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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 May 2013 (30.05.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/075823 A1

(51) International Patent Classification:
A61K 31/381 (2006.01) *A61P 25/14* (2006.01)
A61K 9/70 (2006.01) *A61P 25/28* (2006.01)
A61P 25/16 (2006.01)

(21) International Application Number:
PCT/EP2012/004818

(22) International Filing Date:
21 November 2012 (21.11.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

10 2011 119 043.4		
	22 November 2011 (22.11.2011)	DE
61/667,528	3 July 2012 (03.07.2012)	US
61/667,507	3 July 2012 (03.07.2012)	US
10 2012 013 421.5	3 July 2012 (03.07.2012)	DE
10 2012 013 439.8	3 July 2012 (03.07.2012)	DE

(71) Applicants: **ALFRED E. TIEFENBACHER (GMBH & CO. KG)** [DE/DE]; Van-der-Smissen-Str. 1, 22767 Hamburg (DE). **AMW GMBH** [DE/DE]; Birkerfeld 11, 83627 Warngau (DE).

(72) Inventors: **SAHR, Florian**; Frühlingstr. 33, 83607 Holzkirchen (DE). **LANG, Susanne**; Marktplatz 18d, 83607 Holzkirchen (DE). **RYBACH, Simon**; Langenfelder Damm 90, 22525 Hamburg (DE). **FITZNER, Ansgar**; Unnastrasse 21, 20253 Hamburg (DE).

(74) Agent: **FELDMANN, Ute**; Patent Law Firm Feldmann, Karl-Liebknecht-Str. 5, 10178 Berlin (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,

[Continued on next page]

(54) Title: TRANSDERMAL THERAPEUTIC SYSTEM COMPRISING ROTIGOTINE AND CRYSTALLIZATION INHIBITOR

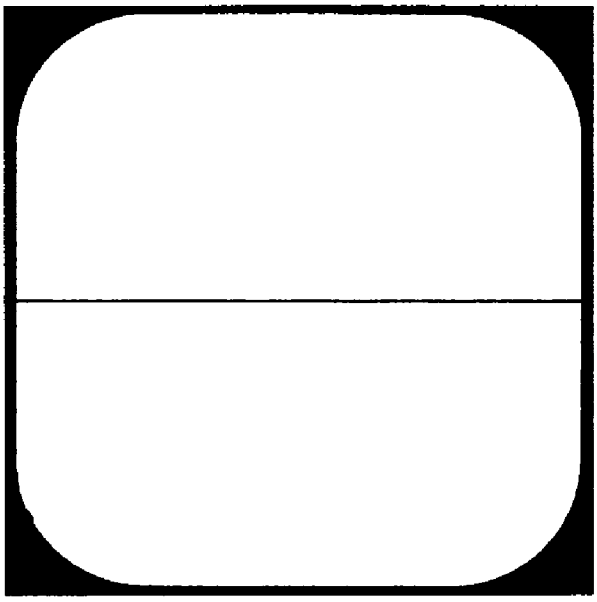


Fig. 2g)

(57) Abstract: The present invention relates to an inventive transdermal therapeutic system (TTS) comprising rotigotine, a pharmaceutically acceptable adhesive comprising styrene butadiene block copolymer and a crystallization inhibitor, an inventive matrix with an extended release of rotigotine suitable for a transdermal therapeutic system, an inventive production method of a respective matrix or a respective TTS comprising rotigotine, as well as uses of the inventive matrix and the inventive TTS.

WO 2013/075823 A1

TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

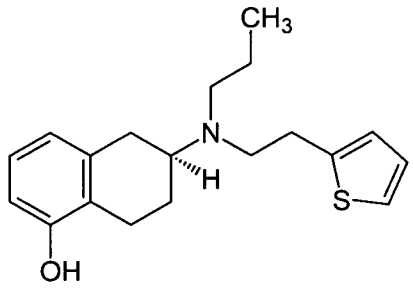
Transdermal Therapeutic System comprising Rotigotine and Crystallization Inhibitor

Technical Field:

The present invention relates to an inventive transdermal therapeutic system (TTS) comprising rotigotine, a pharmaceutically acceptable adhesive comprising styrene butadiene block co-polymer and a crystallization inhibitor, an inventive matrix with an extended release of rotigotine suitable for a transdermal therapeutic system, an inventive production method of a respective matrix or a respective TTS comprising rotigotine, as well as uses of the inventive matrix and the inventive TTS.

Background Art:

Rotigotine is the international non-proprietary name (INN) of the compound [(–)-(S)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol (CAS Nr.: 99755-59-6; MW: 315.47) with the following chemical structure:



At present two crystalline forms of the rotigotine base are known, namely polymorphic form I and polymorphic form II (see WO 2009/068520), which respectively can be distinguished on the basis of their different physicochemical parameters, in particular the different powder X-ray diffractograms, Raman spectra and melting points. The polymorphic form II of rotigotine is more stable at room temperature than the polymorphic form I, which is again more stable than the amorphous form of rotigotine.

Rotigotine is a non-ergoline dopamine agonist for all dopamine receptors, whereby the highest *in vitro* affinity is measured for the D_3 receptor, followed by the affinity for the D_2 receptor, which is approximately 10-fold smaller, and the affinity for the D_1 receptor, which is approximately 100-fold smaller. The intrinsic activity is also high for all dopamine receptors, whereby the highest intrinsic affinity can again be measured for the D_3 receptor.

At present it is known, that rotigotine can be used in the treatment, alleviation and/or prophylaxis of patients, which suffer from or at least with a certain probability fall ill with the following diseases: Parkinson's disease (described in WO 2002/089777), Parkinson Plus Syndrome (described in WO 2005/092331), depression (described in WO 2005/009424), Restless Legs Syndrome (described in WO 2003/092677), loss of dopaminergic neurons (described in WO 2005/063237) and pain (WO 2007/147556).

At present the following pharmaceutical formulations of rotigotine are known: application as a TTS (WO 99/49852), as a depot formulation (WO 2002/015903), as a iontophoretic device (WO 2002/015903) and as an intranasal formulation (WO 2005/63236).

The application of rotigotine in form of a TTS has a high value, in particular as rotigotine is already commercialized as in form of a transdermal therapeutic patch (Neupro® from UCB, also marketed by Bayer as Leganto®).

Rotigotine can be present in transdermal therapeutic systems in form of its free base, in particular in polymorphic form I and/or polymorphic form II (Neupro®). Rotigotine can alternatively be present in form of the hydrochloric salt (WO 94/07468) or a rotigotine prodrug can be used (WO 2004/012721).

The commercially available product Neupro® comprises, as disclosed in WO 02/89777, the rotigotine base in a silicon based adhesive matrix of the following formulation:

	[% based on the total weight of the adhesive mixture]
silicon adhesive (BIO-PSA Q7-4301)	44.5
silicon-adhesive (BIO-PSA Q7-4201)	44.5
Povidone (K90)	2.0
sodium metabisulfite (E223)	0.0006
ascorbyl palmitate (E304)	0.02
DL-alpha-tocopherol (E307)	0.05
rotigotine 0.45 mg/cm^2	9

For the pharmaceutical product Neupro® it has been shown in the year 2007 that the shelf life is insufficient and that during storage of the Neupro® patches at room temperature crystals appear, namely rotigotine in polymorphic form II. Rotigotine in crystalline form, however, cannot or only in limited amount be released from the matrix and, thus, cannot fully with respect to the dose pass into the organism. Thus, there exists the risk that the treatment, alleviation and/or prophylaxis with the respective Neupro® patch does not yield the full effect. The market authorization holder, at the time Schwarz Pharma, has modified the production process of the Neupro® patch, however, this could not fully eliminate the crystallization of the polymorphic form II of rotigotine (see „Scientific conclusions and grounds for the amendment of the marketing authorization of Neupro presented by the EMEA (now EMA)", published at „Neupro-H-C-626-II-24 : EPAR - Scientific Conclusion" dated 1 Januar 2009 on the website of the European Medicines Agency - EMA). The marketing authorization for Neupro® was withdrawn with respect to the USA and was restricted in Europe to the effect, that Neupro® is only allowed to be marketed at cold chain conditions with storage between 2 °C and 8 °C up to 18 months after production, as significant crystallization based on the total area of the transdermal therapeutic system still occurs.

As storage of transdermal therapeutic systems comprising rotigotine by means of cold chain at 2 °C to 8 °C is on one hand error prone (breakdown of cooling systems, inappropriate storage at the patient's home) and on the other hand can reduce the patient compliance, the need exists to provide a transdermal therapeutic system comprising rotigotine, that does not need to be stored at cool chain conditions at 2 °C to 8 °C and at the same time shows a crystallization of rotigotine, which is in line with the market authorization requirements, i.e. a crystallization of up to 20 area-%, preferably up to 15 area-%, more preferably up to 10 area-% and furthermore preferably up to 5 area-% respectively based on the matrix area of the transdermal therapeutic systems when stored at room temperature for up to 24 months.

Disclosure of Invention:

The aforementioned problem is solved by means of the claimed inventive subject matter. Preferred embodiments are described in the dependent claims as well as in the following description.

Accordingly a first aspect of the invention relates to a transdermal therapeutic system comprising or consisting of i) a backing layer, ii) a matrix layer, which comprises a physiologically effective amount of rotigotine [(–)-(S)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol], whereby the matrix layer is deposited at least on part of the backing layer, and iii) a protective foil to be removed prior to use, which is deposited at least on part of the surface of

the matrix layer, characterized in that the matrix layer further comprises or consists of a styrene butadiene block copolymer as a pharmaceutically acceptable adhesive and a pharmaceutically acceptable crystallization inhibitor as well as optionally one or more further pharmaceutical excipients.

A second aspect of the invention relates to a matrix for extended release of rotigotine comprising or consisting of a physiologically effective amount of rotigotine [(–)-(S)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol], a pharmaceutically acceptable adhesive comprising or consisting of a styrene butadiene block copolymer and a pharmaceutically acceptable crystallization inhibitor as well as optionally one or more further pharmaceutical excipients.

A third aspect of the invention relates to a method for producing a matrix for extended release of rotigotine comprising or consisting of the following steps:

a. Provision of rotigotine,
b. Provision of a pharmaceutically acceptable adhesive comprising or consisting of styrene butadiene block copolymer,
c. Provision of a crystallization inhibitor,
d. Optionally provision of one or more further pharmaceutically acceptable excipients,
e. Production of a matrix by mixing the provided components according to steps a.) to d.) with one or more suitable diluents, whereby the matrix comprises rotigotine in a physiologically effective amount.

A fourth aspect of the invention relates to a use of an inventive matrix or a matrix obtainable according to an inventive production method of a transdermal therapeutic system, preferably for treatment, alleviation, and/or prophylaxis of Parkinson's Disease, Parkinson Plus Syndrome, a depression, Restless Legs Syndrome, loss of dopaminergic neurons and/or pain.

A fifth aspect of the invention relates to a method for producing a transdermal therapeutic system comprising or consisting of i) a backing layer, ii) a matrix layer, which comprises a physiologically effective amount of rotigotine [(–)-(S)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol], whereby the matrix layer is deposited at least on part of the backing layer, and iii) a protective foil to be removed prior to use, which is deposited at least on part of the surface of the matrix layer, characterized in that the matrix layer further comprises or consists of a styrene butadiene block copolymer as a pharmaceutically acceptable adhesive and a pharmaceutically acceptable crystallization inhibitor as well as optionally one or more further pharmaceutical excipients, comprising or consisting of the following steps:

a. Provision of rotigotine,

b. Provision of a pharmaceutically acceptable adhesive comprising styrene butadiene block copolymer,

c. Provision of a crystallization inhibitor,

d. Optionally provision of one or more further pharmaceutically acceptable excipients,

e. Production of a matrix by mixing the provided components according to steps a.) to d.) with one or more suitable diluents, whereby the matrix comprises rotigotine in a physiologically effective amount,

f. Provision of a protective foil and production of a double layered active agent containing laminate by depositing of at least part of the matrix produced in step e.) on at least part of the protective foil (matrix layer) and optionally drying of the double layered active agent containing laminate at suitable drying conditions,

g. Provision of a backing layer and production of a three layered active agent containing laminate as transdermal therapeutic system by depositing the backing layer on at least part of the surface of the matrix layer of the double layered laminate of step f.) and

h. Optionally division of the three layered active agent containing laminate of step g.) in two or more transdermal therapeutic systems.

A sixth aspect of the invention relates to a use of an inventive transdermal therapeutic system or a transdermal therapeutic system obtainable according to an inventive production method for treatment, alleviation and/or prophylaxis of a Parkinson's disease, a Parkinson Plus Syndrome, a depression, a Restless Legs Syndrome, loss of dopaminergic neurons and/or pain.

A seventh aspect of the invention relates to a method for treatment, alleviation and/or prophylaxis of a Parkinson's disease, a Parkinson Plus Syndrome, a depression, a Restless Legs Syndrome, loss of dopaminergic neurons and/or pain by application of an inventive transdermal therapeutic system or a transdermal therapeutic system obtainable according to an inventive production method to a subject, that suffers from or is expected to fall ill with Parkinson's disease, a Parkinson Plus Syndrome, a depression, a Restless Legs Syndrome, loss of dopaminergic neurons and/or pain.

The aforementioned inventive embodiments can – as far it is reasonable in view of a technical expert – comprise any possible combination of the preferred inventive embodiments, which are disclosed in the following and in particular in the dependent claims.

Brief Description of Drawing:

The figures show photographic images of top views on inventive transdermal therapeutic systems comprising an adhesive, rotigotine and a crystallization inhibitor as well as comparative systems comprising an adhesive and rotigotine without crystallization inhibitor, whereby possible formation of crystals is visible.

Figures 1a, 1b, 1c, 1d, 1e, 1f, 1g: Top views on the matrix area of a TTS (patch) comprising 7 wt.-% rotigotine, 93 wt.-% adhesive without crystallization inhibitor (comparative system): a) directly after production, b) after storage of 4 weeks at room temperature, c) after storage of 11 weeks at room temperature, d) after storage of 4 weeks at accelerated storage conditions, e) after storage of 11 weeks at accelerated storage conditions, f) after storage of 26 weeks at room temperature and g) after storage for 26 weeks at accelerated conditions

Figures 2a, 2b, 2c, 2d, 2e, 2f, 2g: Top views on the matrix area of an inventive TTS (patch) comprising 7 wt.-% rotigotine, 88 wt.-% adhesive and 5 % Copovidone as crystallization inhibitor: a) directly after production, b) after storage of 4 weeks at room temperature, c) after storage of 11 weeks at room temperature, d) after storage of 4 weeks at accelerated storage conditions, e) after storage of 11 weeks at accelerated storage conditions, f) after storage of 26 weeks at room temperature and g) after storage for 26 weeks at accelerated conditions

Figures 3a, 3b, 3c, 3d, 3e, 3f, 3g: Top views on the matrix area of TTS (patch) comprising 9 wt.-% rotigotine, 91 wt.-% adhesive without crystallization inhibitor (comparative system): a) directly after production, b) after storage of 4 weeks at room temperature, c) after storage of 11 weeks at room temperature, d) after storage of 4 weeks at accelerated storage conditions, e) after storage of 11 weeks at accelerated storage conditions, f) after storage of 26 weeks at room temperature and g) after storage for 26 weeks at accelerated conditions

Figures 4a, 4b, 4c, 4d, 4e, 4f, 4g: Top views on a matrix area of an inventive TTS (patch) comprising 9 wt.-% rotigotine, 86 wt.-% adhesive and 5 % Copovidone as crystallization inhibitor: a) directly after production, b) after storage of 4 weeks at room temperature, c) after storage of 11 weeks at room temperature, d) after storage of 4 weeks at accelerated storage conditions, e) after storage of 11 weeks at accelerated storage conditions, f) after storage of 26 weeks at room temperature and g) after storage for 26 weeks at accelerated conditions

Figures 5a, 5b, 5c, 5d, 5e, 5f, 5g: Top views on the matrix area of TTS (patch) comprising 11 wt.-% rotigotine, 89 wt.-% adhesive without crystallization inhibitor (comparative system): a) directly after production, b) after storage of 4 weeks at room temperature, c) after storage of 11 weeks at room temperature, d) after storage of 4 weeks at accelerated storage conditions, e) after storage of 11 weeks at accelerated storage conditions, f) after storage of 26 weeks at room temperature and g) after storage for 26 weeks at accelerated conditions

Figures 6a, 6c, 6d, 6e, 6f, 6g: Top views on a matrix area of an inventive TTS (patch) comprising 11 wt.-% rotigotine, 84 wt.-% adhesive and 5 % Copovidone as crystallization inhibitor: a) directly after production, c) after storage of 11 weeks at room temperature, d) after storage of 4 weeks at accelerated storage conditions, e) after storage of 11 weeks at accelerated storage conditions, f) after storage of 26 weeks at room temperature and g) after storage for 26 weeks at accelerated conditions

Detailed Description of the Invention:

The inventors have surprisingly identified that an inventive matrix in particular when used in a transdermal therapeutic system (see figures 2, 4 and 6) in comparison to the prior art without crystallization inhibitor (see figures 1, 3 and 5) exhibits no or a strongly reduced crystallization of rotigotine during storage of the TTS for 4 or 11 weeks on the one hand at room temperature / room humidity, and on the other hand at accelerated storage conditions [30 °C / 65 % relative (rH), according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH guideline) Q 1 A (R2)]. These results give reason to the assumption that an inventive transdermal therapeutic system can be stored and commercialized without the need of using cool chain conditions and at the same time exhibit crystallization in line with the market authorization requirements, i.e. exhibit crystals up to 24 months after production when stored at room temperature of up to 20 area-%, preferably 0 to 15 area-%, more preferably 0 to 10 area-%, even more preferably 0 to 5 area-%, in particular preferably 0 to 2 area-% respectively based on the matrix area (see figures) of the inventive transdermal therapeutic system.

Furthermore the inventors have surprisingly identified that an inventive matrix in particular for use in a transdermal therapeutic system exhibits after storage in comparison to the prior art a smaller amount of rotigotine degradation products. As degradation products crystallize in the matrix and, thus, can act as crystallization nucleus, the reduction of the amount of decomposition products on the one hand improves the stability over storage and, thus, the shelf life of the inventive TTS and on the other hand reduces the risk of physiological side effects caused by the rotigotine gradation products.

Furthermore the inventors have surprisingly identified that the inventive matrix as a self-adhesive matrix exhibits an excellent adherence on the skin, i.e. that after 24 hours at least 70 area-%, preferably more than 80 area-%, further preferred more than 90 area-% of the inventive matrix is in direct contact with the skin, i.e. adheres to the skin and is not detached. In this respect it is to be considered that the release of the active agent, presently rotigotine, out of the matrix can only occur in that area of the matrix, which is in direct contact with the skin and

is not detached therefrom. In other words, a smaller matrix area which is in direct contact with the skin, i.e. adheres to the skin, is proportional to a smaller amount of release and, thus, skin permeation of the active agent, presently rotigotine. The inventors could in this respect show by means of *in vitro* experiments with the inventive TTS (procedure according to the modified Franz-Cell System) in comparison to the Neupro® patch of the prior art improved skin permeation rates of up to 400 µg/cm^2 and day.

Despite the excellence adherence the inventive matrix can be excellently removed from the skin after the end of the application (generally after 24 hours), preferably without so called "adhesive residue" (matrix residue on the skin in the area of the border of the TTS).

The inventive matrix and the inventive transdermal therapeutic system respectively can comprise rotigotine preferably in free base form and/or as pharmaceutically acceptable salt, preferably as rotigotine hydrochloride, and/or as pharmaceutically acceptable rotigotine solvate, preferably rotigotine hydrate, and/or as pharmaceutically acceptable rotigotine prodrug, preferably as pharmaceutically acceptable rotigotine ester. In particular preferred is the use of rotigotine in free base form and/or as pharmaceutically acceptable salt, preferably rotigotine hydrochloride. Within the context of the present invention the term rotigotine is used synonymously for all inventive applicable embodiments of rotigotine unless it is explicitly referred to a specific embodiment.

Rotigotine in form of its free base can inventively be used as polymorphic form I and/or polymorphic form II. The use of rotigotine in form of its free base is inventively preferred, as rotigotine can directly be released from the matrix and can permeate through the skin due to its lipophilicity and can directly provide its physiological effect.

Rotigotine is comprised in the inventive matrix in particular for use in an inventive transdermal therapeutic system in a physiologically effective amount, preferably 0.45 mg rotigotine / 1 cm^2 matrix or a multiple thereof, e.g., 2.25 mg rotigotine / 5 cm^2 matrix, whereby the inventive TTS releases 1 mg rotigotine within 24 hours.

The percentaged weight proportion (wt.-%) of rotigotine based on the total weight of the inventive matrix or based on the matrix layer of the inventive transdermal therapeutic system respectively can vary between 4 to 15 wt.-%, preferably 5 to 12 wt.-%, further preferred between 7 and 9 wt.-%.

The inventive matrix or the inventive transdermal therapeutic system respectively comprises as pharmaceutically acceptable adhesive one, two, three, four or more different styrene butadiene block copolymers. A styrene butadiene block copolymer to be used in accordance with the present invention preferably facilitates that the inventive matrix or the matrix layer of the

inventive TTS respectively is self adhesive. Commonly applicable styrene butadiene block copolymers can be used for the present invention.

Styrene butadiene block copolymers consist in general of at least two blocks, one hard non-elastomeric block S of polystyrene having a glass transition temperature above 20 °C, and a soft, elastomeric block B of polybutadiene having a glass transition temperature below 20 °C. Such styrene butadiene block copolymers comprise in general block copolymers of the S-B type, the $(S\text{-}B)_n$ type, the S-B-S type, the $S\text{-}(B\text{-}S)_n$ type, the S-B-S-B type and the S-B-S-B-S type, wherein „n" means, that the polymer chains are coupled at this position, i.e. that in this case a radial polymer is present. The disclosure regarding styrene butadiene block copolymers made in „Kunststoff Handbuch, Band 4, Polystyrol, Hanser Verlag München, 1996" is incorporated into the present application. Depending on the number of blocks one also can distinguish diblock copolymers (e.g. of the S-B type), triblock copolymers (e.g. of the S-B-S type) and multiblock copolymers (e.g. of the S-B-S-B-S type). Furthermore one can distinguish between linear and radial block copolymers, wherein the radial block copolymers represent branched block copolymers with multiple arms. A subgroup of the radial block copolymers are the hyper branched block copolymers (also called star block copolymers) with more than 4 arms. Furthermore it is possible that some of the blocks, preferably the soft block B exhibits an alternating or randomly distributed (statistically) monomer incorporation.

Preferably the styrene butadiene block copolymers to be used in accordance with the present invention are selected from the group consisting of

a. A linear styrene butadiene block copolymer of the S-B type, that optionally contains a monomer block with randomly distributed monomer incorporation, preferably of a soft block B,

b. A radial or hyper branched styrene butadiene block copolymer of the $(S\text{-}B)_n$ type, that optionally contains one or more monomer blocks with randomly distributed monomer incorporation, preferably of a soft block B,

c. A linear or radial styrene butadiene block copolymer of the S-B-S type, that optionally contains one or more monomer blocks with randomly distributed monomer incorporation, preferably of a soft block B,

d. A radial or hyper branched styrene butadiene block copolymer of the $S\text{-}(B\text{-}S)_n$ type, that optionally contains one or more monomer blocks with randomly distributed monomer incorporation, preferably of a soft block B,

e. A linear or radial styrene butadiene block copolymer of the S-B-S-B type, that optionally contains one or more monomer blocks with randomly distributed monomer blocks, preferably of a soft block B,

f. A linear or radial styrene butadiene block copolymer of the S-B-S-B-S type, that optionally contains one or more monomer blocks with randomly distributed monomer incorporation, preferably of a soft block B, and

g. Mixtures thereof.

The styrene butadiene block copolymer of the present invention is preferably selected from one, two, three, four or more styrene butadiene block copolymers of the hereinbefore described groups a.), b.), c.), f.) and g.).

Preferred examples of industrially obtainable block copolymers according to group b.) to be used in accordance of the present invention comprise or consist of

- Solprene 9618 (Dynasol Elastomers), which represents a hyper branched styrene butadiene block copolymer of the $(S-B)_n$ type with a styrene amount of 31 wt.-% and a melt flow index of approximately 13 g / 10 min (ISO 1133), and

- Vector 2411 (Dexco Polymers), which represents a radial styrene butadiene block copolymer of the $(S-B)_n$ type with a styrene amount of 30 wt.-% and a melt flow index of less than 1 g / 10 min (ISO 1133).

Preferred examples of block copolymers according to group c.) to be used in accordance with the present invention comprise or consist of

- Vector 4461 (Dexco Polymers), which represents a linear styrene butadiene triblock copolymer of the S-B-S type with a styrene amount of 43 wt.-% and a melt flow index of approximately 23 g / 10 min (ISO 1133),

- Kraton D1101 (Kraton Polymer US), which represents a linear styrene butadiene block copolymer of the S-B-S type with a styrene amount of approximately 31 wt.-% and a melt flow index of less than 1 g / 10 min (ISO 1133),

- Globalprene 3411 (LCY Elastomers), which represents a radial styrene butadiene block copolymer of the S-B-S type with a styrene amount of 30 wt.-%,

- Kraton D1102 (Kraton Polymer US), which represents a linear styrene butadiene block copolymer of the S-B-S type with a styrene amount of approximately 30 wt.-% and a melt flow index of 6 to 14 g / 10 min (ISO 1133), and

- Tufprene and Asaprene-T (Asahi Kasei), which represent a styrene butadiene block copolymers of the S-B-S type with a styrene amount of 40 wt.-% and 30 wt.-% respectively and a melt flow index of 20 g / 10 min and 25 g / 10 min (ISO 1133) respectively.

A preferred example of an industrially obtainable block copolymer according to group f.) to be used in accordance with the present invention comprises or consists of Stereon (Firestone

Polymers), which represents a styrene butadiene multiblock copolymer of the S-B-S-B-S type with a styrene content of 10 wt.-%.

Preferred examples of industrially obtainable block copolymers according to groups a.) and c.) for the mixture according to group g.) comprise or consist of Duro-Tak 6911 or Duro-Tak 611 (Henkel Corp.).

In a particularly preferred embodiment of the present invention Duro-Tak 6911 and Duro-Tak 611, more preferably Duro-Tak 6911 are used as self adhesive adhesives for the inventive matrix or the inventive transdermal therapeutic system respectively.

Industrially obtainable pharmaceutically acceptable adhesives to be used in accordance with the present invention can generally comprise further components in addition to the inventively applicable styrene butadiene block copolymer, preferably one or more inventively applicable tackifiers and/or one or more antioxidants, which inhibit or reduce the oxidation of the copolymer.

That or the inventively applicable styrene butadiene block copolymers can comprise a weight amount of 25 to 40 wt.-%, preferably 28 to 38 wt.-%, further preferred 30 to 35 wt.-% respectively based on the weight of the inventive matrix or the matrix layer of the inventive TTS.

The inventive matrix in particular for use in the inventive transdermal therapeutic system can comprise alternatively or cumulatively to the aforementioned inventive adhesives one, two, three or more adhesive materials selected from the following group: (cross linked) polyacrylates, optionally additionally comprising further suitable monomer compounds, such as vinyl acetate, acryl amide or N-vinyl pyrrolidone; polysiloxanes, preferably polydimethylsiloxanes, polydiethylsiloxanes, polydiphenylsiloxanes (which comprise amine resistant or non amine resistant adhesives); ethylene vinyl acetate; synthetic and/or natural polyispoprenes; styrene isoprene styrene triblock copolymers (SIS); styrene ethylene butylene styrene triblock copolymers (SEBS); polyisobutylene (PIB); and polyvinyl ether.

In a cumulatively or alternatively preferred embodiment a suitable crystallization inhibitor of the inventive matrix or the inventive transdermal therapeutic system can be selected from the group consisting of colloidal silica; polymers or copolymers comprising or consisting of vinylpyrrolidone, preferably polyvinylpyrrolidone (Povidone), polyvinylpolypyrrolidone (PVPP; Crospovidone), vinylpyrrolidone vinylacetate copolymer (Copovidone); poly(vinyl acetate) (PVA); cellulose ester, preferably cellulose acetate butyrate, cellulose acetate propionate, cellulose phthalate; cellulose ether, preferably hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, ethylcellulose; acrylic polymers (polyacrylates), preferably copolymers of methacrylic acid and methylmethacrylate or ethylacrylate, ammonio methacrylate copolymers, butylmethacrylate dimethylaminoethylmethacrylate methylmethacrylate copolymer, ethylacry-

late methylmethacrylate copolymer, methylacrylate methylmethacrylate methacrylic acid copolymer; sugar and/or sugar alocohols, preferably sorbitol, mannitol, maltitol, isomalt; gelatine; dextrin; dextran; starch and starch derivatives; sterols, preferably cholesterol and gallic acids; colophony, beeswax, microcrystalline wax and/or polyethylene glycol. Polyvinylpyrrolidone (Povidone) and/or vinylpyrrolidone vinylacetate copolymer (Copovidone) are in particular preferred to reduce the crystallization of rotigotine.

The inventively applicable crystallization inhibitor(s) are commonly used with a weight amount (total weight), which effectively reduces the crystallization of rotigotine. In a preferred embodiment the inventively applicable crystallization inhibitor(s) (total weight) comprise a weight amount of 1 to 12 wt.-%, preferably 2 to 10 wt.-%, further preferably 3 to 8 wt.-%, more preferably 4 to 6 wt.-%, most preferably 5 wt.-% or more based on the weight of the inventive matrix or the matrix layer of the inventive TTS respectively.

In a further preferred embodiment the inventive matrix or the inventive transdermal therapeutic system respectively comprises one or more further pharmaceutical excipients, whereby preferably as little further different excipients are used as possible. In a preferred embodiment the further excipient(s) are selected from:

a. One, two, three, four or more pharmaceutically acceptable tackifiers, preferably selected from the group consisting of oils, e.g. avocado oil or palm oil; hydrocarbon resins, which are produced from aliphatic and/or aromatic monomers and/or dicyclopentadiene and can optionally be hydrogenated; natural resins (rosin), resin acids, e.g. abietic acid and pimaric acid or mixtures thereof; hydrogenated or partly hydrogenated resin acids, e.g. dihydro or tetrahydro abietic acid or mixtures thereof; resin acid ester, e.g. ester with methanol, triethylene glycol, glycerol or pentaerythritol; alcohols based on resin acids, e.g. hydroabietic alcohol; derivatives of resin acids, e.g. modified resin acids with maleic acid or fumaric acid anhydride or dimers of resin acids and/or (poly)terpene resins; and/or

b. One, two, three, four or more pharmaceutically acceptable emulsifiers, preferably selected from the group consisting of fatty acid ester, particularly preferred sorbitan fatty acid ester, more particularly preferred sorbitan oleate, sorbitan palmitate, sorbitan monostearate and sorbitan trioleate; polyoxyethylene sorbitan fatty acid ester (polysorbate), preferably polysorbate 20, 40 or 60; polyethylene glycol 15 hydroxystearate, polyethylene glycol, monoglycerides, preferably glycerol monooleate and glycerol monostearate; di and/or triglycerides, e.g. glycerol palmitostearate, caprylocaproyl macrogol glyceride, and/or diethylene glycol monooleate, preferably sorbitan fatty acids, e.g. sorbitan monostearate and/or polyoxyethylene sorbitan fatty acid ester (polysorbate); and/or

c. One, two, three, four or more pharmaceutically acceptable permeation enhancers, preferably selected from the group consisting of glycerol, fatty acids, e.g. lauric acid, oleic acid, linolenic acid or palmitic acid; fatty acid ester, e.g. isopropyl myristate and glycerol monostearate; mono and dibasic alcohols with up to 24 carbon atoms, e.g., 1,2-propanediol, 1,3-propanediol, 1,2-ethanediol, glycerol or dodecanol, terpene resins, amides and/or urea; and/or

d. One, two, three or more pharmaceutically acceptable antioxidants, preferably selected from the group consisting of tocopherol, sesame oil, acorbinic acid and the respective salts or derivatives thereof, e.g. ascorbyl palmitate; butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), gallic acid ester (e.g. methyl, ethyl, propyl, amyl, butyl, lauryl gallate and further gallic acid ester), monothioglycerol, sodium and/or potassium disulfite, sodium sulfite, sodium disulfite, hydroquinones and/or pyrocatechol; preferably tocopherol; ascorbyl palmitate; and/or sodium and/or potassium disulfite.

The inventive use of tackifiers according to a.) is cumulatively or alternatively preferred, as thereby the adherence to the human or animal skin of the inventive matrix or the inventive transdermal therapeutic system is respectively increased and, thus, the release of rotigotine and, thus, the skin permeation of rotigotine can also be increased. One or more saturated (synthetic) hydrocarbons are particularly preferred for use in the present invention. Natural or hydrogenated resin esters or terpene resins can alternatively or cumulatively be as suitable tackifiers. In this respect we refer to the "Presentation to The Society of Adhesion & Interface (Korea), August 2001, ExxonMobil Chemical Korea/B.H.An: Escorez, Hydrocarbon Tackifier Resins", which content in relation to the hydrocarbon tackifier resins, which are particularly preferred as inventive tackifiers, is incorporated into the present application.

The inventively applicable tackifiers have preferably a softening point (ring and ball method) of 10 °C to 150 °C.

Examples for such inventively applicable tackifiers are tackifiers with a softenting point (ring and ball method) of 10-15 °C such as Wingtack 10 (Cray Valley HSC), tackifiers with a softening point (ring and ball method) of 84-90 °C such as Wingtack 86 (Sartomer), tackifiers with a softening point (ring and ball method) of 95-105 °C such as Eastotac H100 (Eastman Chemical Co.) and tackifiers with a softening point (ring and ball method) of 125-135 °C such as Eastotac H130R (Eastman Chemical Co.).

Further examples for inventively applicable tackifiers are Arkon (Hydrogenated Hydrocarbon Resin), e.g. Arkon P-90 or MP-90 (Arakawa Chemical Ind.), Escorez 1000, 2000 or 5000 series, e.g. Escorez 5300 (ExxonMobil Chemical Co. Ltd.), Foral and Foralyn (Hydrogenated Rosin and Rosin ester), e.g. Foral AX, 85 or 105 and Foralyn 5020, 90 or 110 (Eastman

Chemical Co.), Hariester 100 or 110 (Harima Chemical Inc.), Pensel Rosin Ester, e.g. Pensel GA90 or GA100 (Arakawa Chemical Ind.), Pentalyn Synthetic Resin, e.g. Pentalyn C, H, 601-M or 702-M or H-E (Eastman Chemical Co.), Pinecrystal Hydrogenated Rosin, e.g. Pinecrystal KE-100 or KE-311 (Arakawa Chemical Co. Ltd.), Permalyn Resin, e.g. Permalyn 2085 or 5110 (Eastman Chemical Co.) and Staybelite Resin or Staybelite Ester 5, 7 or 10 (Eastman Chemical Co.).

The inventively applicable tackifier(s) are commonly used with a weight amount (total weight), which additionally increases the adherence of the adhesive. Industrially obtainable inventively applicable adhesives comprising styrene butadiene block copolymers may already contain inventively applicable tackifiers in a sufficient amount, whereby optionally in addition to the amount of tackifier already present in the industrially obtainable and applicable adhesive tackifiers can be added to the inventive matrix or the matrix layer of the inventive TTS. A preferred embodiment comprises an amount of 30 to 70 wt.-%, preferably 35 to 65 wt.-%, further preferably 45 to 55 wt.-% of the inventively applicable tackifiers (total weight) based on the weight of the inventive matrix or the matrix layer of the inventive TTS respectively.

To achieve particularly good adherence properties of the inventive TTS to the skin, the weight ratio of the block copolymer according to a.) to the block copolymer according to c.) to the tackifiers in the inventive matrix or the matrix layer of the inventive TTS can in a preferred inventive embodiment respectively be, e.g. 2-40 : 2-25 : 30-70. Preferred sub-ranges of the range 30-70 wt.-% of the tackifier are 40-70 wt.-% and 40-65 wt.-%.

The inventive use of emulsifiers according to b.) is cumulatively or alternatively preferred to improve the homogeneity in the coating solution. It is advantageous to disclaim the use of emulsifiers as further pharmaceutical excipients for the inventive matrix in particular for use of the inventive matrix in an inventive TTS.

The inventively applicable emulsifier(s) are commonly used with a weight amount (total weight), which improves the homogeneity of the coating solution. A preferred embodiment comprises an amount of 1 to 10 wt.-%, preferably 2 to 7 wt.-%, further preferred 2 to 5 wt.-% of the inventively applicable emulsifiers (total weight) based on the weight of the inventive matrix or the matrix layer of the inventive TTS respectively.

The inventive use of permeation enhancers according to c.) is cumulatively or alternatively preferred to increase the skin permeation of rotigotine into the organism.

The inventively applicable permeation enhancer(s) are commonly used with a weight amount (total weight), which improves the skin permeation of rotigotine into the organism (commonly by the interaction of rotigotine with the stratum corneum). A preferred embodiment comprises an amount of 2 to 11 wt.-%, preferably 3 to 10 wt.-% further preferred 5 to 9 wt.-% of the in-

ventively applicable permeation enhancers, preferably fatty acid ester, such as isopropyl myristate and glycerol monostearate, more preferably isopropyl myristate (total weight) based on the weight of the inventive matrix or the matrix layer of the inventive TTS respectively.

The inventive use of antioxidants according to d.) is cumulatively or alternatively preferred to improve the chemical stability of rotigotine. As the inventive matrix in particular when used for the inventive TTS already comprises an excellent chemical stability of rotigotine, the use of antioxidants, in particular of antioxidants selected from the following group can be disclaimed: tocopherol, sesamol, acorbinic acid and the respective salts or derivatives thereof, e.g. ascorbyl palmitate; butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), gallic acid ester (e.g. methyl, ethyl, propyl, amyl, butyl, lauryl gallate and further gallic acid ester), monothioglycerol, sodium and/or potassium disulfite, sodium sulfite, sodium disulfite, hydroquinones and/or pyrocatechol.

As already explained hereinbefore, antioxidants can already be present in industrially obtainable inventively applicable adhesives with a common weight amount of approximately up to 1 wt.-% based on the weight of the industrial applicable adhesive to improve the stability of the polymer. Respectively suitable antioxidants are listed in the following and are not considered to be pharmaceutically acceptable antioxidants according to d.) within the context of the present invention, so that they are disclaimed from the optional disclaimer regarding antioxidants: i) amines or amine derivatives, preferably alkylated N-phenyl-1-naphthylamine, such as e.g. N-octyl-N-phenyl-1-naphthylamine, octylated N-phenyl-1-naphthylamine, and/or butylated N-phenyl-1-naphthylamine; ii) phenoles or phenol derivatives, e.g. 2,6-di-tert.-butyl-4-nonylphenol, 2,6-di-tert.-butyl-4-sec.-nonylphenol, 6-tert.-butyl-2,4-xylenol, penterythritol tetrakis (3-(3,5-di-tert.-butyl-4-hydroxyphenyl)propionate), octadecyl-3-(3,5-di-tert.-butyl-4-hydroxyphenyl)-propionate, octyl-3-(3,5-di-tert.-butyl-4-hydroxyphenyl)-propionate, branched C7-C9 alkylic ester of 3-(3,5-di-tert.-butyl-4-hydroxyphenyl)-propionic acid, and/or 1,3,5-trimethyl-2,4,6-tris(3,5-di-tert.-butyl-4-hydroxybenzyl)benzene; iii) phosphites, preferably aryl- and/or alkyl-organophosphites, such as e.g. triphenyl phosphite, tris(2,4-di-tert.-butylphenyl) phosphite, trilauryl phosphite, or trisnonylphenyl phosphite; or iv) mixtures of two, three or more of the aforementioned antioxidants. Industrially obtainable antioxidants for improvement of the polymerstability within the adhesive are e.g. Isonox® (SI Group, Inc.), Ethanox® (Albemarle Corporation), Ethaphos® (Albemarle Corporation), Irgafos® (BASF SE) and Irganox® (BASF SE) and they are in particular preferably be disclaimed from the disclaimer regarding antioxidants.

In contrast to the aforementioned antioxidants, the inventively applicable antioxidants according to d.) are commonly used with a weight amount (total weight), which improves the stability of rotigotine in the inventive matrix or the inventive TTS. A preferred embodiment comprises

an amount of 0.001 to 1 wt.-%, preferably 0.01 to 0.5 wt.-%, further preferred 0.05 to 0.1 wt.-% of the inventively applicable antioxidants (total weight) based on the weight of the inventive matrix or the matrix layer of the inventive TTS respectively.

An inventive transdermal therapeutic system comprising rotigotine can comprise common matrix area weights. The matrix area weight of an inventive transdermal therapeutic system ranges in a preferred embodiment from 30 to 110 g/m^2, further preferred from 40 to 110 g/m^2.

Common patch forms and patch sizes can be used for inventive transdermal therapeutic systems. In a preferred embodiment rectangular inventive transdermal therapeutic systems, preferably TTS with one or more rounded corners and / or patches up to 80 cm^2 or less can be used.

Common backing layers for TTS can be used as inventively applicable backing layers for the inventive transdermal therapeutic systems, whereby the inventively applicable backing layer is preferably impermeable for the active agent and is preferably a polyester foil, e.g. made from polyethylene terephthalate.

All common protective foils for TTS can inventively be used as protective foil for the inventive transdermal therapeutic system, whereby the inventively applicable protective foil is preferably impermeable for the active agent and is preferably a siliconized polyester foil, e.g. made from polyethylene terephthalate.

All aforementioned embodiments in relation to the matrix and the components thereof can be used for the inventive matrix according to the second aspect of the invention.

All aforementioned embodiments in relation to the matrix and the components thereof can be used for the inventive method for producing a matrix for extended rotigotine release according to the third aspect of the invention.

In a preferred embodiment of the inventive process the components according to steps a.) to d.) are partly or all, separate of partly in combination be predissolved in a suitable diluent. In a further preferred embodiment the components of steps a.) and c.) are predissolved in a suitable diluent. Suitable diluents can be selected from the group consisting of acetone, ethanol, *n*-propanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, toluene, ethyl acetate, dimethyl sulfoxide, water, dioxane, hexane and/or heptane, preferably acetone, ethyl acetate, toluene and/or heptane are used. Preferably the crystallization inhibitor is predissolved in ethyl acetate or ethanol, more preferably ethanol. The same suitable diluents as mentioned hereinbefore also serve as diluent additives during manufacture, wherein preferably ethyl acetate, heptane and/or acetone, more preferably a mixture of heptane and acetone, more preferably a mixture of heptane : acetone 70 : 30 (V/V) is used with respect to the present invention.

When producing the inventive matrix the components according to steps a.) to d.) are agitated as long as a homogenous solution is obtained, which preferably does not comprise any visually visible components.

According to the fourth aspect of the invention the inventive matrix or the matrix obtainable according to the inventive method for producing a matrix is used for a transdermal therapeutic system, i.e. is used for the production of a transdermal therapeutic system. Preferably the inventive matrix is used for the treatment, alleviation and/or prophylaxis of a Parkinson's disease, a Parkinson Plus syndrome, a depression, a Restless Legs syndrome, a loss of dopaminergic neurons and/or pain.

According to the fifth aspect of the invention there is claimed a method for producing a transdermal therapeutic system comprising or consisting of i) a backing layer, ii) a matrix layer, which comprises a physiologically effective amount of rotigotine [(–)-(S)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol], whereby the matrix layer is deposited at least on part of the backing layer, and iii) a protective foil to be removed prior to use, which is deposited at least on part of the surface of the matrix layer, characterized in that the matrix layer further comprises or consists of a styrene butadiene block copolymer as a pharmaceutically acceptable adhesive and a pharmaceutically acceptable crystallization inhibitor as well as optionally one or more further pharmaceutical excipients. The preferred embodiments relating to the components of the inventive transdermal therapeutic system according to the first aspect of the invention as well as the preferred embodiments relating to the process steps a.) to e.) according to the third aspect of the invention are also applicable to the present fifth aspect of the invention.

With respect to the process step f.) of the inventive production method of a transdermal therapeutic system a sufficient amount of inventive matrix is deposited on the inventively commonly applicable protective foil (matrix layer) so that a double layered active agent containing laminate is produced, which is optionally dried at suitable drying conditions.

With respect to the process step g.) of the inventive production method of a transdermal therapeutic system an inventively commonly applicable backing layer is deposited (laminated) on the matrix layer of the inventive transdermal therapeutic system so that a three layered active agent containing laminate as inventive transdermal therapeutic system is produced. Optionally, the three layered laminate produced in step g.) is subsequently in step h.) divided in two, three, four, five or more separate inventive transdermal therapeutic systems, e.g. by means of die cutting.

Alternatively the coating order in process steps f.) and g.) according to the aforementioned method of the fifth aspect of the present invention can be exchanged, so that according to

process step f.) the inventive matrix is first deposited on the backing layer so that the double layered active agent containing laminate is produced and optionally dried and subsequently according to process step g.) the protective layer is deposited on the double layered laminate.

The sixth aspect of the invention relates to the use of an inventive transdermal therapeutic system or a transdermal therapeutic system obtainable according to the inventive production method for the treatment, alleviation and/or prophylaxis of Parkinson's disease, Parkinson Plus syndrome, depression, Restless Legs syndrome, loss of a dopaminergic neurons and/or pain.

The seventh aspect of the invention relates to a method for treatment, alleviation and/or prophylaxis of a Parkinson's disease, Parkinson Plus syndrome, depression, Restless Legs syndrome, loss of dopaminergic neurons and/or pain by application of an inventive transdermal therapeutic system or a transdermal therapeutic system obtainable according to an inventive production method to a subject, that suffers from or is expected to fall ill with Parkinson's disease, a Parkinson Plus Syndrome, a depression, a Restless Legs Syndrome, loss of dopaminergic neurons and/or pain.

The present invention will be described in the following on the basis of exemplary embodiments, which merely serve as examples and which shall not limit the scope of the present protective right.

Examples:

Part A: Method for producing inventive transdermal therapeutic systems

Executive Example 1: Method for producing an inventive transdermal therapeutic system comprising rotigotine, styrene butadiene block copolymer, Copovidone (crystallization inhibitor)

6.25 g rotigotine (equal to 5 wt.-% based on the total matrix weight, predissolved in acetone) and 6.25 g copovidone (equal to 5 wt.-% based on the total matrix weight, predissolved in ethyl acetate) are added to 193.97 g adhesive solution (Duro-Tak 6911, solid content 58 wt.-%, diluted in toluene/heptane) and are adjusted with ethyl acetate. The mixture is stirred until homogeneity by means of a mechanical stirrer. This coating mass is deposited in form of a thin layer by means of a suitable coating device (e.g. doctor blade) on an inert protective foil (e.g. polyester foil) and is dried for 15 – 20 min at 70 °C. Subsequent to the drying step the adhesive layer (area weight of 50 g/m^2) of the double layered active agent containing laminate is laminated with a second foil (backing layer, e.g. polyester). From the three layered laminate

patches of respective sizes (presently 5 cm^2) are die cut by means of a rotating laboratory punch. The patches respectively contain an amount of 0.45 mg/cm^2 rotigotine.

The individual features of the aforementioned executive example can be separately combined with the individual preferred inventive embodiments of the general description.

Executive example 2: Method for producing an inventive transdermal therapeutic system comprising rotigotine, styrene butadiene block copolymer, Copovidone (crystallization inhibitor) and sorbitan monostearate (emulsifier)

11.25 g rotigotine (equal to 9 wt.-% based on the total matrix weight, predissolved in acetone), 2.5 g copovidone (equal to 2 wt.-% based on the total matrix weight, predissolved in ethyl acetate) and 2.5 g sorbitan monostearate (Span 60, equal to 2 wt.-% based on the total matrix weight) are added to 187.5 g adhesive solution (DuroTak 6911, solid content 58 wt.-%, diluted in toluene/heptane) and adjusted with ethyl acetate to a solid content of 35 wt.-%. The mixture is stirred until homogeneity by means of a mechanical stirrer. This coating mass is deposited in form of a thin layer by means of a suitable coating device (e.g. doctor blade) on an inert protective foil (e.g. polyester foil) and is dried for 15 – 20 min at 70 °C. Subsequent to the drying step the adhesive layer (area weight of 50 g/m^2) of the double layered active agent containing laminate is laminated with a second foil (backing layer, e.g. polyester). From the three layered laminate patches of respective sizes (presently 5 cm^2) are die cut by means of a rotating laboratory punch. The patches respectively contain an amount of 0.45 mg/cm^2 rotigotine.

The individual features of the aforementioned executive example can be separately combined with the individual preferred inventive embodiments of the general description.

Executive example 3: Method for producing an inventive transdermal therapeutic system comprising rotigotine, styrene butadiene block copolymer, Copovidone (crystallization inhibitor) and isopropyl myristate (permeation enhancer)

11.25 g rotigotine (equal to 9 wt.-% based on the total matrix weight, predissolved in acetone), 2.5 g copovidone (equal to 2 wt.-% based on the total matrix weight, predissolved in ethyl acetate) and 2.5 g isopropyl myristate (equal to 2 wt.-% based on the total matrix weight) are added to 187,5 g adhesive solution (DuroTak 6911, solid content 58 wt.-%, diluted in toluene/heptane) and adjusted with ethyl acetate to a solid content of 35 wt.-%. The mixture is stirred until homogeneity by means of a mechanical stirrer. This coating mass is deposited in form of a thin layer by means of a suitable coating device (e.g. doctor blade) on an inert protective foil (e.g. polyester foil) and is dried for 15 – 20 min at 70 °C. Subsequent to the drying

step the adhesive layer (area weight of 50 g/m^2) of the double layered active agent containing laminate is laminated with a second foil (backing layer, e.g. polyester). From the three layered laminate patches of respective sizes (presently 5 cm^2) are die cut by means of a rotating laboratory punch. The patches respectively contain an amount of 0.45 mg/cm^2 rotigotine.

The individual features of the aforementioned executive example can be separately combined with the individual preferred inventive embodiments of the general description.

Executive example 27: Method for producing an inventive transdermal therapeutic system comprising rotigotine, styrene butadiene block copolymer, Copovidone (crystallization inhibitor), isopropyl myristate (permeation enhancer) and dodecanol (permeation enhancer)

11.25 g rotigotine (equal to 9 wt.-% based on the total matrix weight, predissolved in acetone), 6.25 g Copovidone (equal to 5 wt.-% based on the total matrix weight, predissolved in ethanol), 6.25 g isopropyl myristate (equal to 5 wt.-% based on the total matrix weight), and 6.25 g dodecanol (equal to 5 wt.-% based on the total matrix weight) are added to 163.8 g adhesive solution (DuroTak 6911, solid content 58 wt.-%, dissolved in toluene/heptane) and adjusted with a mixture of heptane and acetone (70:30) to a solid content of 35 wt.-%. The mixture is stirred until homogeneity by means of a mechanical stirrer. This coating mass is deposited in form of a thin layer by means of a suitable coating device (e.g. doctor blade) on an inert protective foil (e.g. polyester foil) and is dried for 15 – 20 min at 70 °C. Subsequent to the drying step the adhesive layer (area weight of 50 g/m^2) of the double layered active agent containing laminate is laminated with a second foil (backing layer, e.g. polyester). From the three layered laminate patches of respective sizes (presently 5 cm^2) are die cut by means of a rotating laboratory punch. The patches respectively contain an amount of 0.45 mg/cm^2 rotigotine.

The individual features of the aforementioned executive example can be separately combined with the individual preferred inventive embodiments of the general description.

The following exemplary embodiments have been produced in accordance with the hereinbefore described production instructions, wherein the percentage values refer to the percentage weight amount of the respective compound based on the total weight of the inventive matrix layer.

Executive example	Rotigotine	Copovidone (crystallization inhibitor)	Isopropyl-myristate (permeation enhancer)	Dodecanol (permeation enhancer)	Sorbitan monostearate (emulsifier)	Styrene butadiene block copolymer Duro-Tak	Remarks

						6911	
1	5 %	5 %	-	-	-	90 %	inventive
2	9 %	2 %	-	-	2 %	87%	inventive
3	9 %	2 %	2 %	-	-	87%	inventive
4	7 %	5 %	-	-	-	88 %	inventive
5	9 %	2 %	-	-	-	89 %	inventive
6	9 %	5 %	-	-	-	86 %	inventive
7	9 %	8 %	-	-	-	83 %	inventive
8	11 %	5 %	-	-	-	84 %	inventive
9	7 %	5 %	8 %	-	-	80 %	inventive
10	9 %	8 %	2 %	-	-	81%	inventive
11	9 %	5 %	8 %	-	-	78 %	inventive
12	9 %	2 %	2 %	-	2 %	85 %	inventive
13	9 %	8 %	2 %	-	2 %	79 %	inventive
14	5 %	0 %	-	-	-	95 %	compara-tive example
15	7 %	0 %	-	-	-	93 %	compara-tive example
16	9 %	0 %	-	-	-	91 %	compara-tive example
17	11 %	0 %	-	-	-	89 %	compara-tive example
18	7 %	4 %	5 %	-	-	84 %	inventive
19	7 %	4 %	8 %	-	-	81 %	inventive
20	7 %	5 %	5 %	-	-	83 %	inventive
21	7 %	6 %	8 %	-	-	79 %	inventive
22	7 %	7 %	8 %	-	-	78 %	inventive
23	9 %	4 %	5 %	-	-	82 %	inventive
24	9 %	4 %	8 %	-	-	79 %	inventive
25	9 %	4.5 %	8 %	-	-	78.5 %	inventive
26	9 %	5 %	5 %	-	-	81 %	inventive
27	9 %	5 %	5 %	5 %	-	76 %	inventive
28	9 %	6 %	-	-	-	85 %	inventive
29	9 %	6 %	8 %	-	-	77 %	inventive
30	9 %	6 %	8 %	8 %	-	69 %	inventive
31	9 %	6 %	9 %	-	-	76 %	inventive
32	9 %	6 %	10 %	-	-	75 %	inventive

33	9 %	7 %	8 %	-	-	76 %	inventive

Part B: Investigations on the crystallization behaviour of the inventive transdermal therapeutic system in comparison to the transdermal therapeutic systems according to the prior art

The present invention provides in particular transdermal therapeutic systems comprising rotigotine, which shows an improved, i.e. reduced crystallization behaviour of rotigotine in the inventive matrix layer of the inventive transdermal therapeutic system.

The crystallization behaviour was conducted as follows on inventive transdermal therapeutic systems as well as transdermal therapeutic systems of the prior art, which are in particular described in part A:

Photographic images in top view of the matrix area of the patch produced according to part A as inventive transdermal therapeutic system or as comparative system were conducted by means of a macroscope of the company Leica (Z16 APO A, 5-fold enlargement) directly after production (initially), after 4 or 11 or 26 weeks storage at room temperature as well as at accelerated conditions [30 °C / 60 % rH according to ICH-Guideline Q 1 A (R2)] (see figures 1, 2, 3, 4, 5 and 6). Crystallization can be detected visually or by means of a software, preferably by means of Leica Application Suite Version 3.6.0 (Leica Microsystems (Switzerland) Limited, Leica Microsystems CMS GmbH).

Figures 1a, 1b, 1c, 1d, 1e, 1f, and 1g show top views of the matrix area of a TTS (patch) comprising 7 wt.-% rotigotine, 93 wt.-% adhesive without crystallization inhibitor (comparative system) (executive example: 15): a) directly after production, b) after 4 weeks storage at room temperature, c) after 11 weeks storage at room temperature, d) after 4 weeks storage at accelerated conditions, e) after 11 weeks storage at accelerated conditions, f) after 26 weeks at room temperature and g) after 26 weeks at accelerated conditions, whereby it is apparent that no crystals can be visually identified initially with respect to the comparative system, however, after already 4 weeks storage at room temperature as well as at accelerated conditions. After 11 weeks storage at accelerated conditions as well as 26 weeks storage at room temperature and accelerated conditions nearly the whole matrix area of the comparative system is already nearly fully crystallized.

Figures 2a, 2b, 2c, 2d, 2e, 2f, 2g show top views of the inventive matrix area of a TTS (patch) comprising 7 wt.-% rotigotine, 88 wt.-% adhesive and 5 % Copovidone as crystallization inhibitor (executive example: 4): a) directly after production, b) after 4 weeks storage at room tem-

perature, c) after 11 weeks storage at room temperature, d) after 4 weeks storage at accelerated conditions, e) after 11 weeks storage at accelerated conditions, f) after 26 weeks at room temperature and g) after 26 weeks at accelerated conditions, whereby it is apparent that with respect to the inventive patch no crystallization can be identified initially as well as for all storage conditions.

Figures 3a, 3b, 3c, 3d, 3e, 3f, 3g show top views of the matrix area of a TTS (patch) comprising 9 wt.-% rotigotine, 91 wt.-% adhesive without crystallization inhibitor (comparative system) (executive example: 16): a) directly after production, b) after 4 weeks storage at room temperature, c) after 11 weeks storage at room temperature, d) after 4 weeks storage at accelerated conditions, e) after 11 weeks storage at accelerated conditions, f) after 26 weeks at room temperature and g) after 26 weeks at accelerated conditions, whereby it is apparent that no crystals can be visually identified initially with respect to the comparative system, however, after already 4 weeks storage at room temperature as well as at accelerated conditions. After 11 weeks storage at accelerated conditions as well as 26 weeks storage at room temperature and accelerated conditions nearly the whole matrix area of the comparative system is already nearly fully crystallized.

Figures 4a, 4b, 4c, 4d, 4e, 4f, 4g show top views of the matrix area of an inventive TTS (patch) comprising 9 wt.-% rotigotine, 86 wt.-% adhesive and 5 % Copovidone as crystallization inhibitor) (executive example: 6): a) directly after production, b) after 4 weeks storage at room temperature, c) after 11 weeks storage at room temperature, d) after 4 weeks storage at accelerated conditions, e) after 11 weeks storage at accelerated conditions, f) after 26 weeks at room temperature and g) after 26 weeks at accelerated conditions, whereby it is apparent that with respect to the inventive parch no crystallization can be identified initially as well as for all storage conditions up to 11 weeks. After storage for 26 weeks at room temperature and accelerated conditions crystals can only sporadically be visually identified.

Figures 5a, 5b, 5c, 5d, 5e, 5f, 5g show top views of the matrix area of a TTS (patch comprising 11 wt.-% rotigotine, 89 wt.-% adhesive without crystallization inhibitor (comparative system) (executive example: 17): a) directly after production, b) after 4 weeks storage at room temperature, c) after 11 weeks storage at room temperature, d) after 4 weeks storage at accelerated conditions, e) after 11 weeks storage at accelerated conditions, f) after 26 weeks at room temperature and g) after 26 weeks at accelerated conditions, whereby it is apparent that with respect to the comparative system already initially crystals are present and already after 4 weeks storage at room temperature as well as at accelerated conditions crystals can be visually identified over the whole matrix area.

Figures 6a, 6c, 6d, 6e, 6f, 6g show top views of the matrix area of an inventive TTS (patch) comprising 11 wt.-% rotigotine, 84 wt.-% adhesive and 5 % Copovidone as crystallization inhibitor (executive example: 8): a) directly after production, c) after 11 weeks storage at room temperature, d) after 4 weeks storage at accelerated conditions, e) after 11 weeks storage at accelerated conditions, f) after 26 weeks at room temperature and g) after 26 weeks at accelerated conditions, whereby it is apparent that initially as well as after storage for 4 weeks at accelerated conditions hardly no crystals can be identified. After storage at room temperature for 11 weeks and 26 weeks as well as accelerated conditions for 11 weeks crystals can only sporadically be visually identified. After storage at accelerated conditions for 26 weeks larger crystals can be visually identified, however, the crystals are still detached.

On the basis of the present results it can be concluded that the inventive transdermal therapeutic systems exhibit no or at least a strongly reduced crystallization of rotigotine when stored for 4 and 11 weeks as well as 26 weeks respectively on the one hand at room temperature / humidity and on the other hand at accelerated conditions. These results give reason to the assumption that an inventive transdermal therapeutic system can be stored and commercialized without the need of using cool chain conditions and at the same time exhibit crystallization in line with the market authorization requirements, i.e. exhibit crystals up to 24 months after production when stored at room temperature of up to 20 area-%, preferably 0 to 15 area-%, more preferably 0 to 10 area-%, even more preferably 0 to 5 area-%, in particular preferably 0 to 2 area-% respectively based on the matrix area (see figures) of the inventive transdermal therapeutic system.

Claims:

1. Transdermal therapeutic system comprising or consisting of i) a backing layer, ii) a matrix layer, which comprises a physiologically effective amount of rotigotine [(–)-(S)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol], whereby the matrix layer is deposited at least on part of the backing layer, and iii) a protective foil to be removed prior to use, which is deposited at least on part of the surface of the matrix layer, characterized in that the matrix layer further comprises or consists of a styrene butadiene block copolymer as a pharmaceutically acceptable adhesive and a pharmaceutically acceptable crystallization inhibitor as well as optionally one or more further pharmaceutical excipients.

2. Transdermal therapeutic system according to claim 1, characterized in that the matrix layer comprises rotigotine as free base and/or as pharmaceutically acceptable salt, and/or as pharmaceutically acceptable solvate and/or as pharmaceutically acceptable rotigotine prodrug.

3. Transdermal therapeutic system according to claim 1 or 2, characterized in that the styrene butadiene block copolymer in the matrix layer is selected from the group consisting of

   a. A linear styrene butadiene block copolymer of the S-B type, that optionally contains a monomer block with randomly distributed monomer incorporation, preferably of a soft block B,

   b. A radial or hyper branched styrene butadiene block copolymer of the $(S\text{-}B)_n$ type, that optionally contains one or more monomer blocks with randomly distributed monomer incorporation, preferably of a soft block B,

   c. A linear or radial styrene butadiene block copolymer of the S-B-S type, that optionally contains one or more monomer blocks with randomly distributed monomer incorporation, preferably of a soft block B,

   d. A radial or hyper branched styrene butadiene block copolymer of the $S\text{-}(B\text{-}S)_n$ type, that optionally contains one or more monomer blocks with randomly distributed monomer incorporation, preferably of a soft block B,

   e. A linear or radial styrene butadiene block copolymer of the S-B-S-B type, that optionally contains one or more monomer blocks with randomly distributed monomer blocks, preferably of a soft block B,

f. A linear or radial styrene butadiene block copolymer of the S-B-S-B-S type, that optionally contains one or more monomer blocks with randomly distributed monomer incorporation, preferably of a soft block B, and

g. Mixtures thereof.

4. Transdermal therapeutic system according to one of the claims 1 to 3, characterized in that the crystallization inhibitor is selected from the group consisting of colloidal silica; polymers or copolymers comprising or consisting of vinylpyrrolidone; poly(vinyl acetate) (PVA); cellulose ester; cellulose ether; acrylic polymers (polyacrylates); sugar and/or sugar alocohols; gelatine; dextrin, dextran; starch and starch derivatives; sterols; colophony, beeswax, microcrystalline wax and/or polyethylene glycol.

5. Transdermal therapeutic system according to one of the claims 1 to 4, characterized in that the one or more further pharmaceutical excipients are selected from the group consisting of:

a. One or more tackifiers, and/or

b. One or more emulsifiers, and/or

c. One or more permeation enhancers, and/or

d. One or more antioxidants.

6. Matrix for extended release of rotigotine comprising or consisting of a physiologically effective amount of rotigotine [(–)-(S)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol], a pharmaceutically acceptable adhesive comprising or consisting of a styrene butadiene block copolymer and a pharmaceutically acceptable crystallization inhibitor as well as optionally one or more further pharmaceutical excipients.

7. Method for producing a matrix for extended release of rotigotine comprising or consisting of the following steps:

a. Provision of rotigotine,

b. Provision of a pharmaceutically acceptable adhesive comprising or consisting of styrene butadiene block copolymer,

c. Provision of a crystallization inhibitor,

d. Optionally provision of one or more further pharmaceutically acceptable excipients,

e. Production of a matrix by mixing the provided components according to steps a.) to d.) with one or more suitable diluents, whereby the matrix comprises rotigotine in a physiologically effective amount.

8. Use of a matrix according to claim 6 or obtainable according to claim 7 for the production of a transdermal therapeutic system.

9. Method for producing a transdermal therapeutic system comprising or consisting of i) a backing layer, ii) a matrix layer, which comprises a physiologically effective amount of rotigotine [(–)-(S)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol], whereby the matrix layer is deposited at least on part of the backing layer, and iii) a protective foil to be removed prior to use, which is deposited at least on part of the surface of the matrix layer, characterized in that the matrix layer further comprises or consists of a styrene butadiene block copolymer as a pharmaceutically acceptable adhesive and a pharmaceutically acceptable crystallization inhibitor as well as optionally one or more further pharmaceutical excipients, comprising or consisting of the following steps:

a. Provision of rotigotine,

b. Provision of a pharmaceutically acceptable adhesive comprising styrene butadiene block copolymer,

c. Provision of a crystallization inhibitor,

d. Optionally provision of one or more further pharmaceutically acceptable excipients,

e. Production of a matrix by mixing the provided components according to steps a.) to d.) with one or more suitable diluents, whereby the matrix comprises rotigotine in a physiologically effective amount,

f. Provision of a protective foil and production of a double layered active agent containing laminate by depositing of at least part of the matrix produced in step e.) on at least part of the protective foil (matrix layer) and optionally drying of the double layered active agent containing laminate at suitable drying conditions,

g. Provision of a backing layer and production of a three layered active agent containing laminate as transdermal therapeutic system by depositing the backing layer on at least part of the surface of the matrix layer of the double layered laminate of step f.) and

h. Optionally division of the three layered active agent containing laminate of step g.) in two or more transdermal therapeutic systems.

10. Use of a transdermal therapeutic system according to claim 1 to 5 or a transdermal therapeutic system obtainable according to a claim 9 for treatment, alleviation and/or prophylaxis of a Parkinson's disease, a Parkinson Plus Syndrome, a depression, a Restless Legs Syndrome, loss of dopaminergic neurons and/or pain.

11. Method for treatment, alleviation and/or prophylaxis of a Parkinson's disease, a Parkinson Plus Syndrome, a depression, a Restless Legs Syndrome, loss of dopaminergic neurons and/or pain by application of a transdermal therapeutic system according to one of claims 1 to 5 or a transdermal therapeutic system obtainable according to claim 9 to a subject, that suffers from or is expected to fall ill with Parkinson's disease, a Parkinson Plus Syndrome, a depression, a Restless Legs Syndrome, loss of dopaminergic neurons and/or pain.

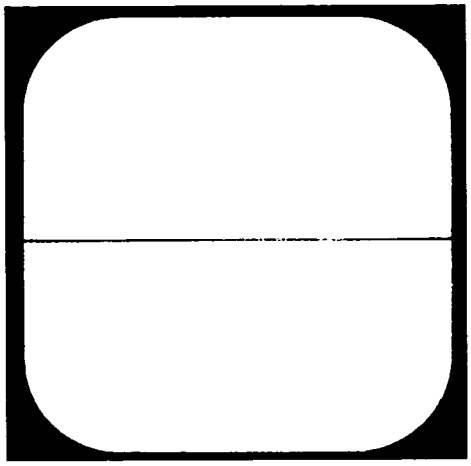


Fig. 1a)

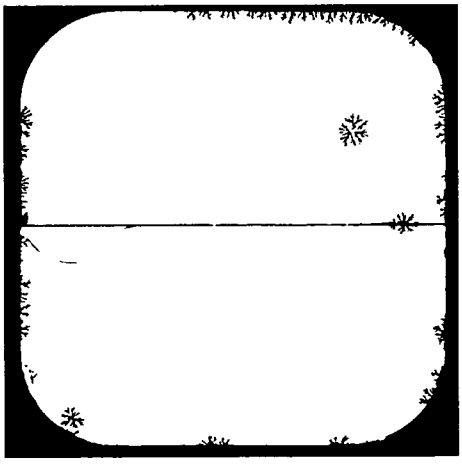


Fig. 1b)

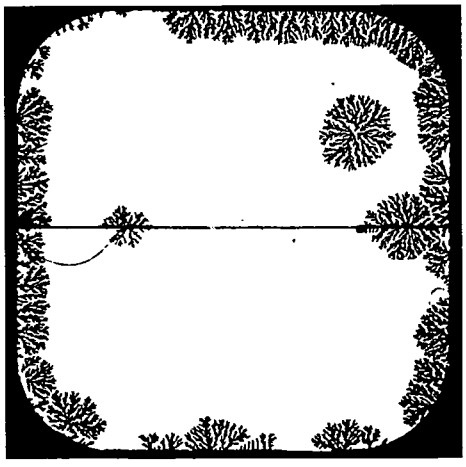


Fig. 1c)

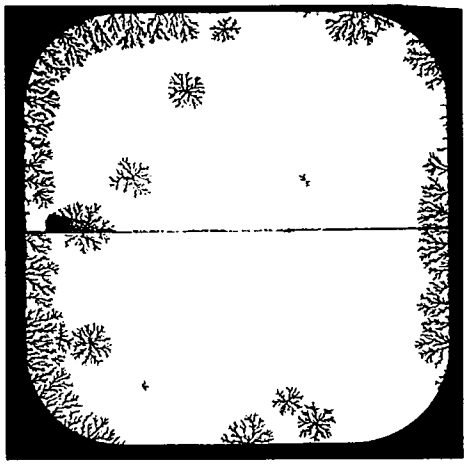


Fig. 1d)

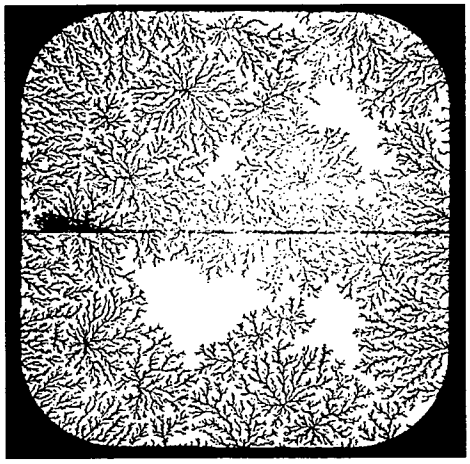


Fig. 1e)

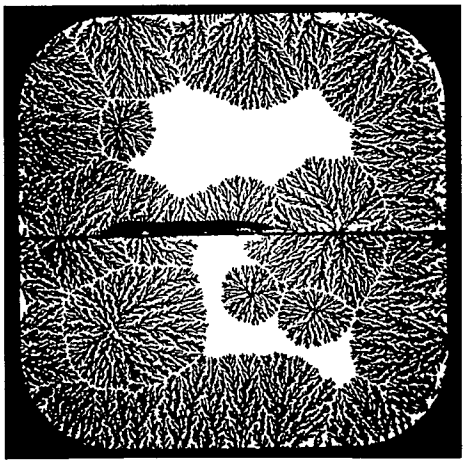


Fig. 1f)

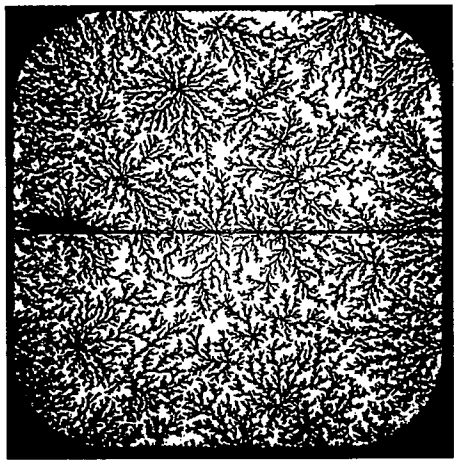


Fig. 1g)

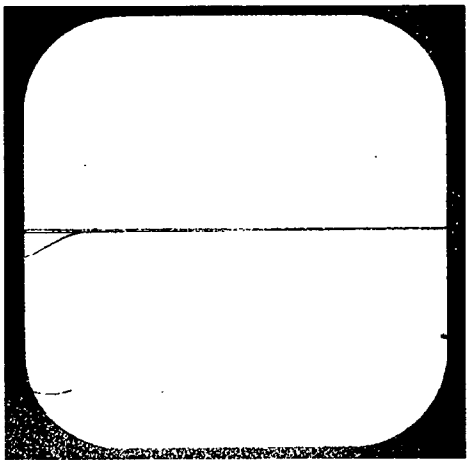


Fig. 2a)

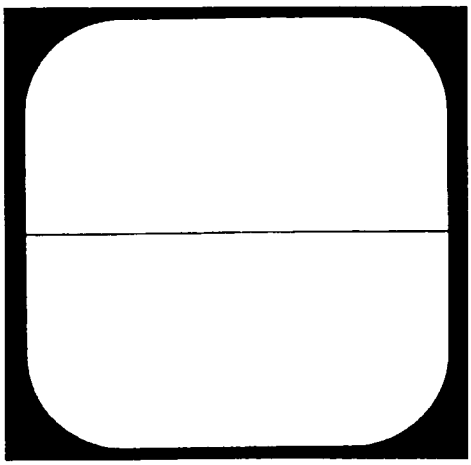


Fig. 2b)

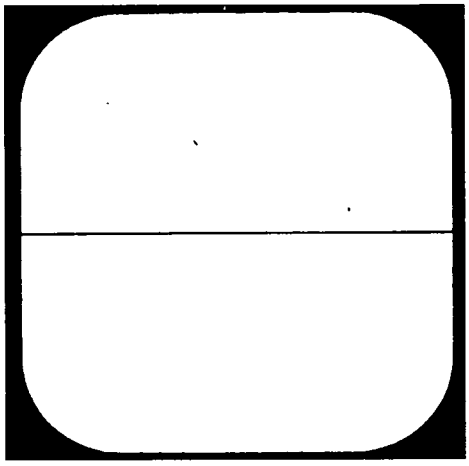


Fig. 2c)

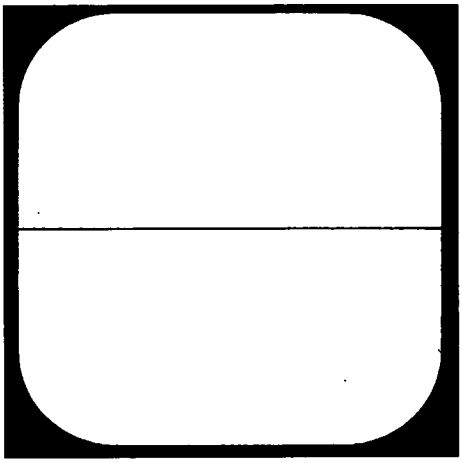


Fig. 2d)

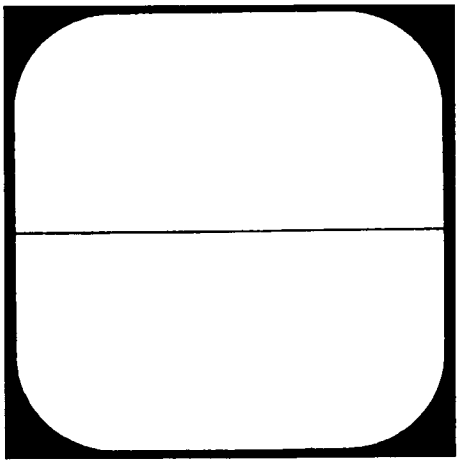


Fig. 2e)

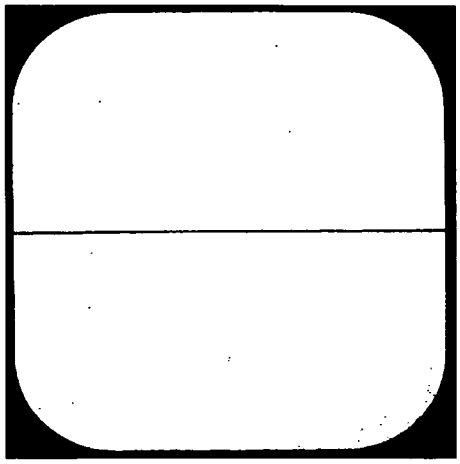


Fig. 2f)

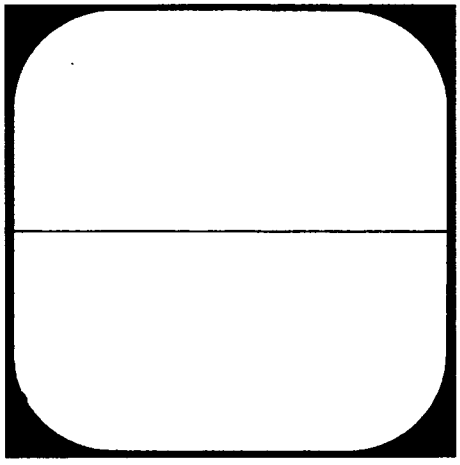


Fig. 2g)

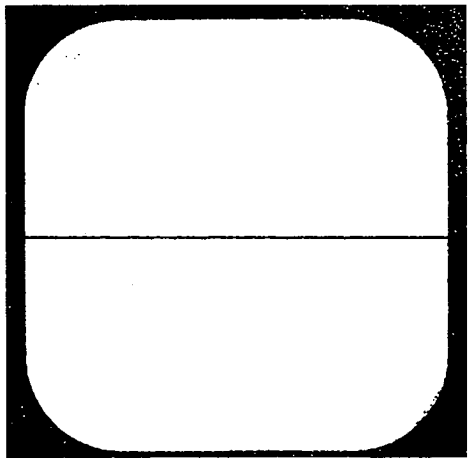


Fig. 3a)

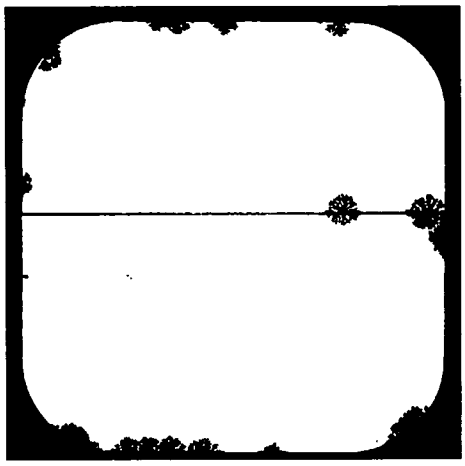


Fig. 3b)

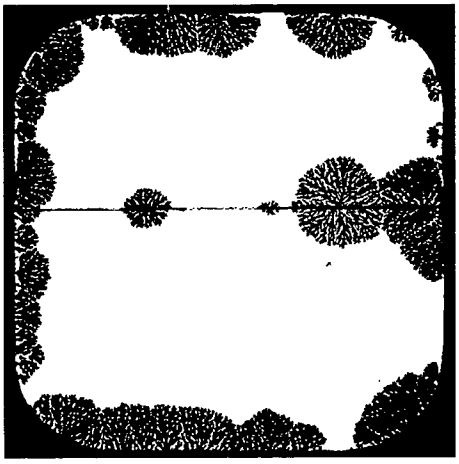


Fig. 3c)

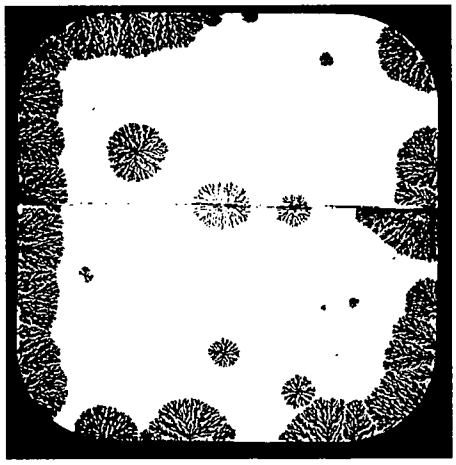


Fig. 3d)

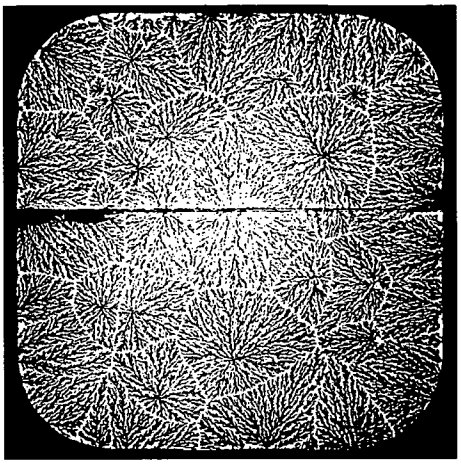


Fig. 3e)

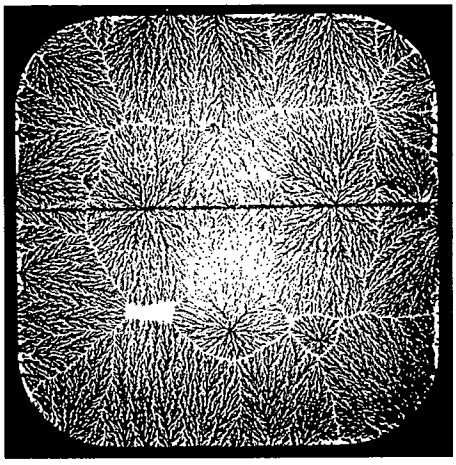


Fig. 3f)

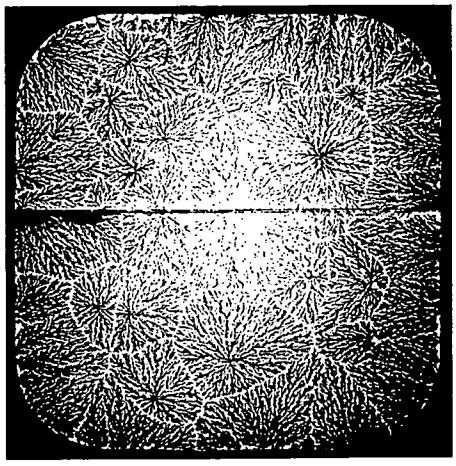


Fig. 3g)

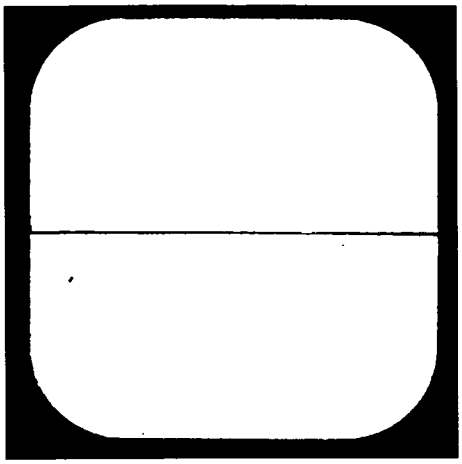


Fig. 4a)

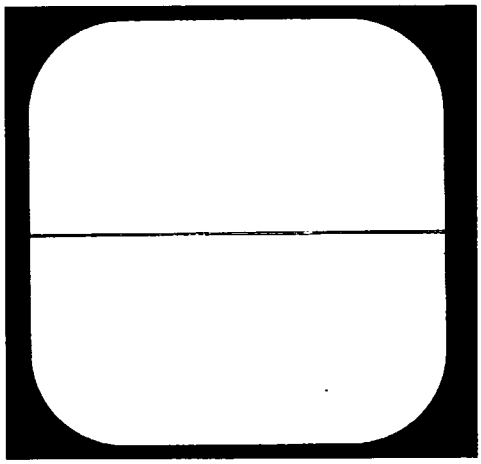


Fig. 4b)

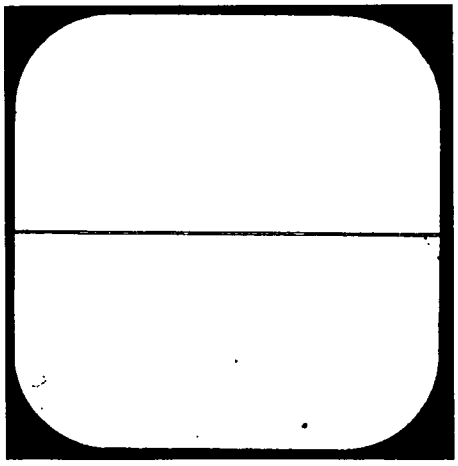


Fig. 4c)

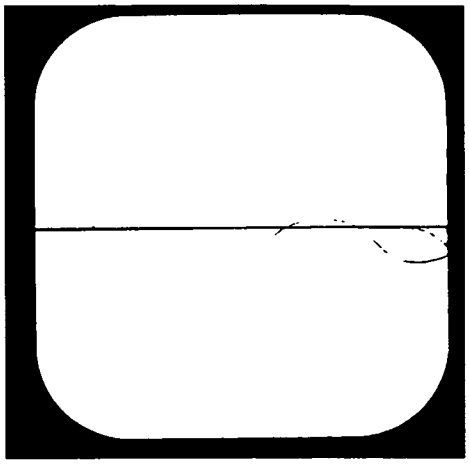


Fig. 4d)

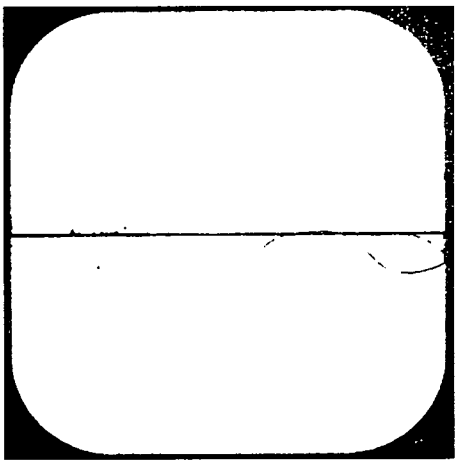


Fig. 4e)

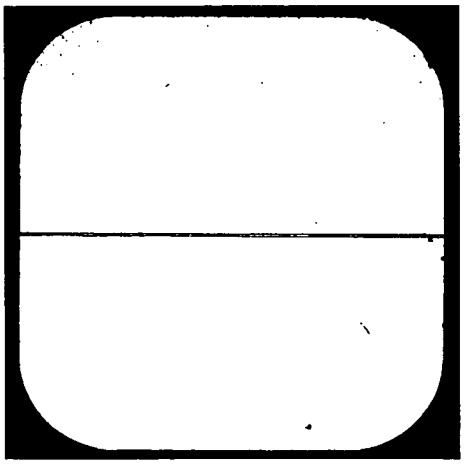


Fig. 4f)

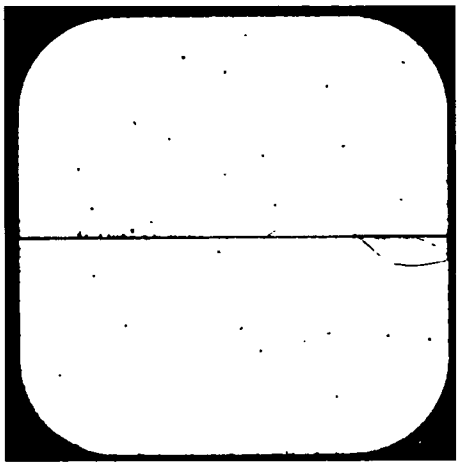


Fig. 4g)

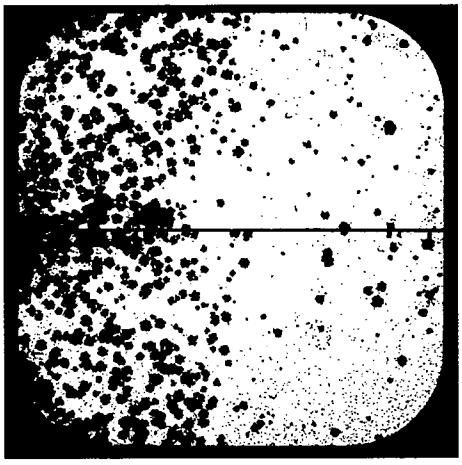


Fig. 5a)

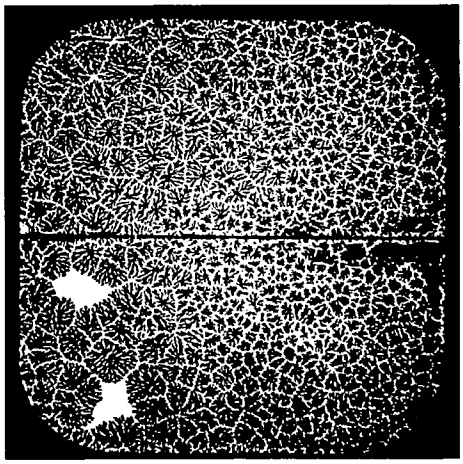


Fig. 5b)

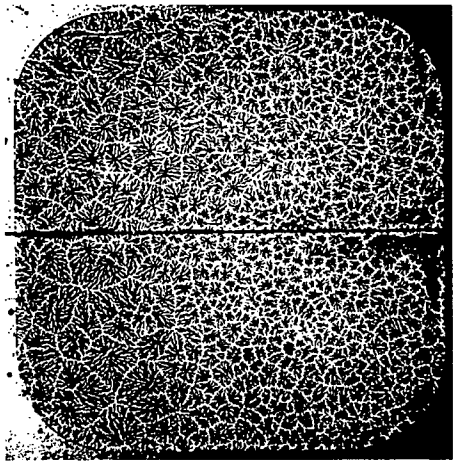


Fig. 5c)

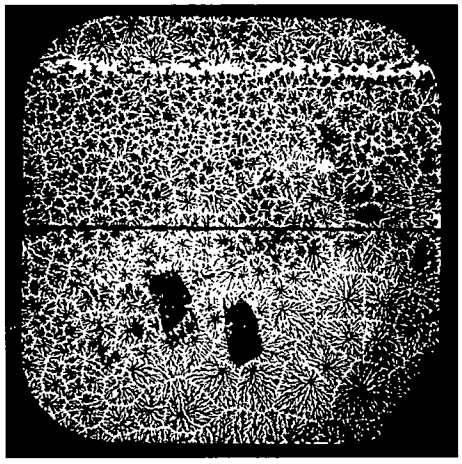


Fig. 5d)

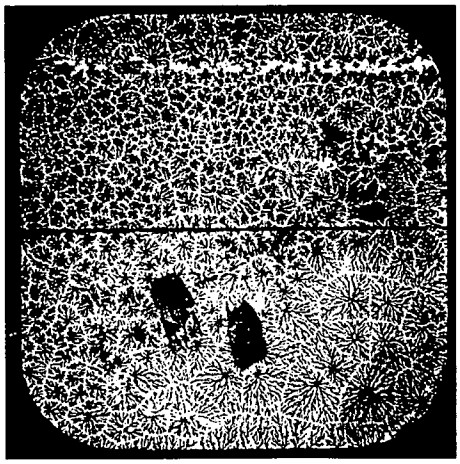


Fig. 5e)

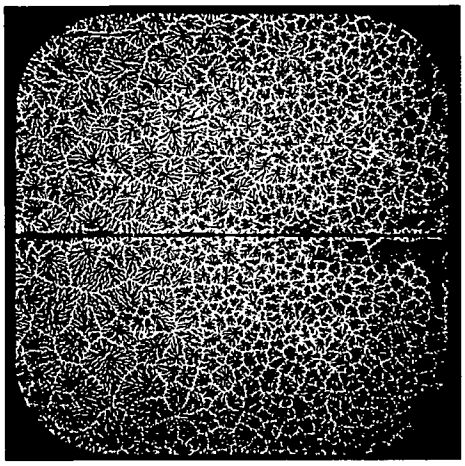


Fig. 5f)

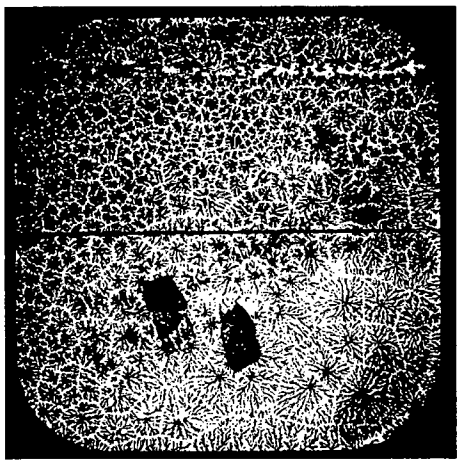


Fig. 5g)

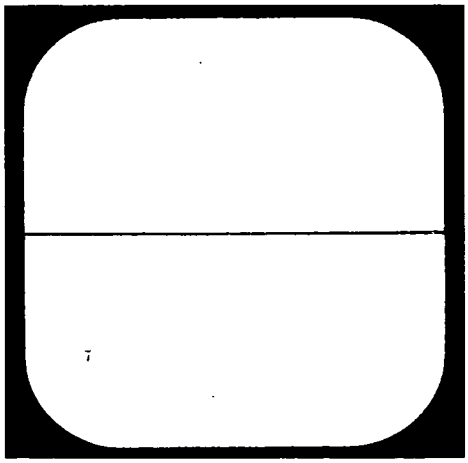


Fig. 6a)

n.a.

Fig. 6b)

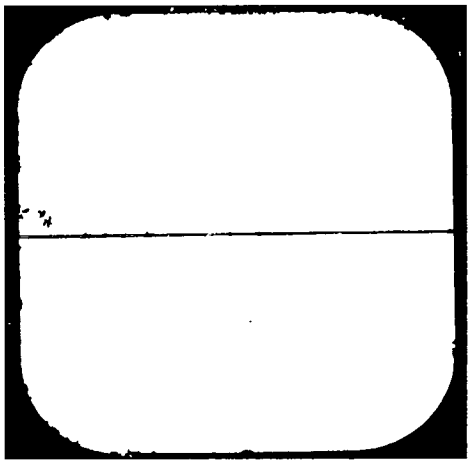


Fig. 6c)

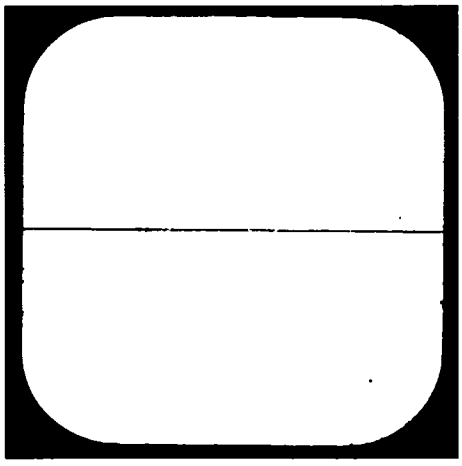


Fig. 6d)

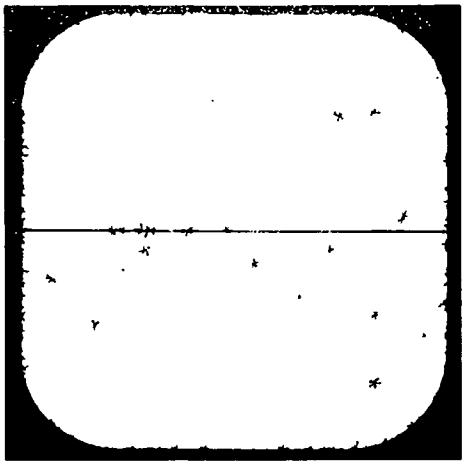


Fig. 6e)

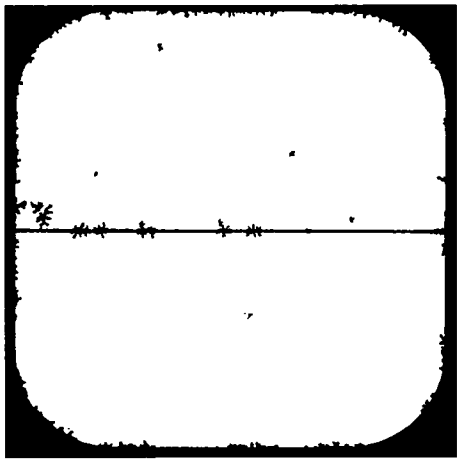


Fig. 6f)

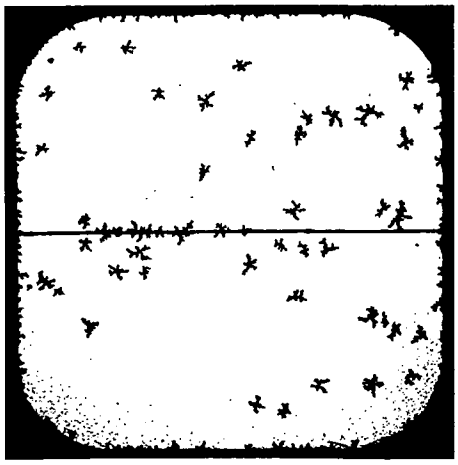


Fig. 6g)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/004818

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/381 A61K9/70 A61P25/16 A61P25/14 A61P25/28
ADD.

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)
A61K

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 practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/012721 A2 (SANOL ARZNEI SCHWARZ GMBH [DE]; BREITENBACH ARMIN [DE]; WOLFF HANS-MIC) 12 February 2004 (2004-02-12) cited in the application page 22, line 20 - line 31; figures 1-4,10 page 26, line 29 - page 27, line 3 -----	1-10
X	US 2004/048779 A1 (SCHOLLMAYER ERWIN [DE]) 11 March 2004 (2004-03-11) paragraphs [0001], [0011] - [0018], [0035], [0050]; example 1 -----	1-10
X	WO 03/092677 A1 (SANOL ARZNEI SCHWARZ GMBH [DE]) 13 November 2003 (2003-11-13) cited in the application page 12, line 1 - line 7 page 15, line 6 - line 11 -----	1-10

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

☒ See patent family 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 application or patent 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
27 February 2013	11/03/2013

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, Fax: (+31-70) 340-3016	Giese, Hans-Hermann

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/004818

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004012721 A2	12-02-2004	AT 324875 T	15-06-2006
		AU 2003269859 A1	23-02-2004
		BR 0311437 A	22-03-2005
		CA 2494361 A1	12-02-2004
		CN 1671364 A	21-09-2005
		DE 10234673 A1	19-02-2004
		DK 1492517 T3	28-08-2006
		EP 1492517 A2	05-01-2005
		EP 1669063 A1	14-06-2006
		ES 2263999 T3	16-12-2006
		HK 1081436 A1	24-09-2010
		JP 4514608 B2	28-07-2010
		JP 2006508908 A	16-03-2006
		KR 20050038007 A	25-04-2005
		MX PA04012150 A	21-09-2005
		PT 1492517 E	29-09-2006
		RU 2304434 C2	20-08-2007
		US 2005260254 A1	24-11-2005
		WO 2004012721 A2	12-02-2004
		ZA 200500457 A	18-07-2005
US 2004048779 A1	11-03-2004	NONE	
WO 03092677 A1	13-11-2003	AT 387912 T	15-03-2008
		AU 2003233233 A1	17-11-2003
		BR 0309837 A	01-03-2005
		CA 2483120 A1	13-11-2003
		CA 2787384 A1	13-11-2003
		CN 1665497 A	07-09-2005
		DE 10220230 A1	27-11-2003
		DK 1501499 T3	23-06-2008
		EP 1501499 A1	02-02-2005
		ES 2301795 T3	01-07-2008
		HK 1072541 A1	27-06-2008
		IL 164861 A	30-06-2011
		JP 2005528413 A	22-09-2005
		JP 2010159302 A	22-07-2010
		MX PA04010687 A	08-06-2005
		NZ 536533 A	26-02-2010
		PT 1501499 E	20-05-2008
		RU 2301063 C2	20-06-2007
		SI 1501499 T1	30-06-2008
		UA 81625 C2	25-01-2008
		WO 03092677 A1	13-11-2003
		ZA 200408862 A	07-07-2005