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(54) **SYSTEME THERAPEUTIQUE TRANSDERMIQUE CONTENANT DE L'ACIDE ACETYLSALICYLIQUE A RESORPTION RENFORCEE**

(54) **TRANSDERMAL, ACETYLSALICYLIC ACID-CONTAINING THERAPEUTIC SYSTEM WITH REINFORCED RESORPTION**

(57) Ce système thérapeutique transdermique contenant de l'acide acétylsalicylique comprend une couche de fond sensiblement imperméable au principe actif et à l'humidité, un réservoir de principe actif et le cas échéant une couche de protection détachable. Ce système thérapeutique transdermique se caractérise en ce qu'il contient du limonène et de l'isosorbide de diméthyle dans un rapport égal à au moins 50 g de limonène par 50 g d'isosorbide de diméthyle dans la zone du principe actif.

(57) A transdermal, acetylsalicylic acid-containing therapeutic system has a substantially active substance- and humidity-impervious backing layer, an active substance reservoir and if required a detachable protecting layer. This transdermal therapeutic system is characterised by a limonene and dimethyl isosorbide content in a mixing ratio of at least 50 g limonene for 50 g dimethyl isosorbide in the area of the active substance.

ABSTRACT

An Acetylsalicylic acid-containing transdermal therapeutic system with an essentially active ingredient- and moisture-impermeable backing layer, an active ingredient reservoir and, where appropriate, a redetachable protective layer is characterized by a content of limonene and dimethyl-isosorbide in a mixing ratio of at least 50:50 (g/g) limonene to dimethylisosorbide in the active ingredient-active region.

Acetylsalicylic acid-containing transdermal therapeutic system with absorption enhancement

The invention relates to an acetylsalicylic acid-containing transdermal therapeutic system with an essentially active ingredient- and moisture-impermeable backing layer, an active ingredient reservoir and, where appropriate, a redetachable protective layer.

Transdermal therapeutic systems (TTS) have already been launched on the market in the medicinal treatment of a number of disorders.

The ability in principle of the active ingredient acetylsalicylic acid to permeate through the human skin and thus be suitable as ingredient of transdermal therapeutic systems is also known. Thus, Rougier et al. (J. Pharm. Sci. 176, 451-454, 1987) have already described the (rather low) dependence of the rate of acetylsalicylic acid uptake into the skin on the selected area of skin.

Acetylsalicylic acid is a relatively safe medicinal substance with a high therapeutic index. In very high doses (more than one gram a day) it is used as antirheumatic agent, in intermediate doses (250-500 mg) as antipyretic/analgesic and in low dosage (30 to 150 mg per day) as platelet aggregation inhibitor. Acetylsalicylic acid is a substance which melts at a low temperature (about 139°C) and shows marked volatility at this temperature.

Because of the unstable ester group, acetylsalicylic acid is susceptible to hydrolysis and transesterification. Various stabilization methods have therefore already been considered, such as elimination of water, alcohols and esters as possible partners in a transesterification or hydrolysis reaction; addition of acetic acid or acetic

anhydride or adjustment to pH 2-3. US-A 4,228,162 also mentions dimethylisosorbide as stabilizing solvent.

A major impediment of the development of acetylsalicylic acid-containing pharmaceutically effective transdermal therapeutic systems is moreover the low permeability, by comparison with the high therapeutic daily dose required, of the active ingredient through the skin. A large number of permeation accelerants have therefore already been proposed as additives, such as azones, carboxylic esters, surface-active substances etc.

US-A 5,164,416 also indicates limonene as permeation-enhancing substance for acetylsalicylic acid but, according to this, its use is restricted to the simultaneous addition of a possibly irritating alkaline additive. Furthermore the permeation rates which can be achieved for acetylsalicylic acid - following this teaching - are still insufficiently high.

It has now been found, surprisingly, that combined addition of limonene and dimethylisosorbide in particular ratios of amounts leads to a considerable improvement, which was not predictable, in acetylsalicylic acid permeation through the skin.

Accordingly, the transdermal therapeutic system according to the invention of the type mentioned at the outset is essentially characterized by a content of limonene and dimethylisosorbide in a mixing ratio of at least 50:50 (g/g) limonene to dimethylisosorbide in the active ingredient-active region.

This solution to the problem is surprising inasmuch as the route to a medicinal form with better bioavailability leads for the skilled person via basic substances which are good

solvents, whereas limonene shows an extremely low solubility for acetylsalicylic acid - even on addition of dimethylisosorbide.

Particular features of the invention are evident from the claims and the following description.

The principle according to the invention can be utilized both in matrix systems and in reservoir/membrane systems. It is also immaterial which polymers, resins and possibly other additives are added as long as the formulation is suitable for delivering the basic substances acetylsalicylic acid, limonene and dimethylisosorbide to the skin.

In the simplest case it is possible for all three characterizing starting materials to be dispersed or dissolved in a solution of basic polymers, and for the mixture to be coated onto a suitable substrate, as a rule a siliconized thermoplastic sheet and, after evaporation of the solvent contents, where appropriate intensified by input of heat, to be covered with another sheet which forms the later rear side of the transdermal therapeutic system. Transdermal therapeutic systems are obtained from such a laminate by cutting out flat structures with the required geometric shape (circle, rounded rectangle etc.).

However, further embodiments may comprise forming a two-layer matrix consisting of a layer on the skin side, which contains the active ingredient in dispersed or dissolved form, and a second layer facing away from the skin, which contains limonene and dimethylisosorbide in the desired mixing ratio. These design variants are, however, only the simplest of a number of possible conceptions of the system known to the skilled person. Thus, matrix systems with more than two layers are, of course, possible

and, where appropriate, further active ingredients can be provided.

Suitable basic polymers for the system according to the invention are, in particular, acrylate copolymers, styrene/diene copolymers, silicone polymers, mixtures of polyisobutylene with suitable thermoplastic resins. This list is far from complete but indicates the wide applicability of the principle according to the invention.

The mixing ratio of limonene to dimethylisosorbide is, in particular, in the range from 50:50 to 99:1, preferably from 85:15 to 95:5 and specifically in the region of 90:10. It is moreover possible and expedient to provide a limonene content which is of the order of magnitude of the acetylsalicylic acid concentration.

Example 1:

20 g of micronized acetylsalicylic acid
30 g of limonene and
1 g of dimethylisosorbide

are dissolved or dispersed in 600 g of an acrylate copolymer solution (solids content: 50% g/g).

The composition is coated onto a siliconized polyester sheet (100 µm thick) to result in a layer with a weight per unit area of 150 g per m^2. Drying takes place under mild conditions by storing at room temperature in the air for 10 hours. The matrix obtained in this way is laminated with another sheet (polyester sheet 15 µm thick), and punches are used to cut out circles with a size of 20 cm^2.

This results in transdermal therapeutic systems which can be applied to the skin directly after detachment of the

siliconized polyester sheet in order to produce the desired therapeutic effect.

Example 2:

1.) 20 g of micronized acetylsalicylic acid are dispersed in 160 g of an acrylate copolymer solution (solids content: 50% g/g). The composition is coated onto a siliconized polyester sheet (100 µm thick) to result in a layer with a weight per unit area of 52 g/m^2. Drying takes place by storing at room temperature in the air for 10 hours. The matrix obtained in this way is laminated with another sheet (polyester sheet 15 µm thick).

2.) 20 g of micronized acetylsalicylic acid are dispersed in 160 g of an acrylate copolymer solution (solids content: 50% g/g). The composition is coated onto a siliconized polyester sheet (100 µm thick) to result in a layer with a weight per unit area of 93 g/m^2. Drying takes place by storing at room temperature in the air for 10 hours.

A circular disc of fabric (cotton) 2.54 cm^2 in size is applied to the adhesive area of the laminate from (2). 8.5 mg of a mixture of 10% (g/g) dimethylisosorbide and 90% (g/g) limonene, which has previously been saturated with acetylsalicylic acid by stirring at room temperature for 5 hours and then filtering, are applied dropwise to the disc of fabric. Laminate from (1) and disc of fabric are covered on the adhesive side with layer (2) so as to result in a sandwich of polyester sheet (15 µm), 52 g/m^2 poly-acrylate with acetylsalicylic acid, doped disc of fabric 2.54 cm^2 and 93 g/m^2 polyacrylate with acetylsalicylic acid, which is then covered on the adhesive side by a siliconized polyester protective sheet with an abhesive action.

7.10 cm^2 circles are cut of this laminate in such a way that the disc of fabric is located in the middle. After application to excized rat skin, the permeation is determined in vitro.

The average permeation found after 48 hours was 632.6 $\mu g/cm^2$ acetylsalicylic acid.

Example 3 (example comparing with Example 2):

Layer 1 and 2 are produced in accordance with Example 2.

A circular disc of fabric (cotton) 2.54 cm^2 in size is applied to the adhesive area of the laminate from (2). 8.5 mg of pure dimethylisosorbide which has previously been saturated with acetylsalicylic acid by stirring at room temperature for 5 hours and then filtering, are applied dropwise to the disc of fabric. Laminate from (1) and disc of fabric are cut out into 7.10 cm^2 specimens in analogy to Example 2. A determination of the permeation of excised rat skin was also carried out in the same way.

The average permeation found after 48 hours was 130.4 $\mu g/cm^2$ acetylsalicylic acid.

Example 4: (example comparing with Example 2):

Layer 1 and 2 are produced in accordance with Example 2.

A circular disc of fabric (cotton) 2.54 cm^2 in size is applied to the adhesive area of the laminate from (2). 8.5 mg of pure limonene which has previously been saturated with acetylsalicylic acid by stirring at room temperature for 5 hours and then filtering, are applied dropwise to the disc of fabric. Laminate from (1) and disc of fabric are cut out into 7.10 cm^2 specimens in analogy to Example 2. A

determination of the permeation of excised rat skin was also carried out in the same way.

The average permeation found after 48 hours was 253.3 $\mu g/cm^2$ acetylsalicylic acid.

Example 5: (example comparing with Example 2):

Layer 1 and 2 are produced in accordance with Example 2.

A circular disc of fabric (cotton) 2.54 cm^2 in size is applied to the adhesive area of the laminate from (2). No dropwise application of medium takes place. Laminate from (1) and disc of fabric are cut out into 7.10 cm^2 specimens in analogy to Example 2. A determination of the permeation of excised rat skin was also carried out in the same way.

The average permeation found after 48 hours was 52.9 $\mu g/cm^2$ acetylsalicylic acid.

Comparison of the permeation results for Examples 2 to 5 clearly shows the superiority of the system according to the invention.

PATENT CLAIMS

1. Acetylsalicylic acid-containing transdermal therapeutic system with an essentially active ingredient- and moisture-impermeable backing layer, an active ingredient reservoir and, where appropriate, a redetachable protective layer, characterized by a content of limonene and dimethylisosorbide in a mixing ratio of at least 50:50 (g/g) limonene to dimethyl-isosorbide in the active ingredient-active region.

2. Transdermal therapeutic system according to Claim 1, characterized by a monolayer or multilayer matrix as active ingredient reservoir, of which at least one layer contains limonene and dimethylisosorbide in a mixing ratio of 50:50 to 99:1 (limonene to dimethyl-isosorbide).

3. Transdermal therapeutic system according to Claim 1 or 2, characterized by a mixing ratio of limonene to dimethylisosorbide of 85:15 to 95:5 (g/g), in particular 90:10.

4. Transdermal therapeutic system according to any of the preceding claims, characterized in that acetyl-salicylic acid, limonene and dimethylisosorbide are present dissolved or dispersed in basic polymers.

5. Transdermal therapeutic system according to any of the preceding claims, characterized by an at least two-layer matrix whose layer facing away from the skin contains limonene and dimethylisosorbide in the stated mixing ratio.

6. Transdermal therapeutic system according to any of the preceding claims, characterized by a limonene content

of the order of magnitude of the acetylsalicylic acid concentration.