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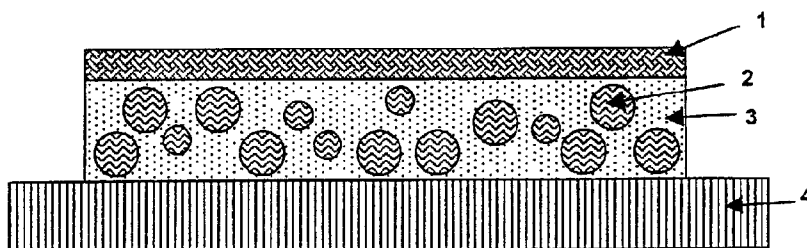
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(54) Title: OCCLUSIVE TRANSDERMAL THERAPEUTIC SYSTEM WIT A NON-OCCLUSIVE BACKING LAYER

(54) Bezeichnung: OKKLUSIVES TRANSDERMALES THERAPEUTISCHES SYSTEM MIT NICHT-OKKLUSIVER RÜCKSCHICHT



(57) Abstract: The inventive system substantially comprises a two-phase adhesive layer that contains an active substance. An inner phase (2) that contains the active substance in dissolved form is embedded in the outer, vapor-impermeable phase (3) in a dispersed form. Combined with an elastic backing layer (1), preferably a warp/weft-elastic fabric, a very thin matrix system is obtained that guarantees an excellent wear comfort and that optimally utilizes the occlusive effect for an increased absorption of the active substance via the skin.

(57) Zusammenfassung: Der erfindungsgemäße System besteht im wesentlichen aus einer wirkstoffhaltigen Klebeschicht, die jedoch zweiphasig ausgeführt wird. In die äußere, wasserdampfsperrende Phase (3) wird eine innere Phase (2), die den Wirkstoff in gelöster Form enthält, dispers eingebettet. In Verbindung mit einer elastischen Rückschicht (1), vorzugsweise einem längs-quer-elastischen Gewebe, ergibt sich ein sehr dünnes Matrixsystem mit ausgezeichnetem Tragekomfort bei gleichzeitig optimaler Ausnutzung der Okklusion zur gesteigerten Wirkstoffaufnahme über die Haut.

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IN THE MATTER OF an Australian
Application corresponding to
PCT Application PCT/EP01/05474

I, Andrew Harvey David SUMPTER BSc,
translator to RWS Group plc, of Europa House, Marsham Way, Gerrards Cross,
Buckinghamshire, England, do solemnly and sincerely declare that I am conversant with the
English and German languages and am a competent translator thereof, and that to the best of
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Date: 30 September 2002

A handwritten signature in black ink, consisting of stylized initials 'AHD' followed by a flourish.

A. H. D. SUMPTER

For and on behalf of RWS Group plc

**Occlusive transdermal therapeutic system with a non-
occlusive backing layer**

Description

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The administration of active substances through the skin is made more difficult in the majority of cases by the low permeability of the skin. Consequently it is in many cases necessary to exploit all of the possibilities available for increasing the permeability. In virtually all cases the absorption of active substances through the skin is promoted by the effect of occlusion. This refers to an accumulation of water vapor in the upper layers of the skin which develops following application of transdermal therapeutic systems (TTS) which include at least one water-vapor-impermeable layer.

The most suitable water-vapor-impermeable layer of a TTS is its backing layer. Consequently, the use of water-vapor-impermeable backing layers is state of the art and is encountered in virtually all market products.

Typically, thin polymer films of polyethylene terephthalate (PET) are used. Precisely these water vapor barrier films, however, are usually inelastic, rigid materials, with little ability to conform to the skin, which do not allow the skin surface to which the TTS is bonded to stretch or compress physiologically. Associated with this is a low level of wear comfort for the patients, especially in the case of relatively large TTS with a surface area upward of about 25 cm². To parts of the body which are under particular mechanical stress, such as the major joints of the extremities, it is virtually impossible to adhesively attach such products durably while retaining full mobility.

Finally, in the case of a TTS with a rigid backing layer of this kind, the period of wear is shortened

because the lack of mechanical compatibility between elastic skin and inelastic TTS results in rapid detachment of such systems: the adhesive layer is unable to lastingly withstand the ongoing mechanical stresses. Elastic films which would be more advantageous in this respect, such as those of polyurethane or ethylene-vinyl acetate (EVA), on the other hand, possess good water vapor permeability and generate little if any occlusion.

10 Wovens or flag substances, finally, when used as backing layers, produce virtually no occlusion which might be of significance for the permeability of the skin.

An alternative option is to give a water vapor barrier construction to one of the other layers of the TTS, in order to be able to utilize the effect of occlusion even with a backing layer which is permeable to water vapor.

In the field of pressure-sensitive adhesive layers, formulations based on pure hydrocarbon polymers are particularly suitable for this purpose. These, however, are very lipophilic polymers, which typically possess low solvency for active pharmaceutical substances. Said substances can then frequently be embedded only in a substantially undissolved form, e.g., as a crystal dispersion, or have to be accommodated completely in an additional, differently formulated, layer.

Undissolved active substances generally result in unsatisfactory release behavior from the TTS, while additional layers complicate the construction of the system and make it more expensive.

In this respect, in accordance with the state of the art, the effect of occlusion can be used only partly or not at all in the case of TTS having an elastic backing layer, especially an elastic woven.

It is an object of the present invention, therefore to develop a transdermal therapeutic system having an elastic backing layer and an active substance layer which has water vapor barrier properties.

This object is achieved by a surprisingly uncomplicated and efficient system construction (Fig. 1).

The presently disclosed invention is aimed to achieve/overcome at least one of the stated objects/prior art disadvantages.

5 The system of the invention is composed essentially of an adhesive layer which comprises active substance but which is configured in two phases. In the outer, water vapour barrier phase (3) an inner phase (2), which contains the active substance in dissolved form, is dispersely embedded. In conjunction with an elastic backing layer (1), preferably a woven possessing
10 longitudinal/transverse elasticity, the result is a very thin matrix system affording excellent wear comfort while at the same time exploiting occlusion to the optimum for the increased absorption of active substance by the skin.

Accordingly there is disclosed herein an occlusive transdermal therapeutic system composed of a water-vapor-permeable and air-permeable elastic backing
15 layer, a matrix layer which comprises one or more active substances, one or more auxiliaries if desired, and one or more permeation enhancers if desired, and a redetachable protective layer, characterized in that the matrix layer is in two phases and is composed of an outer phase, which is substantially impermeable to water vapour and air, and in which an inner phase comprising the active
20 substance is dispersely embedded.

In accordance with standard practice, the pressure-sensitively adhering surface is masked prior to use with a redetachable protective film (4) made of conventional material, eg, siliconized polyethylene terephthalate (PET). Suitable
25 components for the outer and inner phases of the pressure-sensitively adhering matrix, with a view to solvent-based processing, are components which in solution produce a stable emulsion and which also form a stable two-phase system after coating and drying (removal of process solvents).

For the outer phase it is preferred to use polymers from the group of polyisobutylenes, polyisoprene, polybutenes and styrene block polymers with
30 isoprene or butadiene. These polymers have water vapour barrier properties and are suitable as pressure sensitive adhesives when different types having different molecular weights are mixed.

3a

The inner phase can be formed from the solution of the active substance in suitable liquid auxiliaries or else from a solution of the active substance in one or more polymers.

5 Dissolution in a polymer is preferential, since solutions dispersed in the form of droplets, when used as the inner phase, frequently have a tendency to be

exuded or to bleed out when the droplet-containing film is subjected to mechanical stress.

Polymers suitable for the dissolution of the active substance should be compatible with the polymers
5 specified above as being suitable for the outer phase. Compatibility in this context means that in the two-phase mixture there are particularly low interfacial energies, which are manifested in a very high degree of dispersion and a very low tendency of the emulsion to
10 separate. Acrylate polymers and methacrylate copolymers and ethyl-vinyl acetate copolymers have proven highly compatible in this sense. In the case of the (meth)acrylate copolymers, the polymers may also in turn be pressure-sensitively adhering. The result in
15 that case is a layer, embedded into an outer pressure-sensitive adhesive phase comprising hydrocarbon polymers, which is substantially uniform in terms of its viscoelastic properties, something which may have a positive effect on the wear properties on the skin.

20 Among the (meth)acrylate copolymers, those types which contain free carboxyl groups may be of advantage. By neutralizing these groups with suitable alkaline auxiliaries, e.g., potassium hydroxide, it is possible to tailor the hydrophilic/lipophilic balance of such
25 polymers. This may be advantageous for establishing a stable emulsion in a mixture with hydrocarbon polymers. Appropriate active substances are, in particular, non-steroidal antiphlogistics (in German, NSAR for non-steroidal antirheumatics; in English, NSAID for non-steroidal antiinflammatory drugs). These active
30 substances are frequently applied locally, externally, in the region of joints, especially those of the extremities. It is precisely at these application sites, subject to high mechanical stress, that the TTS
35 of the invention prove particularly advantageous. With no claim to completeness, the active substances in question are those from the group of diclofenac or one of its pharmaceutically acceptable salts, preferably the sodium salt, ibuprofen, ketoprofen, fluriprofen,

etofenamate, hydroxyethyl salicylate, meloxicam, piroxicam, lornoxicam, tenoxicam or indomethacin.

Besides the polymers for the outer phase, polymers for the inner phase, where appropriate, and the active
5 pharmaceutical substance, numerous other auxiliaries may be employed as well, such as are known to those skilled in the art for use in TTS.

Thus it is possible, for example, to use permeation enhancers, preferably in the inner phase of the matrix.
10 Suitable permeation enhancers include compounds from the group of low molecular mass monohydric or polyhydric alcohols, fatty acids (preferably oleic acid), fatty alcohols, fatty alcohol ethers, polyoxyethylated fatty alcohols, fatty acid esters
15 (especially monoglycerides and monoesters with propylene glycol), sorbitan fatty acid esters, and polyoxyethylated sorbitan fatty acid esters, and also dimethylisosorbitol.

Also suitable are surfactants which have the capacity
20 to exert a positive influence on the stability of the two-phase matrix layer by lowering the interfacial energy.

Suitable elastic, water-vapor-permeable backing layers
25 include films of polyurethane or ethyl-vinyl acetate copolymers. Particularly suitable, however, are wovens or non-woven flag materials, or composites of such materials. Examples of suitable materials here include cotton, cellulose, viscose, polyurethane or poly-
30 ethylene terephthalate (PET).

Very particular suitability is possessed by PET wovens possessing longitudinal and transverse elasticity.

Example 1

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The transdermal therapeutic system of the invention possesses the following structure and composition (% by weight):

Inner phase:

	Ketoprofen	4.00%
	Oleic acid	4.00%
	Potassium hydroxide	0.58%
5	Aluminum ions	0.008%
	Durotak 387-2353	11.4%

Outer phase:

	Oppanol B10	60.0%
10	Oppanol B100	20.0%

The backing layer used is a bielastic PET woven.

Example 2 (comparative example)

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The transdermal therapeutic system with the standard one-phase structure has the following composition (% by weight):

20	Ketoprofen	10.00%
	Oleic acid	18.00%
	Durotak 387-2052	72.00%

25 The backing layer used is the same longitudinally and transversely elastic PET woven as for the inventive Example 1.

30 For production, ketoprofen and oleic acid are homogeneously dissolved or distributed in the solution of Durotak (National Starch & Chemical) adhesive by stirred incorporation. The one-phase solution obtained is coated onto a redetachable backing film of siliconized polyethylene terephthalate (PET, thickness: 100 μ m) and dried at 80°C in an air-exhaust oven for 10 minutes. The target weight per unit area of the dried adhesive film is 80 g/m².

The dried adhesive film is laminated with a longitudinally and transversely elastic PET woven (100 g/m² basis weight).

Fig. 2 shows in the form of a graph a comparison of the permeation of active substance on human skin in vitro (full skin thickness, n=3, experiments with skin from the same donor). The TTS produced in accordance with
5 the inventive Example 1 achieves very much higher release rates than a conventional TTS produced in accordance with Example 2, despite the fact that the overall amount of active substance (ketoprofen) made available is in fact considerably lower in the
10 inventive TTS than in the comparative TTS.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An occlusive transdermal therapeutic system composed of a water-vapor-permeable and air-permeable elastic backing layer, a matrix layer which comprises one or more active substances, one or more auxiliaries if desired, and
5 one or more permeation enhancers if desired, and a redetachable protective layer, characterized in that the matrix layer is in two phases and is composed of an outer phase, which is substantially impermeable to water vapour and air, and in which an inner phase comprising the active substance is dispersely embedded.
2. The occlusive transdermal therapeutic system of claim 1, characterized in
10 that the elastic backing layer is composed of a longitudinally and transversely elastic woven substrate.
3. The occlusive transdermal therapeutic system of claim 2, characterized in that the woven substrate is composed of polyethylene terephthalate (PET).
4. The occlusive transdermal therapeutic system of any one or more of the
15 preceding claims, characterized in that the water-vapor-impermeable and air-impermeable outer phase of the matrix layer is composed of one or more hydrocarbon polymers.
5. The occlusive transdermal therapeutic system of any one or more of the
20 preceding claims, characterized in that the inner phase of the matrix contains the active substance in dissolved form.
6. The occlusive transdermal therapeutic system of claim 5, characterized in that the active substance is in solution in suitable liquid auxiliaries or in one or more polymers.
7. The occlusive transdermal therapeutic system of claim 4, characterized in
25 that the outer phase of the matrix is composed of one or more polymers from the group of polyisobutylenes, polyisoprene, polybutenes or a styrene block polymer with isoprene or butadiene.

8. The occlusive transdermal therapeutic system of claim 7, characterized in that the outer phase of the matrix is composed of polyisobutylenes of at least two, preferably three, different molecular weights.

5 9. The occlusive transdermal therapeutic system of any one or more of the preceding claims, characterized in that the inner phase of the matrix, containing the active substance in dissolved form, is composed of one or more polymers from the group of acrylate copolymers, methacrylate copolymers or ethyl-vinyl acetate copolymers.

10 10. The occlusive transdermal therapeutic system of claim 9, characterized in that in the case of acrylate or methacrylate copolymers the polymers in question are carboxyl-containing polymers which are preferably in 50-100% neutralized form as sodium or potassium salts.

15 11. The occlusive transdermal therapeutic system of any one or more of the preceding claims, characterized in that the inner phase of the matrix is free from polymers and contains the active substance in solution in at least one liquid auxiliary.

12. The occlusive transdermal therapeutic system of any one or more of the preceding claims, characterized in that the fraction of the inner phase of the matrix is 5-40% by weight of the matrix comprising active substance.

20 13. The occlusive transdermal therapeutic system of claim 12, characterized in that the fraction of the inner phase of the matrix is 10-25% by weight.

14. The occlusive transdermal therapeutic system of any one or more of the preceding claims, characterized in that the matrix comprising active substance amounts to a layer thickness of 60-200 g/m².

25 15. The occlusive transdermal therapeutic system of claim 14, characterized in that the matrix comprising active substance amounts to a layer thickness of 80-120g/m².

16. The occlusive transdermal therapeutic system of any one or more of the preceding claims, characterized in that the inner phase forms a dispersion in the outer phase of the matrix, with a droplet diameter of from 10 nm to 10 μ m.

17. The occlusive transdermal therapeutic system of claim 16, characterized in
5 that the droplet diameter is from 100 nm to 1 μ m.

18. The occlusive transdermal therapeutic system of any one or more of the preceding claims, characterized in that it comprises one or more active substances from the group of non-steroidal antiinflammatory drugs.

19. The occlusive transdermal therapeutic system of claim 18, characterized in
10 that it comprises at least one of diclofenac or one of its pharmaceutically acceptable salts, ibuprofen, ketoprofen, flurbiprofen, etofenamate, hydroxyethyl salicylate, meloxicam, piroxicam, lornoxicam, tenoxicam or indomethacin.

20. The occlusive transdermal therapeutic system of any one or more of the preceding claims, characterized in that the active substance or substances is or
15 are present in the inner phase of the matrix in a concentration range of 50-150% by weight of the saturation solubility of the active substance or of the active substances.

21. The occlusive transdermal therapeutic system of any one or more of the preceding claims, characterized in that it comprises at least one permeation
20 enhancer.

22. The occlusive transdermal therapeutic system of claim 21, wherein the at least one permeation enhancer is in the inner phase of the matrix.

23. The occlusive transdermal therapeutic system of claim 21 or claim 22, characterized in that the permeation enhancer or enhancers are selected from
25 low molecular mass monohydric or polyhydric alcohols, fatty acids, fatty alcohols, fatty alcohol ethers, polyoxy-ethylated fatty alcohols, fatty acid esters, sorbitan

fatty acid esters, polyoxyethylated sorbitan fatty acid esters and dimethyl-isosorbitol.

24. An occlusive transdermal therapeutic system which is substantially as hereinbefore disclosed with reference to Example 1.
- 5 25. An occlusive transdermal therapeutic system which is substantially as hereinbefore disclosed with reference to Figure 1.

DATED this 27th day of October 2004
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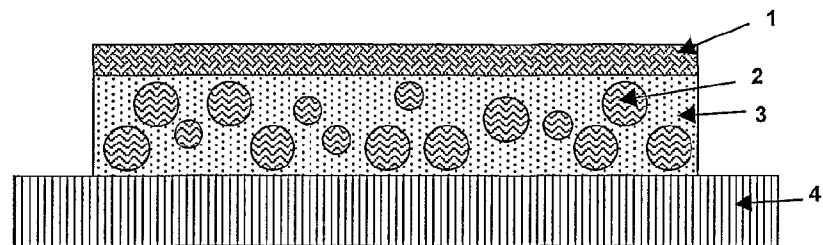
Fig. 1

Fig. 2

