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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

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REF:

EXPEDIENTE 06-038-472

TÍTULO SOLICITADO: "PROCESO PARA LA ELABORACIÓN DE
ARIPIPAZOL ESTÉRIL DE TAMAÑO DE
PARTÍCULA PROMEDIO DESEADO"

PUBLICACIÓN: GACETA 567 DE 31-08-2006, NÚMERO DE
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SOLICITANTE: BRISTOL-MYERS SQUIBB COMPANY

APODERADO: JUAN PABLO CADENA SARMIENTO

TRÁMITE: SUSTENTACIÓN DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, identificado como aparece al pie de mi firma, reconocido apoderado del opositor en el trámite de la referencia, estando dentro de los términos de la prórroga solicitada, por medio del presente escrito me permito ratificar y sustentar los argumentos del escrito de oposición, también radicado dentro del plazo de ley ante esa entidad.

I. RATIFICACIÓN

Reitero a su Despacho la solicitud de negar el beneficio patentario para la totalidad de las reivindicaciones contenidas en el expediente en referencia, por los argumentos que fueron expuestos en el escrito de oposición del 28 de noviembre de 2006.

En efecto, es evidente que en el estado del arte ya se encontraba la solicitud PCT WO 03/026659A1 "LOW HYGROSCOPIC ARIPIRAZOLE DRUG SUBSTANCE AND PROCESSES FOR THE PREPARATION THEREOF" publicada el 3 de abril de 2003, y con prioridades de 2001 y 2002, que revelaba ya la existencia de aripiprazol en forma de Hidrato y su caracterización fisicoquímica por métodos convencionales; en la página 11, líneas 8 a 23, describe Aripiprazol Hidrato A con un tamaño de partícula de 50 micrones o menos, 40 micrones o menos, 35 micrones o menos, 30 micrones o menos que, como se observa, sugiere tamaños de partícula en donde pueden encajar perfectamente los indicados en la solicitud en trámite, es decir, menor de 100 micrones y mayores de 25 micrones.

Otro punto importante para considerar es que en dicha anterioridad menciona que las formas hidratadas de Aripiprazol, más que ventajas, producen un gran número de inconvenientes tanto en la producción como en formulaciones basadas en el mismo, razón por la cual es del caso preguntarse: ¿La solicitud colombiana cumple el requisito de aplicación industrial? ¿Un formulador, teniendo en cuenta las desventajas que proporcionan esas formas hidratadas, incluiría este tipo de forma en sus composiciones? Como las respuestas son en ambos casos negativas, ruego al Despacho considerar que la solicitud que nos ocupa puede incumplir también el requisito de Aplicación Industrial.

Ahora bien, en lo referente a la forma de presentación de monohidrato de una molécula existente en el estado de la técnica como es Aripiprazol, es del caso recordar que nada tiene de novedoso o inventivo el hecho de que un principio activo se encuentre en forma monohidratada, pues resulta evidente que la hidratación o la deshidratación de moléculas son métodos ampliamente conocidos y empleados en la industria química.

Adicionalmente, es bien sabido que mediante la caracterización de simples modificaciones morfológicas en el hábito cristalino es fácil de obtener, como ocurre en este caso, una rápida y simple alteración del tiempo de cristalización, concepto obvio para un técnico en la materia y razón suficiente para reiterar la carencia de nivel inventivo envuelta en la presente solicitud.

En cuanto a los tamaños de partícula, es del caso recordar la Decisión contenida en la resolución N° 30887 del 26 de septiembre de 2002, por la cual se niega la

patente de invención a la solicitud 98005805 "Tabletas de Oxcarbazepina recubiertas de una película y método para la producción de estas formulaciones", en la cual se señaló que "no se traduce en ningún avance sobre el estado de la técnica el modificar una propiedad física de un sólido, como es su tamaño de partícula, con el fin de variar su perfil de disolución y determinar la variación de la biodisponibilidad, puesto que este fenómeno es perfectamente conocido y se encuentra al alcance de cualquier persona con mediana formación farmacotécnica" (Subrayado fuera del texto).

En consecuencia, lo anteriormente discutido y en unión a lo que se expresará en el siguiente punto, demuestra una vez más la falta de nivel inventivo de la solicitud colombiana en trámite.

II. COMPLEMENTO DE INFORMACIÓN

El proceso por el cual se obtienen los cristales de aripiprazol monohidratado en un tamaño de partícula entre 25 micrómetros y 100 micrómetros según las reivindicaciones 3 y 4 de la solicitud en trámite, referido como cristalización por colisión de chorro (Impinging jet crystallization procedure) y descrito en las reivindicaciones 1 a 23, es un procedimiento tecnológico conocido y manejado con bastante anterioridad en procedimientos de obtención de cristales de diversos tipos, tamaños de partícula y de gran variedad de sustancias tal y como se demuestra con los siguientes documentos:

- La patente Americana número 5,314,506 titulada **"CRYSTALLIZATION METHOD TO IMPROVE CRYSTAL STRUCTURE AND SIZE"** publicada el 24 de Mayo de 1994 revela un proceso para la cristalización de un compuesto orgánico farmacéuticamente útil que comprende la utilización de un flujo a presión de una solución elaborada a partir de un solvente y el compuesto orgánico farmacéuticamente útil, y un flujo a presión de un antisolvente, donde dichos flujos a presión colisionan creando una turbulencia alta en el punto de impacto, y donde dichos flujos a presión de solvente y antisolvente tienen una velocidad lineal suficiente para conseguir un intenso y alto micromezclado anterior a la nucleación, seguido de la nucleación y la directa producción de pequeños cristales, donde por lo menos el 95% de dichos cristales tienen un tamaño de partícula igual o menor a 25 micrómetros. Este proceso se refiere a

compuestos farmacéuticos seleccionados de simvastatina, lovastatina, Diltiazem maleato, entre otros y permite la cristalización directa de partículas de alta pureza y alta estabilidad.

- La patente Americana número **6,558,435** titulada **"REACTIVE CRYSTALLIZATION METHOD TO IMPROVE PARTICLE SIZE"** publicada el **06 de Mayo de 2003** revela un proceso para la síntesis y cristalización de un compuesto orgánico de uso farmacéutico, comprendiendo un primer flujo a presión de una solución que comprende un primer solvente y un primer intermediario y un segundo flujo a presión que comprende una segunda solución con un segundo solvente y un segundo intermediario, donde dichos flujos a presión se vierten diametralmente opuestos de tal manera que los flujos opuestos se encuentren en un punto de impacto¹ para crear una película vertical de impacto, creando una turbulencia en el punto de impacto bajo las condiciones de temperatura y presión que permiten la reacción de dichos primero y segundo intermediarios, para conseguir el producto; y que seleccionando el primer y segundo solventes se consigue que el producto sea insoluble en esta nueva mezcla entre el primer y segundo solventes; y que cada flujo a presión tiene la velocidad lineal suficiente para lograr un micromezclado de las soluciones iniciales, seguido por la reacción de primero y segundos intermediarios reactivos, seguida por la nucleación de dicho producto y por ultimo, la producción de cristales con un área superficial alta requerida para una buena biodisponibilidad.
- La patente Americana número **6,302,958** titulada **"SONIC IMPINGING JET CRYSTALLIZATION APPARATUS AND PROCESS"** publicada el **16 de Octubre de 2001** revela: Un nuevo aparato y proceso para obtener cristalización de cristales submicronizados y clasificados según tamaño, útiles en la elaboración de una composición farmacéutica. Los cristales submicronizados y clasificados según tamaño tienen un tamaño promedio de

¹ <http://www.thefreedictionary.com/impingement>.

Noun: 1. **Impingement** - influencing strongly; "they resented the impingement of American values on European culture"

encroachment, impact

influence - causing something without any direct or apparent effort

2. **Impingement** - a sharp collision produced by striking or dashing against something

impaction

crash, smash - the act of colliding with something; "his crash through the window"; "the fullback's smash into the defensive line".

menos de 1 micra, proporcionan un área superficial grande, estabilidad mejorada y alta pureza, y además, de produce cristales que mejoran la biodisponibilidad, aumenta la disolución, disminuye la tasa de descomposición y una vida o tiempo de almacenamiento más largo.

Estos documentos si bien es cierto no hacen referencia al principio activo Aripiprazol, permiten verificar que el procedimiento de cristalización utilizado en la patente Colombiana en trámite no es algo novedoso y si así lo fuere, no proporciona nivel inventivo al mismo; debe admitirse que existen algunas ligeras modificaciones, o variaciones a las condiciones inherentes a la misma técnica tales como temperaturas y presiones, solventes y antisolventes, sin embargo, la obtención de los cristales monohidratados de aripiprazol estériles (como se mencionan en la reivindicación 20 de la patente Colombiana en cuestión) puede derivarse directamente del estudio de documentos como estos.

Así mismo, es importante destacar que el uso de la energía sónica mencionada en la reivindicación 5 de la patente Colombiana en trámite, ya pertenecía al estado de la técnica si se tiene en cuenta que en la reivindicación 1 de la patente Americana US 6,302,958 antes citada, se utiliza energía sónica para favorecer la producción de cristales y que dice textualmente:

What is claimed is:

1. "A process for the crystallization of a pharmaceutical compound comprising positioning a tip of a sonication probe within a gap defined between two or more fluid jets positioned such that fluid jet streams which emerge from said fluid jets impinge in said gap creating a point of high turbulence at the point of impact of said fluid streams, each of said fluid streams having sufficient linear velocity to achieve high intensity micromixing of the solutions prior to nucleation, said sonication probe providing ultrasonic energy in the immediate vicinity of said impinging fluid streams so as to effect nucleation and the direct production of small crystals, at least 95% of said crystals having a diameter of less than 1 micron".

Que si se compara con la reivindicación 5 de la solicitud colombiana en trámite:

5. "Proceso como se define de conformidad con la reivindicación 1, caracterizado porque además incluye la etapa de proporcionar energía ultrasónica en la cercanía inmediata de las corrientes de chorro de colisión, para efectuar nucleación y la producción directa de cristales pequeños de aripiprazol.

Deja en evidencia que, adicional al empleo en ambos documentos de un proceso de "Impinging jet crystallization", existe una etapa de sonicación o de uso de energía sónica para efectuar nucleación y la producción directa de cristales pequeños.

- La publicación científica titulada: **INVESTIGATION OF IMPINGING-JET CRYSTALLIZATION WITH A CALCIUM OXALATE MODEL SYSTEM²** (Publicada el 18 de Julio de 2002) revela:

"Abstract:

An impinging-jet crystallizer was investigated in this work to assess its operational sensitivity and reproducibility for the production of small, monodisperse crystals using calcium oxalate, **a model system capable of forming multiple hydrates. The impinging-jet mixer provides rapid mixing of the reactant solutions through the impingement of two narrow reactant streams at high velocity.** Impinging jet linear velocity and postjetting conditions were studied, with the jet operated in nonsubmerged mode. **Hydrate form and crystal-size distribution (CSD) were determined** using optical microscopy and image analysis techniques. **The impinging jet consistently produced small, monodisperse crystals.** However, at a high level of supersaturation, slight variations in the CSD were observed for apparently identical conditions, suggesting a degree of sensitivity in the system that could lead to difficulty in its application. **An apparent trend between impinging-jet linear velocity and crystal size and number was observed, with more small crystals produced at higher linear velocity."**

Este documento perteneciente al estado del arte, además de confirmar la versatilidad de esta técnica -utilizada en solicitud colombiana en trámite (impinging jet crystallization procedure)- demuestra no solo las ventajas obviamente derivadas de la misma en cualquier proceso de cristalización

² Jean M. Hacherl, Edward L. Paul[†], Helen M. Buettner. Investigation of impinging-jet crystallization with a calcium oxalate model system. AIChE journal (AIChE j.) ISSN 0001-1541 CODEN AICEAC. 2003, vol. 49, n°9, pp. 2352-2362 [11 page(s) (article)] (29 ref.). Received: 18 July 2002; Revised: 19 May 2003. American Institute of Chemical Engineers, New York, NY, ETATS-UNIS (1955) (Revue).

donde se desee obtener cristales de forma y tamaño de partícula definidos, también deja ver la falta de nivel inventivo de la solicitud en trámite.

- La publicación científica titulada **“MODELING AND SIMULATION OF IMPINGING JET CRYSTALLIZERS”³**, aunque su publicación es posterior a la fecha de prioridad de la solicitud colombiana en trámite, es importante resaltar de él que la mayoría de su soporte bibliográfico es anterior a la fecha requerida y que además menciona que el impinging jet crystallizer se conoce por lo menos desde hace 10 años; veamos:

“El cristalizador de colisión de chorro (impinging jet crystallizer) desarrollado por Midler et al. hace más de una década, es reconocido como una tecnología de cristalización industrial altamente reproducible y confiable que produce pequeños cristales con una complicada distribución de tamaño (...) Esta tecnología esta siendo utilizada ampliamente por varios laboratorios farmacéuticos en su producción comercial de fármacos. (...) Numerosos estudios también han sido realizados fuera de la academia en la búsqueda de la industria de un profundo entendimiento de este procedimiento (impinging jet crystallization), el cual puede resultar en un mejor y eficiente proceso de desarrollo y optimización. Para varios antisolventes y sistemas de cristalización reactiva, la dependencia de la distribución del tamaño del cristal con la velocidad de flujo y las concentraciones iniciales han sido investigadas. **(subrayado y negrita fuera del texto).**

Las referencias relacionadas a continuación además de evocar el procedimiento de cristalización discutido, ratifica la anterioridad en el desarrollo y uso de dicho proceso:

1. Dauer, R., J.E. Mokrauer, and W.J. McKeel, **Dual jet crystallizer apparatus**, Merck & Co., Inc. U.S. Patent, 5,578,279, 1996.
2. Mahajan, A.J. and D.J. Kirwan, **Micromixing effects in a two-impinging-jets precipitator**. AIChE Journal, 1996. 42(7), 1801-1814.

³ Xing Yi Woo, Reginald B. H. Tan, Richard D. Braatz. Modeling and Simulation of Impinging Jet Crystallizers. Conferencia realizada en “Annual Meeting of Advances and Case Studies in Crystallization and Post Crystallization Processing.” 13 de Noviembre de 2006: 12:30 PM-3:00 PM Lombard (Hilton San Francisco).

3. Johnson, B.K. and R.K. Prud'homme, **Flash NanoPrecipitation of organic actives and block copolymers using a confined impinging jets mixer**. Australian Journal of Chemistry, 2003. 56(10), 1021-1024.
4. Johnson, B.K. and R.K. Prud'homme, **Chemical processing and micromixing in confined impinging jets**. AIChE Journal, 2003. 49(9), 2264-2282.
5. Mahajan, A.J. and D.J. Kirwan, **Nucleation and growth kinetics of biochemicals measured at high supersaturations**. Journal of Crystal Growth, 1994. 144(3-4), 281-290.

Por todo lo anterior reitero que la solicitud de la referencia incumple los requisitos materiales de patentabilidad establecidos por la Decisión 486 de 2000, razón por la cual no puede ser objeto de privilegio de patente de invención.

III. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de que el Despacho considere oficiosamente, en particular de las allegadas por el suscrito a los expedientes mencionados en este escrito, las siguientes:

- Solicitud Internacional PCT WO 03/026659 A1 **"LOW HYGROSCOPIC ARIPIRAZOLE DRUG SUBSTANCE AND PROCESSES FOR THE PREPARATION THEREOF"** publicada el 3 de abril de 2003, páginas 1 a 6, 11 a 13, 21 a 23.
- La patente Americana **US 5,314,506** titulada **"CRYSTALLIZATION METHOD TO IMPROVE CRYSTAL STRUCTURE AND SIZE"** publicada el 24 de Mayo de 1994. pg 1 y 11.
- La patente Americana **US 6,558,435** titulada **"REACTIVE CRYSTALLIZATION METHOD TO IMPROVE PARTICLE SIZE"** publicada el 06 de Mayo de 2003. pg. 1, 7, 8 y 9.
- La patente Americana número **6,302,958** titulada **"SONIC IMPINGING JET CRYSTALLIZATION APPARATUS AND PROCESS"** publicada el 16 de Octubre de 2001. pg 1 y 6.
- La publicación científica titulada: **INVESTIGATION OF IMPINGING-JET CRYSTALLIZATION WITH A CALCIUM XALATE MODEL SYSTEM**. Publicada el 18 de Julio de 2002.

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- Apartes publicados de la conferencia **"MODELING AND SIMULATION OF IMPINGING JET CRYSTALLIZERS"** realizada en "Annual Meeting of Advances and Case Studies in Crystallization and Post Crystallization Processing." El 13 de Noviembre de 2006, Lombard (Hilton San Francisco, USA).

Señor Superintendente,



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2,379,005 27 March 2002 (27.03.2002) CA

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: LOW HYGROSCOPIC ARIPIPRAZOLE DRUG SUBSTANCE AND PROCESSES FOR THE PREPARATION THEREOF

(57) Abstract: The present invention provides low hygroscopic forms of aripiprazole and processes for the preparation thereof which will not convert to a hydrate or lose their original solubility even when a medicinal preparation containing the aripiprazole anhydride crystals is stored for an extended period.

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DESCRIPTION

LOW HYGROSCOPIC ARIPIPRAZOLE DRUG SUBSTANCE AND
PROCESSES FOR THE PREPARATION THEREOF

DETAILED DESCRIPTION OF THE INVENTION

Field of the Invention

The present invention relates to an improved form of aripiprazole having reduced hygroscopicity and
5 processes for the preparation of this improved form.

Background of the Invention

Aripiprazole, 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydro carbostyryl or 7-{4-
10 [4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydro-2(1H)-quinolinone, is an atypical antipsychotic agent useful for the treatment of schizophrenia (U.S. 4,734,416 and U.S. 5,006,528). Schizophrenia is a common type of psychosis characterized by delusions,
15 hallucinations and extensive withdrawal from others. Onset of schizophrenia typically occurs between the age of 16 and 25 and affects 1 in 100 individuals worldwide. It is more prevalent than Alzheimer's disease, multiple sclerosis, insulin-dependent diabetes
20 and muscular dystrophy. Early diagnosis and treatment can lead to significantly improved recovery and outcome. Moreover, early therapeutic intervention can avert costly hospitalization.

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According to Example 1 of Japanese Unexamined Patent Publication No. 191256/1990, aripiprazole anhydride crystals are manufactured for example by reacting 7-(4-bromobutoxy)-3,4-dihydrocarbostyryl with 1-(2,3-dichlorophenylpiperidine and recrystallizing the resulting raw aripiprazole anhydride with ethanol. Also, according to the Proceedings of the 4th Japanese-Korean Symposium on Separation Technology (October 6-8, 1996), aripiprazole anhydride crystals are manufactured by heating aripiprazole hydrate at 80°C. However, the aripiprazole anhydride crystals obtained by the aforementioned methods have the disadvantage of being significantly hygroscopic.

The hygroscopicity of these crystals makes them difficult to handle since costly and burdensome measures must be taken in order ensure they are not exposed to moisture during process and formulation. Exposed to moisture, the anhydrous form can take on water and convert to a hydrous form. This presents several disadvantages. First, the hydrous forms of aripiprazole have the disadvantage of being less bioavailable and less dissoluble than the anhydrous forms of aripiprazole. Second, the variation in the amount of hydrous versus anhydrous aripiprazole drug substance from batch to batch could fail to meet specifications set by drug regulatory agencies. Third, the milling may cause the drug substance, Conventional Anhydride, to adhere to manufacturing equipment which

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may further result in processing delay, increased operator involvement, increased cost, increased maintenance and lower production yield. Fourth, in addition to problems caused by introduction of moisture during the processing of these hygroscopic anhydrides, the potential for absorbance of moisture during storage and handling would adversely affect the dissolubility of aripiprazole drug substance. Thus shelf-life of the product could be significantly decreased and/or packaging costs could be significantly increased. It would be highly desirable to discover a form of aripiprazole that possessed low hygroscopicity thereby facilitating pharmaceutical processing and formulation operations required for producing dosage units of an aripiprazole medicinal product having improved shelf-life, suitable dissolubility and suitable bioavailability.

Also, Proceedings of the 4th Japanese-Korean Symposium on Separation Technology (October 6-8, 1996) state that, aripiprazole anhydride crystals exist as type-I crystals and type-II crystals; the type-I crystals of aripiprazole anhydride can be prepared by recrystallizing from an ethanol solution of aripiprazole, or by heating aripiprazole hydrate at 80°C; and the type-II crystals of aripiprazole anhydride can be prepared by heating the type-I crystals of aripiprazole anhydride at 130 to 140°C for 15 hours.

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By the aforementioned methods, aripiprazole anhydride type-II crystals having high purity can not be easily prepared in an industrial scale with good repeatability.

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SUMMARY OF THE INVENTION

Thus according to the present invention is provided a form of aripiprazole having reduced hygroscopicity and which is more amenable to pharmaceutical processing and formulation. The inventors of the present invention have discovered that this reduced-hygroscopic form of Aripiprazole is a crystalline substance defined herein as Anhydride B. A particular process for the preparation of this anhydrous crystalline substance has also been discovered and comprises yet another aspect of the present invention. Particularly, it was discovered as part of the present invention that in order to produce Anhydride B having the desired pharmaceutical properties and utilizing the most efficient process, Hydrate A, as defined herein, would have to serve as the intermediate. It was also discovered that a particular sequence of processing had to be implemented in order to form Hydrate A. It was discovered that the preparation of Hydrate A required milling what is defined herein as Conventional Hydrate. Then, Hydrate A can be transformed into Anhydride B through suitable heating as defined herein. Surprisingly, if the

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Conventional Hydrate is first heated and then milled, serious agglomeration sets in rendering the processing commercially unsuitable.

An object of the present invention is to
5 provide novel aripiprazole anhydride crystals.

Moreover, another object of the present invention is to provide aripiprazole anhydride crystals which neither easily convert into hydrates nor substantially decrease the original solubility, even
10 when a pharmaceutical composition comprising aripiprazole anhydride is stored for a long period of time.

Further object of the present invention is to provide preparation methods, in order to obtain
15 aripiprazole anhydride crystals having high purity in an industrial scale with good repeatability.

The present inventors have conducted research works aimed to attain the aforementioned objects. In the course of the research, they have found that the
20 desired aripiprazole anhydride crystals can be obtained when a well-known aripiprazole anhydride is heated at the specific temperature. Further, the present inventors have found that the desired aripiprazole anhydride crystals can be obtained from
25 recrystallization of a well-known aripiprazole anhydride by using the specific solvents. Moreover, the present inventors found that the desired aripiprazole anhydride crystals can be obtained by

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suspending a well-known aripiprazole anhydride in the specific solvent, and heating thus obtained suspension.

The present invention thus completed on the basis of these findings and knowledge.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a thermogravimetric/differential thermogram of the Aripiprazole Hydrate A obtained in Example 1.

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Figure 2 shows the ¹H-NMR spectrum (DMSO-d₆, TMS) of the Aripiprazole Hydrate A obtained in Example 1.

Figure 3 is a powder x-ray diffraction diagram of the Aripiprazole Hydrate A obtained in

15 Example 1.

Figure 4 shows the ¹H-NMR spectrum (DMSO-d₆, TMS) of the Aripiprazole Anhydride Crystals B obtained in Example 2.

Figure 5 is a powder x-ray diffraction diagram of the Aripiprazole Anhydride Crystals B obtained in Example 2.

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Figure 6 is a thermogravimetric/differential thermogram of the aripiprazole hydrate obtained in Reference Example 3.

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Figure 7 is a powder x-ray diffraction diagram of the aripiprazole hydrate obtained in Reference Example 3.

Figure 8 shows thermogravimetric/differential

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According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate 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.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a mean particle size of 50 µm or less.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a mean particle size of 40 µm or less.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a mean particle size of 35 µm or less.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a mean particle size of 30 µm or less.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a mean particle size of 25 µm or less.

According to another embodiment of the first

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aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a mean particle size of 20 μm or less.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a mean particle size range of 40 to 10 μm .

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a mean particle size range of 36 to 14 μm .

According to a second aspect of the present invention is provided a process for the preparation of Hydrate A wherein said process comprises the steps of milling Conventional Hydrate.

According to a first embodiment of the second aspect of the present invention is provided a process for the preparation of Hydrate A comprising the steps of milling Conventional Hydrate wherein said milling is performed by a milling machine.

According to another embodiment of the second aspect of the present invention is provided a process for the preparation of Hydrate A comprising the steps of milling Conventional Hydrate wherein said milling machine is an atomizer, pin mill, jet mill or ball mill.

According to another embodiment of the second aspect of the present invention is provided a process

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for the preparation of Hydrate A comprising the steps of milling Conventional Hydrate wherein said milling machine is an atomizer.

According to another embodiment of the second aspect of the present invention is provided a process for the preparation of Hydrate A comprising the steps of milling Conventional Hydrate wherein said milling machine is an atomizer using a rotational speed of 5000-15000 rpm for the main axis, a feed rotation of 10-30 rpm and a screen hole size of 1-5 mm.

According to various embodiments of a third aspect of the present invention is provided Hydrate A defined according to one or more of the embodiments described herein wherein said Hydrate is made by a process as described herein.

According to a fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity.

According to a first embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said low hygroscopicity is a moisture content of 0.5% or less after placing said drug substance for 24 hours in a dessicator maintained at a temperature of 60°C and a humidity level of 100%.

According to a first embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity

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converts to an aripiprazole hydrate (Hydrate A as defined herein) with a different powder x-ray diffraction spectrum by different peak intensities. Moreover, it was found that Hydrate A loses the sharp
5 dehydration endothermic peak of 123.5°C which characterizes unmilled Conventional Hydrate in thermogravimetric/differential thermal analysis. Thus, the Conventional Hydrate is transformed into Hydrate A after milling Conventional Hydrate and exhibits a
10 gradual dehydration endothermic peak between about 60°C and 120°C with a weak peak at about 71°C.

Yet another aspect of the invention comprised discovering that when heated to a specific temperature of 90-125°C for 3-50hr, this novel aripiprazole hydrate
15 dehydrates gradually avoiding the aggregation phenomenon thought to be caused in conventional aripiprazole hydrate by rapid dehydration, and that aripiprazole anhydride crystals obtained by heating of the novel aripiprazole hydrate to a specific
20 temperature are aripiprazole anhydride crystals with the desired properties.

Characterization of Hydrate A

Particles of "Hydrate A" as used herein have
25 the physicochemical properties given in (1)-(5) below:

(1) It has an endothermic curve which is substantially the same as the thermogravimetric/differential thermal analysis (heating rate 5°C/min)

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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.

5 (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
10 (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
15 (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 $2\theta = 12.6^\circ$,
20 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 particle size of 50 μm or
25 less.

Process for Manufacturing Hydrate A

Hydrate A is manufactured by milling

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Conventional Hydrate. Conventional milling methods can be used to mill Conventional Hydrate. For example, Conventional 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.

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.

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

Characterization of Aripiprazole Anhydride Crystals B

"Aripiprazole Anhydride Crystals B" of the present invention as used herein have the physicochemical properties given in (6)-(12) below.

(6) They have an ^1H -NMR spectrum which is substantially the same as the ^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),

[54] CRYSTALLIZATION METHOD TO
IMPROVE CRYSTAL STRUCTURE AND
SIZE

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538,411, Jan. 13, 1990, abandoned

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[52] U.S. Cl. 23/298 R; 23/299;
423/639; 137/496; 239/421; 239/433; 366/173
[58] Field of Search 137/397, 396; 23/295 R,
23/293 R, 293 A, 293 S, 299; 241/36; 239/420,
421, 433; 366/172, 173, 176, 422/245; 423/639

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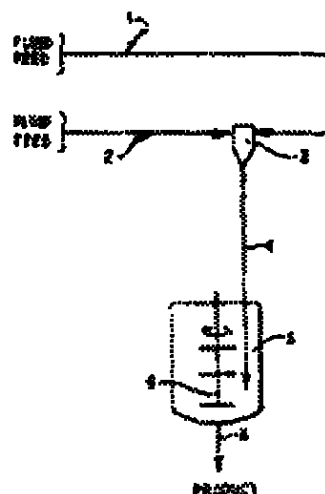
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[57] ABSTRACT

Impinging fluid streams are used in a continuous
crystallization process to achieve high intensity mi-
cromixing of fluids so as to form a homogeneous com-
position prior to the start of nucleation. This process
permits direct crystallization of high surface area par-
ticles of high purity and stability.

28 Claims, 4 Drawing Sheets



The solution was allowed to cool to room temperature then cooled in an ice bath to 5° C. while agitation was continued. The solid was then filtered, washed with water and dried. The crystals were cube-like particles; approximately 95% of the particles were smaller than 3 microns.

What is claimed is:

1. A process for crystallization of an organic pharmaceutical compound comprising contacting one or more jet streams of a feed solution of the organic pharmaceutical compound with one or more jet streams of an anti-solvent, said jet streams impinging to create high turbulence at their point of impact, and each jet stream having sufficient linear velocity to achieve high intensity micronizing of the feed solution and the anti-solvent prior to nucleation, followed by nucleation and the direct production of small crystals, at least 95% of said crystals having a diameter equal to or less than 25 microns.

2. The process of claim 1 wherein at least one of the jet streams comprises a surfactant.

3. The process of claim 1 wherein the pharmaceutical compound is selected from the group consisting of simvastatin, lovastatin, ((3a, 17β)-(1,1-dimethylethyl)-3-oxo-4-azastandrost-1-ene-17-carboxamide), diltiazem maleate, 17β-benzoyl-4-aza-3a-androst-1-ene-3-one, 4'-epi-acetylaminoglycyloxy-vermectin B₁ and (trans-(-)-)-2-[[3-methoxy-2-propoxy-5-(tetrahydro-3-(3,4,5-trimethoxyphenyl)-2-furanylphenyl)sulfonyl]ethanol.

4. The process of claim 1 wherein each jet stream is independently at a temperature in the range of about 24° C. to 70° C.

5. The process of claim 1 wherein substantially all of said crystals have a diameter equal to or less than 20 microns.

6. A process for crystallization of an organic pharmaceutical compound comprising contacting one or more jet streams of a first feed solution of the organic pharmaceutical compound with one or more jet streams of a second feed solution of the organic pharmaceutical compound, said jet streams impinging to create high turbulence at their point of impact, and each jet stream having sufficient linear velocity to achieve high intensity micronizing of the first and second feed solutions prior to nucleation followed by nucleation and the direct production of small crystals, at least 95% of said crystals having a diameter equal to or less than 25 microns.

7. The process of claim 6 wherein the pharmaceutical compound is selected from the group consisting of simvastatin, lovastatin, ((3a, 17β)-(1,1-dimethylethyl)-3-oxo-4-azastandrost-1-ene-17-carboxamide), diltiazem maleate, 17β-benzoyl-4-aza-3a-androst-1-ene-3-one, 4'-epi-acetylaminoglycyloxy-vermectin B₁ and (trans-(-)-)-2-[[3-methoxy-2-propoxy-5-(tetrahydro-3-(3,4,5-trimethoxyphenyl)-2-furanylphenyl)sulfonyl]ethanol.

8. The process of claim 6 wherein two jet streams are used and the two jet streams are substantially diametrically opposed to each other, and the hydrodynamic form of each jet stream remains essentially intact up to the point of impingement.

9. The process of claim 6 wherein at least one of the jet streams comprises a surfactant.

10. The process of claim 6 wherein substantially all of said crystals have a diameter equal to or less than 20 microns.

11. A process for crystallization of an organic pharmaceutical compound comprising contacting two opposing jet streams, one jet stream comprising a feed

solution of the organic pharmaceutical compound and the other jet stream comprising an anti-solvent, said opposing jet streams impinging to create high turbulence at their point of impact, and each jet stream having sufficient linear velocity to achieve high intensity micronizing of the feed solution and the anti-solvent prior to nucleation, followed by nucleation and the direct production of small crystals, at least 95% of said crystals having a diameter equal to or less than 25 microns.

12. The process of claim 11 wherein the linear velocity of the jet streams is at least about 5 meters/sec.

13. The process of claim 12 wherein the linear velocity is greater than 10 meters/sec.

14. The process of claim 13 wherein the linear velocity is between about 20-25 meters/sec.

15. The process of claim 14 wherein the compound to be crystallized is simvastatin, and the process is conducted in a temperature range of about 53-70° C.

16. The process of claim 15 wherein the feed solution is comprised of simvastatin dissolved in 100% methanol, the anti-solvent is comprised of 100% water, and a 41:59 volumetric ratio of feed solution:anti-solvent is used.

17. The process of claim 14 wherein the temperature is between 40-70° C.

18. The process of claim 13 wherein the compound to be crystallized is ((3a, 17β)-(1,1-dimethylethyl)-3-oxo-4-azastandrost-1-ene-17-carboxamide) and the process is conducted at room temperature.

19. The process of claim 18 wherein the feed solution is comprised of ((3a, 17β)-(1,1-dimethylethyl)-3-oxo-4-azastandrost-1-ene-17-carboxamide) dissolved in a 60:40 volumetric ratio of glacial acetic acid:water, the anti-solvent is comprised of 100% water, and a 1.5:1 volumetric ratio of feed solution:anti-solvent is used.

20. The process of claim 13 wherein the compound to be crystallized is lovastatin, and the process is conducted in a temperature range of about 40-56° C.

21. The process of claim 20 wherein the feed solution is comprised of lovastatin dissolved in a 90:10 volumetric ratio of methanol:water, the anti-solvent is comprised of 100% water, and about a 2.6:1 volumetric ratio of feed solution to anti-solvent is used.

22. The process of claim 13 wherein the compound to be crystallized is omeprazole and the process is conducted in temperature range of about 30° to 43° C.

23. The process of claim 22 wherein at least one of the fluids comprises a surfactant.

24. The process of claim 11 wherein at least one of the jet streams comprises a surfactant.

25. The process of claim 11 wherein the organic pharmaceutical compound is selected from the group consisting of simvastatin, lovastatin, ((3a, 17β)-(1,1-dimethylethyl)-3-oxo-4-azastandrost-1-ene-17-carboxamide), diltiazem maleate, 17β-benzoyl-4-aza-3a-androst-1-ene-3-one, 4'-epi-acetylaminoglycyloxy-vermectin B₁ and (trans-(-)-)-2-[[3-methoxy-2-propoxy-5-(tetrahydro-3-(3,4,5-trimethoxyphenyl)-2-furanylphenyl)sulfonyl]ethanol.

26. The process of claim 11 wherein each jet stream is independently at a temperature in the range of about 23° C. to 70° C.

27. The process of claim 11 wherein substantially all of said crystals have a diameter equal to or less than 20 microns.

28. The process of claim 11 wherein the pharmaceutical compound is omeprazole and at least one of the fluids comprises a surfactant.

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(12) **United States Patent**
Am Ende et al.

(10) **Patent No.:** **US 6,558,435 B2**
(45) **Date of Patent:** **May 6, 2003**

(54) **REACTIVE CRYSTALLIZATION METHOD
TO IMPROVE PARTICLE SIZE**

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(65) **Prior Publication Data**

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(52) **U.S. Cl.** 23/300; 544/284; 546/272.4

(58) **Field of Search** 23/295 R, 300;
544/230, 284; 546/276, 272.4

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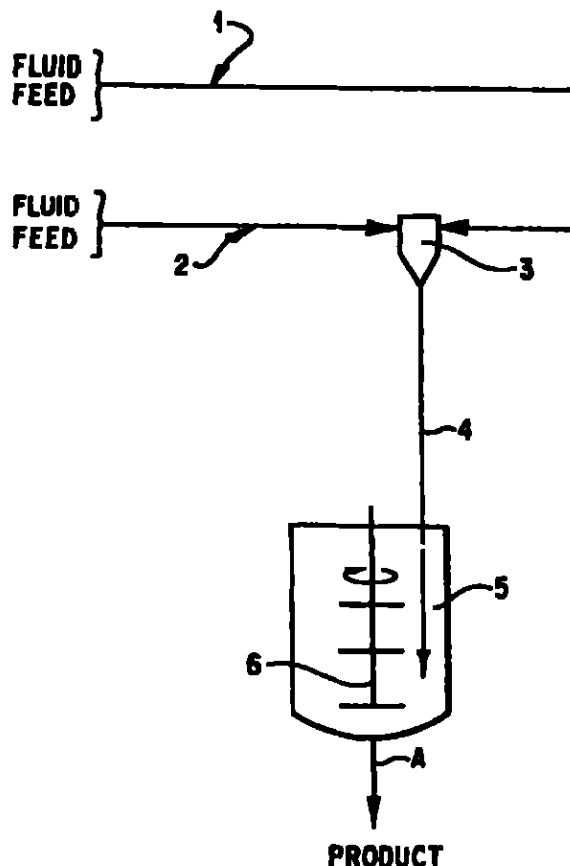
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(57)

ABSTRACT

This invention provides a method of conducting a simulta-
neous chemical reaction and controlled crystallization of the
product employing impinging fluid jet streams containing
reactants capable of producing the product with desired
particle size characteristics.

27 Claims, 2 Drawing Sheets



larger particle size distribution. The modifications to example 1 were: a) 3.1 g of Ziprasidone free base dissolved in 65 volumes of THF was used, b) not hot filtration was performed in preparing the Ziprasidone free base THF solution, and c) the age time for the resulting crystals, after the impingement period, was 55 minutes prior to filtration. The crystals were vacuum filtered, washed with 150 ml of deionized water, and air dried. The dry Ziprasidone hydrochloride monohydrate particles were free flowing. Microscopy revealed the formation of a uniform distribution of crystalline aggregates that give superior filtration and powder properties such as flowability. Thus this method can influence degree of aggregation and provide benefits to bulk handling characteristics. The powder was not sieved prior to Malvern light scattering as it required no delumping. The volume mean particle size, $D[4,3]$, was 104 micron with 90% by volume, D_{90} , less than 210 microns. No particles below 1 micron were measured, indicating no fines were produced.

Example 4

Reaction-Crystallization of Voriconazole Camphorsulfonic Acid Salt to Voriconazole Free Base (U.S. Pat. No. 5,567,817; CAS-1378234-62-9)

28.75 g of Voriconazole R(-)-camphorsulfonic acid salt was dissolved in 120 ml of a 50:50 volume ratio of ethanol and deionized water and placed in a 2L jacketed vessel equilibrated at 30° C. 4 liters of an aqueous solution of sodium acetate (3.4 wt %) was placed in a stainless steel pressure can at room temperature and pressurized to 26 psig with nitrogen. Each vessel was plumbed to individual jets assembled in a chamber similar to the configuration depicted in FIG. 1. The jets were 1/8 inch OD and 0.02 inch ID. The flow of sodium acetate solution was started through the jet at 115 ml/min, controlled via the nitrogen pressure. The Voriconazole camphorsulfonic acid salt solution was then turned on with flow rate of 115 ml/min through the jet. The flow of the two solutions created at impingement zone between the two jets and while crystalline material was observed to be forming in the impingement chamber which flowed down to the receiving vessel that was equilibrated to 5° C.

The jets were run until the Voriconazole salt solution was consumed. The slurry was aged for 10 minutes then vacuum filtered, and washed with 70 ml DI water.

The crystals were dried in a vacuum oven at 50° C. and 10 inches of Hg with an air bleed for 24 hours. The dried material was sieved through a 30 mesh (600 μ m) screen as a means to delump. Differential scanning calorimetry and x-ray diffraction confirmed the complete conversion to the Voriconazole free-base. No unreacted Voriconazole camphorsulfonate was detected.

Dry particle sizing analysis (SympaTec) revealed a volume mean diameter of 22 microns with 90% of particles ($D[v,0.9]$) less than 41 microns and 50% of particles ($D[v,0.50]$) less than 18 microns. Specification of product conventionally obtained by jet milling is 90% less than 130 microns and 50% less than 50 microns.

Example 5

Reactive Crystallization of 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene to Achieve Desired Salt Form and Particle Size Using Submerged Impinging Jets

1.006 grams of 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene free base was dissolved in

30 ml of ethyl acetate and 5 ml. of methanol in a conical shaped centrifuge tube and held at room temperature. In a separate conical shaped centrifuge tube 0.96 g of (L)-tartaric acid was dissolved in 40 mL methanol at room temperature.

A receiving vessel contained 250 ml of methanol and 250 ml of ethyl acetate to which 20 milligrams of jet milled 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene (L)-tartrate were added as seed. The seed had a volume mean diameter of 2.7 microns. The receiver was equipped with magnetic stirrer to suspend the seed in the methanol-ethyl acetate solvent system. The impinging jet apparatus was submerged in the receiver vessel with both jets having inside diameters of 0.007 inches (ID).

Flow of neat methanol and ethyl acetate was initiated through their respective jets at 20 ml/min for 5 seconds from separate reservoirs to establish steady state flow. By way of two 3-way valves the solutions of 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene free base solution and (L)-tartaric acid were switched on so they would impinge each other at the same 20 ml/min flow rate. The velocities through the jets were 13.4 meters/sec. After 1 minute of impingement the flows were stopped and the resulting slurry was allowed to age in the agitated receiver for 5 minutes. The slurry was vacuum filtered and dried at 40° C. overnight and delumped through a 500 micron sieve. Polymorph characterization by x-ray diffraction revealed it to be of the desired polymorphic form. Particle size analysis (AerSizer) resulted in a volume mean diameter of 10 microns with narrow particle size distribution: 5% of particles were less than 5 microns and 95% of the particle were less than 15 microns.

What is claimed is:

1. A process for synthesis and crystallization of a pharmaceutical compound comprising:

contacting one or more liquid jet streams of a solution in a first solvent of a first reactive intermediate and one or more liquid jet streams of a solution in a second solvent of a second reactive intermediate, with each jet stream of said first reactive intermediate substantially diametrically opposite a jet stream of said second reactive intermediate and each jet stream of said second reactive intermediate substantially diametrically opposite a jet stream of said first reactive intermediate when viewed from overhead, so that each jet stream of said first reactive intermediate is directed into a jet stream of said second reactive intermediate and each jet stream of said second reactive intermediate is directed into a jet stream of said first reactive intermediate, such that the liquid streams meet at a point of impingement to create a vertical impingement film and with said jet streams creating turbulence at their point of impact under conditions of temperature and pressure which permit reaction of said first and second reactive intermediates to produce a product; and

selecting said first and second solvents so that said product is insoluble in a mixture of said first and second solvents; and

with each jet stream having sufficient linear velocity to achieve micromixing of said solutions followed by reaction of first and second reactive intermediates, followed by nucleation of said product and production of high surface area crystals of said product that meet bioavailability requirements.

2. The process of claim 1, wherein one of said first and second reactive intermediates is a basic intermediate and the other intermediate is an acidic intermediate.

3. The process of claim 1, wherein one of said first and second reactive intermediates is a zwitterion and the other intermediate is an acid.

4. The process of claim 1, wherein one of said first and second reactive intermediates is a zwitterion and the other intermediate is a base.

5. The process of claim 1, wherein one of said first and second reactive intermediates is an organic salt form and the other intermediate is a neutralizing acid compound.

6. The process of claim 1, wherein one of said first and second reactive intermediates is an organic salt form and the other intermediate is a neutralizing basic compound.

7. The process of claim 1, wherein said product is a pharmaceutically acceptable salt selected from the group consisting of hydrochloride, acetate, besylate, citrate, hydrobromide, D or L lactate, mesylate, succinate, sulfate, D or L tartrate, stearate, tosylate, calcium, potassium, sodium and ethylenediamine.

8. The process of claim 1, wherein said product further comprises aggregates of said high surface area crystals.

9. The process of claim 2, wherein one reactive intermediate is Ziprasidone free base and the other reactive intermediate is aqueous HCl solution.

10. The process of claim 1, wherein said product is Ziprasidone hydrochloride monohydrate.

11. The process of claim 1, wherein said product is Voriconazole free base.

12. The process of claim 2, wherein said basic intermediate is selected from sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, and said acidic intermediate is Voriconazole R-(−)-camphorsulfonic acid salt.

13. The process of claim 1, wherein each of said liquid jet streams emerges from a nozzle having an outlet hole and with each said nozzle from which each jet stream emerges directed sufficiently downward to ensure that said liquid jet streams emerging from each nozzle will not enter said outlet hole of said substantially diametrically opposite nozzle.

14. The process of claim 1, wherein said product produced upon crystallization is solvated.

15. The process of claim 2, wherein one reactive intermediate is 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene free base and the other reactive intermediate is a L-tartaric acid solution.

16. The process of claim 1, wherein said product is 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene (L)-tartrate.

17. The process of claim 1, wherein the linear velocity of the jet streams is at least 5 m/sec.

18. The process of claim 1, wherein a sonication probe is included with said impinging jet streams.

19. A process for synthesis and crystallization of a pharmaceutical compound comprising contacting one or more jet streams of a solution in a first solvent of a first reactive intermediate and one or more jet streams of a solution in a second solvent of a second reactive intermediate, said jet streams impinging to create turbulence at their point of impact under conditions of temperature and pressure which permit reaction of said first and second reactive intermediates to produce a product; and,

selecting said first and second solvents so that said product is insoluble in a mixture of said first and second solvents; and

said jet streams impinging to create turbulence at their point of impact and each jet stream having sufficient linear velocity to achieve micromixing of said solutions followed by reaction of first and second reactive

intermediates, followed by nucleation of said product and production of a crystalline product having small crystals of controlled particle size, wherein said crystals of said product meet bioavailability requirements, wherein said first reactive intermediate is selected from Ziprasidone free base or 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene free base, and said second reactive intermediate is selected from HCl or L-tartaric acid.

20. The process of claim 19, wherein said first reactive intermediate is Ziprasidone free base and said second reactive intermediate is HCl.

21. The process of claim 19, wherein said crystalline product is Ziprasidone hydrochloride monohydrate.

22. The process of claim 19, wherein said first reactive intermediate is 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene free base and said second reactive intermediate is a L-tartaric acid.

23. The process of claim 19 wherein said crystalline product is 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene (L)-tartrate.

24. A process for synthesis and crystallization of a pharmaceutical compound comprising contacting one or more jet streams of a solution in a first solvent of a first reactive intermediate and one or more jet streams of a solution in a second solvent of a second reactive intermediate, said jet streams impinging to create turbulence at their point of impact under conditions of temperature and pressure which permit reaction of said first and second reactive intermediates to produce a product; and

selecting said first and second solvents so that said product is insoluble in a mixture of said first and second solvents, and

said jet streams impinging to create turbulence at their point of impact and each jet stream having sufficient linear velocity to achieve micromixing of said solutions followed by reaction of first and second reactive intermediates, followed by nucleation of said product and production of a crystalline product having small crystals of controlled particle size, wherein said crystals of said product meet bioavailability requirements, wherein said first reactive intermediate is Voriconazole camphorsulfonic acid salt and said second reactive intermediate is a base and wherein said product is Voriconazole free base.

25. The process of claim 24 wherein said base is selected from sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, sodium carbonate and sodium bicarbonate.

26. A process for synthesis and crystallization of a pharmaceutical compound comprising contacting one or more jet streams of a solution in a first solvent of a first reactive intermediate and one or more jet streams of a solution in a second solvent of a second reactive intermediate, said jet streams impinging to create turbulence at their point of impact under conditions of temperature and pressure which permit reaction of said first and second reactive intermediates to produce a product; and

selecting said first and second solvents so that said product is insoluble in a mixture of said first and second solvents; and

said jet streams impinging to create turbulence at their point of impact and each jet stream having sufficient linear velocity to achieve micromixing of said solutions followed by reaction of first and second reactive intermediates, followed by nucleation of said product and production of high surface area crystals of said

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product that meet bioavailability requirements wherein
said first reactive intermediate is selected from Zipra-
sidone free base or 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{2,5}]-hexadeca-2(11),3,5,7,9-pentaene free base, and
said second reactive intermediate is an acid, wherein
said crystalline product is a pharmaceutically accept-
able salt of Ziprasidone or 5,8,14-triazatetracyclo
[10.3.1.0^{2,11}.0^{2,5}]-hexadeca-2(11), 3,5,7,9-pentaene
selected from the group consisting of: hydrochloride,
acetate, hexylate, citrate, hydrobromide, D or L lactate,
mesylate, succinate, sulfate, D or L tartrate, stearate and
tosylate.
27. A process for synthesis and crystallization of a chemi-
cal compound comprising contacting one or more jet
streams of a solution in a first solvent of a first reactive
intermediate and one or more jet streams of a solution in a
second solvent of a second reactive intermediate, said jet
streams impinging to create turbulence at their point of

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impact under conditions of temperature and pressure which
permit reaction of said first and second reactive intermedi-
ates to produce a product; and
selecting said first and second solvents so that said
product is insoluble in a mixture of said first and second
solvents; and
said jet streams impinging to create turbulence at their
point of impact and each jet stream having sufficient
linear velocity to achieve micromixing of said solutions
followed by reaction of first and second reactive
intermediates, followed by nucleation of said product
and production of high surface area crystals of said
product that meet bioavailability requirements, wherein
said first reactive intermediate is a zwitterion and said
second reactive intermediate is a base or an acid.

* * * * *



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(12) **United States Patent**
Lindrud et al.

(10) **Patent No.:** **US 6,302,958 B1**
(45) **Date of Patent:** **Oct. 16, 2001**

(54) **SONIC IMPINGING JET CRYSTALLIZATION APPARATUS AND PROCESS**

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(*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

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(22) **Filed:** Jun. 27, 2000

Related U.S. Application Data

(60) **Provisional application No. 60/117,878, filed on Jan. 29,
1999.**

(51) **Int. Cl.⁷** C30B 7/14

(52) **U.S. Cl.** 117/65; 422/245.1; 23/295.1;
23/300

(58) **Field of Search** 422/245.1; 23/295 R,
23/300; 117/65, 925

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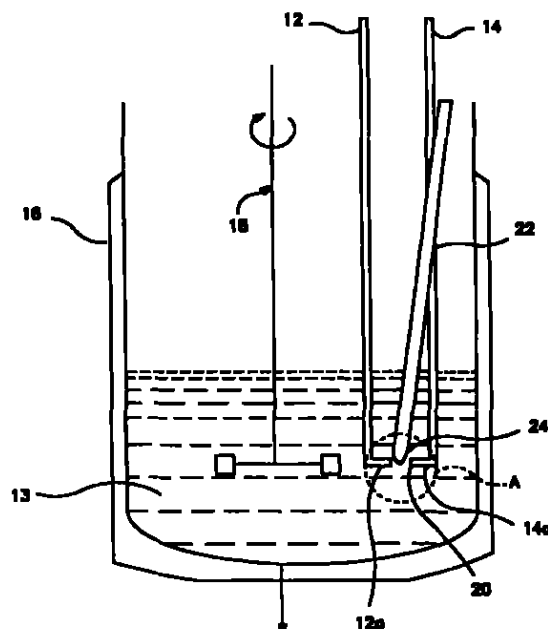
Primary Examiner—Robert Kuncmund

(74) **Attorney, Agent, or Firm**—Shah R. Makujina

(57) **ABSTRACT**

A novel apparatus and process for crystallizing submicron-sized crystals of a pharmaceutical composition. The submicron-sized crystals, which have an average size of less than 1 micron, provide high surface area and product crystals with greatly improved stability and purity, and which afford crystals having improved bioavailability, higher dissolution, decreased decomposition rate and longer shelf-life.

17 Claims, 2 Drawing Sheets



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(4) Upon completion of crystallization, the product was filtered and washed with 2 liters of water (RO quality, filtered). The filter cake was dried in vacuo at 70° C. until dry.

(5) The dry product was delumped by passing it through an 80 mesh screen. API aerosizer assays yield a mean particle size of 0.5324 microns with 95% of particles under 0.8321 microns.

Experiment No.	Mean Size	% <0.5000 μ m	95th percentile
42216-028-10	0.5324 microns	91.563	0.8321 microns

What is claimed is:

1. A process for the crystallization of a pharmaceutical compound comprising positioning a tip of a sonication probe within a gap defined between two or more fluid jets positioned such that fluid jet streams which emerge from said fluid jets impinge in said gap creating a point of high turbulence at the point of impact of said fluid streams, each of said fluid streams having sufficient linear velocity to achieve high intensity micromixing of the solutions prior to nucleation, said sonication probe providing ultrasonic energy in the immediate vicinity of said impinging fluid streams so as to effect nucleation and the direct production of small crystals, at least 95% of said crystals having a diameter of less than 1 micron.

2. The process according to claim 1, wherein two fluid jets are used, said first fluid jet is provided for carrying a first fluid stream, said first fluid stream comprising a combination of DMSO and said pharmaceutical compound, said second fluid jet is provided for carrying a second fluid stream, said second fluid stream comprising water.

3. The process according to claim 2, wherein said first and said second fluid jets are substantially diametrically opposed to each other, such that said first and second fluid streams impinge so as to attain high intensity impact.

4. The process according to claim 1, wherein at least one of said fluid streams comprises a surfactant.

5. The process according to claim 1, wherein said pharmaceutical compound selected from (Z-3-[1-(4-chlorophenyl)-1-(4-methylsulfonylphenyl)methylene]-dihydrofuran-2-one, and [R-(R*,R*)]4-[2-[2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl-4-thiazolyl]benzonitrile.

6. The process according to claim 1, wherein each jet stream is independently at a temperature in the range of about 0° C. to 100° C.

7. The process according to claim 1, wherein substantially all of said crystals have a diameter equal to or less than 1 micron.

8. The process according to claim 1, wherein said gap defined between said fluid jets is 0.4 inches.

9. The process according to claim 1, wherein said tip of said sonication probe is positioned in said gap in the same plane with said fluid jets and at the point where said fluid streams from set fluid jets impinge with one another.

10. The process according to claim 9, wherein said sonication probe provides power in a range of between 30 and 150 watts.

11. A crystallization apparatus for producing submicron-sized particles, which comprises:

- a crystallization flask;
- two or more fluid impinging jets,
- an agitator, and

a sonication probe having a probe tip, wherein said impinging jets, said agitator and said sonication probe are positioned within said crystallization flask, said impinging jets positioned substantially diametrically opposed to each other, and said sonication probe positioned proximate said impinging jets such that said probe tip is positioned such that it is at the same level as the impinging jets.

12. The crystallization apparatus according to claim 11, wherein said apparatus comprises two fluid impinging jets, said first fluid jet is provided for carrying a first fluid stream, said first fluid stream comprising a combination of DMSO and a pharmaceutical compound, said second fluid jet is provided for carrying a second fluid stream, said second fluid stream comprising water.

13. The crystallization apparatus according to claim 12, wherein said first and said second fluid jets are substantially diametrically opposed to each other, such that said first and second fluid streams impinge so as to attain high intensity impact.

14. The crystallization apparatus according to claim 11, wherein said agitator provides an agitation rate of >300 rpm which is maintained throughout the crystallization process.

15. The crystallization apparatus according to claim 11, wherein sonication probe is a 20 khz probe.

16. The crystallization apparatus according to claim 15, wherein said sonication probe provides power to said first and said second fluid streams within said flask in the range from 30 to 50 watts.

17. The process according to claim 1, wherein said pharmaceutical compound is Z-3-[1-(4-chlorophenyl)-1-(4-methylsulfonylphenyl)methylene]-dihydrofuran-2-one or [R-R*,R*)]4-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl-4-thiazolyl]benzonitrile.

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Investigation of Impinging-jet crystallization with a calcium oxalate model system

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ABSTRACT

An impinging-jet crystallizer was investigated in this work to assess its operational sensitivity and reproducibility for the production of small, monodisperse crystals using calcium oxalate, a model system capable of forming multiple hydrates. The impinging-jet mixer provides rapid mixing of the reactant solutions through the impingement of two narrow reactant streams at high velocity. Impinging jet linear velocity and postjetting conditions were studied, with the jet operated in nonsubmerged mode. Hydrate form and crystal-size distribution (CSD) were determined using optical microscopy and image analysis techniques. The impinging jet consistently produced small, monodisperse crystals. However, at a high level of supersaturation, slight variations in the CSD were observed for apparently identical conditions, suggesting a degree of sensitivity in the system that could lead to difficulty in its application. An apparent trend between impinging-jet linear velocity and crystal size and number was observed, with more small crystals produced at higher linear velocity.

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Modeling and Simulation of Impinging Jet Crystallizers

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The impinging jet crystallizer, developed by Midler et al. [1] more than a decade ago, is recognized as a highly reproducible and reliable industrial crystallization technology that produces small crystals with narrow size distribution. The basic principle in this design is to utilize the high intensity micromixing of fluids to achieve a homogeneous composition of high supersaturation before the onset of nucleation. This technology is now being used by various pharmaceutical companies in their commercial drug production [2-4].

Numerous experimental studies have also been carried out by academic as well as industrial researchers to gain a deeper understanding of the impinging jet crystallization process, which can result in more efficient process development and optimization. For various antisolvent and reactive crystallization systems, the dependence of the crystal size distribution on the jet velocity and the inlet concentrations has been investigated [5-7]. Mahajan and Kirwan [5] and Johnson and Prud'homme [8] had characterized the mixing in impinging jets with an overall micromixing time using competitive reactions. The modeling of reactions in impinging jets has been widely studied as well [9, 10]. This paper extends this past computational work to include the population balance equation, with crystal nucleation and growth, to gain a deeper understanding of impinging jet crystallization. The ultimate goal is to speed up the design of impinging jets and tailor the crystal size distribution according to the bioavailability and drug administration requirements.

In this paper, a coupled CFD-Micromixing-Population Balance model [11] was used to simulate the crystallization process in a confined impinging jet crystallizer [8]. In the first part of the study, the CFD-Micromixing algorithm was combined with kinetics of competitive reactions to model the experimental work reported in Johnson and Prud'homme [8]. A parameter sensitivity analysis [12] was performed which guided the selection of model parameters to provide a closer agreement between model predictions and the experimental data.

In the second part of the study, the improved CFD-micromixing model was coupled with the population balance equation to simulate the full crystal size distribution for the antisolvent crystallization of Lovastatin [13] in the confined impinging jet crystallizer. The effects of jet velocity were numerically investigated and compared semi-quantitatively with experimental data in published literature [5]. Good agreement with the experimental data, especially the shape of the distribution, was obtained. The crystal size and distribution width was found to decrease with an increase in inlet jet velocity, which was consistent with the experimental observations. The simulation results showed different degrees of inhomogeneity in the supersaturation and the nucleation and growth rates for different jet velocities.

In the last part of the study, the antisolvent crystallization of two polymorphic forms of L-histidine in the confined impinging jet crystallizer was simulated with the CFD-micromixing-population balance model. The crystal size distribution of the stable and metastable polymorphs was computed for different jet velocities. It was found that, for the range of conditions simulated, the stable polymorph formed a large proportion of the crystals.

To the authors' knowledge, this is the most detailed simulation study on impinging jet crystallizers reported to date. The simulation results show the feasibility of tailoring a specific crystal size distribution or polymorphic ratio by adjusting the operating conditions (for example, jet velocity) of the impinging jet crystallizers. Hence, these computational tools can provide a technological advancement for the process development in the

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pharmaceutical industry by providing more in-depth understanding of the crystallization process, and reducing the number of trial-and-error experiments required to determine the optimum operating conditions, which reduces the amount of API needed for experiments. Consequently, the process design can be performed much earlier during the drug development, where there is a limited amount of API available.

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2020
Bogotá, D.C.,

Doctor:
Juan Pablo Cadena Samiento
Apoderado

Oficio N°: 3276

ASUNTO:	Radicación PCT N°	06-38472
	Trámite	011
	Evento	379
	Actuación	440
	Folios	058

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Tecnoquímicas S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única 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, 09 MAR. 2007.

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2020
Bogotá, D.C.,

Doctor:
Juan Pablo Cadena Sarmiento
Apoderado

Oficio N°: 3271

ASUNTO:

Radicación PCT N°	06-38472
Trámite	011
Evento	379
Actuación	440
Folios	008

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor Reinaldo Pinilla Moreno, en su calidad de apoderado de Procaps S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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


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

El anterior requerimiento fue notificado por fijación en lista de fecha, **09 MAR. 2007**.

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