



(43) International Publication Date
26 November 2015 (26.11.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/177212 A1

(51) International Patent Classification:

A61K 9/70 (2006.01) A61K 47/02 (2006.01)
A61K 47/34 (2006.01)

(21) International Application Number:

PCT/EP2015/061112

(22) International Filing Date:

20 May 2015 (20.05.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

14169031.3 20 May 2014 (20.05.2014) EP

(71) Applicants: LTS LOHMANN THERAPIE-SYSTEME

AG [DE/DE]; Lohmannstraße 2, 56626 Andernach (DE).
UCB PHARMA GMBH [DE/DE]; Alfred-Nobel-Straße
10, 40789 Monheim (DE).

(72) Inventors: EMGENBROICH, Marco; Wagnerstraße 7,

53359 Rheinbach (DE). LEONHARD, Johannes Josef;
Raabstraße 3, 56170 Bendorf (DE). KASSNER, Kristina;
Niedenhof 11, 51427 Bergisch Gladbach (DE). LAP-
PERT, Aurélie; Rue Medaets 63, B-1150 Woluwe Saint
Pierre (BE).

(74) Agent: EHlich, Eva; MAIWALD PATENTANWALTS
GMBH, Elisenhof, Elisenstraße 3, 80335 Munich (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, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, 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, SA, 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, ST, SZ,
TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU,
TJ, 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, KM, ML, MR, NE, SN, TD, TG).

Published:

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

(54) Title: TRANSDERMAL DELIVERY SYSTEM INCLUDING AN INTERFACE MEDIATOR

(57) Abstract: Transdermal therapeutic system for the transdermal administration of a systemically active agent comprising a self-adhesive layer structure, comprising A) a backing layer, and B) a dried biphasic layer, the dried biphasic layer having a) an outer phase having a composition comprising 75% to 100% of a polymer or polymer mixture, and b) an inner phase having a composition comprising at least one active agent, wherein the inner phase forms dispersed deposits in the outer phase, and c) 0.1 % to 3.5% of an interface mediator with a kinematic viscosity of from 10 cSt to 100 000 cSt at 25°C, and and C) optionally an additional skin contact layer.



WO 2015/177212 A1

- 1 -

5 **TRANSDERMAL DELIVERY SYSTEM INCLUDING AN**
 INTERFACE MEDIATOR

TECHNICAL FIELD OF THE INVENTION

10 [001] The present invention relates to a transdermal therapeutic system (TTS) for the transdermal administration of a systemically active agent, processes of manufacture, and uses thereof.

BACKGROUND OF THE INVENTION

15 [002] Transdermal therapeutic systems (TTS) for the transdermal administration of systemically active agents have several advantages over other application systems. In comparison to oral dosage forms, for example, fewer side effects are observed. Furthermore, constant drug levels in the patient can be achieved more easily. Due to the simple mode of application more convenience is accomplished for the patient. In particular, longer administration periods on the skin of human patients are beneficial for the compliance and for constant therapeutic drug levels. As a consequence of longer administration periods, a higher loading of the active agent is required in order to be able to provide therapeutically effective amounts of the active agent over the whole administration period. However, an increase of the active agent loading seems limited, in particular in solvent-based transdermal therapeutic systems. In solvent-based biphasic systems which comprise the active agent in a separate phase dispersed in a matrix, an increased active agent concentration in the TTS matrix may result e.g. in crystallization of the active agent during storage which jeopardizes the therapeutic success due to insufficient permeation rates of the remaining active agent available for skin absorption. Furthermore, an increased concentration of active agent-containing phase in the biphasic system may lead to coalescence of the dispersed phase. In this context, it was found that the size of the dispersed phase including the active agent has an influence on the drug release. A TTS manufactured

20

25

30

- 2 -

5 with large active agent-containing droplets in its biphasic layer may lead to e.g. a more fluctuating drug release or to dose dumping. Smaller droplets provide reliable permeation rates with minimum fluctuation. It is thus believed that by reducing the droplet size of the active-agent containing phase of a biphasic system, a stabilization of the system is achieved, in particular for biphasic systems with an increased drug
10 loading.

[003] So far, a reduction of the droplet sizes in a solvent-based biphasic system is solely achieved by applying mechanical force to a biphasic coating mixture.

Therefore, there remains room for improvement of such transdermal therapeutic systems, and in processes for making them.

15

OBJECTS AND SUMMARY OF THE INVENTION

[004] It is an object of the present invention to provide a transdermal therapeutic system for the transdermal administration of a systemically active agent which
20 provides long-term stability.

[005] It is an object of the present invention to provide a transdermal therapeutic system for the transdermal administration of a systemically active agent providing a continuous administration of therapeutically effective amounts of the active agent for 1 to 7 days during an administration period to the skin of the patient of 1 to 7 days
25 (e.g. 7 days).

[006] It is an object of the present invention to provide a transdermal therapeutic system for the transdermal administration of a systemically active agent providing a reduced fluctuation of the therapeutically effective permeation rate of the active agent for 1 to 7 days during an administration period to the skin of the patient of 1 to
30 7 days (e.g. 7 days).

[007] It is a further object of the present invention to provide a transdermal therapeutic system for the transdermal administration of a systemically active agent which complies with the needs of a convenient application in view of skin tolerance, size and thickness and can easily and cost-effectively be prepared.

- 3 -

5 **[008]** It is also an object of the present invention to provide a method of manufacture of an active agent-containing dried biphasic layer with a small maximum droplet size.

[009] These objects and others are accomplished by the present invention, which according to one aspect relates to a transdermal therapeutic system for the
10 transdermal administration of a systemically active agent comprising a self-adhesive layer structure,
 comprising

 A) a backing layer, and

 B) a dried biphasic layer, the dried biphasic layer having

15 a) an outer phase having a composition comprising 75% to 100% of a polymer or polymer mixture, and

 b) an inner phase having a composition comprising at least one active agent, wherein the inner phase forms dispersed deposits in the outer phase,
 and

20 c) 0.1% to 3.5% of an interface mediator with a kinematic viscosity of from 10 cSt to 100 000 cSt at 25°C,

 and

 C) optionally an additional skin contact layer,

 in particular for use in a method of treatment, wherein therapeutically effective
25 amounts of the systemically active agent are provided for 1 to 7 days by said transdermal therapeutic system during an administration period of 1 to 7 days.

[0010] According to another specific aspect the invention relates to a transdermal therapeutic system for the transdermal administration of rotigotine containing
 2.0 mg/cm² to 4.0 mg/cm² rotigotine base in a self-adhesive layer structure,
30 comprising

 A) a backing layer, and

 B) a dried biphasic layer, the dried biphasic layer having

 a) an outer phase having a composition comprising 75% to 100% of pressure-sensitive adhesive polysiloxane(s), and

- 4 -

- 5 b) an inner phase having a composition comprising rotigotine,
 wherein the inner phase forms dispersed deposits in the outer phase,
 and
 c) 0.1% to 3.5% of a silicone oil with a kinematic viscosity of from 10 cSt
 to 100 000 cSt at 25°C, and
- 10 and
- C) optionally an additional skin contact layer,
 in particular for use in a method of treatment, wherein therapeutically effective
 amounts of the rotigotine base are provided for 1 to 7 days by said transdermal
 therapeutic system during an administration period of 1 to 7 days, in particular for
- 15 use in a method of treating patients suffering from Parkinson's disease, Parkinson's
 plus syndrome, depression, anxiety, AHDS, fibromyalgia, the restless-legs syndrome
 and for use in the treatment or prevention of dopaminergic neuron loss or the
 treatment or prevention of cognitive disorders, dementia or lewy body disease.
- [0011] According to another aspect the invention relates to a transdermal
- 20 therapeutic
 system for the transdermal administration of rotigotine containing 2.0 mg/cm² to
 3.0 mg/cm² rotigotine base in a self-adhesive layer structure, comprising
- A) a backing layer, and
- B) a dried biphasic layer, the dried biphasic layer having
- 25 a) an outer phase having a composition comprising 75% to 100% of
 pressure-sensitive adhesive polysiloxane(s), and
- b) an inner phase having a composition comprising rotigotine,
 wherein the inner phase forms dispersed deposits in the outer phase,
 and
- 30 c) 0.1% to 3.5% of a silicone oil with a kinematic viscosity of from 10 cSt
 to 100 000 cSt at 25°C, and
- and
- C) optionally an additional skin contact layer,

- 5 -

5 in particular for use in a method of treatment, wherein therapeutically effective amounts of rotigotine base are provided for 1 to 7 days by said transdermal therapeutic system during an administration period of 1 to 7 days, in particular for use in a method of treating patients suffering from Parkinson's disease, Parkinson's plus syndrome, depression, anxiety, AHDS, fibromyalgia, the
10 restless-legs syndrome and for use in the treatment or prevention of dopaminergic neuron loss or the treatment or prevention of cognitive disorders, dementia or lewy body disease.

[0012] According to one specific aspect the invention relates to a method of manufacture of an active agent-containing dried biphasic layer comprising the steps
15 of:

- (1) preparing a biphasic coating mixture having an inner phase dispersed in an outer phase:
 - (a) the inner phase comprising the active agent,
 - (b) the outer phase comprising a polymer or polymer mixture,
20 wherein the biphasic coating mixture comprises solvents in sufficient amounts to provide for a viscosity of the coating mixture suitable for coating,
- (2) adding to said biphasic coating mixture an interface mediator, and mixing said coating mixture to provide a suitable dispersion of the inner phase in the outer phase,
- 25 (3) coating said coating mixture on a film to provide a layer of said solvent-containing mixture,
- (4) evaporating said solvents to provide a dried layer with a coating weight to provide said active agent-containing dried biphasic layer with the desired area weight,
- 30 (5) optionally laminating two or more of said dried layers to provide said active agent-containing dried biphasic layer with the desired area weight.

[0013] According to a certain embodiment, the invention relates to a dried biphasic layer obtainable by the method of manufacture described in the previous paragraph.

- 6 -

5 **[0014]** According to another specific aspect the invention relates to a method of manufacture of a transdermal therapeutic system comprising an active agent-containing dried biphasic layer for the transdermal administration of a systemically active agent in accordance with the invention, comprising the steps of:

- 10 (1) preparing a biphasic coating mixture having an inner phase dispersed in an outer phase:
- (a) the inner phase comprising the active agent,
- (b) the outer phase comprising a polymer or polymer mixture,
- wherein the biphasic coating mixture comprises solvents in sufficient amounts to provide for a viscosity of the coating mixture suitable for coating,
- 15 (2) adding to said biphasic coating mixture an interface mediator, and mixing said coating mixture to provide a suitable dispersion of the inner phase in the outer phase,
- (3) coating said coating mixture on a film to provide a layer of said solvent-containing mixture,
- 20 (4) evaporating said solvents to provide a dried layer with a coating weight to provide an active agent-containing dried biphasic layer with the desired area weight,
- (5) optionally laminating two or more of said dried layers to provide an active agent-containing dried biphasic layer with the desired area weight,
- 25 (6) laminating said active agent-containing dried biphasic layer to a backing layer,
- (7) optionally laminating said active agent-containing biphasic layer to an additional skin contact layer,

 preferably wherein for the production of the dried biphasic layer and optionally the additional skin contact layer a pressure-sensitive adhesive mixture of pressure-sensitive adhesive polysiloxanes in heptanes or ethyl acetate is used.

[0015] According to one aspect the invention relates to the use of a silicone oil as interface mediator in a transdermal therapeutic system with an active agent-containing dried biphasic layer having a hydrophilic inner phase and a hydrophobic

- 7 -

5 outer phase for controlling the maximum droplet size of the inner phase of said dried biphasic layer, in particular in a transdermal therapeutic system wherein the active agent is rotigotine base and is present in the dried biphasic layer in an amount of 16% to 26% of the dried biphasic layer.

10 [0016] According to a further aspect the invention relates to the use of an interface mediator to reduce the maximum droplet size of the inner phase in form of dispersed deposits in the outer phase of a dried biphasic layer in a transdermal therapeutic system as described above.

15 [0017] Within the meaning of this invention, the term “transdermal therapeutic system” (or TTS) refers to a system by which the active agent (e.g. rotigotine) is administered systemically and in particular refers to the entire individual unit that is applied to the skin of a patient, and which comprises a therapeutically effective amount of a systemically active agent in a self-adhesive layer structure and optionally an additional larger active-free self-adhesive layer structure (overlying adhesive) on top of the active agent-containing self-adhesive layer structure. During
20 storage, such a TTS is normally located on a detachable protective layer from which it is removed immediately before application to the surface of the patient’s skin. A TTS protected this way may be stored in a blister pack or a side sealed bag.

25 [0018] Within the meaning of this invention, the terms “active”, “active agent” are used synonymously. Unless otherwise indicated the amounts of active agent in the TTS relate to the amount of active agent before administration of the TTS. The amounts of active agent in the TTS after administration are referred to as residual amounts.

30 [0019] Within the meaning of this invention, the terms “active agent-containing self-adhesive layer structure” and “comprising the active agent in a self-adhesive layer structure” have the same meaning and refer to the active agent-containing structure providing the area of release of the active agent.

[0020] Within the meaning of this invention, the term “biphasic” refers to a system of two distinguishable, e.g., visually distinguishable, areas, an outer phase and an inner phase, wherein the inner phase is in form of dispersed deposits within the outer

- 8 -

5 phase. Such deposits are e.g., solid solution droplets. Deposits that are visually distinguishable may be identified by use of a microscope.

[0021] Within the meaning of this invention, the term “dried biphasic layer” refers to a biphasic layer obtained from a solvent-containing coating mixture after coating on a film and evaporating the solvents (solvent-based layer) and is to be
10 distinguished from a biphasic layer obtained from a hot-melt coating mixture (hot-melt-based layer).

[0022] Within the meaning of this invention, the term “polymer mixture” includes mixtures of polymers comprising the same monomer(s) but providing different grades. Polymers of different grades are polymers which are distinguishable by
15 different properties (e.g. the viscosity) and are usually commercially available under different trademarks. E.g., the commercially available products Kollidon® 90 and Kollidon® 30 provide individual grades of polyvinylpyrrolidone, a polymer of the monomer vinylpyrrolidone; the commercially available products Dow Corning® BIO-PSA 7-4201 and BIO-PSA 7-4301 provide individual grades of pressure-
20 sensitive adhesive polysiloxane.

[0023] Within the meaning of this invention, the term “interface mediator” refers to a substance that promotes a maximum separation of an inner phase in an outer phase to allow the inner phase to be uniformly dispersed without exhibiting surface activity. The interface mediator enhances the compatibility of the two separate
25 phases by filling cavities at the interface between the two phases. As a result the inner phase forms dispersed deposits with a minimum size which provide an increase of the dynamic viscosity of the biphasic system. The increased dynamic viscosity further provides a reduced attempt of the inner phase to coalesce and thereby stabilizes the biphasic system.

30 [0024] Within the meaning of this invention, the term “silicone oil” refers to any liquid polymerized siloxane with organic side chains.

[0025] Within the meaning of this invention, the term “solid solution” refers to a mixture of active agent (e.g. rotigotine) and the polymer mixture to provide a single homogeneous phase in form of a solid-state solution.

- 9 -

5 **[0026]** Within the meaning of this invention, the term “pressure-sensitive adhesive” refers to a composition that in particular adheres with finger pressure, is permanently tacky, exerts a strong holding force and should be removable from smooth surface without leaving a residue. The pressure-sensitive adhesive properties of the pressure-sensitive adhesive composition are based on suitable tackifiers, or on a polymer or
10 polymer mixture which is a/are pressure-sensitive adhesive polymer(s), or on both. Pressure-sensitive adhesive polymer(s) are available in solid form or in a mixture with a suitable solvent (e.g. heptane or ethyl acetate). According to a certain embodiment, the polymer or polymer mixture is a/are pressure-sensitive adhesive polysiloxane(s). Examples of useful pressure-sensitive adhesive polysiloxanes which
15 are commercially available include the standard BIO-PSA series (7-4400, 7-4500 and 7-4600 series), the amine compatible (endcapped) BIO-PSA series (7-4100, 7-4200 and 7-4300 series), and the Soft Skin Adhesives series (7-9800) manufactured by Dow Corning. Preferred pressure-sensitive polysiloxanes are heptane- and ethyl acetate-solvated pressure-sensitive adhesive polysiloxanes including BIO-PSA
20 7-4201, BIO-PSA 7-4301, BIO-PSA 7-4202, and BIO-PSA 7-4302.

[0027] Within the meaning of this invention, the term “pressure-sensitive adhesive mixture” refers to a pressure-sensitive adhesive polymer or pressure-sensitive adhesive polymers at least in mixture with a solvent (e.g. heptane or ethyl acetate).

[0028] Within the meaning of this invention, the term “polyvinylpyrrolidone”
25 refers to polyvinylpyrrolidone which is soluble with more than 10% in at least ethanol, preferably also in water, diethylene glycol, methanol, n-propanol, 2-propanol, n-butanol, chloroform, methylene chloride, 2-pyrrolidone, macrogol 400, 1,2 propylene glycol, 1,4 butanediol, glycerol, triethanolamine, propionic acid and acetic acid. Examples of polyvinylpyrrolidones which are commercially available
30 include Kollidon® 12 PF, Kollidon® 17 PF, Kollidon® 25, Kollidon® 30 and Kollidon® 90 F supplied by BASF. The different grades of Kollidon® are defined in terms of the K-Value reflecting the average molecular weight of the polyvinylpyrrolidone grades. Kollidon® 12 PF is characterized by a K-Value range of 10.2 to 13.8, corresponding to a nominal K-Value of 12. Kollidon® 17 PF is

- 10 -

5 characterized by a K-Value range of 15.3 to 18.4, corresponding to a nominal K-Value of 17. Kollidon® 25 is characterized by a K-Value range of 22.5 to 27.0, corresponding to a nominal K-Value of 25, Kollidon® 30 is characterized by a K-Value range of 27.0 to 32.4, corresponding to a nominal K-Value of 30. Kollidon® 90 F is characterized by a K-Value range of 81.0 to 97.2, corresponding to a nominal
10 K-Value of 90. A preferred Kollidon® grade is Kollidon® 90 F.

[0029] Within the meaning of this invention, the term “K-Value” refers to a value calculated from the relative viscosity of polyvinylpyrrolidone in water according to the European Pharmacopoeia (Ph.Eur.) and USP monographs for “Povidone”.

[0030] Within the meaning of this invention, the term “skin contact layer” refers to
15 the part of the TTS which is an additional layer (in addition to the active agent-containing dried biphasic layer) and is in direct contact with the skin of the patient during administration. The sizes of an additional skin contact layer and the active agent-containing self-adhesive layer structure are co-extensive and correspond to the area of release.

20 [0031] Within the meaning of this invention, the term “additional larger active agent-free self-adhesive layer structure” (overlying adhesive) refers to a self-adhesive layer structure that is free of active agent and larger in area than the active agent-containing structure and providing additional area adhering to the skin, but no area of release of the active agent, and enhancing thereby the overall adhesive
25 properties of the TTS.

[0032] Within the meaning of this invention, the term “area weight” refers to the dry weight of an individual layer or the sum of individual layers, except backing layer and release liner, and is provided in g/m^2 . The area weight may be the coating weight of a layer, or the sum of the coating weights of individual layers. Amounts of
30 active agent or polymer in a layer provided in mg/cm^2 or % refer to or are based on the area weight of the layer.

[0033] If not indicated otherwise “%” refers to weight-%.

5

BRIEF DESCRIPTION OF THE DRAWINGS

- [0034] Fig. 1 depicts the rotigotine-containing biphasic coating mixture of Example 1A.
- [0035] Fig. 2 depicts the rotigotine-containing biphasic coating mixture of Example 1B with 1% silicone oil (Dow Corning® Medical Fluid 100 cSt).
- 10 [0036] Fig. 3 depicts the rotigotine-containing biphasic coating mixture of Example 1C with 1% silicone oil (Dow Corning® Medical Fluid 350 cSt).
- [0037] Fig. 4 depicts the rotigotine-containing biphasic coating mixture of Example 1D with 1% silicone oil (Dow Corning® Medical Fluid 1000 cSt).
- 15 [0038] Fig. 5 depicts the rotigotine-containing biphasic coating mixture of Example 1E with 1% silicone oil (Dow Corning® Medical Fluid 12500 cSt).
- [0039] Fig. 6 depicts the rotigotine-containing biphasic coating mixture of Example 2A.
- [0040] Fig. 7 depicts the rotigotine-containing biphasic coating mixture of Example 2B with 1% silicone oil (Dow Corning® Medical Fluid 12500 cSt).
- 20

DETAILED DESCRIPTION**TTS STRUCTURE**

25

[0041] According to a certain embodiment of the invention the transdermal therapeutic system for the transdermal administration of a systemically active agent comprising a self-adhesive layer structure, comprising

30

- A) a backing layer, and
- B) a dried biphasic layer, the dried biphasic layer having
 - a) an outer phase having a composition comprising 75% to 100% a polymer or polymer mixture, and
 - b) an inner phase having a composition comprising at least one active agent,

- 12 -

5 wherein the inner phase forms dispersed deposits in the outer phase,
 and
 c) 0.1% to 3.5% of an interface mediator with a kinematic viscosity of from
 10 cSt to 100 000 cSt at 25°C,

 and

10 C) optionally an additional skin contact layer.

[0042] According to certain embodiments of the invention, the TTS may comprise
in addition to the active agent-containing self-adhesive layer structure attached
thereto a larger active agent-free self-adhesive layer structure, e.g., an overlaying
adhesive, for enhancing the adhesive properties of the overall transdermal therapeutic
15 system. Said active agent-free self-adhesive layer structure comprises also a backing
layer. In certain embodiments, this additional layer is beige colored. The area of said
second active agent-free self-adhesive layer structure adds to the overall size of the
TTS but does not add to the area of release. The pressure-sensitive adhesive
compositions of the active agent-containing and the active agent-free self-adhesive
20 layer structures may be the same or different. E.g., the active agent-free pressure-
sensitive adhesive composition may comprise a pressure-sensitive adhesive polymer
or polymer mixture selected from the group of polysiloxanes or polyisobutylenes.

[0043] A TTS according to the invention is normally located on a detachable
protective layer (release liner) from which it is removed immediately before
25 application to the surface of the patient's skin. A TTS protected this way may be
stored in a blister pack or a side sealed bag.

ACTIVE AGENT-CONTAINING SELF-ADHESIVE LAYER STRUCTURE

30 [0044] In accordance with the invention, the active agent-containing self-adhesive
layer structure comprises a backing layer, an active agent-containing dried biphasic
layer and optionally an additional skin contact layer.

[0045] The size of the active agent-containing self-adhesive layer structure
providing the area of release ranges from 1 cm² to 60 cm², and may be about 5 cm²,

- 13 -

5 about 10 cm², about 20 cm², about 30 cm², about 40 cm², or about 50 cm². The amount of rotigotine provided by the TTS per hour (mg/h) is proportional to the size of the area of release of a TTS and may be used to distinguish TTSs by the dosage strength.

[0046] The active agent-containing self-adhesive layer structure contains a
10 therapeutically effective amount of a systemically active agent. In a preferred embodiment the systemically active agent is an amine functional drug, which has an octanol/water partitioning coefficient $\log P \sim 2.8$ at pH 7.4. In another preferred embodiment the amine functional drug has a pKa of 7.4 to 8.4. In an especially preferred embodiment the amine functional drug has an octanol/water partitioning
15 coefficient $\log P \sim 2.8$ at pH 7.4 and a pKa of 7.4 to 8.4. The pKa value can be measured by standard methods. A particularly preferred method is potentiometric titration of aqueous drug solutions (without addition of organic cosolvents) at room temperature. The octanol/water partitioning coefficients (octan-1-ol/water
20 partitioning coefficients) are determined at pH 7.4, 37°C and an ionic strength of 0.15 in an appropriate buffer solution according to the method described by E. Miyamoto et al. (E. Miyamoto et al. "Physico-chemical Properties of Oxybutynin" Analyst (1994), 119, 1489-1492).

[0047] Particularly preferred amine functional drugs are dopamine D2 agonists, which are useful for example in the treatment of Parkinson's disease. Especially
25 preferred dopamine D2 receptor agonists are aminotetraline compounds, such as 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol (INN: rotigotine).

[0048] Other examples for particularly preferred amine functional drugs are N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-propanamide (INN: fentanyl) which is
30 useful in the treatment of pain and anticholinergic drugs exerting an antispasmodic effect on smooth muscles and inhibiting the muscarinic action of acetylcholin on smooth muscles. Examples of such anticholinergic drugs which are useful in the present invention are 4-diethylamino-2-butynyl phenylcyclohexylglycolate (INN: oxybutynine) and 2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)

- 14 -

5 phenyl isobutyrate (INN: fesoterodine). Oxybutynine and fesoterodine are useful in the treatment of urinary incontinence. It will be understood by a person skilled in the art that the amine functional drugs, such as rotigotine, fentanyl, oxybutynine and fesoterodine, may all exist in various isomeric forms. It has to be understood that in this case the amine functional drug may be any single isomer or a mixture of
10 different isomers. If the amine functional group contains asymmetric carbon atoms, any single enantiomer or a mixture of enantiomers may be used. Rotigotine, fentanyl oxybutynine and fesoterodine all contain one asymmetric carbon atom. Hence, the S- or R-enantiomer or the racemate or any other enantiomer mixture of these compounds may be used as the amine functional drug.

15 [0049] According to certain embodiments of the invention, the systemically active agent is selected from the group consisting of rotigotine, fentanyl, oxybutynine, and fesoterodine, rotigotine is preferred.

[0050] According to certain embodiments of the invention, the active agent-containing self-adhesive layer structure may contain a therapeutically effective
20 amount of rotigotine from 0.1 mg/cm² to 10.0 mg/cm², in particular from 0.1 mg/cm² to 5.0 mg/cm², or from 0.3 mg/cm² to 3.0 mg/cm².

[0051] Rotigotine exists in two different polymorphic states, Polymorphic Form I and Polymorphic Form II, which can be differentiated by their melting point, infrared (IR) spectroscopy, solid state nuclear magnetic resonance (SSNMR) or Raman
25 spectroscopy as well as differential scanning calorimetry (DSC) and X-ray powder diffraction (XRD). The different physicochemical characteristics of the two polymorphic forms of rotigotine are for example described in WO 2009/068520. For the TTS according to one aspect of the invention, Polymorphic Form II is preferred.

30

DRIED BIPHASIC LAYER

[0052] The dried biphasic layer contains an outer and an inner phase. According to certain embodiments of the invention, the outer phase is hydrophobic and the inner phase is hydrophilic.

- 15 -

- 5 **[0053]** The active agent-containing biphasic layer may be coated at any area weight, but is preferably coated at an area weight of about 30 g/m² to about 400 g/m², or of about 30 g/m² to about 200 g/m², or of about 100 g/m² to about 200 g/m².
- [0054]** In a specific embodiment, the active agent-containing dried biphasic layer contains the active agent (e.g. rotigotine) in an amount of 1% to 30%, 10% to 26%,
10 or 16% to 30%, or 16% to 26% of the dried biphasic layer.
- [0055]** According to a certain embodiment, the dried biphasic layer has an area weight of about 100 g/m² to about 200 g/m² and the active agent (e.g. rotigotine) is present in an amount of 16% to 26% of the dried biphasic layer.
- [0056]** The dried biphasic layer is obtained from a solvent-containing biphasic
15 coating mixture after coating on a film and evaporating the solvents. The obtained layer (solvent-based layer) is to be distinguished from a biphasic layer obtained from a hot-melt coating mixture (hot melt-based layer). A biphasic layer obtained from a hot-melt coating mixture is characterized by different physico-chemical properties.
- [0057]** According to a certain embodiment of the invention, the active agent-
20 containing dried biphasic layer is in direct contact with the skin.
- [0058]** According to a certain other embodiment of the invention, the active agent-containing self-adhesive layer structure comprises an additional skin contact layer which is also in the form of a dried biphasic layer and may be manufactured containing the active agent (e.g. rotigotine).
- 25 **[0059]** The dried biphasic layer of the TTS according to the invention may further comprise one or more anti-oxidants. Suitable anti-oxidants are sodium metabisulfite, ascorbyl palmitate, tocopherol and esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate, preferably sodium metabisulfite, ascorbyl palmitate and tocopherol. The anti-oxidants may be
30 conveniently present in an amount of from about 0.001% to about 0.5% of the dried biphasic layer.
- [0060]** The dried biphasic layer according to the invention may further comprise in addition to the above mentioned ingredients other various excipients or additives, for example from the group of solubilizers, fillers, tackifiers, substances which influence

- 16 -

5 the barrier properties of the stratum corneum in the sense of increasing the active agent permeability, pH regulators, and preservatives. Suitable permeation enhancers may be selected from the group of fatty alcohols, fatty acids, fatty acid esters, fatty acid amides, glycerol or its fatty acid esters, N-methylpyrrolidone, terpenes such as limonene, [alpha]-pinene, [alpha]-terpineol, carvone, carveol, limonene oxide, pinene
10 oxide, 1,8-eucalyptol and most preferably ascorbyl palmitate. In a preferred embodiment, the TTS according to the invention does not contain a penetration enhancer.

OUTER PHASE

15

[0061] In certain embodiments of the present invention, the outer phase of the active agent-containing dried biphasic layer has a composition comprising 75% to 100% of a polymer or polymer mixture. The polymer or polymer mixture in the outer phase may be (a) hydrophobic polymer(s).

20 [0062] In a certain embodiment of the invention, the composition of said outer phase is a pressure-sensitive adhesive composition.

[0063] In certain other embodiments of the invention, the polymer or polymer mixture in the outer phase is a/are pressure-sensitive adhesive polymer(s).

[0064] Pressure-sensitive adhesive polymers being suitable for solvent-containing
25 coating mixtures exhibit a dynamic viscosity of above 150 Pa·s at a temperature of 160 °C.

[0065] In certain embodiments of the invention, the polymer or polymer mixture in the outer phase is a/are pressure-sensitive adhesive polymer(s) selected from the group of polysiloxanes, or polyisobutylenes, preferably the polymer or polymer
30 mixture in the outer phase is a/are pressure-sensitive adhesive polysiloxane(s). Pressure-sensitive adhesive polysiloxanes provide for suitable tack for quick bonding to various skin types, including wet skin, suitable adhesive and cohesive qualities, long lasting adhesion to the skin of up to 7 days, a high degree of flexibility, a permeability to moisture, and compatibility to many actives and film-substrates. It is

- 17 -

- 5 possible to provide them with sufficient amine resistance and therefore enhanced stability in the presence of amines. Such pressure-sensitive adhesive polymers are based on a resin-in-polymer concept wherein, by condensation reaction of silanol end blocked polydimethylsiloxane with a silica resin, a polysiloxane is prepared which for amine stability the residual silanol functionality is additionally capped with
- 10 trimethylsiloxy groups. The dimethiconol content contributes to the viscous component of the visco-elastic behavior, and impacts the wetting and the spreadability properties of the adhesive. The resin acts as a tackifying and reinforcing agent, and participates in the elastic component. The correct balance between dimethiconol and resin provides for the correct adhesive properties.
- 15 **[0066]** The adhesive strength of the pressure-sensitive polysiloxanes may be sufficient for the desired skin contact. In certain embodiments of the invention a plasticizer or a tackifying agent is incorporated into the formulation to improve the adhesive characteristics of the biphasic layer. It may be advantageous in an individual case to improve the tack by adding small amounts of tackifiers.
- 20 **[0067]** In certain embodiments of the invention, the polysiloxane(s) is/are amine-resistant. In further embodiments of the invention the polysiloxane(s) is/are amine-resistant being a product of the condensation reaction of silanol endblocked polydimethylsiloxane with a silica resin and the residual silanol functionality being capped with trimethylsiloxy groups.
- 25 **[0068]** Preferred pressure-sensitive adhesive polymers are supplied and used in solvents like heptane, ethyl acetate or other volatile silicone fluids. For the present invention pressure-sensitive adhesive mixtures of pressure-sensitive adhesive polysiloxane(s) in heptane or ethyl acetate are preferred. The solids content is usually between 60% and 80 %.
- 30 **[0069]** The preferred pressure-sensitive adhesive mixtures of pressure-sensitive adhesive polysiloxane(s) in heptane in accordance with the invention are characterized by a solution viscosity at 25°C and 60 % solids content in heptane of more than 150 mPa s, or from about 200 mPa s to about 700 mPa s, in particular from about 350 mPa s to about 600 mPa s, more preferred from about 480 mPa s to

- 18 -

5 about 550 mPa s, or most preferred of about 500 mPa s or alternatively from about 400 mPa s to about 480 mPa s, or most preferred of about 450 mPa s. These may also be characterized by a complex viscosity at 0.01 rad/s at 30°C of less than about 1×10^9 Poise or from about 1×10^5 to about 9×10^8 Poise, or more preferred from about 1×10^5 to about 1×10^7 Poise, or most preferred about 5×10^6 Poise or alternatively
10 more preferred from about 2×10^7 to about 9×10^8 Poise, or most preferred about 1×10^8 Poise.

[0070] The preferred pressure-sensitive adhesive mixtures of pressure-sensitive adhesive polysiloxane(s) in ethyl acetate in accordance with the invention are characterized by a solution viscosity at 25°C and 60 % solids content in ethyl acetate
15 of more than 350 mPa s, or from about 400 mPa s to about 1500 mPa s, in particular from about 600 mPa s to about 1300 mPa s, more preferred from about 1100 mPa s to about 1300 mPa s, or most preferred of about 1200 mPa s or alternatively from about 700 mPa s to about 900 mPa s, or most preferred of about 800 mPa s. These may also be characterized by a complex viscosity at 0.01 rad/s at 30°C of less than
20 about 1×10^9 Poise or from about 1×10^5 to about 9×10^8 Poise, or more preferred from about 1×10^5 to about 1×10^7 Poise, or most preferred about 5×10^6 Poise or alternatively more preferred from about 2×10^7 to about 9×10^8 Poise, or most preferred about 1×10^8 Poise.

[0071] According to a certain embodiment, a pressure-sensitive adhesive mixture
25 of a pressure-sensitive adhesive polysiloxane in heptane characterized by a solution viscosity at 25°C and about 60% solids content in heptane of 500 mPa s and a pressure-sensitive adhesive polysiloxane in heptane characterized by a solution viscosity at 25°C and about 60% solids content in heptane of 450 mPa s is preferred.

[0072] According to a certain other embodiment, a pressure-sensitive adhesive
30 mixture of a pressure-sensitive adhesive polysiloxane in ethyl acetate characterized by a solution viscosity at 25°C and about 60% solids content in ethyl acetate of 1200 mPa s and a pressure-sensitive adhesive polysiloxane in ethyl acetate characterized by a solution viscosity at 25°C and about 60% solids content in ethyl acetate of 800 mPa s is preferred.

- 19 -

5 **[0073]** Suitable pressure-sensitive adhesive polysiloxanes may be obtained from Dow Corning® BIO-PSA Standard Silicone Adhesives. Preferred pressure-sensitive adhesive mixtures of pressure-sensitive adhesive polysiloxane(s) in heptane are the BIO-PSA 7-4301 and BIO-PSA 7-4201 Silicone Adhesives, and in ethyl acetate the BIO-PSA 7-4302 and BIO-PSA 7-4202 Silicone Adhesives. According to certain
10 embodiments of the invention, a mixture of BIO-PSA 7-4301 and BIO-PSA 7-4201 is preferred and according to certain other embodiments a mixture of BIO-PSA 7-4302 and BIO-PSA 7-4202 is preferred. According to certain embodiments the preferred mixtures provide a 50:50 ratio, according to certain other embodiments the mixtures provide a 60:40, or 70:30 ratio. A higher amount of BIO-PSA 7-4301, or
15 BIO-PSA 7-4302, respectively, is preferred for a biphasic layer which provides the skin contact layer. According to a certain embodiment of the invention, the TTS comprises a mixture of BIO-PSA 7-4301 and BIO-PSA 7-4201 in a ratio of 30:70 in the outer phase of the rotigotine-containing biphasic layer and a mixture of BIO-PSA 7-4301 and BIO-PSA 7-4201 in a ratio of 70:30 in the outer phase of the additional
20 skin contact layer.

[0074] BIO-PSA 7-4301 has a solution viscosity at 25°C and about 60% solids content in heptane of 500 mPa s and a complex viscosity at 0.01 rad/s at 30°C of 5×10^6 Poise. BIO-PSA 7-4201 has a solution viscosity at 25°C and about 60% solids content in heptane of 450 mPa s and a complex viscosity at 0.01 rad/s at 30°C of
25 1×10^8 Poise. BIO-PSA 7-4302 has a solution viscosity at 25°C and about 60% solids content in ethyl acetate of 1200 mPa s and a complex viscosity at 0.01 rad/s at 30°C of 5×10^6 Poise. BIO-PSA 7-4202 has a solution viscosity at 25°C and about 60% solids content in heptane of 800 mPa s and a complex viscosity at 0.01 rad/s at 30°C of 1×10^8 Poise.

30

5

INNER PHASE

[0075] According to the invention, the inner phase comprises the active agent. According to one aspect of the invention, the inner phase also comprises a hydrophilic agent forming a solid solution with the active agent.

10 [0076] In order to form a solid solution with the active agent a hydrophilic agent may be present in the inner phase. In a certain embodiment of the present invention this hydrophilic agent is a hydrophilic polymer or polymer mixture. The hydrophilic polymer(s) is/are selected from the group consisting of

- polyvinylpyrrolidones having a K-Value of from 10 to 200,
- 15 - copolymers of vinyl caprolactam, vinylacetate and ethylene glycol,
- copolymers of vinylpyrrolidone and vinylacetate,
- copolymers of ethylene and vinylacetate,
- polyethylene glycols,
- polypropylene glycols,
- 20 - acrylic polymers,
- modified celluloses.

[0077] In a further embodiment of the present invention, the hydrophilic polymer(s) is/are selected from the group consisting of:

- polyvinylpyrrolidones having a K-Value of from 10 to 200,
- 25 - copolymers of vinyl caprolactam, vinylacetate and ethylene glycol,
- copolymers of vinylpyrrolidone and vinylacetate,
- copolymers of ethylene and vinylacetate,
- polyethylene glycols,
- polypropylene glycols,
- 30 - copolymers of dimethylaminoethyl methacrylate, butyl methacrylate and methyl methacrylate,
- copolymers of methacrylic acid and methyl methacrylate,
- hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate.

- 21 -

5 **[0078]** In accordance with a certain specific embodiment of the invention the polymer in the inner phase comprises polyvinylpyrrolidone(s), in particular having a K-Value of from 10 to 200, or 90.

[0079] According to the invention, the inner phase forms dispersed deposits in the outer phase of the biphasic layer. According to a specific embodiment of the
10 invention, the maximum droplet size of the dispersed deposits is from 5 μm to 25 μm .

INTERFACE MEDIATOR

15 **[0080]** According to the invention the interface mediator is present in the biphasic layer in an amount of 0.1% to 3.5%. Useful concentrations of the interface mediator are in particular 0.1% to 3%, or 0.1% to 2%, or 0.1% to 1.5%.

[0081] According to the present invention the interface mediator has a kinematic viscosity of from about 10 cSt to about 100 000 cSt at 25°C, preferably from about
20 100 cSt to about 100 000 cSt, or about 200 cSt to about 100 000 cSt, or about 500 cSt to about 100 000 cSt, or about 800 cSt to about 100 000 cSt, or about 1 000 cSt to about 100 000 cSt, or about 10 000 cSt to about 100 000 cSt at 25 °C, or a kinematic viscosity of from about 100 cSt to about 30 000 cSt, or about 200 cSt to about 30 000 cSt, or about 500 cSt to about 30 000 cSt, or about 800 cSt to about
25 30 000 cSt, or about 1 000 cSt to about 30 000 cSt, or about 10 000 cSt to about 30 000 cSt at 25 °C, or a kinematic viscosity of from about 100 cSt to about 15 000 cSt, 200 cSt to about 15 000 cSt, or about 500 cSt to about 15 000 cSt, or about 800 cSt to about 15 000 cSt, or about 1 000 cSt to about 15 000 cSt, or about 10 000 cSt to about 15 000 cSt at 25 °C.

30 **[0082]** The methods of measuring the kinematic viscosity are known, follow standardized procedures and provide interchangeable results.

[0083] As known for the skilled person, the viscosimeters are calibrated with certified viscosity reference standards. Certified viscosity reference standards are certified by a laboratory that has been shown to meet the requirements of ISO 17025

- 5 (initially issued by the International Organization for Standardization in 1999,
reviewed in 2005) by independent assessment. Viscosity standards shall be traceable
to master viscometer procedures described in standard method ASTM D2162
(originally approved in 1963, ASTM D2162-13 revised in 2013), the internationally
10 recognized method for viscosity reference standards under ISO/IEC 17025
guidelines.
- [0084] The standard test method for the determination of the kinematic viscosity is
ASTM D445 (originally approved in 1937, ASTM D445-12 revised in 2012) which
corresponds to ISO 3104. The range of kinematic viscosities covered by this test
method is from 0.2 to 300 000 cSt. The specification of ASTM D445, which refers to
15 the standard calibration method ASTM D2162, lists about 20 different capillary
viscometers, e.g. Ubbelohde and Cannon type viscometers, useful for determining
the kinematic viscosity according to the standard test method. However, as stated in
ASTM D445, it is not intended to restrict the test method to the use of only those
viscometers listed in the specification. The kinematic viscosity according to the
20 present invention can thus be determined by any calibrated viscometer covering the
desired kinematic viscosity range. Ubbelohde viscometers, for example, cover a
kinematic viscosity range of from about 0.3 cSt to about 100 000 cSt (see, e.g.,
ASTM D445-12) and are useful viscometers for the determination of the kinematic
viscosity of from about 10 cSt to about 100 000 cSt at 25°C.
- 25 [0085] The kinematic viscosity according to the invention may, e.g., be determined
by the standard test method ASTM D445, e.g. ASTM D445-12, e.g., using
Ubbelohde viscometers calibrated with the standard method ASTM D2162, e.g.
ASTM D2162-13.
- [0086] The kinematic viscosity according to the present invention can likewise be
30 determined by measuring the dynamic viscosity of the interface mediator. The
kinematic viscosity is the ratio of the dynamic viscosity to the density of the
substance. Suitable viscometers for the determination of the dynamic viscosity are
rotational viscometers such as Brookfield cup/spindle viscometers and cone/plate
viscometers. Standard test methods that are suitable for determining the dynamic

5 viscosity are ASTM D1084 (e.g., ASTM D1084-08) and ASTM D4287 (e.g., ASTM D4287-00). The methods provide interchangeable results if the viscosimeters are calibrated with certified viscosity reference standards.

[0087] A possible practicable method is that the standard test method ASTM D445 (e.g., ASTM D445-12) is used for measuring kinematic viscosities of less than
10 1 000 cSt at 25 °C, e.g. for measuring a kinematic viscosity of about 20 cSt, about 100 cSt or about 350 cSt, and that one of the standard test methods for measuring the dynamic viscosity, ASTM D1084 (e.g., ASTM D1084-08) or ASTM D4287 (e.g., ASTM D4287-00), is used for determining kinematic viscosities of about 1 000 cSt or more at 25 °C, e.g. for determining a kinematic viscosity of about 1 000 cSt, or
15 about 12 500 cSt as described in Dow Corning's Corporate Test Methods CTM 0004 and CTM 0050. For determining kinematic viscosities of about 1 000 cSt or more at 25 °C, e.g. for determining a kinematic viscosity range of from about 1 000 cSt to about 100 000 cSt at 25°C, the standard test method ASTM D1084 is practicable.

[0088] According to one aspect of the invention, the interface mediator is used to
20 reduce the maximum droplet size of the dispersed deposits of the inner phase in the outer phase in a dried biphasic layer of a transdermal therapeutic system as described above. Without wishing to be bound to any theory it is believed that this effect is achieved by filling cavities at the interface between the dispersed inner phase and the outer phase and thereby enhancing the compatibility of the two separate phases and
25 promoting a maximum separation/dispersion of the inner phase in the outer phase.

[0089] According to certain embodiments of the invention, the interface mediator is hydrophobic when the outer phase is hydrophobic.

[0090] In accordance with certain embodiments of the invention, the interface mediator is a silicone oil, preferably with a kinematic viscosity of about 10 cSt to
30 about 100 000 cSt, or about 100 cSt to about 30 000 cSt, or about 10 000 cSt to about 15 000 cSt (e.g. Dow Corning® Medical Fluid).

[0091] Preferably, the silicone oil has a kinematic viscosity of from about 100 cSt to about 100 000 cSt, or about 200 cSt to about 100 000 cSt, or about 500 cSt to about 100 000 cSt, or about 800 cSt to about 100 000 cSt, or about 1 000 cSt to about

- 24 -

- 5 100 000 cSt, or about 10 000 cSt to about 100 000 cSt at 25 °C, or a kinematic viscosity of from about 100 cSt to about 30 000 cSt, or about 200 cSt to about 30 000 cSt, or about 500 cSt to about 30 000 cSt, or about 800 cSt to about 30 000 cSt, or about 1 000 cSt to about 30 000 cSt, or about 10 000 cSt to about 30 000 cSt at 25 °C, or a kinematic viscosity of from about 100 cSt to about
- 10 15 000 cSt, 200 cSt to about 15 000 cSt, or about 500 cSt to about 15 000 cSt, or about 800 cSt to about 15 000 cSt, or about 1 000 cSt to about 15 000 cSt, or about 10 000 cSt to about 15 000 cSt at 25 °C.

[0092] According to one aspect of the invention, a silicone oil is used as interface mediator in a transdermal therapeutic system with an active agent-containing dried

15 biphasic layer having a hydrophilic inner phase and a hydrophobic outer phase for controlling the maximum droplet size of the inner phase of said dried biphasic layer, in particular in a transdermal therapeutic system wherein the active agent is rotigotine base and is present in the dried biphasic layer in an amount of 16% to 26% of the dried biphasic layer.

20

SKIN CONTACT LAYER

[0093] The TTS in accordance with the invention may comprise an additional skin contact layer which is an adhesive layer.

- 25 [0094] According to a certain embodiment, the additional skin contact layer has a pressure-sensitive adhesive composition comprising pressure-sensitive polymers selected from polysiloxanes, or polyisobutylenes. A pressure-sensitive adhesive composition comprising pressure-sensitive adhesive polysiloxane(s) is preferred according to a certain embodiment of the invention.

- 30 [0095] The additional skin contact layer may be manufactured active agent-free or active agent-containing.

5

METHOD OF MANUFACTURE

[0096] According to one aspect, the invention relates to a method of manufacture of an active agent-containing dried biphasic layer comprising the steps of:

- 10 (1) preparing a biphasic coating mixture having an inner phase dispersed in an outer phase:
 - (a) the inner phase comprising the active agent,
 - (b) the outer phase comprising a polymer or polymer mixture,wherein the biphasic coating mixture comprises solvents in sufficient amounts to provide for a viscosity of the coating mixture suitable for coating,
- 15 (2) adding to said biphasic coating mixture an interface mediator, and mixing said coating mixture to provide a suitable dispersion of the inner phase in the outer phase,
- (3) coating said coating mixture on a film to provide a layer of said solvent-containing mixture,
- 20 (4) evaporating said solvents to provide a dried layer with a coating weight to provide said active agent-containing dried biphasic layer with the desired area weight,
- (5) optionally laminating two or more of said dried layers to provide said active agent-containing dried biphasic layer with the desired area weight.

25 in particular to a dried biphasic layer obtainable by said process.

[0097] According to one further aspect, the invention relates to a method of manufacture of a transdermal therapeutic system comprising an active agent-containing dried biphasic layer, comprising the steps of:

- 30 (1) preparing a biphasic coating mixture having an inner phase dispersed in an outer phase:
 - (a) the inner phase comprising the active agent,
 - (b) the outer phase comprising a polymer or polymer mixture,wherein the biphasic coating mixture comprises solvents in sufficient amounts to provide for a viscosity of the coating mixture suitable for coating,

- 26 -

- 5 (2) adding to said biphasic coating mixture an interface mediator, and
 mixing said coating mixture to provide a suitable dispersion of the inner phase
 in the outer phase,
- (3) coating said coating mixture on a film to provide a layer of said solvent-
 containing mixture,
- 10 (4) evaporating said solvents to provide a dried layer with a coating weight to
 provide an active agent-containing dried biphasic layer with the desired area
 weight,
- (5) optionally laminating two or more of said dried layers to provide an active
 agent-containing dried biphasic layer with the desired area weight,
- 15 (6) laminating said active agent-containing dried biphasic layer to a backing layer,
 (7) optionally laminating said active agent-containing biphasic layer to an
 additional skin contact layer.

[0098] According to a certain embodiment of the invention, a pressure-sensitive
adhesive mixture of pressure-sensitive adhesive polysiloxanes in heptane or ethyl
20 acetate is used for the production of the biphasic layer and optionally the additional
 skin contact layer.

[0099] Useful solvents for dissolving the polymer mixture comprising at least two
hydrophilic polymers are alcohols (e.g. ethanol), acetone and methyl ethyl ketone,
ethanol is preferred. The composition comprising 75 % to 100% of a polymer or a
25 polymer mixture may be dissolved in heptanes, hexanes, toluene, or ethyl acetate,
 preferably in heptane or ethyl acetate.

[00100] According to a certain embodiment of the invention, the active agent-
containing dried biphasic layer is laminated to an additional skin contact layer and
wherein the preparation of the skin contact layer comprises the steps of:

- 30 (1) providing an adhesive coating mixture,
 (2) coating said adhesive coating mixture on a film in an amount to provide
 the desired area weight,
 (3) drying said coated adhesive composition to provide a skin contact layer
 with the desired area weight.

5

METHOD OF TREATMENT / MEDICAL USE

[00101] According to one aspect, the transdermal therapeutic system in accordance with one specific aspect of the invention containing rotigotine as active agent and as described above in detail is for use in a method of treatment, in particular for use in a method of treating patients suffering from Parkinson's disease, Parkinson's plus syndrome, depression, anxiety, AHDS, fibromyalgia, the restless-legs syndrome and for use in the treatment or prevention of dopaminergic neuron loss or the treatment or prevention of cognitive disorders, dementia or lewy body disease.

10 [00102] The method comprises in particular the application of the TTS for 7 days on the skin of a human patient. According to other methods in accordance with the invention the TTS can be applied for at least 1 day, or 3 days, or 4 days on the skin of a human patient. A 7 day-application is preferred.

[00103] The TTS according to the invention is in particular for use in a method of treatment by applying a transdermal therapeutic system for 7 days on the skin of a human patient. According to other aspects of the invention, the TTS is for use in a method of treatment by applying a transdermal therapeutic system for at least 1 day, 3 days, or 4 days on the skin of a human patient. A 7 day-application is preferred.

20 [00104] According to certain embodiments of the invention, therapeutically effective amounts of the active agent (e.g. rotigotine) are provided for 1 to 7 days by said transdermal therapeutic system during an administration period of 1 to 7 days.

[00105] A multi-day TTS according to the invention has the advantage of allowing for a reduced application frequency compared to daily applied transdermal therapeutic systems. This is particularly advantageous for patients suffering from severe dopaminergic disorders, like Parkinson's disease, as these patients often experience motor disabilities which make the frequent handling and administration of transdermal therapeutic systems difficult. At the same time, the number of skin application sites to be treated with transdermal therapeutic systems during a long-term medication is reduced. A prolongation of the medication interval e.g. from

25
30

- 28 -

5 1 day to at least 3 or even at least 7 days minimizes the potential risk of skin lesions associated with repeated TTS stripping from the patients' skin at skin application sites selected for repeated TTS administration. E.g., for the once-daily TTS Neupro® 14 different skin application sites are necessary for repeated TTS application to avoid skin irritation, whereas with a once-weekly TTS only 3 skin application sites are
10 necessary. In addition, the influence of inter- and intra-individually differing lag-times on the absorption of the active agent (e.g. rotigotine), which may be associated with the daily replacement of active agent-containing transdermal therapeutic systems in the case of low skin permeability and which may cause therapeutically unwanted fluctuations of the plasma levels of the active agent (e.g. rotigotine), can
15 be eliminated by the multi-day TTS of the present invention. Finally, the replacement of a daily TTS administration by one single administration for several days, for example by an administration once or twice weekly, contributes to the reduction of the costs of the respective medication by saving material and production time.
[00106] According to certain embodiments of the invention, therapeutically effective
20 amounts of the active agent (e.g. rotigotine) are provided for 3 days by the transdermal therapeutic system according to the invention during an administration period of 3 days, preferably for 4 days during an administration period of 4 days, or for 7 days during an administration period of 7 days.

25

EXAMPLES

[00107] The present invention will now be more fully described with reference to the accompanying examples. It should be understood, however, that the following description is illustrative only and should not be taken in any way as a restriction of
30 the invention.

EXAMPLE 1

[00108] Preparation of the biphasic coating mixture:

- 29 -

- 5 [00109] At first, an ethanolic polyvinylpyrrolidone (PVP) solution containing 12.8% by weight of Kollidon 90F was manufactured.

[00110] The composition of the PVP solution is summarized in Table 1 below.

[00111] Table 1

Excipients	Quantity [g]	Quantity [%]
Ascorbyl palmitate	0.25	0.11
Alpha tocopherol	0.62	0.28
Sodium metabisulfite solution 10% (w/w)	0.226	0.006
Polyvinylpyrrolidone (Kollidon 90F)	50.00	12.83
Ethanol	338.6	86.89
Total amount	389.695	100.00

- 10 [00112] 50.00 g PVP (Kollidon 90F), 0.62 g DL- α -Tocopherol, 0.25 g ascorbyl palmitate and 0.226 g of an aqueous sodium metabisulfite solution (10 % by weight) were mixed with 338.6 g anhydrous ethanol to obtain a clear solution.

[00113] The composition of the rotigotine-containing biphasic coating mixture is summarized in Table 2 below.

- 15 [00114] Table 2

Excipients	Quantity [g]	Quantity [%]
PVP solution	19.00	19.79
Rotigotine	5.50	5.73
BIO-PSA 7-4201 (73.5%)	36.00	37.50
BIO-PSA 7-4301 (74.6%)	35.50	36.98
Total amount	96.00	100.00

[00115] 19.0 g of the stabilized PVP solution and 5.50 g rotigotine of polymorphic form II were mixed and heated to 60 °C for 90 min until a clear solution was obtained.

- 20 [00116] 36.00 g silicone adhesive BIO-PSA 7-4201 (73.5 % by weight in n-heptane) and 35.50 g silicone adhesive BIO-PSA 7-4301 (74.6 % by weight in n-heptane)

- 30 -

- 5 were added to the obtained solution of rotigotine, PVP and antioxidants and stirred for 40 min.

[00117] At the end of the manufacture of the 100 g rotigotine-containing biphasic coating mixture, it was split into five samples of approximately 20 g. One sample was stored at room temperature without further treatment (Example 1A).

- 10 [00118] In order to investigate the influence of an interface mediator on the droplet size distribution in the biphasic coating mixture silicone oils with different viscosities (100 cSt, 350 cSt, 1000 cSt and 12500 cSt) were added under stirring at a concentration of 1% by weight to the other four samples resulting in Examples 1B-E.

[00119] The composition of the mixtures is summarized in Table 3 below.

- 15 [00120] Table 3

	1B (100 cSt)	1C (350 cSt)	1D (1 000 cSt)	1E (12 500 cSt)
Drug containing mass (1A)	20.0 g	20.0 g	20.0 g	20.0 g
Silicone oil	0.2 g	0.2 g	0.2 g	0.2 g
Total amount	20.2 g	20.2 g	20.2 g	20.2 g

- [00121] Microscopic pictures were taken of the biphasic coating mixture after preparation. Figure 1 shows a microscopic picture of the biphasic coating mixture of Example 1A. Figures 2-5 show microscopic pictures of the biphasic coating mixture of Examples 1 B-1E.
- 20

[00122] During the microscopic investigation the droplet size (diameter) was determined. The maximum droplet sizes in the rotigotine-containing biphasic coating mixture are summarized in Table 4 below.

[00123] Table 4

Mixture	1A	1B	1C	1D	1E
Maximum droplet size	28 μm	20 μm	17 μm	15 μm	13 μm

5

EXAMPLE 2

[00124] The composition of the rotigotine-containing biphasic coating mixture (Example 2A) is summarized in Table 5 below.

[00125] Table 5

Example 2A	Composition solid	Composition solution
Exipients	[%]	[%]
Ethanol	-	14.902
Ethanol dilution	-	12.078
Polyvinylpyrrolidone (Kollidon 90 F)	8.00	4.401
Sodium metabisulfite solution 10% (w/w)	0.0036	0.020
Ascorbyl palmitate	0.0401	0.0220
All-rac-Tocopherol	0.0994	0.0547
Rotigotine	18.00	9.902
BIO-PSA 7-4301 (71.5%)	36.93	28.413
BIO-PSA 7-4201 (71.5%)	36.93	28.413
n-Heptane	-	1.796
Total amount	100.0	100.0

10

[00126] The composition of the rotigotine-containing biphasic coating mixture with 1% silicone oil (Example 2B) is summarized in Table 6 below.

5 [00127] Table 6

Example 2B	Composition solid	Composition solution
Excipients	[%]	[%]
Ethanol	-	26.98
Polyvinylpyrrolidone (Kollidon 90 F)	8.00	4.40
Sodium metabisulfite solution 10% (w/w)	0.0036	0.020
Ascorbyl palmitate	0.0401	0.022
All-rac-Tocopherol	0.0994	0.055
Rotigotine	18.00	9.90
BIO-PSA 7-4301 (71.5%)	36.02	27.71
BIO-PSA 7-4201 (71.5%)	36.02	27.71
Silicone oil (12500 cSt)	1.817	1.000
n-Heptane	-	2.19
Total amount	100.0	100.0

[00128] Preparation of the rotigotine-containing biphasic coating mixture (step 1):

[00129] 8.80 g polyvinylpyrrolidone (PVP, Kollidon 90F), 0.109 g

DL- α -Tocopherol, 0.044 g ascorbyl palmitate and 0.040 g of an aqueous sodium
 10 metabisulfite solution (10 % by weight) were mixed with 53.96 g anhydrous ethanol to obtain a clear solution (2000 rpm, propeller stirrer).

[00130] 19.8 g rotigotine of polymorphic Form II were added while stirring at 600 rpm and heated to 60 °C for 60 min.

[00131] 55.42 g silicone adhesive 7-4201 (71.5 % by weight in n-heptane), 55.42 g
 15 silicone adhesive 7-4301 (71.5 % by weight in n-heptane) and, in case of Example 2B, 2.00 g silicone oil (12500 cSt) were added to the obtained solution of rotigotine, PVP and antioxidants and stirred at 1200 rpm for 5 min (turbine stirrer).

[00132] Preparation of the transdermal therapeutic system (TTS) (step 2):

[00133] The mixture obtained in step 1 was coated onto two sheets of a suitable
 20 polyester release liner (e.g. Scotchpak™ 9755) to obtain two rotigotine-containing

- 33 -

5 biphasic layers each having a coating weight of 75 g/m^2 . The coated release liner sheets were placed in a drying oven and dried at 50°C for about 30 min and then at 115°C for about 10 min. The first dried rotigotine-containing layer was laminated with (1) a polyester-type backing foil and (2) the second rotigotine-containing layer after removal of the release liner from the surface of the first rotigotine-containing layer to provide the rotigotine-containing self-adhesive layer structure having an area weight of 150 g/m^2 . Finally, individual systems (TTS) having a size of 10 cm^2 were punched out of the complete laminate and sealed into pouches.

[00134] Microscopic pictures of the rotigotine-containing biphasic coating mixture were taken using a Nikon Microscope with a Leica camera. Figure 6 and 7 show microscopic pictures of the rotigotine-containing biphasic coating mixture of Example 2A and 2B.

[00135] During the microscopic investigation the droplet size (diameter) was determined. The maximum droplet sizes found in the respective dried biphasic layers in Figures 6 and 7 are listed in Table 7 below.

20 [00136] Table 7

Mixture	Example 2A without silicone oil	Example 2B with 1% silicone oil
Maximum droplet size	36 μm	21 μm

- 34 -

5 **The invention relates in particular to the following further items:**

1. Transdermal therapeutic system for the transdermal administration of a systemically active agent comprising a self-adhesive layer structure, comprising
 - 10 A) a backing layer, and
 - B) a dried biphasic layer, the dried biphasic layer having
 - a) an outer phase having a composition comprising 75% to 100% of a polymer or polymer mixture, and
 - b) an inner phase having a composition comprising at least one active agent,
15 wherein the inner phase forms dispersed deposits in the outer phase, and
 - c) 0.1% to 3.5% of an interface mediator with a kinematic viscosity of from 10 cSt to 100 000 cSt at 25°C,and
 - 20 C) optionally an additional skin contact layer.
2. Transdermal therapeutic system in accordance with item 1 comprising 0.1% to 3% of an interface mediator.
- 25 3. Transdermal therapeutic system in accordance with item 1 or 2 comprising 0.1% to 2% of an interface mediator.
4. Transdermal therapeutic system in accordance with any one of items 1 to 3 comprising 0.1% to 1.5% of an interface mediator.
- 30 5. Transdermal therapeutic system in accordance with any one of items 1 to 4, wherein the outer phase is hydrophobic and the inner phase is hydrophilic.

- 35 -

- 5 6. Transdermal therapeutic system in accordance with any one of items 1 to 5,
wherein said outer phase is a pressure-sensitive adhesive composition.
7. Transdermal therapeutic system in accordance with any one of items 1 to 6,
wherein said polymer or polymer mixture in the outer phase is a/are hydrophobic
10 polymer(s).
8. Transdermal therapeutic system in accordance with item 7, wherein the
hydrophobic polymer or polymer mixture in the outer phase is a/are pressure-
sensitive adhesives polymer(s) selected from the group of polysiloxanes, or
15 polyisobutylenes.
9. Transdermal therapeutic system in accordance with item 8, wherein the
hydrophobic polymer or polymer mixture is a/are pressure-sensitive adhesive
polysiloxane(s).
- 20 10. Transdermal therapeutic system in accordance with item 9, wherein the
polysiloxane(s) is/are amine-resistant.
11. Transdermal therapeutic system in accordance with item 9, wherein the
25 polysiloxane(s) is/are amine-resistant being a product of the condensation reaction of
silanol endblocked polydimethylsiloxane with a silica resin and the residual silanol
functionality being capped with trimethylsiloxy groups.
12. Transdermal therapeutic system in accordance with any one of items 1 to 11,
30 wherein for the production of the dried biphasic layer and optionally the additional
skin contact layer a pressure-sensitive adhesive mixture of pressure-sensitive
adhesive polysiloxane(s) in heptane is used.
13. Transdermal therapeutic system in accordance with item 12, wherein the
35 pressure-sensitive adhesive mixture is characterized by a solution viscosity at 25°C
and 60% solids content in heptane of more than 150 mPa s.

- 36 -

- 5
14. Transdermal therapeutic system in accordance with item 12, wherein the pressure-sensitive adhesive mixture is characterized by a solution viscosity at 25°C and 60% solids content in heptane of from about 200 mPa s to about 700 mPa s.
- 10
15. Transdermal therapeutic system in accordance with item 12, wherein the pressure-sensitive adhesive mixture is characterized by a solution viscosity at 25°C and 60% solids content in heptane of from about 350 mPa s to about 600 mPa s.
- 15
16. Transdermal therapeutic system in accordance with any one of items 1 to 11, wherein for the production of the dried biphasic layer and optionally the additional skin contact layer a pressure-sensitive adhesive mixture of pressure-sensitive adhesive polysiloxane(s) in ethyl acetate is used.
- 20
17. Transdermal therapeutic system in accordance with item 16, wherein the pressure-sensitive adhesive mixture is characterized by a solution viscosity at 25°C and 60% solids content in ethyl acetate of more than 350 mPa s.
- 25
18. Transdermal therapeutic system in accordance with item 16, wherein the pressure-sensitive adhesive mixture is characterized by a solution viscosity at 25°C and 60% solids content in ethyl acetate of from about 400 mPa s to about 1500 mPa s.
- 30
19. Transdermal therapeutic system in accordance with item 16, wherein the pressure-sensitive adhesive mixture is characterized by a solution viscosity at 25°C and 60% solids content in ethyl acetate of from about 600 mPa s to about 1300 mPa s.
- 35
20. Transdermal therapeutic system in accordance with any one of items 9 to 19, wherein the pressure-sensitive adhesive polysiloxane(s) is/are characterized by a complex viscosity at 0.01 rad/s at 30°C of less than 1×10^9 Poise.

- 37 -

- 5 21. Transdermal therapeutic system in accordance with any one of items 9 to 19,
wherein the pressure-sensitive adhesive polysiloxane(s) is/are characterized by a
complex viscosity at 0.01 rad/s at 30°C of from about 1×10^5 to about 9×10^9 Poise.
- 10 22. Transdermal therapeutic system in accordance with any one of items 1 to 11,
wherein for the production of the dried biphasic layer and optionally the additional
skin contact layer a pressure-sensitive adhesive mixture of a pressure-sensitive
adhesive polysiloxane in heptane characterized by a solution viscosity at 25°C and
about 60% solids content in heptane of 500 mPa s and a pressure-sensitive adhesive
polysiloxane in heptane characterized by a solution viscosity at 25°C and about 60%
15 solids content in heptane of 450 mPa s is used.
- 20 23. Transdermal therapeutic system in accordance with any one of items 1 to 11,
wherein for the production of the dried biphasic layer and optionally the additional
skin contact layer a pressure-sensitive adhesive mixture of a pressure-sensitive
adhesive polysiloxane in ethyl acetate characterized by a solution viscosity at 25°C
and about 60% solids content in ethyl acetate of 1200 mPa s and a pressure-sensitive
adhesive polysiloxane in ethyl acetate characterized by a solution viscosity at 25°C
and about 60% solids content in ethyl acetate of 800 mPa s is used.
- 25 24. Transdermal therapeutic system in accordance with any one of items 1 to 23,
wherein the inner phase comprises a hydrophilic agent and the systemically active
agent forms a solid solution with the hydrophilic agent.
- 30 25. Transdermal therapeutic system in accordance with item 24, wherein the
hydrophilic agent in the inner phase is a hydrophilic polymer or polymer mixture.
- 35 26. Transdermal therapeutic system in accordance with any one of items 24 and 25,
wherein the hydrophilic polymer or polymer mixture in the inner phase is selected
from the group consisting of
- polyvinylpyrrolidones having a K-Value of from 10 to 200,

- 38 -

- 5 - copolymers of vinyl caprolactam, vinylacetate and ethylene glycol,
 - copolymers of vinylpyrrolidone and vinylacetate,
 - copolymers of ethylene and vinylacetate,
 - polyethylene glycols,
 - polypropylene glycols,
10 - acrylic polymers,
 - modified celluloses.
27. Transdermal therapeutic system in accordance with any one of items 24 and 25,
wherein the hydrophilic polymer or polymer mixture in the inner phase is selected
15 from the group consisting of
 - polyvinylpyrrolidones having a K-Value from 10 to 200,
 - copolymers of vinyl caprolactam, vinylacetate and ethylene glycol,
 - copolymers of vinylpyrrolidone and vinylacetate,
 - copolymers of ethylene and vinylacetate,
20 - polyethylene glycols,
 - polypropylene glycols,
 - copolymers of dimethylaminoethyl methacrylate, butyl methacrylate and
 methyl methacrylat,
 - copolymers of methacrylic acid and methyl methacrylat,
25 - hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate
 succinate.
28. Transdermal therapeutic system in accordance with any one of items 25 to 27,
wherein the hydrophilic polymer or polymer mixture in the inner phase is a/are
30 polyvinylpyrrolidone(s).
29. Transdermal therapeutic system in accordance with item 27, wherein the
polyvinylpyrrolidone(s) in the inner phase is a/are polyvinylpyrrolidone(s) having a
K-Value of from 10 to 200, in particular 90.

- 39 -

- 5 30. Transdermal therapeutic system in accordance with any one of items 1 to 29,
wherein the outer phase is hydrophobic and the interface mediator is hydrophobic.
31. Transdermal therapeutic system in accordance with any one of items 1 to 30;
wherein the interface mediator is a silicone oil.
- 10 32. Transdermal therapeutic system in accordance with item 30, wherein the silicone
oil exhibits a kinematic viscosity of about 100 cSt to about 30 000 cSt.
33. Transdermal therapeutic system in accordance with item 30 or 31, wherein the
15 silicone oil exhibits a kinematic viscosity of about 10 000 cSt to about 15 000 cSt.
34. Transdermal therapeutic system in accordance with any one of items 1 to 33,
wherein the active agent is selected from the group of rotigotine, fentanyl,
oxybutynine, and fesoterodine.
- 20 35. Transdermal therapeutic system in accordance with any one of items 1 to 34,
wherein the active agent is rotigotine base or a pharmaceutically acceptable salt
thereof.
- 25 36. Transdermal therapeutic system in accordance with item 35, wherein the
transdermal therapeutic system contains 0.1 mg/cm^2 to 10.0 mg/cm^2 of rotigotine
base in said self-adhesive layer structure.
- 30 37. Transdermal therapeutic system in accordance with any one of items 35 to 36,
wherein the transdermal therapeutic system contains 0.1 mg/cm^2 to 5.0 mg/cm^2 of
rotigotine base in said self-adhesive layer structure.
- 35 38. Transdermal therapeutic system in accordance with any one of items 35 and 36,
wherein the transdermal therapeutic system contains 0.3 mg/cm^2 to 3.0 mg/cm^2 of
rotigotine base in said self-adhesive layer structure.

- 40 -

5

39. Transdermal therapeutic system in accordance with item 35, wherein the transdermal therapeutic system contains 0.3 mg/cm^2 to 1.0 mg/cm^2 of rotigotine base in said self-adhesive layer structure.

10

40. Transdermal therapeutic system in accordance with item 35, wherein the transdermal therapeutic system contains 1.0 mg/cm^2 to 1.5 mg/cm^2 of rotigotine base in said self-adhesive layer structure.

15

41. Transdermal therapeutic system in accordance with item 35, wherein the transdermal therapeutic system contains 1.5 mg/cm^2 to 5.0 mg/cm^2 of rotigotine base in said self-adhesive layer structure.

20

42. Transdermal therapeutic system in accordance with any one of items 35 to 41, wherein the transdermal therapeutic system contains 2.0 mg/cm^2 to 4.0 mg/cm^2 , preferably 2.0 mg/cm^2 to 3.0 mg/cm^2 of rotigotine base in said self-adhesive layer structure.

25

43. Transdermal therapeutic system in accordance with any one of items 35 to 42, wherein rotigotine base is present in an amount of 1% to 30% of said dried biphasic layer.

30

44. Transdermal therapeutic system in accordance with any one of items 35 to 43, wherein rotigotine base is present in an amount of 10% to 26% of said dried biphasic layer, preferably of 16% to 26% of said dried biphasic layer.

45. Transdermal therapeutic system in accordance with any one of items 35 to 43, wherein rotigotine base is present in an amount of 16% to 30% of said dried biphasic layer.

- 41 -

- 5 46. Transdermal therapeutic system in accordance with any one of items 1 to 45,
wherein the dried biphasic layer has an area weight of about 30 g/m² to about
200 g/m².
- 10 47. Transdermal therapeutic system in accordance with any one of items 1 to 46,
wherein the dried biphasic layer has an area weight of about 100 g/m² to about
200 g/m².
- 15 48. Transdermal therapeutic system in accordance with any one of items 1 to 47,
wherein the biphasic layer has an area weight of about 100 g/m² to about 200 g/m²
and wherein rotigotine base is present in an amount of 16% to 26% of said biphasic
layer.
- 20 49. Transdermal therapeutic system in accordance with any one of items 1 to 48,
wherein the dried biphasic layer comprises an anti-oxidant selected from the group
consisting of sodium metabisulfite, ascorbyl palmitate, tocopherol and esters thereof,
ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate.
- 25 50. Transdermal therapeutic system in accordance with any one of items 1 to 49,
wherein the skin contact layer has a pressure-sensitive adhesive composition
comprising pressure-sensitive polymers selected from polysiloxanes, or
polyisobutylenes.
- 30 51. Transdermal therapeutic system in accordance with any one of items 1 to 50,
wherein the skin contact layer has a pressure-sensitive adhesive composition
comprising pressure-sensitive adhesive polysiloxane.
- 35 52. Transdermal therapeutic system in accordance with any one of items 1 to 51,
wherein the skin contact layer is manufactured active agent-free or active agent-
containing.

- 42 -

- 5 53. Transdermal therapeutic system in accordance with any one of items 1 to 52 providing a maximum droplet size of the dispersed deposits of 5 μm to 25 μm .
54. Transdermal therapeutic system in accordance with any one of items 1 to 53, wherein therapeutically effective amounts of the systemically active agent are
10 provided for 1 to 7 days by said transdermal therapeutic system during an administration period on the skin of a human patient of 1 to 7 days.
55. Transdermal therapeutic system in accordance with any one of items 1 to 54, wherein therapeutically effective amounts of the systemically active agent are
15 provided for 3 days by said transdermal therapeutic system during an administration period on the skin of a human patient of 3 days.
56. Transdermal therapeutic system in accordance with any one of items 1 to 55, wherein therapeutically effective amounts of the systemically active agent are
20 provided for 4 days by said transdermal therapeutic system during an administration period on the skin of a human patient of 4 days.
57. Transdermal therapeutic system in accordance with any one of items 1 to 56, wherein therapeutically effective amounts of the systemically active agent are
25 provided for 7 days by said transdermal therapeutic system during an administration period on the skin of a human patient of 7 days.
58. Transdermal therapeutic system in accordance with any one of items 1 to 57 for use in a method of treatment.
30
59. Transdermal therapeutic system in accordance with any one of items 35 to 58 for use in a method of treating patients suffering from Parkinson's disease, Parkinson's plus syndrome, depression, anxiety, AHDS, fibromyalgia, the restless-legs syndrome and for use in the treatment or prevention of dopaminergic neuron loss or the
35 treatment or prevention of cognitive disorders, dementia or lewy body disease.

5

60. Use of an interface mediator to reduce the maximum droplet size of the dispersed deposits of a transdermal therapeutic system in accordance with any one of items 1 to 59.

10 61. Use of a silicone oil as interface mediator in a transdermal therapeutic system with an active agent-containing dried biphasic layer having a hydrophilic inner phase and a hydrophobic outer phase for controlling the maximum droplet size of the inner phase of said dried biphasic layer.

15 62. Use of a silicone oil as interface mediator in a transdermal therapeutic system according to item 61, wherein the active agent is rotigotine base and is present in the dried biphasic layer in an amount of 16% to 25% of the dried biphasic layer.

63. Method of manufacture of an active agent-containing dried biphasic layer
20 comprising the steps of:

- (1) preparing a biphasic coating mixture having an inner phase dispersed in an outer phase:
 - (a) the inner phase comprising the active agent,
 - (b) the outer phase comprising a polymer or polymer mixture,
- 25 wherein the biphasic coating mixture comprises solvents in sufficient amounts to provide for a viscosity of the coating mixture suitable for coating,
- (2) adding to said biphasic coating mixture an interface mediator, and mixing said coating mixture to provide a suitable dispersion of the inner phase in the outer phase,
- 30 (3) coating said coating mixture on a film to provide a layer of said solvent-containing mixture,
- (4) evaporating said solvents to provide a dried layer with a coating weight to provide said active agent-containing dried biphasic layer with the desired area weight,

- 44 -

- 5 (5) optionally laminating two or more of said dried layers to provide said active agent-containing dried biphasic layer with the desired area weight.

64. Dried biphasic layer obtainable by a process in accordance with item 63.

- 10 65. Method of manufacture of a transdermal therapeutic system in accordance with any one of items 1 to 59 comprising an active agent-containing dried biphasic layer comprising the steps of:

- (1) preparing a biphasic coating mixture having an inner phase dispersed in an outer phase:
- 15 (a) the inner phase comprising the active agent,
 (b) the outer phase comprising a polymer or polymer mixture,
 wherein the biphasic coating mixture comprises solvents in sufficient amounts to provide for a viscosity of the coating mixture suitable for coating,
- (2) adding to said biphasic coating mixture an interface mediator, and
- 20 mixing said coating mixture to provide a suitable dispersion of the inner phase in the outer phase,
- (3) coating said coating mixture on a film to provide a layer of said solvent-containing mixture,
- (4) evaporating said solvents to provide a dried layer with a coating weight to
- 25 provide an active agent-containing dried biphasic layer with the desired area weight,
- (5) optionally laminating two or more of said dried layers to provide an active agent-containing dried biphasic layer with the desired area weight,
- (6) laminating said active agent-containing dried biphasic layer to a backing layer,
- 30 (7) optionally laminating said active agent-containing biphasic layer to an additional skin contact layer.

66. Transdermal therapeutic system obtainable by a process in accordance with item 65.

5 67. Transdermal therapeutic system for the transdermal administration of a rotigotine containing 2.0 mg/cm^2 to 4.0 mg/cm^2 rotigotine base in a self-adhesive layer structure, comprising

A) a backing layer, and

10 B) a dried biphasic layer, the dried biphasic layer having

a) an outer phase having a composition comprising 75% to 100% of pressure-sensitive adhesive polysiloxane(s), and

b) an inner phase having a composition comprising rotigotine base, wherein the inner phase forms dispersed deposits in the outer phase,

15 and

c) 0.1% to 3.5% of a silicone oil with a kinematic viscosity of from 10 cSt to 100 000 cSt at 25°C ,

and

C) optionally an additional skin contact layer.

20

68. Transdermal therapeutic system for the transdermal administration of rotigotine containing 2.0 mg/cm^2 to 3.0 mg/cm^2 rotigotine base in a self-adhesive layer structure, comprising

25 A) a backing layer, and

B) a dried biphasic layer, the dried biphasic layer having

a) an outer phase having a composition comprising 75% to 100% of pressure-sensitive adhesive polysiloxane(s), and

b) an inner phase having a composition comprising rotigotine base, wherein the inner phase forms dispersed deposits in the outer phase, and

30

c) 0.1% to 3.5% of a silicone oil with a kinematic viscosity of from 10 cSt to 100 000 cSt at 25°C ,

and

- 46 -

- 5 C) optionally an additional skin contact layer,
for use in a method of treatment providing therapeutically effective amounts of
rotigotine base for 7 days by said transdermal therapeutic system during an
administration period on the skin of a human patient of 7 days.
- 10 69. Transdermal therapeutic system for the transdermal administration of rotigotine
containing 2.0 mg/cm^2 to 3.0 mg/cm^2 rotigotine base in a self-adhesive layer
structure, comprising
- A) a backing layer, and
- B) a dried biphasic layer, the dried biphasic layer having
- 15 a) an outer phase having a composition comprising 75% to 100% of
 pressure-sensitive adhesive polysiloxane(s), and
- b) an inner phase having a composition comprising rotigotine base,
 wherein the inner phase forms dispersed deposits in the outer phase,
 and
- 20 c) 0.1% to 3.5% of a silicone oil with a kinematic viscosity of from 10 cSt
 to 100 000 cSt at 25°C,
- and
- C) optionally an additional skin contact layer,
for use in a method of treatment of patients suffering from Parkinson's disease,
25 Parkinson's plus syndrome, depression, anxiety, AHDS, fibromyalgia, the restless-
legs syndrome and for use in the treatment or prevention of dopaminergic neuron
loss or the treatment or prevention of cognitive disorders, dementia or lewy body
disease by providing therapeutically effective amounts of rotigotine base for 7 days
by said transdermal therapeutic system during an administration period on the skin of
30 a human patient of 7 days.

5

CLAIMS

1. Transdermal therapeutic system for the transdermal administration of a systemically active agent comprising a self-adhesive layer structure, comprising
 - 10 A) a backing layer, and
 - B) a dried biphasic layer, the dried biphasic layer having
 - a) an outer phase having a composition comprising 75% to 100% of a polymer or a polymer mixture, and
 - b) an inner phase having a composition comprising at least one active agent
 - 15 wherein the inner phase forms dispersed deposits in the outer phase, and
 - c) 0.1% to 3.5% of an interface mediator with a kinematic viscosity of from 10 cSt to 100 000 cSt at 25°C,and
 - 20 C) optionally an additional skin contact layer.
2. Transdermal therapeutic system in accordance with claim 1, wherein the outer phase is hydrophobic and the inner phase is hydrophilic.
 - 25 3. Transdermal therapeutic system in accordance with claims 1 or 2, wherein said outer phase is a pressure-sensitive adhesive composition.
 4. Transdermal therapeutic system in accordance with any one of claims 1 to 3, wherein said polymer or polymer mixture in the outer phase is a/are hydrophobic
 - 30 polymer(s).
 5. Transdermal therapeutic system in accordance with claim 4, wherein the hydrophobic polymer or polymer mixture is a/are pressure-sensitive adhesive polysiloxane(s).

- 48 -

- 5
6. Transdermal therapeutic system in accordance with any one of claims 1 to 5, wherein the inner phase comprises a hydrophilic agent and the systemically active agent forms a solid solution with the hydrophilic agent.
- 10
7. Transdermal therapeutic system in accordance with claim 6, wherein the hydrophilic agent in the inner phase is a hydrophilic polymer or polymer mixture.
8. Transdermal therapeutic system in accordance with claim 7, wherein the hydrophilic polymer or polymer mixture in the inner phase is a/are
- 15 polyvinylpyrrolidone(s).
9. Transdermal therapeutic system in accordance with any one of claims 1 to 8, wherein the outer phase is hydrophobic and the interface mediator is hydrophobic.
- 20
10. Transdermal therapeutic system in accordance with any one of claims 1 to 9, wherein the interface mediator is a silicone oil.
11. Transdermal therapeutic system in accordance with claim 10, wherein the silicone oil exhibits a kinematic viscosity of about 100 cSt to about 30 000 cSt.
- 25
12. Transdermal therapeutic system in accordance with any one of claims 1 to 11, wherein the active agent is selected from the group of rotigotine, fentanyl, oxybutynine, and fesoterodine.
- 30
13. Transdermal therapeutic system in accordance with any one of claims 1 to 12, wherein the active agent is rotigotine base or a pharmaceutically acceptable salt thereof.
14. Transdermal therapeutic system in accordance with any one of claims 1 to 13,
- 35 wherein the skin contact layer has a pressure-sensitive adhesive composition comprising pressure-sensitive adhesive polysiloxane.

5

15. Transdermal therapeutic system in accordance with any one of claims 1 to 14, wherein the skin contact layer is manufactured active agent-free or active agent-containing.

10 16. Transdermal therapeutic system in accordance with any one of claims 1 to 15 providing a maximum droplet size of the dispersed deposits of 5 μm to 25 μm .

17. Transdermal therapeutic system in accordance with any one of claims 1 to 16, wherein therapeutically effective amounts of the systemically active agent are
15 provided for 1 to 7 days by said transdermal therapeutic system during an administration period on the skin of a human patient of 1 to 7 days.

18. Transdermal therapeutic system in accordance with any one of claims 1 to 17, wherein therapeutically effective amounts of the systemically active agent are
20 provided 7 days by said transdermal therapeutic system during an administration period on the skin of a human patient of 7 days.

19. Transdermal therapeutic system in accordance with any one of claims 1 to 18 for use in a method of treating patients suffering from Parkinson's disease, Parkinson's
25 plus syndrome, depression, anxiety, AHDS, fibromyalgia, the restless-legs syndrome and for use in the treatment or prevention of dopaminergic neuron loss or the treatment or prevention of cognitive disorders, dementia or lewy body disease.

20. Use of a silicone oil as interface mediator to reduce the maximum droplet size of
30 the dispersed deposits of a transdermal therapeutic system in accordance with any one of claims 1 to 19.

21. Use of a silicone oil as interface mediator in a transdermal therapeutic system with an active agent-containing dried biphasic layer having a hydrophilic inner phase

- 50 -

- 5 and a hydrophobic outer phase for controlling the maximum droplet size of the inner phase of said dried biphasic layer.

22. Use of a silicone oil as interface mediator in a transdermal therapeutic system according to claim 21, wherein the active agent is rotigotine base and is present in
10 the dried biphasic layer in an amount of 16% to 26% of the dried biphasic layer.

23. Method of manufacture of an active agent-containing dried biphasic layer comprising the steps of:

- 15 (1) preparing a biphasic coating mixture having an inner phase dispersed in an outer phase:
(a) the inner phase comprising the active agent,
(b) the outer phase comprising a polymer or polymer mixture,
wherein the biphasic coating mixture comprises solvents in sufficient amounts to provide for a viscosity of the coating mixture suitable for coating,
20 (2) adding to said biphasic coating mixture an interface mediator, and mixing said coating mixture to provide a suitable dispersion of the inner phase in the outer phase,
(3) coating said coating mixture on a film to provide a layer of said solvent-containing mixture,
25 (4) evaporating said solvents to provide a dried layer with a coating weight to provide said active agent-containing dried biphasic layer with the desired area weight,
(5) optionally laminating two or more of said dried layers to provide said active agent-containing dried biphasic layer with the desired area weight.

30

24. Dried biphasic layer obtainable by a process in accordance with claim 23.

25. Method of manufacture of a transdermal therapeutic system in accordance with any one of claims 1 to 19 comprising an active agent-containing dried biphasic layer
35 comprising the steps of:

- 51 -

- 5 (1) preparing a biphasic coating mixture having an inner phase dispersed in an outer phase:
(a) the inner phase comprising the active agent,
(b) the outer phase comprising a polymer or polymer mixture,
wherein the biphasic coating mixture comprises solvents in sufficient amounts
10 to provide for a viscosity of the coating mixture suitable for coating,
(2) adding to said biphasic coating mixture an interface mediator, and
mixing said coating mixture to provide a suitable dispersion of the inner phase
in the outer phase,
(3) coating said coating mixture on a film to provide a layer of said solvent-
15 containing mixture,
(4) evaporating said solvents to provide a dried layer with a coating weight to
provide an active agent-containing dried biphasic layer with the desired area
weight,
(5) optionally laminating two or more of said dried biphasic layers to provide an
20 active agent-containing dried biphasic layer with the desired area weight,
(6) laminating said active agent-containing dried biphasic layer to a backing layer,
(7) optionally laminating said active agent-containing biphasic layer to an
additional skin contact layer.
- 25 26. Transdermal therapeutic system obtainable by a process in accordance with claim 25.
27. Transdermal therapeutic system for the transdermal administration of rotigotine
containing 2.0 mg/cm^2 to 4.0 mg/cm^2 rotigotine base in a self-adhesive layer
30 structure,
comprising
A) a backing layer, and
B) a dried biphasic layer, the dried biphasic layer having

- 52 -

- 5 a) an outer phase having a composition comprising 75% to 100% of
 pressure-sensitive adhesive polysiloxane(s), and
 b) an inner phase having a composition comprising rotigotine base,
 wherein the inner phase forms dispersed deposits in the outer phase,
 and
10 c) 0.1% to 3.5% of a silicone oil with a kinematic viscosity of from 10 cSt
 to 100 000 cSt at 25°C,
and
 C) optionally an additional skin contact layer.
- 15 28. Transdermal therapeutic system for the transdermal administration of rotigotine
containing 2.0 mg/cm² to 3.0 mg/cm² rotigotine base in a self-adhesive layer
structure,
comprising
 A) a backing layer, and
20 B) a dried biphasic layer, the dried biphasic layer having
 a) an outer phase having a composition comprising 75% to 100% of
 pressure-sensitive adhesive polysiloxane(s), and
 b) an inner phase having a composition comprising rotigotine base,
 wherein the inner phase forms dispersed deposits in the outer phase,
25 and
 c) 0.1% to 3.5% of a silicone oil with a kinematic viscosity of from 10 cSt
 to 100 000 cSt at 25°C,
and
 C) optionally an additional skin contact layer,
30 for use in a method of treatment providing therapeutically effective amounts of
rotigotine base for 7 days by said transdermal therapeutic system during an
administration period on the skin of a human patient of 7 days.

- 53 -

- 5 29. Transdermal therapeutic system for the transdermal administration of rotigotine
containing 2.0 mg/cm^2 to 3.0 mg/cm^2 rotigotine base in a self-adhesive layer
structure, comprising
- A) a backing layer, and
 - B) a dried biphasic layer, the dried biphasic layer having
 - 10 a) an outer phase having a composition comprising 75% to 100% of
pressure-sensitive adhesive polysiloxane(s), and
 - b) an inner phase having a composition comprising rotigotine base,
wherein the inner phase forms dispersed deposits in the outer phase,
and
 - 15 c) 0.1% to 3.5% of a silicone oil with a kinematic viscosity of from 10 cSt
to 100 000 cSt at 25°C ,
- and
- C) optionally an additional skin contact layer,
- for use in a method of treatment of patients suffering from Parkinson's disease,
20 Parkinson's plus syndrome, depression, anxiety, AHDS, fibromyalgia, the restless-
legs syndrome and for use in the treatment or prevention of dopaminergic neuron
loss or the treatment or prevention of cognitive disorders, dementia or lewy body
disease by providing therapeutically effective amounts of rotigotine base for 7 days
by said transdermal therapeutic system during an administration period on the skin of
25 a human patient of 7 days.

Figure 1

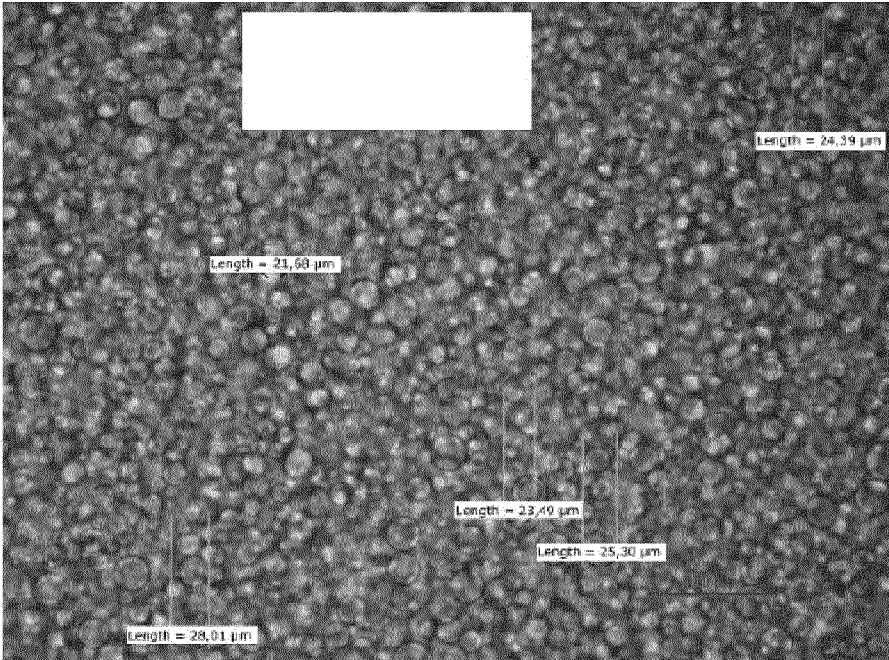


Figure 2

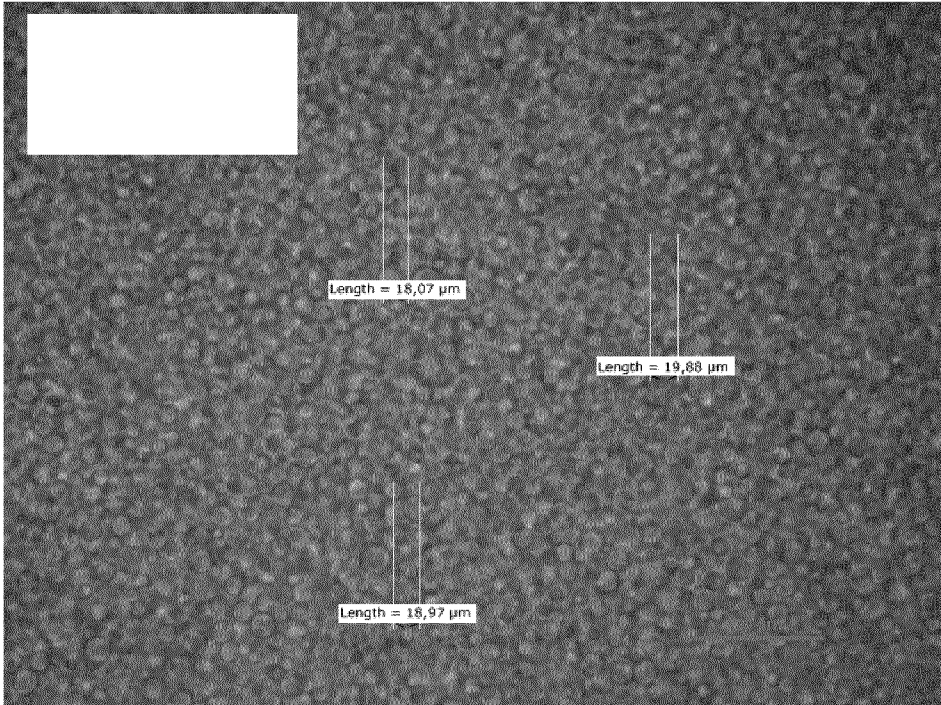


Figure 3

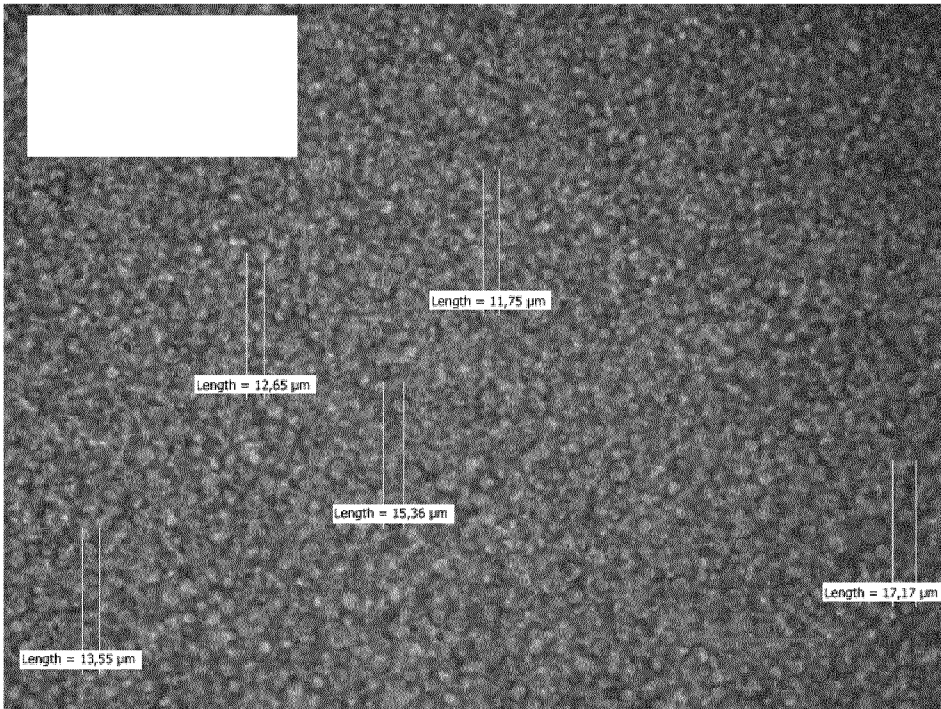


Figure 4

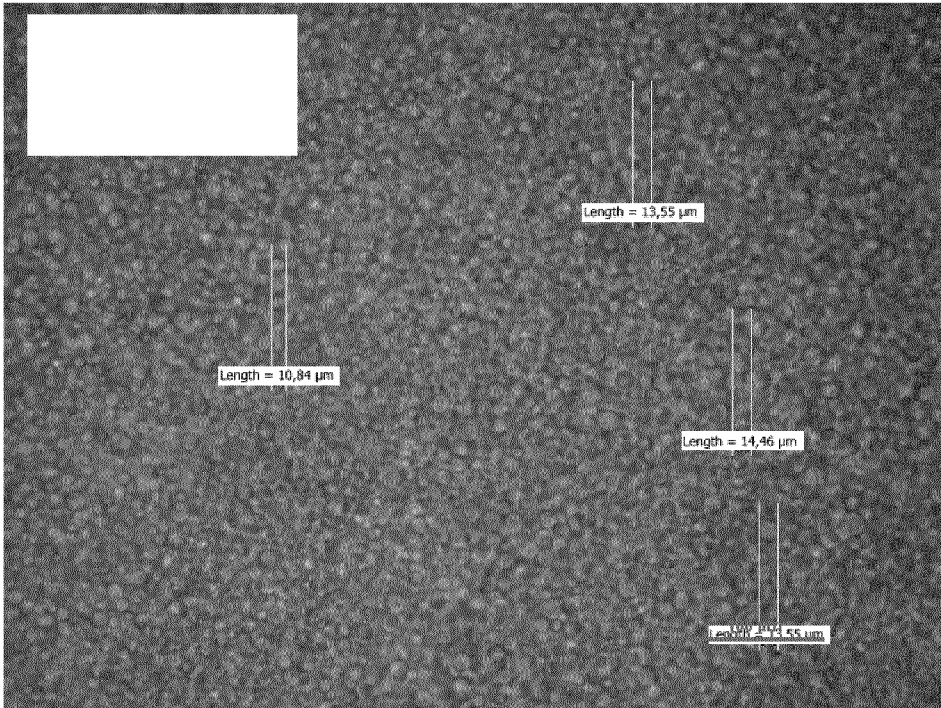


Figure 5

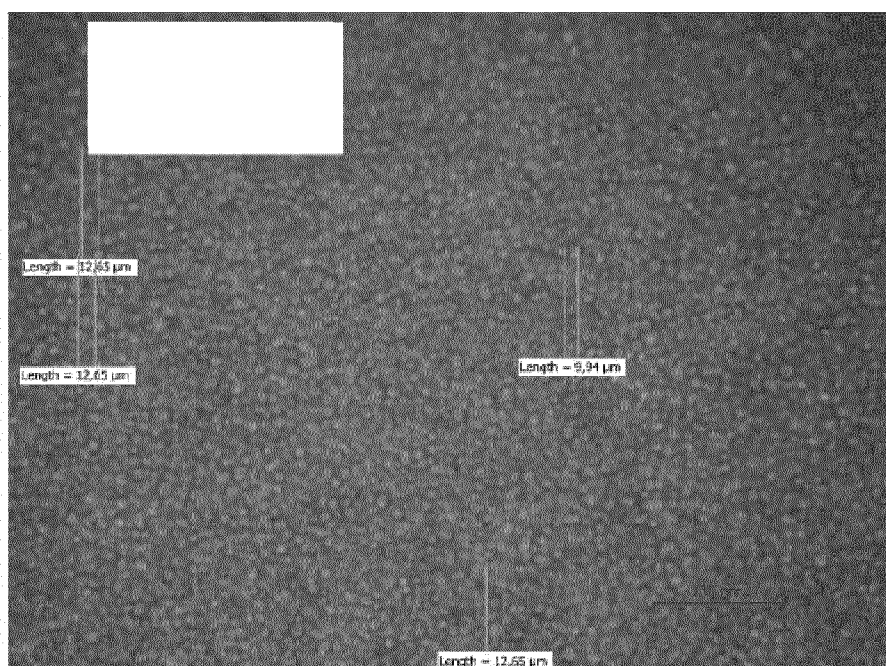


Figure 6

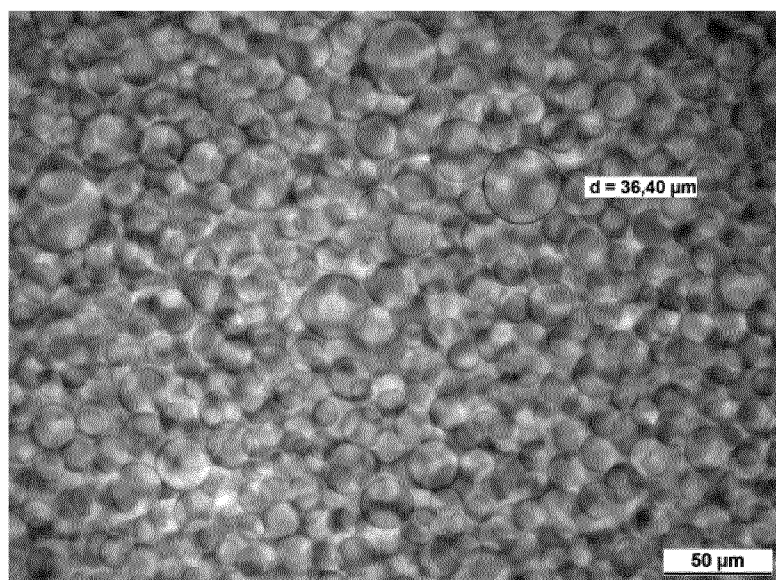
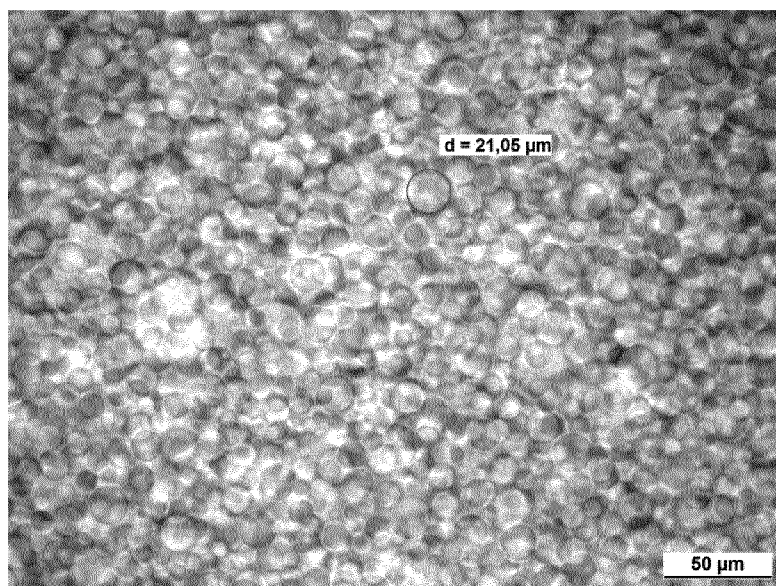


Figure 7



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/061112

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/70 A61K47/34 A61K47/02
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 03/015678 A1 (LAVIPHARM LAB INC [US]) 27 February 2003 (2003-02-27) claims 1,10,11,14; figures 1,2 -----	1-29
X	WO 2013/088254 A1 (LOHMANN THERAPIE SYST LTS [DE]) 20 June 2013 (2013-06-20) claims 1-17; figures 1-4 -----	1-29
X,P	WO 2014/079573 A1 (UCB PHARMA GMBH [DE]; LOHMANN THERAPIE SYST LTS [DE]) 30 May 2014 (2014-05-30) claims; figure 10; examples -----	1-29
X,P	WO 2014/195352 A1 (LOHMANN THERAPIE SYST LTS [DE]) 11 December 2014 (2014-12-11) claims 1-17; figures 1-4 ----- -/-	1-29



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

16 July 2015

Date of mailing of the international search report

30/07/2015

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Giese, Hans-Hermann

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/061112

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 89/10108 A1 (CYGNUS RESEARCH CORP [US]) 2 November 1989 (1989-11-02) the whole document claim 1; example 2 -----	1-29
X	WO 2011/076879 A1 (UCB PHARMA GMBH [DE]; LOHMANN THERAPIE SYST LTS [DE]; WOLFF HANS-MICHA) 30 June 2011 (2011-06-30) the whole document paragraphs [0021], [0066] - [0070]; claim 1 -----	1-29
A	WO 01/01967 A1 (LOHMANN THERAPIE SYST LTS [DE]; MUELLER WALTER [DE]) 11 January 2001 (2001-01-11) claim 1 -----	1-29
A	US 2010/119585 A1 (HILLE THOMAS [DE] ET AL) 13 May 2010 (2010-05-13) the whole document claim 1 -----	1-29

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2015/061112

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03015678	A1	27-02-2003	CA 2460352 A1 27-02-2003 EP 1453447 A1 08-09-2004 NZ 531789 A 27-01-2006 US 2003060479 A1 27-03-2003 WO 03015678 A1 27-02-2003
WO 2013088254	A1	20-06-2013	AR 089201 A1 06-08-2014 AU 2012327247 A1 27-06-2013 CA 2858531 A1 20-06-2013 CL 2014001559 A1 03-10-2014 CN 104114161 A 22-10-2014 CO 7000779 A2 21-07-2014 CR 20140321 A 13-11-2014 DE 112012005185 T5 28-08-2014 EA 201491164 A1 30-10-2014 EP 2790685 A1 22-10-2014 GB 2512007 A 17-09-2014 JP 2015500329 A 05-01-2015 KR 20140101858 A 20-08-2014 PE 23412014 A1 17-01-2015 PH 12014501231 A1 08-09-2014 TW 201338813 A 01-10-2013 US 2014363487 A1 11-12-2014 WO 2013088254 A1 20-06-2013
WO 2014079573	A1	30-05-2014	AU 2013350037 A1 11-06-2015 CA 2887085 A1 30-05-2014 CN 104736146 A 24-06-2015 TW 201431570 A 16-08-2014 WO 2014079573 A1 30-05-2014
WO 2014195352	A1	11-12-2014	EP 2810646 A1 10-12-2014 TW 201509416 A 16-03-2015 WO 2014195352 A1 11-12-2014
WO 8910108	A1	02-11-1989	AT 119019 T 15-03-1995 AU 633500 B2 04-02-1993 AU 3853089 A 24-11-1989 CA 1325381 C 21-12-1993 DE 68921473 D1 06-04-1995 DE 68921473 T2 22-06-1995 DK 241090 A 05-10-1990 EP 0409910 A1 30-01-1991 IE 891070 L 08-10-1989 JP H0575727 B2 21-10-1993 JP H03504977 A 31-10-1991 NO 904317 A 28-11-1990 NZ 228637 A 26-10-1990 PT 90240 A 10-11-1989 US 4906463 A 06-03-1990 WO 8910108 A1 02-11-1989
WO 2011076879	A1	30-06-2011	AU 2010334805 A1 03-05-2012 CA 2767068 A1 30-06-2011 CN 102665699 A 12-09-2012 CN 104189912 A 10-12-2014 EA 201270657 A1 28-12-2012 EP 2515887 A1 31-10-2012

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2015/061112

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
		JP 2013515041 A	02-05-2013	
		KR 20120107971 A	04-10-2012	
		US 2012322845 A1	20-12-2012	
		WO 2011076879 A1	30-06-2011	

WO 0101967	A1	11-01-2001	AT 234081 T	15-03-2003
			AU 774740 B2	08-07-2004
			AU 5222000 A	22-01-2001
			BR 0012152 A	12-03-2002
			CA 2374930 A1	11-01-2001
			CN 1356895 A	03-07-2002
			CZ 20014514 A3	13-03-2002
			DK 1191927 T3	26-05-2003
			EP 1191927 A1	03-04-2002
			ES 2194736 T3	01-12-2003
			HK 1047234 A1	29-07-2005
			HU 0201763 A2	28-12-2002
			JP 4428899 B2	10-03-2010
			JP 2003503445 A	28-01-2003
			MX PA02000118 A	27-02-2003
			NZ 515953 A	30-06-2003
			PL 352361 A1	11-08-2003
			PT 1191927 E	31-07-2003
			TR 200103845 T2	21-05-2002
			TW I255723 B	01-06-2006
			TW I256311 B	11-06-2006
			WO 0101967 A1	11-01-2001

US 2010119585	A1	13-05-2010	AR 064268 A1	25-03-2009
			AU 2007323387 A1	29-05-2008
			BR PI0719115 A2	10-12-2013
			CA 2670290 A1	29-05-2008
			CN 101528207 A	09-09-2009
			DE 102006054731 A1	29-05-2008
			EP 2094249 A2	02-09-2009
			EP 2769714 A1	27-08-2014
			HK 1132921 A1	19-09-2013
			JP 2010510259 A	02-04-2010
			JP 2014028844 A	13-02-2014
			KR 20090082410 A	30-07-2009
			NZ 575500 A	22-12-2011
			RU 2009123368 A	27-12-2010
			TW 200836776 A	16-09-2008
			US 2010119585 A1	13-05-2010
			WO 2008061625 A2	29-05-2008
			ZA 200901695 A	27-01-2010
