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54. **TITULO** TABLETAS DE DERAMCICLANO-FUMARATO

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71. **SOLICITANTE** EGIS GYÓGYSZERGYÁR RT.

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74. **APODERADO** JUAN PABLO CADENA SARMIENTO

22. **SANTAFE DE BOGOTA, D.C.**

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1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	Nombre: EGIS GYÓGYSZERGYÁR RT. Dirección: Keresztúri út 30-38, H-1106 Budapest, Hungría Nacionalidad o Domicilio: Hungría Lugar de Constitución: Hungría Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: JUAN PABLO CADENA SARMIENTO Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número 80 410.337 TP 57492
4 INVENTOR (ES) (72)	Nombre: Pál FEKETE, Lászlóné MAROSHELYI, Zsolt ZSIGMOND, Lászlóné GÓRA, Magdolna LEVENTISZNÉ HUSZÁR, Istvánné JÁMBOR, József TARI Dirección: Csernyus u. 15, H-1147 Budapest (HU), Linda tér, 5, H-1165 Budapest (HU), Borsó u. 8, H-1173 Budapest (HU), Nagy S. u. 42, H-2117 Isaszeg (HU), Virányos út 24/A, H-1125 Budapest (HU), Somlókert u. 47/a, H-1182 Budapest (HU), Tóalmás u. 27, H-I 172 Budapest (HU) (Respectivamente) Nacionalidad o Domicilio: Hungría (Respectivamente)	

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10 ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $443.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso. Fotocopia Autenticada
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
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11 FIGURA CARACTERÍSTICA:

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NOMBRE: JUAN PABLO CADENA SARMIENTO

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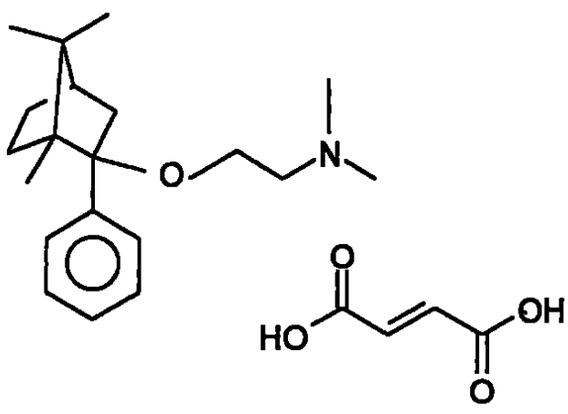

(I)

(57) Abstract: The invention relates to tablets comprising deramciclane-fumarate of the Formula (I) whereby said tablets contain (related to the total weight) more than 50 % by weight of deramciclane-fumarate, 5-20 % by weight of a binder, 5-20 % by weight of microcrystalline cellulose having an average particle size below 30 μm, 1-10 % by weight of a disintegrant, 0.5-4 % by weight of a lubricant, 0.5-4 % by weight of an anti-adhesive agent and 0-30 % by weight of a filler. Deramciclane-fumarate is a known anxiolytic active ingredient.

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DERAMCICLANE-FUMARATE TABLETS

TECHNICAL FIELD OF THE INVENTION

The invention relates to deramciclane-fumarate tablets of high active ingredient content and a process for the preparation thereof.

STATE OF THE ART

It is known that (1R,2S,4R)-(-)-2-dimethylaminoethoxy-2-phenyl-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2-(E)-butenedioate (1:1) of the Formula I (referred to furtheron as deramciclane-fumarate) is a valuable anxiolytic pharmaceutical active ingredient (GB 2,065,122; EP 1 052 245).

The preparation of the active ingredient and pharmaceutical compositions containing the same - i.e. tablets - is described in GB 2,065,122.

Deramciclane-fumarate is a white crystalline powder which according to practical experience possesses extremely unfavourable tabletting properties.

The following properties of deramciclane-fumarate are very unfavourable from the point of view of the production of tablets:

- weak cohesion;
- high elasticity;
- strong adhesion;
- low water solubility.

Due to the weak cohesion characteristics of deramciclane-fumarate on compression of the particles of the active ingredient acceptable tablet strength can not be obtained. When filling 300 mg of deramciclane-fumarate powder into a die cavity of 10 mm diameter of an eccentric press machine and thereafter pressing with a compression force of 5-40 kN, the crushing strength of the tablets does not exceed 10 N. In case of suitably compressible materials the attainable crushing strength is higher than 100 N.

The highly elastic behaviour of the particles of the active ingredient means that under the effect of compression force the volume of the deramciclane-fumarate particles is decreased, whereupon when compression is no more exerted, the particles regain their original form to a significant extent and due to said elastic re-conversion the bonds formed during compression among the particles are broken up. Said disruption of the bonds

takes place along the maximal force planes formed within the tablet and this causes the lamination of the tablet structure. In case of conveniently compressible materials having low elasticity the internal structure of the tablet is homogenous and no laminate structure is formed.

The low tablet crushing strength and lamination can be eliminated by using a large amount of a binder. However, a large amount of the binder prolongs the disintegration time of the tablet in aqueous medium to an excessive extent and additionally it slows down the dissolution of the active ingredient; accordingly tablets of unsuitable quality are obtained.

Due to the strongly adhesive properties of deramciclane-fumarate on the one hand during compression high friction forces are formed between the side of the tablets and the wall of die, which result in a damage of the tablet when it is removed from the die. On the other hand the tablets stick to the surface of the punches and therefore the surface of the tablet becomes uneven. This drawback can be eliminated in principle by adding a large amount of a lubricant; however, this measure has serious disadvantages; it decreases the strength of the tablets to an undesired extent, due to the hydrophobic character it considerably slows down the disintegration of tablet in aqueous medium, it also slows down the dissolution of the active ingredient and for

the reasons stated above tablet of unsuitable quality are obtained.

In addition to the low water solubility of deramciclane-fumarate the weak cohesion properties and strong adhesion are still more problematic because the required larger amount of the binders on the one hand and the lubricants on the other make the fast dissolution of the active ingredient impossible.

Because of the problems discussed above the tablet formulations described in GB 2,065,122 are unsuitable for industrial scale manufacture of deramciclane-fumarate tablets.

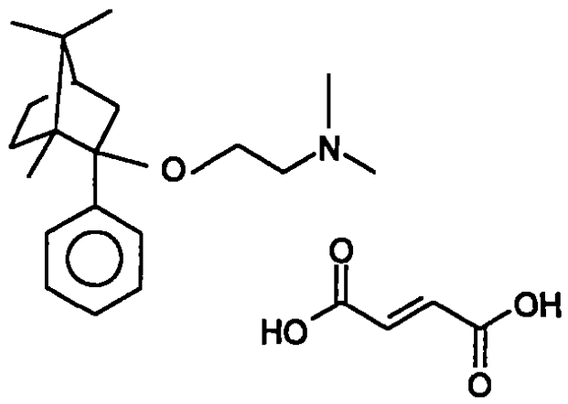
The tablet formulations disclosed in GB 2,065,122 are particularly unsuitable for the preparation of deramciclane-fumarate tablets having an active ingredient content above 50 % by weight. However, both the manufacturers and the patients prefer tablets having such a high active ingredient content. From the point of view of the manufacturers the smaller tablet weight requires less auxiliary agents and a shorter labour time, a higher batch size, less analytical tests, i.e. lower manufacturing costs. The patients can swallow smaller tablets more easily and this improves the patient compliance.

SUMMARY OF THE INVENTION

The object is the invention is the development of deramciclane-fumarate tablets which have an active ingredient content above 50 % by weight and can be readily compressed into tablets.

A further object of the present invention is the elaboration of a process suitable for the preparation of such tablets.

The present invention is directed to tablets comprising deramciclane-fumarate of the Formula



I.

whereby said tablets contain (related to the total weight) more than 50 % by weight of deramciclane-fumarate, 5-20 % by weight of a binder, 5-20 % by weight of microcrystalline cellulose having an average particle size below 30 μm, 1-10 % by

weight of a disintegrant, 0.5-4 % by weight of a lubricant, 0.5-4 % by weight of an anti-adhesive agent and 0-30 % by weight of a filler.

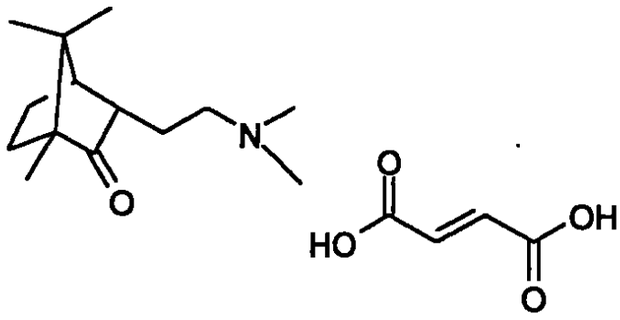
DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the recognition that if microcrystalline cellulose having a particle size below 30 μm is used in the granulating liquid, the particles of such microcrystalline cellulose form a layer on the surface of deramciclane-fumarate particles and thus decrease the adhesion properties of the granules. Thus the amount of lubricants and anti-adhesive agents required in the tablet can be reduced and in this manner non-sticking tablets having appropriate strength can be manufactured. The tablets according to the present invention possess good mechanical strength, disintegrate easily and quickly in aqueous medium and the active ingredient content is promptly dissolved.

The deramciclane-fumarate content of the tablets according to the present invention is 50-88 % by weight, preferably 50-78 % by weight.

According to a preferred embodiment of the present invention there are provided tablets comprising as active ingredient

(1R,2S,4R)-(-)-2-dimethylaminoethoxy-2-phenyl-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2-(E)-butenedioate (1:1) of the Formula I which contain not more than 0.2 % by weight of (1R,3S,4R)-(-)-3-(2-N,N-dimethylaminoethyl)-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2-one-(E)-butenedioate (1:1) of the Formula



II.

Such high purity deramciclane-fumarate is described in EP 1 052 245.

The deramciclane-fumarate tablets of the present invention can comprise any binder suitable for the purposes of the manufacture of tablets. Such binders are disclosed e.g. in the chapter National Formulary of the US Pharmacopoeia [USP23/NF18 page 2206 (United States Pharmacopeial Convention, Inc., 1995)]. Thus as binder preferably polyvinyl pyrrolidone, gum-arabic, alginic acid, sodium carboxymethyl cellulose, dextrine, ethyl cellulose, gelatine, liquid sugar, guar gum, hydroxypropyl methyl cellulose, methyl cellulose, polyethylene oxide, pre-gelatinised starch or sugar syrup, particularly polyvinyl pyrroli-

done (povidone) or a copolymer of vinyl pyrrolidone and vinyl acetate (co-povidone) can be used.

The tablets according to the present invention contain 5-20 % by weight, preferably 5-12 % by weight, particularly 6-9 % by weight of a binder (related to the total weight of the tablet).

The granulating liquid used for dissolving the binder can be preferably water, ethanol, isopropanol or a mixture thereof containing said solvents in any ratio. Microcrystalline cellulose having a average particle size not higher than 30 μm is suspended in the granulating liquid, whereupon the powder of the active ingredient is granulated with said granulating suspension directly without adding further auxiliary agents. Granulating can be carried out by the wet granulating method whereby the above granulating suspension is added to the powder of the active ingredient in a high shear mixer. According to another procedure granulation is performed by the spraying method whereby the above granulating suspension is sprayed onto the powder of the active ingredient in a fluidization spraying apparatus.

Microcrystalline cellulose having an average particle size of 30 μm or below is generally designated by No. 105. The most frequently used commercially available products are Avicel 105, Vivapur 105 and Elcema 105. The brochures of the manu-

facturers recommend the use of microcrystalline cellulose of this type as inert carrier, or alternatively as auxiliary agent useful in the manufacture of suspension and suppositories in order to prevent sedimentation.

Nowadays in the manufacture of tablets microcrystalline cellulose having an average particle size of at least 50 μm is used. Microcrystalline cellulose having an average particle size of 50 μm is generally denoted by No. 101, while microcrystalline cellulose having an average particle size of 90-100 μm is generally designated as No. 102.

According to the state of the art various microcrystalline cellulose types are used by admixing microcrystalline cellulose with the active ingredient and optionally with other auxiliary agent in powder form and thereafter subjecting the powder mixture to direct tabletting by compression. If the flowing properties and/or the compressability of the powder mixture are not suitable, the wet granulating method is used whereby the powder mixture is granulated with a solution of a binder and/or the binding agent is used as powder and the powder mixture is granulated by a suitable solvent, the granules are dried, sieved, admixed with a lubricant and compressed to tablets. In the case of direct compression technology generally microcrystalline cellulose having an average particle size of at least 90 μm are

used. In the wet granulation process generally microcrystalline cellulose having an average particle size of 50 μm is applied. Recently microcrystalline cellulose containing about 2 % by weight of colloidal silicium dioxide has been used; this microcrystalline cellulose is called as silicified microcrystalline cellulose, and marketed under the name Prosolv.

It has not been described in prior art and it is new that microcrystalline cellulose having an average particle size below 30 μm suspended in a granulating liquid and used for granulation is suitable for the improvement of the tabletting properties of deramciclane-fumarate active ingredient which can generally be compressed to tablets only with high difficulties.

The granules comprising deramciclane-fumarate prepared as described above are thereafter admixed with disintegrating agent(s), lubricant(s), anti-adhesive auxiliary agent(s) and/or filler(s) and the homogenized mixture thus obtained is compressed into tablets.

As disintegrating agent excipients conventionally used in pharmaceutical compositions for such purposes can be used, e.g. various types of starch, preferably corn starch, potato or wheat starch, sodium carboxymethyl starch, sodium carboxymethyl cellulose, lower substituted hydroxypropyl cellulose or

crosslinked polyvinylpyrrolidone or a mixture thereof, particularly sodium carboxymethyl cellulose.

The disintegrating agent content of the tablets is 1-10 % by weight, preferably 2-8 % by weight, particularly 3-5 % by weight, related to the total weight of the composition.

As lubricant excipients generally used in pharmaceutical compositions for this purpose can be used, preferably magnesium stearate, calcium stearate, stearic acid, sodium steraril fumarate, hydrogenated vegetable oils or sugar esters, particularly magnesium stearate.

The lubricant content is 0.5-4 % by weight, preferably 0.5-2 % by weight, particularly preferably 1.0-1.5 % by weight, related to the total weight of the tablets.

As anti-adhesive agent excipients generally used in pharmaceutical compositions for this purpose can be used, preferably talc, colloidal and/or micronized silicium dioxide particularly colloidal silicium dioxide.

The amount of the anti-adhesive agent is 0.5-4 % by weight, preferably 0.5-2 % by weight, particularly 1.1-1.5 % by weight, related to the total weight of the tablet.

The pharmaceutical compositions of the present invention contain as filler preferably microcrystalline cellulose or having a particle size of at least 50 μm or silicified microcrystalline cellulose.

The amount of the filler is 0-30 % by weight, preferably 10-30 % by weight, particularly 20-30 % by weight, related to the total amount of the tablets.

According to a further aspect of the present invention there is provided a process for the preparation of deramciclane-fumarate containing tablets which comprises granulating more than 50 % by weight of deramciclane-fumarate (related to the total weight of the tablet) with 5-20 % by weight of microcrystalline cellulose having an average particle size below 30 μm, suspended in a solution of 5-20 % by weight of a binder; homogenizing the granules obtained with 1-15 % by weight of a disintegrant, 0.5-4 % by weight of a lubricant, 0.5-4 % by weight of an anti-adhesive agent and 0-30 % by weight of a binder; and thereafter compressing the mixture to tablets.

According to a preferred form of realization of the process of the present invention the granulation of more than 50 % by weight of deramciclane-fumarate (related to the total weight of

the tablet) is carried out with 5-10 % by weight of microcrystalline cellulose having an average particle size below 30 μm, suspended in an aqueous solution of 5-10 % by weight of a binder. The composition of the granulating suspension is determined - similarly to conventionally used granulating liquids - so that in case of high stear granulation the suspensions should still be easily handable, while in case of fluidization spraying granulation it should be suitably sprayable. The determination of the concentration of the binder belongs to the knowledge of the skilled art worker. The amount of microcrystalline cellulose is 5-20 %, related to the total weight of the granulating liquid.

According to a preferred form of realization of the process of the present invention a solution of the binder formed with water, ethanol or isopropanol can be used.

The granulating and tabletting step can be carried out by conventional methods of pharmaceutical industry by using the granulating suspension prepared above.

According to a particularly preferable form of realization of the process of the present invention one can accomplish granulation more than 50 % by weight of deramciclane-fumarate (related to the total weight of the tablet) with 6-9 % by weight of microcrystalline cellulose having an average particle size below

30 μm, suspended in an aqueous solution of 6-9 % by weight of povidone; homogenizing the granules thus obtained with 3-5 % by weight of sodium carboxymethyl cellulose, 1-1.5 % by weight of magnesium stearate, 1-1.5 % by weight of colloidal silicium dioxide and 20-30 % by weight of microcrystalline cellulose having an average particle size above than 50 μm; and compressing the mixture to tablets.

The tablets of the present invention have suitable crushing strength and can be particularly preferably used in film coating process where the mechanical stress is very high. Film coating of the tablets can be carried out by known methods of pharmaceutical industry. Thus for this purpose e.g. film coating compositions marketed under the name Opadry can be used, whereby hydroxypropyl methyl cellulose (Opadry I and Opadry II) or polyvinyl alcohol (Opadry II HP) are applied as film forming polymer.

Further details of the present invention are to be found in the following Examples without limiting the scope of protection to said Examples.

Example 1

The granulating solution is prepared by dissolving 245 g of copovidone in 1500 ml of water and thereafter dispersing in the solution 245 g of microcrystalline cellulose type No. 105 having an average particle size below 30 μm.

The granules are prepared by introducing 1470 g of deramciclane-fumarate into the container of a Glatt WSG 1 type fluidizing granulating apparatus, maintaining the active ingredient in fluidized state by air stream having a temperature of 40°C and thereafter spraying the granulating liquid thus obtained onto the powder within about 45 minutes. The granules formed are dried and sieved on a sieve having a hole-size of 1 mm.

To 224 g of the granules thus obtained 24 g of sodium carboxymethyl cellulose disintegrant, 4.0 g of magnesium stearate lubricant and as filler 35 g of Prosolv SMCC 90 (microcrystalline cellulose having an average particle size of 100 μm and containing 2 % by weight of colloidal silicium dioxide) are added. The homogenized mixture thus obtained is compressed on a Fette E XI type press machine into biconvex form tablets weighing 160 mg and having a diameter of 8 mm. The deramciclane base content of the tablets is 60.7 mg; the deramciclane-fumarate content of the tablets amounts to 52.5 % by weight.

During compression no sticking was observed on the surface of punches or the tablets. The internal surface of the broken (crushed) tablets was homogenous and free of lamination.

On measuring the critical parameters of the tablets according to the methods of the European Pharmacopoeia the following results are obtained:

WO 2004/105743

Compressing force	Friability	Disintegration	Resistance to crushing	Height	Weight	Dissolution (%)		
	(%)	(min)	(N)	(mm)	(mg)	5 min	15 min	30 min
6 KN	0 33	2 3	54	3 93	162 0			
10 KN	0 3	3 5	61	3 81	162 4	85 2	96 8	98 6
14 KN	0 43	5 3	66	3 69	159 0			
18 KN	0 46	5 7	68	3 66	158 7			
20 KN	0 38	6 5	70	3 66	158 2			

PCT/HU2004/000058

Taking into consideration the requirements of the European Pharmacopoeia the quality of deramciclane-fumarate tablets prepared according to Example 1 is highly favourable.

The requirements of European Pharmacopoeia (Ph. Eur.) are as follows:

Tablet parameter	Specification of Ph. Eur.
Deviation of the weight of the tablet:	
below 80 mg	± 10 %
between 80-250 mg	± 7.5 %
above 250 mg	± 5 %
Active ingredient of the tablet:	
nominal value	± 5 %
Deviation of active ingredient content:	
average value	± 15 %
Disintegration time	max. 15 min.
Friability	max. 1 %
Strength of the tablet*	no specification
Dissolution of the active ingredient	no general specification*

*most severe requirement: within 15 minutes more than 85 % of the active ingredient should be dissolved.

[Note for guigance on the investigation of bioavailability and bioequivalence, EMEA (European Agency for the Evaluation of Medical Products), 1999].

Test methods:

4th European Pharmacopoeia

2.9.1 Disintegration of tablets and capsules

2.9.3 Dissolution test for solid dosage forms

2.9.7 Friability of uncoated tablets

2.9.8 Resistance to crushing of tablets

Example 2

Granules having the composition shown in the following table are prepared from the granule according to Example 1, whereupon the homogenized mixture is compressed into tablets on a Fette E XI press machine into biconvex form tablets weighing 160 mg and having a diameter of 8 mm. The deramciclane base content of the tablets is 60.7 mg, the deramciclane-fumarate content of the tablets amounts to 52.5 mg.

No. of experiment	21.	22.	23.	24.	25.
Granules	224.0 g	224.0 g	224.0 g	224.0 g	224.0 g
Sodium-carboxymethyl-cellulose	18.0 g	12.0 g	12.0 g	12.0 g	12.0 g
Microcrystalline cellulose (102)	70.0 g	66.0 g	74.0 g	72.0 g	70.0 g
Magnesium stearate	5.4 g	6.0 g	6.0 g	6.0 g	6.0 g
Colloidal silicium-dioxide	2.6 g	12.0 g	4.0 g	6.0 g	8.0 g

During compression no sticking was observed on the surface of punches or the tablets. The internal surface of the broken (crushed) tablets was homogenous and free of lamination.

On measuring the critical parameters of the tablets according to the methods of the European Pharmacopoeia the following results are obtained:

No of experiment	21		22		23		24		25	
Compressing force	Resistance to crushing	Disintegration	Resistance to crushing	Disintegration	Resistance to crushing	Disintegration	Resistance to crushing	Disintegration	Resistance to crushing	Disintegration
	(N)	(min)	(N)	(min)	(N)	(min)	(N)	(min)	(N)	(min)
6 KN	76 3	3 0	63 6	1 8	70 2	2 9	80 8	2 2	72 3	2 4
10 KN	100 2	5 0	88 4	4 2	98 4	5 8	104 2	3 6	103 7	4 2
14 KN	107 6	5,5	106 1	4 6	121 9	6 2	121 3	5 2	119 4	6 0
18 KN	94 1	6 2	112 2	5 1	138 6	7 7	142 2	6 5	136 8	7 3

Taking into the consideration the relevant specifications of the European Pharmacopoeia the quality of the deramciclane-fumarate tablets prepared according to Example 2 is highly favourable.

Example 3

The granules are prepared by introducing 1470 g of deramciclane-fumarate into the container of a fluidization granulating apparatus type Glatt WSG 1 and keeping the active ingredient in fluidized condition by air stream having a temperature of 40°C. A granulating liquid having a composition shown in the following table is sprayed on the powder. The granules thus obtained are dried and sieved on a 1 mm hole-size sieve.

No. of experiment	31.	32.	33.	34.	35.
Copovidone	140.0 g	192.5 g	245.0 g	--	--
Microcrystalline cellulose (105)	140.0 g	192.5 g	245.0 g	200.0 g	185.0 g
Povidone K 30	--	--	--	100.0 g	135.0 g
Purified water	1500 g	1500 g	1500 g	1200 g	1000 g

A homogenized product having the composition disclosed in the following Table is prepared from the above granules. The homogenized mixture is compressed into tablets on a Fette E XI press machine into biconvex form tablets weighing 160 mg and having a diameter of 8 mm. The deramciclane base content of the tablets is 60.7 mg, the deramciclane-fumarate content of the tablets amounts to 52.5 % by weight.

No. of experiment	31.	32.	33.	34.	35.
Granules	200.0 g	212.0 g	224.0 g	228.0 g	238.0 g
Sodium-carboxymethyl-cellulose	12.0 g	12.0 g	12.0 g	14.0 g	14.0 g
Microcrystalline cellulose (102)	96.0 mg	84.0 mg	72.0 mg	60.0 g	50.0 g
Magnesium stearate	6.0 g	6.0 g	6.0 g	12.0 g	12.0 g
Colloidal silicium-dioxide	6.0 g	6.0 g	6.0 g	6.0 g	6.0 g

During compression no sticking was observed on the surface of punches or the tablets. The internal surface of the broken (crushed) tablets was homogenous and free of lamination.

On measuring the critical parameters of the tablets according to the methods of the European Pharmacopoeia the following results are obtained:

No of experiment	31		32		33		34		35	
Compressing force	Resistance to crushing	Disintegration	Resistance to crushing	Disintegration	Resistance to crushing	Disintegration	Resistance to crushing	Disintegration	Resistance to crushing	Disintegration
	(N)	(min)	(N)	(min)	(N)	(min)	(N)	(min)	(N)	(min)
6 KN	34 9	0 3	43 0	1 1	48 5	1 6	42 8	1 3	47 3	1 9
10 KN	50 0	0 8	74 7	2 1	79 3	3 7	60 4	2 6	69 3	2 6
14 KN	66 5	0 9	102	4 9	112 4	5 3	63 9	3 2	64 4	3 0
18 KN	73 2	0 9	112 3	5 9	121 4	6 5	56 8	4 0	68 4	3 6

Taking into the consideration the relevant specifications of the European Pharmacopoeia the quality of the deramciclane-fumarate tablets prepared according to Example 3 is highly favourable.

Example 4

The granulating solution is prepared by dissolving 175 g of povidone K30 type polyvinyl pyrrolidone in 1000 ml of water and dispersing in the solution 175 g of No. 105 type microcrystalline cellulose having an average particle size below 30 μm.

The granules are prepared by introducing 1453 g of deramciclane-fumarate into the container of a Glatt WSG 1 type fluidizing granulating apparatus and keeping the active ingredient in fluidized condition by air stream having a temperature of 40°C. Thereafter the above granulating liquid is sprayed onto the powder within about 30 minutes. The granules thus obtained are dried and sieved on a 1 mm hole-size sieve.

The granules thus obtained are homogenized into a blend having the composition disclosed in the above table. The blends are compressed on a Fette E XI press machine into biconvex form tablets having a diameter of 8 mm; the active ingredient content of the tablets is always 60 mg deramciclane base. Depending on the composition of the granulating liquid the deramciclane-

fumarate content of the tablets varies between 51.8 and 60.3 % by weight.

No. of experiment	41.	42.	43.*	44.	45.*
Granules	206.0 g	206.0 g	206.0 g	206.0 g	206.0 g
Sodium-carboxymethyl-cellulose	12.0 g	6.0 g	--	12.0 g	12.0 g
Microcrystalline cellulose (102)	90.0 mg	90.0 mg	90.0 mg	45.0 g	--
Magnesium stearate	6.0 g	6.0 g	6.0 g	6.0 g	6.0 g
Colloidal silicium dioxide	6.0 g	6.0 g	6.0 g	6.0 g	6.0 g

During compression no sticking was observed on the surface of punches or the tablets. The internal surface of the broken (crushed) tablets was homogenous and free of lamination.

The critical parameters of the tablets were determined in accordance with the corresponding specification of the European Pharmacopoeia. The results obtained are summarized in the following Table:

No of experiment	41		42		43		44		45	
Compressing force	Resistance to crushing	Disintegration	Resistance to crushing	Disintegration	Resistance to crushing	Disintegration	Resistance to crushing	Disintegration	Resistance to crushing	Disintegration
	(N)	(min)	(N)	(min)	(N)	(min)	(N)	(min)	(N)	(min)
6 KN	51 8	1 5	48 4	1 3	53 7	4 3	26 7	1 6	23 8	2 1
10 KN	703	2 3	64 8	2 5	55 9	7 3	46 9	2 4	24 1	2 4
14 KN	75 3	2 5	69 3	3 3	58 1	8 1	49 3	2 8	29 0	2 6
18 KN	78 2	3 0	72 4	4 9	60 2	9 7	48 5	3 1	23 1	2 6

Experiments 43 and 45 are of comparative character. The composition No. 43 contains no disintegrating agent and therefore the disintegration time of the tablets is significantly longer. Contrary to the present invention composition No. 45 contains no microcrystalline cellulose having an average particle size of at least 50 μm and the strength of the tablets does not reach the required crushing strength of at least 40 N.

Example 5

The granulating solution is prepared by dissolving 245 g of povidone K30 type polyvinyl pyrrolidone in 1500 ml of water and dispersing in the solution 245 g of type No. 105 microcrystalline cellulose having an average particle size below 30 μm.

The granules are prepared by introducing 1470 g of deramciclane-fumarate into the container of a Glatt WSG 1 type fluidizing granulating apparatus and keeping the active ingredient in fluidized state by air stream having a temperature of 40°C. The granulating liquid thus obtained is sprayed onto the powder within about 30 minutes. The granules thus formed are dried and sieved on a 1 mm hole-size sieve.

The granules thus obtained are admixed with 105 g of sodium carboxymethyl cellulose, 52.5 g of magnesium stearate, 52.5 g

of colloidal silicium dioxide and 630 g of microcrystalline cellulose (No. 102, average particle size 90 μm). The blend is compressed into biconvex form tablets weighing 160 mg and having a diameter of 8 mm on a Fette E XI eccentric press machine or a Manesty Betapress rotating press machine under 55 r.p.m. The deramciclane base content of the tablets is 60.7 mg, the deramciclane-fumarate content of the tablets is 52.5 % by weight.

During compression no sticking was observed on the surface of punches or the tablets. The internal surface of the broken (crushed) tablets was homogenous and free of lamination.

On measuring the critical parameters of the tablets according to the methods of the European Pharmacopoeia the following results are obtained:

No. of experiment	51.		52.	
	Fette E XI eccentric press machine		Betapress rotating press machine	
Compressing force	Resistance to crushing	Disintegration time	Resistance to crushing	Disintegration time
	(N)	(min.)	(N)	(min.)
6 KN	50.3	2.0	--	--
10 KN	81.6	4.1	84.5	4.6
14 KN	99.4	5.4	104.5	5.5
18 KN	112.2	6.5	--	--

The compressability of the granules is suitable and not dependent on the type of the press machine used.

Example 6

The granulating solution is prepared by dissolving 600 g of povidone K30 type polyvinyl pyrrolidone in 3.6 kg of water and dispersing in the solution 600 g of microcrystalline cellulose type No. 105 having an average particle size below 30 μm.

The granules are prepared by introducing 4.98 g of deramciclane-fumarate into the container of a Glatt WSG 5 type fluidizing granulating apparatus and keeping the active ingredient in fluidized state by air stream having a temperature of 60°C. The granulating solution is sprayed on the powder within about 60 minutes. The granules formed are dried and sieved on a 1 mm hole-size sieve.

The granules thus obtained are admixed with 360 g of sodium carboxymethyl cellulose, 180 g of magnesium stearate, 180 g of colloidal silicium dioxide and 2.70 kg of microcrystalline cellulose (No. 102 having an average particle size of 90 μm). The blend is compressed on a Manesty Betapress rotating press machine into biconvex formed tablets weighing 80 mg and having a diameter of 6 mm, or weighing 160 mg and having a diameter of 8 mm respectively. The deramciclane base content of the tablets is 30 mg/tablet and 60 mg/tablet respectively, the deramciclane-fumarate content of the tablets amounts to 51.8 % by weight.

During compression no sticking was observed on the surface of punches or the tablets. The internal surface of the broken (crushed) tablets was homogenous and free of lamination.

On measuring the critical parameters of the tablets according to the methods of the European Pharmacopoeia the following results are obtained:

No. of experiment	61.			62.		
	Weight 80 mg, diameter 6 mm 30 mg deramciclane base			Weight 160 mg, diameter 8 mm 60 mg deramciclane base		
Compressing force	Resistance to crushing	Disintegration time	Dissolution 15 min.	Resistance to crushing	Disintegration time	Dissolution 15 min.
	(N)	(min.)	(%)	(N)	(min.)	(%)
4 KN	44.7	1.3				
7 KN	53.1	3.0	96.4	56.1	1.1	
10 KN	61.7	3.3	94.0	83.4	2.8	92.9

In view of the relevant specifications of the European Pharmacopoeia the quality of the deramciclane-fumarate tablets thus obtained is highly favourable. On the basis of the mechanical characteristics the tablets are suitable for filmcoating.

Example 7

The granulating solution is prepared by dissolving 2.0 kg of povidone K30 type polyvinyl pyrrolidone in 12 kg of water and dispersing in the solution 2.0 kg of No. 105 microcrystalline cellulose having an average particle size below 30 μm.

The granules are prepared by introducing 16.61 kg of deramciclane-fumarate into the container of a Glatt GPCG 15 type fluidizing granulating apparatus and keeping the active ingredient in fluidized state by air stream having a temperature of 60°C. The granulating solution thus obtained is sprayed on the powder within about 80 minutes. The granules thus formed are dried and sieved on a 1 mm hole-size sieve.

The granules thus obtained are admixed with 1.2 kg of sodium carboxymethyl cellulose, 0.40 kg of magnesium stearate, 0.40 kg of colloidal silicium dioxide and 8.99 kg of microcrystalline cellulose (No. 102, an average particle size of 90 μm). The blend is compressed on a Manesty Betapress rotating press machine under 60 r.p.m. into biconvex formed tablets weighing 80 mg, having a diameter of 6 mm and weighing 160 mg, having a diameter of 8 mm, respectively. The deramciclane base content of the tablets amount to 30 mg/tablet and 60 mg/tablet,

respectively. The deramciclane-fumarate content of the tablets is 51.8 % by weight.

During compression no sticking was observed on the surface of punches or the tablets. The internal surface of the broken (crushed) tablets was homogenous and free of lamination.

On measuring the critical parameters of the tablets according to the methods of the European Pharmacopoeia the following results are obtained:

No. of experiment	71.			72.		
	Weight 80 mg, diameter 6 mm 30 mg deramciclane base			Weight 160 mg, diameter 8 mm 60 mg deramciclane base		
Compressing force	Resistance to crushing	Disintegration	Dissolution 15 min.	Resistance to crushing	Disintegration	Dissolution 15 min.
	(N)	(min.)	(%)	(N)	(min.)	(%)
8 kN	58	4.5	94.6			
12 kN				94	4.2	91.4

In view of the relevant specifications of the European Pharmacopoeia the quality of the deramciclane-fumarate tablets thus prepared is highly favourable. On the basis of the mechanical characteristics the tablets are suitable for filmcoating.

Example 8 (comparative example)

As a comparison deramciclane tablets are prepared by omitting in the granulating liquid according to Example 5 the microcrystalline cellulose type No. 105 (particle size below 30 μm) and replacing it by increasing the amount of microcrystalline cellulose by adding No. 102 type microcrystalline cellulose (particle size 90 μm) to the granules.

The granules are prepared by introducing 1470 g of deramciclane-fumarate into the container of a Glatt WSG 1 type fluidizing granulating apparatus and keeping the active ingredient in fluidized state by air stream having a temperature of 40°C. A solution of 245 g povidone K30 type polyvinyl pyrrolidone formed with 1500 ml of water is sprayed onto the powder within about 30 minutes. The granules thus formed are dried and sieved on a 1 mm hole-size sieve.

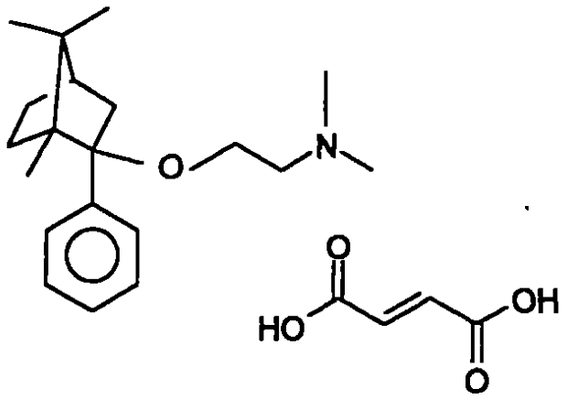
The granules thus obtained are admixed with 105 g of sodium carboxymethyl cellulose, 52.5 g of magnesium stearate, 52.5 g

of colloidal silicium dioxide and 875 g of microcrystalline cellulose (No. 102, an average particle size 90 μm). The blend is compressed on a Fette E XI eccentric press machine or a Manesty Betapress rotating press machine under 55 r.pm. into biconvex formed tablets weighing 160 mg and having a diameter of 8 mm. The deramciclane base content of the tablets is 60.7 mg, the deramciclane-fumarate content of the tablets amounts to 52.5 % by weight.

During the compression of tablets a layer is formed on the pressing tool, the surface of the tablets became cloudy; the quality of the tablets is unsatisfactory and the tablets are unsuitable for industrial scale manufacture.

What we claim is:

1. Tablets comprising deramciclane-fumarate of the Formula



I.

whereby said tablets contain (related to the total weight) more than 50 % by weight of deramciclane-fumarate, 5-20 % by weight of a binder, 5-20 % by weight of microcrystalline cellulose having an average particle size below 30 μm, 1-10 % by weight of a disintegrant, 0.5-4 % by weight of a lubricant, 0.5-4 % by weight of an anti-adhesive agent and 0-30 % by weight of a filler.

2. Tablets according to Claim 1 comprising 50-88 % by weight, preferably 50-78 % by weight of deramciclane-fumarate.

3. Tablets according to Claim 1 comprising as binder polyvinyl pyrrolidone, gum-arabic, alginic acid, sodium carboxymethyl cellulose, dextrine, ethyl cellulose, gelatine, liquid sugar, guar gum, hydroxypropyl methyl cellulose, methyl cellulose, polyethylene oxide, pre-gelatinised starch or sugar syrup.

4. Tablets according to Claim 3 comprising as binder polyvinyl pyrrolidone.

5. Tablets according to Claim 3 or 4 comprising 5-12 % by weight of a binder.

6. Tablets according to Claim 5 comprising 6-9 % by weight of a binder.

7. Tablets according to Claim 1 comprising 5-15 % by weight of microcrystalline cellulose having an average particle size below 30 μm.

8. Tablets according to Claim 7 comprising 6-9 % by weight of microcrystalline cellulose having an average particle size below 30 μm.

9. Tablets according to Claim 1 comprising as disintegrant starch, preferably maize, potato or wheat starch, sodium carboxymethyl starch, sodium carboxymethyl cellulose, lower substituted hydroxypropyl cellulose or crosslinked polyvinyl pyrrolidone or a mixture thereof.

10. Tablets according to Claim 9 comprising as disintegrant sodium carboxymethyl cellulose.

11. Tablets according to Claim 9 or 10 comprising 2-8 % by weight of a disintegrant.

12. Tablets according to Claim 11 comprising 3-5 % by weight of said disintegrant.

13. Tablets according to Claim 1 comprising as lubricant magnesium stearate, calcium stearate, stearic acid, sodium stearil fumarate, hydrogenated vegetable oils or sugar esters.

14. Tablets according to Claim 13 comprising as lubricant magnesium stearate.

15. Tablets according to Claim 13 or 14 comprising said lubricant in an amount of 0.5-2 % by weight.

16. Tablets according to Claim15 comprising said lubricant in an amount of 1.0-1.5 % by weight.

17. Tablets according to Claim 1 comprising as anti-adhesive agent colloidal silicium dioxide.

18. Tablets according to Claim 17 comprising colloidal silicium dioxide in an amount of 0.5-2 % by weight.

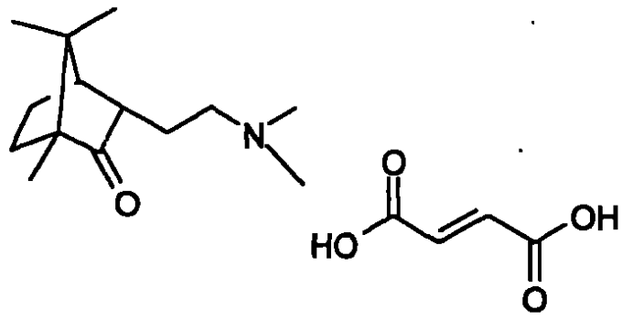
19. Tablets according to Claim 18 comprising colloidal silicium dioxide in an amount of 1.0-1.5 % by weight.

20. Tablets according to Claim 1 comprising as filler microcrystalline cellulose having a particle size of at least 50 μm or microcrystalline cellulose containing colloidal silicium dioxide.

21. Tablets according to Claim 20 comprising said filler in an amount of 10-30 % by weight.

22. Tablets according to Claim 21 comprising said filler in an amount of 20-30 % by weight.

23. Tablets according to Claim 1 comprising as active ingredient (1R,2S,4R)-(-)-2-dimethylaminoethoxy-2-phenyl-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2-(E)-butenedioate (1:1) of the Formula I which contains not more than 0.2 % by weight of (1R,3S,4R)-(-)-3-(2-N,N-dimethylaminoethyl)-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2-one-(E)-butenedioate (1:1) of the Formula



II.

24. Process according to Claim 1 for the preparation of deramciclane-fumarate containing tablets which comprises granulating more than 50 % by weight of the deramciclane-fumarate (related to the total weight of the tablet) with 5-20 % by weight of microcrystalline cellulose having an average particle size below 30 μm, suspended in a solution of 5-20 % by weight of a binder; homogenizing the granules obtained with 1-15 % by weight of a disintegrant, 0.5-4 % by weight of a lubricant, 0.5-4 % by weight of an anti-adhesive agent and 0.30 %

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by weight of a binder; and thereafter compressing the mixture to tablets.

25. Process according to Claim 23 which comprises using a solution of a binder formed with water, ethanol or isopropanol.

26. Process according to Claim 22 or 23 which comprises granulating more than 50 % by weight of deramciclane-fumarate (related to the total weight of the tablet) with 6-9 % by weight of microcrystalline cellulose having an average particle size below 30 μm, suspended in an aqueous solution of 6-9 % by weight of povidone; homogenizing the granules thus obtained with 3-5 % by weight of sodium carboxymethyl cellulose, 1-1.5 % by weight of magnesium stearate, 1-1.5 % by weight of colloidal silicium dioxide and 20-30 % by weight of microcrystalline cellulose having an average particle size above than 50 μm; and compressing the mixture to tablets.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HU2004/000058

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/13 A61K9/20 C07C217/12 A61P25/22

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P C07C

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, MEDLINE

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

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
28 September 2004	05/10/2004

Name and mailing address of the ISA	Authorized officer
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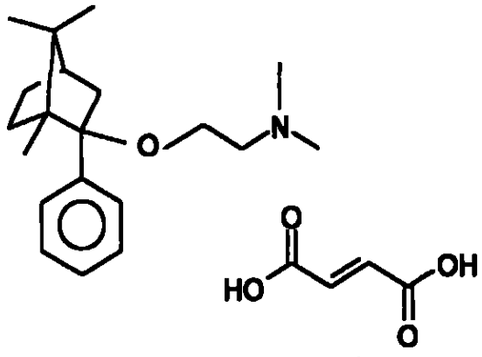
(54) Título: TABLETAS DE DERAMCICLANO-FUMARATO



(I)

(57) Extracto: La invención se refiere a tabletas que comprenden deramciclano-fumarato de la Fórmula (I) por lo cual dichas tabletas contiene (en relación con el peso total) más de 50 % en peso de deramciclano-fumarato, 5-20 % en peso de un aglutinante, 5-20 % en peso de celulosa microcristalina con un tamaño medio de partícula inferior a 30 µm, 1-10 % en peso de un desagregante, 0.5-4 % en peso de un lubricante, 0.5-4 % en peso de un agente anti-adhesivo y 0-30 % en peso de un relleno. Deramciclano-fumarato es un conocido ingrediente activo ansiolítico.

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TABLETAS DE DERAMCICLANO-FUMARATO

CAMPO TÉCNICO DE LA INVENCIÓN

La invención se refiere a tabletas de deramciclano-fumarato, con alto contenido de ingrediente activo, y a un proceso para su preparación.

ESTADO DEL ARTE

Se sabe que (1R,2S,4R)-(-)-2-dimetilaminoetoxi-2-fenil-l,7,7-trimetil-biciclo[2.2.1]heptano-2-(E)-butenodioato (1:1) de la Fórmula I (denominado en lo sucesivo deramciclano-fumarato) es un valioso ingrediente activo farmacéutico, ansiolítico, (GB 2,065,122; EP 1 052 245).

La preparación del ingrediente activo y composiciones farmacéuticas que contienen el mismo – es decir, tabletas – se describe en GB 2,065,122.

Deramciclano-fumarato es un polvo cristalino blanco que, de acuerdo con la experiencia práctica, posee propiedades de compactación (***"tabletting properties"***) en extremo desfavorables.

Las siguientes propiedades del deramciclano-fumarato son muy desfavorables desde el punto de vista de la producción de tabletas:

- poca cohesión;
- alta elasticidad;
- fuerte adhesión;
- baja solubilidad en agua.

Debido a las características de poca cohesión del deramciclano-fumarato en la compresión de las partículas del ingrediente activo, no es posible obtener una resistencia aceptable de las tabletas. Cuando se depositan 300 mg de polvo de deramciclano-fumarato en la cavidad de una matriz de 10 mm de

diámetro de una prensa excéntrica y luego se compacta con una fuerza de compresión de 5-40 kN, la resistencia a la trituración de las tabletas no supera los 10 N. En el caso de materiales adecuadamente comprimibles, la resistencia a la trituración que puede logarse es superior a los 100 N.

El comportamiento elevadamente elástico de las partículas del ingrediente activo significa que, bajo el efecto de la fuerza de compresión, el volumen de las partículas de deramciclano-fumarato disminuye, tras lo cual, cuando ya no se ejerce más compresión, las partículas recuperan su forma original en una medida significativa y, debido a dicha recuperación elástica, los enlaces formados durante la compresión entre las partículas, se rompen. Dicho rompimiento de los enlaces tiene lugar a lo largo de los planos de fuerza máxima formados dentro de la tableta, y esto produce la laminación de la estructura de la tableta. En el caso de materiales convenientemente comprimibles con baja elasticidad, la estructura interna de la tableta es homogénea y no se forma una estructura laminada.

La baja resistencia de la tableta a la trituración y la laminación pueden eliminarse empleando una gran cantidad de un aglutinante. No obstante, una gran cantidad del aglutinante prolonga el tiempo de disgregación de la tableta en medio acuoso en una magnitud excesiva y, adicionalmente, desacelera la disolución del ingrediente activo; por consiguiente, se obtienen tabletas de calidad inadecuada.

Debido a las propiedades fuertemente adhesivas del deramciclano-fumarato, de una parte, durante la compresión se forman elevadas fuerzas de fricción entre la cara de la las tabletas y la pared de la matriz, lo cual resulta en un daño de la tableta cuando se extraen de la matriz. Por otra parte, las tabletas se pegan a la superficie de los punzones y, por lo tanto, la superficie de la tableta no es uniforme. Esta desventaja puede eliminarse, en principio, agregando una gran cantidad de un lubricante; sin embargo, esta medida tiene serias desventajas; disminuye la resistencia de las tabletas en un grado

indeseado; debido al carácter hidrófobo el lubricante desacelera considerablemente la desagregación de la tableta en un medio acuoso, y ralentiza asimismo la disolución del ingrediente activo y, por las razones ya expuestas, se obtienen tabletas de calidad inapropiada.

Aparte de la baja solubilidad en agua del deramciclano-fumarato, las propiedades de poca cohesión y fuerte adhesión son aún más problemáticas porque, de un lado, la gran cantidad requerida de los aglutinantes y los lubricantes, del otro, hacen imposible la rápida disolución del ingrediente activo.

Debido a los problemas discutidos anteriormente, las formulaciones de tableta descritas en GB 2,065,122 son inadecuadas para la manufactura a escala industrial de tabletas de deramciclano-fumarato.

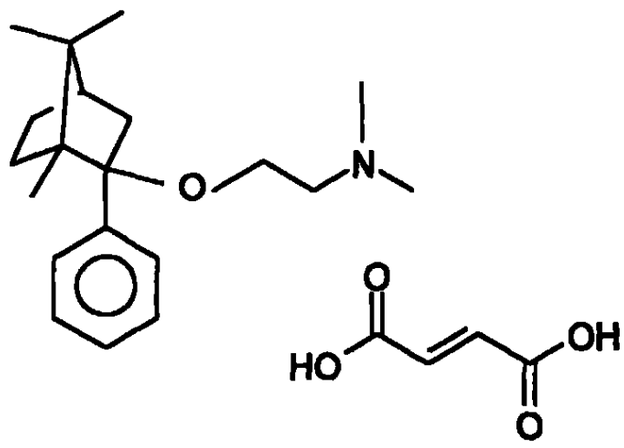
Las formulaciones de tableta divulgadas en GB 2,065,122 son particularmente inadecuadas para la preparación de tabletas de deramciclano-fumarato con un con un contenido de ingrediente activo por encima de 50 % en peso. No obstante, tanto los fabricantes como los pacientes prefieren tabletas con un contenido de ingrediente activo tan alto como ése. Desde el punto de vista de los fabricantes el menor peso de la tableta requiere menos agentes auxiliares y un tiempo de mano de obra más corto, un tamaño de lote más grande, menos pruebas analíticas, es decir, menores costos de producción. Los pacientes pueden tragar tabletas más pequeñas con mayor facilidad, y esto mejora el cumplimiento terapéutico del paciente.

SUMARIO DE LA INVENCIÓN

El objeto de la invención es el desarrollo de tabletas de deramciclano-fumarato que tengan un contenido de ingrediente activo por encima del 50 % en peso y puedan comprimirse fácilmente en tabletas.

Otro objeto de la presente invención es la elaboración de un proceso adecuado para la preparación de tales tabletas.

La presente invención se dirige a tabletas que comprenden deramciclano-fumarato de la Fórmula



I.

por lo cual dichas tabletas contienen (en relación con el peso total) más de 50 % en peso de deramciclano-fumarato, 5-20 % en peso de un aglutinante, 5-20 % en peso de celulosa microcristalina con un tamaño medio de partícula inferior a 30 µm, 1-10 % en peso de un desagregante, 0.5-4 % en peso de un lubricante, 0.5-4 % en peso de un agente anti-adhesivo y 0-30 % en peso de un relleno.

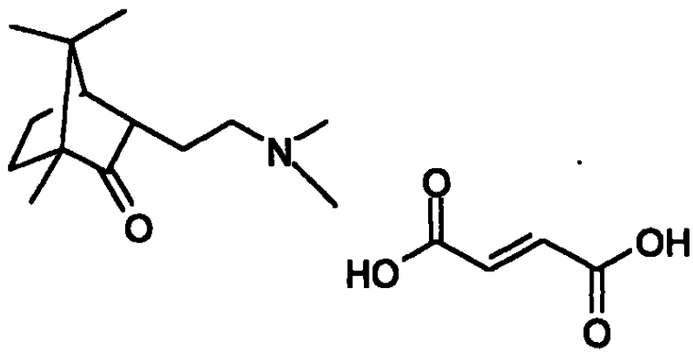
DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La presente invención se basa en el reconocimiento de que si celulosa microcristalina, con un tamaño de particular inferior a 30 µm, se utiliza en el líquido de granulación, las partículas de tal celulosa microcristalina forman una capa en la superficie de las partículas de deramciclano-fumarato y, por consiguiente, disminuyen las propiedades de adhesión de los gránulos. Por lo tanto, puede reducirse la cantidad de lubricantes y agentes anti-adhesivos requeridos en la tableta y, de esta manera, manufacturarse

tabletas no adherentes que tengan una resistencia apropiada. Las tabletas de acuerdo con la presente invención poseen excelente resistencia mecánica, se disgregan fácil y rápidamente en un medio acuoso y el contenido de ingrediente activo se disuelve prontamente.

El contenido de deramciclano-fumarato de las tabletas de acuerdo con la presente invención es 50-88 % en peso, preferiblemente 50-78 % en peso.

De acuerdo con una incorporación preferida de la presente invención se proveen tabletas que comprenden como ingrediente activo (1R,2S,4R)-(-)-2-dimetilaminoetoxi-2-fenil-1,7,7-trimetil-biciclo[2.2.1]heptano-2-(E)-butenodioato (1:1) de la Fórmula I, las cuales no contienen más de 0.2 % en peso de (1R,3S,4R)-(-)-3-(2-N,N-dimetilammoetil)-1,7,7-trimetil-biciclo[2.2.1]heptano-2-ona-(E)-butenodioato (1:1) de la Fórmula



II.

Tal deramciclano-fumarato de alta pureza se describe en EP 1 052 245.

Las tabletas de deramciclano-fumarato de la presente invención pueden comprender cualquier aglutinante apropiado para los propósitos de la manufactura de tabletas. Tales aglutinantes se divulgan, por ejemplo en el capítulo Colección Nacional de Fórmulas de la Farmacopea de los Estados Unidos [USP23/NF18 página 2206 (United States Pharmacopeial Convention, Inc., 1995)]. Por consiguiente puede emplearse como aglutinante preferiblemente polivinilpirrolidona, goma arábiga, ácido algínico, carboximetilcelulosa sódica, dextrina, etilcelulosa, gelatina, azúcar líquido, goma de guar, hidroxipropilmetilcelulosa, metilcelulosa, óxido de

polietileno, almidón pre-gelatinizado jarabe de azúcar, particularmente polivinilpirrolidona (povidona) o un copolímero de vinilpirrolidona y acetato de vinilo (copovidona).

Las tabletas de acuerdo con la presente invención contienen 5-20 % en peso, preferiblemente 5-12 % en peso, particularmente 6-9 % en peso de un aglutinante (en relación con el peso total de la tableta).

El líquido de granulación usado para disolver el aglutinante puede ser preferiblemente agua, etanol, isopropanol o una mezcla de los mismos que contenga dichos disolventes en cualquier proporción. Celulosa microcristalina con un tamaño medio de partícula no superior a 30 µm se suspende en el líquido de granulación, tras lo cual el polvo del ingrediente activo se granula con dicha suspensión de granulación directamente sin agregar otros agentes auxiliares. La granulación puede llevarse a cabo por el método de granulación por la vía húmeda, por lo cual la suspensión de granulación mencionada se agrega al polvo del ingrediente activo en un mezclador supercortante (***"a high shear mixer"***). De acuerdo con otro procedimiento, la granulación se realiza mediante el método de aspersión mediante el cual la suspensión de granulación mencionada se rocía sobre el polvo del ingrediente activo en un aparato de aspersión con fluidización.

Celulosa microcristalina con un tamaño medio de partícula de 30 µm ó menos se designa generalmente por No. 105. Los productos disponibles en el comercio usados con más frecuencia son Avicel 105, Vivapur 105 y Elcema 105. Los folletos de los fabricantes recomiendan el uso de celulosa microcristalina de este tipo como excipiente inerte, o alternativamente como agente auxiliar útil en la manufactura de suspensiones y supositorios con el fin de evitar la sedimentación.

Actualmente, en la manufactura de tabletas se utiliza celulosa microcristalina con un tamaño medio de partícula de por lo menos 50 µm.

Celulosa microcristalina con un tamaño medio de partícula de 50 µm se denota generalmente por No. 101, mientras que celulosa microcristalina con un tamaño medio de partícula de 90-100 µm se designa generalmente como No. 102.

De acuerdo con el estado del arte se emplean varios tipos de celulosa microcristalina mezclando celulosa microcristalina con el ingrediente activo y, de manera opcional, con otro agente auxiliar en forma de polvo y, seguidamente, sometiendo la mezcla de polvo a un proceso de compactación directo por compresión. Si las propiedades de deslizamiento y/o la compresibilidad de la mezcla de polvo no son apropiadas, se recurre al método de granulación por vía húmeda, por lo cual la mezcla de polvo se granula con una solución de un aglutinante y/o el agente aglutinante se usa como polvo y la mezcla de polvo se granula con un disolvente apropiado, los gránulos se secan, se tamizan, se mezclan con un lubricante y se comprimen en tabletas. En el caso de la tecnología de compresión directa, se emplea generalmente celulosa microcristalina con un tamaño medio de partícula de por lo menos 90 µm. En el proceso de granulación por la vía húmeda se aplica generalmente celulosa microcristalina con un tamaño medio de partícula de 50 µm. Recientemente se ha utilizado celulosa microcristalina con un contenido de alrededor de 2 % en peso de dióxido de silicio coloidal; esta celulosa microcristalina se denomina celulosa microcristalina silicificada, y se comercializa bajo la marca Prosolv.

No se ha descrito en el arte previo y es nuevo que la celulosa microcristalina con un tamaño medio de partícula inferior a 30 µm, suspendida en un líquido de granulación y empleada para granular, es adecuada para mejorar las propiedades de compactación del ingrediente activo deramciclano-fumarato, el cual puede comprimirse generalmente en tabletas sólo con grandes dificultades.

Los gránulos que comprenden deramciclano-fumarato preparados como se

describe anteriormente se mezclan luego con agente(s) desagregante(s), lubricante(s), agente(s) anti-adhesivo(s) auxiliar(es) y/o relleno(s) y la mezcla homogeneizada así obtenida se comprime en tabletas.

Como agente desagregante pueden emplearse excipientes utilizados convencionalmente en composiciones farmacéuticas para tales propósitos, por ejemplo varios topos de almidón, preferiblemente almidón de maíz, almidón de papa o trigo, almidón carboximetílico sódico, carboximetilcelulosa sódica, hidroxipropilcelulosa sustituida inferior o polivinilpirrolidona cruzadamente enlazada o una mezcla de las mismas, particularmente carboximetilcelulosa sódica.

El contenido de agente desagregante de las tabletas es 1-10 % en peso, preferiblemente 2-8 % en peso, particularmente 3-5 % en peso, en relación con el peso total de la composición.

Como lubricante, pueden emplearse excipientes usados generalmente en composiciones farmacéuticas para este propósito, preferiblemente estearato de magnesio, estearato de calcio, ácido esteárico, estearilfumarato sódico, aceites vegetales hidrogenados o ésteres de azúcar, particularmente estearato de magnesio.

El contenido de lubricante es 0.5-4 % en peso, preferiblemente 0.5-2 % en peso, particularmente preferiblemente 1.0-1.5 % en peso, en relación con el peso total de las tabletas.

Como agente anti-adhesivo, pueden emplearse excipientes utilizados generalmente en composiciones farmacéuticas para este propósito, preferiblemente talco, dióxido de silicio coloidal y/o micronizado, particularmente dióxido de silicio coloidal.

La cantidad del agente anti-adhesivo es 0.5-4 % en peso, preferiblemente

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0.5-2 % en peso, particularmente 1.1-1.5 % en peso, en relación con el peso total de la tableta.

Las composiciones farmacéuticas de la presente invención contienen como relleno preferiblemente celulosa microcristalina o con un tamaño de partícula de por lo menos 50 μm o celulosa microcristalina silicificada.

La cantidad del relleno es 0-30 % en peso, preferiblemente 10-30 % en peso, particularmente 20-30 % en peso, en relación con el peso total de las tabletas.

De acuerdo con un aspecto adiciona de la presente invención se provee un proceso para la preparación de tabletas que contienen deramciclano-fumarato, el cual comprende granular más de 50 % en peso de deramciclano-fumarato (en relación con el peso total de la tableta) con 5-20 % en peso de celulosa microcristalina con un tamaño medio de partícula inferior a 30 μm, suspendida en una solución de 5-20 % en peso de un aglutinante; homogeneizar los gránulos obtenidos con 1-15 % en peso de una desagregante, 0.5-4 % en peso de un lubricante, 0.5-4 % en peso de un agente anti-adhesivo y 0-30 % en peso de un aglutinante; y seguidamente comprimir la mezcla en tabletas.

De acuerdo con una forma preferida de realización del proceso de la presente invención, la granulación de más de 50 % en peso de deramciclano-fumarato (en relación con el peso total de la tableta) se lleva a cabo con 5-10 % en peso de celulosa microcristalina con un tamaño medio de partícula inferior a 30 μm, suspendida en una solución acuosa de 5-10 % en peso de un aglutinante. La composición de la suspensión de granulación se determina – análogamente a líquidos de granulación empleados convencionalmente – de modo que en el caso granulación ultracortante (***"high shear granulation"***) las suspensiones deben ser aún fácilmente manejables, mientras que en el caso de granulación de aspersión con

fluidización debe ser apropiadamente atomizable. La determinación de la concentración del aglutinante pertenece al conocimiento del operario experto en el arte. La cantidad de celulosa microcristalina es 5-20 %, en relación con el peso total del líquido de granulación.

De acuerdo con una forma preferida de realización del proceso de la presente invención puede usarse una solución del aglutinante formada con agua, etanol o isopropanol.

El paso de granular y compactar puede llevarse a cabo por métodos convencionales de la industria farmacéutica usando la suspensión de granulación preparada más arriba.

De acuerdo con una forma particularmente preferida de realización del proceso de la presente invención se puede lograr la granulación de más de 50 % en peso de deramciclano-fumarato (en relación con el peso total de la tableta) con 6-9 % en peso de celulosa microcristalina con un tamaño medio de partícula inferior a 30 μm, suspendida en una solución acuosa de 6-9 % en peso de povidona; homogeneizando los gránulos así obtenidos con 3-5 % en peso de carboximetilcelulosa sódica, 1-1.5 % en peso de estearato de magnesio, 1-1.5 % en peso de dióxido de silicio coloidal y 20-30 % en peso de celulosa microcristalina con un tamaño medio de partícula superior a 50 μm; y comprimiendo la mezcla en tabletas.

Las tabletas de la presente invención tienen una resistencia de trituración apropiada y, en particular, pueden usarse preferiblemente en procesos de recubrimiento con película donde el esfuerzo mecánico es muy alto. El recubrimiento con película de las tabletas puede llevarse a cabo por métodos conocidos de la industria farmacéutica. Así, para este propósito, pueden utilizarse por ejemplo composiciones de recubrimiento comercializadas bajo la marca Opadry, para lo cual hidroxipropilmetilcelulosa (Opadry I y Opadry II) o alcohol polivinílico (Opadry II HP) se aplican como polímero

formador de película.

Otros detalles de la presente invención tienen que encontrarse en los siguientes Ejemplos sin limitar el ámbito de protección a dichos Ejemplos.

Ejemplo 1

La solución de granulación se prepara disolviendo 245 g de copovidona en 1500 ml de agua y, a continuación, dispersando en la solución 245 g de celulosa microcristalina tipo No. 105 con un tamaño medio de partícula inferior a 30 μm.

Los gránulos se preparan introduciendo 1470 g de deramciclano-fumarato en el tanque de un aparato de granulación con fluidización Glatt tipo WSG 1, manteniendo el ingrediente activo en estado fluidizado por chorro de aire con una temperatura de 40°C y, seguidamente, rociando el líquido de granulación así obtenido sobre el polvo en alrededor de 45 minutos. Los gránulos formados se secan y se ciernen en un tamiz con un tamaño de orificio de 1 mm.

A 224 g de los gránulos así obtenidos 24 g se agregan disgregador de carboximetilcelulosa sódica, 4.0 g de lubricante estearato de magnesio y como relleno 35 g de Prosolv SMCC 90 (celulosa microcristalina con un tamaño medio de partícula de 100 μm y que contenía 2 % en peso de dióxido de silicio coloidal). La mezcla homogeneizada así obtenida se comprime en una prensa Fette E tipo XI en tabletas de forma biconvexa que pesan 160 mg y con un diámetro de 8 mm. El contenido base de deramciclano de las tabletas es 60.7 mg; el contenido de deramciclano-fumarato de las tabletas asciende a 52.5 % en peso.

Durante la compresión no se observó adherencia en la superficie de los punzones o las tabletas. La superficie interna de las tabletas rotas (trituradas) era homogénea y libre de laminación.

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Al medir los parámetros críticos de las tabletas de acuerdo con los métodos de la Farmacopea Europea se obtienen los siguientes resultados:

Fuerza de compresión	Friabilidad	Disgregación	Resistencia a la trituración	Altura	Peso	Disolución (%)		
	(%)	(min.)	(N)	(mm)	(mg)	5 min.	15 min.	30 min.
6KN	0.33	2.3	54	3.93	162.0			
10 kN	0.3	3 5	61	3 81	162.4	85.2	96.8	98.6
14 kN	0.43	5.3	66	3.69	159.0			
18 kN	0.46	5.7	68	3.66	158.7			
20 kN	0 38	6.5	70	3.66	158 2			

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Teniendo en cuenta los requerimientos de la Farmacopea Europea la calidad de las tabletas de deramciclano-fumarato preparadas de acuerdo con Ejemplo 1 es altamente favorable.

Los requerimientos de la Farmacopea Europea (Ph. Eur.) son los siguientes:

Parámetro de la tableta	Especificación de Ph. Eur.
Desviación del peso de la tableta:	± 10 %
menos de 80 mg	± 7.5 %
entre 80-250 mg	± 5%
más de 250 mg	
Ingrediente activo de la tableta:	
Valor nominal	± 5%
Desviación del contenido de ingrediente activo:	
Valor promedio	± 5%
Tiempo de desagregación	máx. 15 min.
Friabilidad	máx. 1%
Resistencia de la tableta*	sin especificación
Disolución del ingrediente activo	sin especificación general*

*Requerimiento más severo: en un lapso de 15 minutos debe disolverse más de 85 % del ingrediente activo.

[Para orientación sobre la investigación de la biodisponibilidad la bioequivalencia, téngase en cuenta a EMEA (European Agency for the Evaluation of Medical Products), 1999].

Métodos de prueba:
Farmacopea Europea 4ª Edición

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2.9.1 Desagregación de tabletas y cápsulas

2.9.3 Prueba de disolución para formulaciones farmacéuticas sólidas

2.9.7 Friabilidad de tabletas no recubiertas

2.9.8 Resistencia a la trituración de las tabletas

Ejemplo 2

Gránulos con la composición indicada en la siguiente tabla se preparan del gránulo de acuerdo con Ejemplo 1, tras lo cual la mezcla homogeneizada se comprime en una prensa Fette E XI en tabletas de forma biconvexa que pesan 160 mg y con un diámetro de 8 mm. El contenido base de deramciclano de las tabletas es 60.7 mg, el contenido de deramciclano-fumarato de las tabletas asciende a 52.5 mg.

No. de experimento	21.	22.	23.	24.	25.
Gránulos	224.0 g	224.0 g	224.0 g	224.0 g	224.0 g
Carboximetilcelulosa sódica	18.0 g	12.0 g	12.0 g	12.0 g	12.0 g
Celulosa microcristalina (102)	70.0 g	66.0 g	74.0 g	72.0 g	70.0 g
Estearato de magnesio	5.4 g	6.0 g	6.0 g	6.0 g	6.0 g
Dióxido de silicio coloidal	2.6 g	12.0 g	4.0 g	6.0 g	8.0 g

Durante la compresión no se observó adherencia en la superficie de los punzones o las tabletas. La superficie interna de las tabletas rotas (trituradas) era homogénea y libre de laminación.

Al medir los parámetros críticos de las tabletas de acuerdo con los métodos de la Farmacopea Europea se obtienen los siguientes resultados:

No. de experimento	21.		22		23.		24.		25.	
Fuerza de compresión	Resistencia a la trituración	Disgregación	Resistencia a la trituración	Disgregación	Resistencia a la trituración	Disgregación	Resistencia a la trituración	Disgregación	Resistencia a la trituración	Disgregación
	(N)	(min.)	(N)	(min.)	(N)	(min)	(N)	(min.)	(N)	(min.)
6 kN	76.3	3.0	63.6	1.8	70.2	2.9	80.8	2.2	72.3	2.4
10 kN	100.2	5.0	88.4	4.2	98.4	5.8	104.2	3.6	103.7	4.2
14 kN	107.6	5 5	16.1	4 6	121 9	6.2	121.3	5.2	119.4	6.0
18 kN	94 1	6.2	112 2	5.1	138.6	7.7	142 2	6.5	136 8	7 3

Teniendo en cuenta las especificaciones relevantes de la Farmacopea Europea la calidad de las tabletas de deramciclano-fumarato preparadas de acuerdo con Ejemplo 2 es altamente favorable.

Ejemplo 3

Los gránulos se preparan introduciendo 1470 g de deramciclano-fumarato en el tanque de un aparato de granulación con fluidización tipo Glatt WSG 1 y manteniendo el ingrediente activo en estado fluidizado mediante chorro de aire con una temperatura de 40°C. Un líquido de granulación que tiene una composición indicada en la siguiente tabla se rocía sobre el polvo. Los gránulos así obtenidos se secan y se cernen en una criba con tamaño de orificio 1 mm.

No. de experimento	31.	32.	33.	34.	35.
Copovidona	140.0 g	192.5 g	245.0 g	--	--
Celulosa microcristalina (105)	140.0 g	192.5 g	245.0 g	200.0 g	185.0 g
Povidona K30	--	--	--	100.0 g	135.0 g
Agua purificada	1500 g	1500 g	1500 g	1200 g	1000 g

Un producto homogeneizado que tiene la composición divulgada en la siguiente Tabla se prepara a partir de los gránulos anteriores. La mezcla homogeneizada se comprime en tabletas en una prensa Fette E XI en tabletas de forma biconvexa que pesan 160 mg y con un diámetro de 8 mm. El contenido base de deramciclano de las tabletas es 60.7 mg, el contenido de deramciclano-fumarato de las tabletas asciende a 52.5 % en peso.

No. de experimento	31.	32.	33.	34.	35.
Gránulos	200.0 g	212.0 g	224.0 g	228,0 g	238.0 g
Carboxi-metilcelulosa sódica	12.0 g	12.0 g	12.0 g	14.0 g	14.0 g
Celulosa microcristalina (102)	96.0 mg	84.0 mg	72.0 mg	60.0 g	50.0 g
Estearato de magnesio	6.0 g	6.0 g	6.0 g	12.0 g	12.0 g
Dióxido de silicio coloidal	6.0 g	6.0 g	6.0 g	6.0 g	6.0 g

Durante la compresión no se observó adherencia en la superficie de los punzones o las tabletas. La superficie interna de las tabletas rotas (trituradas) era homogénea y libre de laminación.

Al medir los parámetros críticos de las tabletas de acuerdo con los métodos de la Farmacopea Europea se obtienen los siguientes resultados:

No. de experimento	31.		32.		33.		34.		35.	
Fuerza de compresión	Resistencia a la trituración	Disgregación	Resistencia a la trituración	Disgregación	Resistencia a la trituración	Disgregación	Resistencia a la trituración	Disgregación	Resistencia a la trituración	Disgregación
	(N)	(min.)	(N)	(min.)	(N)	(min.)	(N)	(min.)	(N)	(min.)
6 kN	34.9	0.3	43.0	1 1	48.5	1 6	42.8	1.3	47.3	1.9
10 kN	50.0	0.8	74.7	2.1	79.3	3.7	60.4	2 6	69.3	2 6
14 kN	66.5	0 9	102..	4.9	112.4	5.3	63 9	3.2	64.4	3.0
18 kN	73.2	0.9	112.3	5.9	121.4	6.5	56.8	4 0	68.4	3.6

Teniendo en cuenta las especificaciones relevantes de la Farmacopea Europea la calidad de las tabletas de deramciclano-fumarato preparadas de acuerdo con Ejemplo 3 es altamente favorable.

Ejemplo 4

La solución de granulación se prepara disolviendo 175 g de povidona K30 tipo polivinilpirrolidona en 1000 ml de agua y dispersando en la solución 175 g de No. 105 tipo celulosa microcristalina con un tamaño medio de partícula inferior a 30 μm.

Los gránulos se preparan introduciendo 1453 g de deramciclano-fumarato en el tanque de un aparato de granulación con fluidización Glatt tipo WSG 1 y manteniendo el ingrediente activo en estado fluidizado mediante chorro de aire con una temperatura de 40°C. Seguidamente el anterior líquido de granulación se rocía sobre el polvo en alrededor de 30 minutos. Los gránulos así obtenidos are se secan y se ciernen en una criba con tamaño de orificio 1 mm.

Los gránulos así obtenidos se homogeneizan en una mezcla que tiene la composición divulgada en la tabla anterior. Las mezclas se comprimen en una prensa Fette E XI en tabletas de forma biconvexa con un diámetro de 8 mm; el contenido de ingrediente activo de las tabletas es siempre 60 mg de base de deramciclano. Dependiendo de la composición del líquido de granulación el contenido de deramciclano-fumarato de las tabletas varía entre 51.8 y 60.3 % en peso.

No. de ex-perimento	41.	42.	43.*	44.	45.*
Gránulos	206.0 g	206.0 g	206.0 g	206.0 g	206.0 g
Carboximetil-celulosa sódica	12.0 g	6.0 g		12.0 g	12.0 g.

80
49

Celulosa microcristalina (102)	90.0 mg	90.0 mg	90.0 mg	45.0 g	--
Estearato de magnesio	6.0 g	6.0 g	6.0 g	6.0 g	6.0 g
Dióxido de silicio coloidal	6.0 g	6.0 g	6.0 g	6.0 g	6.0 g

Durante la compresión no se observó adherencia en la superficie de los punzones o las tabletas. La superficie interna de las tabletas rotas (trituradas) era homogénea y libre de laminación.

Los parámetros críticos de las tabletas se determinaron de acuerdo con la correspondiente especificación de la Farmacopea Europea. Los resultados obtenidos se resumen en la siguiente Tabla:

No. de experimento	41.		42		43		44.		45.	
Fuerza de compresión	Resistencia a la trituración	Disgregación	Resistencia a la trituración	Disgregación	Resistencia a la trituración	Disgregación	Resistencia a la trituración	Disgregación	Resistencia a la trituración	Disgregación
	(N)	(min.)	(N)	(min)	(N)	(min.)	(N)	(min.)	(N)	(min)
6 kN	51.8	1.5	48.4	1.3	53.7	4.3	26.7	1.6	23 8	2.1
10 kN	703	2.3	64.8	2.5	55.9	7.3	46.9	2.4	24 1	2.4
14 kN	75.3	2.5	69 3	3.3	58 1	8.1	49.3	2.8	29 0	2 6
18 kN	78.2	3.0	72.4	4 9	60.2	9.7	48 5	3 1	23.1	2.6

Experimentos 43 y 45 son de carácter comparativo. La composición No. 43 no contiene agente desagregante y, por consiguiente, el tiempo de desagregación de las tabletas es significativamente más largo. Contrario a la composición No. 45 de la presente invención no contiene celulosa microcristalina con un tamaño medio de partícula de por lo menos 50 μm y la resistencia de las tabletas no alcanza la resistencia requerida a la trituración de por lo menos 40 N.

Ejemplo 5

La solución de granulación se prepara disolviendo 245 g de povidona K30 tipo polivinilpirrolidona en 1500 ml de agua y dispersando en la solución 245 g de tipo No. 105 celulosa microcristalina con un tamaño medio de partícula inferior a 30 μm.

Los gránulos se preparan introduciendo 1470 g de deramciclano-fumarato en el tanque de un aparato de granulación con fluidización Glatt tipo WSG 1 y manteniendo el ingrediente activo en estado fluidizado por chorro de aire con una temperatura de 40°C. El líquido de granulación así obtenido se rocía sobre el polvo en alrededor de 30 minutos. Los gránulos así formados se secan y se ciernen en una criba con tamaño de orificio 1 mm.

Los gránulos así obtenidos se mezclan con 105 g de carboximetilcelulosa sódica, 52.5 g de estearato de magnesio, 52.5 g de dióxido de silicio coloidal y 630 g de celulosa microcristalina (No. 102, tamaño medio de partícula 90 μm). La mezcla de comprime en tabletas de forma biconvexa que pesan 160 mg y con un diámetro de 8 mm en un prensa excéntrica o una prensa rotativa Manesty Betapress a 55 r.p.m. El contenido base de deramciclano de las tabletas es 60.7 mg, el contenido de deramciclano-fumarato de las tabletas es 52.5 % en peso.

Durante la compresión no se observó adherencia en la superficie de los

punzones o las tabletas. La superficie interna de las tabletas rotas (trituradas) era homogénea y libre de laminación.

Al medir los parámetros críticos de las tabletas de acuerdo con los métodos de la Farmacopea Europea se obtienen los siguientes resultados:

No. de experimento	51.		52.	
	Prensa excéntrica Fette E XI		Prensa rotativa Betapress	
Fuerza de compresión	Resistencia a la trituración	Tiempo de desagregación	Resistencia a la trituración	Tiempo de desagregación
	(N)	(min.)	(N)	(min.)
6KN	50.3	2.0	–	–
10 kN	81.6	4.1	84.5	4.6
14 kN	99.4	5.4	104.5	5.5
18 kN	112.2	6.5	–	–

La compresibilidad de los gránulos es apropiada y no depende del tipo de prensa usada.

Ejemplo 6

La solución de granulación se prepara disolviendo 600 g de povidona K30 tipo polivinilpirrolidona en 3.6 kg de agua y dispersando en la solución 600 g de celulosa microcristalina tipo No. 105 con un tamaño medio de partícula inferior a 30 μm.

Los gránulos se preparan introduciendo 4.98 g de deramciclano-fumarato en el tanque de un aparato de granulación con fluidización Glatt tipo WSG 5 y manteniendo el ingrediente activo en estado fluidizado por chorro de aire

con una temperatura de 60°C. La solución de granulación se rocía sobre el polvo en alrededor de 60 minutos. Los gránulos formados se secan y se ciernen en una criba con tamaño de orificio 1 mm.

Los gránulos así obtenidos se mezclan con 360 g de carboximetilcelulosa sódica, 180 g de estearato de magnesio, 180 g de dióxido de silicio coloidal y 2.70 kg de celulosa microcristalina (No. 102 con un tamaño medio de partícula de 90 μm). La mezcla se comprime en una prensa rotativa Manesty Betapress en tabletas de forma biconvexa que pesan 80 mg y con un diámetro de 6 mm, o que pesaban 160 mg y con un diámetro de 8 mm respectivamente. El contenido base de deramciclano de las tabletas es 30 mg/tableta y 60 mg/tableta respectivamente, el contenido de deramciclano-fumarato de las tabletas asciende a 51.8 % en peso.

Durante la compresión no se observó adherencia en la superficie de los punzones o las tabletas. La superficie interna de las tabletas rotas (trituradas) era homogénea y libre de laminación.

Al medir los parámetros críticos de las tabletas de acuerdo con los métodos de la Farmacopea Europea se obtienen los siguientes resultados:

No. de experimento	61.			62.		
	Peso 80 mg, diámetro 6 mm 30 mg base de deramciclano			Peso 160 mg, diámetro 8 mm 60 mg base de deramciclano		
Fuerza de compresión	Resistencia a la trituración	Tiempo de desagregación	Disolución 15 min.	Resistencia a la trituración	Tiempo de desagregación	Disolución 15 min.
	(N)	(min.)	(%)	(N)	(min.)	(%)
4 kN	44.7	1.3				
7 kN	53.1	3.0	96.4	56.1	1.1	
10 kN	61.7	3.3	94.0	83.4	2.8	92.9

En vista de las especificaciones relevantes de la Farmacopea Europea la

calidad de las tabletas de deramciclano-fumarato así obtenidas es altamente favorable. Sobre la base de las características mecánicas, las tabletas son aptas para recubrimiento de película.

Ejemplo 7

La solución de granulación se prepara disolviendo 2.0 kg de povidona K30 tipo polivinilpirrolidona en 12 kg de agua y dispersando en la solución 2.0 kg de No. 105 celulosa microcristalina con un tamaño medio de partícula inferior a 30 μm.

Los gránulos se preparan introduciendo 16.61 kg de deramciclano-fumarato en el tanque de un aparato de granulación con fluidización Glatt tipo GPCG 15 y manteniendo el ingrediente activo en estado fluidizado por chorro de aire con una temperatura de 60°C. La solución de granulación así obtenida se rocía sobre el polvo en alrededor de 80 minutos. Los gránulos así formados se secan y se ciernen en una criba con tamaño de orificio 1 mm.

Los gránulos así obtenidos se mezclan con 1.2 kg de carboximetilcelulosa sódica, 0.40 kg de estearato de magnesio, 0.40 kg de dióxido de silicio coloidal y 8.99 kg de celulosa microcristalina (No. 102, un tamaño medio de partícula de 90 μm). La mezcla se comprime en una prensa rotativa Manesty Betapress a 60 r.p.m. en tabletas de forma biconvexa que pesan 80 mg, con un diámetro de 6 mm y que pesan 160 mg, con un diámetro de 8 mm, respectivamente. El contenido base de deramciclano de las tabletas asciende a 30 mg/tableta y 60 mg/tableta, respectivamente. El contenido de deramciclano-fumarato de las tabletas es 51.8 % en peso.

Durante la compresión no se observó adherencia en la superficie de los punzones o las tabletas. La superficie interna de las tabletas rotas (trituradas) era homogénea y libre de laminación.

Al medir los parámetros críticos de las tabletas de acuerdo con los métodos de la Farmacopea Europea se obtienen los siguientes resultados:

No. de experimento	71.			72.		
	Peso 80 mg, diámetro 6 mm 30 mg base de deramciclano			Peso 160 mg, diámetro 8 mm 60 mg base de deramciclano		
Fuerza de compresión	Resistencia a la trituración	Tiempo de desagregación	Disolución 15 min.	Resistencia a la trituración	Tiempo de desagregación	Disolución 15 min.
	(N)	(min.)	(%)	(N)	(min.)	(%)
8 kN	58	4.5	94.6			
12 kN				94	4.2	91.4

En vista de las especificaciones relevantes de la Farmacopea Europea la calidad de las tabletas de deramciclano-fumarato así preparadas es altamente favorable. Sobre la base de las características mecánicas, las tabletas son adecuadas para recubrimiento de película.

Ejemplo 8 (Ejemplo Comparativo)

Como comparación se preparan tabletas de deramciclano omitiendo en el líquido de granulación de acuerdo con Ejemplo 5 la celulosa microcristalina tipo No. 105 (tamaño de partícula inferior a 30 μm) y reemplazándola aumentando la cantidad de celulosa microcristalina agregando No. 102 tipo celulosa microcristalina (tamaño de partícula 90 μm) a los gránulos.

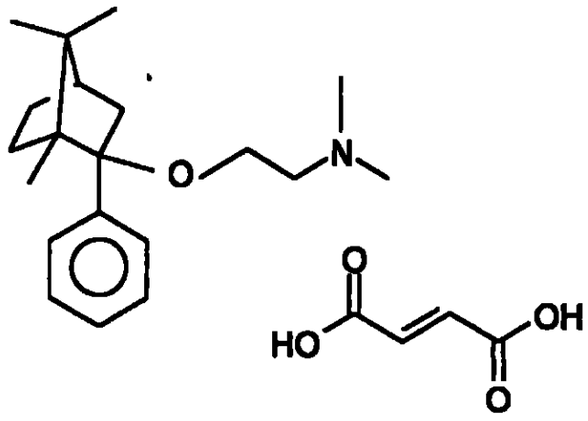
Los gránulos se preparan introduciendo 1470 g de deramciclano-fumarato en el tanque de un aparato de granulación con fluidización Glatt tipo WSG 1 y manteniendo el ingrediente activo en estado fluidizado por chorro de aire con una temperatura de 40°C. Una solución de 245 g povidona K30 tipo polivinilpirrolidona formada con 1500 ml de agua se rocía sobre el polvo en alrededor de 30 minutos. Los gránulos así formados se secan y se cieman en una criba con tamaño de orificio 1 mm.

Los gránulos así obtenidos se mezclan con 105 g de carboximetilcelulosa sódica, 52.5 g de estearato de magnesio, 52.5 g de dióxido de silicio coloidal y 875 g de celulosa microcristalina (No. 102, un tamaño medio de partícula 90 μm). La mezcla se comprime en una prensa excéntrica Fette E XI o una prensa rotativa Manesty Betapress a 55 r.pm. en tabletas de forma biconvexa que pesan 160 mg y con un diámetro de 8 mm. El contenido base de deramciclano de las tabletas es 60.7 mg, el contenido de deramciclano-fumarato de las tabletas asciende a 52.5 % en peso.

Durante la compresión de las tabletas se forma una capa en la herramienta de prensado, la superficie de las tabletas se volvió nebulosa; la calidad de las tabletas no es satisfactoria y las tabletas son inapropiadas para manufactura a escala industrial.

Lo que reivindicamos es:

1. Tabletas que comprenden deramciclano-fumarato de la Fórmula



I.

por lo cual dichas tabletas contienen (en relación con el peso total) más de 50 % en peso de deramciclano-fumarato, 5-20 % en peso de un aglutinante, 5-20 % en peso de celulosa microcristalina con un tamaño medio de partícula inferior a 30 μm, 1-10 % en peso de un desagregante, 0.5-4 % en peso de un lubricante, 0.5-4 % en peso de un agente anti-adhesivo y 0-30 % en peso de un relleno.

2. Tabletas de acuerdo con la Reivindicación 1 que comprenden 50-88 % en peso, preferiblemente 50-78 % en peso de deramciclano-fumarato.

3. Tabletas de acuerdo con Reivindicación 1 que comprenden como aglutinante polivinilpirrolidona, goma arábiga, ácido algínico, carboximetilcelulosa sódica, dextrina, etilcelulosa; gelatina, azúcar líquido, goma de guar, hidroxipropilmetilcelulosa, metilcelulosa, óxido de polietileno, almidón pre-gelatinizado o jarabe de azúcar.

4. Tabletas de acuerdo con Reivindicación 3 que comprenden como aglutinante polivinilpirrolidona.

5. Tabletas de acuerdo con Reivindicación 3 ó 4 que comprenden 5-12 % en peso de un aglutinante.

6. Tabletas de acuerdo con Reivindicación 5 que comprenden 6-9 % en peso de un aglutinante.

7. Tabletas de acuerdo con Reivindicación 1 que comprenden 5-15 % en peso de celulosa microcristalina con un tamaño medio de partícula inferior a 30 µm.

8. Tabletas de acuerdo con Reivindicación 7 que comprenden 6-9 % en peso de celulosa microcristalina con un tamaño medio de partícula inferior a 30 µm.

9. Tabletas de acuerdo con Reivindicación 1 que comprenden como desagregante almidón, preferiblemente almidón de maíz, papa o trigo, almidón de carboximetilo sódico, carboximetilcelulosa sódica, hidroxipropilcelulosa sustituida inferior o polivinilpirrolidona enlazada cruzadamente o una mezcla de las mismas.

10. Tabletas de acuerdo con Reivindicación 9 que comprenden como desagregante carboximetilcelulosa sódica.

11. Tabletas de acuerdo con Reivindicación 9 ó 10 que comprenden 2-8 % en peso de un desagregante.

12. Tabletas de acuerdo con Reivindicación 11 que comprenden 3-5 % en peso de dicho desagregante.

13. Tabletas de acuerdo con Reivindicación 1 que comprenden como lubricante estearato de magnesio, estearato de calcio, ácido esteárico, estearilfumarato de sodio, aceites vegetales hidrogenados o ésteres de azúcar.

60
59

14. Tabletas de acuerdo con Reivindicación 13 que comprenden como lubricante estearato de magnesio.

15. Tabletas de acuerdo con Reivindicación 13 ó 14 que comprenden dicho lubricante en una cantidad de 0.5-2 % en peso.

16. Tabletas de acuerdo con Reivindicación 15 que comprenden dicho lubricante en una cantidad de 1.0-1.5 % en peso.

17. Tabletas de acuerdo con Reivindicación 1 que comprenden como agente anti-adhesivo dióxido de silicio coloidal.

18. Tabletas de acuerdo con Reivindicación 17 que comprenden dióxido de silicio coloidal en una cantidad de 0.5-2 % en peso.

19. Tabletas de acuerdo con Reivindicación 18 que comprenden dióxido de silicio coloidal en una cantidad de 1.0-1.5 % en peso.

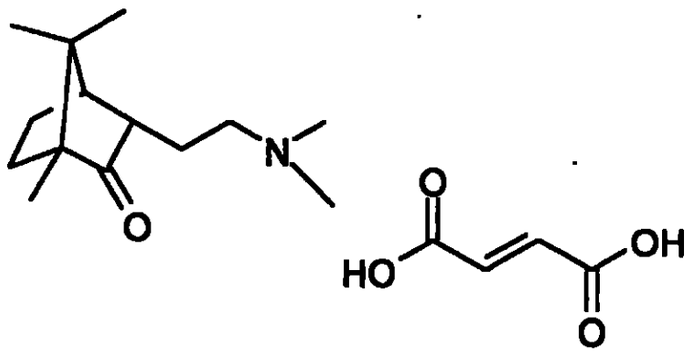
20. Tabletas de acuerdo con Reivindicación 1 que comprenden como relleno celulosa microcristalina con un tamaño de partícula de por lo menos 50 μm o celulosa microcristalina que contiene dióxido de silicio coloidal.

21. Tabletas de acuerdo con Reivindicación 20 que comprenden dicho relleno en una cantidad de 10-30 % en peso.

22. Tabletas de acuerdo con Reivindicación 21 que comprenden dicho relleno en una cantidad de 20-30 % en peso.

23. Tabletas de acuerdo con Reivindicación 1 que comprenden como ingrediente activo (1R,2S,4R)-(-)-2-dimetilaminoetoxi-2-fenil-1,7,7-trimetil-biciclo [2.2.1]heptano-2-(E)-butenodioato (1:1) de la Fórmula I que contiene no más de 0.2 % en peso de (1R,3S,4R)-(-)-3-(2-N,N-

dimetilaminoetil)-1,7,7-trimetil-biciclo[2.2.1]heptano-2-ona-(E)-butenodioato (1:1) de la Fórmula



II.

24. Proceso de acuerdo con Reivindicación 1 para la preparación de tabletas que contienen deramciclano-fumarato, el cual comprende granular más de 50 % en peso del deramciclano-fumarato (en relación con el peso total de la tableta) con 5-20 % en peso de celulosa microcristalina con un tamaño medio de partícula inferior a 30 μm, suspendida en una solución de 5-20 % en peso de un aglutinante; homogeneizar los gránulos obtenidos con 1-15 % en peso de un desagregante, 0.5-4 % en peso de un lubricante, 0.5-4 % en peso de un agente anti-adhesivo y 0.30 % en peso de un aglutinante; y, a continuación, comprimir la mezcla en tabletas.

25. Proceso de acuerdo con Reivindicación 23 que comprende usar una solución de un aglutinante formado con agua, etanol o isopropanol.

26. Proceso de acuerdo con Reivindicación 22 ó 23 que comprende granular más de 50 % en peso de deramciclano-fumarato (en relación con el peso total de la tableta) con 6-9 % en peso de celulosa microcristalina con un tamaño medio de partícula inferior a 30 μm, suspendida en una solución acuosa de 6-9 % en peso de povidona; homogeneizar los gránulos así obtenidos con 3-5 % en peso de carboximetilcelulosa sódica, 1-1.5 % en peso de estearato de magnesio, 1-1.5 % en peso de dióxido de silicio coloidal y 20-30 % en peso de celulosa microcristalina con un tamaño medio de partícula superior a 50 μm; y comprimir la mezcla en tabletas.

AS: 100.020

2005 JUL 08

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

ADVOPATENT
P.O. Box 11
H-1251 Hungary
HONGRIE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Registered letter

Date of mailing (day/month/year)	04.07.2005
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
17121 KB	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/HU2004/000058	03.06.2004	03.06.2003

Applicant
EGIS GYOGYSZERGYAR RT.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Oberhauser, A

Tel. +49 89 2399-8139

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
17121 KB		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/HU2004/000058	03.06.2004	03.06.2003

International Patent Classification (IPC) or national classification and IPC
A61K31/13, A61K9/20, C07C217/12, A61P25/22

Applicant
EGIS GYOGYSZERGYAR RT.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.12.2004	04.07.2005

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer
Telephone No. +49 89 2399- 8654
Uhl, M.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/HU2004/000058

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-37 as originally filed

   Claims, Numbers

   1-26 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/HU2004/000058

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-26
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-26
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-26
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/HU2004/000058

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Prior art does not disclose tablets comprising deramciclane-fumarate containing more than 50% of the active principle and among other components 5-20 % microcrystalline cellulose having an average particle size below 30μm. Subject matter of claims 1-26 is thus regarded to be novel over the prior art (Art. 33(2) EPC).

There is no hint in the prior art, that with such components a high dosage form (more than 50%) of deramciclane is obtainable. Prior art tablets of this active principle have 12,5% as highest concentration. Microcrystalline cellulose with an average particle size below 30m seems is used rarely in tabletting and there is no hint that high dosage forms can be obtained by such special combination of excipients (Art. 33(3) EPC).

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TRATADO SOBRE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

Remitente:
OFICINA ENCARGADA DEL EXAMEN PRELIMINAR INTERNACIONAL

A:

ADVOPATENT
P.O. Box 11
H-1251
HUNGRÍA

PCT

COMUNICACIÓN SOBRE EL ENVÍO DEL INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

(Regla 71.1 PCT)

	Fecha de envío *(Día/Mes/Año)* 04.07.2005
No, de Expediente del Solicitante o Apoderado 17121 KB	COMUNICACIÓN IMPORTANTE

No. de Solicitud Internacional	Fecha Internacional de Presentación *(día/mes/año)*	Fecha de Prioridad *(día/mes/año)*
PCT/HU2004/000058	03.06.2004	03.06.2003

Solicitante
EGIS GYOGYSZERGYAR RT.

1. Se comunica al solicitante que la oficina encargada del examen preliminar internacional le envía con el presente el informe de examen preliminar internacional, elaborado para la solicitud internacional, en caso dado con los anexos correspondientes.

2. Una copia del informe, en caso dado con los anexos correspondientes se hace llegar a la Oficina Internacional para su envío posterior a todas las oficinas seleccionadas.

3. A solicitud de una oficina seleccionada, la Oficina Internacional preparará una traducción del informe (pero no de los anexos) al inglés y la remitirá a esta oficina.

4. **RECORDATORIO**

Para ingresar en la fase nacional el solicitante, dentro de los 30 meses a partir de la fecha de prioridad (o en algunas oficinas incluso después), tiene que realizar ante cada oficina seleccionada ciertos actos (entrega de traducciones y desembolso de honorarios nacionales) (Artículo 39 (1)) (véase también la información remitida por la Oficina Internacional en el Formulario PCT/IB/301).

Si se tiene que enviar a una oficina seleccionada una traducción de la solicitud internacional, entonces esta traducción tiene que incluir traducciones de todos los anexos al informe de examen preliminar internacional. Es obligación del solicitante elaborar dichas traducciones y hacerlas llegar directamente a las oficinas seleccionadas respectivas.

Mayores detalles en cuanto a los plazos normativos y los requisitos de las oficinas seleccionadas se desprenden del Volumen II de la guía PCT para solicitantes.

Se llama la atención del solicitante al Artículo 33(5), que establece que los criterios de novedad, actividad inventiva y posibilidad de aplicación industrial descritos en Artículo 33(2) a (4) sirven meramente los propósitos del examen preliminar internacional y que "todo Estado Contratante puede aplicar criterios adicionales o diferentes para efectos de decidir si la invención reivindicada es patentable o no" (véase también Artículo 27 (5)). Los criterios adicionales pueden incluir, por ejemplo, exención de patentabilidad y los requerimientos, si se permite la divulgación, y de claridad y soporte de las reivindicaciones.

Nombre y dirección postal de la Oficina Encargada del Examen Preliminar Internacional	Empleado Autorizado
Oficina Europea de Patentes D-80298 Munich Tel.: +49 89 2399 – 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	**Oberhauser, A** Tel.: +49 89 2399-8139

Formulario PCT/IPEA/416 (Enero 2004)

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TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

(Capítulo II del Tratado de Cooperación en Materia de Patentes)

(Artículo 36 y Regla 70 PCT)

No. de Expediente del Solicitante o Apoderado	PROCEDIMIENTO POSTERIOR	Véase formulario PCT/IPEA/416
17121 KB		
No. Solicitud Internacional	**Fecha Internacional de Presentación** *(día/mes/año)*	**Fecha de Prioridad** *(día/mes/año)*
PCT/HU2004/000058	03.06.2004	03.06.2003
Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC		
A61K31/13, A61K9/20, C07C217/12, A61P25/22		
Solicitante		
EGIS GYOGYSZERGYAR RT.		

1. El presente informe es el informe de examen preliminar internacional, establecido por esta Oficina Encargada del Examen Preliminar Internacional bajo Artículo 35 y transmitido a solicitante de acuerdo con el Artículo 36.
2. El presente INFORME comprende un total de 4 hojas, inclusive esta portada
3. Este importe se acompaña igualmente por ANEXOS, que comprenden:
   a. ☐ *(enviado al solicitante y a la Oficina Internacional)* un total de hojas, como sigue:
      ☐ hojas de la descripción, reivindicaciones y/o dibujos que se han corregido y constituyen la base de el presente informe y/o hojas que contienen rectificaciones autorizadas por esta Oficina (véase Regla 70.16 y Sección 607 de las Instrucciones Administrativas).
      ☐ hojas que reemplazan hojas anteriores, pero que esta Oficina considera que contienen una corrección que va más allá de la divulgación en la solicitud internacional tal como se presentó, como se indica en el ítem 4 de Cuadro No. I y el Cuadro Adicional.
   b. ☐ (enviado a la Oficina Internacional únicamente) un total de (indicar tipo y número de medios electrónicos)) ,que contiene un listado de secuencias y/o tablas relacionadas con este asunto, en formato de lectura por computador únicamente, como se indica en el Cuadro Adicional Relativo al Listado de Secuencias (véase Sección 802 de las Instrucciones Administrativas).
4. El presente informe contiene datos con respecto a los siguientes puntos:
   - ☒ Cuadro No. I Base del Informe
   - ☐ Cuadro No. II Prioridad
   - ☐ Cuadro No. III Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial
   - ☐ Cuadro No. IV Uniformidad deficiente de la invención
   - ☒ Cuadro No. V Declaración justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración
   - ☐ Cuadro No. VI Ciertos documentos enumerados
   - ☐ Cuadro No. VII Ciertas deficiencias del registro internacional
   - ☐ Cuadro No. VIII Ciertas observaciones relacionadas con la solicitud internacional

Fecha de presentación de la petición	Fecha de la preparación de el presente informe
29.12.2004	04.07.2005
Nombre y dirección postal de la Oficina Encargada del Examen Preliminar Internacional	**Empleado Autorizado**
Oficina Europea de Patentes D-80298 Munich Tel.: +49 89 2399 – 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Teléfono No.: +49 89 2399-8654

Cuadro No. I Base del informe

1. En lo concerniente al idioma: El presente informe se basa en la solicitud internacional en el idioma en el cual se presentó, salvo indicación en contrario consignada bajo este punto.

   ☐ El presente informe se basa en traducciones del idioma original al siguiente idioma INGLÉS, que es el idioma de una traducción suministrada para los efectos de:
   - ☐ la búsqueda internacional (según las reglas 12.3 y 23.1 (b))
   - ☐ la publicación de la solicitud internacional (según la regla 12.4).
   - ☐ el examen preliminar internacional (según las reglas 55.2 y/o 55.3).

2. Con respecto a los elementos de la solicitud internacional, este informe se basa en *(hojas intercambiables que se han suministrado a la oficina receptora en respuesta a una invitación bajo Artículo 14 se tienen en este informe por "presentadas originalmente" y no se anexan a este informe):*

   Descripción, páginas

   1-37 versión original

   Reivindicaciones, No.

   1-26 versión original

   ☐ Un listado de secuencias y/o cualquier tabla(s) relacionada(s)– véase Cuadro Adicional relativo al Listado de Secuencias

3. ☐ Las correcciones han resultado en la cancelación de:
   - ☐ la descripción, páginas
   - ☐ las reivindicaciones, Nos.:
   - ☐ los dibujos, hojas/figs.
   - ☐ el listado de secuencias *(especificar)*
   - ☐ cualquier tabla(s) relacionada con el listado de secuencias *(especificar)*

4. ☒ El presente informe se preparó como si no se hubieran hecho (algunas de) las correcciones anexadas a este informe y enumeradas a continuación ya que éstas, por las razones aducidas, en concepto de la oficina van más allá del contenido de divulgación en la versión presentada originalmente (Regla 70.2 (c)).
   - ☐ la descripción, páginas:
   - ☐ las reivindicaciones, Nos.
   - ☐ los dibujos, hojas/figs.
   - ☐ el listado de secuencias *(especificar)*
   - ☐ cualquier tabla(s) relacionada con el listado de secuencias *(especificar)*

   ** Si se aplica el punto 4, algunas o todas estas hojas pueden estar marcadas como "reemplazadas."*

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No. PCT/HU2004/000058

Cuadro No. V Declaración motivada bajo Artículo 35(2) en cuanto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración

1. DECLARACIÓN

Novedad (N)	Sí:	Reivindicaciones 1-26
	No:	Reivindicaciones
Actividad inventiva (IS)	Sí:	Reivindicaciones 1-26
	No:	Reivindicaciones
Posibilidad de Aplicación Industrial (IA)	Sí:	Reivindicaciones 1-26
	No:	Reivindicaciones

2. Documentos y explicaciones (Regla 70.7)

Véase hoja separada

Ref: Cuadro No. V
Declaración motivada en cuanto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración

El arte previo no divulga tabletas que comprendan deramciclano-fumarato con un contenido superior al 50% del principio activo y, entre otros componentes, 5-20 % de celulosa microcristalina con un tamaño medio de partícula inferior a 30 μm. Por consiguiente, el asunto de las reivindicaciones 1-26 se considera novedoso sobre el arte previo (Art. 33(2) EPC).

En el arte previo no existe una sugerencia en el sentido de que, con tales componentes, pueda obtenerse una formulación farmacéutica elevada (más del 50%) de deramciclano. Las tabletas del arte previo de este principio activo tienen 12,5% como concentración máxima. Aparentemente la celulosa microcristalina con un tamaño medio de particular inferior a 30 μm se usa raramente en compactación de tabletas y no existe sugerencia en el sentido de que puedan obtenerse formulaciones farmacéuticas elevadas mediante tal combinación especial de excipientes (Art. 33(3) EPC).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
17121 KB		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/HU2004/000058	03/06/2004	03/06/2003
Applicant		
EGIS GYOGYSZERGYAR RT.		

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

This International Search Report consists of a total of 4 sheets.

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

1. **Basis of the report**
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. [ ] Certain claims were found unsearchable (See Box II).

3. [ ] Unity of invention is lacking (see Box III).

4. With regard to the title,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the drawings,
   a. the figure of the drawings to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU2004/000058

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/13 A61K9/20 C07C217/12 A61P25/22

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

E. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P C07C

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 694 299 A (EGYT GYOGYSZERVEGYESZETI GYAR) 31 January 1996 (1996-01-31) example 1	1-26
A	US 4 342 762 A (MEZEI TIBOR ET AL) 3 August 1982 (1982-08-03) example 23	1-26
A	WO 00/37055 A (ABBOTT LAB) 29 June 2000 (2000-06-29) claim 1	1-26

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

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 September 2004	05/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Uhl, M

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HU2004/000058

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0694299 A	31-01-1996	HU 72441 A2	29-04-1996
		AT 205707 T	15-10-2001
		AU 701585 B2	04-02-1999
		AU 2325195 A	18-01-1996
		BE 1009060 A3	05-11-1996
		CA 2153083 A1	02-01-1996
		CN 1126590 A ,B	17-07-1996
		DE 69522764 D1	25-10-2001
		DE 69522764 T2	04-07-2002
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HU2004/000058

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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PCT

REQUEST

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

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 17121 KB

Box No. I TITLE OF INVENTION

DERAMCICLANE-FUMARATE TABLETS

Box No. II APPLICANT ☐ This person is also inventor

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

EGIS GYÓGYSZERGYÁR RT.

Budapest
Keresztúri út 30-38., H-1106
Hungary

Telephone No.

Facsimile No.

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

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

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

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

FEKETE, Pál

Budapest
Csernyus u. 15., H-1147
Hungary

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

Applicant's registration No. with the Office

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

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

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

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

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

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

ADVOPATENT Office of Patent and Trademark Attorneys

Budapest
P.O.Box 11, H-1251
Hungary

Telephone No. (36-1) 201-1528

Facsimile No. (36-1) 201-1692

Teleprinter No.

Agent's registration No. with the Office

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

77
76

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

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

MAROSHELYI, Lászlóné

Budapest
Linda tér 5, H-1165
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

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

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

ZSIGMOND, Zsolt

Budapest
Borsó u. 8., H-1173
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
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GÓRA, Lászlóné

Iszaszeg
Nagy S. u. 42., H-2117
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
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LEVENTISZNÉ HUSZÁR, Magdolna

Budapest
Virányos út 24/A, H-1125
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

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

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

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

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

JÁMBOR, Istvánné

Budapest
Somlókert u. 47/a, H-1182
Hungary

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

Applicant's registration No. with the Office

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State *(that is, country)* of residence: Hungary

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

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TARI, József

Budapest
Tóalmás u. 27., H-1172
Hungary

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

Applicant's registration No. with the Office

State *(that is, country)* of nationality: Hungary

State *(that is, country)* of residence: Hungary

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

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

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

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

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

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

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

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

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

Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

☐ DE Germany is not designated for any kind of national protection

☐ KR Republic of Korea is not designated for any kind of national protection

☐ RU Russian Federation is not designated for any kind of national protection

(The check-boxes above may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law, of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)

Box No. VI PRIORITY CLAIM

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

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 03/June/2003 03/06/2003	P 03 01537	Hungary		
item (2)				
item (3)				

☐ Further priority claims are indicated in the Supplemental Box.

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

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

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

.....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

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

ISA / EP .....

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

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

Box No. VIII DECLARATIONS

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

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

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) In paper form, the following number of sheets:

request (including declaration sheets)	:	5
description (excluding sequence listing and/or tables related thereto)	:	37
claims	:	6
abstract	:	1
drawings	:	
Sub-total number of sheets	:	0
sequence listing	:	
tables related thereto	:	
(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)		
Total number of sheets	:	490

(b) ☐ only in computer readable form (Section 801(a)(i))
- (i) ☐ sequence listing
- (ii) ☐ tables related thereto

(c) ☐ also in computer readable form (Section 801(a)(ii))
- (i) ☐ sequence listing
- (ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the
- ☐ sequence listing: .....
- ☐ tables related thereto: .....

(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:	Number of items
1. ☒ fee calculation sheet	:
2. ☐ original separate power of attorney	:
3. ☐ original general power of attorney	:
4. ☐ copy of general power of attorney; reference number, if any:	:
5. ☐ statement explaining lack of signature	:
6. ☐ priority document(s) identified in Box No. VI as item(s):	:
7. ☐ translation of international application into *(language)*:	:
8. ☐ separate indications concerning deposited microorganism or other biological material	:
9. ☐ sequence listing in computer readable form *(indicate type and number of carrier(s))*	
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:
(ii) ☐ *(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column	:
10. ☐ tables in computer readable form related to sequence listing *(indicate type and number of carriers)*	
(i) ☐ copy submitted for the purposes of international search under Section 802(b-*quater*) only (and not as part of the international application)	:
(ii) ☐ *(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quater*)	:
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column	:
11. ☐ other *(specify)*:	:

Figure of the drawings which should accompany the abstract:	Language of filing of the international application: English

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

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

(KARÁCSONYI, Béla)
European Patent Attorney (130 870)

For receiving Office use only

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

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International Application No.

Date stamp of the receiving Office

Applicant's or agent's file reference

Applicant

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . HUF | 10,000.- T

2. SEARCH FEE . . . . . EUR | 1,550.- S

International search to be carried out by EPO

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

3. INTERNATIONAL FILING FEE

Where items (b) and/or (c) of Box No. IX apply, enter Sub-total number of sheets
Where items (b) and (c) of Box No. IX do not apply, enter Total number of sheets } _____

i1 first 30 sheets . . . . . CHF | 1,400.- i1

i2 19 (number of sheets in excess of 30) x 15 CHF (fee per sheet) = | 285.- i2

i3 additional component (only if sequence listing and/or tables related thereto are filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)):

400 x _____ (fee per sheet) = | _____ i3

Add amounts entered at i1, i2 and i3 and enter total at I . . . . CHF | 1,685.- I

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

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . | _____ P

5. TOTAL FEES PAYABLE . . . . . | _____ TOTAL

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

MODE OF PAYMENT

☐ authorization to charge deposit account (see below) ☐ postal money order ☐ cash ☐ coupons

☐ cheque ☒ bank draft ☐ revenue stamps ☐ other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

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

Receiving Office: RO/ _____

Deposit Account No.: _____

Date: _____

Name: _____

Signature: _____

☐ Authorization to charge the total fees indicated above.

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

☐ Authorization to charge the fee for priority document.

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

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 17121 KB
International application No. PCT/HU2004/000058	International filing date *(day/month/year)* 03/June/2004 03/06/2004	(Earliest) Priority date *(day/month/year)* 03/June/2003 03/06/2003
Title of invention DERAMCICLANE FUMARATE TABLETS		

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	Telephone No.
EGIS GYÓGYSZERGYÁR RT. Budapest kereszturi ut 30-38., H-1106 Hungary	Facsimile No.
	Teleprinter No.
	Applicant's registration No. with the Office
State *(that is, country)* of nationality: Hungary	State *(that is, country)* of residence: Hungary

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	
FEKETE, Pál Budapest Csernyus u. 15., H-1147 Hungary	
State *(that is, country)* of nationality: Hungary	State *(that is, country)* of residence: Hungary

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	
MAROSHELYI, Lászlóné Budapest Linda rér 5., H-1165 Hungary	
State *(that is, country)* of nationality: Hungary	State *(that is, country)* of residence: Hungary

☒ Further applicants are indicated on a continuation sheet.

International application No.
PCT/HU2004/000058

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

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

ZSIGMOND, Zsolt

Budapest
Borsó u. 8., H-1173
Hungary

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Hungary	Hungary

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

GÓRA, Lászlóné

Isaszeg
Nagy S. u. 42., H-2117
Hungary

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Hungary	Hungary

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

LEVENTISZNÉ HUSZÁR, Magdolna

Budapest
Virányos út 24/A, H-1125
Hungary

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

JÁMBOR, Istvánné

Budapest
Somlókert u. 47/a., H-1182
Hungary

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Hungary	Hungary

[X] Further applicants are indicated on another continuation sheet.

International application No
PCT/HU2004/000058

Continuation of Box No. II APPLICANT(S)

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State *(that is, country)* of nationality:	State *(that is, country)* of residence:

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

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet

85

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Sheet No. 4

International application No. PCT/HU2004/000058

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

The following person is [X] agent [ ] common representative

and [ ] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*	Telephone No.
ADVOPATENT Office of Patent and Trademark Attorneys Budapest P.O.Box 11, H-1251 Hungary	Facsimile No.
	Teleprinter No.
	Agent's registration No. with the Office

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

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

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

   [X] the international application as originally filed

   the description: [X] as originally filed; [ ] as amended under Article 34

   the claims: [X] as originally filed; [ ] as amended under Article 19 (together with any accompanying statement); [ ] as amended under Article 34

   the drawings: [ ] as originally filed; [ ] as amended under Article 34

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

3. [ ] The applicant wishes the start of the international preliminary examination to be postponed until the expiration of the applicable time limit under Rule 69.1(d).

4. [ ] The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule *54bis*.1(a).

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

Language for the purposes of international preliminary examination: English

[X] which is the language in which the international application was filed.

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

[ ] which is the language of publication of the international application.

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

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

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Sheet No 5.

International application No.
PCT/HU2004/000058

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1 translation of international application	:	sheets	☐	☐
2 amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5 letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

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

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

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

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

(KARÁCSONYI. Béla)
European Patent Attorney
Re. No. 130 870

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

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

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
   ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.
6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54*bis*.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54*bis*.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54*bis*.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

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CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/HU2004/000058	For International Preliminary Examining Authority use only
Applicant's or agent's file reference 17121 KB	Date stamp of the IPEA

Applicant
EGIS GYÓGYSZERGYÁR RT..
FEKETE, Pál et al.

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee ..... EUR	1530,-	P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)* ..... EUR	129,-	H	
3 Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box ... EUR	1659,- TOTAL		

MODE OF PAYMENT

- ☐ authorization to charge deposit account with the IPEA (see below)
- ☐ cash
- ☐ cheque
- ☐ revenue stamps
- ☐ postal money order
- ☐ coupons
- ☒ bank draft
- ☐ other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

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

IPEA/ _____

☐ Authorization to charge the total fees indicated above.

Deposit Account No.: _____

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

Date: _____

Name: _____

Signature: _____

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 06000003 00000000 Folios: 87
Fecha (AMD): 2006-01-02 09:12:55
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente	( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud	( )	( )
- Descripción de la invención	( )	( )
- Dibujos de ser estos pertinentes.	( )	( )
- Comprobante de Pago de las tasas establecidas		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud		
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable

Fecha: 2 de Dic de 2005