Transdermal therapeutic system (TTS) for delivering active ingredient through the skin to a body and method for application to the skin

The invention relates to a transdermal therapeutic system (TTS) for delivering active ingredient through the skin to a human or animal body, comprising a matrix which contains active ingredient and has a self-adhesive active layer which faces the skin and can be covered before its application with a detachable protective layer, and a covering layer which outwardly demarcates the matrix.

Transdermal therapeutic systems represent medicinal forms in which the medicinal substance is made systemically available in the body through the barrier layer of the skin.

As so-called single dose units they are characterized in respect of their dosage strength by the release ($g/cm^2/t$) or ($\mu g/cm^2/t$), generally "amount of medicinal substance (g or µg)/area/unit time". In contrast to administration forms such as tablets or films, in respect of divisibility of the dose to be given these TTS are divisible only with great difficulty or not at all. With tablets or films on the other hand divisibility for the purpose of adapting the dosage to the patient's requirements is achieved without difficulty by breaking notches or, in the case of films, by providing lines of weakness. On the other hand, division of a TTS for example by cutting along an identification line is extremely problematical. This is because such a division leads to nonuniform products or to divided systems which are questionable especially in respect of their self-adhesiveness and ability to make contact with the skin. It is obvious that, for example, a semicircular sheet-like structure will display problems of adhesion at the corners of the semicircle, and these may lead to unwanted

detachment. This is a very great disadvantage because an intended rate of delivery of active ingredient through the skin requires secure adhesive contact with the skin over a predetermined period. A TTS in the form of a laminate applied to the skin is highly endangered in respect of the detachment which is to be avoided, as a consequence of the stretching and flexing of the skin by a body in motion. Such a danger can be avoided only by not dividing a TTS by cutting.

Based on this experience, the invention is based on the object of indicating a TTS and a method for its application which permits adaptation of the dosage to particular patient requirements, without cutting, and in the case of a uniform product leads to a divided system which can be accurately predetermined and which involves no difficulties and is reliable in respect of its ability to make contact with the skin.

Accurate dosage, tailored to the therapeutic requirements of a patient from case to case, on application of a TTS, and thus achievement of the abovementioned object, is attained in a simple manner and, in particular, without worsening the mechanical properties of a TTS according to the invention by covering the active layer of the matrix at the time of application in a part-zone of its active ingredient-delivery area facing the skin by a barrier layer which is impermeable for active ingredient.

This results in an active ingredient flux into the skin from the area zone covered by the barrier layer being prevented.

The barrier layer may consist of film-forming polymers such as hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, vinylpyrrolidone/vinyl acetate 60:40 copolymer,

ethylcellulose, acrylic and methacrylic ester copolymers with trimethylammoniummethyl acrylate, copolymers of dimethylaminomethacrylic acid and neutral methacrylic esters, shellac, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polymers of methacrylic acid and methacrylic esters, ethyl acrylate/methyl methacrylate 70:30 copolymer, methacrylic acid/methyl acrylate 50:50 copolymer, gelatin, polyvinyl acetate, methacrylate, acrylate dispersions, polyether/polyamide block copolymers, polyethylene/methyl methacrylate block copolymers, polyurethanes, polyester block copolymers, polyiso-butylene/styrene/styrene copolymers, styrene/butadiene/ styrene/isoprene copolymers, ethylene/vinyl acetate copolymers, polyamide, nitrocellulose, and other lacquer and film formers known to the skilled person. The addition of plasticizers to these film formers emerges as inevitable in accordance with the required flexibility needed for the film.

This barrier layer can be designed to be self-adhesive in the form of a laminate in the layer facing the skin, in which case the self-adhesive layer may optionally contain active ingredient. Suitable constituents for this purpose are all commercially available adhesives known to the skilled person and also employed for wound management in the form of dressings and plasters, such as, for example, adhesives based on acrylates, polyisobutylene, silicones etc.

However, it is also possible for the barrier layer not to be self-adhesive on the skin side, but the self-adhesive finish additionally increases the security of wearing of the TTS.

Because the amount of active ingredient delivered to the skin from the self-adhesive matrix is diffusion-controlled and directly proportional to the area of

contact, it is possible to neglect lateral diffusion out of the matrix zone with a barrier against the skin over the application period. The following simplified calculation example may illustrate this:

Assuming that a TTS is loaded with 10 mg of active ingredient, and supposing that 5 mg are released over an area of 30 cm^2 over a period of 24 h, this results in a release of 0.17 $mg/cm^2/24$ h. Assuming the layer thickness of the matrix to be 50 µm and the degree of covering to be 50%, the resulting cylindrical surface area of the matrix (possible area for lateral diffusion) is 0.069 cm^2, corresponding to a release of 0.011 mg/24 h, equivalent to 0.23%.

Besides this negligible effect of lateral diffusion, account must be taken of the fact that the covering by the barrier layer produces a "cavity zone" in the edge zone, depending on the layer thickness, and this effectively reduces the area of contact with the skin in the region of the adhesive "remaining matrix area". If the layer thickness of the barrier layer in this case is 20 µm and there is assumed to be a radius enlargement of 100 µm, this effectively means an area enlargement of the barrier layer in the abovementioned example (50% covering) of 0.95%.

In order to achieve a balance of these two effects, it is, therefore, advantageous to keep the layer thickness of the barrier layer as small as possible and additionally to restrict the size of the unavoidable "contact-free cavity" by making the side of the barrier layer facing the skin self-adhesive.

The system which is partly inactivated with a barrier layer before application for the purpose of adjusting a defined dose is distinguished from previous systems in that in production only one dose strength or

else 2 - 3 graded dose strengths are produced and can subsequently be adjusted further in a graded manner in respect of the active ingredient flux immediately before application by standardized barrier layers, for example in the form of circular segments. For example, a TTS without barrier layer might be used for therapy of a particular pathological state in an adult, whereas the TTS is arranged before application for the same purpose in a child with a considerably lower body weight to give a correspondingly reduced active ingredient flux.

In clinical test series it is possible by means of these inventive measures to carry out dosage tests accurately and straightforwardly.

Further details, features and advantages of the invention are evident from the following explanation of an exemplary embodiment depicted diagrammatically in the drawings. These show:

Fig. 1 a perspective view of a TTS with applied barrier layer;

Fig. 2 the TTS in the section along a plane of section II-II in layer 1;

Fig. 3 in the section of the plane of section II-II in layer 1 a TTS and a barrier layer immediately before joining together;

The transdermal therapeutic system depicted in Fig. 1 for delivering active ingredient through the skin to a human or animal body comprises a matrix 5 which contains the active ingredient and has a self-adhesive active layer 2 which faces the skin and can be covered before its application with a detachable protective layer 11, and a covering layer 1 which outwardly demarcates the matrix 5

and is impermeable for active ingredient. The latter layer can consist of the same material as the barrier layer 3 which is likewise impermeable for active ingredient, corresponding to the previous list of suitable film-forming polymers such as hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone etc. In the case of these TTS provided immediately before application to a site, selected for this purpose, on the human skin, the active layer 2 of the matrix 5 is covered at the time of application by a barrier layer 3, which is impermeable for active ingredient, in a part-zone 6 of its active ingredient-delivery area facing the skin, so that an active ingredient flux into the skin from the matrix zone 6 is prevented.

As is further evident from Fig. 1, the barrier layer 3 is provided with an adhesive layer 4 on the skin side. Although the self-adhesive finish of the barrier layer 3 on the skin side with an adhesive layer 4 results in a plaster which is optimal in respect of comfort of wearing and secure adhesion to the skin, the scope of the invention is likewise intended to include an administration form in which the barrier layer 3 is not self-adhesive on the skin side.

Fig. 2 shows the appearance of a section of a plaster or TTS according to the invention with a structure corresponding to that in Fig. 1. In this, number 1 denotes a covering layer, which is impermeable for active ingredient, of the matrix 5 whose active layer 2 is covered in a central part-zone 6 by a barrier layer 3 with adhesive layer 4 on the skin side before application, so that an active ingredient flux into the skin from this part-zone 6 is prevented. It can be assumed with reference to the above statements concerning the lateral diffusion 9 and the cavity zone 8 resulting in an edge zone of the barrier layer 3, with the corresponding calculation examples, that

the influence of these two defects is negligibly small and therefore the amount of active ingredient delivered to the skin from the self-adhesive matrix corresponds to the ratio of the circular area of the matrix 5 to the circular area of the barrier layer 3. The active ingredient flux from the circular ring-shaped remaining area of the edge zone 7 is then effectively multiplied by the degree of release of x $mg/cm^2/24$ h.

In this case, the barrier layer 3 may have a layer thickness between 1 µm and 40 µm, preferably between 5 µm and 30 µm and particularly preferably between 10 µm and 20 µm. In a preferred embodiment of the TTS, both the active layer 2 of the matrix 5 and the barrier layer 3 are preferably each designed with a circular area, and the diameter of the barrier layer 3 is less than the diameter of the active layer 2.

As Fig. 3 furthermore shows, the plaster according to the invention with its components, namely on the one hand the matrix 5 with its covering layer 1 and a detachable protective layer 11 for the active layer 2, and the barrier layer 3 finished by the adhesive layer 4, which is initially covered with a detachable protective layer 10, is to be arranged, for example, loosely together in one package. The plaster can thus be stored separately from the barrier layer in one package.

In a method for application of a TTS to the skin for dosable delivery of active ingredient through the skin to a body, comprising a matrix 5 which contains the active ingredient and has an active layer 2 which is self-adhesive to the skin and is covered before application with a detachable protective layer 11, and a covering layer 1 which covers the matrix 5 outwardly and is impermeable for active ingredient, the procedure is first to detach the protective layer 11 from the matrix 5 to expose the self-

adhesive active layer 2 onto which then the barrier layer 3 is placed as shown by the broken-line arrows and is fastened self-adhesively by gentle pressure, after which the protective layer 10 is pulled off from its adhesive layer 4 as shown by the arrow 12. The TTS designed according to the invention is now ready for sticking onto an intended site on a patient's skin. In this case, the active layer 2 of the matrix 5 is then inactivated in accordance with a previously determinable limitation of its active ingredient delivery rate which is set up per unit time and active area ($mg/cm^2/24$ h) in a part-zone of its active area by the barrier layer 3 which is impermeable for active ingredient.

Patent Claims

1. Transdermal therapeutic system (TTS) for delivering active ingredient through the skin to a human or animal body, comprising a matrix (5) which contains the active ingredient and has a self-adhesive active layer (2) which faces the skin and can be covered before its application with a detachable protective layer (11), and a covering layer (1) which outwardly demarcates the matrix (5) and is impermeable for active ingredient, characterized in that the active layer (2) of the matrix (5) is covered at the time of application in a part-zone (6) of its active ingredient-delivery area facing the skin with a barrier layer (3) which is impermeable for active ingredient.

2. TTS according to Claim 1, characterized in that the barrier layer (3) is provided on the skin side with an adhesive layer (4) which may itself contain active ingredient.

3. TTS according to Claim 1, characterized in that the barrier layer (3) does not have a self-adhesive finish on the skin side.

4. TTS according to one or more of Claims 1 to 3, characterized in that the barrier layer (3) has a layer thickness between 1 µm and 40 µm.

5. TTS according to one or more of Claims 1 to 3, characterized in that the barrier layer (3) has a layer thickness between 5 µm and 30 µm.

6. TTS according to one or more of Claims 1 to 3, characterized in that the barrier layer (3) has a layer thickness between 10 µm and 20 µm.

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7. TTS according to one or more of Claims 1 to 6, characterized in that both the active layer (2) of the matrix (5) and the barrier layer (3) are preferably each designed with a circular area, and in that the diameter of the barrier layer (3) is less than the diameter of the active layer.

8. TTS according to one or more of Claims 1 to 7, characterized in that the barrier layer (3) is a sheet-like structure which is arranged to cover the active layer (2) of the matrix in such a way that a circular ring-shaped edge zone (7) of the active layer (2) remains.

9. TTS according to any of the preceding claims, characterized in that it is stored separately from the barrier layer in one package.

10. Method for application of a TTS to the skin for dosable delivery of active ingredient through the skin to a body, comprising a matrix (5) which contains the active ingredient and has an active layer (2) which is self-adhesive to the skin and is covered before application with a detachable protective layer, and a covering layer (1) which covers the matrix (5) outwardly and is impermeable for active ingredient, characterized in that the active layer (2) of the matrix (5) is inactivated before its application to the skin in accordance with a predeterminable limitation of its active ingredient delivery rate which is set up per unit time and active area ($mg/cm^2/24\ h$) in a part-zone of its active area by application of a barrier layer (3) which is impermeable for active ingredient.

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