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(54) **Transzdermális terápiás rendszer buprenorfin hatóanyag adagolására**

Transdermal therapeutic system for administering the active substance buprenorphine

Description

[0001] The present invention relates to a transdermal therapeutic system with at least one carboxylic acid which determines the solubility of the buprenorphine in the matrix layer and is likewise absorbable, for pain therapy with significantly increased active substance utilization.

[0002] The active ingredient buprenorphine (17-(cyclopropyl-methyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-6,14-ethenomorphinan-7-methanol) is a partially synthetic opiate whose advantage over other compounds from this substance class lies in a higher activity. This means that analgesia can be achieved in cancer or tumor patients with very unfavourable diagnosis in the final stage with daily doses of around 1 mg. In this context, an advantage of buprenorphine over the synthetic opioid fentanyl and its analogues is that the addictive potential of buprenorphine is lower than that of these compounds. The disadvantage is that, owing to the high molecular weight of buprenorphine, namely 467.64 daltons, it is difficult to effect its transdermal absorption.

[0003] In spite of this, transdermal systems containing buprenorphine (e.g. Transtec® or Norspan®) are already commercially available. German Patent DE 39 39 376 C1 describes their functionality. The active ingredient is in homogeneous solution in a polyacrylate matrix with a carboxylic acid serving as permeation enhancer and solubilizer.

[0004] Systems in which the active ingredient is in homogeneous solution are commonly distinguished by low active substance utilization. The reason for this is that the thermodynamic activity of the active ingredient, which determines the delivery of active ingredient, decreases in the course of administration as a result of the decreasing active ingredient loading. Uniform delivery of active ingredient over the entire administration time is achievable only through a relatively high active ingredient loading in comparison to the amount to be delivered. The published data for Transtec® 35 which is a product marketed in Europe suggest, for example, an

active substance utilization of only 17% over the administration period. Given that buprenorphine is an expensive active ingredient, higher active substance utilization would be a substantial advantage from a costs standpoint.

[0005] A very low loading of the system with buprenorphine, which is a narcotic, and a resultant minimal residual content following application in the systems used, is additionally very desirable in view of safety aspects.

[0006] Thus, it was the object of the present invention to develop a TTS which makes the active ingredient buprenorphine, whose transdermal absorption is difficult to effect, available for transdermal administration with significantly increased active substance utilization.

[0007] This object is achieved in accordance with the invention in a surprising way by means of a transdermal therapeutic system for administering buprenorphine to the skin, wherein the TTS comprises an active ingredient-impermeable backing layer, at least one pressure-sensitive adhesive matrix layer comprising the active ingredient buprenorphine and at least one carboxylic acid, and, optionally, a protective layer to be detached before use. The matrix layer is constructed on the basis of polysiloxanes or polyisobutylene. The buprenorphine is in solution in the carboxylic acid or the carboxylic acids, and this solution is in dispersion in the form of droplets in the matrix layer. This is all the more surprising in view of the fact that buprenorphine, due to its known physicochemical properties, in particular its poor solubility, its comparatively high melting point of 216 °C and, as already mentioned, its high molecular weight, tends readily towards crystallization. For this reason a solvent with at least one acidic group is used in order to prevent the buprenorphine crystallization during the storage of the pharmaceutical form. Both buprenorphine itself and carboxylic acids have an extremely low solubility in polysiloxanes or polyisobutylene. Thus, it is possible to dissolve buprenorphine in a carboxylic acid and to disperse this solution in the form of droplets in a matrix layer prepared on the

basis of polysiloxanes, preferably amine-resistant dimethyl-polysiloxanes, more preferably a mixture of an amine-resistant and a non-amine-resistant dimethyl-polysiloxane, wherein the non-amine-resistant dimethyl-polysiloxane is present at no more than 40% by weight, preferably 2% to 20% by weight, or polyisobutylene as base polymer. In this case, it is important that the mixture of buprenorphine and carboxylic acid or carboxylic acids is in liquid form.

[0008] Generally, the carboxylic acids employed are sparingly soluble in the organic solvents of the adhesives. Thus, the liquid mixture of buprenorphine and carboxylic acid can be dispersed in the solution of the adhesive, wherein the dispersion is retained after removal of the solvent. In such a matrix layer, the solubility of the buprenorphine is virtually only dependent on the amount of the carboxylic acid or carboxylic acids. The amount of the dispersed solution can amount to up to 40% by weight, wherein it is preferred that 20% by weight are not exceeded. Preferably, the droplet size itself should not exceed 50 µm. The preferred size depends additionally on the thickness of the matrix layer.

[0009] Figure 1 shows a schematic representation of such a mono-layer self-adhesive system. In Figure 2 a system with a skin contact layer is depicted; Figure 3 shows a multilayer system with an over-plaster. In these figures are:

1 backing layer
2 matrix layer based on polysiloxanes with dispersed droplets of a buprenorphine-carboxylic acid solution
3 protective layer to be removed before use
4 skin contact layer based on a polyacrylate adhesive
5 pressure-sensitive adhesive layer without buprenorphine
6 backing layer (e.g. skin-coloured)

[0010] Since carboxylic acids can likewise be absorbed through the skin, their amount in the system decreases during the time of application and hence also the saturation solubility of the buprenorphine. Thereby, the decrease in the thermodynamic activity of buprenorphine caused by the delivery is compensated. The choice of the carboxylic acid is guided by the absorption through the skin, which is just as quick, and preferably quicker, compared with buprenorphine. It is preferred to use carboxylic acids which are liquid at skin temperature. The carboxylic acid or the carboxylic acids is or are selected from the group consisting of oleic acid, laevulinic acid, linoleic acid and linolenic acid. Given proper execution, it is possible to achieve supersaturated states during the time of application. In supersaturated systems, the thermodynamic activity of the active ingredient and hence also the permeation rate per area unit is increased in accordance with the supersaturation factor. Advantageously, it is thus possible to minimize the delivery area and also the area of the system. During storage, both buprenorphine and the acid remain in the polymer matrix, so that during this time the system is at most saturated and recrystallization of the active ingredient is excluded.

[0011] A further aspect of the invention concerns the effect that in such systems, if the delivery of the acid is too quick, the rise in thermodynamic activity can lead to an excessive increase in the permeation rate after application. The consequence is that the TTS is prematurely exhausted as a result of the excessively rapid delivery of active ingredient. It has now been found that this kind of effect is prevented by addition of a further layer based on polyacrylates. This layer is preferably located between the active ingredient-containing polymer matrix layer and the skin, or else between matrix layer and backing layer. This additional layer is preferably executed as self-adhesive skin contact layer.

[0012] The solubility of buprenorphine in polyacrylates is significantly higher than in polysiloxanes or polyisobutylene and, depending on the precise composition, reaches up to about 10 per cent by weight. Since the overall system has thus a higher

saturation solubility for buprenorphine, the degree of supersaturation caused by the delivery of the acid is reduced by redistribution of the buprenorphine from the matrix layer into the polyacrylate layer. The delivery of active ingredient is thus more uniform, and a premature exhaustion of the system is prevented. It has been found that in one preferred embodiment with a loading of the the matrix layer of about 0.4 mg of buprenorphine and the use of the carboxylic acid laevulinic acid, per cm^2 a skin contact layer with a coating weight of 15-30 g/m^2 is sufficient to achieve the desired effect.

[0013] Regarding the monomers used for producing the polyacrylate adhesive, there are basically no limitations. Based on theoretical considerations, however, adhesives without free carboxyl groups are preferred as they are unable to immobilize the basic buprenorphine via formation of salts.

[0014] Figure 2 shows a schematic representation of such a system; the preparation is described in Example 1. The thickness of the matrix layer and the skin contact layer must in each case be optimized as a function of the chosen active ingredient concentration in the matrix layer and the amount of active ingredient per unit area, respectively. The amount or concentration of the acid in the matrix layer depends on its dissolution ability for buprenorphine. In the case of the preferred use of laevulinic acid, buprenorphine and the acid are used in equal proportions by weight. The chosen concentration of both substances of 7% to 9% by weight has proved to be suitable, but can also be chosen differently without affecting the performance of the TTS, when taken into account for the selection of the coating weight.

[0015] Transdermal therapeutic systems according to Example 1 were compared in a pharmacokinetics study in humans with already marketed TTS as a reference system. It was found that a 17 cm^2 system according to Example 1 with a buprenorphine content of 6.3 mg corresponds to a 25 cm^2 reference TTS with an active ingredient content of 20 mg. Taking into account the declared delivery of the reference product

of 35 µg/h TTS, an active substance utilization of 17% for the reference product and an active substance utilization of 53% for a TTS according to Example 1 is achieved. This clearly shows that with transdermal systems according to Example 1, the objective of a substantially improved active substance utilization was achieved. Thus, with the TTS according to the invention with buprenorphine as active ingredient, it is possible to achieve in vivo active substance utilizations of at least 30%, preferably at least 40%, more preferably at least 50%. Additionally, it is advantageous that these systems can be used with a surface area of approximately 30% less than the reference systems due to the higher permeation rate.

[0016] A particular advantage is that this improved active substance utilization allows for the loading of the system with the narcotic buprenorphine to be further reduced, and thus for a further minimization of the residual buprenorphine content in the used systems after application.

[0017] The transdermal therapeutic systems according to the invention can be provided with different release profiles and in different dose strengths. As already described above, the active ingredient release profile can be influenced by, for example, appropriate variation of the layer thickness of the active ingredient-containing matrix and/or the skin contact layer, or by altering the concentration of active ingredient in the matrix. The dose strength of the TTS according to the invention can be modified, for example, by varying the surface area of the active ingredient-containing matrix, while keeping the composition and layer thickness of the matrix and skin contact layer the same, in order to thereby obtain different dose strengths. Preferably, it is thus possible to obtain transdermal therapeutic systems which have comparable properties with transdermal therapeutic systems already on the market.

[0018] By providing TTS with different dosage levels, it is possible to adjust a patient individually on the amount of active ingredient he or she requires.

Furthermore, it becomes possible to set up the delivery of active ingredient to the patient in such a way that he or she is titrated in a way which is known in principle by means of an appropriate dosage scheme to the amount of active ingredient he or she needs. In such a scheme, the amount of active ingredient administered to the patient is increased accordingly by means, for example, of sequential administration of transdermal therapeutic systems with different dose strengths. The sequential increase in the dose of active ingredient may allow for a further reduction in the side effects which may possibly arise in the course of administration of the active ingredient buprenorphine. Examples of the sequential adaptation of the delivery of active ingredient to a patient by means of appropriate dosing schemes are described in, for example, patent applications WO 2006/030030 A2 and EP 1572167. Thus, the present invention also comprises systems, e.g. kits, which comprise several TTS according to the invention with different dose strengths.

[0019] The transdermal therapeutic systems according to the invention may be shaped to allow for a subdivision of the TTS into different sub-units. Such divisibility also allows for further modification of the TTS to the individual active ingredient required by a patient or the use of the TTS for implementation of an appropriate dosing scheme. Advantageously, the divisible TTS thus contains a plethora of polymer matrix regions which are spatially separated by active ingredient-free regions. The TTS can then be divided along the active ingredient-free regions, e.g. by cutting, in order to separate one or more polymer matrix regions from the rest of the TTS. Examples of the structure of divisible TTS variants are described in, e.g., patent applications WO 2003/079962 A2 and WO 02/41878 A2.

[0020] The transdermal therapeutic systems according to the invention can be used and modified for different durations of administration, respectively. The TTS according to the invention can, for example, be applied for at least 12 h or 24 h. Preferably, the individual TTS of the invention can, however, also be used over an

application duration of at least 72 h, 84 h or 96 h. Longer application durations, however, are also possible, such as, for example, 120 h, 144 h or 168 h.

[0021] The invention is further illustrated by the following examples, however, without thereby restricting the scope of the invention:

Example 1

[0022]

A In a stainless steel vessel, 3.65 kg of buprenorphine are suspended in 3.65 kg of laevulinic acid and 2.6 kg of ethanol. Under stirring, 60.6 kg of a polysiloxane adhesive in the form of a solution in n-heptane having a solids content of 74% by weight and 9.72 kg of heptane are added. The mixture is stirred until the buprenorphine base is fully dissolved to give 80.22 kg of a buprenorphine-containing adhesive solution with 4.55% of buprenorphine with a solids content of 64.8% (adhesive solution 1).

B For the skin contact layer, a polyacrylate adhesive prepared from 2-ethylhexyl acrylate, vinyl acetate and 2-hydroxyethyl acrylate is used. 31.87 kg of a solution of this adhesive with a solids content of 51% by weight is admixed with 6.5 kg of ethyl acetate and 1.91 kg of oleic acid, in pure form or as a mixture with other carboxylic acids, to give, following homogenization, approximately 40 kg of active ingredient-free polyacrylate solution (adhesive solution 2).

C Auxiliary means known to the person skilled in the art are used to coat a film, which has been treated so as to be abhesive for the chosen adhesive, with the buprenorphine-containing adhesive solution 1. The coating thickness is chosen such that removal of the solvents results in a coating weight of the matrix layer

of 55 g/m^2. The concentration of buprenorphine and laevulinic acid in this layer is 7% to 9% by weight. The backing layer of the subsequent system is then laminated onto the "dried" matrix layer. Adhesive solution 2 is likewise coated onto an abhesively treated film (the protective film to be which is to be removed before the systems are used) and the organic solvents are removed. The coating thickness of the resulting skin contact layer ought to amount to approximately 20 g/m^2 after removal of the solvents. The abhesively treated film is then removed from the matrix layer which was produced first, and the matrix layer is laminated onto the skin contact layer.
The individual systems can now be punched from the resulting total laminate.

[0023] In specific embodiments, a TTS as described above can be provided with an over-plaster of larger surface area, preferably with rounded corners, comprising a pressure-sensitive adhesive matrix layer which is free of active ingredient and has a preferably skin-coloured backing layer. This is advantageous when the skin contact layer does not adhere sufficiently to the skin on the basis of its physical properties alone and/or when the buprenorphine-containing matrix layer has pronounced corners (square or rectangular shapes) for the purpose of avoiding waste.

Example 2 - 5

[0024] Preparation is carried out according to Example 1, only the concentrations and layer thickness of the matrix layer is varied in accordance with Table 1.

Example 6

[0025] As Example 6, the commercial product Transtec® from Grünenthal GmbH was used.

Table 1: Composition of the buprenorphine-containing TTS relative to the active ingredient matrix

Example	Area weight matrix layer [g/m²]	Buprenorphine content in the matrix layer [% by weight]	Buprenorphine content [mg/cm²]	Laevulinic acid content Laminate 1 [% by weight]
1	55	7	0.385	7
2	60	7	0.42	7
3	65	8.4	0.546	8.4
4	80	7	0.56	7

[0026] Using these TTS, in vitro experiments were carried out with the Franz diffusion cell, which is known to a person skilled in the art, using epidermis from human full-thickness skin. For this purpose, diecuts with an area of 2.54 cm^2 were punched from laminates and were tested against diecuts of the commercial product Transtec®, respectively. Transtec® is commercially available in three different dose strengths, which are, however, proportional to their surface area. The concentrations of buprenorphine in the acceptor medium of the Franz cell were measured (Tab. 2). Additionally, after the experiment, the TTS were analyzed for their buprenorphine and laevulinic acid content. The results of the analyses of Example 1 are shown in table and graph form alongside those of the further examples.

Table 2: Average cumulative amounts of buprenorphine in micrograms/hour, released at the Franz cell from the TTS according to the invention.

Example	2 h	4 h	8 h	24 h	32 h	48 h	56 h	72 h
1	< d.l.	0.015	0.118	1.79	3.40	7.56	13.6	21.1
2	< d.l.	0.007	0.062	0.87	1.72	5.3	9.63	19.3
3	0.013	0.027	0.076	0.689	1.36	4.7	9.15	21.5
4	0.035	0.071	0.184	1.64	3.27	8.86	12.9	25.9

Transtec®	n.d.	0.061	0.167	2.35	n.d.	11.4	n.d.	25.4

[0027] When the cumulative flux rates of Table 2 are compared with one another, it is seen that all permeation rates of the TTS according to the invention are situated in the same order of magnitude as those of the commercial product Transtec®. Despite the fact that the Franz cell is not a substitute for clinical trials, but is instead used in order to discriminate between different TTS formulations, can the results presented in Table 2 be evaluated to show that the TTS of Example 1 delivers just as much buprenorphine as Transtec® under in vitro conditions. As already described above, a TTS according to Example 1 was compared in a pharmacokinetics study in humans with this already marketed TTS as reference system, and for the reference product an active substance utilization of 17% TTS was demonstrated in comparison to an active substance utilization of 53% for a TTS according to Example 1.

[0028] After the permeation studies, all of the example TTS according to the invention were analysed for their residual laevulinic acid content. The residual amounts and the relative quantities of laevulinic acid delivered, as calculated from the residual amounts, are shown in Table 3.

Table 3: Release of laevulinic acid

Example	Laevulinic acid content [mg/cm²]	Residual laevulinic acid in TTS [mg/cm²]	Released laevulinic acid [%]
1	0.385	0.025	93.5
2	0.42	0.026	93.8
3	0.546	0.033	94
4	0.56	0.039	93

[0029] Table 3 illustrates that in accordance with the teaching of the invention the TTS deplete of laevulinic acid during use and thus bring about the surprisingly high utilization of the active ingredient buprenorphine.

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Transzdermális terápiás rendszer buprenorfin hatóanyag adagolására

Szabadalmi igénypontok:

1. Transzdermális terápiás rendszer buprenorfin bőrre történő adagolására, amely rendszer tartalmaz hatóanyagot át nem eresztő fedőréteget, legalább egy, nyomásra érzékeny tapadó mátrix réteget, amely tartalmazza a buprenorfin hatóanyagot és tartalmaz legalább egy karbonsavat, és a rendszer adott esetben tartalmaz egy használat előtt leválasztható védőréteget, azzal jellemezve, hogy a mátrix réteg polisziloxán- vagy poliizobutilén alapúként van kialakítva, a buprenorfin fel van oldva a karbonsavban vagy karbonsavakban, és ez az oldat cseppek formájában diszpergálva van a mátrix rétegben, és a mátrix réteg diffúziót lehetővé tevő kontaktusban van egy poliakrilát-alapú, öntapadó, a bőrrel érintkezésbe kerülő réteggel.

2. Az 1. igénypont szerinti transzdermális terápiás rendszer, azzal jellemezve, hogy a polisziloxán amin-rezisztens dimetilpolisziloxán.

3. Az 1. igénypont szerinti transzdermális terápiás rendszer, azzal jellemezve, hogy a polisziloxán amin-rezisztens és nem-amin-rezisztens dimetilpolisziloxán keveréke, ahol a nem-amin-rezisztens dimetilpolisziloxán legfeljebb 40 tömeg% mennyiségben van jelen.

4. Az előző igénypontok közül egy vagy több szerinti transzdermális terápiás rendszer, azzal jellemezve, hogy a karbonsav gyorsabban diffundál a bőrbe, mint a buprenorfin hatóanyag.

5. Az előző igénypontok közül egy vagy több szerinti transzdermális terápiás rendszer, azzal jellemezve, hogy a diszpergált oldat mennyisége legfeljebb 40 tömeg%, előnyösen legfeljebb 20 tömeg%.

6. Az előző igénypontok közül egy vagy több szerinti transzdermális terápiás rendszer, azzal jellemezve, hogy a karbonsav folyékony a bőr hőmérsékletén.

7. A 6. igénypont szerinti transzdermális terápiás rendszer, azzal jellemezve, hogy a karbonsavat az olajsav, levulinsav, linolsav és a linolénsav által alkotott csoportból választjuk.

8. A 7. igénypont szerinti transzdermális terápiás rendszer, azzal jellemezve, hogy a buprenorfin és a levulinsav azonos tömegarányban van jelen.

9. Az 1. igénypont szerinti transzdermális terápiás rendszer, azzal jellemezve, hogy a poliakrilát ragasztóanyag nem rendelkezik szabad karboxilcsoporttal.

10. Az előző igénypontok közül egy vagy több szerinti transzdermális terápiás rendszer, azzal jellemezve, hogy in vivo körülmények között legalább 30 %-os, előnyösen legalább 40 %-os és még előnyösebben legalább 50 %-os hatóanyag-kihasználást érünk el.

11. Az előző igénypontok közül egy vagy több szerinti transzdermális terápiás rendszer fájdalomterápiás kezelésben való alkalmazásra.

Fig 1

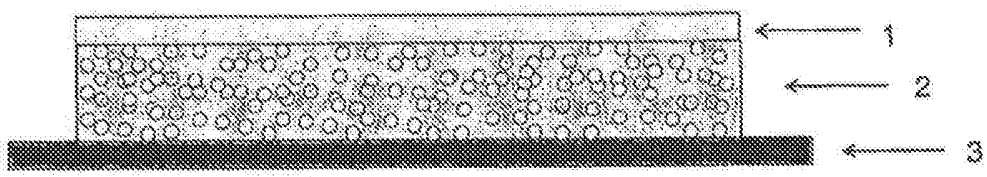

Fig 2

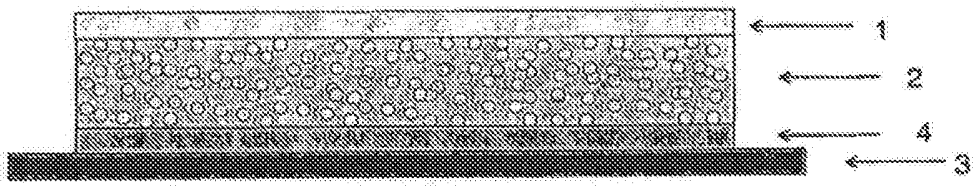

Fig 3