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Castillo Grau & Asociados
ABOGADOS

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
Ciudad.-

SUPERINDUSTRIA Y COMERCIO
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Re.: Expediente No. 00 – 28.932
Solicitud de Patente

Por el presente escrito me permito manifestarle que interpongo el RECURSO DE REPOSICIÓN contra la Resolución No. 25369 de Septiembre 30 del 2005.

Este recurso tiene como propósito el que Usted revoque la mentada providencia para disponer en su lugar la concesión del privilegio de invención que aquí se solicita.

Para este efecto, me sustento entonces en los siguientes argumentos:

- El rechazo de esta solicitud se basa en un cierto número de asunciones hechas por el Examinador que de hecho son equivocadas. Por ejemplo, en la página (5), primer párrafo, el Examinador sostiene:

  "Se aclara, además, que el ser un polimorfo es una característica inherente al compuesto y el hecho de definirla ahora en esta solicitud no lo hace nuevo"

  Esto es incorrecto ! si siendo un polimorfo era inherente, cualquier compuesto podría existir alguna vez en un estado único "polimórfico". Es evidente que esto no es correcto y que es una contradicción en términos. En el caso de la sal de ácido maleico de 5-[4-[2-(N-methyl-N-(2-pyridilo)amino)ethoxy]benzyl] Thiazolidina-2, 4-dione, hay varias formas polimórficas diferentes. Polimorfismo no es predecible ni inherente.

El Examinador también afirmó en la página 11, renglón cuatro (a continuación de la fórmula) que lo que fue obtenido
"no se obtuvo de forma pura, o que por alguna razón se tuvo otro compuesto diferente después del proceso de síntesis"

Tal afirmación es incorrecta y sugiere que el Examinador no entiende polimorfismo o su análisis. Como el término para presentar este recurso es extremadamente corto, habida cuenta además de la distancia, deseamos referir al Examinador a la publicación de Tecnología Farmacéutica publicada en Agosto del 2004 y que puede ser localizado en la siguiente página web: "http://www.findarticles.com/p/articles/mi_mOEEH/is_8_28/ai_n6361510#continue" en la cual claramente se observa que diferentes polimorfos del mismo compuesto tendrán diferentes espectral y contornos XRPD. Por lo que se puede afirmar que aunque los polimorfos tengan la misma estructura y el mismo nombre, difieren su spectra y patronos XRPD.

Poliformismo es la existencia de diferentes clases de arreglos cristalinos del mismo compuesto químico. Como tal, es inevitable y de sentido común que los polimorfos del mismo compuesto químico tengan la misma estructura y el mismo nombre. La afirmación formulada por el Examinador de que el polimorfo reivindicado carece de novedad y/o altura inventiva sobre el estado de la técnica porque el compuesto reivindicado tiene el mismo nombre que el arte conocido no tiene simplemente ningún sentido. El solicitante está reclamando un polimorfo específico que no está revelado en el estado de la técnica ni tampoco se sugiere su existencia en lo conocido.

D1 no enseña el mismo compuesto como el que se reivindica actualmente. Por los datos físicos presentados, es claro que revela una forma polimórfica diferente. Lo mismo ocurre con los demás estados de la técnica citados.

El Examinador está equivocado cuando afirma que "de este compuesto ya se conocía su existencia".

Castillo Grau & Asociados
ABOGADOS

Mi cliente no se encuentra en posición de suministrar otros comentarios adicionales ya que los argumentos de rechazo del Examinador parecen estar basados en malos entendidos de la química de polimorfos.

Le ruego entonces se sirva autorizar la concesión de este privilegio.

Recibiré notificaciones en la Secretaría de su Despacho y en mi oficina de abogado, en la Carrera 13 No. 37 – 43, Piso 12 en esta ciudad.

Le ruego proceder en consecuencia.

De Ustedes atentamente,

REPUBLICA DE COLOMBIA GONZALO L. DELGADO CASTRO NOTARIA 28 DE BOGOTA

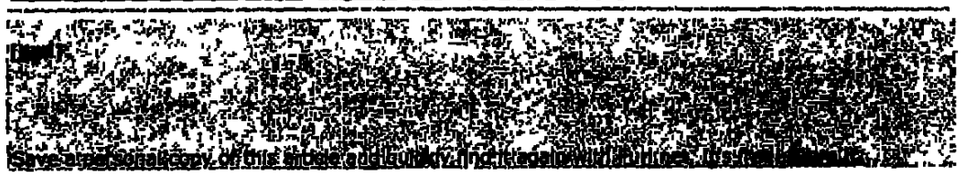
GERMAN CASTILLO GRAU
T.P. No. 2.978 del C.S.J.
C.C. No. 17.017.671 de Bogotá

El anterior memorial fué presentado personalmente por
Germán de Jesús Castillo Grau
quien se identificó con C. de C. No. 17.017.671
de Bogotá
Tarjeta Profesional No. 2978 C.S. de J.
Bogotá, D. E. -9 NOV 2005

REPUBLICA DE COLOMBIA GONZALO L. DELGADO CASTRO NOTARIA 28 DE BOGOTA

Solid-state NMR spectroscopy for pharmaceutical analysis: solid-state nuclear magnetic resonance spectroscopy is an emerging technique for the analysis of pharmaceuticals. Some of its applications include the identification of polymorphs or amorphous material, quantitation, structure determination, and the analysis of intact formulations

Pharmaceutical Technology, August, 2004 by Thomas J. Offerdahl



Approximately 90% of pharmaceuticals are marketed as solid dosage forms (1). Changes in the solid-state properties of these products can affect solubility, bioavailability, and stability (2). In addition, the processing and formulation of a drug may affect purity (i.e., polymorphism and/or amorphous content), dissolution characteristics, chemical and physical stability, and bioavailability. The Food and Drug Administration requires pharmaceutical companies to monitor and control solid-state properties because these properties have a direct effect on drug potency and effectiveness (3).

The ability to detect solid-state changes in a formulation depends on the analytical technique used to characterize the sample. Scientists use differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), Fourier transform infrared (FT-IR), and Raman spectroscopy as well as X-ray powder diffraction (XRD) to analyze pharmaceuticals in the solid state. Each technique provides information about a sample.

DSC and TGA characterize the physical properties of a specific solid (e.g., the melting point or the hydration state) of the active pharmaceutical ingredient (API) but have limited utility in the study of solid-state changes in a formulation compared with spectroscopic methods. FT-IR and Raman spectroscopy provide insight into the individual components in a formulation and, in some cases, are highly sensitive to solid-state changes. X-ray methods, either single crystal or powder diffraction, reveal extremely detailed information about the crystalline structure of the API in the solid state. XRD, in particular, can detect formulation solid-state form changes (e.g., polymorphism), although it is generally limited to the detection and quantitation of crystalline species in a formulation.

Solid-state nuclear magnetic resonance (NMR) spectroscopy is a powerful technique for characterizing pharmaceutical formulations Each API solid-state form, inclusive of amorphous states, usually exhibits a unique spectrum. NMR spectroscopy can often separate excipient peaks and the API peaks into different regions of a spectrum Moreover, in solid-state NMR spectroscopy, quantitation of mixtures of polymorphic forms can be performed without first preparing standard curves One disadvantage, however, is the instrumentation's high cost and operational complexity.

Basics of NMR spectroscopy

Theory Commonly observed NMR nuclei such as [sup 1]H or [sup 13]C have a spin quantum number I = 1/2 and therefore have a magnetic moment. When these nuclei are placed in a static magnetic field, the nuclei begin to precess because the magnetic moment is fixed at an angle of 54 74[degrees] with respect to the static magnetic field The precession frequency, called the Larmor frequency, is

[omega] = [[gamma] sub.nuc][B.sub 0]

In which [omega] is the precession frequency in rad/s, [[gamma] sub nuc] is the isotope's unique magnetogyric ratio, and [B sub.0] is the strength of the static magnetic field For example, [sup 1]H in a magnetic field of 9 4 T will have a Larmor frequency of 400 MHz

The magnetic moments can line up either with ([alpha] state) or against ([beta] state) the static magnetic field The population difference between the two spin states is governed by the Boltzmann distribution

[DELTA][N sub 0] = [Ne.sup [DELTA]E/KT]

In which N is the number of nuclei present, [DELTA]E = [gamma]h[B sub 0]/2[pi], k is the Boltzmann constant, and T is the temperature in Kelvin The NMR signal is proportional to the population difference With increasing magnetic field, a larger [DELTA]E produces a bigger population difference and a larger NMR signal In Fourier transform NMR spectroscopy, the nuclei are perturbed from equilibrium and the precessing spins produce an alternating current in a coil The resulting signal, or free induction decay (FID), is processed to produce the NMR spectrum

Solution-state NMR spectroscopy. Solution-state NMR spectroscopy elucidates the structure of many organic molecules because researchers can consistently predict or interpret the NMR spectrum for small organic molecules The rapid motion of the molecules in solution creates high-resolution NMR spectra with linewidths less than 1 Hz, with an average acquisition time of a [sup 1]H NMR spectrum less than 1 min Because of the high resolution that is possible in a solution NMR spectrum, the

structure of the molecule often can be determined (4, 5) This technique can be easily automated and can be used in conjunction with other solution techniques such as liquid chromatography More advanced NMR pulse sequences such as DEPT, INEPT, NOESY, and REDOR are two-dimensional NMR pulse sequences that allow researchers to observe the molecular dynamics and give insight into its structure Higher magnetic field strengths, currently at 21.1 T ([sup.1]H = 900 MHz), and better magnet designs allow scientists to apply solution-state NMR spectroscopy to study the structure and associated dynamics of large, complex molecules such as proteins.

Solid-state NMR spectroscopy Solid-state NMR spectroscopy is an emerging technique for analyzing various API forms In contrast to solution-state NMR spectroscopy, in which a high degree of molecular mobility exists and rotational averaging is conducted, solid-state NMR methods involve little or no molecular mobility NMR spectra of a solid sample, therefore, generate very broad peaks as a result of two prominent interactions dipolar coupling and chemical shift anisotropy (CSA).

Dipolar couplings are through-space interactions between the magnetic moments of two or more nuclei Because nuclei have magnetic moments, the "magnet" of one nucleus influences the neighboring field of another nucleus. The magnitude of the dipolar coupling has a 1/[r sup 3]-dependence and is proportional to the magnetogyric ratios of the coupled nuclei This coupling is either homonuclear or heteronuclear Most often, only [sup.1]H-[sup 13]C heteronuclear dipolar interactions are significant in solid-state [sup 13]C NMR spectroscopy because the low natural abundance of [sup.13]C (1 1%) means that the probability that two [sup.13]C nuclei are in close proximity is very small

CSA is the other main broadening factor in solid-state NMR spectra. When a sample is placed in a magnetic field, the individual crystallites exhibit various orientations with respect to the magnetic field, thereby creating a range of chemical shifts for the sample, often called a powder pattern. Powder patterns may be ~200 ppm broad for [sp sup 2] hybridized carbons (e.g., carbonyl, aromatic) If multiple sites are present, as is typical for APIs, the result is a broad, featureless NMR spectrum High-power decoupling and/or magic-angle spinning (MAS) can almost eliminate the effects of these two interactions

High-power [sup 1]H decoupling can greatly reduce or eliminate the [sup.1]H-[sup.13]C dipolar interactions. During the acquisition of FID, a continuous radio frequency (RF) pulse at the [sup 1]H Larmor frequency is applied to the sample. The [sup 1]H spins rapidly "flip" between the [alpha] and [beta] states such that the [sup.13]C nucleus sees only the average dipolar interaction, which is zero.

Magic-angle spinning averages the chemical-shift anisotropy Andrew (6) and Lowe (7) independently discovered this technique. When a sample spins rapidly at 54 74[degrees] (the magic angle) relative to a static magnetic field, the anisotropic component of the chemical shift is either partially or completely averaged to the isotropic chemical shift, thereby yielding high-resolution solid-state NMR spectra This angle dependence also reduces the dipolar interaction When the spinning speed is less than the width of the powder pattern, spinning sidebands appear at multiples of the spinning speed This magic angle, calculated using average Hamiltonian theory, can be rationalized by simpler means. The body diagonal of a cube is 54.74[degrees], so if a sample is spinning about that axis of rotation, then the individual vectors from each nuclei will spend an equal amount of time in all three axes, thereby averaging out the CSA

Cross-polarization (CP) provides a four-fold signal enhancement for [sup.13]C experiments It also shortens acquisition delay times because the recycle delay is determined by the [sup.1]H relaxation rate, which often is much slower than that of a [sup.13]C nuclei (8) Stejskal and Schaefer described the combination of these three techniques (CP, MAS, and high-power decoupling) in 1977 (9). Figure 1 shows the solid-state NMR spectrum of hexamethylbenzene, a common solid-state NMR standard, obtained using multiple pulse sequences The use of CP reduced the acquisition time by a factor of nine and greatly improved the sensitivity

[FIGURE 1 OMITTED]

Probe designs and pulse-sequence designs for solid-state NMR spectroscopy have advanced significantly since the development of the CPMAS NMR experiment. Initial MAS speeds were slow, but improved technologies and materials have increased spinning speeds to 50 kHz (3,000,000 rpm) Other improvements include the design of new pulse sequences For example, the use of the total sideband suppression (TOSS) experiment removes the spinning sidebands present in a MAS NMR spectrum (see Figure 1) (10). The interrupted-decoupling experiment can differentiate methyl and quaternary carbons from methines and methylenes (11) Recently, two-dimensional pulse sequences that normally are used in solution have been applied to solid samples. One example is the heteronuclear correlation (HETCOR) experiment, in which assignments are made on the basis of the connectivities between two different nuclei (12).

Advantages and disadvantages of solid-state NMR spectroscopy

Solid-state NMR spectroscopy offers several advantages over other analytical techniques NMR spectroscopy is a selective technique that allows researchers to focus on a specific nucleus of interest (I e , [sup 13]C, [sup 19]F, [sup 15]N) Moreover, if the molecule has specific reactive sites,

the use of isotopic labeling can increase the sensitivity of those particular sites by two orders of magnitude Solid-state NMR spectroscopy is not greatly affected by particle size; in fact, intact tablets of the correct diameter can be analyzed directly Formulations also can be analyzed directly, without the need to extract the API from the matrix Typically excipient peaks lie in a region of the NMR spectrum that does not overlap with many of the peaks from the API Techniques such as spectral subtraction can even remove the excipient peaks from the spectrum

Solid-state NMR spectroscopy makes it possible to directly observe API-excipient interaction occurring in a tablet, which is critical to the investigation of stability and bioavailability issues Solid-state NMR spectroscopy is highly sensitive to changes in the local environment such that it can detect small changes that are sometimes not seen in PXRD patterns In addition, polymorphs are readily identified because of the change in the chemical shift of a specific peak and, in contrast to XRD, even amorphous material can be observed easily.

NMR spectroscopy is inherently quantitative the intensity of the peaks is directly proportional to the number of magnetically equivalent nuclei. When the technique is conducted properly, quantitation can be performed without the need for a standard curve. This capability is extremely useful when a specific polymorph cannot be isolated at a high enough purity for use in generating a standard curve, which is a necessary step in other analytical techniques

Solid-state NMR spectroscopy also has some disadvantages The technique is nonroutine and requires a highly trained operator The instrumentation is generally more expensive than that used for the other analytical techniques discussed. Solid-state NMR spectroscopy is difficult to automate, meaning that individual samples must be switched manually, which limits sample throughput. For the analysis of pharmaceutical materials, solution NMR spectroscopy generally involves [sup 1]H NMR spectroscopy because of its high natural abundance and Larmor frequency. This is not possible in the solid state because of high dipolar interactions Solid-state [sup 1]H NMR spectroscopy generates broad peaks, usually spanning 20-30 ppm. Analysis of pharmaceuticals in the solid-state requires [sup.13]C NMR spectroscopy. However, because the natural abundance of [sup 13]C is 1.1% and the Larmor frequency is approximately one-fourth that of [sup.1]H, [sup.13]C NMR spectroscopy is ~6000 times less sensitive than [sup 1]H NMR spectroscopy This, of course, leads to longer acquisitions because of the increased number of transients required for adequate signal-to-noise Moreover, for some samples the relaxation time between transients can be as short as a second to as long as an hour or even longer. So acquiring a simple one-dimensional solid-state NMR spectrum could take from a couple of minutes to several days. Isotopic enrichment of certain sites in

the molecule shortens the acquisition time by increasing the sensitivity; however, it also increases the expense of the analysis

Applications of solid-state NMR spectroscopy to pharmaceutical solids

This section discusses some of the current literature describing the use of solid-state NMR spectroscopy to characterize pharmaceuticals and shows some spectra of several over-the-counter medications with different API loading levels. These spectra show the ability of solid-state NMR spectroscopy to characterize formulations, to quantify polymorphic mixtures, to differentiate polymorphic forms, and to complement the information provided by other analytical techniques

Solid-state NMR spectroscopy of pharmaceutical dosage forms. Solid-state NMR spectroscopy is uniquely suited to studying intact formulations The selectivity of the technique and its nondestructive nature allow direct analysis of intact formulations. For this article, the author tested several over-the-counter medications using solid-state NMR spectroscopy. Analysis was conducted on site using an NMR spectrometer (Unityplus, Varian Inc , Palo Alto, CA) and an Oxford 9.4 T ([sup 1]H = 399.870 MHz, [sup 13]C = 100 557 MHz) narrow-bore magnet Samples were obtained from a local pharmacy store and gently broken apart with a mortar and pestle These fragments were packed in a [Si sub.3][N sub 4] 7-mm rotor, placed in a double resonance CPMAS probe, and spun from 3500 to 4000 Hz

Ibuprofen is a very simple molecule with a relatively fast relaxation rate. A fast relaxation rate and moderate loading of the API (approximately 40%) lead to a very fast acquisition time Figure 2 shows the resulting spectrum in which the API peaks are readily identified among those peaks owing to the excipients (marked with an asterisk)

Ibuprofen represents a relatively ideal case: a fast relaxation rate and moderate API loading Therefore, to better demonstrate the ability of solid-state NMR spectroscopy to deal with a range of APIs and drug loadings, the author tested a set of similar heartburn relieving medications, each having different API loads. cimetidine 200 mg (70.9% w/w), ranitidine 75 mg (50.9% w/w), nizatidine 75 mg (21 3% w/w), and famotidine 10 mg (4.9% w/w). Figure 3 shows the resultant spectra The excipient peaks are easily identifiable as well as the peaks owing to the specific API, all of which appear crystalline because of the sharp peaks seen in the NMR spectra. The individual peaks from the API all have different chemical shifts, thereby making it relatively simple to determine which API is present in the formulation or whether there is a mixture of APIs present in the formulation At the lowest loading level, only the methyl peak appears because time constraints limited full optimization of the NMR parameters for acquisition

[FIGURES 2-3 OMITTED]

Pharmaceutical analysts also use solid-state NMR spectroscopy to study products with low API loading. Figure 4 shows that one can obtain a usable spectrum of loperamide hydrochloride in 2-mg (1 2% w/w) API loading. The most intense peaks in the NMR spectrum are attributed to the excipients, but a few low-intensity peaks owing to the API also are visible. When the NMR conditions are fully optimized, significantly better spectra are obtainable. Isotopic enrichment would have lowered the loading level, perhaps down to 0 01% w/w in an ideal case.

[FIGURE 4 OMITTED]

Quantitation of drug forms. Under ideal circumstances, an NMR spectrum in the solid state should be quantitative Solid-state NMR spectra, however, are often not quantitative because they are usually acquired with a CP experiment In this type of experiment, the peak areas in the NMR spectrum are a result of the amount of the specific molecular form in the sample and the dynamics involved with the magnetization transfer from the abundant spin (normally [sup.1]H) to the dilute (normally [sup.13]C) spin These dynamics must be taken into account to achieve accurate results. Gao used this approach to determine the composition of polymorphic mixtures of delavirdine mesylate (13).

Binary mixtures of a minor polymorphic or pseudopolymorphic form were mixed with a major form and quantitation was performed. Taking the CP dynamics into account, the author used multiple contact times to measure the change in magnetization transfer with respect to time. The initial buildup of magnetization was attributed to the rate of transfer of magnetization from [sup.1]H to [sup 13]C, characterized by the heteronuclear cross-polarization rate constant [T sub CH] The decrease of the intensity over time is a result of one of the proton relaxation rates, [T sub 1[rho]]. Calculations revealed that the isopropyl methyl carbon peaks--the peaks that were used for the quantitation--had the same [T sub 1[rho]] rates for all of the forms

Quantitation, therefore, could be carried out directly on the basis of the peak area to provide a relative measure of the one form with respect to the other. The areas of the peak corresponding to each of the polymorphic forms were taken and the experimental weight percent was determined for each polymorphic form Experimental results agreed to within 1% (absolute error) of the actual amount present (see Table I) Moreover, a plot of the actual weight percent versus the NMR determined weight percent confirmed the overall accuracy of the method. The data fit the expected straight line with a slope near one and an intercept near zero.

Assigning the NMR spectrum of aspartame forms

Numerous articles discuss using solid-state NMR spectroscopy for identifying and characterizing polymorphic systems. Solid-state NMR spectroscopy can identify the number of crystallographically-

inequivalent molecules in the unit cell on the basis of the number of peaks for each carbon. However, this can make it even more difficult to assign the peaks in the NMR spectrum to a specific carbon in the molecule, because chemical shift values in the solid state can be as much as 10 ppm different from their values in solution (14). Aspartame exists in several different forms Forms I and II are hemihydrate, and Form III is dihemihydrate. The [sup 13]C CPMAS NMR spectra of these three forms are easily distinguishable (see Figure 5) Form I has only one peak per carbon, which indicates that only one crystallographically inequivalent molecule in the unit cell, which agrees with the crystal structure The other two forms show up to three resonances for several of the carbons, indicating multiple crystallographically inequivalent molecules in the unit cell To assign the spectra, the authors synthesized aspartame in which all of the carbons were [sup 13]C. By combining high speed MAS with very strong [sup.1]H decoupling powers, the authors were able to obtain high-resolution NMR spectra of uniformly [sup 13]C-labeled aspartame Two-dimensional exchange experiments were then used to assign the individual resonances for the resolved peaks.

[FIGURE 5 OMITTED]

Comparison to other analytical techniques

Pharmaceutical scientists use several analytical techniques to fully characterize a sample. Sometimes these techniques provide contradictory information A recent article by Padden et al highlights the use of PXRD and solid-state NMR spectroscopy for identifying different forms of a new artificial sweetener Neotame, a derivative of aspartame (15). Neotame exists in multiple polymorphic forms (16) Several of these forms were generated via dehydration and were successfully analyzed by PXRD and solid-state [sup 13]C CPMAS NMR spectroscopy. In the study, a sample containing a mixture of two anhydrous polymorphic forms was allowed to rehydrate for several days. Solid-state NMR spectroscopy showed that a transformation was occurring, and at one stage of the rehydration, as many as five different polymorphic forms were present (see Figure 6). Interestingly, the PXRD patterns did not change during the rehydration experiment. The researchers concluded that the NMR experiment was observing changes in the local conformation of the molecules, which the PXRD method did not identify because the long-range order was not affected

[FIGURE 6 OMITTED]

Conclusion

Solid-state nuclear magnetic resonance spectroscopy is a valuable technique for analyzing pharmaceuticals Using this technique, researchers can evaluate formulations in a nondestructive manner and gain far more information than by using other methods NMR spectroscopy can readily identify the contributions of excipients, and in some cases, eliminate them Polymorphs, polymorphic

transitions, and amorphous forms can be easily identified, and quantitation can be performed without the need of a standard curve

Table I. Comparison of actual versus NMR-determined weight percents for a physical mixture of delavirdine mesylate polymorphs (13).

Actual weight percent	NMR-determined weight percent
2.00	2.7
3.00	2.8
5 00	5.4
10.00	9 4
15 00	14.5
19 90	20.2
25.00	24.0
50.00	48 7

Acknowledgment

I would like to thank Drs Gary Silvey, Marty Power, and Jeff Botts for their contributions to this work.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

RESPUESTA AL RECURSO DE REPOSICIÓN

2020
Bogotá, D C , Marzo 29 de 2006

Abogado
GERMÁN CASTILLO GRAU

REFERENCIA:	Radicación No	00 028 932
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No	
	Folios	00

TÍTULO "Nuevos compuestos antidiabéticos"

En atención al Recurso de Reposición interpuesto, se hacen las siguientes aclaraciones

1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el nuevo capítulo descriptivo comprendido en los folios 5 - 16 y el nuevo capítulo reivindicatorio de los folios 119 - 122 de la solicitud en estudio

2. Objeto de la Invención

El objeto de la presente solicitud de patente de invención consiste en

Las reivindicaciones 1 - 8, 11, 12, se refieren a un polimorfo de la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona

Las reivindicaciones 9 y 14 - 18 mencionan un proceso para preparar un polimorfo que se caracteriza por la disolución del compuesto en acetona a elevada temperatura ó siembra en etanol desnaturalizado a elevada temperatura, de cristales del polimorfo y posterior enfriamiento de manera que se produce la cristalización del polimorfo, después de lo cual se recupera

La reivindicación 10 se refiere a una composición que contiene un polimorfo de la reivindicación 1 y un vehículo

La reivindicación 13 se refiere al uso del polimorfo.

El problema planteado en esta solicitud es la necesidad de proporcionar un nuevo producto farmacéutico para tratamiento y/o profilaxis de diabetes mellitus.

Para resolver este problema técnico la solicitud en estudio proporciona un polimorfo de la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etox[]bencil]-tiazolidin-2,4-diona.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 23 K 31/12 // 31/425 // 31/44; C 07 D 417/12; A 61 P 3/10.

También se reivindica prioridad de las Solicitudes de Patente de Gran Bretaña 9909473.2 de abril 23 de 1999 y 9912196.4 de mayo 25 de 1999, con respecto a las cuales la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Respuesta a los Argumentos del Solicitante

En atención a los argumentos del solicitante se hacen las siguientes aclaraciones:

1. Dice el solicitante en el folio 146 que el ser polimorfo no es algo inherente a un compuesto, porque si así fuese, "cualquier compuesto podría existir alguna vez en un estado único polimórfico".

Se aclara al solicitante que el polimorfismo sí es inherente al compuesto porque un técnico no puede formar un cristal de un compuesto que no tiene la capacidad de cristalizar en varias formas; y en cambio, es posible que haciendo sistemáticamente los cambios apropiados de polaridad (solventes), pH, velocidad de agitación, temperatura, encuentre las condiciones en las cuales se formen, de manera espontánea, los cristales que el compuesto es capaz de conformar. Y para esto se sigue una secuencia previamente establecida se busca el estado cristalino más estable. Justamente por esto, no es cierta la expresión según la cual "cualquier compuesto podría existir alguna vez en un estado único polimórfico", porque cada compuesto, de acuerdo con el ordenamiento tridimensional de las moléculas tiene capacidad para formar uno ó mas estados cristalinos.

La secuencia de cristalización del compuesto en diversos tipos de solventes con diferentes rangos de polaridad, con los cuales se producen diversas formas cristalinas, no puede considerarse inventiva, porque esta es una serie de ensayos sistemáticos que se realiza normalmente para purificar y caracterizar el compuesto después de ser sintetizado.

2. Dice el solicitante en el folio 147 que aunque los polimorfos tengan la misma estructura y el mismo nombre, difieren su espectro y su patrón XRPD.

Se aclara al solicitante que justamente porque conservan la misma estructura y el mismo nombre, los polimorfos son las diversas formas externas de los cristales en que pueden conformarse las moléculas del compuesto. Y como ya se explicó, no hay nivel inventivo ni en el proceso de cristalización ni en los cristales obtenidos.

3. Reitera el solicitante que por el hecho de mencionar esta solicitud un polimorfo, es nuevo e inventivo y piensa que no es cierta la expresión según la cual "de este compuesto ya se conocía sus existencia".

Se reitera al solicitante que no es nuevo y no es inventivo, por las razones ya expuestas. Efectivamente "de este compuesto ya se conocía su existencia" porque D1, D2 y D3 mencionaban formas cristalinas de la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona y su proceso de otención (ver folios 79 – 100); así que no es nuevo.
No es inventivo porque:

(a) el compuesto de esta solicitud ya era conocido en las anterioridades, de la misma manera que el hecho de recristalizarlo en un solvente orgánico, así que para una persona conocedora de la materia era evidente el cristalizarlo de manera similar, teniendo en cuenta lo enseñado por las anterioridades;
(b) las reivindicaciones de esta solicitud no mencionan una característica que conceda un efecto diferente o especial a la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona ni a las composiciones, según esta solicitud, que pueda considerarse como un aporte a la técnica, porque es el mismo compuesto, así que es obvio para una persona versada en la materia; porque el compuesto presenta las mismas propiedades anti diabéticas y no presenta propiedades sorprendentes ó inesperadas que resuelvan algún problema en la técnica, cuando se compara con el compuesto del estado del arte. Puesto que no se observa una ventaja comparativa sorprendente con respecto al compuesto enseñado en la anterioridad, es claro que no hay nivel inventivo.
(c) el problema planteado en esta solicitud que era la necesidad de proporcionar un producto farmacéutico para tratamiento y/o profilaxis de diabetes mellitas se resuelve con un polimorfo de la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona. Este polimorfo no constituye un aporte a la técnica porque lo normal durante el desarrollo de un medicamento es realizar una secuencia de cristalizaciones del compuesto, en las que se varía el solvente de cristalización y luego, de entre los cristales obtenidos, se lleva a escala industrial aquel que es más puro y más estable. Así que el polimorfo mencionado es obvio y evidente para una persona versada en la materia;
(d) el resultado obtenido: cristal de la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona no es inesperado;
(e) no parece haberse superado un prejuicio técnico anterior, con el cristal de la sal del ácido maléico de la 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]-tiazolidin-2,4-diona, el proceso, ni las composiciones propuestas.

De manera que las reivindicaciones 1 -18 no tienen **nivel inventivo.**

4. Conclusión

Teniendo en cuenta lo anterior, se recomienda ratificar la negación del privilegio solicitado para las reivindicaciones 1 - 18, folios 119 - 122.

Bogotá, D. C., Marzo 27 de 2006

CONCEPTO TÉCNICO 544	JEFE DIVISIÓN NUEVAS CREACIONES	EXAMINADOR TÉCNICO 202007