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A B O G A D O S

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

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REF: Expediente 08 012.143

**TÍTULO SOLICITADO: FORMULACIONES FARMACÉUTICAS SÓLIDAS
SUBLINGUALES CONTENIENDO MELOXICAM.**

PUBLICACIÓN: Gaceta 604 de 29/05/2009, N° de publicación 199.

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SOLICITANTE: WORLD-TRADE IMPORT-EXPORT, WTIE, AG.

APODERADO: DILIA MARÍA RODRÍGUEZ D'ALEMAN.

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi 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 **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar la oposición presentada oportunamente ante ese Despacho, en los siguientes términos:

I. COMPLEMENTO DE INFORMACIÓN

Comendidamente me permito presentar los argumentos que demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 16 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario, veamos:

En primer lugar, y refiriéndonos a la carencia de nivel inventivo de la solicitud colombiana en trámite, es importante resaltar, que como cualquier persona medianamente versada en la materia debe reconocer, las tabletas sublinguales, así como los procesos mediante los cuales pueden obtenerse dichas formulaciones, se encuentran ampliamente descritas en el estado de la técnica. Las tabletas sublinguales y bucales son comprimidos destinados a situarse bajo la lengua o a mantenerse en la cavidad oral, donde se disuelven ya sea para ejercer un efecto local o sistémico. Así mismo dichos comprimidos pueden tener una lenta liberación del fármaco o en otros casos una liberación inmediata, características que pueden manipularse a través de la inserción u omisión de ciertos excipientes¹.

En otras palabras, la inclusión de cualquier tipo de principio activo dentro de este tipo de formulaciones farmacéuticas (tabletas sublinguales) no sustenta nivel inventivo alguno, puesto que dicha inclusión corresponde a una práctica común y cotidiana en la industria farmacéutica, que involucra la realización de los respectivos ensayos de preformulación y formulación que garanticen la eficacia, efectividad, seguridad y estabilidad del medicamento con unas características predefinidas para el respectivo tipo de formulación farmacéutica. Lo anterior también puede sustentarse en la versatilidad con que este tipo de formulaciones sublinguales ha incluido con anterioridad otros tipos de fármacos, tales como nitroglicerina², aspirina³, fármacos beta-2-miméticos⁴ y calcitonina⁵.

En otro aspecto, y esta vez refiriéndonos a la absoluta falta de novedad de la solicitud colombiana en cuestión, es importante exponer la existencia de documentos que contienen información que describe con anterioridad la esencia de todo lo contenido en el capítulo reivindicatorio de la solicitud colombiana en trámite, veamos:

¹ Vila Jato J.L. Tecnología Farmacéutica. Volumen II. Páginas 142 y 143.

² Patente americana US3789119: STABILIZED MOLDED SUBLINGUAL NITROGLYCERIN TABLETS.

³ Patente americana US4206209: Sublingual aspirin tablet.

⁴ Patente Europea EP0306422B1: Galenical forms of 2-beta-mimetics for perlingual and sublingual administration.

⁵ Patente Europea EP0438147A2: Pharmaceutical compositions and dosage forms for the oral administration of calcitonin.

La patente americana US 2003/0161875 publicada el 28 de agosto de 2003 y titulada "FAST DISSOLVING TABLETS OF CYCLOOXYGENASE- ENZYME INHIBITORS" revela:

The present invention relates to fast dissolving tablets for oral administration comprising a therapeutically effective amount of drug(s) that acts selectively as a cyclooxygenase-2 (COX-2) enzyme inhibitor, which disintegrate quickly in mouth. The tablets are particularly suitable for patients who have difficulty in swallowing.

(...)

5. The tablet according to claim 4 wherein the COX-2 inhibitor is selected from the group consisting of meloxicam, rofecoxib, celecoxib, valdecoxib, parecoxib, nabumetone, nimesulide and etodolac.

(...)

8. The tablet according to claim 2 wherein the pharmaceutical excipients comprises binders, disintegrants, lubricants, glidants, colouring agents, flavouring agents and sweeteners.

Como se puede apreciar claramente, en esta anterioridad se hace mención explícita de formulaciones farmacéuticas de Meloxicam de rápida disolución en la boca, las cuales están compuestas por exactamente los mismos excipientes que se mencionan en la solicitud colombiana en trámite, con lo cual queda en evidencia la ausencia de novedad de la composición allí descrita.

La publicación internacional WO 02/085331 publicada el 31 de Octubre de 2002 y titulada "FAST DISINTEGRATING MELOXICAM TABLET" revela:

The present invention relates to a fast disintegrating tablet comprising meloxicam or a pharmaceutically acceptable salt thereof, starch or various starches, glidant and at least one additional excipient.

(...)

A tablet, fast disintegrating in water, consisting essentially of meloxicam or a pharmaceutically acceptable salt thereof, starch or various starches, a glidant and at least one additional excipient, characterized in that at least one of the additional excipients is water soluble.

(...)

7. A tablet according to one of claims 1 to 5, consisting essentially of meloxicam or a pharmaceutically acceptable salt thereof, maize starch or a mixture of maize and rice starch, hydrated silicon dioxide, lactose and magnesium stearate.
8. A tablet according to one of claims 1 to 7, comprising 1 to 20 mg of meloxicam in form of the free base.

Como se puede apreciar en esta anterioridad, nuevamente se menciona de manera explícita una tableta de fácil desintegración bucal, en donde los excipientes que hacen parte de dicha formulación corresponden nuevamente a los mismos mencionados por la solicitud colombiana en trámite, y además, la cantidad de Meloxicam que pueden contener las formulaciones de esta anterioridad incluyen las cantidades del mismo principio activo que se reivindican en la solicitud en cuestión.

Para finalizar, en la reivindicación 5 de la solicitud colombiana en cuestión, el solicitante hace mención de las características que pueden hacer parte del envase que contiene las formulaciones farmacéuticas que describe en el mismo capítulo reivindicatorio. Sea lo primero resaltar, que de ninguna manera las características de un envase pueden sustentar algún tipo de novedad o de nivel inventivo, al menos que dichas características correspondan a un envase no convencional, y cuyas características busquen sustentar la invención de un nuevo tipo de envase, lo que claramente no corresponde al caso de la solicitud colombiana. Por el contrario, y como cualquier persona medianamente versada en la materia debe reconocer, los materiales tales como el polietileno de alta o baja densidad, polietileno tereftalato, cloruro de polivinilo, polipropileno, poliestireno, vidrios tipo I, II, III o IV, corresponden a los materiales de mayor uso en la industria farmacéutica, y su elección corresponde a las características y clase de formulación que van a ser contenidas en el envase.

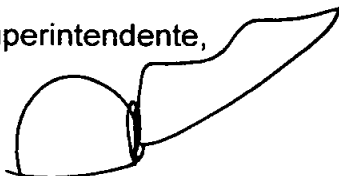
En conclusión, la solicitud colombiana en trámite, carece irrefutablemente de los requisitos fundamentales para otorgársele el privilegio de patente de invención, en primer lugar porque carece de nivel inventivo al involucrar formulaciones farmacéuticas cuyas características y métodos de obtención se encuentran ampliamente descritos en el mismo estado de la técnica, y en segundo lugar, porque dichas formulaciones carecen de novedad, tanto porque el contenido de Meloxicam, como los excipientes que componen dichas formulaciones, ya se habían descrito en el mismo estado de la técnica para obtener formulaciones farmacéuticas del mismo tipo.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales, y que en consecuencia el Despacho decrete, además de la negación de la solicitud en comento, el archivo del expediente que lo contiene.

III. ANEXOS

- ❖ La patente americana US 2003/0161875 publicada el 28 de agosto de 2003 y titulada "FAST DISSOLVING TABLETS OF CYCLOOXYGENASE- ENZYME INHIBITORS".
- ❖ La publicación internacional WO 02/085331 publicada el 31 de Octubre de 2002 y titulada "FAST DISINTEGRATING MELOXICAM TABLET".
- ❖ Vila Jato José Luis. Tecnología Farmacéutica. Volumen II. Paginas 142 y 143.
- ❖ Portadas de las patentes americanas US3789119 y las patentes europeas EP0306422B1 y EP0438147A2.

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.



US 20030161875A1

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0161875 A1****Murpani et al.**(43) **Pub. Date: Aug. 28, 2003**(54) **FAST DISSOLVING TABLETS OF
CYCLOOXYGENASE-2 ENZYME
INHIBITORS**(22) **Filed: Feb. 27, 2002****Publication Classification**(76) **Inventors: Deepak Murpani, New Delhi (IN);
Vinod Kumar Arora, New Delhi (IN);
Rajiv Malik, New Delhi (IN)**(51) **Int. Cl.⁷ A61K 31/415; A61K 9/20**(52) **U.S. Cl. 424/465; 514/406****Correspondence Address:****JAYADEEP R. DESHMUKH
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PRINCETON, NJ 08540 (US)**(57) **ABSTRACT**(21) **Appl. No.: 10/085,664**

The present invention relates to fast dissolving tablets for oral administration comprising a therapeutically effective amount of drug(s) that acts selectively as a cyclooxygenase-2 (COX-2) enzyme inhibitor, which disintegrate quickly in mouth. The tablets are particularly suitable for patients who have difficulty in swallowing.

FAST DISSOLVING TABLETS OF CYCLOOXYGENASE-2 ENZYME INHIBITORS

FIELD OF THE INVENTION

[0001] The present invention relates to fast dissolving tablets for oral administration comprising a therapeutically effective amount of drug(s) that acts selectively as a cyclooxygenase-2 (COX-2) enzyme inhibitor, which disintegrate quickly in mouth. The tablets are particularly suitable for patients who have difficulty in swallowing.

BACKGROUND OF THE INVENTION

[0002] Nonsteroidal anti-inflammatory drugs (NSAIDs) exert anti-inflammatory and analgesic effects through the inhibition of prostaglandin synthesis by blocking cyclooxygenase (COX) enzyme activity. COX enzyme has two isoforms: COX-1 and COX-2. COX-2 enzyme is inducible by inflammation, whereas COX-1 is present in most tissues as the house keeper enzyme. The inhibition of COX-1 is therefore undesirable whereas on the other hand inhibition of COX-2 enzyme accounts for the therapeutic benefits.

[0003] COX-2 inhibitors are the latest addition to the growing armamentarium of anti-inflammatory drugs. Much of the recent research has focussed upon efficacious methods for development of drug delivery of COX-2 enzyme inhibitors to treat inflammation associated maladies.

[0004] The ability of COX-2 inhibitors to selectively block formation of pro-inflammatory prostaglandins while sparing those that guard the gastrointestinal tract makes them an attractive choice for long term use, such as in rheumatoid arthritis or osteoarthritis.

[0005] Rheumatoid arthritis and osteoarthritis are old age diseases associated with joint pain, stiffness, inflammation or swelling. Many elderly persons have difficulty in taking conventional oral dosage forms like solutions, suspensions, tablets and capsules, because of hand tremors and dysphagia. Moreover, increase intake of water for swallowing conventional dosage forms results in frequent urination and nocturia.

[0006] Swallowing problems are also common in mentally ill, the developmentally disabled, and patients who are uncooperative, on reduced liquid-intake plans, or are nauseated. In cases such as motion sickness, sudden episodes of allergic attack or coughing, and an unavailability of water, swallowing the conventional tablets becomes difficult. Consequently, there is a need to provide a fast dissolving dosage form of COX-2 inhibitors for oral administration which disintegrates and dissolves rapidly in saliva without the need for drinking water.

SUMMARY OF THE INVENTION

[0007] It is an object of the present invention to provide a fast dissolving tablet which comprises a therapeutically effective amount of drug(s) that acts as a cyclooxygenase-2 enzyme (COX-2) inhibitor for oral administration which disintegrate quickly in the mouth. The tablets prepared by the present invention disintegrate and dissolve in the oral cavity in less than about 30 seconds without the need of water. The fast dissolving tablet of COX-2 of the present invention process has pleasant mouth feel and there is no after taste or grittiness.

[0008] The fast dissolving tablets according to the present inventions comprises a therapeutically effective amount of COX-2 inhibitor, a filler, and optionally other pharmaceutical excipients.

[0009] Direct compression is the preferred method because of the above advantages. Accordingly, the present invention provides a process for the preparation of fast dissolving tablets comprising a therapeutically effective amount of drug(s) that acts as a cyclooxygenase-2 (COX-2) inhibitor for oral administration.

[0010] The fast dissolving tablets of the present invention can either be produced by conventional methods like wet granulation, dry granulation and direct compression or by specialized techniques like tablet molding and freeze drying.

[0011] Since the pharmaceutical industry is constantly making efforts to increase the efficiency of tableting operations and reduce costs by utilizing the smallest amount of floor space and labor as possible for a given operation, increasing attention is being given to direct compression of tablet preparation.

[0012] Direct compression is regarded as a relatively quick process where the powdered materials are compressed directly without changing the physical and chemical properties of the drug. The advantages of direct compression include

[0013] (i) few manufacturing steps, as granulation step is eliminated

[0014] (ii) elimination of heat and moisture and therefore better

[0015] a. physical stability such as no change in crystallinity and polymorphic form of the drug, and

[0016] b. chemical stability

[0017] (iii) use of conventional equipment and commonly available excipients; and

[0018] (iv) low cost and less manpower.

[0019] The process comprises:

[0020] a) blending a therapeutically effective amount of COX-2 inhibitors with filler and optionally, other pharmaceutical acceptable excipients, for a time sufficient to form a homogeneous mixture.

[0021] b) compressing the homogeneous mixture obtained in step (a) to form the fast dissolving tablet of COX-2 inhibitor.

DETAILED DESCRIPTION OF THE INVENTION

[0022] According to the present invention, the "COX-2 inhibitor" as used herein to embrace compounds that specifically/selectively, or preferentially inhibits cyclooxygenase-2 over cyclooxygenase-1. Illustrative examples of COX-2 enzyme inhibitors that are advantageously administered by the pharmaceutical compositions of this invention include "specific inhibitors" such as celecoxib, rofecoxib, parecoxib, valdecoxib, and the like or "preferential inhibitors" such as meloxicam, nimesulide, etodolac, nabumetone, and the like.

[0023] "Therapeutically effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

[0024] Fillers of the present invention can be selected from any such pharmaceutically acceptable excipient, which gives bulk to the COX-2 inhibitor composition and which is physically and chemically compatible with COX-2 inhibitor; preferably those fillers may be selected from alkali earth metal salts such as directly compressible dicalcium phosphate dihydrate, tricalcium phosphate, calcium sulfate, calcium carbonate, calcium hydroxide, aluminium hydroxide, magnesium silicate, aluminium magnesium hydroxide; carbohydrates such as directly compressible maltose, maltitol, sorbitol, mannitol, glucose, sucrose, xylitol, lactose, lactose monohydrate, erythritol, fructose, maltodextrins; celluloses such as microcrystalline cellulose, calcium carboxy methyl cellulose; starches such as pregelatinized starch, potato starch, maize starch; clays such as kaolin and polyethylene glycols (PEG) such as PEG 4000; or mixtures thereof.

[0025] The effective amount of the fillers found useful in the present invention is in the range of about 10 to about 95 weight percent, preferably about 25 to about 85 weight percent, and most preferably about 80 weight percent of the COX-2 inhibitor compositions of this invention. One of the preferred fillers is directly compressible mannitol.

[0026] The direct compression excipients are chosen such that they have good flow and compressible characteristics and prevent segregation of powders in the hopper and thereby help in direct compression.

[0027] The optional pharmaceutical excipients of this invention may be selected from the binders, disintegrants, lubricants, glidants, colouring agents, flavouring agents and sweeteners which are chemically and physically compatible with COX-2 enzyme inhibitors.

[0028] The direct compression method for preparing tablets requires a material that not only is free-flowing but also sufficiently cohesive to act as a binder. Materials such as microcrystalline cellulose, microcrystalline dextrose, mannitol, directly compressible dicalcium phosphate, amylose and polyvinylpyrrolidone have such properties.

[0029] Disintegrants preferred for the present invention may be selected from starches or modified starches such as sodium starch glycolate, corn starch, potato starch or pregelatinized starch; clays such as bentonite, montmorillonite or veegum; celluloses such as microcrystalline cellulose, hydroxypropyl cellulose or carboxymethyl cellulose; alginates such as sodium alginate or alginic acid; cross-linked cellulose such as croscarmellose sodium; gums such as guar gum or xanthan gum; cross-linked polymers such as crospovidone; effervescent agent such as sodium bicarbonate and citric acid; or mixtures thereof.

[0030] The effective amount of a disintegrant found useful for the COX-2 inhibitor compositions of this invention is in

the range of about 1.0 to about 10.0 weight percent, preferably about 1.5 to about 2.5 weight percent and most preferably about 2.0 weight percent of the COX-2 inhibitor compositions by this invention. The preferred disintegrant is croscarmellose sodium.

[0031] The lubricants of the present invention may be selected from talc, magnesium stearate, calcium stearate, stearic acid, magnesium lauryl sulphate and hydrogenated vegetable oil. Soluble lubricants include sodium benzoate, a mixture of sodium benzoate and sodium acetate, sodium chloride, leucine, sodium stearyl fumarate and PEG 4000.

[0032] The effective amount of lubricant found useful in the present invention is in the range of about 0.25 to about 4 weight percent, preferably about 0.5 to about 2 weight percent, and most preferably 1.0 weight percent of the COX-2 inhibitor compositions of this invention. The preferred lubricant is magnesium stearate.

[0033] The glidants of the present invention may be selected from colloidal silicon dioxide and talc.

[0034] The coloring agent of the present invention may be selected from any colorant used in pharmaceuticals which is approved and certified by the FDA.

[0035] The flavouring agent of the present invention include both natural and artificial flavours such as artificial vanilla, cinnamon, various fruit flavours, both individual and mixed; mints such as peppermint, menthol; essential oils such as thymol, eucalyptol and methyl salicylate and the like. The flavours are generally utilized in amounts that will vary depending upon the individual flavour, and may range in amounts of about 0.5% to about 3% by weight of the final composition weight.

[0036] The sweeteners for the present invention include both natural and artificial sweeteners. The sweeteners may include, among others, water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolyzed starch, or corn syrup solids and sugar alcohols such as sorbitol, xylitol, mannitol and mixtures thereof; water-soluble artificial sweeteners such as the soluble saccharin salts, cyclamate salts, acesulfam-K and the like, and free acid form of saccharin and dipeptide based sweeteners. The amount of sweetener will vary with the desired sweeteners selected for a particular tablet composition.

[0037] The process of the present invention comprises sieving of the COX-2 inhibitors, fillers, disintegrants, binders, glidants, colouring agents, flavouring agents and sweeteners, through a suitable sieve and admixing them to make a uniform blend. The lubricant is also passed through the suitable sieve and mixed with the blend. The blend is directly compressed using the suitable tooling.

[0038] The tablets made by the present inventive process disintegrate/dissolve in less than about 30 seconds preferably in about 25 seconds. The process of this invention for preparing rapidly dissolving tablet may be used for any strength of COX-2 inhibitor tablets without deviating from this invention.

[0039] The present invention is illustrated by, but by no means limited to, the following examples:

EXAMPLE 1

[0040]

<u>Rofecoxib mouth dissolving tablets-25 mg.</u>	
Ingredient	Quantity (mg)
Rofecoxib	25.28
Aspartame	0.35
Mannitol	166.67
Croscarmellose sodium	4.00
Colloidal silicon dioxide	1.00
Mixed fruit flavour	0.70
Magnesium stearate	2.00
Total	200.00

[0041] 1. Rofecoxib, aspartame, mannitol, croscarmellose sodium, colloidal silicon dioxide and mixed fruit flavour are sifted through the sieve #44 BSS and admixed for about 15 minutes to make a uniform blend.

[0042] 2. Magnesium stearate is passed through sieve #100 BSS and mixed with the blend of step 1 for sufficient time.

[0043] 3. Uniform blend of step 2 is directly compressed using 9 mm, round biconcave tooling to make the tablets of about 3.8 ± 0.1 mm thickness.

[0044] The mouth dissolving tablets prepared by the above composition and process had hardness in the range of 2.2 to about 4.0 Kp. The disintegration time in water was less than 15 seconds, whereas the mouth dissolving time was less than 25 seconds. The friability was about 0.4% w/w. The mouth dissolving rofecoxib tablets are tested in 1% sodium lauryl sulphate (SLS) according to the procedure described in the United States Pharmacopoeia XXIII, Apparatus 1 @ 100 rpm and found to have the following release profile:

Time (Minutes)	% Rofecoxib dissolved
15	74
30	83
45	88

EXAMPLE 2

[0045]

Ingredient	Quantity (mg)
Rofecoxib	50.56
Aspartame	0.70
Mannitol	333.34
Croscarmellose sodium	8.0
Colloidal silicon dioxide	2.0

-continued

Ingredient	Quantity (mg)
Mixed fruit flavour	1.4
Magnesium stearate	4.0
Total	400.0

[0046] The procedure of Example 1 was followed to prepare the tablets of above composition.

[0047] The rofecoxib mouth dissolving tablet of 50 mg strength had an average weight of 400 ± 20 mg, thickness of 4.9 ± 0.2 mm, hardness of 4.5-5.0 Kp, disintegration time of less than 20 seconds, mouth dissolving time of about 25 seconds, friability of about 0.44% w/w and dissolution upto 86% in 45 minutes.

EXAMPLE 3

[0048]

<u>Nimesulide mouth dissolving tablet-100 mg.</u>	
Ingredient	Quantity (mg)
Nimesulide	100.00
Aspartame	4.5
Mannitol	318.75
Croscarmellose sodium	10.5
Colloidal silicon dioxide	2.25
Orange flavour	4.5
Monosodium citrate	5.0
Magnesium stearate	4.5
Total	450.0

[0049] The procedure of Example 1 was followed to prepare the above tablets.

[0050] The nimesulide mouth dissolving tablet of 100 mg strength had an average weight of 450 ± 22.5 mg, thickness of 5.7 ± 0.2 mm, hardness of 2-5 Kp, disintegration time of less than 20 seconds, mouth dissolving time of about 25 seconds and friability of about 0.9% w/w.

[0051] While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We claim:

1. A fast dissolving tablet which comprises a therapeutically effective amount of drug(s) that acts as a cyclooxygenase-2 (COX-2) inhibitor for oral administration.

2. The tablet according to claim 1 wherein the tablet comprises a therapeutically effective amount of COX-2 inhibitor, a filler and optionally, other pharmaceutical excipients.

3. The tablet according to claim 1 wherein the fast dissolving tablet dissolves in the mouth.

4. The tablet according to claim 1 or 2 wherein the drug(s) that acts as a cyclooxygenase-2 (COX-2) inhibitor is specific or preferential COX-2 inhibitor.

5. The tablet according to claim 4 wherein the COX-2 inhibitor is selected from the group consisting of meloxi-

cam, rofecoxib, celecoxib, valdecoxib, parecoxib, nabumetone, nimesulide and etodolac.

6. The tablet according to claim 2 wherein the filler may be selected from the group consisting of alkali earth metal salts, carbohydrates, celluloses, starches, clays and polyethylene glycols, and mixtures thereof.

7. The tablet according to claim 9 wherein the filler may be selected from the group consisting of directly compressible dicalcium phosphate dihydrate, tricalcium phosphate, calcium sulfate, calcium carbonate, calcium hydroxide, aluminium hydroxide, magnesium silicate, aluminium magnesium hydroxide, maltose, maltitol, sorbitol, mannitol, glucose, sucrose, xylitol, lactose, lactose monohydrate, erythritol, fructose, maltodextrins, microcrystalline cellulose, calcium carboxy methyl cellulose, pregelatinized starch, potato starch, maize starch, kaolin, polyethylene glycol 4000, and mixtures thereof.

8. The tablet according to claim 2 wherein the pharmaceutical excipients comprises binders, disintegrants, lubricants, glidants, colouring agents, flavouring agents and sweeteners.

9. The tablet according to claim 8 wherein the binders may be selected from the group consisting of microcrystalline cellulose, mannitol, microcrystalline dextrose, directly compressible dicalcium phosphate, amylose and polyvinylpyrrolidone.

10. The tablet according to claim 8 wherein the disintegrant is selected from the group consisting of starches or modified starches, clays, celluloses, algin, cross-linked celluloses, gums, cross-linked polymers, effervescent agents, and mixtures thereof.

11. The tablet according to claim 10 wherein the disintegrant is selected from the group consisting of sodium starch glycolate, corn starch, potato starch, pregelatinized starch, bentonite, montmorillonite, veegum, microcrystalline cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, alginic acid, croscarmellose sodium, guar gum, xanthan gum, crospovidone, sodium bicarbonate and citric acid, and mixtures thereof.

12. The tablet according to claim 8 wherein the lubricants may be selected from the group consisting of talc, magnesium stearate, calcium stearate, stearic acid, magnesium lauryl sulphate and hydrogenated vegetable oil, sodium benzoate, sodium acetate, sodium chloride, leucine, sodium stearyl fumarate, PEG 4000, and mixtures thereof.

13. The tablet according to claim 8 wherein the glidants may be selected from the group consisting of colloidal silicon dioxide and talc.

14. The tablet according to claim 8 wherein the colouring agents may be selected from any colorant used in pharmaceuticals which is approved and certified by the FDA.

15. The tablet according to claim 8 wherein the flavouring agent may be selected from the group consisting of natural and artificial flavours, mints and essential oils or the mixtures thereof.

16. The tablet according to claim 15 wherein the flavouring agent may be selected from the group consisting of peppermint, menthol, artificial vanilla, cinnamon, various fruit flavours, both individual and mixed, thymol, eucalyptol and methyl salicylate and the like.

17. The tablet according to the claim 8 wherein the sweetener may be selected from the group consisting of natural and artificial sweeteners.

18. The tablet according to the claim 17 wherein the sweetener may be selected from the group consisting of monosaccharides, disaccharides, polysaccharides, partially hydrolyzed starch, corn syrup solids, sugar alcohols, water-soluble artificial sweeteners, and mixtures thereof.

19. The tablet according to the claim 18 wherein the sweetener may be selected from the group consisting of xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, sorbitol, xylitol, mannitol, soluble saccharin salts, cyclamate salts, acesulfam-K and free acid form of saccharin and dipeptide based sweeteners, and mixtures thereof.

20. A mouth dissolving tablet of COX-2 inhibitor consisting of a COX-2 inhibitor, croscarmellose sodium, mannitol, aspartame, colloidal silicon dioxide, magnesium stearate and flavouring agent.

21. A process for preparing a fast dissolving tablet according to claim 2 comprising the steps of:

(a) blending a therapeutically effective amount of COX-2 inhibitor, a filler, and optionally, other pharmaceutical excipients;

(b) compressing the homogeneous mixture obtained in step (a).

22. The process according to claim 21 wherein the blend is granulated before compression.

23. The process according to claim 22 wherein the granulation is done by wet or dry granulation methods.

24. The process according to claim 23 wherein the dry granulation is done by slugging or roller compaction.

* * * * *

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: FAST DISINTEGRATING MELOXICAM TABLET

(57) Abstract: The present invention relates to a fast disintegrating tablet comprising meloxicam or a pharmaceutically acceptable salt thereof, starch or various starches, glidant and at least one additional excipient.

Fast disintegrating Meloxicam Tablet

Field of the invention

5

The present invention relates to a fast disintegrating tablet comprising meloxicam or a pharmaceutically acceptable salt thereof, starch or various starches, glidant and at least one additional excipient.

10 Background of the invention

Meloxicam [2H-1,2-benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-1,1-dioxide] is a non-steroidal antiinflammatory drug (NSAID) with antiinflammatory, antipyretic and analgetic activity.

15 Meloxicam has a low solubility in acidic or neutral medium.

The preparation of a pharmaceutical tablet formulation of meloxicam, is disclosed in PCT/EP 98/05456 as a mixing of meloxicam with special additives using different production processes (co-milling, co-grinding, co-kneading etc.) and several processing steps to build a multilayered tablet which provides an improved solubility

20 and bioavailability of meloxicam.

EP 0 945 134 describes the preparation of a meloxicam tablet comprising various additives and a salt of meloxicam, preferrably the meglumin salt or sodium salt of meloxicam using the direct pressing method. However the disintegration thereof in water is very slowly.

25

Description of the invention

The problem underlying the present invention is to provide a tablet of meloxicam, which is able to fast disintegration in water and which is obtainable by a simple

30 method of manufacture.

Thus it has surprisingly been found that the problem underlying the invention is solved by a tablet consisting essentially of meloxicam or a pharmaceutically

acceptable salt thereof, starch or various starches, a glidant and at least one additional excipient, wherein at least one of the additional excipients is water soluble. According to the invention further auxiliary agents known in the state of the art may be used for the preparation of the tablets. Auxiliary agents are as a rule lubricants, water soluble excipients, glidants, sweeteners, souring agents and flavouring agents, which are known from the state of the art. Lubricants are preferably selected from the group consisting of magnesium stearate, stearic acid, magnesium lauryl sulfate and sodium stearyl fumarate, more preferably magnesium lauryl sulfate and magnesium stearate. Water soluble excipients are preferably selected from the group consisting of lactose, glucose, erythritol, dextrose, maltose, fructose, sucrose, sorbitol and mannitol. Glidants are preferably selected from the group consisting of hydrated silicon dioxide, talc and synthetic aluminum silicate. Sweeteners are preferably selected from the group consisting of aspartame and monoammonium glycyrrhizinate. Souring agents are preferably selected from the group consisting of mono sodium fumarate, anhydrous citric acid, citric acid, ascorbic acid and tartaric acid. Flavoring agents, which are natural or synthetic, are preferably selected from the group consisting of 1-menthol, lemon oil and orange oil.

According to the invention the term pharmaceutically acceptable salt stands for a meloxicam salt of an organic or inorganic base, as for example the meglumin, sodium, potassium or ammonium salt.

In a preferred embodiment the present invention relates to a tablet, wherein the water soluble excipients are chosen from the group comprising lactose, glucose, erythritol, dextrose, maltose, fructose, sucrose, sorbitol and mannitol, more preferably lactose or glucose, most preferably lactose.

According to the invention the term lactose stands for native lactose, lactose monohydrate or modified lactose, preferably granulated lactose monohydrate.

In a further preferred embodiment the present invention relates to a tablet, wherein glidants are chosen from the group of hydrated silicon dioxide, talc and synthetic aluminum silicate, preferably hydrated silicon dioxide.

In a further preferred embodiment of the present invention the starch or various starches are chosen from the group comprising native starch, gelatinized starch, partly gelatinized starch, starch powder, starch granules, chemically modified starch and swellable physically modified starch, preferably starch powder or partly
5 gelatinized starch, more preferably starch powder.

Moreover the starch powder may be derived from any starch-containing plant source. This includes normal maize, hybrids like white maize, waxy maize and high-amylose-containing maizes, wheat, potato, rice, sorghum, tapioca or cassava.

10 In a further preferred embodiment of the present invention the starch or various starches are chosen from the group comprising rice starch, maize starch and potato starch, preferably rice starch or maize starch, most preferably maize starch or a mixture of rice starch and maize starch.

15 In a particularly preferred embodiment of the present invention the meloxicam salt is the sodium or meglumin salt, preferably the meglumin salt.

In a mostly preferred embodiment of the present invention the tablet consists essentially of meloxicam or a pharmaceutically acceptable salt thereof, maize starch,
20 hydrated silicon dioxide, lactose and magnesium stearate.

In a particularly preferred embodiment of the present invention the concentration of meloxicam is 1 to 25 mg/tablet, preferably 4 to 18 mg/tablet, more preferably 5 mg/tablet, 7,5 mg/tablet, 10 mg/tablet or 15 mg/tablet, wherein the amount given
25 relates to the active ingredient in form of the free base.

In another particularly preferred embodiment of the present invention the concentration of starch in a tablet is in the range from 20 to 50 % (w/w), preferably 25 to 48 % (w/w), more preferably 35 to 45 % (w/w), particularly preferred about 40 %
30 (w/w).

In a further particularly preferred embodiment of the present invention the concentration of the water soluble excipient, in particular of lactose, in a tablet is in

the range from 40 to 80% (w/w), preferably 42 to 70% (w/w), more preferably 45 to 65 % (w/w), particularly preferred about 50 % (w/w).

In a further particularly preferred embodiment of the present invention the
5 concentration of the lubricant, in particular of magnesium stearate, in a tablet is in
the range from 0,2 to 0,6% (w/w), preferably 0,3 to 0,5% (w/w), more preferably
0,4 % (w/w), and the concentration of glidant, in particular of hydrated silicon
dioxide, in a tablet is in the range from 0,05 to 1,0 % (w/w), preferably 0,1 to 0,5%
(w/w), more preferably 0,35 % (w/w).

10 More particularly preferred according to the present invention is a tablet, which is
obtainable by a direct dry pressing method.

Most preferably the tablet according to the invention is free of cellulose.

15 As a rule the tablet according to the invention has a weight in the range of 20 to 800
mg/tablet, preferably 40 to 400 mg/tablet, more preferably 80 to 300 mg/tablet, most
preferably 90 to 260 mg/tablet, particularly preferred about 170 mg/tablet or 255
mg/tablet.

20 The invention will be further illustrated by the examples of tablet compositions given
in Table 1. The invention should not be limited to these examples. According to the
present invention the compositions are manufacturable to tablets by the direct
pressing method, which is described for instance in DRUG AND THE
25 PHARMACEUTICAL SCIENCES, Vol.71, Goeran Alderborn and Christer Nystroem,
Pharmaceutical Powder Compaction Technology, 419 - 428, Marcel Dekker, inc.,
Uppsala University, Sweden, 1996.

A suitable method of manufacturing the directly compressible composition is to
prepare e.g. a blend of meloxicam, lactose, starch and hydrated silicon dioxide by
30 mixing the ingredients 30 minutes in a conventional mixer. Subsequently magnesium
stearate is added and the composition is blended for further 5 minutes.

Table 1 Compositions of meloxicam for fast disintegrating tablets.

Values are given in [mg].

Example	1	2	3	4	5	6
Meloxicam	10.0	10.0	10.0	10.0	15.0	15.0
Lactose monohydrate	90.7	90.2	90.7	91.2	85.7	136.0
Maize starch	68.0	68.0	51.0	34.0	51.0	76.5
Rice starch	---	---	17.0	34.0	17.0	25.5
Hydrated silicon dioxide	0.6	1.1	0.6	0.1	0.6	0.9
Magnesium stearate	0.7	0.7	0.7	0.7	0.7	1.1
Total weight	170.0	170.0	170.0	170.0	170.0	255.0

5

Disintegration experiments have been conducted according to the disintegration test, which is described in the Japanese Pharmacopoeia (JP XIII). The tested tablets were prepared by the direct pressing method from the compositions shown in Table 1.

Test results are shown in Table 2.

10

Table 2. Test fluid: water (the volume of the fluid in the beaker is such that, at the lowest point of the downward stroke, the top of the basket is on a level with the surface of the fluid), temperature 37 ± 2 °C. The apparatus is adjusted so as to raise and lower the basket smoothly at a constant frequency of 29 to 32 cycles per

15 minutes. 6 tablets were tested for each batch.

Example	1	2	3	4	5	6
Diameter [mm]	7	8	8	8	8	9
Average of thickness [mm]	3.2	2.7	2.7	2.7	2.6	3.1
Disintegration time [sec]	25	17	19	37	21	29

Claims

1. A tablet , fast disintegrating in water, consisting essentially of meloxicam or a pharmaceutically acceptable salt thereof, starch or various starches, a glidant and
5 at least one additional excipient, characterized in that at least one of the additional excipients is water soluble.
2. A tablet according to claim 1, characterized in that the water soluble excipients are chosen from the group comprising lactose, glucose, erythritol, maltose,
10 fructose, dextrose, sucrose, sorbitol and mannitol.
3. A tablet according to claim 1 or 2, characterized in that the glidant is hydrated silicon dioxide.
- 15 4. A tablet according to one of claims 1 to 3, characterized in that the starch or various starches are chosen from the group comprising native starch, gelatinized starch, partly gelatinized starch , starch powder, starch granules, chemically modified starch and swellable physically modified starch.
- 20 5. A tablet according to one of claims 1 to 4, characterized in that the starch or various starches are chosen from the group comprising rice starch, maize starch and potato starch.
6. A tablet according to one of claims 1 to 5, characterized in that the starch is maize
25 starch or a mixture of maize and rice starch.
7. A tablet according to one of claims 1 to 5, consisting essentially of meloxicam or a pharmaceutically acceptable salt thereof, maize starch or a mixture of maize and rice starch, hydrated silicon dioxide, lactose and magnesium stearate.
30
8. A tablet according to one of claims 1 to 7, comprising 1 to 20 mg of meloxicam in form of the free base.

9. A tablet according to one of claims 1 to 8, characterized in that the concentration of starch in a tablet is in the range from 20 to 50 % (w/w).
10. A tablet according to one of claims 1 to 9, characterized in that the concentration
5 range of the water soluble excipient in a tablet is in the range from 40 to 80% (w/w).
11. A tablet according to one of claims 1 to 10, characterized in that the tablet is
10 produced by a direct dry pressing method.
12. A tablet according to one of claims 1 to 11, characterized in that it is free of cellulose.
13. A tablet according to one of claims 1 to 12, characterized in that the weight of the
15 whole tablet is in the range of 20 to 800 mg.

United States Patent [19]

Fusari et al.

[11] 3,789,119

[45] Jan. 29, 1974

[54] STABILIZED MOLDED SUBLINGUAL NITROGLYCERIN TABLETS

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[22] Filed: June 1, 1971

[21] Appl. No.: 149,072

[52] U.S. Cl. 424/78, 264/117, 424/298,
424/349, 424/358, 424/361

[51] Int. Cl. A61k 27/12

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(1951) "Tablets of Glyceryl Trinitrate"

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[57] ABSTRACT

Pharmaceutical compositions containing minor proportions of nitroglycerin and a non-volatile, water-soluble solvent in combination with a major proportion of a solid, water-soluble pharmaceutical carrier. Those compositions, in the form of tablets suitable for sublingual administration, can be produced by wetting a substantially dry mixture of the nitroglycerin and the solid, water-soluble pharmaceutical carrier with a solvent mixture containing a non-volatile, water-soluble solvent and a volatile solvent, forming the wetted mixture into tablets, and removing the volatile solvent.

4 Claims, No Drawings



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(54) **Nouvelles formes galéniques de bêta-2-mimétiques pour administration par voie per- et sublinguale**

Galenische 2-beta-Mimetik-Formen für die per- und sublinguale Verabreichung
Galenical forms of 2-beta-mimetics for perlingual and sublingual administration

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edition, 1975, pages 684 et 1577

Remarques:
Le dossier contient des informations techniques
présentées postérieurement au dépôt de la
demande et ne figurant pas dans le présent fascicule.

EP 0 306 422 B1

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59 **Pharmaceutical compositions and dosage forms for the oral administration of calcitonin.**

57 New pharmaceutical compositions containing a calcitonin as active principle and suitable for oral administration in the form of peribuccal and sublingual tablets are described, in which the active principle is homogenized with a mixture of solid excipients, said excipients consisting of a diluent, a lubricant, a disintegrating agent in the case of sublingual tablets, and a binder in the case of peribuccal tablets.

Said compositions enable the same pattern of hematologic levels to be obtained for the same unit dose as obtainable by conventional intramuscular administration.

EP 0 438 147 A2

CAPÍTULO 2: FORMAS SÓLIDAS ORALES

arativas entre los distintos lotes. El
cacia clínica; sin embargo, su incu
isiga una eficacia completa.

piecen que al menos un 75% del fármaco debe disolverse en 45 minutos. Con obje
to de reducir la variabilidad interlaboratorio en los test de disolución, la USP sugie
re el uso de discos estándares de ácido salicílico y prednisona como calibradores
del equipo de disolución.

2.2.11. Comprimidos especiales

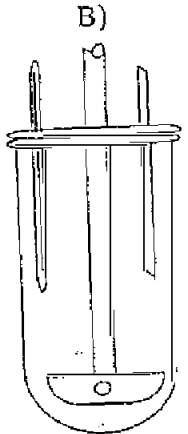
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enta la misma actividad terapéutica.
ar estudios sobre la velocidad de
nante de su absorción.
de gran importancia en el control de
o solubles, es preciso señalar que
isponibilidad, que debe ser evaluada
esultados obtenidos *in vitro* e *in vivo*
en considerarse buenos indicadores
lación ensayada.
entos para llevar a cabo este ensayo
los recogidos en la USP: método del
s se presentan en la figura 2.55.

Se incluye dentro de esta categoría a aquellos comprimidos que presentan algu
na característica farmacotécnica diferente de las descritas para los comprimidos
convencionales. Los comprimidos especiales de mayor utilización (sublinguales y
bucales, masticables, efervescentes, multicapa, vaginales, de implantación, de libe
ración sostenida y recubiertos) se describen a continuación.

A) Comprimidos sublinguales y bucales

Son comprimidos destinados a situarse bajo la lengua (sublinguales) o a man
tenerse en la cavidad oral (bucales), donde se disuelven lentamente liberando el
principio activo para producir un efecto local o ser absorbidos a través de la mucos
y ejercer un efecto sistémico. En general, presentan pequeño tamaño y una for
ma plana u oval. Los comprimidos bucales deben disolverse con lentitud, para lo
cual en su formulación se evita la presencia de agentes disgregantes y se incorpo
ran aglutinantes enérgicos (gelatina, goma arábica, carboximetilcelulosa...) y lubri
cantes de acción hidrofóbica, del tipo del estearato magnésico, que contribuyen a
aumentar el tiempo de disgregación. Además, se utilizan fuerzas elevadas de com
presión para obtener comprimidos duros. Se pueden administrar de esta forma hor
monas como la metiltestosterona, el citrato de oxitocina, la progesterona, antisép
ticos y antibióticos, etc.

Los comprimidos sublinguales suelen contener fármacos que serían destruidos o
inactivados a su paso por el tracto gastrointestinal. En general, están concebidos para
que el principio activo se ceda lentamente, de manera que la velocidad de liberación
sea del mismo orden de magnitud que la de absorción para asegurar el máximo apro
vechamiento de la dosis administrada. Si la liberación se produjera muy rápidamen
te, la mucosa no estaría en situación de absorber toda la cantidad de fármaco disuel
ta, por lo que una parte de éste sería deglutida junto con la saliva. Por el contrario, en
ciertos casos especiales, cuando se recurre a esta forma de administración para el tra
tamiento de situaciones urgentes, como la angina de pecho o el asma, los comprimi
dos sublinguales deben disolverse fácilmente, permitiendo una rápida absorción del
fármaco, por lo que para su obtención se emplean bajas fuerzas de compresión y se
les dota de una forma lenticular y de gran superficie. De este modo se administran
fármacos tales como la nitroglicerina, el clorhidrato de isoproterenol, el sulfato de iso
prenalina, el dinitrato de isosórbida, la ketanserina, etc.



de disolución. A) Método de cestillo. B) Mé
toleta

in para llevar a cabo el ensayo, junto
monografía de las farmacopeas, do
ico que debe disolverse en un período
erimientos de disolución de la USP

Estos tipos de comprimidos se suelen endulzar con azúcar y otros edulcorantes sintéticos de mayor actividad, aromatizándose con aceites esenciales, todo con objeto de mejorar su palatabilidad y evitar que un mal sabor estimule el flujo salivar con el consiguiente riesgo de deglución.

B) *Comprimidos masticables*

Los comprimidos masticables, destinados a ser fragmentados con los dientes posteriormente tragados, constituyen una alternativa en la administración de fármacos en pacientes que plantean dificultades para deglutir los comprimidos enteros. Como base diluyente se utiliza normalmente el manitol, ya que tiene una sabor agradable (aproximadamente un 70% del poder edulcorante del azúcar), proporciona sensación de frescor y puede enmascarar sabores desagradables. Además, el hecho de no ser higroscópico le convierte en el excipiente ideal para preparar comprimidos masticables que contengan fármacos sensibles a la humedad. El manitol puede llegar a constituir un 50% del total de la formulación y, en ocasiones, puede sustituirse total o parcialmente por otros edulcorantes como el sorbitol, la lactosa, la dextrosa y la glucosa. Estos comprimidos suelen incorporar, asimismo, polvo de cacao y otras sustancias aromáticas; no requieren la presencia de disgregantes, ya que los dientes realizan la función de desintegración, pero contienen una proporción relativamente alta de aglutinantes. Se preparan por granulación húmeda y utilizando fuerzas de compresión moderadas. Entre los fármacos presentados en esta forma destacan los preparados vitamínicos, los antiácidos, algunos antineoplásicos y antibióticos y el ácido acetilsalicílico.

C) *Comprimidos efervescentes*

Los comprimidos efervescentes son diseñados para conseguir una rápida disolución en agua, con liberación simultánea de dióxido de carbono, previa a su administración. Se preparan por compresión de los componentes activos junto con mezclas de ácidos orgánicos, como el cítrico o el tartárico, y un carbonato, habitualmente bicarbonato sódico, aunque también pueden utilizarse los de potasio, calcio, metionina o lisina, con el fin de evitar el aporte de sodio. Cuando el comprimido se pone en contacto con agua, se inicia la reacción química entre el bicarbonato y el ácido para formar la sal sódica de este ácido con producción de dióxido de carbono. Esta reacción es bastante rápida, completándose en un minuto o menos. La efervescencia, además de contribuir a una rápida disgregación, produce una sensación agradable que enmascara el mal sabor de algunos fármacos.

Estos comprimidos pueden prepararse por granulación húmeda o seca mediante calor. En el primer caso se procede a la preparación por separado de dos granulaciones que contengan los componentes ácidos y básicos, respectivamente, o bien por el método

convencional, pero empleando o el isopropanol, incapaces de desmenuzarse por calor requiere el mezclado en seco incorporando el ácido cítrico en su formulación para calientan para liberar el agua de la matriz del agente granulante. Obviamente, para los fármacos solubles, como los polietilenglicoles, se utiliza la sacarina, ya que el azúcar no se disuelve al comprimido. En general, se utilizan analgésicos, descongestivos, antihistamínicos, etc.

Dado que este tipo de comprimidos, deben tomarse precauciones en su administración, así, a los tubos metálicos con tapa de aluminio, habitualmente gel de sílice, o al envase de plástico termosellados que garanticen la integridad del producto.

El ensayo de disgregación, para verificar la liberación total, previa liberación de burbujas de gas, el comprimido en un vaso de precipitados, la operación debe repetirse con seis unidades.

D) *Comprimidos multicapa*

Un comprimido multicapa está constituido por uno sobre otro en varias capas paralelas. El comprimido es sometido a una compresión final para incorporar en un recipiente. Se utilizan para incorporar en un comprimido física o químicamente, como por ejemplo, el ácido ascórbico mezclados con paracetamol, para producir este tipo de comprimidos de liberación prolongada. Para producir este tipo de comprimidos especiales, ya descritas en el apartado anterior.

E) *Comprimidos vaginales*

Los comprimidos vaginales están diseñados para ser principio activo en la cavidad vaginal. Se utilizan para la retención en la vagina. Están ideados para el tratamiento de la mucosa, fundamentalmente en el tratamiento de infecciones, antifúngicos, antisépticos o astríngentes, en el caso de los esteroides. En su formulación, los fármacos solubles, como la glucosa y la lactosa, para la conservación de la flora bacteriana, deben tamponarse.

24

2020
Bogotá, D.C.,

Doctora:
Dilia María Rodríguez D'Aleman
Apoderada

Oficio N°: 13873

ASUNTO:	Radicación PCT N°	08-12143
	Trámite	011
	Evento	378
	Actuación	440
	Folios	008

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Cielo Ángela Peña Rodríguez, en su calidad de apoderada de Procaps S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

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

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


ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (C).

El anterior oficio fue notificado por fijación en lista de fecha,

04 DIC. 2009

202021

25

2020
Bogotá, D.C.,

Doctora:
Dilia María Rodríguez D'Aleman
Apoderada

Oficio N°: 13874

ASUNTO:	Radicación PCT N°	08-12143
	Trámite	011
	Evento	378
	Actuación	440
	Folios	029

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

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

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


ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (C).

04 DIC. 2009

El anterior oficio fue notificado por fijación en lista de fecha,_____.

202021

26

2020
Bogotá, D.C.,

Doctora:
Dilia María Rodríguez D'Aleman
Apoderada

Oficio N°: 13873

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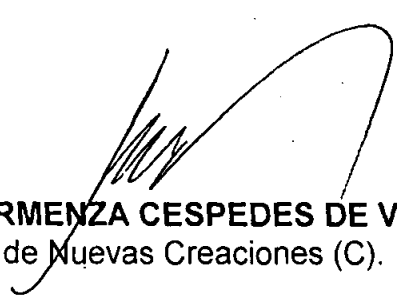
ASUNTO:	Radicación PCT N°	08-12143
	Trámite	011
	Evento	378
	Actuación	440
	Folios	008

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comunidad Andina, se le comunica que la oposición de Ángela Peña Rodríguez, en su calidad de apoderada, no cumple con los requisitos formales exigidos por la ley al momento de

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

2 OPOSITORES

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 10 del capítulo quinto del título primero de la Circular Única N° 001 de 2009.


ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (C).

El anterior oficio fue notificado por fijación en lista de fecha,

04 DIC. 2009

202021

2020
Bogotá, D.C.,

Doctora:
Dilia María Rodríguez D'Aleman
Apoderada

Oficio N°: 13874

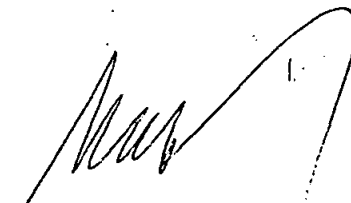
ASUNTO:

Radicación PCT N°	08-12143
Trámite	011
Evento	378
Actuación	440
Folios	029

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

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

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



ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (C).

04 DIC. 2009

El anterior oficio fue notificado por fijación en lista de fecha, _____.

202021