQUIBB COMPANY LAWRENCEVILLE-PRINCETON ROAD P.O. BOX 4000 PRINCETON NJ 08543-4000	RECEIVED Int'l Patent Law NOV 14 2001 Docketed Item <i>RES.</i> Due Date 12/6/01 (PCT Articles 3(4)(i) and 14(1) and Rule 26)	145 PCT INVITATION TO CORRECT DEFECTS IN THE INTERNATIONAL APPLICATION
		Date of mailing (day/month/year) 06 NOV 2001
Applicant's or agent's file reference CT2545ACIP		REPLY DUE within ONE MONTH from the above date of mailing
International application No. PCT/US01/31530		International filing date (day/month/year) 09 OCT 01
Applicant BRISTOL-MYERS SQUIBB COMPANY		

1. ☒ The applicant is hereby invited, within the time limit indicated above, to correct, in the international application as filed, the defects specified on the attached
 - ☐ Annex A
 - ☐ Annex B1 (text matter of the international application as filed)
 - ☒ Annex C1 (drawings of the international application as filed)
2. ☐ The applicant is hereby invited, within the time limit indicated above, to correct, in the translation of the international application furnished under Rule 12.3, the defects specified on the attached
 - ☐ Annex A
 - ☐ Annex B2 (text matter of the translation of the international application)
 - ☐ Annex C2 (drawings of the translation of the international application)

Additional observations (if necessary):

HOW TO CORRECT THE DEFECTS?

Correction must be submitted by filing a replacement sheet embodying the correction and a letter accompanying the replacement sheet, which shall draw attention to the difference between the replaced sheet and the replacement sheet. A correction may be stated in a letter only if it is of such a nature that it can be transferred from the letter to the record copy without adversely affecting the clarity and direct reproducibility of the sheet onto which the correction is to be transferred (Rule 26.4).

ATTENTION

Failure to correct the defects will result in the international application being considered withdrawn by this receiving Office (see Rule 26.5 for further details).

A copy of this invitation and any attachments has been sent to the International Bureau

☐ and the International Searching Authority.

Name and mailing address of the receiving Office Assistant Commissioner for Patents Box PCT Washington, D.C. 20231 Facsimile No.	Authorized officer <i>dp</i> Chief of PCT PCT Operations - (APD Team) (703) 305-3688 (703) 305-0280 FAX Telephone No.
---	---

ANNEX C1 TO FORM PCT/RO/106

International application No.

PCT/US01/31530

The receiving Office has found that, with regard to the presentation of the drawings of the international application as filed, the physical requirements are not complied with to the extent that compliance therewith is necessary for:

1. ☒ reasonably uniform international publication (Rules 11 and 26.3(a)(i)) (defects to be specified):

Sheets containing drawings:

- a. ☐ the sheets do not admit of direct reproduction.
- b. ☐ the sheets are not free from creases, cracks, folds.
- c. ☐ one side of the sheets is not left unused.
- d. ☐ the paper of the sheets is not flexible/strong/white/smooth/non-shiny/durable.
- e. ☐ the drawings do not commence on a new sheet.
- f. ☐ the sheets are not connected as prescribed (Rule 11.4(b)).
- g. ☐ the sheets are not A4 size (29.7cm x 21cm).
- h. ☐ the minimum margins on the sheets are not as prescribed Fig. (top: 2.5cm; left side: 2.5cm; right side: 1.5cm; bottom: 1cm).
- i. ☐ the file reference number indicated on the sheets does not appear in the left-hand corner of the sheets, within 1.5cm of the top of the sheets.
- j. ☐ the file reference number exceeds the maximum of 12 characters.
- k. ☐ the sheets are not free from frames around usable or used surfaces.
- l. ☒ the sheets are not numbered in consecutive Arabic numerals (e.g. 1/3, 2/3, 3/3).
- m. ☐ the sheet numbers are not centered at the top or bottom of the sheets.
- n. ☐ the sheet numbers are in the margin (see h. above for the size of the margins).
- o. ☐ the sheets contain alterations/overwritings/interlineations/too many erasures.
- p. ☒ the sheets contain photocopy marks.

Drawings (Rule 11.13):

- a. ☐ do not admit of direct reproduction.
- b. ☐ contain unnecessary text matter.
- c. ☐ contain words so placed as to prevent translation without interference with lines thereof.
- d. ☒ are not executed in durable black color; the lines are not uniformly thick and well-defined. Fig. ALL
- e. ☐ contain cross-sections not properly hatched.
- f. ☐ would not be properly distinguishable in reduced reproduction.
- g. ☐ contain scales not represented graphically.
- h. ☒ contain numbers, letters and reference lines lacking simplicity and clarity. Fig. ALL
- i. ☐ contain lines drafted without the aid of drafting instruments.
- j. ☐ contain disproportionate elements of a figure not necessary for clarity.
- k. ☐ contain numbers and letters of height less than 0.32 cm.
- l. ☐ contain letters not conforming to the Latin, and where customary, Greek alphabets.
- m. ☐ contain figures on two or more sheets which form a single complete figure but which are not able to be assembled without concealing parts thereof.
- n. ☐ contain figures which are not properly arranged and clearly separated.
- o. ☐ contain different figures not numbered in consecutive Arabic numerals.
- p. ☐ contain different figures not numbered independent of the numbering of the sheets.
- q. ☐ are not restricted to reference signs mentioned in the description.
- r. ☐ do not contain reference signs that are mentioned in the description.
- s. ☐ contain the same feature denoted by different reference signs.
- t. ☐ are not arranged in an upright position, clearly separated from one another.
- u. ☐ are not presented sideways with the top of the figures at the left side of the sheets.

2. ☐ satisfactory reproduction (Rules 11 and 26.3(b)(i)).

Further observations (if necessary):

Shading or solid black objective figure number

New drawings are required

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
SHAH R. MAKUJINA
BRISTOL-MYERS SQUIBB COMPANY
LA WRENCEVILLE-PRINCETON ROAD
P.O. BOX 4000
PRINCETON, NJ 08543-4000

RECEIVED
BRIS PATENT LAW

PCT
SEP 08 2003

WRITTEN OPINION
Docketed Item

Due Date (PCT Rule 66)

Date of Mailing
(day/month/year)

05 SEP 2003

Applicant's or agent's file reference

CT2545ACIP

REPLY DUE

within 2 months/days from
the above date of mailing

International application No.

International filing date (day/month/year)

Priority date (day/month/year)

PCT/US01/31530

09 October 2001 (09.10.2001)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 9/14, 9/20 and US Cl.: 424/489, 464, 465

Applicant

BRISTOL-MYERS SQUIBB COMPANY

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 09 February 2004 (09.02.2004)

Name and mailing address of the IPEA/US
Mail Stop PCT, Attn: IPEA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer
Amy Pulliam

Telephone No. 703-308-1235

WRITTEN OPINION

International application No.

PCT/US01/31530

I. Basis of the opinion

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed
- ☒ the description:
 pages 1-47, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____
- ☒ the claims:
 pages 48-57, as originally filed
 pages NONE, as amended (together with any statement) under Article 19
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____
- ☒ the drawings:
 pages 1-7, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____
- ☐ the sequence listing part of the description:
 pages NONE, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
 These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."

WRITTEN OPINION

International application No.
PCT/US01/31530

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims <u>1-45</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-45</u>	NO
Industrial Applicability (IA)	Claims <u>1-45</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-45 lack an inventive step under PCT Article 33(3) as being obvious over WO 98/03064 to FMC CORPORATION. FMC CORPORATION teach a composition useful as an excipient for increasing the disintegration rate of solid dosage forms of active agents in pharmaceutical formulations. FMC CORPORATION teaches that superdisintegrants which may be employed include croscarmellose sodium, crospovidone, sodium starch glycolate and the like (page 4, lines 25-30). Additionally, FMC CORPORATION teaches the use of lubricants, such as talc, and glidants such as silica (page 7, lines 4-10). Additionally, the reference teaches that as co-disintegrants, substances such as diamomaceous silica (earth) and calcium silicate can be used (page 5, lines 4-9). FMC CORPORATION also teaches the use of binders, such as microcrystalline cellulose or lactose (page 9, lines 30-31). Therefore, FMC CORPORATION teaches a composition for increased disintegration comprising the components claimed by Applicant.

FMC CORPORATION does not specifically teach the active agents claimed by Applicant. However, FMC CORPORATION teaches an excipient for use in general pharmaceutical formulations. One of ordinary skill in the art would expect this formulation to be used with pharmaceutical active agents in general. Absent a showing of criticality, it is within the skill of the ordinary worker to use well known active agents in a generically disclosed formulation.

Additionally, FMC CORPORATION does not teach all of the particulars regarding the calcium silicate. It is the position of the examiner, however, that FMC CORPORATION teaches the use of calcium silicate, for the same reason claimed by Applicant. Calcium silicate will have the same properties, regardless of the formulation it is found in. Therefore, the particular properties claimed by Applicant, absent a showing of criticality or unexpected results, is not found to render novelty to the claims. Therefore, this invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-45 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

WRITTEN OPINION

150
International application No.
PCT/US01/31530

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

MAKUJINA, Shah, R.
Bristol-Myers Squibb Company
Laurenceville-Princeton Road
PO Box 4000
Princeton, NJ 08543-4000
ETATS-UNIS D'AMERIQUE

MAY 05 2003

Date of mailing(day/month/year) 17 April 2003 (17.04.03)		Docketed Item	
Applicant's or agent's file reference CT2545ACIP		Due Date Attorney (SRM)	
International application No. PCT/US01/31530		International filing date(day/month/year) 09 October 2001 (09.10.01)	Priority date(day/month/year)
Applicant BRISTOL-MYERS SQUIBB COMPANY			

IMPORTANT NOTICE

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

KP, KR

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 17 April 2003 (17.04.03) under No. 03/030868
4. **TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase**

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Judith Zahra

Facsimile No.(41-22) 740.14.35

Telephone No.(41-22) 338.91.11

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/31530

A. CLASSIFICATION OF SUBJECT MATTER												
IPC(7) : A61K 9/14, 9/20												
US CL : 424/489, 464, 465												
According to International Patent Classification (IPC) or to both national classification and IPC												
B. FIELDS SEARCHED												
Minimum documentation searched (classification system followed by classification symbols) U.S. : 424/489, 464, 465												
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched												
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EAST/ WEST												
C. DOCUMENTS CONSIDERED TO BE RELEVANT												
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.										
Y	WO 98/03064 A1 (FMC CORPORATION) 29 January 1998 (28.01.1998), page 4, lines 25-30, page 7, lines 4-36, page 9, lines 15, 30, 31, page 6, line 29 - page 7, line 2, page 4, lines 1-15.	1-41										
☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.												
* Special categories of cited documents: <table border="0"> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"E" earlier application or patent published on or after the international filing date</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	"P" document published prior to the international filing date but later than the priority date claimed	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention											
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone											
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art											
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family											
"P" document published prior to the international filing date but later than the priority date claimed												
Date of the actual completion of the international search 14 December 2001 (14.12.2001)		Date of mailing of the international search report 12 FEB 2002										
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230		Authorized officer Amy Pulliam <i>Felicia D. Roberts for</i> Telephone No. 703-308-1235										

183
153

04-32557

SUPERINDUSTRIA Y COMERCIO

SISTEMA DE REGISTRO I

Fecha 19/05/2004

| MANTENIMIENTO DE PROTOCOLOS

|Numero : 19358

|Fecha : 07/05/1999

|Conferido: BRISTOL-MYERS SQUIBB COMPANY
|

|Pais : US ESTADOS UNIDOS DE AMERICA

|Ciudad : 82 PRINCETON, NEW JERSEY

|Represent: S Sustituir: S Desistir: S

No. Radicacion: 99 28346 Clase: 0 Seev: 0 Seac: 0

|scncia Codigo Ctr

Nombre

| 1 340 A CASTRO DUQUE RAMIRO

| 2 3002 GOMEZ MEJIA HECTOR
|

| Encontrados (1/1) registro(s)

138
154

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

PATENTE DE INVENCION

MODELO DE UTILIDAD

USUARIO RADICADOR

- Indicación de que se solicita la concesión de una patente.
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.
- Descripción de la invención.
- Dibujos de ser estos pertinentes.
- Comprobante de Pago de las tasas establecidas.

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COMPLETA ()

INCOMPLETA () ()

DISEÑO INDUSTRIAL ()

- Indicación de que se solicita el registro de Diseño Industrial
- Datos de identificación del solicitante o de la persona que presenta la solicitud.
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.
- Comprobante de pago de las tasas establecidas

() ()
() ()
() ()
() ()

COMPLETA ()

INCOMPLETA () ()

ESQUEMA DE TRAZADO ()

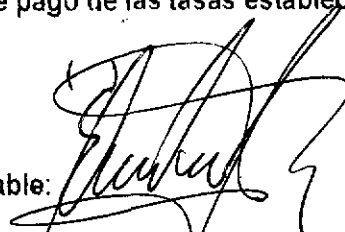
- Indicación de que solicita el registro de un Esquema de trazado.
- Datos de identificación del solicitante o de la persona que presenta la solicitud.
- Representación gráfica del esquema de trazado
- Comprobante de pago de las tasas establecidas.

() ()
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() ()

COMPLETA

INCOMPLETA () ()

Firma Responsable:



SUPERINDUSTRIA Y COMERCIO

Radicacion : 04032557 00000000

Folios: 152

Fecha:

Fecha (AMD): 2004-04-06 16:29:01

Trámite : 011 PCT-PATENT 379 FASE NACT 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES



2020
Bogotá, D.C.,

Doctor:
RAMIRO CASTRO DUQUE
Apoderado
BRISTOL-MYERS SQUIBB COMPANY

Oficio N° 05218

ASUNTO:	Radicación N°	04-32557
	Solicitud internacional	PCT/US01/31530
	Fecha inicio fase nacional	09/05/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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


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

El anterior requerimiento fue notificado por fijación en lista de fecha, 2-7 Mayo 2004

202060

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 382 2695
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia