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(54) Titre : SYSTEME THERAPEUTIQUE TRANSDERMIQUE CONTENANT DU FENTANYLE ET DES SUBSTANCES APPARENTEES

(54) Title: TRANSDERMAL THERAPEUTIC SYSTEM CONTAINING FENTANYL OR RELATED SUBSTANCES

(57) Abrégé/Abstract:
The invention relates to a transdermal therapeutic system (TTS), comprising a backing layer, which is permeable to the active ingredient, at least one matrix layer, comprising fentanyl or an active agent analogous to fentanyl, based on polyacrylate and a protective layer to be removed before usage, characterised in that the polyacrylate polymer is self-adhesive, free of carboxyl groups, has a saturation solubility for fentanyl of 3 to 20 wt. %, preferably of 4 to 12 and particularly of 5 to 10 wt. % and the layers contain at least 80 % of the included active ingredient in a molecularly-dispersed, dissolved form.

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(54) Title: TRANSDERMAL THERAPEUTIC SYSTEM WITH FENTANYL OR RELATED SUBSTANCES

(54) Bezeichnung: TRANSDERMALES THERAPEUTISCHES SYSTEM MIT FENTANYL BZW. VERWANDTEN SUBSTANZEN

(57) Abstract: The invention relates to a transdermal therapeutic system (TTS), comprising a backing layer, which is permeable to the active ingredient, at least one matrix layer, comprising fentanyl or an active agent analogous to fentanyl, based on polyacrylate and a protective layer to be removed before usage, characterised in that the polyacrylate polymer is self-adhesive, free of carboxyl groups, has a saturation solubility for fentanyl of 3 to 20 wt. %, preferably of 4 to 12 and particularly of 5 to 10 wt. % and the layers contain at least 80 % of the included active ingredient in a molecularly-dispersed, dissolved form.

(57) Zusammenfassung: Die Erfindung bezieht sich auf ein transdermales therapeutisches System (TTS) bestehend aus einer wirkstoffundurchlässigen Rücksicht, zumindest einer Fentanyl oder einen fentanylanalogen Wirkstoff enthaltenden Matrixschicht auf Basis von Polyacrylat und einer vor Gebrauch zu entfernenden Schutzschicht, das dadurch gekennzeichnet ist, dass das Polyacrylatpolymer selbstklebend und frei von Carboxylgruppen ist, für Fentanyl eine Sättigungslöslichkeit zwischen 3 und 20 Gewichtsprozenten, bevorzugt eine Sättigungslöslichkeit zwischen 4 und 12 und besonders bevorzugt eine Sättigungslöslichkeit zwischen 5 und 10 Gewichtsprozenten aufweist, und dass die wirkstoffhaltigen Schichten mindestens 80 Gewichtsprozent des eingearbeiteten Wirkstoffs in molekulardispers gelöster Form enthalten.

WO 03/018075 A3

Transdermal therapeutic system containing fentanyl or related substances

Description

Fentanyl and fentanyl-analogous substances such as sulfentanyl, carfentanyl, lofentanyl and alfentanyl are extremely efficacious analgesics. The requirement for only a low dose and their physicochemical properties such as the n-octanol/water partition coefficient, melting point and the molecular weight make possible the transdermal administration of these substances in an efficacious amount and their pharmacokinetic properties such as the rapid metabolization and the relatively narrow therapeutic index make transdermal administration desirable.

In fact, a TTS containing fentanyl as active compound has been on the market for some years. This system is a "reservoir system". A reservoir system is understood here as meaning a system which contains the active compound in a liquid or gelatinous preparation in a sachet formed from an impermeable film, which serves as a back layer, and an active compound-permeable membrane, the membrane additionally being provided with an adhesive layer for fixing the system to the skin. In this specific case, fentanyl is dissolved in a mixture of ethanol and water. Further details of this system can be taken from US patent specification 4,588,580 or DE-C 35 26 339, which both contain a detailed description.

Reservoir systems, however, have the disadvantage that in the case of a leak in the reservoir sachet the active compound-containing reservoir filling comes in contact with the skin over a wide area and the active compound is absorbed in excessively high doses. This is very dangerous, especially in the case of fentanyl and

its derivatives, since an overdose very rapidly leads to respiratory depression and therefore fatal incidents. A number of such fatal or near-fatal incidents are described in *Clinical Pharmacokinet,* **2000**, 38(1), 59-89.

In one aspect, the invention relates to a transdermal therapeutic system (TTS) consisting of: an active compound-impermeable back layer; at least one matrix layer based on polyacrylate and comprising fentanyl or a fentanyl-analogous active compound; and a protective film to be removed before use, wherein the polyacrylate is self-adhesive and free of carboxyl groups and has a saturation solubility for fentanyl of between 3 and 20% by weight, and wherein the active compound-containing layers contain at least 80% by weight of the incorporated active compound in molecularly disperse dissolved form.

The invention makes available a transdermal therapeutic system containing fentanyl or fentanyl analogs, which offers the user increased safety against an inadvertent absorption of overdoses.

This is possible according to the invention in that, instead of the reservoir system, a matrix system is employed in which the active compound is incorporated directly into a self-adhesive polyacrylate and thus, even in the case of damage to the system, cannot come into contact with the skin over a greater area than afforded by the TTS. In such a system, the active compound is generally completely, but to at least 80%, dissolved in molecularly disperse form in this polymer, the saturation solubility of the active compound in the polymer being between 3 and 20% by weight. Furthermore, it has surprisingly been shown that when using polyacrylate adhesives for the production of TTS containing fentanyl and its analogs, only adhesives without free carboxyl groups are suitable.

Such matrix systems in the simplest case consist of a back layer, which is impermeable to the active compound, of a self-adhesive active compound-containing layer and of a protective layer to be removed before use. In complicated embodiments of such systems is additionally also added a membrane controlling the release of active compound, which is normally further provided with an adhesive layer for fixing the system to the skin.

The active compound-containing layers of such a matrix system according to this invention consist of

polyacrylates. Since free functional groups increase the saturation solubility of fentanyl and its derivatives in polyacrylate adhesives above the preferred range, the polyacrylate adhesives which are best suited are those which have no free functional groups and are only prepared from esters of acrylic and/or methaycrylic acid and optionally other vinyl compounds without free functional groups such as vinyl acetate. However, in the synthesis of the adhesive, monomers having free hydroxyl groups such as 2-hydroxyethyl acrylate or 2-hydroxyethyl methacrylate can be tolerated up to a content of 20% by weight. Polyacrylates are prepared by free-radical polymerization using acrylic and/or methacrylic acid derivatives. Such derivatives are, for example, esters. By way of example of such derivatives, acrylic and methacrylic acid derivatives may be mentioned, in particular esters of alcohols having 1 to 8 C atoms, which optionally contain one hydroxyl group, such as 2-ethylhexyl acrylate, n-octyl acrylate, propyl acrylate, n- or isobutyl acrylate, 2-hydroxyethyl acrylate and dimethylaminoethyl acrylate or the corresponding methacrylates. Additionally, other polymerizable vinyl compounds without free functional groups such as, for example, vinyl acetate can also be used, e.g. in amounts of up to 50% by weight. The polymers thus prepared are also described as random copolymers, as solely the quantitative distribution of the monomers employed and chance decide the composition of the polymer chains.

If the polymers contain free hydroxyl groups, the possibility exists of additionally crosslinking the polymer chains by polyvalent cations such as Al^{3+} or Ti^{4+} or reactive substances such as melamine. Use is made of this possibility in order to increase the molecular weight and thus to improve the cohesion of the polymers. The possibility of the crosslinkage of polyacrylates, in particular of polyacrylate adhesives,

is particularly valuable if the plasticizing action of the active compound dissolved in the polymers or the plasticizing action of other auxiliaries has to be compensated. The adhesive is usually used in the form of a solution. Solvents used are, for example, ethyl acetate, hexane or heptane, ethanol or their mixtures. These are removed during the preparation of the TTS.

Table 1 shows the results of permeation studies which have been obtained using an adhesive with and an adhesive without free carboxyl groups (but without hydroxyl groups). In both adhesives, the active compound was incorporated in a concentration of 5 percent by weight. The permeation study was carried out by means of the Franz diffusion cells known to the person skilled in the art and using human skin.

Table 1: Results of permeation studies using adhesives with and without free carboxyl groups

Formulation	Cumulated amount of permeated active compound [µg/cm^2] Mean value of n = 3 *				
	4 h	8 h	24 h	48 h	72 h
1	0.00	0.00	0.44	1.71	3.51
2	0.0	0.2	4.0	14.7	28.24

* skin used: female lower abdominal skin

Formulation 1: polyacrylate adhesive with 4.8% by weight of free carboxyl groups

Formulation 2: neutral polyacrylate adhesive without free carboxyl groups but with 5.2% by weight of free hydroxyl groups

The results show that a neutral adhesive without free carboxyl groups is markedly superior to a carboxyl group-containing adhesive with respect to the permeation rates achievable.

An important characteristic of each active compound-containing polymer in TTS technology is the saturation solubility of the chosen polymer for the respective active compound. This parameter is important because the thermodynamic activity of the active compound in the matrix does not depend on the absolute amount of active compound dissolved, but rather on the ratio of the actual concentration to the saturation concentration. Since the active compound on application of the TTS to the skin must disperse in the skin and in the process bring into line not concentrations, but activities, it is important for achieving a permeation rate which is as high as possible to choose as high as possible a thermodynamic activity of the active compound in the TTS. This means that the solubility of the active compound in the active compound-containing parts of the TTS must not be too high, since otherwise the active compound concentration in the TTS must be quite high in order to achieve an adequately high thermodynamic activity. This is unadvantageous if the active compound disadvantageously influences the physical properties of the active compound-containing parts of the system in the high concentration and/or the active compound is very expensive. In the case of fentanyl, both reasons are true, it additionally still having to be taken into consideration that fentanyl and its derivatives belong to the narcotics and for this reason alone it is therefore desirable to incorporate as little active compound in the TTS as possible and/or to make the utilization of active compound, i.e. the ratio of active compound released during the wearing time of the TTS to the content of the unworn TTS, as large as possible.

From this point of view, the saturation solubility of the active compound-containing layers for a three-day TTS should not be below 3 percent by weight and not above 20 percent by weight. At higher saturation

solubilities, even with a high specific permeation rate, the utilization of active compound is too poor, and the TTS is not readily marketable for commercial reasons because of the expensive active compound. Preferably, for these reasons the saturation solubility is between 4 and 12 and particularly preferably between 5 and 10, percent by weight.

The saturation solubility of fentanyl and its analogs can additionally be reduced by the addition of substances which do not have good dissolving properties for the active compound. Such substances are, for example, liquid hydrocarbons such as dioctylcyclohexane, liquid paraffin, hydrocarbon resins such as polyterpenes, in particular polypinene, or polar substances such as glycerol, di- and triglycerol or polyethylene glycols, e.g. having a molecular weight from 200 to 1000. These substances can form a homogeneous mixture with the polyacrylate adhesive or else be contained therein as a separate phase. Glycerol and its derivatives especially are already present in low concentrations in the matrix as a separate phase, e.g. in the form of droplets. By means of the addition of such substances, it is in particular also possible to compensate the higher saturation solubility in adhesives having free hydroxyl groups.

Table 2 contains some data regarding the saturation solubilities of fentanyl in some of these substances.

Table 2: Saturation solubilities of fentanyl in solubility-decreasing additives

Substance	**Saturation solubility [% by weight]**
Polyethylene glycol 400	7.5
Glycerol	< 1.5
Diglycerol	< 1.5
Dioctylcyclohexane	< 1.9
Paraffin, liquid	< 1.5

The influence of such additives can be recognized by means of comparative permeation studies.

In table 3, the results of permeation studies with matrices based on a neutral polyacrylate adhesive having free hydroxyl groups with and without such additives and of a polyacrylate adhesive without other free functional groups are compared. All formulations contain fentanyl in a concentration of 5% by weight.

Table 3. Comparative permeation studies using formulations with and without solubility-decreasing additives

Formulation	Cumulated amount of permeated active compound [µg/cm^2] Mean value of n = 3 *				
	4 h	8 h	24 h	48 h	72 h
2	0.00	0.23	7.89	32.82	64.17
3	0.798	4.46	29.6	68.9	103.1
4	0.805	4.87	32.6	74.7	113.2

* skin: human epidermis, female breast skin

Formulation 2: 5% by weight fentanyl in a neutral polyacrylate adhesive with 5.2% free hydroxyl groups

Formulation 3:	fentanyl	5.0%
	polyacrylate adhesive, neutral with 5.2% free hydroxyl groups	55.0%
	polypinene	15.0%
	glycerol	10.0%
	dioctylcyclohexane	15.0%

Formulation 4: 5% by weight of fentanyl in a polyacrylate adhesive without free functional groups

The results of the permeation study show that the permeation rate can be significantly improved by the addition of substances reducing the solubility of the active compound in the matrix. Approximately the same results are achieved by the use of an adhesive without free functional groups, which even without additives has a low dissolving capacity for the active compound.

From the permeation data, the respective TTS sizes can be calculated for various TTS strengths. The results are listed in table 4.

Table 4: TTS sizes calculated from permeation data

Release rate	**Calculated area sizes [cm^2]**				
	Form. 1	**Form. 2***	**Form. 2****	**Form. 3**	**Form. 4**
25 µm/h	513	63.7	28.1	17.45	15.9
50 µm/h	1026	127.4	56.2	34.9	31.8
75 µm/h	1539	191.1	84.3	52.35	47.7
100 µm/h	2052	254.8	112.4	69.8	63.6

* calculated on the basis of the permeation data from table 1

** calculated on the basis of the permeation data from table 2

The result of the calculation shows that carboxyl group-containing adhesives at a fentanyl concentration of 5% even at the lowest dose lead to TTS which are too large for practical use. Although quite large TTS are also calculated in the case of the hydroxyl group-containing adhesives, the possibility exists here due to the increase in the fentanyl concentration to arrive at TTS having a size suitable for practical use with concentrations which are not too high, i.e. at most 20%. Simplified, it can be assumed here that the thermodynamic activity and thus also the permeation rates depend linearly on the concentration, as long as the active compound is present completely dissolved.

By use of the solubility-lowering auxiliaries in formulations having hydroxyl group-containing polyacrylate adhesives or by the use of polyacrylate adhesives without free functional groups, even at a fentanyl concentration of 5%, TTS are obtained which have an acceptable size, even in the highest dose of 100 µg/h. Of course, the possibility also offers itself here of further reducing the system area by increasing the fentanyl concentration.

Fentanyl and its derivatives, as already mentioned at the outset, have a narrow therapeutic index. This means that for the action, on the one hand, a certain threshold value which must be exceeded with respect to the plasma concentration, on the other hand unacceptable side-effects rapidly occur at higher concentrations. It is therefore advantageous if the system additionally contains a control membrane and thus the active compound flow through the skin is restricted to a maximum value independently of the individual skin condition. Such membranes preferably consist of a copolymer of ethylene and vinyl acetate (EVA polymer) or are microporous films based on polyethylene or polypropylene. The prior art includes

membranes of this type. In the case of the EVA polymers, the active compound permeability depends on the content of vinyl acetate and the thickness of the membrane. Membranes having a VA content of between 2 and 25 percent by weight and a thickness of between 25 and 100 µm, preferably between 40 and 100 µm, are customary, there being scarcely any limitations in practice with respect to the vinyl acetate content and the thickness. For the particular formulation, both parameters must be chosen accordingly in order to guarantee restriction to the desired maximum flow from the TTS. In the case of the microporous membranes, the substance transport does not take place through the polymer, but only through the pores found in these membranes. The number and size of the pores in this case determines the maximum release rate of the TTS.

Customarily, such membranes are provided with an adhesive film for fixing the TTS to the skin. Adhesive films based on self-adhesive polyacrylates or self-adhesive polysiloxanes are particularly suitable for fentanyl and its derivatives. The advantage of polysiloxanes here is that the active compound in these polymers is very poorly soluble and therefore the active compound loading of the TTS does not have to be increased unnecessarily by the use of an additional adhesive film. Adhesive films of this type, however, can also be used in systems which contain no membranes, but matrix layers having lower adhesive power.

As in any TTS, of course, there is also the possibility here of reducing the barrier properties of the human horny layer by the use of permeation-promoting substances. Such substances are, for example, fatty acids, fatty alcohols, fatty acid esters, esters of glycerol with medium- or long-chain fatty acids and glycols such as 1,2-propanediol. All substances can be employed here which are physiologically acceptable and

compatible with the active compound and the other excipients.

In summary, it is to be observed the matrix systems within the meaning of this invention show satisfactory to good permeation rates and also make possible the production of TTS having an acceptable size. At the same time, an endangering of the patient by an excessively high absorption of active compound as a result of a leak is impossible. Overall, matrix systems based on polyacrylate adhesives within the meaning of this invention are thus an important advance in relation to the known prior art for fentanyl and its analogs with respect to patient safety.

Examples:

Example 1 (formulation 1, 2, 4)

Fentanyl (free base) is dissolved in the solution of the adhesive in heptane/ethyl acetate. The amount of fentanyl is in this case calculated such that, based on the solids content of the adhesive solution, a concentration of 5.0% results. The resulting material is coated using a doctor blade onto a siliconized polyester film protective layer to be removed before use, in a thickness such that, after the removal of the solvent, a weight of the coating of about 80 g/m^2 results. After the removal of the solvent, the dried film is laminated with a thin polyester film (back layer of the TTS), and the finished TTS are stamped out of the complete laminate.

Example 2 (formulation 3):

5.0 g of fentanyl, 15.0 g of polypinene, 10.0 g of glycerol, 15.0 g of dioctylcyclohexane and 110 g of the adhesive solution having a solids content of 50.0% are combined and stirred until the fentanyl has dissolved.

The resulting material is coated using a doctor blade onto a siliconized polyester film (protective layer to be removed before use) in a thickness such that, after the removal of the solvent, a weight of the coating of about 80 g/m^2 results. After the removal of the solvent, the dried film is laminated with a thin polyester film (back layer of the TTS) and the finished TTS are stamped out of the complete laminate.

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CLAIMS:

1. A transdermal therapeutic system (TTS) consisting of: an active compound-impermeable back layer; at least one matrix layer based on polyacrylate and comprising fentanyl or a fentanyl-analogous active compound; and a protective film to be removed before use, wherein the polyacrylate is self-adhesive and free of carboxyl groups and has a saturation solubility for fentanyl of between 3 and 20% by weight, and wherein the active compound-containing layers contain at least 80% by weight of the incorporated active compound in molecularly disperse dissolved form.

2. The TTS as claimed in claim 1, wherein the polyacrylate has a saturation solubility of between 4 and 12% by weight for fentanyl.

3. The TTS as claimed in claim 2, wherein the polyacrylate has a saturation solubility of between 5 and 10% by weight for fentanyl.

4. The TTS as claimed in any one of claims 1 to 3, wherein the polyacrylate has no free functional groups and is synthesized only from monomers of acrylic or methacrylic acid esters and, optionally, additionally from other polymerizable vinyl compounds without free functional groups in amounts of up to 50% by weight.

5. The TTS as claimed in claim 4, wherein the additional polymerizable vinyl compound is vinyl acetate.

6. The TTS as claimed in any one of claims 1 to 5, wherein the monomer mixture on which the polyacrylate is based contains up to 20% by weight of monomers having free functional groups in the form of 2-hydroxyethyl acrylate and/or methacrylate.

7. The TTS as claimed in any one of claims 1 to 6, which additionally contains a control membrane as a further layer.

8. The TTS as claimed in claim 7, which additionally contains a self-adhesive layer situated toward the skin on the membrane for fixing to the skin.

9. The TTS as claimed in claim 7or 8, wherein the control membrane consists of an ethylene/vinyl acetate copolymer, or of a microporous film based on polyethylene or polypropylene.

10. The TTS as claimed in claim 9, wherein the ethylene/vinyl acetate copolymer has a vinyl acetate content of up to 25% by weight.

11. The TTS as claimed in claim 9 or 10, wherein the control membrane has a thickness of between 25 and 100 µm.

12. The TTS as claimed in claim 11, wherein the control membrane has a thickness of between 40 and 100 µm.

13. The TTS as claimed in any one of claims 1 to 12, wherein the active compound-containing layers additionally contain a substance for improving the permeation rate through human skin.

14. The TTS as claimed in claim 13, wherein the substance is a glycol, a fatty acid, a fatty acid ester, a fatty alcohol or a glycerol ester.

15. The TTS as claimed in any one of claims 1 to 14, wherein the active compound-containing layers contain a substance which lowers the solubility of the active compound in said layers.

16. The TTS as claimed in claim 15, wherein the substance is a hydrocarbon which is liquid at room temperature, a hydrocarbon resin, or polyethylene glycol or glycerol.

17. The TTS as claimed in claim 16, wherein the hydrocarbon is dioctylcyclohexane or paraffin, and the hydrocarbon resin is a polypinene resin.

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