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A B O G A D O S

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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EXPEDIENTE 07-032-749

TÍTULO SOLICITADO: "FORMA FARMACÉUTICA DE IBUPROFENO DE LIBERACIÓN MODIFICADA."

PUBLICACIÓN: Gaceta 594 de 31 de Julio de 2008, N° de publicación 611.

PRIORIDAD : US 60/614.932 de 30/09/2004

SOLICITANTE: SCOLR PHARMA, INC.

APODERADO: LAURA MICHELSEN NIÑO

TRÁMITE: REMISION DE INFORMACION

JOSÉ LUIS REYES VILLAMIZAR, mayor y vecino de Bogotá, identificado como aparece al pie de la firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, en el trámite de la referencia, con el propósito de coadyuvar con la entidad en la decisión que sobre dicha solicitud de patente habrá de adoptar próximamente, de manera respetuosa me permito remitir información complementaria para demostrar que la pretensión de obtener patente de invención sobre una forma farmacéutica de ibuprofeno de liberación modificada, no puede ser objeto de privilegio de patente a la luz de las normas subregionales aplicables.

II. COMPLEMENTO DE INFORMACION

Con el propósito de reiterar que la solicitud colombiana en trámite carece de los requisitos de patentabilidad establecidos por los artículos 14, 16 y 18 de la

Decisión 486 y que, me permito brindar otros argumentos que complementan los ya presentados, veamos:

EN CUANTO A LA CLARIDAD DE LA SOLICITUD

Se observa que el nuevo capítulo reivindicatorio no supera las objeciones realizadas por el Señor Examinador, en cuanto al requisito de claridad por que la nueva reivindicación 4 reclama la composición por medio de su viscosidad, parámetro que depende de las características estructurales de la composición, de manera que la viscosidad no puede ser considerada como una característica técnica esencial de la solicitud de patente.

Por otro lado, aunque se ha modificado la redacción del capítulo reivindicatorio, los problemas de concisión y sustento persisten en la medida en que las diferencias en el número de polímeros, el tipo de polímero, la concentración y los aditivos sobre las propiedades de la tableta y su efectividad son muy amplios de forma que no sería reproducible la composición reclamada de forma inequívoca dado que los rangos de cada componente son muy extensos; es evidente entonces que lo reclamado es una generalización no verificada de los ejemplos descritos.

Por otra parte, en el aparte 2.2 (página 1 de memorial radicado el 21.02.2011) el solicitante argumenta que: *"Igualmente, el señor examinador se refiere a que las cláusulas 1 y 10 no establecen el tipo de polímero; que no establecen un rango específico de ibuprofeno; que no se limitan los agentes diluyentes aminoácidos con base en la descripción; y, que no se limita el uso de carbonato de sodio" y menciona en el numeral 2.3 que: "... no es claro el porqué se define que no se ha especificado o limitado los compuestos incluidos, si en reivindicaciones dependientes de éstas, se definen claramente los tipos de polímeros, diluyentes y la limitación del uso de carbonatos de sodio. Es de aclarar que en los ejemplos de la descripción se revela el "perfil de liberación" de la forma de dosificación sólida, de manera que ayudan a ilustrar e interpretar la invención y la materia que se desea proteger y que está contenida en las reivindicaciones, tanto en aquellas principales como en sus dependientes. En forma particular, se define una dosis sólida que logra un perfil de liberación, con las cantidades limitadas de ibuprofeno entre 300 y 800 mg, por lo que se ha ilustrado en la descripción varios ejemplos donde se ha modificado las dosis a varios puntos intermedios para sustentar tal*

afirmación. Hacer un estudio para todos los rangos entre 300 y 800 mg, sería innecesario, lo mismo que puntualizar una cantidad de ibuprofeno, toda vez que la combinación propuesta es aplicable a varias cantidades posibles. Debe ser claro, que la intención de la presente no es proteger el ibuprofeno, por el contrario, el objeto de la presente es proteger una novedosa forma farmacéutica que incluye entre otros, ibuprofeno y que comprende una mejorada disolución dentro del organismo después de su administración. A lo largo de estos ejemplos en la descripción, se especifica que la forma de dosificación sólida es una tableta comprimida monolítica, con una cantidad de ibuprofeno que varía en varios ejemplos y sobre la cual se estudia su comportamiento en el marco de la combinación novedosa, entre otros, que incluye uno o más polímeros hidrofílicos comprendiendo dos diferentes viscosidades y que en conjunto hacen de la forma a proteger como novedosa y diferente a las formas farmacéuticas conocidas que incluyen ibuprofeno: esto excluye las tabletas que son bi-capas o con partes que están en de forma granulado o embebidos en una matriz. Con la configuración propuesta y con estos componentes como se define en la reivindicación principal y se especifican o particularizan en sus cláusulas dependientes, los inventores han mostrado que el perfil de liberación exigido se puede alcanzar (ver ejemplos), mejorando su biodisponibilidad y actuación dentro del organismo. Esta es una característica importante de la invención, a saber, lograr una "bi-modalidad" de perfil de liberación, en la que se libera al menos el veinte por ciento del ibuprofeno en dos horas tras la administración oral de ibuprofeno y luego liberar en una proporción relativamente constante durante al menos ocho horas con al menos el setenta por ciento de ibuprofeno en un periodo de no más de catorce horas". El subrayado es nuestro.

Como se observa, el Señor Solicitante explica la amplitud y la poca claridad de las reivindicaciones tomando en cuenta los ejemplos y la descripción sin tener en cuenta que es el tenor de las reivindicaciones el que confiere el alcance de la protección (ver Art 51 D. 486). Por otra parte, en la argumentación presentada el Señor Solicitante defiende únicamente el intervalo de concentración de ibuprofeno, pero es totalmente silencioso en los demás componentes que en últimas son parte de la solicitud por tratarse de una "novedosa forma farmacéutica" como él mismo lo menciona; de esta forma el Señor Solicitante insiste en la no definición del tipo de polímero, ni los aminoácidos ni tampoco los diluyentes, compuestos que le dan la estructura, función y resuelven el problema técnico propuesto.

Continuando con el análisis, el Señor Solicitante además falla en interpretar la función de las reivindicaciones al mencionar que *"...con estos componentes como se define en la reivindicación principal y se especifican o particularizan en sus cláusulas dependientes..."*, está pasando por alto, que es la reivindicación principal la que debe presentar las características técnicas estructurales que definen la materia que se desea proteger, entendiéndose que son éstas las que hacen novedoso e inventivo el objeto de la solicitud, mientras que las reivindicaciones dependientes se refieren a modalidades particulares del objeto reclamado, y no en las que la especifican o particularizan los componentes, como el Señor Solicitante presume.

Así mismo, es necesario entender además, como lo menciona el Manual Andino de Patentes en su numeral 4. 5. 2 sobre las reivindicaciones dependientes, que "Una reivindicación dependiente es patentable si la reivindicación independiente de la cual se deriva es también patentable..." Por tal razón se llama la atención al Despacho de la SIC para que determine la claridad, concisión y sustento de la reivindicación principal sobre la base de lo anteriormente presentado y bajo la siguiente óptica: la nueva reivindicación 1 que es la que define la invención, incluye la expresión *"forma farmacéutica sólida para la administración oral modificada (...) que comprende:"* según la cual se habla de modificar la administración oral, más no la liberación del principio activo.

Dicha nueva reivindicación 1 enseña que comprende: *"...uno o más polímeros hidrofílicos comprendiendo dos diferentes viscosidades..."*, en este fragmento no muestra cuántos ni cuáles son los polímeros empleados, dejando abierta la selección de múltiples alternativas posibles, de manera que cualquier mezcla de polímeros podría entrar dentro del alcance de esta reivindicación.

Además hace mención a dos polímeros con viscosidades diferentes y no deja claro si se refiere a una característica estructural o si es un resultado de la concentración del mismo polímero; de ninguna manera se puede considerar que este fragmento muestre claramente las características de los polímeros que desea proteger.

La mencionada nueva reivindicación 1 continúa de la siguiente manera: *"...de 300 o 800 mg de ibuprofeno en la forma farmacéutica sólida uniformemente dispersos*

en dicho polímero..." sin especificar la cantidad realmente efectiva, y luego menciona: "...un diluyente disperso en dicho polímero hidrofílico en una cantidad en el intervalo del 10% al 35 % en peso de ibuprofeno... dicho diluyente que comprende una sal alcalina metálica, un aminoácido de cadena lateral de neutra a alcalina, croscarmelosa o una sal de la misma, o cualquier combinación de dos de dichos diluyentes...", en estos fragmentos se observa que no se especifican el diluyente ni las combinaciones y que por su amplitud dichas combinaciones obedecen a un número indeterminado y no soportado por la descripción, y por ultimo menciona: "...y un aditivo inerte de la fórmula disperso en dicho polímero hidrofílico en una cantidad en el intervalo del 15 % al 75% en peso de ibuprofeno, dicho aditivo de la fórmula que comprende celulosa microcristalina, sílice, estearato de magnesio, ácido esteárico, lactosa, almidón pre-gelatinizado, fosfato dicalcico o una combinación de cualquiera de los mismos, en donde la forma farmacéutica sólida es una tableta comprimida monolítica..." de este aparte se puede observar la carencia de una definición clara y concisa de, en este caso, los aditivos de la composición.

EN CUANTO A LA PATENTABILIDAD DE LA SOLICITUD

El Solicitante argumenta en el aparte 3.3. (página 2 de memorial radicado en 21.02.2011): *"... D1 revela una forma farmacéutica de un agente activo de liberación gástrica modificada que está constituido por un agente activo disuelto en una matriz polimérica que contiene un polímero hidrofílico, un agente aglutinante y una sustancia no polimérica soluble en agua; y, D2 define una composición farmacéutica en forma de tableta (comprimido) compuesta por un vehículo base constituido por la mezcla de hidroxipropilmetil celulosa (HPMC) de alta viscosidad y baja viscosidad, Ibuprofeno, un agente de unión o aglutinante y otros excipientes."* En el parte 3.4 dice (página 3 de memorial radicado en 21.02.2011): *"Diferimos de la apreciación del señor examinador en la medida que ninguno de los documentos D1 o D2, definen una dosis uniformemente dispersada que comprende una combinación de ibuprofeno con uno o más polímeros hidrofílicos comprendiendo dos diferentes viscosidades, un aditivo en disolución y una formulación de aditivo."*

Frente a las argumentaciones anteriormente citadaS, y teniendo en cuenta el nuevo capítulo de reivindicaciones, se observa que la característica técnica

esencial de la composición reclamada está en la combinación de ibuprofeno con uno (1) o mas polímeros con dos (2) viscosidades diferentes; sin embargo, no se enseña en la reivindicación principal modificada cuales son los polímeros empleados y las características técnicas que les permiten lograr dos viscosidades diferentes; de manera que, a la luz de lo presentado en la reivindicación 1 los documentos mencionados por el Examinador – D1 US6548083 y D2 US5009895– si logran afectar los requisitos de patentabilidad de la solicitud en mención. (Cabe resaltar nuevamente que los aditivos y los diluyentes reclamados son numerosos y sus rangos son pocos específicos por lo cual D1 y D2 afectan los requerimientos de patentabilidad de la presente solicitud.)

En el aparte 3.5 (página 3 memorial radicado 21.02.2011) el Solicitante dice: “... D1, se dirige a una forma de dosificación que se adapta para la retención en el estómago, útil para la entrega prolongada de una formulación de un agente activo en un ambiente fluido (Ver resumen). Esto se logra mediante la utilización de una banda de material insoluble que rodea una matriz de polímero que se hincha al entrar en contacto con los fluidos del estómago, la banda de material insoluble (p.e. el número 15 en las figuras 1b-4d, 6 y 7), de manera que impide que la parte cubierta de la matriz polimérica se hinche y proporcione un segmento de forma de dosificación con la rigidez suficiente para soportar las contracciones de la expulsión del estómago y el retraso del mismo hasta que el agente activo se haya dispensado poco a poco.” En contraste a lo allí revelado, el Solicitante argumenta lo siguiente en el aparte 3.6: “... la invención reivindicada en la presente es una tableta monolítica comprimida, no comprende bandas insolubles que se necesitan para lograr los propósitos incluyen el logro de una liberación bimodalidad, además, en forma de tabletas comprimidas monolítica, donde la invención reivindicada excluye la necesidad de cualquier tipo de granulación. Para esto, dirigimos su atención a los ejemplos 7, 9 y 12-14 de la presente solicitud, donde se define que tableta es monolítica y se forma a partir de todos los ingredientes para conformar un comprimido, que en comparación no comprende una etapa de granulación para su conformación”

Si tenemos en cuenta lo anterior, vemos que a partir de D1, tal y como lo señala el Solicitante, se observa que enseña formas farmacéuticas con bandas a su

alrededor de material insoluble¹ (párrafo 28, D1) que además contienen polímeros (párrafo 29 a 30, D1)² de varias clases. Sin embargo, se agrega que D1 reivindica una forma farmacéutica que contiene: un agente de reserva que comprende un ingrediente activo, adaptado a liberar el agente activo por un periodo de tiempo prolongado y una capa de una matriz polimérica que promueve la retención de la forma farmacéutica (párrafo 57, D1)³.

Se tiene entonces que en contraste con lo argumentado por el Solicitante, D1 ya revelaba las características técnicas esenciales que reclama la presente solicitud de patente: un ingrediente activo contenido en una matriz polimérica, la cual además podría estar constituida por uno o más polímeros.

Si a esto se agrega que en la nueva la reivindicación 1 el Solicitante no presenta de forma explícita los polímeros ni las viscosidades de cada uno en la composición, NO es posible establecer estas las características técnicas que lo hacen diferente la composición divulgada por D1. Entonces, la nueva reivindicación 1 al reclamar dos viscosidades desconocidas de polímeros desconocidos no da elementos para que el experto en la materia logre una forma farmacéutica esencialmente diferente de la composición revelada por D1.

¹ D1, US 6548083 [00028] In still another aspect, the active agent dosage form comprises (a) a therapeutically-effective amount of an active agent, (b) a polymer matrix in which the active agent is dissolved or dispersed, the polymer matrix including a high molecular weight, water-soluble polymer and a hydroattractant such as a water-insoluble polymer, and, optionally, non-polymeric water-soluble excipients and polymers of molecular weight of less than 10,000 grams per mole, the polymer matrix having an outer surface for exposure to the environment of use, and (c) a band of insoluble material circumscribing a portion of the outer surface of the polymer matrix.

² [00029] Examples of water soluble polymers are sodium and calcium polyacrylic acid, polyacrylic acid, polymethacrylic acid, polymethylvinylether co-maleic anhydride, polyvinylpyrrolidone, polyethylene oxide, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, hydroxymethyl methacrylate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, methyl cellulose, maltodextrin, xanthan gum, tragacanth gum, agar, gellan gum, kayara gum, alginic acids, pectins, pre-gelatinized starch, and polyvinyl alcohol, and blends of those polymers. Particularly useful polymer blends are those which form association polymers in the low pH environment of the stomach, such as mixtures of polyacrylic acid and polyethylene oxide or mixtures of polyacrylic acid and polyvinylpyrrolidone.

[00030] Examples of hydroattractants are water insoluble polymers such as low substituted hydroxypropyl cellulose, ion exchange resins, microcrystalline cellulose, cross-linked sodium or calcium carboxymethyl cellulose, cellulose fiber, cross-linked polyvinyl pyrrolidone, cross-linked polyacrylic acid, cross-linked Amberlite resin, alginates, chitin, colloidal magnesium-aluminum silicate, corn starch granules, wheat starch granules, rice starch granules, potato starch granules, zein, soya polysaccharide, and sodium carboxymethyl starch, and blends of these hydroattractants.

[00031] Examples of non-polymeric water soluble excipients include sugars, such as mannitol, sorbitol, sucrose, lactose, fructose, maltose; salts such as sodium chloride, potassium chloride, calcium sulfate; the amino acids alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine; buffering agents such as citric acid, sodium citrate, potassium citrate, succinic acid, fumaric acid, sodium acetate, sodium phosphate monobasic, tartaric acid, sodium potassium tartrate; surface active agents such as poloxamers, polysorbates, lecithin and the like; and effervescing couples such as citric acid blended with sodium bicarbonate, and similar blends. Maltodextrin, having a molecular weight of about 400 to 4000 grams per mole, and polymers having similar properties are example of a low molecular weight polymeric materials useful in this invention.

³ (57)What is claimed is: 1. An active agent dosage form comprising: an active agent reservoir comprising an active agent, the active agent reservoir being adapted to deliver the active agent over a prolonged period to a stomach of a subject; and a layer of polymer matrix provided around the active agent reservoir and including a swellable, water-soluble polymer and a water insoluble hydroattractant, the layer of polymer matrix being configured to promote gastric retention of the dosage form.

Por otro lado, con relación a la argumentación que la tableta de la presente solicitud es monolítica y la de D1 no, se observa que este hecho no parece ser la característica técnica esencial de la presente solicitud de patente, así mismo, no hay nada en el capítulo reivindicatorio ni en el memorial de respuesta al requerimiento según el artículo 45 que aporte pruebas que demuestren de que este tipo de tableteado de la forma farmacéutica es el que le otorga un efecto técnico superior al logrado por las tabletas del estado del arte; se observa entonces que ni la forma de tableteado, ni las viscosidades de los polímeros que el Señor Solicitante menciona como elementos distintivos de lo reclamado sobre la materia que comprende el estado del arte demuestran ser elementos que logren un efecto técnico superior o diferente al esperado.

En otro aspecto, el Solicitante argumenta en el aparte 3.7. (página 3 de memorial radicado en 21.02.2011): *“Con respecto a la patente D2, allí se enseña un sistema de liberación de orden cero (lineal). Enseña gránulos dispersos en dos tipos diferentes de HPMC para modular y lograr la liberación de orden cero. Como se mencionó anteriormente, la presente, por el contrario, recita una tableta monolítica que no requiere de granulación y ello se define claramente en la descripción. En D2, con base en el “Proceso” expuesto de la columna 3, se define una preparación inicial de un lote de gránulos de ibuprofeno lisina que contiene PVP. Estos gránulos son posteriormente mezclados con diversos excipientes en forma licuada para formar una mezcla que posteriormente se comprime, por lo que sobre los comprimidos formados no puede decirse, que es “monolítico”) por naturaleza.”* En el aparte 3.8. (página 3 de memorial radicado en 21.02.2011): *“La presente solicitud tiene por objeto una tableta que tiene una bi-funcionalidad donde tiene una liberación inmediata de ibuprofeno dentro de las 2 horas seguido por una liberación constante relativa de ibuprofeno por 8 horas. Por el contrario, ninguna de estas anterioridades D1 o D2 define una tableta de dispersión uniforme ausente de capas, gránulos, etc.”*

Frente a los argumentos anteriores presentados por el Señor Solicitante se anota que en ninguna parte del cuerpo de las reivindicaciones se muestra la forma de preparación y según la descripción no parece que el efecto técnico de liberación del activo sea logrado por la ausencia de granulación; también se deja de presente que teniendo en cuenta las características técnicas estructurales de la

composición reclamada se observa que son fácilmente derivables del estado del arte, especialmente de D1 y D2, ya que revelaban composiciones con ibuprofeno en matrices poliméricas, lo cual demuestra que cualquier experto medio en el área habría sugerido el incluir el ibuprofeno a una matriz polimérica sin granular previamente.

Por otro lado, no se encuentran estudios de comparación entre otras composiciones como las de D1 y D2 y las formas farmacéuticas acá reclamadas que demuestren que las últimas resuelven el problema técnico planteado y superar o mejorar el resultado alcanzado por las composiciones ya conocidas.

Como complemento, se anota que existían otras anterioridades que también proponían como problema técnico objetivo la necesidad de una formulación de ibuprofeno en el cual no se granulara dicho activo, como es el caso de la patente americana US 4,904,477 titulada: "Spray dried ibuprofen compositions", en la cual, se presenta una composición de ibuprofeno por la técnica de spray dried que supera los problemas relacionados con la granulación húmeda del ibuprofeno, veamos:

" [00006] The present invention provides a spray dried ibuprofen composition which is directly compressible into tablets. The spray dried compositions are free flowing and simplify production of tablets to a simple mixing and tableting operation with the necessity of only small amounts of conventional tableting lubricants and with a minimal rejection rate of underweight or imperfect tablets. Moreover, tablets formed from the spray dried compositions have good physical stability in respect of friability, disintegration and dissolution properties, and have excellent bioavailability associated with high dosage levels of ibuprofen.

[00007] The spray dried ibuprofen compositions of this invention comprise finely divided ibuprofen in a gelatinized starch matrix and are of a generally spherical shape. The spray dried compositions comprise ibuprofen, as a disintegrant croscovidone, croscarmellose sodium and/or sodium starch glycolate, pregelatinized starch, colloidal silica and as a wetting agent polyvinylpyrrolidone and/or sodium lauryl sulfate."

De lo anterior se puede concluir que por lo menos desde la fecha de presentación de la solicitud de patente US4,904,477 en julio 13 de 1989, ya eran conocidas composiciones que no requerían la granulación del ibuprofeno por vía húmeda y

que sugerían ya al experto en la materia la posibilidad de mejorar las formas farmacéuticas que contienen dicho agente activo por medio de la no granulación del mismo, adicionalmente, la reivindicación principal de dicha anterioridad ya mostraba que el ibuprofeno estaba en combinación con algún polímero, tal como se describe a continuación:

(57) We claim:

1. A spray dried ibuprofen composition in powder form suitable for direct compression into tablets consisting essentially of about 80% to about 90% by weight ibuprofen, about 2% to about 6% by weight of a disintegrant selected from the class consisting of crospovidone, croscarmellose sodium and sodium starch glycolate, about 8% to about 12% by weight pregelatinized starch, and about 0.2% to about 2% by weight of a wetting agent selected from the class consisting of polyvinylpyrrolidone and sodium lauryl sulfate, the powder having been spray dried from a dispersion in water of the ibuprofen, the disintegrant, the gelatinized starch and the wetting agent.

Esto permite concluir que en el estado de la técnica ya habían muchas enseñanzas a partir de las cuales el experto medio habría podido sugerir formulaciones como las reclamadas por la presente solicitud de patente.

Para finalizar con nuestro análisis, el Solicitante expresa: “... *un primer objeto de la presente invención es proporcionar una forma farmacéutica de dosis de liberación modificada, que comprende una tableta uniformemente dispersada de liberación de la dosis del activo de manera inmediata, inicialmente para proporcionar después una dosis de liberación extendida, y ninguno de los antecedentes expuestos puede compararse con ésta, dado que la función, la composición y su objeto son diferentes.*” Nuevamente nos permitimos citar las anterioridades D1 y D2, las cuales presentan formas farmacéuticas capaces de modificar la liberación del principio activo dado que en su composición contienen ingredientes activos en matrices de uno o más polímeros, de manera que D1 y D2 si están relacionados con el objeto de la presente solicitud toda vez que proveen formas farmacéuticas para entrega de principios activos con excipientes que permiten tal propósito y, por lo que las enseñanzas ya presentadas si llevarían a cualquier experto en la materia a lograr procurar una formulación como la planteada en la presente solicitud.

De igual forma, la patente americana antes mencionada, US 4,904,477 ya presentaba composiciones que contenían ibuprofeno sin necesidad de la

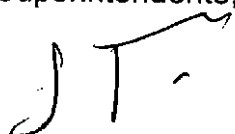
granulación por vía húmeda y con componentes como la croscarmelosa –de manera similar a lo reclamado por el Señor Solicitante – lo que demuestra una vez más que los elementos de todas las anterioridades mencionadas si constituyen claves para que el experto en la técnica lograra llegar a la composición acá reclamada, dejando además en evidencia que los resultados presentados en el memorial (aparte 2.3 página 2 del memorial radicado 21.02.2011) y en la descripción no eran inesperados a partir de lo divulgado por la materia que comprende el estado del arte.

Por todo lo anterior, le solicito Señor Superintendente, que analice los argumentos citados con el rigor y detenimiento habituales y que decrete, además de la negación de la solicitud en comento, el archivo del citado expediente.

III. ANEXOS

- Patente americana US 4,904,477 de julio 13 de 1989.

Señor Superintendente,



JOSÉ LUÍS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A 44.655 del C.S.J.

12

United States Patent [19]

Ho et al.

[11] **Patent Number:** 4,904,477[45] **Date of Patent:** Feb. 27, 1990[54] **SPRAY DRIED IBUPROFEN
COMPOSITIONS**[75] **Inventors:** Ying T. R. Ho, Haddonfield; Robert
G. Blank, Vineland, both of N.J.[73] **Assignee:** American Home Products
Corporation, New York, N.Y.[21] **Appl. No.:** 378,480[22] **Filed:** Jul. 13, 1989**Related U.S. Application Data**

[63] Continuation of Ser. No. 71,116, Jul. 8, 1987, abandoned.

[51] **Int. CL⁴** A61K 9/20[52] **U.S. Cl.** 424/465; 424/479;
424/492; 424/494; 424/497; 424/498[58] **Field of Search** 424/465, 479, 480, 492,
424/494, 497, 498[56] **References Cited****U.S. PATENT DOCUMENTS**

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Primary Examiner—Mark L. Bell*Assistant Examiner*—David M. Brunsman*Attorney, Agent, or Firm*—John W. Routh[57] **ABSTRACT**

A spray dried ibuprofen composition suitable for direct compression into tablets comprising a spray dried dispersion in water of ibuprofen, pregelatinized starch, a disintegrant and a wetting agent for the ibuprofen.

7 Claims, No Drawings

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SPRAY DRIED IBUPROFEN COMPOSITIONS

This application is a continuation of application Ser. No. 071,116, filed July 8, 1987, now abandoned.

BACKGROUND OF THE INVENTION

The invention relates to spray dried compositions comprising agglomerates of ibuprofen in a gelatinized starch matrix and to a method for manufacture thereof.

The commercial analgesic, aspirin, can be dry-mixed with starch and is then directly compressible into tablets. The commercial analgesic acetaminophen, on the other hand, cannot be similarly dry mixed and directly compressed but must be further processed such as, for example, by wet granulation; by spray drying acetaminophen with pre-gelatinized starch as described in European Pat. Appln. EP 40,472; or by fluidizing acetaminophen and cross-linked sodium carboxymethyl cellulose in hot air, pulverizing the mixture with pregelatinized starch paste, and drying as described in Fr. Demande FR 2,496,461.

The commercial analgesic ibuprofen is also different from aspirin in that it cannot be dry-mixed with starch and directly compressed into tablets. In the past, most ibuprofen tablets have been prepared from a wet granulation of a binder and ibuprofen which is dried, mixed with lubricants and disintegrating agents and compressed into tablets. This process involves several processing steps and is disadvantageous because of the equipment costs, time involved and higher rejection rate. A dry granulation process is described in U.S. Pat. No. 4,609,675.

SUMMARY OF THE INVENTION

The present invention provides a spray dried ibuprofen composition which is directly compressible into tablets. The spray dried compositions are free flowing and simplify production of tablets to a simple mixing and tableting operation with the necessity of only small amounts of conventional tableting lubricants and with a minimal rejection rate of underweight or imperfect tablets. Moreover, tablets formed from the spray dried compositions have good physical stability in respect of friability, disintegration and dissolution properties, and have excellent bioavailability associated with high dosage levels of ibuprofen.

The spray dried ibuprofen compositions of this invention comprise finely divided ibuprofen in a gelatinized starch matrix and are of a generally spherical shape. The spray dried compositions comprise ibuprofen, as a disintegrant croscopolvidone, croscarmellose sodium and/or sodium starch glycolate, pregelatinized starch, colloidal silica and as a wetting agent polyvinylpyrrolidone and/or sodium lauryl sulfate.

The proportions of ingredients in the spray dried ibuprofen compositions can be adjusted within limits to provide a free flowing, dust free powder suitable for feed to a high speed table press. The proportions generally range from about 80% to about 90% by weight ibuprofen, about 1.5% to about 6% by weight disintegrant, about 8% to about 12% by weight pregelatinized starch, about 0.10% to about 0.35% by weight colloidal silica, and about 0.2% to about 2.0% by weight wetting agent.

The spray dried compositions of the invention have several properties which make them especially suitable for charging to a high speed tablet press. One such

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property is the free flow characteristic as evidenced by a low angle of repose when collected, for example, in a beaker from a funnel positioned above the beaker. The free flow characteristic permits faster tablet compression with less weight variation between tablets. Another such property is the natural lubricity of the spray dried compositions, requiring only minimal amount of tableting lubricants such as, for example, stearic acid. In general, the lower the lubricant level, the faster the dissolution of the tablet.

DETAILED DESCRIPTION OF THE INVENTION

The ibuprofen is available commercially, for example, from Ethyl Corporation, Baton Rouge, La. A suitable pharmaceutical grade is marketed as a powder with a particle distribution of 100-250 microns.

Croscarmellose sodium is a cross-linked polymer of carboxymethylcellulose sodium and is available in Type A and Type B depending upon the degree of substitution. Type A is preferred for the compositions of this invention. It is sold under the trade name ACDISOL and is available from FMC Corporation, 200 Market Street, Philadelphia Pa. 19103, U.S.A.

Pregelatinized starch is starch that has been chemically and/or mechanically processed to rupture all or part of the granules separated from the mature grain of corn in the presence of water. It is available from National Starch and Chemical Corp., Bridgewater, N.J. U.S.A. as STARCH 1551.

The colloidal silica is a commercial product and is available commercially in USP and NF grades. It is marketed by Degussa Corp., Teterboro, N.J. U.S.A. and a suitable grade is marketed under the tradename AEROSIL 200.

Polyvinylpyrrolidone is available commercially in U.S.P. grade under the generic name povidone and is marketed by GAF Corporation, 140 West 51st. Street, New York, N.Y. 10020 under the trademark PLASDONE K. A suitable grade is PLASDONE K-29/32 which has a molecular weight of about 29,000-32,000. Croscopolvidone are cross linked insoluble homopolymers of polyvinylpyrrolidone also known as polyvinylpyrrolidone. It is also available from GAF Corporation under the trademark POLYPLASDONE-XL-X.

Sodium lauryl sulfate is a commercial product in USP grade. Preferably it is used in powder form to promote blending and is available from Albright Wilens, 180 Old Tappan Road, Old Tappan, N.J., U.S.A., under the tradename EMPICOL, and a suitable grade is EMPICOL 0303. Sodium starch glycolate is available commercially and is marketed by Generichem Corp., 85 Main Street, Little Falls, N.J. under the trademark PRIMOJEL.A. It is made from potato starch.

Spray dryers can be of the usual laboratory or commercial type. Suitable spray dryers are manufactured by Buchi Laboratories-Technik AG, by the Anhydro Company of Attleboro, Mass. and Niro Atomizer Inc., of Columbia, Md.

The spray dryer employed in the first six examples was a Niro Portable Spray Dryer, Model No. 21231-0001. The operating conditions include a variable air inlet temperature, a variable air pressure of compressed air driving the atomizer wheel, and a variable feed rate.

The invention will be further illustrated by the following examples in which the spray dried compositions were prepared using the procedure described therein.

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In the examples where indicated there were employed ibuprofen, STARCH 1551 brand of pregelatinized starch, AEROSIL 200 brand of colloidal silica, AC-DISOL Type A brand of croscarmellose sodium and PLASDONE K-29/32 brand of povidone, EMPICOL 0303 brand of sodium lauryl sulfate, and PRIMOJEL brand of sodium starch glycolate.

The invention will be further illustrated by the following examples in which the spray dried compositions were prepared using the procedures described therein.

EXAMPLE 1

In this example the feed mixture charged to the spray dryer was composed of the following materials.

	Grams Ingredient	Weight % Ingredient in Suspension	Weight % Ingredient in Powder
Ibuprofen	1000	35.9	85
Pregelatinized Starch	140	4.0	11.9
Croscarmellose Sodium	28	.77	2.4
Colloidal Silica	3	.08	0.26
Povidone	5	.14	0.43
Purified Water, deionized	2414		
	3590		

The water was placed in a stainless steel mixing vessel equipped with a Lightnin mixer. The povidone, croscarmellose sodium, and colloidal silica were slowly added to the water with mixing and mixing was continued for 5 minutes. The ibuprofen powder was slowly dispersed in the mixture and mixed for 30 minutes until homogeneous. The pregelatinized starch was then slowly added and mixed until homogeneous.

The spray dryer was operated with a feed rate of 30 to 35 grams per minute and an air outlet temperature of 60° to 65° C. The atomizer pressure was 2.2 to 2.3 bar.

The product from the spray dryer was a fine powder with a moisture content of 1.17%.

EXAMPLE 2

In this example the feed mixture charged to the spray dryer was composed of the following materials.

	Grams Ingredient	Weight % Ingredient in Suspension	Weight % Ingredient in Powder
Ibuprofen	500	23.94	85
Pregelatinized Starch	50	2.39	8.5
Croscarmellose Sodium	35	1.67	5.94
Colloidal Silica	1.5	.07	0.25
Povidone	2	.09	0.34
Purified Water, deionized	1500		100%
	2088.5		

The water was placed in a stainless steel mixing vessel equipped with a Lightnin mixer. Slowly added to the water with mixing were the croscarmellose sodium, the colloidal silica and the povidone. Mixing was continued for 5 minutes. The ibuprofen was then slowly added to the mixture and mixing was continued for 30 minutes. The pregelatinized starch was then added and mixing continued for 20 minutes.

The spray dryer was operated with a feed rate of 20-25 grams per minute and the air inlet heater was set to produce an air outlet temperature of 60°-65° C. The atomizer pressure was 4 bar.

The product from the spray drier was a fine powder.

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EXAMPLE 3

In this example the feed mixture charged to the spray dryer was composed of the following materials.

	Grams Ingredient	Weight % Ingredient in Powder
Ibuprofen	500	85
Pregelatinized Starch	62.5	10.63
Croscarmellose Sodium	20.0	3.40
Colloidal Silica	1.5	0.17
Povidone	4.0	0.68
Purified Water, deionized	1512	100%
	2100	

The water was placed in a stainless steel mixing vessel equipped with a Lightnin mixer. Slowly added to the water with mixing were the croscarmellose sodium, the colloidal silica and the povidone. Mixing was continued for 5 minutes. The ibuprofen was then slowly added to the mixture and mixing was continued for 30 minutes. The pregelatinized starch was then added and mixing continued for 2 hours.

The spray dryer was operated with a feed rate of 30 grams per minute and the air inlet heater was set to produce an air outlet temperature of 60°-65° C. The atomizer pressure was 80 p.s.i.

The product from the spray drier was a fine powder of about 40 microns with a moisture content of 0.4% and a bulk density of 0.401 grams per cubic centimeter.

The above spray dried powder was blended into a formulation for a compressed tablet as follows:

	Grams Per Batch	Milligrams Per Tablet
Spray Dried Powder (85% ibuprofen)	152.95	235.3
Croscarmellose Sodium, Type A	9.75	15.0
Pregelatinized Starch	19.50	30.0
Compressible starch	16.25	25.0
Colloidal Silica	0.13	0.2
Sodium lauryl sulfate	0.33	0.5
Stearic acid	1.30	2.0
		308.0

The compression mix for tableting was prepared by separately mixing the spray dried powder with the croscarmellose sodium, the pregelatinized starch and the compressible starch for 10 minutes in a PK-blender and then mixing with a pre-screened (30 mesh Tyler) mixture of the colloidal silica, the sodium lauryl sulfate and the stearic acid powder.

The compression mix was tabletted on a Stokes Rotary Press using tablet tooling set up for double compression with a release pressure of 2.6 tons at a RPM of 14. The compression mix showed good flow characteristics.

The tablets were divided into two batches and the physical characteristics of the tablets are shown below:

	Batch 1	Batch 2
Average weight, mg/tab	308-309	308-310
Thickness, inch	0.206-0.208	0.206-0.208
Hardness, Strong Cobb Units	6-8	4-6
Disintegration Time, minutes	1.25-1.50	1.25

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	Batch 1	Batch 2
Friability, USP Test	0-0.1	0-0.1

EXAMPLE 4

In this example the feed mixture charged to the spray dryer was composed of the following materials.

	Grams Ingredient	Weight % Ingredient in Powder
Ibuprofen	500	85
Pregelatinized Starch	62.5	10.63
Sodium Starch Glycolate	20.0	3.40
Colloidal Silica	1.5	0.26
Povidone	4.0	0.68
Purified Water, deionized	1512	
	2100	

The water was placed in a stainless steel mixing vessel equipped with a Lightnin mixer. Slowly added to the water with mixing were the sodium starch glycolate, the colloidal silica and the povidone. Mixing was continued for 5 minutes. The ibuprofen was then slowly added to the mixture and mixing was continued for 30 minutes. The pregelatinized starch was then added and mixing continued for 1 hour.

The spray dryer was operated with a feed rate of 32 grams per minute and the air inlet heater was set to produce an air outlet temperature of 60°-65° C. The atomizer pressure was 80 p.s.i.

The product from the spray drier was a fine powder of about 40 microns with a moisture content of 0.8% and a bulk density of 0.380 grams per cubic centimeter. The particle size distribution (Tyler screen) was, as percent retained on 100 mesh, 0.5%; retained on 200 mesh, 7.5%; retained on 325 mesh, 68.2% and greater than 325 mesh, 24.2%.

The above spray dried powder was blended into a formulation for a compressed tablet as follows:

	Milligrams Per Tablet
Spray Dried Powder (85% ibuprofen)	257.4
Sodium starch glycolate	10.0
Pregelatinized Starch	20.0
Compressible starch	40.0
Magnesium Stearate	0.8
Stearic acid	2.0
	330.0

The compression mix for tableting was prepared by separately mixing the spray dried powder with the sodium starch glycolate, the pregellatinized starch and the compressible starch for 8 minutes in a PK-blender and then mixing with a pre-screened (30 mesh Tyler) mixture of the magnesium stearate and the stearic acid powder.

The compression mix was tabletted on a Stokes Rotary Press using tablet tooling set up for double compression with a release pressure of 2.6 tons at a RPM of 14. The cmpression mix showed good flow characteristics.

The physical characteristics of the tablets are shown below:

	Batch
Average weight, mg/tab	330
Thickness, inch	0.212-0.216
Hardness, Strong Cobb Units	4-6
Friability, USP Test	0-0.1

EXAMPLE 5

In this example the feed mixture charged to the spray dryer was composed of the following materials.

	Grams Ingredient	Weight % Ingredient in Powder
Ibuprofen	500	84.96
Pregelatinized Starch	60	10.20
Croscarmellose Sodium	25	4.25
Colloidal Silica	1.5	0.25
Sodium Lauryl Sulfate	2.0	0.34
Purified Water, deionized	1500	100%
	2088.5	

The water was placed in a stainless steel mixing vessel equipped with a Lightnin mixer. Slowly added to the water with mixing were the croscarmellose sodium, the colloidal silica and sodium lauryl sulfate. Mixing was continued for 5 minutes. The ibuprofen was then slowly added to the mixture and mixing was continued for 30 minutes. The pregelatinized starch was then added and mixing continued for 20 minutes.

The spray dryer was operated with a feed rate of 20-25 milliliters per minute and the air inlet heater was set to produce an air outlet temperature of 60°-63° C. The atomizer pressure was 3.5 bar.

The product from the spray drier was a fine powder. The above spray dried powder was blended into a formulation for a compressed tablet as follows:

	Milligrams Per Tablet
Spray Dried Powder (85% ibuprofen)	233.3
Croscarmellose Sodium, Type A	20.0
Pregelatinized Starch	60.0
Colloidal Silica	0.20
Sodium lauryl sulfate	0.50
Stearic acid	2.0
	320.0

The compression mix for tableting was prepared by separately mixing the spray dried powder with the croscarmellose sodium, the pregellatinized starch and the compressible starch for 10 minutes in a PK-blender and then mixing with a pre-screened (30 mesh Tyler) mixture of the colloidal silica, the sodium lauryl sulfate and the stearic acid powder.

The compression mix was tabletted on a Stokes Rotary Press using tablet tooling set up for double compression with a release pressure of 2.6 tons at a RPM of 14. The compression mix showed good flow characteristics.

The physical characteristics of the tablets are shown below:

	Batch
Average weight, mg/tab	320

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	Batch
Thickness, inch	0.212-0.215
Hardness, Strong Cobb Units	4-5
Disintegration Time, minutes	1-1.25
Friability, USP Test	0-0.1

EXAMPLE 6

In this example the feed mixture charged to the spray dryer was composed of the following materials.

	Grams Ingredient	Weight % Ingredient in Powder
Ibuprofen	500	85.03
Pregelatinized Starch	50	8.5
Croscarmellose Sodium	35	5.59
Colloidal Silica	1.5	0.26
Sodium Lauryl Sulfate	1.5	0.26
Purified Water, deionized	1400	100%

The water was placed in a stainless steel mixing vessel equipped with a Lightnin mixer. Slowly added to the water with mixing were the croscarmellose sodium, the colloidal silica and the sodium lauryl sulfate. Mixing was continued for 5 minutes. The ibuprofen was then slowly added to the mixture and mixing was continued for 30 minutes. The pregelatinized starch was then added and mixing continued for 20 minutes.

The spray dryer was operated with a feed rate of 15-17 milliliters per minute and the air inlet heater was set to produce an air outlet temperature of 60°-65° C. The atomizer pressure was 3.5 bar.

The product from the spray dryer was a fine powder.

The above spray dried powder was blended into a formulation for a compressed tablet as follows:

	Milligrams Per Tablet
Spray Dried Powder (85% ibuprofen)	235.3
Croscarmellose Sodium, Type A	20.0
Pregelatinized Starch	30.0
Compressible Starch	20.00
Colloidal Silica	0.20
Sodium lauryl sulfate	0.50
Stearic acid	2.0
	308.0

The compression mix for tableting was prepared by separately mixing the spray dried powder with the croscarmellose sodium, the pregellatinized starch and the compressible starch for 10 minutes in a PK-blender and then mixing with a pre-screened (30 mesh Tyler) mixture of the colloidal silica, the sodium lauryl sulfate and the stearic acid powder.

The compression mix was tabletted on a Stokes Rotary Press using tablet tooling set up for double compression with a release pressure of 2.6 tons at a RPM of 14. The compression mix showed good flow characteristics.

EXAMPLE 7

In this example the feed mixture charged to the spray dryer was composed of the following materials.

	Grams Ingredient	Weight % Ingredient in Powder
Ibuprofen	500.0	88.07
Pregelatinized Starch	50.0	8.81
Crospovidone NF, XL	10.0	1.76
Colloidal Silica	1.5	0.26
Povidone	6.25	1.10
Purified Water, deionized	1512	100%
	2100	

The water was placed in a stainless steel mixing vessel equipped with a Lightnin mixer. Slowly added to the water with mixing were the crospovidone, the colloidal silica and the povidone. Mixing was continued for 5 minutes. The ibuprofen was then slowly added to the mixture and mixing was continued for 30 minutes. The pregelatinized starch was then added and mixing continued for 2 hours. The change to the spray dryer contained 30% solids.

The spray dryer was operated with a feed rate of 30 grams per minute and the air inlet heater was set to produce an air outlet temperature of 60°-65° C. The atomizer pressure was 80 p.s.i.

The product from the spray dryer was a fine powder of about 40 microns with a moisture content of 0.4% and a bulk density of 0.401 grams per cubic centimeter.

The above spray dried powder was blended into a formulation for a compressed tablet as follows:

	Grams Per Batch	Milligrams Per Tablet
Spray Dried Powder (88% ibuprofen)	113.6	227.2
Croscarmellose Sodium, Type A	9.0	18.0
Pregelatinized Starch	15.0	30.0
Compressible starch	15.0	30.0
Colloidal Silica	0.15	0.3
Sodium lauryl sulfate	0.30	0.6
Stearic acid	1.00	2.0
		308.1

The compression mix for tableting was prepared by separately mixing the spray dried powder with the croscarmellose sodium, the pregellatinized starch and the compressible starch for 10 minutes in a PK-blender and then mixing with a pre-screened (30 mesh Tyler) mixture of the colloidal silica, the sodium lauryl sulfate and the stearic acid powder.

The compression mix was tabletted on a Stokes Rotary Press using tablet tooling set up for double compression with a release pressure of 2.6 tons at a RPM off 14. The compression mix showed good flow characteristics.

The tablets were divided into two batches and the physical characteristics of the tablets are shown below:

	Batch
Average weight, mg/tab	308-309
Thickness, inch	0.206-0.209
Hardness, Strong Cobb Units	4-6
Disintegration Time, minutes	1-1.5
Friability, USP Test, 4 min.	0-0.1

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EXAMPLE 8

In this example, four large size runs were made with an eight foot diameter Bowen Pilot Unit spray dryer. The charges to the runs are shown in the following table in terms of weight percentage of each ingredient and solids content of the dispersion to the spray dryer. Typically, the solids were added to the water in the Dryer Feed Slurry Make-up Tank and agitated for two hours. The final viscosity ranged between 175-200 cps, the temperature between 24°-26° C., and the pH about 5.4

The spray dryer was operated at an air inlet temperature of 138°-143° C., an air outlet temperature of 60°-65° C., an atomizer RPM of 19,000-21,000 and a feed rate of about 120 pounds per hour. The yield was about 95%.

The spray dried powder from Run 1 typically had a loose bulk density of 0.372 grams per cubic centimeter, a moisture content of 1.0 per cent, and a sieve fraction % Alpine retained on +200 mesh of 14.9, and retained on +325 mesh of 49.0.

The spray dried powder from Run 2 typically had a loose bulk density of 0.354 grams per cubic centimeter, a moisture content of 0.86 per cent, and a sieve fraction % Alpine retained on +200 mesh of 13.5 and retained on +325 mesh of 42.0. The flow rate through the bulk densiometer was 43 seconds and the angle of repose was 39°.

The spray dried powder from Run 3 typically had a loose bulk density averaging 0.359 grams per cubic centimeter, a moisture content averaging 0.95 per cent, and a sieve fraction % Alpine retained on +200 mesh averaging 12.1 and retained on +325 mesh averaging 39.1.

The spray dried powder from Run 4 typically had a loose bulk density averaging 0.362 grams per cubic centimeter, a moisture content of 1.19 and a sieve fraction % Alpine retained on +200 mesh of 4.1 and retained on +325 mesh of 25.1. The flow rate through the bulk densiometer was 42 seconds and the angle of repose was 39°.

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Ingredient	Percent	Weight Kilograms
Croscarmellose Sodium	3.50	14.0
Colloidal Silica	0.25	1.0
Povidone	1.00	4.0
Ibuprofen	85.00	340.0
Total	100.00%	400.0
Deionized, Filtered Water	246 gallons	
Percent Solids	30%	

The solids were added to the water in the Dryer Feed Slurry Make-up Tank and agitated for 55 hours.

After 42 hours 10 additional gallons of water were added to the tank to maintain the solids content at about 30%. The final viscosity ranged between 500 to 750 cps, the temperature between 22.2 and 32.2° C. and the pH was 5.47.

The spray dryer was charged over a single day period from 1127 until 1647 hours. The spray dryer was operated at an air inlet temperature of 270°-275° F., an air outlet temperature of about 140° F., an atomizer RPM of 18,639 and a feed rate of about 0.77-0.82 gallons per minute. The yield was about 95%.

Samples of product from the spray dryer were taken periodically and the loose bulk density, moisture content and particle size distribution are shown in the following table. The spray dried material was collected into 7 drums.

Time	Moisture %	LBD g/cc	Sieve +200	Fraction +325	
1127	.73	.350	9.8	34.1	Drum 1
1147	1.0	.354	14.0	37.2	
1207	0.96	.356	10.9	38.6	
1233	0.98	.353	16.3	41.2	
1253			16.6	42.9	Drum 2
1314	.93	.349	15.6	43.2	
1334					
1346	.89	.360	17.7	44.3	
1415	.86	.356	15.8	42.0	Drum 3
1435	.91	.340	12.5	41.3	

Ingredient	Run #1		Run #2		Run #3		Run #4	
	Percent	Weight Kilograms	Percent	Weight Pounds	Percent	Weight Kilograms	Percent	Weight Kilograms
Pregelatinized Starch	10.00%	9.091	10.47	20.94	10.25	8.441	10.25	8.441
Croscarmellose Sodium	3.50%	3.182	3.41	6.82	3.50	2.882	3.50	2.882
Colloidal Silica	0.30%	0.273	0.27	0.54	0.25	0.206	0.25	0.206
Povidone	1.20%	1.091	0.85	1.70	1.00	0.824	1.00	0.824
Ibuprofen	85.00%	77.274	85.00	170.00	85.00	70.0	85.00	70.0
Total	100.00%	90.91	100%	200.00	100%	82.353	100%	82.353
Deionized, Filtered Water		56 gallons		56 gallons		51 gallons		51 gallons
Percent Solids	30% Solids		30% Solids		30% Solids		30% Solids	

EXAMPLE 9

In this example, a semi-production run was made on the Bowen Pilot Unit spray dryer used in the previous example. The dry ingredients in the charge to the spray dryer, as shown below, were dry blended in a PK blender for 30 minutes.

Ingredient	Percent	Weight Kilograms
Pregelatinized Starch	10.25	41.0

1500						
1520	.88	.344	10.4	42.7	Drum 4	
1540			14.5	43.3		
1600	.91	.343	11.8	40.5		
1630	.90	.341	10.8	39.5	Drum 5	
1650	.88	.340	10.0	37.9		
1720	1.06	.334	15.2	40.5	Drum 6	
1740		.350	20.6	46.0		
1810	.93	.349	17.1	48.4	Drum 7	
1830						

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The flow rate, as measured in seconds required to empty a funnel having a top opening of four and one-quarter inches in diameter, a bottom opening of three-quarter inch in diameter and a height of 12 inches, was determined and the angle of repose was determined by collecting the flow from the funnel in a 400 milliliter Nalgene beaker placed 4 inches below the funnel, the beaker having a top diameter of 3½ inches, a bottom diameter of 2½ inches and a height of 4½ inches, measuring the distance from the top of the beaker to the top of the powder, and extrapolating from a conversion table. The results are shown below:

	Spray Dried Powder		
	Flow Rate, Seconds	Angle Of (°) Repose	Loose Bulk Density (gm/cc)
Drum 1	56	37	0.397
Drum 2	47	38	0.386
Drum 3	48	37	0.401
Drum 4	43	37	0.404
Drum 5	65	39	0.395
Drum 6	43	36	0.404
Drum 7	35	42	0.395

For optimum tableting results, the loose bulk density is in the range of about 0.35 to 0.38 grams per cubic centimeter, the moisture content is less than 1% and the particle distribution is such that the sieve fraction % Alpine retained on +200 mesh ranges from about 10 to about 15% and retained on +325 ranges from about 40 to about 60%. The angle of repose is between about 20° to about 50°, preferably about 35° to about 45°.

EXAMPLE 10

Tablets were made from the spray dried powders from Examples 8 and 9 each with the formulation below:

Ingredient	Milligrams Per Tablet
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Spray Dried Powder	236.0
Pregelatinized Starch	22.5
Compressible Starch	22.5
Croscarmellose Sodium, Type A	18.0

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Ingredient	Milligrams Per Tablet
Colloidal Silica	0.45
Sodium lauryl sulfate	0.75
Stearic acid	1.80
Total	302.0

The compression mix for tableting was prepared by separately mixing the spray dried powder with the croscarmellose sodium, the pregelatinized starch and the compressible starch for 10 minutes in a PK-blender and then mixing with a pre-screened (30 mesh Tyler) mixture of the colloidal silica, the sodium lauryl sulfate and the stearic acid powder. The flow rate through the bulk densiometer, the bulk density and the angle of repose were measured and are shown in the following table.

	Compression Mix		
	Flow Rate Seconds	Loose Bulk Density (gm/cc)	Angle of Repose (°)
Run 1	45	0.394	36
Run 2	38	0.398	27
Run 3	—	—	—
Run 4	—	—	—
Drum 1	46	0.439	25
Drum 2	52	0.476	18
Drum 3	48	0.454	29
Drum 4	33	0.423	27
Drum 5	49	0.463	21
Drum 6	42	0.453	25
Drum 7	46	0.461	26

The compression mix was tabletted on a Stokes Rotary Press using tablet tooling set up for double compression with a release pressure of 2.6 tons at a RPM of 14. The compression mix showed good flow characteristics.

The physical characteristics of the tablets are shown below:

	Example 8				Example 9
	Run 1	Run 2	Run 3	Run 4	Drum 2
Average weight, mg/tablet	298	298	297	297	300
Thickness, inch	0.209-0.212	0.210-0.212	0.207-0.210	0.208-0.211	0.206-0.211
Hardness, Strong Cobb Units	4.5-6.5	5.5-6.5	4.5-5.5	4.0-5.5	5.5-6.5
Disintegration Time, minutes	1.73-2	1.41-1.67	3-4	4.75-5.25	2-2.25
Dissolution Rate, minutes*	5	4	5.6	6	4
Friability, USP	—	0.17	1.176	—	—
A Friability Stress	—	—	0.5	—	0.5

*Dissolution By FDA Method.
Ibuprofen Tablets, Capsules & Caplets
(Time for 80% to be dissolved)

EXAMPLE 11

Tablets were made from the spray dried powders from Example 10, Drums 5, 3 and 4 respectively, from the following ingredients in the amounts listed.

Ingredient	Run #1		Run #2		Run #3	
	Milligrams Per Tablet	Grams	Milligrams Per Tablet	Grams	Milligrams Per Tablet	Grams
Spray Dried Powder	236.00	6726	236.00	7080	236.00	7080
Pregelatinized Starch	22.40	641.25	25.00	750	25.00	750
Starch	—	—	19.80	600	24.80	600
Compressible Modified Starch	22.40	641.25	—	—	—	—
Croscarmellose Sodium, Type A	18.00	513	18.00	540	—	—
Crospovidone XL	—	—	—	—	13.00	540

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-continued

Ingredient	Run #1		Run #2		Run #3	
	Milligrams Weight		Milligrams Weight		Milligrams Weight	
	Per Tablet	Grams	Per Tablet	Grams	Per Tablet	Grams
Colloidal Silica	0.65	14.25	0.65	13.5	0.65	13.5
Sodium Lauryl Sulfate	0.75	19.95	0.75	22.5	0.75	22.5
Stearic Acid, TP	1.80	51.3	1.80	54	1.80	54
	302.00		302.00		302.00	

The spray dried powder was screened through a #12 mesh screen and added to a PK blender, followed by the pregelatinized starch, the compressible starch, the croscarmellose sodium or crospovidone, and the mixture was blended for 8 minutes. The colloidal silica, sodium lauryl sulfate and the stearic acid were screened through a #30 mesh screen, added to the PK blender and blended for 9 minutes. The flow rate, the loose bulk density and the angle of repose of the compression were measured and are shown below.

	Compression Mix		
	Flow Rate	Angle of Repose	Loose Bulk Density
Run 1	49	21	0.403
Run 2	48	29	0.454
Run 3	33	27	0.423

The compression mix was tableted on a Stokes Rotary Press Model BB-2, a 35 station press with 10.5 millimeter (0.71 concavity) tooling at 14 RPM for one hour and 30 minutes. The compression mix showed good flow characteristics.

The physical characteristics of the tablets are shown below:

	Run 1	Run 2	Run 3
Average weight, mg/tablet	302-305	303	303
Thickness, inch	0.203-0.206	0.203-0.206	0.205-0.209
Hardness, Strong Cobb Units	5-8	5-7	6.5-7.5
Disintegration Time, minutes	2-2.25	4.16-4.67	2.27-2.40
Dissolution Rate, minutes*	5.5	5	6
Friability, USP	0	0	0
Content Uniformity	±3.6%	±3.61	±4.31
Moisture Content, %	1.31	1.38	1.88

*Dissolution By FDA Method
Ibuprofen Tablets, Capsules
(Time for 80% to be dissolved)

EXAMPLE 12

An 8 kilogram batch of the tablets from Example 11, Run 1 was sugar coated with a coating procedure described below in a Colton 20 inch coating pan rotating at 30 RPM. The various coating materials were poured by hand from a small container or sprayer over the rotating tablets (about 26,500).

A seal coat was applied in the amount of 159 ml from a small sprayer during a period of three minutes. The seal was Opaglos GS-2-0310, a shellac type seal coat marketed by Colorcon Inc. West Point, Pa. After spraying was complete, the tablets were permitted to tumble for 2 minutes and then the tablets were removed from the coating pan and placed in an oven-humidifier at 40° C. for 8 hours. The seal coat was applied in the amount of 0.006 mg/tablet.

A sub coat was applied to 7.5 kilograms of the seal coated tablets (about 24,193). The sub coat contained the ingredients in the amounts listed below:

Ingredient	Weight Percent	Weight Grams
Sucrose, NF	67.3%	4038
Microcrystalline Cellulose,	5.2%	312
Deionized Water	27.5%	16.30
		6000

The microcrystalline cellulose was added to the water in a mixing vessel equipped with a stirrer and mixed for 2 minutes at 40 RPM. The suspension was heated to 60° C. and the sucrose was added while mixing. The suspension was maintained at 60°-65° during the time the sub coat was applied in about 18 applications of 200 ml per application, each application being followed by a tumbling period of 10 minutes followed by a warm (30°-35°) air drying interlude of 5 minutes.

The average tablet weight from the over-humidifier is about 310 milligrams and the target weight for the tablet with the subcoat is 425 milligrams. Beginning with the fifteenth application, tablets were weighed to obtain an average tablet weight prior to the next application.

A coloring coat was next applied in about 14 applications at the rate of 60 ml. per application, each application being followed by a tumbling period of 4 minutes followed by a warm (30°-35°) air drying interlude of 2 minutes. The target average tablet weight is 450 milligrams. The coloring coat was a mixture of ingredients in the amounts shown below:

Ingredient	Weight Percent	Weight Grams
Sucrose, NF	63.2%	448
Coloring	11.7%	175
Deionized Water	25.1%	376.5

The water was heated to 60° C. and the sucrose was added with stirring and cooled to 40° C. Add the coloring agent to the solution and mix for 5 minutes. Maintain the solution at 45° C. during the period of application to the tablets.

A polishing step was next employed in which a mixture of Opaglos GS-2-0310 and carnauba wax was applied to the tumbling tablets in an amount respectively of 0.028 and 0.1 milligram per tablet. Tumbling was continued for 30 minutes to complete the tablet coating procedure.

The coated tablets were tested for dissolution characteristics in accordance with the method suggested by the FDA for ibuprofen tablets. This test method differs from the USP test method in that 80% of the ibuprofen is dissolved in 60 minutes at 50 RPM using a Type 2 paddle. The dissolution time was 12 minutes for the coated tablets of this example.

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We claim:
1. A spray dried ibuprofen composition in powder form suitable for direct compression into tablets consisting essentially of about 80% to about 90% by weight ibuprofen, about 2% to about 6% by weight of a disintegrant selected from the class consisting of croscopol-
done, croscarmellose sodium and sodium starch glyco-
late, about 8% to about 12% by weight pregelatinized
starch, and about 0.2% to about 2% by weight of a
wetting agent selected from the class consisting of poly-
vinylpyrrolidone and sodium lauryl sulfate, the powder
having been spray dried from a dispersion in water of
the ibuprofen, the disintegrant, the gelatinized starch
and the wetting agent.
2. The spray dried composition of claim 1 wherein
the wetting agent is polyvinylpyrrolidone.

3. The spray dried composition of claim 1 wherein
the wetting agent is sodium lauryl sulfate.
4. The spray dried composition of claim 1 wherein
the disintegrant is croscarmellose sodium.
5. A compression mix for compressed tablets contain-
ing ibuprofen consisting essentially of, as the ibuprofen
component, the spray dried ibuprofen composition in
powder form of claim 1, and additionally containing
starch, a disintegrant and a wetting agent.
6. In a coated compressed tablet containing ibu-
profen, the improvement which comprises incorporat-
ing into the compressed tablet as the ibuprofen compo-
nent the spray dried ibuprofen composition of claim 5.
7. The improved coated compressed tablet of claim 6
wherein the tablet is a sugar coated compressed tablet.
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