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(54) Title: METHOD FOR ADJUSTING THE RELEASE OF ACTIVE AGENT IN A TRANSDERMAL DELIVERY SYSTEM

(57) **Abrégé/Abstract:**

Use of an additive in a transdermal therapeutic system with an active agent-containing layer in the form of a biphasic layer having a hydrophilic inner phase and a hydrophobic outer phase, wherein the inner phase comprises the additive and an active agent dissolved therein, wherein the additive has a higher affinity to water than to the active agent, for the control of the permeation rate of the active agent in a manner which is independent from its concentration in the biphasic layer, wherein the maintenance of the permeation rate is proportional to the amount of active agent in the biphasic layer.

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(54) **Title:** METHOD FOR ADJUSTING THE RELEASE OF ACTIVE AGENT IN A TRANSDERMAL DELIVERY SYSTEM(57) **Abstract:** Use of an additive in a transdermal therapeutic system with an active agent-containing layer in the form of a biphasic layer having a hydrophilic inner phase and a hydrophobic outer phase, wherein the inner phase comprises the additive and an active agent dissolved therein, wherein the additive has a higher affinity to water than to the active agent, for the control of the permeation rate of the active agent in a manner which is independent from its concentration in the biphasic layer, wherein the maintenance of the permeation rate is proportional to the amount of active agent in the biphasic layer.

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**METHOD FOR ADJUSTING THE RELEASE OF ACTIVE AGENT IN A
TRANSDERMAL DELIVERY SYSTEM**

TECHNICAL FIELD OF THE INVENTION

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[001] The present invention relates to the use of an additive for the control of the permeation rate of the active agent in a transdermal therapeutic system (TTS) and a corresponding method of adjusting the period of permeation of a transdermal therapeutic system.

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BACKGROUND OF THE INVENTION

[002] Transdermal therapeutic systems are designed to provide constant dosing of the active agent across the skin and into the bloodstream during the administration period. TTS thus require less frequent dosing and provide constant blood levels during the dosing period avoiding fluctuating blood levels in danger of either being associated with increased side effects or insufficient treatment. Useful dosing periods range from 1 day to 7 days, whereas 7 days are in particular attractive due to the convenient weekly exchange schedule. On the other hand it is technically challenging to provide TTS with constant release rates for time periods as needed and in particular for long periods of time as a 7 days period. A concentration dependent release relying on the concentration gradient between the TTS and the blood stream has limits in terms of dosing intervals and needs a large amount of active in the TTS in excess of the active actually permeating and thus being administered and which is only present for providing the driving force for diffusion. It is thus advantageous to have a mechanism of release which is independent of the concentration of the active in the TTS and thus has the ability to provide the total amount of active in the TTS for administration and which allows the tailoring of the period of administration by the total amount of active in the TTS.

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OBJECTS AND SUMMARY OF THE INVENTION

[003] It is an object of the present invention to provide a system for the control of the release of an active agent from a transdermal therapeutic system which is
5 independent from the active agent concentration.

[004] It is an object of the present invention to provide a system for the control of the release of an active agent from a transdermal therapeutic system which allows the adjusting of the period of administration by adjusting the amount of active in the TTS.

10 [005] It is an object of the present invention to provide a system for the control of the release of active agent from a transdermal therapeutic system which makes use of the total amount of active in the TTS.

[006] This object is accomplished by the present invention, which relates to the use of an additive in a transdermal therapeutic system with an active agent-
15 containing layer in the form of a biphasic layer having a hydrophilic inner phase and a hydrophobic outer phase,
wherein the inner phase comprises

the additive and an active agent dissolved therein,

wherein the additive has a higher affinity to water than to the active agent,
20 for the control of the permeation rate of the active agent in a manner which is independent from its concentration in the biphasic layer, wherein the maintenance of a permeation rate is proportional to the amount of active agent in the biphasic layer.

[006a] This object is also accomplished by the present invention, which relates to use of an additive in a transdermal therapeutic system with an active agent-
25 containing layer in the form of a biphasic layer having a hydrophilic inner phase and a hydrophobic outer phase, wherein the hydrophilic inner phase comprises the additive and an active agent dissolved therein, wherein the additive has a higher affinity to water than to the active agent, and is a hygroscopic polymer or a mixture of hygroscopic polymers selected from the group consisting of
30 polyvinylpyrrolidones, copolymers of vinyl caprolactam, vinylacetate and ethylene glycol, copolymers of vinylpyrrolidone and vinylacetate, copolymers of ethylene and vinylacetate, polyethylene glycols, polypropylene glycols, acrylic polymers, and modified celluloses, wherein the active agent is rotigotine; and wherein the

hydrophobic outer phase is a pressure-sensitive adhesive composition comprising a polymer or polymer mixture which is/are pressure-sensitive adhesive polymer(s) selected from the group consisting of polysiloxanes, polyisobutylenes, polyacrylates, copolymers of styrene and butadiene, and copolymers of styrene and isoprene;

5 for the control of the permeation rate of the active agent in a manner which is independent from a concentration of the active agent in the biphasic layer, wherein the maintenance of the permeation rate is proportional to the amount of active agent in the biphasic layer.

[007] This object is also accomplished by the present invention, which relates to a method of adjusting the period of permeation of a transdermal therapeutic system by

- providing a transdermal therapeutic system with an active agent-containing layer in the form of a biphasic layer having a hydrophilic inner phase and a hydrophobic outer phase, wherein the inner phase comprises
15 the additive and an active agent dissolved therein, wherein the additive has a higher affinity to water than to the active agent,
- adjusting the amount of active in the inner phase of the biphasic layer to the desired administration period.

20 [007a] This object is also accomplished by the present invention, which provides a method of adjusting the period of permeation of a transdermal therapeutic system by

- providing a transdermal therapeutic system with an active agent-containing layer in the form of a biphasic layer having a hydrophilic inner phase and a hydrophobic outer phase,
25 wherein the hydrophilic inner phase comprises an additive and an active agent dissolved therein, wherein the additive has a higher affinity to water than to the active agent, and is a hygroscopic polymer or a mixture of hygroscopic polymers selected from the group consisting of polyvinylpyrrolidones, copolymers of vinyl caprolactam, vinylacetate and ethylene glycol, copolymers of vinylpyrrolidone and vinylacetate, copolymers of ethylene and vinylacetate, polyethylene glycols, polypropylene glycols, acrylic polymers, and modified
30 celluloses, wherein the active agent is rotigotine; and wherein the

hydrophobic outer phase is a pressure-sensitive adhesive composition comprising a polymer or polymer mixture which is/are pressure-sensitive adhesive polymer(s) selected from the group consisting of polysiloxanes, polyisobutylenes, polyacrylates, copolymers of styrene and butadiene, and copolymers of styrene and isoprene; and

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- adjusting the amount of active in the inner phase of the biphasic layer to a desired administration period.

[008] Without wishing to be bound to any theory it is believed that the additive which forms a solution with the active agent and has a higher affinity to water than to the active agent takes up cutaneous water during application of the TTS to the skin of a patient and thereby displacing dissolved active agent. The displaced molecules of active agent are subject to a high driving force for the diffusion out of the TTS to the skin and into the skin. The diffusion and thereby the permeation rate of the active agent is thus independent from the concentration of active agent in the TTS and is

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maintained over the desired administration period in accordance with the total amount of active agent in the TTS.

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[009] In accordance with the invention, the permeation rate is determined by an *in vitro* permeation test performed over an extended period of time using a 51 μm thick membrane consisting of an ethylene vinyl acetate (EVA) copolymer with 9% vinyl acetate (CoTranTM Membrane, 3M) and the Paddle over Disk apparatus described in the United States Pharmacopeia (USP). Phosphate buffer pH 4.5 was used as acceptor medium (900 ml; 32 °C; 50 rpm). The permeation rate of the active agent into the acceptor medium was determined in regular intervals using a validated UV photometric or HPLC method, determination by HPLC is preferred. In accordance

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with the invention, the permeation rate is independent from the concentration of active agent in the biphasic system of the TTS. That is, the permeation rate provided by the TTS according to the invention does not change significantly, i.e., is constant within 20% points, preferably within 15% points, more preferably within 10% points, when the concentration of active agent in the biphasic layer is amended, e.g.

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within a range of the active agent concentration from 1% to 30%, preferably from 1% to 26%. Additionally, the maintenance of a permeation rate of a certain TTS is proportional to the amount of active agent in the biphasic layer. That is, for the provision of a sufficient and continuous permeation rate of active agent over several

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days, a corresponding higher amount of active agent in mg/cm^2 is required than for a TTS designed for a 1-day administration of active agent. According to the invention, the maintenance of a permeation rate of active agent is proportional within 20% points, preferably within 15% points, more preferably within 10% points to the amount of active agent in the biphasic layer.

5 **[0010]** Within the meaning of this invention, the parameter “permeation of the active agent” is provided in $\mu\text{g}/\text{cm}^2$ and relates to the amount of active agent permeated at a certain elapsed time within the total time period of permeation as measured in an *in vitro* permeation test. The value is a mean value of at least

10 **[0011]** Within the meaning of this invention, the parameter “permeation rate” is provided in $\mu\text{g}/\text{cm}^2/\text{hr}$ and is calculated from the amount of active agent permeating during a certain sample interval, e.g. from hour 8 to hour 12, as measured through an EVA membrane in $\mu\text{g}/\text{cm}^2$, divided by the hours of said sample interval, e.g. 4 hours.

15 **[0012]** In accordance with the invention, the skin permeation rate is determined by an *in vitro* permeation test performed over an extended period of time using dermatomized human skin of about 300 μm thickness in a flow cell setup. A phosphate buffered saline (PBS) pH 6.2 was used as acceptor medium (32 °C). The permeation rate of the active agent into the acceptor medium was determined in

20 regular intervals using a validated UV photometric or HPLC method, determination by HPLC is preferred. In accordance with the invention, the skin permeation rate is independent from the concentration of active agent in the biphasic system of the TTS. That is, the permeation rate provided by the TTS according to the invention does not change significantly, i.e., is constant within 20% points, preferably within

25 15% points, more preferably within 10% points, when the concentration of active agent in the biphasic layer is amended, e.g. within a range of the active agent concentration from 1% to 30%, preferably from 1% to 26%. Additionally, the maintenance of a skin permeation rate of a certain TTS is proportional to the amount of active agent in the biphasic layer. That is, for the provision of a sufficient and

30 continuous skin permeation rate of active agent over several days, a corresponding

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higher amount of active agent in mg/cm^2 is required than for a TTS designed for a 1-day administration of active agent. According to the invention, the maintenance of a skin permeation rate of active agent is proportional within 20% points, preferably within 15% points, more preferably within 10% points to the amount of active agent
5 in the biphasic layer.

[0013] Within the meaning of this invention, the parameter “skin permeation of the active agent” is provided in $\mu\text{g}/\text{cm}^2$ and relates to the amount of active agent permeated at a certain elapsed time within the total time period of permeation as measured in an *in vitro* skin permeation test. The value is a mean value of at least
10 3 experiments.

[0014] Within the meaning of this invention, the parameter “skin permeation rate” is provided in $\mu\text{g}/\text{cm}^2/\text{hr}$ and is calculated from the amount of active agent permeating during a certain sample interval, e.g. from hour 9 to hour 12, as measured through skin in $\mu\text{g}/\text{cm}^2$, divided by the hours of said sample interval, e.g. 3 hours.

15 **[0015]** Within the meaning of this invention, the term “transdermal therapeutic system” (or TTS) refers to a system by which the active agent is administered systemically and in particular refers to the entire individual unit that is applied to the skin of a patient, and which comprises an effective amount of the active agent in a self-adhesive layer structure and optionally an additional larger active-free self-
20 adhesive layer structure (overlying adhesive) on top of the active agent-containing self-adhesive layer structure. During 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 **[0016]** Within the meaning of this invention, the term “active agent-containing self-adhesive layer structure” refers to the active agent-containing structure providing the area of release of the active agent during administration. The overlying adhesive adds to the overall size of the TTS but does not add to the area of release. The active agent-containing self-adhesive layer structure comprises a backing layer, an active
30 agent-containing biphasic layer and optionally an additional skin contact layer.

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[0017] 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 phase. Such deposits are e.g., solid solution deposits. Deposits that are visually
5 distinguishable may be identified by use of a microscope.

[0018] Within the meaning of this invention, the term “biphasic layer” refers to the final biphasic layer solidified after coating the coating mixture by e.g. drying a solvent-containing coating mixture or cooling a hot-melt coating mixture. Solvent-containing coating mixtures are preferred according to the invention. The biphasic
10 layer may also be manufactured by laminating two or more layers (e.g. dried layers) of the same composition to provide the desired area weight.

[0019] 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
15 distinguished from a biphasic layer obtained from a hot-melt coating mixture (hot-melt-based layer).

[0020] Within the meaning of this invention, the term “log P” is dimensionless and refers to the logarithm of the octanol/water partition coefficient which is defined as the ratio of the solubility concentration of a compound in octanol (a non-polar
20 solvent) to its solubility concentration in water (a polar solvent). The higher the partition coefficient, the more non-polar the compound. Log P values are generally inversely related to aqueous solubility and known as a measure of lipophilicity. The octanol/water partitioning coefficients (octan-1-ol/water partitioning coefficients) are determined at pH 7.4, 37°C and an ionic strength of 0.15 in an appropriate buffer
25 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).

[0021] Within the meaning of this invention, the term “hygroscopic” is the ability of a substance to absorb water.

[0022] The TTS according to the invention is manufactured with starting materials
30 containing a minimum amount of water.

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[0023] Within the meaning of this invention, the term “solid solution” refers to a mixture of active agent and the additive to provide a single homogeneous phase in form of a solid-state solution.

[0024] Within the meaning of this invention, the terms “polymer mixture” includes
5 mixtures of polymers comprising the same monomer(s) but providing different grades. Polymers of different grades are polymers which are distinguishable by 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
10 monomer vinylpyrrolidone; the commercially available products Dow Corning® BIO PSA 7-4201 and BIO PSA 7-4301 provide individual grades of pressure-sensitive adhesive polysiloxane.

[0025] Within the meaning of this invention, the term “pressure-sensitive adhesive composition” refers to a composition that in particular adheres with finger pressure,
15 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 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
20 mixture with a suitable solvent (e.g. heptanes 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 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
25 and 7-4300 series), the Soft Skin Adhesives series (7-9800), and the BIO-PSA Hot Melt Adhesives manufactured by Dow Corning. Preferred pressure-sensitive polysiloxanes are heptane- and ethyl acetate-solvated pressure-sensitive adhesive polysiloxanes including BIO-PSA 7-4201, BIO-PSA 7-4301, BIO-PSA 7-4202, and BIO-PSA 7-4302.

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[0026] 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., heptanes or ethyl acetate).

[0027] Within the meaning of this invention, the term “polyvinylpyrrolidone”
5 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
10 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
15 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
20 K-Value of 90. Preferred Kollidon® grades are Kollidon® 30 and Kollidon® 90 F.

[0028] 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”.

[0029] Within the meaning of this invention, the term “area weight” refers to the
25 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 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.

30 [0030] If not indicated otherwise “%” refers to weight-%.

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] Fig. 1 depicts the permeation rate of Example 1, Example 2 and Example 3.

5 [0032] Fig. 2 depicts the skin permeation rate of Example 5, Example 6 and Example 7.

DETAILED DESCRIPTION

10 [0033] In accordance with the invention, the additive is used in a transdermal therapeutic system with an active agent-containing layer in the form of a biphasic layer having a hydrophilic inner phase and a hydrophobic outer phase, wherein the inner phase comprises
the additive and an active agent dissolved therein,
15 wherein the additive has a higher affinity to water than to the active agent, for the control of the permeation rate of the active agent in a manner which is independent from its concentration in the biphasic layer, wherein the maintenance of a permeation rate is proportional to the amount of active agent in the biphasic layer.

[0034] In accordance with the invention, there is a method of adjusting the period
20 of permeation of a transdermal therapeutic system by

- providing a transdermal therapeutic system with an active agent-containing layer in the form of a biphasic layer having a hydrophilic inner phase and a hydrophobic outer phase, wherein the inner phase comprises
25 the additive and an active agent dissolved therein, wherein the additive has a higher affinity to water than to the active agent,
- adjusting the amount of active in the inner phase of the biphasic layer to the desired administration period.

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[0035] According to the invention, the additive forms a solid solution with the active agent.

[0036] The additive in accordance with the invention may be a hygroscopic composition. According to certain embodiments, the additive is a hygroscopic polymer or a mixture of hygroscopic polymers. The hygroscopic polymer or the mixture of hygroscopic polymers may be able to take up water from about 1% up to about 60%, preferably from about 10% up to about 60%, more preferably from about 30% up to about 60%.

[0037] According to certain embodiments, the additive is a hygroscopic polymer or a mixture of hygroscopic polymers selected from the group consisting of:

- polyvinylpyrrolidones,
- copolymers of vinyl caprolactam, vinylacetate and ethylene glycol,
- copolymers of vinylpyrrolidone and vinylacetate,
- copolymers of ethylene and vinylacetate,
- polyethylene glycols,
- polypropylene glycols,
- acrylic polymers,
- modified celluloses.

[0038] According to certain specific embodiments, the additive is a hygroscopic polymer or a mixture of hygroscopic polymers selected from the group consisting of:

- polyvinylpyrrolidones having a K-Value of at least 80, or from 80 to 200,
- polyvinylpyrrolidones having a K-Value of less than 80, or from 10 to 79,
- copolymers of vinyl caprolactam, vinylacetate and ethylene glycol,
- copolymers of vinylpyrrolidone and vinylacetate,
- copolymers of ethylene and vinylacetate,
- polyethylene glycols,
- polypropylene glycols,
- copolymers of dimethylaminoethyl methacrylate, butyl methacrylate and methyl methacrylate,
- copolymers of methacrylic acid and methyl methacrylate,

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- hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinates.

[0039] According to certain embodiments, the additive is a polyvinylpyrrolidone having a K-Value of at least 80, or from 80 to 200, or a mixture of polyvinylpyrrolidone having a K-Value of at least 80, or from 80 to 200, and

5 polyvinylpyrrolidone having a K-Value of less than 80, or from 10 to 79.

[0040] According to a certain embodiment the additive is not solely a polyvinylpyrrolidone, in particular a PVP having a K value of at least 80, or from 80 to 200.

[0041] According to certain embodiments, the amount of the additive ranges from
10 0.1 mg/cm² to 10.0 mg/cm², or from 0.1 mg/cm² to 5.0 mg/cm², or from 0.3 mg/cm² to 3.0 mg/cm² of the biphasic layer. The additive may be present in the biphasic layer in a concentration of about 1% to about 20%, or of about 1% to about 15%, of about 1% to about 10%.

[0042] Useful active agents for the TTS according to the invention may have a log
15 P value of about 2.8 to about 6, or of about 3 to about 6, preferably of more than 3 to about 6, or of more than 3 to about 5.

[0043] According to certain embodiments, the active agent has a water solubility of about 1 mg/L to less than 100 mg/L, or of about 5 mg/L to about 50 mg/L, or of about 5 mg/L to about 25 mg/L, preferably the active agent has a log P value of more
20 than 3 to about 6 and a water solubility of about 5 mg/L to about 50 mg/L.

[0044] In a preferred embodiment the active agent is an amine functional drug, which has a log P value of about 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 a log P value of about 2.8 at pH 7.4 and a pKa of 7.4 to
25 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.

[0045] Particularly preferred amine functional drugs are dopamine D2 agonists, which are useful for example in the treatment of Parkinson's disease. Especially
30 preferred dopamine D2 receptor agonists are aminotetraline compounds, such as

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5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol (INN: rotigotine).

[0046] Other examples for particularly preferred amine functional drugs are N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-propanamide (INN: fentanyl) which is
5 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)
10 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
15 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.

20 [0047] According to certain embodiments of the invention, the active agent is selected from the group consisting of rotigotine, fentanyl, oxybutynine, and fesoterodine.

[0048] According to a certain embodiment the active agent is not rotigotine base.

[0049] According to a certain specific embodiment the additive is not solely
25 polyvinylpyrrolidone, in particular a PVP having a K value of at least 80, or from 80 to 200, and the active agent is not rotigotine base.

[0050] According to certain embodiments, the ratio of active agent to the additive is 1:0.2 to 1:1, preferably 1:0.2 to 1:0.8, or 1:0.4 to 1:0.6.

[0051] In accordance with the invention, the active agent may be present in any
30 concentration in the biphasic layer of the TTS. According to certain embodiments,

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the active agent is present in a concentration of about 1% to about 30%, preferably of about 2% to about 25%, or of about 5% to about 25% of the biphasic layer.

[0052] According to certain embodiments, the active agent is present in an amount of 0.1 mg/cm² to 10.0 mg/cm² of the biphasic layer, preferably in an amount of 0.3
5 mg/cm² to 1.0 mg/cm², or 1.0 mg/cm² to 1.5 mg/cm², or 1.5 mg/cm² to 5.0 mg/cm².

[0053] The biphasic layer of the TTS according to the invention contains a hydrophobic outer and a hydrophilic inner phase. According to a certain preferred embodiment, the hydrophilic inner phase forms dispersed deposits in the outer phase.

[0054] The biphasic layer may be coated at any area weight, but is preferably
10 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.

[0055] According to certain embodiments, the biphasic layer is manufactured having a hydrophilic inner phase containing 90% to 100%, preferably 95% to 100%, or 99% to 100% of a solution consisting of said additive and the active agent.

15 [0056] According to certain embodiments, the biphasic layer is a dried biphasic layer. The dried biphasic layer is obtained from a solvent-containing biphasic 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).

20 [0057] The 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
25 conveniently present in an amount of from about 0.001 to about 0.5% of the biphasic layer.

[0058] The 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
30 the barrier properties of the stratum corneum in the sense of increasing the active

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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
5 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.

[0059] In accordance with the invention, the outer phase of the biphasic layer of the TTS is a hydrophobic outer phase. According to a certain embodiment of the
10 invention, the hydrophobic outer phase is a pressure-sensitive adhesive composition.

[0060] According to a certain embodiment of the invention, the hydrophobic outer phase is a pressure-sensitive adhesive composition comprising a polymer or polymer mixture which is a/are pressure-sensitive adhesives polymer(s) selected from the group of polysiloxanes, polyisobutylenes, polyacrylates, copolymers of styrene and
15 butadiene, copolymers of styrene and isoprene, preferably selected from the group of polysiloxanes, or polyisobutylenes.

[0061] Pressure-sensitive adhesive polymers being suitable for a hot-melt coating exhibit a dynamic viscosity of no more than 60 Pa·s, no more than 80 Pa·s, no more than 100 Pa·s, no more than 120 Pa·s or at most 150 Pa·s at a temperature of 160 °C.
20 Depending on the dynamic viscosity of the pressure-sensitive adhesive polymer(s) at 160 °C, the addition of a softener, such as waxes, silicone oils, glycerin, condensates from glycerin with fatty acids or polyols, or laurylacetate, or, in particular, glycerolmonolaurate, laurylacetate, waxes of the formula R-C(O)-OR', alkylmethylsiloxane waxes, siloxated polyether waxes, organic waxes or glycerin,
25 may be required to adjust the viscosity of the pressure-sensitive adhesive polymer(s) in a suitable manner during hot-melt manufacturing processes.

[0062] Pressure-sensitive adhesive polymers being suitable for solvent-containing coating mixtures exhibit a dynamic viscosity of above 150 Pa·s at a temperature of 160 °C and therefore require the addition of a softener in order to be suitable for a
30 hot-melt manufacturing process.

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[0063] According to a certain embodiment of the invention, the pressure-sensitive adhesive composition does not contain a softener, which after the addition to an pressure-sensitive adhesive composition lowers the viscosity of said pressure-sensitive adhesive composition to no more than 60 Pa·s, no more than 80 Pa·s, no more than 100 Pa·s, no more than 120 Pa·s or at most 150 Pa·s at a temperature of 160 °C.

[0064] According to a certain embodiment of the invention, the outer phase does not contain a pressure-sensitive adhesive composition having a dynamic viscosity of no more than 60 Pa·s, no more than 80 Pa·s, no more than 100 Pa·s, no more than 120 Pa·s or at most 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, polyisobutylenes, polyacrylates, copolymers of styrene and butadiene, copolymers of styrene and isoprene, preferably selected from the group of polysiloxanes, or polyisobutylenes.

[0066] In a certain preferred embodiment of the invention, the polymer or polymer 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 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 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

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agent, and participates in the elastic component. The correct balance between dimethiconol and resin provides for the correct adhesive properties.

[0067] 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.

[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 %.

[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 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 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 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

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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 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
5 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 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
10 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 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
15 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.

[0073] Suitable pressure-sensitive adhesive polysiloxanes may be obtained from Dow Corning® BIO-PSA Standard Silicone Adhesives. Preferred pressure-sensitive
20 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 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
25 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.

[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
30 5×10^6 Poise. BIO-PSA 7-4201 has a solution viscosity at 25°C and about 60% solids

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content in heptane of 450 mPa s and a complex viscosity at 0.01 rad/s at 30°C of
1×10⁸ 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 5×10⁶ Poise. BIO-PSA 7-4202 has a solution viscosity at 25°C and about 60%
5 solids content in heptane of 800 mPa s and a complex viscosity at 0.01 rad/s at 30°C
of 1×10⁸ Poise.

[0075] According to certain embodiments of the invention, therapeutically effective
amounts of the active agent are provided for 1 to 7 days by the transdermal
therapeutic system during an administration period to the skin of the patient of 1 to 7
10 days.

[0076] According to certain embodiments of the invention, therapeutically effective
amounts of the active agent are provided for 1 day by the transdermal therapeutic
system according to the invention during an administration period to the skin of the
patient of 1 day.

15 **[0077]** According to certain embodiments of the invention, therapeutically effective
amounts of the active agent are provided for 3 days by the transdermal therapeutic
system according to the invention during an administration period to the skin of the
patient of 3 days, preferably for 4 days during an administration period to the skin of
the patient of 4 days, or for 7 days during an administration period to the skin of the
20 patient of 7 days.

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EXAMPLES

[0078] 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 the invention.

EXAMPLE 1

[0079] The composition of the active agent-containing biphasic coating mixtures is summarized in Table 1 below.

[0080] Table 1

	Solid	Solution
Excipients	[%]	[%]
Rotigotine	7.50	4.665
Polyvinylpyrrolidone (Kollidon 90 F)	3.33	2.07
Ethanol	-	14.04
Sodium metabisulfite solution (10% w/w)	0.0015	0.0093
Ascorbyl palmitate	0.017	0.010
DL- α -Tocopherol	0.042	0.026
BIO-PSA Q7-4301 (70.0% w/w)	53.47	47.515
BIO-PSA Q7-4201 (70.0% w/w)	35.64	31.67
Total	100.00	100.005

[0081] Preparation of the rotigotine-containing biphasic coating mixture (step 1):

[0082] 6.66 g polyvinylpyrrolidone (PVP, Kollidon 90 F), 0.083 g DL- α -Tocopherol, 0.033 g ascorbyl palmitate and 0.030 g of an aqueous sodium metabisulfite solution (10 % by weight) were mixed with 25.93 g anhydrous ethanol to obtain a clear solution (300 - 2000 rpm, propeller stirrer). 15.00 g rotigotine of

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polymorphic Form II were added while stirring at 300 rpm and heated to 60 °C for 90 min. This mixture was added to 152.80 g silicone adhesive BIO-PSA 7-4301 (70.0 % by weight in n-heptane) and 101.84 g silicone adhesive BIO-PSA 7-4201 (70.0 % by weight in n-heptane) were added and stirred at 2000 rpm for 10 min
5 (turbine stirrer) to obtain a stable dispersion.

[0083] Preparation of the transdermal therapeutic system (TTS) (step 2):

[0084] The mixture obtained in step 1 was coated onto a suitable polyester release liner (e.g. Scotchpak™ 9744). The coated release liner sheets were placed in a drying oven and dried at 50 °C for about 30 min and then at 110 °C for about 10 min. The
10 coating thickness was chosen such that removal of the solvents results in an area weight of the rotigotine-containing layer of 60 g/m². The rotigotine-containing layer was laminated with a polyester-type backing foil.

[0085] Finally, individual systems (TTS) having a size of 10 cm² were punched out of the rotigotine-containing self-adhesive layer structure and sealed into pouches.

15

EXAMPLE 2

[0086] The composition of the active agent-containing biphasic coating mixtures is summarized in Table 2 below.

20

[0087] Table 2

	Solid	Solution
Excipients	[%]	[%]
Rotigotine	9.00	5.48
Polyvinylpyrrolidone (Kollidon 90 F)	4.00	2.43
Ethanol	-	16.48
Sodium metabisulfite solution (10% w/w)	0.0018	0.011
Ascorbyl palmitate	0.020	0.012
DL- α -Tocopherol	0.050	0.031
BIO-PSA Q7-4301 (70.0% w/w)	43.46	37.78
BIO-PSA Q7-4201 (70.0% w/w)	43.46	37.78
Total	100.00	100.00

[0088] Preparation of the rotigotine-containing biphasic coating mixture (step 1):

- [0089] 7.01 g polyvinylpyrrolidone (PVP, Kollidon 90F), 0.089 g DL- α -
 5 Tocopherol, 0.035 g ascorbyl palmitate and 0.031 g of an aqueous sodium
 metabisulfite solution (10 % by weight) were mixed with 47.45 g anhydrous ethanol
 to obtain a clear solution (300 - 2000 rpm, propeller stirrer). 15.76 g rotigotine of
 polymorphic Form II were added while stirring at 300 rpm and heated to 60 °C for
 90 min. This mixture was added to 108.75 g silicone adhesive BIO-PSA 7-4301
 10 (70.0 % by weight in n-heptane) and 108.75g silicone adhesive BIO-PSA 7-4201
 (70.0 % by weight in n-heptane) were added and stirred at 2000 rpm for 10 min
 (turbine stirrer) to obtain a stable dispersion.

[0090] Preparation of the transdermal therapeutic system (TTS) (step 2):

- [0091] The mixture obtained in step 1 was coated onto a suitable polyester release
 15 liner (e.g. Scotchpak™ 9744). The coated release liner sheets were placed in a drying
 oven and dried at 50 °C for about 30 min and then at 110 °C for about 10 min. The
 coating thickness was chosen such that removal of the solvents results in an area

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weight of the rotigotine-containing layer of 50 g/m². The rotigotine-containing layer was laminated with a polyester-type backing foil.

[0092] Finally, individual systems (TTS) having a size of 10 cm² were punched out of the rotigotine-containing self-adhesive layer structure and sealed into pouches.

5

EXAMPLE 3

[0093] The composition of the active agent-containing biphasic coating mixtures is summarized in Table 3 below.

10 [0094] Table 3

	Solid	Solution
Excipients	[%]	[%]
Ethanol	-	10.750
Polyvinylpyrrolidone (Kollidon 90 F)	8.000	4.560
Sodium metabisulfite solution 10% (w/w)	0.0036	0.020
Ascorbyl palmitate	0.0401	0.0228
all-rac-Tocopherol	0.0994	0.0566
Rotigotine	18.00	10.260
BIO PSA 7-4302 (60%)	36.93	35.080
BIO PSA 7-4202 (60%)	36.93	35.080
Ethyl acetate	-	4.175
Total	100.00	100.00
Solids content		57.0 %

[0095] Preparation of the rotigotine-containing biphasic coating mixture (step 1):

[0096] To a solution of 13.68 g polyvinylpyrrolidone (PVP, Kollidon 90F) in 32.23 g ethanol and 12.52 g ethyl acetate, 0.171 g DL- α -tocopherol, 0.068 g ascorbyl palmitate and 0.062 g of an aqueous sodium metabisulfite solution (10 % by weight) were added and mixed to obtain a clear solution (1000 rpm, propeller stirrer).

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105.24 g silicone adhesive BIO-PSA 7-4202 (60 % by weight in ethyl acetate) and
105.24 g silicone adhesive BIO-PSA 7-4302 (60 % by weight in ethyl acetate) were
added to the obtained PVP solution and stirred at 500 rpm until complete mixing.
30.78 g rotigotine of polymorphic Form II were added while stirring. The mixture
5 was heated up to 40 °C and stirred at 500 rpm for a minimum of 60 min until a
homogenous dispersion was obtained.

[0097] Preparation of the transdermal therapeutic system (TTS) (step 2):

[0098] The mixture obtained in step 1 was coated onto two sheets of a suitable
polyester release liner (e.g. Scotchpak™ 9755). The coated release liner sheets were
10 placed in a drying oven and dried at 50 °C for about 30 min and then at 115 °C for
about 10 min. The coating thickness was chosen such that removal of the solvents
results in a coating weight of each of the two rotigotine-containing layers of 75 g/m².
The first 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
15 from the surface of the first layer to provide the rotigotine-containing self-adhesive
layer structure with a rotigotine-containing biphasic layer having an area weight of
150 g/m².

[0099] Finally, individual systems (TTS) having a size of 10 cm² were punched out
of the rotigotine-containing self-adhesive layer structure and sealed into pouches.

20

EXAMPLE 4

[00100] In Example 4, the *in-vitro* permeation of Examples 1 to 3 was evaluated by
a membrane permeation test using a 51 µm thick membrane consisting of an ethylene
25 vinyl acetate (EVA) copolymer with 9% vinyl acetate (CoTran™ Membrane, 3M)
and the Paddle over Disk apparatus described in the United States Pharmacopeia
(USP). Phosphate buffer pH 4.5 was used as acceptor medium (900 ml; 32 °C;
50 rpm). TTS with an area of 10 cm² of Example 1, 2 and 3 were tested. The
permeation of rotigotine into the acceptor medium was measured by HPLC. The
30 results are shown in Tables 4 and 5 and Figure 1.

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[00101] Table 4

rotigotine permeation [$\mu\text{g}/\text{cm}^2$] n=3 (SD)			
Time [h]	Example 1	Example 2	Example 3
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
4	23.26 (0.92)	28.00 (1.55)	37.27 (4.40)
8	63.42 (1.84)	74.67 (2.16)	82.49 (7.09)
12	115.33 (2.16)	125.67 (2.80)	128.82 (4.17)
16	166.67 (2.64)	179.33 (2.42)	183.90 (2.07)
20	220.03 (2.99)	232.67 (1.63)	235.10 (2.48)
24	272.01 (4.10)	284.83 (0.75)	287.11 (2.31)
28	324.33 (4.42)	336.50 (1.05)	339.69 (2.26)
32	376.14 (5.34)	386.83 (1.83)	392.64 (1.98)
36	411.96 (2.53)	431.50 (3.39)	445.75 (1.95)
40	427.08 (2.17)	457.67 (7.06)	498.61 (1.63)
44	433.77 (1.47)	468.67 (9.79)	551.23 (1.58)
48	-	-	602.71 (1.72)
52	-	-	656.10 (1.77)
56	-	-	709.57 (2.04)
60	-	-	762.62 (2.69)
64	-	-	815.21 (3.78)
68	-	-	867.34 (4.32)
72	-	-	919.19 (5.34)
76	-	-	969.86 (5.59)
80	-	-	1021.38 (6.16)
84	-	-	1073.09 (6.43)
88	-	-	1123.22 (7.52)
92	-	-	1172.30 (8.19)
96	-	-	1221.74 (9.81)

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100	-	-	1271.46 (10.86)
104	-	-	1320.81 (11.32)
108	-	-	1369.46 (12.72)
112	-	-	1415.27 (13.63)
116	-	-	1460.86 (13.10)
120	-	-	1507.33 (14.18)
124	-	-	1553.71 (15.26)
128	-	-	1600.48 (16.81)
132	-	-	1646.49 (17.41)
136	-	-	1691.47 (19.29)
140	-	-	1736.65 (20.78)
144	-	-	1780.74 (21.97)
148	-	-	1825.03 (22.41)
152	-	-	1869.91 (24.75)
156	-	-	1914.56 (25.78)
160	-	-	1958.29 (26.57)
164	-	-	2000.87 (27.32)
168	-	-	2045.11 (28.02)
172	-	-	2087.75 (29.56)
176	-	-	2130.92 (30.79)
180	-	-	2174.24 (32.05)
184	-	-	2216.06 (35.01)
188	-	-	2257.11 (35.84)
192	-	-	2299.36 (37.55)

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[00102] Table 5

rotigotine permeation rate [$\mu\text{g}/\text{cm}^2/\text{h}$] n=3 (SD)			
Time [h]	Example 1	Example 2	Example 3
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
4	5.82 (0.23)	7.00 (0.39)	9.32 (1.10)
8	10.04 (0.31)	11.67 (0.26)	11.30 (0.77)
12	12.98 (0.39)	12.75 (0.27)	11.58 (1.12)
16	12.83 (0.32)	13.42 (0.20)	13.77 (1.11)
20	13.34 (0.34)	13.33 (0.26)	12.80 (0.11)
24	13.00 (0.47)	13.04 (0.29)	13.00 (0.18)
28	13.08 (0.38)	12.92 (0.26)	13.14 (0.16)
32	12.95 (0.65)	12.58 (0.34)	13.24 (0.13)
36	8.96 (0.80)	11.17 (0.44)	13.28 (0.02)
40	3.78 (0.44)	6.54 (1.03)	13.21 (0.19)
44	1.67 (0.48)	2.75 (0.69)	13.15 (0.10)
48	-	-	12.87 (0.06)
52	-	-	13.35 (0.09)
56	-	-	13.37 (0.36)
60	-	-	13.26 (0.26)
64	-	-	13.15 (0.28)
68	-	-	13.03 (0.18)
72	-	-	12.96 (0.26)
76	-	-	12.67 (0.10)
80	-	-	12.88 (0.16)
84	-	-	12.93 (0.09)
88	-	-	12.53 (0.28)
92	-	-	12.27 (0.17)
96	-	-	12.36 (0.41)
100	-	-	12.43 (0.34)

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104	-	-	12.34 (0.12)
108	-	-	12.16 (0.36)
112	-	-	11.45 (0.25)
116	-	-	11.40 (0.13)
120	-	-	11.62 (0.28)
124	-	-	11.60 (0.27)
128	-	-	11.69 (0.40)
132	-	-	11.50 (0.18)
136	-	-	11.25 (0.47)
140	-	-	11.30 (0.37)
144	-	-	11.02 (0.30)
148	-	-	11.07 (0.27)
152	-	-	11.22 (0.61)
156	-	-	11.16 (0.26)
160	-	-	10.93 (0.20)
164	-	-	10.64 (0.28)
168	-	-	11.06 (0.31)
172	-	-	10.66 (0.44)
176	-	-	10.79 (0.40)
180	-	-	10.83 (0.41)
184	-	-	10.45 (0.74)
188	-	-	10.26 (0.24)
192	-	-	10.56 (0.43)

EXAMPLE 5

[00103] The composition of the rotigotine-containing biphasic coating mixture is summarized in Table 6 below.

[00104] Table 6

	Solid	Solution
Excipients	[%]	[%]
Ethanol	-	12.28
Ethyl acetate	-	3.39
Polyvinylpyrrolidone (Kollidon 90 F)	4.00	2.28
Polyvinylpyrrolidone (Kollidon 30)	6.00	3.42
Sodium metabisulfite solution 10% (w/w)	0.0045	0.03
Ascorbyl palmitate	0.04	0.02
all-rac-Tocopherol	0.10	0.06
Rotigotine	18.00	10.26
BIO PSA 7-4302 (60%)	35.93	34.13
BIO PSA 7-4202 (60%)	35.93	34.13
Total	100.00	100.00
Solids content		57.0 %

[00105] Preparation of the rotigotine-containing biphasic coating mixture (step 1):

- [00106] 13.68 g polyvinylpyrrolidone (PVP, Kollidon 90F) and 20.53 g
5 polyvinylpyrrolidone (PVP, Kollidon 30) were dissolved in 73.67 g ethanol and
20.53 g ethyl acetate. 0.34 g DL- α -tocopherol, 0.14 g ascorbyl palmitate and 0.15 g
of an aqueous sodium metabisulfite solution (10 % by weight) were added and mixed
to obtain a clear solution (1000 rpm, propeller stirrer). 204.81 g silicone adhesive
BIO-PSA 7-4202 (60 % by weight in ethyl acetate) and 204.81 g silicone adhesive
10 BIO-PSA 7-4302 (60 % by weight in ethyl acetate) were added to the obtained PVP
solution and stirred at 500 rpm until complete mixing. 61.56 g rotigotine of
polymorphic Form II were added while stirring. The mixture was heated up to 40 °C
and stirred at 500 rpm for a minimum of 60 min until a homogenous dispersion was
obtained.

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[00107] Preparation of the transdermal therapeutic system (TTS) (step 2):

[00108] The mixture obtained in step 1 was coated onto two sheets of a suitable polyester release liner (e.g. Scotchpak™ 9755). 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 coating thickness was chosen such that removal of the solvents results in a coating weight of each of the two rotigotine-containing layers of 80-82 g/m². The first 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 layer to provide the rotigotine-containing self-adhesive layer structure with a rotigotine-containing biphasic layer having a coating weight of 160-164 g/m². Finally, individual systems (TTS) having a size of 10 cm² were punched out of the rotigotine-containing self-adhesive layer structure and sealed into pouches.

EXAMPLE 6

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[00109] The composition of the rotigotine-containing biphasic coating reservoir mixture is identical to Example 5.

[00110] The composition of the rotigotine-free skin contact layer is summarized in Table 7 below.

20 [00111] Table 7

	Solid	Solution
Excipients	[%]	[%]
BIO PSA 7-4302 (60%)	80.00	80.00
BIO PSA 7-4202 (60%)	20.00	20.00
Total	100.00	100.00

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[00112] Preparation of the rotigotine--free adhesive mixture (step 1):

[00113] 80.01 g silicone adhesive BIO-PSA 7-4202 (60 % by weight in ethyl acetate) were added to 320.01 g silicone adhesive BIO-PSA 7-4302 (60 % by weight in ethyl acetate) and stirred at 500 rpm until complete mixing.

5 [00114] Preparation of the rotigotine--free skin layer (TTS) (step 2):

[00115] The adhesive mixture obtained in step 1 was coated onto sheets of a suitable polyester release liner (e.g. Scotchpak™ 9755). 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 coating thickness was chosen such that removal of the solvents
10 results in a coating weight of each of the adhesive layer of 28 g/m².

[00116] Preparation of the rotigotine-containing biphasic coating mixture (step 3) is identical to step 1 in Example 5.

[00117] Preparation of the transdermal therapeutic system (TTS) (step 4):

[00118] The mixture obtained in step 3 was coated onto sheets of a suitable polyester
15 release liner (e.g. Scotchpak™ 9755). 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 coating thickness was chosen such that removal of the solvents results in a coating weight of the rotigotine-containing layer of 139g/m². The rotigotine-containing layer was laminated with (1) a polyester-type backing foil and (2) the
20 rotigotine--free skin layer after of step 2 to provide the rotigotine-containing self-adhesive layer structure with a rotigotine-containing biphasic layer having a coating weight of 167 g/m². Finally, individual systems (TTS) having a size of 10 cm² were punched out of the rotigotine-containing self-adhesive layer structure and sealed into
25 pouches.

EXAMPLE 7

[00119] The composition of the rotigotine-containing biphasic coating mixture as rotigotine-containing skin contact layer is summarized in Table 8 below.

[00120] Table 8

	Solid	Solution
Excipients	[%]	[%]
Ethanol	-	7.84
Polyvinylpyrrolidone (Kollidon 90 F)	3.33	1.93
Sodium metabisulfite solution 10% (w/w)	0.015	0.01
Ascorbyl palmitate	0.02	0.01
all-rac-Tocopherol	0.04	0.02
Rotigotine	7.50	4.34
BIO PSA 7-4302 (60%)	71.29	68.68
BIO PSA 7-4202 (60%)	17.82	17.17
Total	100.00	100.00
Solids content		57

[00121] Preparation of the rotigotine-containing biphasic coating mixture (step 1):

[00122] 3.34 g polyvinylpyrrolidone (PVP, Kollidon 90F) were dissolved in 13.56 g ethanol. 0.02 g DL- α -tocopherol, 0.04 g ascorbyl palmitate and 0.15 g of an aqueous sodium metabisulfite solution (10 % by weight) were added and mixed to obtain a clear solution (1000 rpm, propeller stirrer). 29.70 g silicone adhesive BIO-PSA 7-4202 (60 % by weight in ethyl acetate) and 118.80 g silicone adhesive BIO-PSA 7-4302 (60 % by weight in ethyl acetate) were added to the obtained PVP solution and stirred at 500 rpm until complete mixing. 7.51 g rotigotine of polymorphic Form II were added while stirring. The mixture was heated up to 40 °C and stirred at 500 rpm for a minimum of 60 min until a homogenous dispersion was obtained.

[00123] Preparation of the transdermal therapeutic system (TTS) (step 2):

[00124] The mixture obtained in step 1 was coated onto sheets of a suitable polyester release liner (e.g. Scotchpak™ 9755). 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 coating thickness was chosen such that removal of the solvents results in a

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coating weight of each of the rotigotine-containing layer of 28 g/m². The rotigotine-containing layer was laminated with (1) a polyester-type backing foil and (2) the the rotigotine-containing layer of Example 6 with a coating weight of 188-192 g/m² after removal of the release liner from the surface of the first layer to provide the
5 rotigotine-containing self-adhesive layer structure with a rotigotine-containing biphasic layer having a total coating weight of 160-164 g/m². Finally, individual systems (TTS) having a size of 10 cm² were punched out of the rotigotine-containing self-adhesive layer structure and sealed into pouches.

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EXAMPLE 8

[00125] In Example 8, the *in-vitro* skin permeation of Examples 5, 6 and 7 was evaluated by *in-vitro* skin permeation test performed over 192 hours using dermatomized human skin of about 300 μm thickness in a flow cell setup. A
15 phosphate buffered saline (PBS) pH 6.2 was used as acceptor medium (32 °C) and the area of the acceptor cells was 0.52cm². Samples were taken every hour for the first 6 hours, every 3 hours until 18 hours and every 6 hours for the remaining time of the experiments. The permeation of rotigotine into the acceptor medium was determined by HPLC. The results are shown in Tables 9 and 10 and Figure 2.

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[00126] Table 9

rotigotine skin permeation [$\mu\text{g}/\text{cm}^2$] n=3 (SD)			
Time [h]	Example 5	Example 6	Example 7
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1	0.08 (0.06)	0.11 (0.02)	0.12 (0.01)
2	0.40 (0.07)	0.43 (0.15)	0.77 (0.56)
3	1.57 (0.16)	1.35 (0.60)	2.48 (1.61)
4	3.95 (0.38)	3.08 (1.24)	5.24 (2.89)
5	7.57 (0.73)	5.69 (1.98)	9.04 (4.28)
6	12.36 (1.20)	9.18 (2.79)	13.91 (5.69)
9	32.46 (3.07)	24.19 (5.30)	32.94 (9.63)
12	58.53 (5.22)	44.27 (7.71)	57.17 (13.11)
15	88.64 (7.35)	67.75 (10.09)	85.12 (16.34)
18	121.66 (9.38)	93.70 (12.50)	115.73 (19.40)
21	156.98 (11.35)	121.63 (14.84)	148.41 (22.29)
24	193.94 (13.04)	150.86 (17.22)	182.68 (25.08)
30	272.15 (16.19)	213.11 (22.01)	255.45 (30.34)
36	353.62 (18.88)	278.34 (26.84)	331.15 (35.72)
42	437.33 (21.09)	345.64 (31.65)	409.14 (40.97)
48	522.53 (22.85)	414.33 (36.44)	488.38 (46.06)
54	608.55 (24.49)	484.11 (41.37)	568.40 (51.16)
60	695.40 (25.73)	554.21 (46.28)	649.42 (56.18)
66	781.61 (26.99)	624.16 (50.92)	729.93 (60.86)
72	868.28 (28.02)	694.63 (55.52)	810.85 (65.41)
78	955.51 (28.77)	765.50 (60.06)	892.13 (69.80)
84	1040.63 (30.06)	836.39 (64.27)	973.52 (74.00)
90	1124.99 (32.68)	907.33 (68.39)	1055.32 (78.31)
96	1210.24 (35.12)	978.08 (72.67)	1137.45 (82.47)
102	1296.73 (37.18)	1049.66 (76.80)	1220.56 (86.66)

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108	1384.60 (38.69)	1121.75 (81.20)	1303.98 (90.84)
114	1473.52 (39.81)	1194.00 (85.44)	1387.47 (95.07)
120	1563.25 (40.67)	1267.62 (90.44)	1471.27 (99.28)
126	1653.44 (41.87)	1342.30 (95.93)	1554.91 (103.32)
132	1743.80 (42.84)	1416.98 (101.50)	1638.61 (107.32)
138	1834.18 (43.78)	1492.10 (107.37)	1722.20 (111.18)
144	1924.70 (44.69)	1567.82 (113.79)	1805.90 (115.12)
150	2015.42 (45.48)	1643.71 (120.18)	1889.45 (119.23)
156	2106.00 (46.33)	1718.18 (125.54)	1972.81 (123.60)
162	2196.52 (47.00)	1792.63 (130.85)	2055.97 (128.00)
168	2286.50 (47.82)	1866.46 (136.22)	2138.73 (132.36)
174	2375.57 (48.91)	1938.38 (140.51)	2220.66 (136.65)
180	2462.37 (51.96)	2009.42 (144.89)	2301.77 (140.58)
186	2549.97 (54.03)	2079.95 (149.31)	2382.35 (144.54)
192	2637.99 (55.34)	2150.31 (153.14)	2462.66 (148.56)

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[00127] Table 10

rotigotine skin permeation rate [$\mu\text{g}/\text{cm}^2/\text{h}$] n=3 (SD)			
Time [h]	Example 5	Example 6	Example 7
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1	0.09 (0.06)	0.11 (0.02)	0.14 (0.03)
2	0.32 (0.03)	0.32 (0.17)	0.66 (0.55)
3	1.17 (0.09)	0.92 (0.46)	1.70 (1.05)
4	2.38 (0.22)	1.73 (0.63)	2.76 (1.28)
5	3.61 (0.35)	2.61 (0.74)	3.80 (1.39)
6	4.79 (0.47)	3.48 (0.81)	4.86 (1.41)
9	6.70 (0.62)	5.00 (0.85)	6.34 (1.31)
12	8.69 (0.72)	6.69 (0.84)	8.08 (1.16)
15	10.04 (0.71)	7.83 (0.83)	9.32 (1.08)
18	11.00 (0.68)	8.65 (0.84)	10.20 (1.02)
21	11.77 (0.67)	9.31 (0.81)	10.89 (0.96)
24	12.32 (0.57)	9.74 (0.81)	11.42 (0.93)
30	13.04 (0.54)	10.37 (0.81)	12.13 (0.88)
36	13.58 (0.47)	10.87 (0.81)	12.62 (0.90)
42	13.95 (0.39)	11.22 (0.81)	13.00 (0.88)
48	14.20 (0.31)	11.45 (0.80)	13.21 (0.85)
54	14.34 (0.29)	11.63 (0.82)	13.34 (0.85)
60	14.47 (0.22)	11.68 (0.82)	13.50 (0.84)
66	14.37 (0.21)	11.66 (0.78)	13.42 (0.78)
72	14.44 (0.17)	11.74 (0.78)	13.49 (0.76)
78	14.54 (0.13)	11.81 (0.78)	13.55 (0.73)
84	14.19 (0.62)	11.81 (0.73)	13.56 (0.70)
90	14.06 (0.92)	11.82 (0.73)	13.63 (0.72)
96	14.21 (0.73)	11.79 (0.78)	13.69 (0.69)
102	14.42 (0.57)	11.93 (0.77)	13.85 (0.70)

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108	14.64 (0.33)	12.02 (0.82)	13.90 (0.70)
114	14.82 (0.20)	12.04 (0.80)	13.92 (0.71)
120	14.95 (0.15)	12.27 (0.84)	13.97 (0.70)
126	15.03 (0.20)	12.45 (0.92)	13.94 (0.68)
132	15.06 (0.16)	12.45 (0.94)	13.95 (0.67)
138	15.06 (0.16)	12.52 (1.00)	13.93 (0.65)
144	15.09 (0.15)	12.62 (1.09)	13.95 (0.67)
150	15.12 (0.14)	12.65 (1.08)	13.92 (0.70)
156	15.10 (0.15)	12.41 (0.90)	13.89 (0.74)
162	15.09 (0.12)	12.41 (0.89)	13.86 (0.75)
168	15.00 (0.14)	12.31 (0.90)	13.79 (0.75)
174	14.85 (0.18)	11.99 (0.88)	13.66 (0.75)
180	14.47 (0.54)	11.84 (0.95)	13.52 (0.70)
186	14.60 (0.35)	11.75 (0.98)	13.43 (0.71)
192	14.67 (0.22)	11.73 (0.91)	13.39 (0.73)

CLAIMS

1. Use of an additive in a transdermal therapeutic system with an active agent-containing layer in the form of a biphasic layer having a hydrophilic inner phase and
5 a hydrophobic outer phase,
wherein the hydrophilic inner phase comprises the additive and an active agent dissolved therein,
wherein the additive has a higher affinity to water than to the active agent,
and is a hygroscopic polymer or a mixture of hygroscopic polymers selected
10 from the group consisting of:
- polyvinylpyrrolidones,
- copolymers of vinyl caprolactam, vinylacetate and ethylene glycol,
- copolymers of vinylpyrrolidone and vinylacetate,
- copolymers of ethylene and vinylacetate,
15 - polyethylene glycols,
- polypropylene glycols,
- acrylic polymers, and
- modified celluloses;
wherein the active agent is rotigotine; and
20 wherein the hydrophobic outer phase is a pressure-sensitive adhesive composition comprising a polymer or polymer mixture which is/are pressure-sensitive adhesive polymer(s) selected from the group consisting of polysiloxanes, polyisobutylenes, polyacrylates, copolymers of styrene and butadiene, and copolymers of styrene and isoprene;
25 for the control of the permeation rate of the active agent in a manner which is independent from a concentration of the active agent in the biphasic layer, wherein the maintenance of the permeation rate is proportional to the amount of active agent in the biphasic layer.
- 30 2. The use in accordance with claim 1, wherein said additive forms a solid solution with the active agent.

3. The use in accordance with claim 1 or 2, wherein said active agent has a water solubility of about 1 mg/L to less than 100 mg/L.
4. The use in accordance with any one of claims 1 to 3, wherein the active agent
5 is present in a concentration of about 1% w/w to about 30% w/w of the biphasic layer.
5. The use in accordance with any one of claims 1 to 4, wherein the active agent is present in an amount of 0.1 mg/cm² to 10.0 mg/cm² of the biphasic layer.
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6. The use in accordance with any one of claims 1 to 5, wherein said hygroscopic polymer or said mixture of hygroscopic polymers is/are able to take up water from about 1% up to about 60%.
- 15 7. The use in accordance with any one of claims 1 to 6, wherein the amount of said additive ranges from 0.1 mg/cm² to 10.0 mg/cm² of the biphasic layer.
8. The use in accordance with any one of claims 1 to 7, wherein said additive is present in the biphasic layer in a concentration of about 1% w/w to about 20% w/w.
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9. The use in accordance with any one of claims 1 to 8, wherein the biphasic layer has an area weight of about 30 g/m² to about 400 g/m².
10. The use in accordance with any one of claims 1 to 9, wherein the transdermal
25 therapeutic system is formulated to release amounts of active agent for 1 to 7 days upon application to the skin of a patient during an administration period of 1 to 7 days.
11. Method of adjusting the period of permeation of a transdermal therapeutic
30 system by:

- providing a transdermal therapeutic system with an active agent-containing layer in the form of a biphasic layer having a hydrophilic inner phase and a hydrophobic outer phase,
 - wherein the hydrophilic inner phase comprises an additive and an active agent dissolved therein,
 - wherein the additive has a higher affinity to water than to the active agent, and is a hygroscopic polymer or a mixture of hygroscopic polymers selected from the group consisting of:
 - polyvinylpyrrolidones,
 - copolymers of vinyl caprolactam, vinylacetate and ethylene glycol,
 - copolymers of vinylpyrrolidone and vinylacetate,
 - copolymers of ethylene and vinylacetate,
 - polyethylene glycols,
 - polypropylene glycols,
 - acrylic polymers, and
 - modified celluloses;
 - wherein the active agent is rotigotine; and
 - wherein the hydrophobic outer phase is a pressure-sensitive adhesive composition comprising a polymer or polymer mixture which is/are pressure-sensitive adhesive polymer(s) selected from the group consisting of polysiloxanes, polyisobutylenes, polyacrylates, copolymers of styrene and butadiene, and copolymers of styrene and isoprene;
- adjusting the amount of active in the inner phase of the biphasic layer to a desired administration period.

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12. The method in accordance with claim 11, wherein said additive forms a solid solution with the active agent.

13. The method in accordance with claim 11 or 12, wherein said active agent has a water solubility of about 1 mg/L to less than 100 mg/L.

14. The method in accordance with any one of claims 11 to 13, wherein the active agent is present in a concentration of about 1% w/w to about 30% w/w of the biphasic layer.
- 5 15. The method in accordance with any one of claims 11 to 14, wherein the active agent is present in an amount of 0.1 mg/cm² to 10.0 mg/cm² of the biphasic layer.
16. The method in accordance with any one of claims 11 to 15, wherein said hygroscopic polymer or said mixture of hygroscopic polymers is/are able to take up
10 water from about 1% up to about 60%.
17. The method in accordance with any one of claims 11 to 16, wherein the amount of said additive ranges from 0.1 mg/cm² to 10.0 mg/cm² of the biphasic layer.
15
18. The method in accordance with any one of claims 11 to 17, wherein said additive is present in the biphasic layer in a concentration of about 1% w/w to about 20% w/w.
- 20 19. The method in accordance with any one of claims 11 to 18, wherein the biphasic layer has an area weight of about 30 g/m² to about 400 g/m².
20. The method in accordance with any one of claims 11 to 19, wherein the transdermal therapeutic system is formulated to release amounts of active agent for 1
25 to 7 days upon application to the skin of a patient during an administration period of 1 to 7 days.

Figure 1

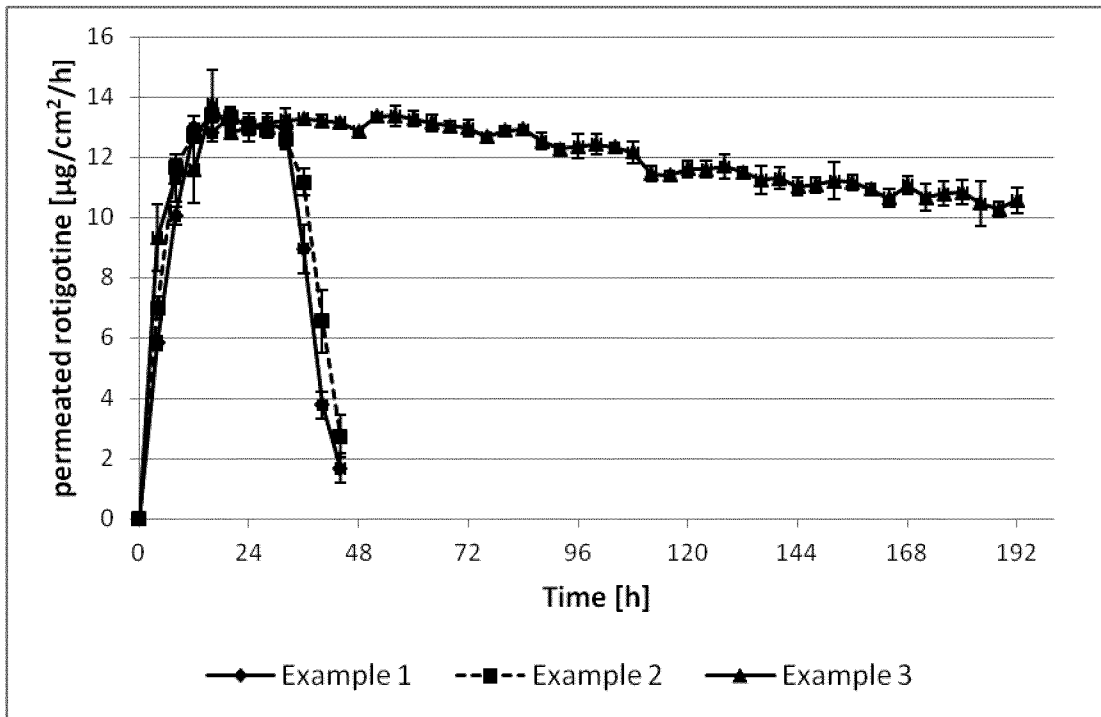


Figure 2

