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(54) Title: TRANSDERMAL THERAPEUTIC SYSTEM (TTS) WITH ROTIGOTINE

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


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Transdermal Therapeutic System (TTS) with Rotigotine

Technical Field:

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

Prior 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:

![Chemical Structure of Rotigotine]

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 D₃ receptor, followed by the affinity for the D₂ receptor,
which is approximately 10-fold smaller, and the affinity for the D₁ 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 D₃ 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 TVS (WO 99/49852), as a depot formulation (WO 2002/015903), as an 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 commercial 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]

<table>
<thead>
<tr>
<th>Component</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>silicon adhesive (BIO-PSA Q7-4301)</td>
<td>44.5</td>
</tr>
<tr>
<td>silicon-adhesive (BIO-PSA Q7-4201)</td>
<td>44.5</td>
</tr>
<tr>
<td>Povidone (K90)</td>
<td>2.0</td>
</tr>
<tr>
<td>sodium metabisulfite (E223)</td>
<td>0.0006</td>
</tr>
<tr>
<td>ascorbyl palmitate (E304)</td>
<td>0.02</td>
</tr>
<tr>
<td>DL-alpha-tocopherol (E307)</td>
<td>0.05</td>
</tr>
<tr>
<td>rotigotine</td>
<td>0.45 mg/cm²</td>
</tr>
</tbody>
</table>
It is object of the present invention to provide a transdermal therapeutic system with one or more of the following properties:

- Rotigotine amount smaller or equal to 9 mg rotigotine/TTS [WO 99/49852 page 10: 20 cm²; example 2: 50 g matrix/m² = 0.1 g matrix/20 cm² with 9 % rotigotine = 9 mg rotigotine/20 cm²].

- Skin permeation of rotigotine equal or higher that 300 µg/cm² within 24 hours application to the skin [WO 99/49852 example 2 with Fig. 1].

- Skin permeation of rotigotine of up to 25 pg/cm² and hour.

- Preferably no addition of antioxidants for the reduction of the rotigotine oxidation, e.g. selected from the group consisting of tocopherol, sesamoil, ascorbinic acid and the 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.

- Little and preferably no crystallization after storage at room temperature.

**Brief Description of the 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 comprises or consists of a styrene butadiene block copolymer as a pharmaceutically acceptable adhesive 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 com-
prising or consisting of a styrene butadiene block copolymer 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. Optionally provision of one or more further pharmaceutically acceptable excipients,

d. Production of a matrix by mixing the provided components according to steps a.) to c.) 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 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. Optionally provision of one or more further pharmaceutically acceptable excipients,

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

e. 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 d.) 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,

f. 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 e.) and

g. Optionally division of the three layered active agent containing laminate of step f.) 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.

**Detailed Description of the Invention:**

The inventors have surprisingly identified that the inventive matrix as a self-adhesive matrix exhibits an excellent adherence on the skin, i.e. which after 24 hours at least 70 area-%, preferably more than 80 area-%, further preferably 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 of the active agent 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/cm² and day.

Despite the excellent 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 cm² matrix or a multiple thereof, e.g., 2.25 mg rotigotine / 5 cm² matrix, whereby the inventive TTS releases 1 mg rotigotine within 24 hours.

The percentage 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 preferably 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 facilitates that the inventive matrix or the matrix layer of the inventive TTS respectively is self adhesive. All 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 comprises a glass transition temperature below 20 °C. Such styrene butadiene block copolymers comprise in general block copolymers of the S-B type, the (S-B)_n type, the S-B-S type, the S-(B-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 Munchen, 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-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-(B-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.), a), f.) and g.).

A preferred example of an industrially obtainable block copolymer according to group a.) to be used in accordance with the present invention comprises or consists of Solprene 1205 (Dynasol Elastomers), which represents a linear styrene butadiene random block copolymer of the S-B type, with a styrene content of 25 wt.-%.

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 about 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 about 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 about 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 about 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 691 1 or Duro-Tak 611 (Henkel Corp.).

In a particularly preferred embodiment of the present invention Duro-Tak 691 1 and Duro-Tak 611, more preferably Duro-Tak 691 1 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 preferably 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 polyisopropenes; styrene isoprene styrene triblock copolymers (SIS); styrene ethylene butylene styrene triblock copolymers (SEBS); polyisobutylene (PIB); and polyvinyl ether.

In a further preferably 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 preferably sorbitan fatty acid ester, more particularly preferably 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; preferred permeation enhancers are dodecanol and fatty acid ester, such as isopropyl myristate and glycerol monostearate, and more preferred isopropyl myristate; 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 and/or

e. One, two, three, four or more pharmaceutically acceptable crystallization inhibitors, preferably selected from the group consisting of colloidal silica; polymers or copolymers comprising or consisting of vinlypyrrolidone, preferably polyvinylpyrrolidone (Povidone), polyvinylpolypyrrolidone (PVPP; Crospovidone), vinylpyrrolidone vinylacetate copolymer (Copovidone); polyvinyl acetate) (PVA); cellulose ester, preferably cellulose acetate bu-
tyrate, 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, ethylacrylate methylmethacrylate copolymer, methylacrylate methylmethacrylate methacrylic acid copolymer; sugar and/or sugar alcohols, preferably sorbitol, mannitol, maltitol, isomalt; gel- atine; dextrin; dextran; starch and starch derivatives; sterols, preferably cholesterol and gallic acids; colophony, beeswax, micro crystalline wax and/or polyethylene glycol.

Polyvinylpyrrolidone (Povidone) and/or vinylpyrrolidone vinylacetate copolymer (Copovidone) are in particular preferred to reduce the crystallization of rotigotine.

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 as inventive tackifiers according to a.) Natural or hydrogenated resin esters or terpene resins can alternatively or cumulatively be used 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 softening 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 or 5690 (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 Esters, 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 of the tackifier are 40-70 and 40-65.

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, further preferably 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 preferably 5 to 9 wt.-% of the
inventively applicable permeation enhancers, preferably dodecanol and 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. Thus, on the one hand the side effects of the degradation products can be reduced and at the same time the shelf life of the inventive TTS can be increased. 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, sesamoil, ascorbic 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 pyrocate chol.

As already explained hereinbefore, antioxidants can already be present in industrially obtainable inventively applicable adhesives with a common weight amount of about 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-xylene, penterythritol tetrais (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. phenolic antioxidants of the BNX series (Mayzo Inc.), 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 preferably 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.

The inventive use of crystallization inhibitors according to e) is cumulatively or alternatively preferred, as thereby the crystallization of rotigotine can be reduced, preferably up to 20 area-%, preferably 0 to 15 area-%, more preferably 0 to 10 area-%, even more preferably up to 0 to 5 area-%, in particular preferably up to 0 to 2 area-% of crystals for a storage at room temperature up to 24 months after production respectively based on the matrix area of the inventive transdermal therapeutic system. Crystallization can be determined by means of photographic images, e.g. with a macroscope of the company Leica (Z16 APO A, 5-fold enlargement) in top view of the matrix area of the inventively produced TTS (patch) after respective storage at room temperature or at accelerated conditions [30 °C / 60 % rH according to ICH-guideline Q 1 A (R2)] respectively, wherein the determination can be visually or supported by a software, preferably by means of Leica Application Suite Version 3.6.0 (Leica Microsystems (Switzerland) Limited, Leica Microsystems CMS GmbH). Based on the present results it can be assumed that the inventive transdermal therapeutic systems exhibit no or a strongly reduced crystallization of rotigotine during storage of the TTS for 4 or 11 or 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.

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.-%, even more preferably at least 5 wt.-% 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/m², further preferred from 40 to 110 g/m².

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 cm² 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 c.) are partly or all, separate of partly in combination be 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, dimethylsulfoxide, 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 c.) are agitated as long as a homogenous solution is obtained, which preferably does not comprise any visually viewable 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 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 d.) 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 e.) 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 f.) 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 f.) is subsequently in step g.) 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 e.) and f.) 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 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.

**Further embodiments of the invention**

1. Transdermal therapeutic system with a backing layer, which is impermeable for active agents, a self-adhesive reservoir with an amount of active agent as well as a removable protective foil,

   Wherein the reservoir comprises

   - a self-adhesive adhesive with
   - a styrene butadiene block copolymer and
   - an tackifier and

   = rotigotine or a rotigotine-derivative as active agent.

   With respect to the present invention the term „reservoir“ is used synonymously with the term „matrix“ or ”matrix layer“ and the term ”tackifier“ inventively refers always to pharmaceutically acceptable tackifiers. The aforementioned inventive embodiment 1 can be combined with all features of the first inventive aspect.

2. Transdermal therapeutic system according to inventive embodiment 1 with rotigotine as free base or as pharmaceutically acceptable salt, in particular as hydrochloride, or with a pharmaceutically rotigotine ester as rotigotine prodrug. The aforementioned inventive embodiment 2 can be combined with all features of the first inventive aspect.
3. Transdermal therapeutic system according to inventive embodiment 1 or 2 with 6 to 20 wt.-% rotigotine or rotigotine derivative (based on the reservoir weight). The aforementioned inventive embodiment 3 can be combined with all features of the first inventive aspect.

4. Transdermal therapeutic system according to one of the aforementioned inventive embodiments with a styrene butadiene block copolymer of the following group:

(a) a hyper branched polystyrene polybutadiene block copolymer

- with a percentual di-block amount of about 25 to about 75 % and in particular less than about 50 %,

wherein the hyper branched polystyrene polybutadiene polystyrene block copolymer comprises

- a ratio of light scattering molecular weight MW (of a non-di-block polymer) to GPC molecular weight (of a non-di-block polymer) of more than 1,4 and

- a ratio of light scattering molecular weight MW (of a non-di-block polymer) to light scattering molecular weight MW (of a di-block polymer) of more than 5, wherein

- the weight average of the molecular weight each of the arms of the hyper branched polystyrene polybutadiene polystyrene block copolymer is less than about 100,000,

(b) linear, radial or random block copolymer with general formula A-B-A, wherein

- the polymer end blocks A are non-elastomeric polymer block, which as homopolymers have a glass transition temperature of more than 20°C and

- comprise styrene homopolymers, while

- the elastomeric polymer middle block B is derived from butadiene,

(c) random styrene butadiene block copolymers and

(d) mixtures thereof.

The aforementioned inventive embodiment 4 can be combined with all features of the first inventive aspect, wherein with respect to the aforementioned formulas the term „A“ refers to the styrene amount and relates to „S“ of the first inventive aspect and „B“ refers as with respect to the first inventive aspect to the butadiene amount.
5. Transdermal therapeutic system according to inventive embodiment 4, wherein the weight average of the molecular weight of each arm of the hyper branched polystyrene polybutadiene polystyrene block copolymer is about 20,000 to about 80,000 Da. The aforementioned inventive embodiment 5 can be combined with all features of the first inventive aspect.

6. Transdermal therapeutic system according to inventive embodiment 5, wherein the hyper branched polystyrene polybutadiene polystyrene block copolymer comprises at least about 10 and in particular at least about 13 arms. The aforementioned inventive embodiment 6 can be combined with all features of the first inventive aspect.

7. Transdermal therapeutic system according to at least one of the aforementioned inventive embodiment with a hydrogenated synthetic hydrocarbon as adherence enhancer. The aforementioned inventive embodiment 7 can be combined with all features of the first inventive aspect.

8. Transdermal therapeutic system according to at least one of the aforementioned inventive embodiments, wherein the self-adhesive adhesive comprises about 30 to about 70 wt.-% tackifier (based on the weight of the adhesive). The aforementioned inventive embodiment 8 can be combined with all features of the first inventive aspect.

9. Transdermal therapeutic system according to at least one of the aforementioned inventive embodiments with 60 to 90 wt.-% self-adhesive adhesive (based on the reservoir weight). The aforementioned inventive embodiment 9 can be combined with all features of the first inventive aspect.

10. Transdermal therapeutic system according to at least one of the aforementioned inventive embodiments with DuroTak 691 1A as self-adhesive adhesive. The aforementioned inventive embodiment 10 can be combined with all features of the first inventive aspect, wherein DuroTak 691 1A is not correct but relates to DuroTak 691 1.

11. Transdermal therapeutic system according to at least one aforementioned inventive embodiment with an amount of emulsifier. The aforementioned inventive embodiment 11 can be combined with all aspects of the first inventive aspect.

12. Transdermal therapeutic system according to inventive embodiment 10 with sorbitan fatty acid ester, in particular sorbitan monostearate as emulsifier. The inventive embodiment 12 can be combined with all features of the first inventive aspect.
13. Transdermal therapeutic system according to inventive embodiment 10 or 11 with 2 to 10 wt.-% emulsifier (based on the reservoir weight). The aforementioned inventive embodiment 13 can be combined with all features of the first inventive aspect.

14. Transdermal therapeutic system according to at least one aforementioned inventive embodiment with a reservoir area weight of 30 to 110 g/m² and in particular 40 to 110 g/m². The aforementioned inventive embodiment 14 can be combined with all features of the first inventive aspect.

15. Transdermal therapeutic system according to at least one aforementioned inventive embodiment, wherein the patch size is 40 cm² or less. The aforementioned inventive embodiment 15 can be combined with all features of the first inventive aspect.

Furthermore the aforementioned inventive embodiments 1 to 15 can be described as follows:

The problem underlying the present invention is solved by a transdermal therapeutic system with a backing layer, which is impermeable for active agents, a self-adhesive reservoir with an amount of active agent as well as a removable protective foil, whereby the reservoir comprises:

- a self-adhesive adhesive with
- a styrene butadiene block copolymer and
- a tackifier and

= rotigotine or a rotigotine-derivative as active agent.

Rotigotine can be used with the inventive transdermal therapeutic system as rotigotine derivative as free base or as pharmaceutically acceptable salt, in particular hydrochloride, or as pharmaceutically acceptable rotigotine ester as rotigotine prodrug.

The inventive transdermal therapeutic system can comprise 6 to 12 wt.-% rotigotine or rotigotine derivative (based on the reservoir weight).

With respect to the inventive transdermal therapeutic system the styrene butadiene block copolymer can be a block copolymer of the following group:

(a) a hyper branched polystyrene polybutadiene block copolymer

= a block copolymer of the following group:

(a) a hyper branched polystyrene polybutadiene block copolymer
- with a percentual di-block amount of about 25 to about 75 % and in particular less than about 50 %,

wherein the hyper branched polystyrene polybutadiene polystyrene block copolymer comprises

- a ratio of light scattering molecular weight \( \text{MW} \) (of a non-di-block polymer) to GPC molecular weight (of a non-di-block polymer) of more than 1.4 and

- a ratio of light scattering molecular weight \( \text{MW} \) (of a non-di-block polymer) to light scattering molecular weight \( \text{MW} \) (of a di-block polymer) of more than 5, wherein

- the weight average of the molecular weight each of the arms of the hyper branched polystyrene polybutadiene polystyrene block copolymer is less than about 100,000 Da,

(b) linear, radial or random block copolymer with general formula A-B-A, wherein

- the polymer end blocks A are non-elastomeric polymer block, which as homopolymers have a glass transition temperature of more than 20 °C and

- comprise styrene homopolymers, while

- the elastomeric polymer middle block B is derived from butadiene,

(c) random styrene butadiene block copolymers and

(d) mixtures thereof.

An example for a block copolymer according to (a) is Solprene 9681, which is a hyper branched SBS-block copolymer (Dynasol) with a styrene amount of about 30%, a melt flow index of about 12 g/10 min (ISO 1133) and a percentual di-block amount of about 50%.

Examples for block copolymers according to (b) are

- Vector 4461 (Exxon Mobil Chemical Co.), which is a block copolymer of about 30 % styrene as end block and about 70 % butadiene polymer as middle block, wherein the melt flow index of the block copolymer is 10-16 g/10 min (ISO 1133) and the percentual di-block amount is 0.

- Kraton 1102 (Kraton Polymer US), which is a block copolymer of about 30 % styrene as end block and about 70 % butadiene polymer as middle block, wherein the melt flow index of the block copolymer is 14 g/10 min (ISO 1133) and the percentual di-block amount is about 17 %,
- Globalprene 6302 (LCY Elastomers), which is a block copolymer of about 30 % styrene as end block and about 70 % butadiene polymer as middle block, wherein the melt flow index of the block copolymer is less than 1 g/10 min (ISO 1133) and the percentual di-block amount is minimal, and

- Kraton 1101 or D1101 (Kraton Polymer US) respectively, which is a block copolymer of about 31 % styrene as end block and about 69 % butadiene polymer as middle block, wherein the melt flow index of the block copolymer is less than 1 g/10 min (ISO 1133) and the percentual di-block amount is about 17 %.

An example for a block copolymer according to (c) comprises DuroTak 691 1A or DuroTak 611.

An example for a mixture according to (d) is a mixture of Kraton D1101 and Solprene 9618; which can be present in a weight ratio of 6 : 27.

The weight average of the molecular weight each of the arms of the hyper branched polystyrene polybutadiene polystyrene block copolymer can be with respect to the inventive transdermal therapeutic system about 20,000 to about 80,000 Da.

Furthermore can the inventive transdermal therapeutic system comprise the hyper branched polystyrene polybutadiene polystyrene block copolymer with at least about 10 and in particular at least 13 arms.

Furthermore the inventive transdermal therapeutic system can comprise an optionally hydrogenated synthetic hydrocarbon as tackifier.

Examples of such tackifiers are tackifiers with a softening point (ring and ball method) of 95-105 °C such as Eastotac H100 (Eastman Chemical Co.), a tackifier with a softening point (ring and ball method) of 125-135 °C, such as Eastotac H130R (Eastman Chemical Co.), a tackifier with a softening point (ring and ball method) of 84-90 °C, such as Wingtack 86 (Sartomer; aromatic modified hydrocarbon tackifier) and a tackifier with a softening point (ring and ball method) of 10-15 °C such as Wingtack 10 (Sartomer; aliphatic hydrocarbon tackifier).

Suitable are also natural or hydrogenated rosin esters or terpenes. In this respect we refer also to the "Presentation to The Society of Adhesion & Interface"(Korea), August 2001, ExxonMobil Chemical Korea/B.H.An: Escorez, Hydrocarbon Tackifier Resins".

The weight ratio of block copolymer according to (a) to block copolymer according to (b) to tackifier can e.g. be 2-40 : 2-25 : 30-70. Preferred sub ranges of the range 30-70 tackifier are 40-70 and 40-65.
The inventive therapeutic system can also comprise 30 to 70 wt.-% of the self adhesive adhesive (based on the weight content of the adhesive).

Self adhesive adhesives comprising the aforementioned properties are disclosed in the prior art, wherein reference is made to the full content of WO 2009/026085. The self adhesive adhesives disclosed in this document have, however, up to now not been proposed for transdermal therapeutic systems with active agent content.

WO 2009/026085 discloses in particular specific embodiments of the self adhesive adhesives, mainly with respect to styrene butadiene block copolymer, the tackifiers, further components and their content. Reference is particularly made with respect to the examples. Methods for determination of the molecular weights are also disclosed therein.

Reference is furthermore made to the full content of WO 2005/003248. The self adhesive adhesives with the styrene block copolymer of the structure A-B-A disclosed in this document have also not been proposed for use as transdermal therapeutic systems with active agent content.

Furthermore the inventive transdermal therapeutic system can comprise 60 to 90 wt.-% self adhesive adhesive (based on the reservoir weight).

DuroTak 6911A is a preferred example for a self adhesive adhesive with respect to the inventive transdermal therapeutic system.

Furthermore the inventive transdermal therapeutic system can comprise an emulsifier content.

The emulsifier can be a sorbitan fatty acid ester, in particular sorbitan monostearate.

The inventive transdermal therapeutic system can comprise 2 to 10 wt.-% emulsifier (based on the reservoir weight content).

Furthermore the inventive transdermal therapeutic system can comprise

- on or more oils, resins and/or saturated hydrocarbons in liquid form in particular as tackifiers, such as e.g., avocado oil, palm oil, paraffin, and/or colophony and/or

- one or more enhancers, such as fatty acids, e.g., palmitic acid, alcohols, such as Dodecanol, and/or fatty acid ester, such Span60 (sorbitan monostearate), isopropyl myristate and/or glycerol monostearate and/or

- stabilizers, such as Span 60, Kollidones such as polyvinylpyrrolidon (PVP), natural oils and/or polyethylenglycol.
The use of PVP for transdermal therapeutic systems with a rotigotine content is already disclosed in the prior art, cf. as WO 201 1/076879.

Furthermore the inventive transdermal therapeutic system can comprise a reservoir area weight of 30 to 110 g/m² and in particular 40 to 110 g/m².

Finally the inventive transdermal therapeutic system can have a patch size of up to 40 cm² or less.

The inventive transdermal therapeutic system can furthermore contain one or more permeation enhancers, such as fatty acids, e.g. oleic acid or linolenic acid or ester thereof, e.g. isopropyl myristate.

The protective foil impermeable for active agents can be a polyester foil, e.g. made from polyethylene terephthalate.

The removable protective foil can be a siliconized polyester foil, e.g. made from polyethylene terephthalate.

The present invention is 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:

Example 1

0.45 g (9 wt.-%) rotigotine (free base) is predissolved in 1 g acetone. The predissolution is added to a mixture of 0.2 g (4 %) phosphate buffer (pH 6), 0.2 g (4 wt.-%) silicon oil (Medical Fluid), 0.2 g (4 wt.-%) sorbitan monostearate (Span 60) and 1 g acetone. The resulting mixture is added to 3.95 g (79 wt.-%) DuroTak 691 1 and is then agitated for 12 h. The resulting coating mass is deposited onto a polyester foil (polyethylene terephthalate; Primeliner PET 75 micro m 1S), which is on one side siliconized, and then dried at 70 °C for 20 min. The double layered laminate is subsequently laminated with a polyester foil (Hostaphan MN 23 DMF). Patches with different sizes are die cut from the now three layered laminate patches.

The individual features of the aforementioned executive example can separately be inventively combined with the general description of the invention.

Example 2

0.45 g (9 wt.-%) rotigotine (free base) is predissolved in 1 g acetone. The predissolution is added to a mixture of 0.2 g (4 wt.-%) silicon oil (Medical Fluid), 0.2 g (wt.-%) sorbitan monostearate (Span 60) and 1 g acetone. The resulting mixture is added to 4.15 g (83 wt.-%) of a solution (solid content 57 wt.-%) comprising a mixture of block copolymers (Kraton D 1101 and Solprene 9618 in weight ratio 6:27) and tackifiers (Wingtack 86 and Wingtack 10 in weight ratio 40.5:26) in admixture with toluene and heptane (weight ratio 66:34). The weight ratio of block copolymer to tackifier is 33:66.5. It is subsequently stirred for 12 h. The resulting coating mass is deposited on a polyester foil (polyethylene terephthalate; Primeliner PET 75 micro m 1S), which is siliconized on one side, and then dried at 70 °C for 20 minutes. The two layered laminate is subsequently laminated with a polyester foil (Hostaphan MN 23 DMF). From the now three layered laminate patches of different sizes are die cut.

The individual features of the aforementioned executive example can separately be inventively combined with the general description of the invention.

Example 3

Example 2 is repeated, wherein instead of the mixture of block copolymer Kraton 1102 and instead of the mixture of tackifiers Eastotac H100 is used.

The individual features of the aforementioned executive example can separately be inventively combined with the general description of the invention.
Example 4

Example 2 is repeated, wherein instead of the mixture of block copolymer Kraton 1102 and instead of the mixture of tackifiers Eastotac H130R is used.

The individual features of the aforementioned executive example can separately be inventively combined with the general description of the invention.

Example 5:

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 691, solid content 58 wt.-%, dissolved 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/m²) 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 cm²) are die cut by means of a rotating laboratory punch. The patches respectively contain an amount of 0.45 mg/cm² rotigotine.

The individual features of the aforementioned executive example can separately be inventively combined with the general description of the invention.

Example 6:

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 (equal to 2 wt.-% based on the total matrix weight) are added to 187.5 g adhesive solution (DuroTak 691, solid content 58 wt.-%, dissolved 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/m²) 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 cm²) are die cut by means of a rotating laboratory punch. The patches respectively contain an amount of 0.45 mg/cm² rotigotine.
The individual features of the aforementioned executive example can separately be inventively combined with the general description of the invention.

**Example 7:**

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.-%, dissolved 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/m²) 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 cm²) are die cut by means of a rotating laboratory punch. The patches respectively contain an amount of 0.45 mg/cm² rotigotine.

The individual features of the aforementioned executive example can separately be inventively combined with the general description of the invention.

**Example 31:**

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/m²) 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 cm²) are die cut by means of a rotating laboratory punch. The patches respectively contain an amount of 0.45 mg/cm² rotigotine.
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.

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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 comprises or consists of a styrene butadiene block copolymer as a pharmaceutically acceptable adhesive 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-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-(B-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 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 and/or
   e. One or more pharmaceutically acceptable crystallization inhibitors.

5. 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 as well as optionally one or more further pharmaceutical excipients.

6. 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. Optionally provision of one or more further pharmaceutically acceptable excipients,
   d. Production of a matrix by mixing the provided components according to steps a.) to c.) with one or more suitable diluents, whereby the matrix comprises rotigotine in a physiologically effective amount.

7. Use of a matrix according to claim 5 or obtainable according to claim 6 for the production of a transdermal therapeutic system.

8. 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 pro-
ective 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 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 or consisting of styrene butadiene block copolymer,

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

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

e. 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 d.) 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

f. 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 e.) and

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

9. Use of a transdermal therapeutic system according to claim 1 to 4 or a transdermal therapeutic system obtainable according to a claim 8 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.

10. 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 4 or a transdermal therapeutic system obtainable according to claim 8 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.
**INTERNATIONAL SEARCH REPORT**

**PCT/EP2012/004817**

### A. CLASSIFICATION OF SUBJECT MATTER


### 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

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* 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) on which the application is based
- **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
- **A** document member of the same patent family

**Date of the actual completion of the international search**

21 February 2013

**Date of mailing of the international search report**

04/03/2013

**Name and mailing address of the ISA**

European Patent Office, P.B. 5816 Patentlaan 2 NL - 2280 HV Rijswijk

Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

**Authorized officer**

Gi ese, Hans-Hermann

Form PCT/ISA/210 (second sheet) (April 2005)
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### INTERNATIONAL SEARCH REPORT

Information on patent family members

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