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**Bevan et al.**

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[54] **TRANSDERMAL SYSTEM FOR SIMULTANEOUS DELIVERY OF A NUMBER OF ACTIVE PRINCIPLES**

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[21] Appl. No.: **08/849,688**

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[57] **ABSTRACT**

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A novel system for percutaneously delivering at least two active principles, consisting of at least two juxtaposed devices. The system includes (i) a first device containing a mixture of all the active principles in which at least one first active principle (A) is present in an amount enabling the effective therapeutic dose to be delivered, and at least one second active principle (B) is present in an amount smaller than the amount needed to deliver the effective therapeutic dose; and (ii) one or more additional devices each containing a single active principle (B) selected from those in the first device and provided in an amount smaller than the amount needed to deliver the effective therapeutic dose, said additional device(s) being designed to top up the amount of each of the active principles (B) in the system until the effective therapeutic dose is achieved.

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[52] **U.S. Cl.** ..... **424/448**; 424/449

[58] **Field of Search** ..... 424/449, 448

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**20 Claims, No Drawings**

**TRANSDERMAL SYSTEM FOR  
SIMULTANEOUS DELIVERY OF A NUMBER  
OF ACTIVE PRINCIPLES**

This Application is a 371 of PCT/FR95/01696, filed Dec. 9, 1995.

**FIELD OF THE INVENTION**

The present invention relates to systems for the transdermal delivery of a number of active principles simultaneously, said systems being designed so as to facilitate adjustment of the delivered doses of one or more active principles and reduce the surface area of such systems in order to improve safety and comfort when used by the patient.

**PRIOR ART**

There are numerous devices currently in existence for the transdermal delivery of an active principle.

The composition of these devices is defined for the purpose of (i) ensuring a good physicochemical stability of the active principle over time, and (ii) obtaining an optimal transdermal absorption flux per unit surface area. Thus the dose of active principle delivered in the course of a treatment is mainly determined by the surface area of the device applied to the skin.

Now, this surface area must not be so large as to cause physical discomfort when the device is used and produce a device whose size and esthetic appearance would rule out its use altogether. The device must also have good adhesion and cohesion properties, making it easy, pleasant and discreet to apply when used.

Thus devices containing a single active principle are produced at the present time and satisfy these demands, i.e. they are effective, small and comfortable and neither creep nor become detached during use.

On the other hand, the production of such efficient systems for the delivery of two active principles, or even more than two active principles, still presents numerous problems which become increasingly difficult to solve as the number of active principles to be delivered increases.

A first known technical solution among those envisaged in the prior art involves transdermal systems which consist of a single device containing all the active principles mixed together. Such systems are described for example in patent documents EP-A-0 285 563, WO-A-92/07589, WO-A-92/07590 and WO-A-94/06383. Although these systems have the advantage of being small, they prove generally very complex, if not impossible, to perfect.

In fact, by virtue of their nature and their physicochemical properties, the active principles behave in different ways towards the corneal layer and often have important influences on the composition of the device.

Because the skin has different permeabilities to the active principles, each active principle has a different absorption flux. It therefore proves virtually impossible to obtain the desired therapeutic dose of each active principle to be delivered by simultaneously using the same absorption area and the same formulation.

Furthermore, if it is necessary to readjust the delivered dose of at least one of the active principles during clinical development, it is impossible to modify the delivered dose of this active principle independently of those of the other active principles without having to change the formulation of the other components.

Similarly, it is also common for one and the same system for the transdermal delivery of a number of active principles to be used for delivering several dosages of these active principles according to the patients or pathological conditions treated.

This will be done by choosing different surface areas of said system on account of the fact that the dose of active principle delivered will be proportional to the surface area applied to the skin.

In the case of such a system for the delivery of a number of active principles where different posologies are required, if at least two active principles do not remain in the same dose ratio for all the chosen posologies, or if one active principle is delivered at a fixed dose, it will be impossible to obtain the different desired posologies by varying the surface area of the device, since in this case the doses of each active principle vary simultaneously as a function of the surface area and in constant dose ratios.

In both the above cases, therefore, the benefit of the work already put in is lost and comfortable systems with good fluxes and good physical properties are forsaken.

Now, the choice of components forming part of the formulation of the device becomes very rapidly restricted as the number of active principles increases, the latter often imposing conflicting constraints.

In fact, the active principles may be partially or totally incompatible with certain constituents of the formulation (resins, solvents, plasticizers, polymers, skin absorption promoters, etc.). They may have different solubilities and stability temperatures and some of them recrystallize over time, degrade when applied or can only be used in the composition at concentrations which are too low to obtain the intended therapeutic dosage. Likewise, there is no universal skin absorption promoter for all active principles in order to increase their transdermal fluxes. Therefore, to administer different active principles, it is often necessary to use several promoters or solvents. Now, the introduction of any new substance may cause or raise problems of irritation and the system's cohesion or adhesion.

By the same token, this set of constraints (compatibility, solubility, etc.) also affects the different constituents of the formulation other than the active principles, thereby exacerbating the difficulties of optimizing their role in the formulation and benefiting from the specific advantages they can bring.

In practice, this first technical solution is not workable and leads to an impasse or, at best, to devices hampered by obvious disadvantages for the use of this type of pharmaceutical form.

A second known solution for the simultaneous delivery of a number of active principles consists in producing a system formed of several transdermal devices applied to the skin, each device containing a single active principle. Such systems are described for example in patent documents WO-A-94/06383, WO-A-90/06736 and WO-A-94/13354.

This avoids the above problems of compatibility, stability and adjustment of the desired dosage. Attainment of the desired dose of each active principle is then defined by the surface area of each device.

It is this which constitutes the main disadvantage of this solution, because such a system generally has a large overall surface area, its size increasing with the number of active principles.

Now, in general, the larger a transdermal system is, the more difficult it is to use. This is because it becomes harder

to optimize its adhesion and cohesion properties over the whole of the surface area which is to come into contact with the skin.

Thus, the larger the system is, the greater will be the risk of increasing the likelihood of creep of the adhesive mass and hence soiling of the clothes, sensations of pulling, discomfort or even irritation of the skin or cohesive rupture when the system is removed, making the system less manageable and acceptable.

Furthermore, as the dose delivered over time is determined by the surface area of the device applied to the skin, any increase in surface area increases the risk of partial or total detachment of the system or puckering, which can result in a loss of activity because of non-uniform contact with the skin, particularly over curved parts of the body or parts which frequently move.

Similarly, in the case of a reservoir, an inhomogeneous distribution over the whole of the surface area which is to come into contact with the skin necessarily modifies the dose released and does not allow the desired therapeutic activity to be achieved. Thus, in the case of an excessively large reservoir system, where the liquid or semiliquid (solution or gel) containing the active principle tends to stagnate in the lower part of the reservoir under the action of gravity, the surface area utilized will be reduced and the system will ultimately be less effective.

Another disadvantage of a large system, whatever its nature may be, is the risk that it will be poorly accepted by the patient because it is too visible and therefore difficult to conceal.

The esthetic appearance and the discreetness of the transdermal system, possibly combined with a sensation of physical discomfort, are actually important parameters for the acceptability of the product and the patient's compliance with the therapeutic treatment.

All these problems therefore detract from the comfort of the system when in use or, even worse, from its therapeutic efficacy when used by the patient.

The solutions of the prior art are therefore unsatisfactory because they do not succeed in reconciling the possibility of simply adapting the delivered doses of each of the active principles with the production of a system of small overall surface area, allowing safer and more comfortable use when the system is applied to the skin.

#### OBJECT OF THE INVENTION

In the field of the simultaneous transdermal delivery of a number of active principles, it would therefore be desirable to provide a novel technical solution which enables the desired compromise to be reached without the above-mentioned disadvantages.

It is this object which the present invention proposes to achieve through the production of a system for the simultaneous transdermal delivery of at least two active principles which makes it possible simply to adjust the dose of each active principle to be delivered, while at the same time having a reduced total surface area.

#### SUBJECT OF THE INVENTION

The above-mentioned object is achieved through the production, as a novel industrial product, of a novel system for the transdermal delivery of at least two active principles which consists of at least two juxtaposed (or associated) devices, said system being characterized in that it comprises

- (i) a first device containing a mixture of all the active principles in which at least one first active principle (A)

is present in an amount which enables the effective therapeutic dose to be delivered, and at least one second active principle (B) is present in an amount which is less than that required to deliver the effective therapeutic dose, and

- (ii) one or more additional devices each containing a single active principle (B) selected from those present in the first device and provided in an amount which is less than that required to deliver the effective therapeutic dose, said additional device or devices making up the amount of each of the active principles (B) present in the system until the effective therapeutic dose is obtained.

#### DETAILED DESCRIPTION OF THE INVENTION

The expression "transdermal system" in the present invention denotes the association of at least two devices for the purpose of simultaneously delivering all the active principles by application to the skin.

"Device" is understood here as meaning any system used to deliver at least one active principle transdermally. Such devices are generally classed in two major categories:

- reservoir devices, in which the active principle or principles are dissolved in a solvent acting as a vector for transporting the active principle across an adhesive or non-adhesive microporous membrane; and
- matrix devices, in which the active principle or principles are dissolved or dispersed in a polymer network forming the matrix, which can be self-adhesive or non-adhesive.

These devices can be monolayer or multilayer (also called lamellar), i.e. formed by the superposition of several matrices or reservoirs which may or may not contain one or more active principles, said matrices or reservoirs optionally being separated by microporous membranes.

The association of at least two devices according to the invention can be carried out by techniques known to those skilled in the art, for example by sticking onto a support coated with adhesive, juxtaposed double coating or heat sealing onto a single support. The devices will have a single support in the above cases, but it is also possible to manufacture a system in which each device has an identical or different independent support, association being effected by juxtaposition of the devices, for example by heat sealing, or by associating the devices on an additional support, always by the same techniques.

The support used may be any support generally employed in occlusive or non-occlusive transdermal systems, of variable thickness, which is impermeable to the constituents of the devices.

Preferred supports will be for example in the form of a polyethylene, polypropylene or polyester film, a composite consisting of polyethylene and a vinyl acetate/ethylene copolymer, an aluminized film or else a foam.

In practical terms, the whole of the system or each of the devices may be covered with a protective layer or film which can be peeled off before the system is used, it being possible for said system itself to be packaged in a leaktight protection such as, for example, a polyethylene/aluminum composite.

A device according to the present invention can be made of the materials familiar to those skilled in the art, for example natural or synthetic polymers (such as acrylics or derivatives thereof, silicones, block copolymers, vinyl acetate/ethylene copolymers, rubbers and derivatives thereof, etc.), according to the properties of the active

principles to be delivered. Other appropriate known products generally used by those skilled in the art may be associated with said active principles, examples being solubilizing agents, plasticizers, resins, stabilizers, bulking agents or skin permeation promoters.

Likewise, the membranes which may be employed are those generally used in the art in the field of transdermal systems, examples being a film of ethylene/vinyl acetate copolymer.

In the case where one or more matrix devices are used in the system according to the present invention, said matrix devices are manufactured by the coating techniques generally known in the art, either in a solvent phase or by the so-called hot melt technique (i.e. in the absence of a solvent).

Likewise, in the case where devices of the reservoir type are used, said devices are manufactured by the techniques known in the art, an example being creation of the reservoir by heat-sealing the support onto a membrane and simultaneously or non-simultaneously filling the reservoir.

In both cases, in the context of industrial production, the size of the devices is set to the appropriate dimensions, according to the amount of active principle or principles present per unit surface area, to give the chosen doses of active principles to be delivered by the system over a given time.

The transdermal system according to the invention can have any geometric shape: square, rectangular, circular or oval. The different devices can be arranged either side-by-side or concentrically, each device then completely surrounding the previous one, or any other geometric construction can be used. The devices can optionally be separated or surrounded by one or more additional layers, which can be adhesive in order to help hold the unit together if necessary.

Any combination of active principles capable of being applied transdermally and exerting either a topical or a systemic action can be used within the framework of the present invention.

The following possible associations may be mentioned among these combinations:

- (a) one or more estrogens with one or more progestins, natural or synthetic, for contraceptive purposes or in the treatment of the symptoms of menopause, for example estradiol, ethynylestradiol, estriol and derivatives thereof in association with norethisterone acetate, norgestrel, levonorgestrel, desogestrel, norgestimate, lynestrenol, gestodene, nomegestrol acetate or dienogest;
- (b)  $\beta$ -blocker and diuretic compounds useful especially in cardiovascular diseases, for example timolol, pindolol, bufradol, indenolol or nipradinol in association with amilofide or hydrochlorothiazide;
- (c) corticoid and antihistamine compounds useful especially in the treatment of allergies, for example methylprednisolone, prednisolone, hydrocortisone, beclomethazone or triamcinolone in association with astemizole, dexchlorpheniramine, cetirizine, diphenylhydromine chloride or chloro-pheniramine;
- (d) analgesic and anti-inflammatory compounds useful especially in the treatment of pain, for example acetylsalicylic acid, paracetamol or noramidopyrine in association with mefenamic acid, flufenamic acid, diclofenac, oxyphen-butazone, ibuprofen, naxoprene or fenbufene; and
- (e) antibacterial and antibiotic compounds useful especially in the treatment of infections, for example

amoxycillin in association with clavulanic acid, sulfamethoxazole in association with trimethoprim, erythromycin in association with acetylsulfafurazole or erythromycin in association with tetracycline.

Advantageously, a system in which the active principles to be delivered simultaneously are chosen on the one hand from estrogen compounds and on the other hand from progestin compounds is particularly recommended.

#### BEST MODE

The best mode of carrying out the invention consists in using a system for the transdermal delivery of two active principles (A and B), characterized in that it comprises

- (i) a first matrix device which is a matrix containing in its bulk the active principle A in an amount which enables the effective therapeutic dose to be delivered, and the active principle B in an amount which is less than that necessary to deliver the effective therapeutic dose, and
- (ii) a second matrix device which is a matrix containing in its bulk the active principle B in an amount which makes up the amount present in said first matrix device until its effective therapeutic dose is obtained.

In other words, a system is recommended which consists of two juxtaposed (or associated) matrices, this system being such that a first matrix which contains a mixture of the two active principles, where one of the two is delivered at a dose which is less than its effective therapeutic dose, is combined with a second matrix which contains this same active principle and which enables its effective therapeutic dose to be delivered.

This system is very useful for the simultaneous delivery of an estrogen and a progestin, in particular for the simultaneous delivery of different doses of 17- $\beta$ -estradiol, between 25 and 100  $\mu$ g per 24 hours, and different doses of norethisterone acetate, between 100 and 800  $\mu$ g per 24 hours, in 17- $\beta$ -estradiol/norethisterone acetate dose ratios of  $\frac{1}{4}$  to  $\frac{1}{8}$  respectively, said doses being therapeutically effective in the treatment of the symptoms of menopause and the resulting cardiovascular risks.

The advantages and characteristics of the invention will be understood more clearly from the following description of Examples of systems produced according to the invention and experiments comparing them with systems described in the prior art. Of course, these details taken as a whole do not in any way imply a limitation but are given by way of illustration. The systems according to the invention and the comparative systems are produced by different combinations of the matrix devices described below.

#### EXAMPLE 1 (device 1)

47.8 g of LEVAPREN® 450P (an ethylene/vinyl acetate copolymer (abbreviated to EVA below) marketed by BAYER), 48 g of crotamiton [N-ethyl-2-N-(2-methylphenyl)-2-butanamide] (marketed by BOEHRINGER INGELHEIM), 0.2 g of IRGANOX® B215 (an antioxidant marketed by CIBA-GEIGY) and 115.53 g of ethyl acetate are placed in a vessel. The mixture is heated for 5 hours until the EVA has completely dissolved. It is stirred at room temperature for 1 hour and 4 g of norethisterone acetate (abbreviated to NETA below), previously dissolved in 20 g of tetrahydrofuran, are then added. The mixture obtained is stirred for about 30 minutes until it is completely homogeneous; it is then left to stand until the bubbles have totally disappeared. The mass obtained is coated onto a siliconized polyester film at room temperature (15–25° C.) to give a deposit of material of (100±10) g/m<sup>2</sup>. The unit

obtained is heated at 70° C. for 30 minutes and then transferred to a polyethylene support. The resulting product is then cut to appropriate dimensions. If necessary, the cut products are packaged in sachets, envelopes or leaktight enclosures.

#### EXAMPLE 2 (device 2)

The procedure is analogous to Example 1 above using 49.8 g of LEVAPREN® 450P, 44 g of crotamiton, 0.2 g of IRGANOX® B215, 116.2 g of ethyl acetate, 2 g of 17- $\beta$ -estradiol and 4 g of norethisterone acetate (added at the same time as the 17- $\beta$ -estradiol), these two hormones being dissolved together in 30 g of tetrahydrofuran.

#### EXAMPLE 3 (device 3)

20.7 g of ELVAX® 46L and 6.9 g of ELVAX® 46 (ethylene/vinyl acetate copolymers marketed by DU PONT) and 6 g of ETHOCEL® (ethyl cellulose marketed by DOW CHEMICAL) are placed in a vessel, with stirring, and heated to about 130° C. 1.2 g of 17- $\beta$ -estradiol and 18.9 g of EUTANOL® G (2-octyldodecanol marketed by HENKEL) are then incorporated gradually at 130° C., with continued stirring, and the mixture is stirred until it is completely homogeneous. 6.3 g of SURFADONE® LP300 (N-dodecyl-2-pyrrolidone marketed by GAF CORPORATION) are then added at a temperature of the order of 100 to 110° C. and stirring is continued until the mixture is perfectly homogeneous. The mixture obtained is coated, at a temperature between 100 and 140° C., onto an antiadhesive temporary intermediate support, especially a siliconized polyester film, at a rate of (100±10) g/m<sup>2</sup>. The matrix obtained is transferred to a polyethylene support.

#### EXAMPLE 4 (device 4)

The procedure is identical to Example 3 except that 11 g of ELVAX® 46L, 11 g of ELVAX® 46, 5 g of ETHOCEL®, 15 g of EUTANOL® G, 5 g of SURFADONE® LP300, 1 g of 17- $\beta$ -estradiol and 2 g of norethisterone acetate are used in this case.

#### EXAMPLE 5 (device 5)

The procedure is identical to Example 3 except that 33.75 g of ELVAX® 46L, 11.25 g of ELVAX® 46, 10 g of ETHOCEL®, 30.5 g of EUTANOL® G, 4 g of norethisterone acetate and 10.5 g of SURFADONE® LP300 are used in this case.

#### EXAMPLE 6 (device 6)

13.35 g of KRATON G® 1657 (a poly(styrene/ethylene/butylene/styrene) three-block copolymer marketed by SHELL), 0.1 g of IRGANOX® 565 (an antioxidant marketed by CIBA-GEIGY), 12.5 g of ZONATAC® 105L (a tackifying resin marketed by ARIZONA CHEMICAL), 10.25 g of PARAPOL® 950 (an n-butene/isobutylene copolymer marketed by EXXON CHEMICAL), 10.25 g of EUTANOL® G (2-octyldodecanol marketed by HENKEL), 3 g of SURFADONE® LP300 (N-dodecyl-2-pyrrolidone marketed by GAF CORPORATION) and 25.6 g of cyclohexane are placed in a 250 ml beaker. The mixture is stirred for 6 hours, while being heated at 60° C., until the constituents have completely dissolved. 0.55 g of norethisterone acetate, previously dissolved in 2.75 g of tetrahydrofuran, is then added. The mixture obtained is stirred for 30 minutes until it is completely homogeneous, and then left to stand until the bubbles have totally disappeared. The mixture

obtained is coated onto a siliconized polyester film at a rate of (100±10) g/m<sup>2</sup> at room temperature (15–25° C.). After heating at 70° C. for 0.5 hour, the matrix obtained is transferred to a polyethylene support. The product is then cut to appropriate dimensions and packaged in sachets if necessary.

#### EXAMPLE 7 (device 7)

13.8 g of VECTOR® 4211D [a poly(styrene/isoprene/styrene) three-block copolymer marketed by EXXON CHEMICAL], 23.85 g of ECR® 385 (a tackifying resin marketed by EXXON CHEMICAL), 0.1 g of IRGANOX® 565 (an antioxidant marketed by CIBA-GEIGY), 3.5 g of SURFADONE® LP300 (N-dodecyl-2-pyrrolidone marketed by BOEHRINGER INGELHEIM), 7.5 g of LAUROGLYCOL® (a mixture of the monoester and diester of propylene glycol and lauric acid, marketed by GATTEFOSSE) and 19.8 g of ethyl acetate are placed in a 250 ml beaker. This mixture is stirred, while being heated at 60° C., until the compounds have completely dissolved. A solution of 1.25 g of norethisterone acetate, previously dissolved in 6.25 g of tetrahydrofuran, is then added. The resulting mixture is stirred for about 30 minutes until it is completely homogeneous. It is left to cool until the bubbles have totally disappeared. The resulting mass is coated onto a siliconized polyester film at a rate of (110±10) g/m<sup>2</sup> at room temperature (15–20° C.). The coating produced is heated at 50° C. for at least 30 minutes and then transferred to a polyethylene support. The product is cut into shapes of the desired dimensions.

The advantages of the present invention were illustrated by carrying out ex vivo permeation tests on the abdominal skin of male nude mice according to the following protocol:

The amounts of hormones (i.e. steroids) released by a transdermal device with a surface area of 2.54 cm<sup>2</sup>, previously cut out with a hollow punch and deposited on a 3.14 cm<sup>2</sup> disk of abdominal skin of a male nude mouse, are measured in a static glass cell, thermostated at 37° C., which has a receiving compartment with a volume of 11.5 ml containing a receiving phase made up of an isotonic solution/PEG<sub>400</sub> mixture (75/25; v/v).

Samples of the receiving solutions are taken at 2, 4, 6, 8, 12, 16, 20 and 24 hours and assayed by liquid chromatography. To allow for the variability of the results associated with the intrinsic permeability of the skin samples, each permeation experiment for a sample of transdermal device is performed on a minimum of 3 to 5 skin samples. The result given is the mean obtained for each device from these experiments.

The following mean skin absorption fluxes were thus obtained for 17- $\beta$ -estradiol ( $F_{ES}$ ) and/or norethisterone acetate ( $F_{NETA}$ ) in the case of devices 1 to 7:

Device 1:  $F_{NETA}=0.35\pm 0.16 \mu\text{g}/\text{cm}^2/\text{h}$

Device 2:  $F_{ES}=0.2\pm 0.07 \mu\text{g}/\text{cm}^2/\text{h}$   $F_{NETA}=0.39\pm 0.1 \mu\text{g}/\text{cm}^2/\text{h}$

Device 3:  $F_{ES}=0.61\pm 0.08 \mu\text{g}/\text{cm}^2/\text{h}$

Device 4:  $F_{ES}=0.57\pm 0.13 \mu\text{g}/\text{cm}^2/\text{h}$   $F_{NETA}=0.57\pm 0.17 \mu\text{g}/\text{cm}^2/\text{h}$

Device 5:  $F_{NETA}=0.5\pm 0.03 \mu\text{g}/\text{cm}^2/\text{h}$

Device 6:  $F_{NETA}=0.47\pm 0.05 \mu\text{g}/\text{cm}^2/\text{h}$

Device 7:  $F_{NETA}=0.89\pm 0.12 \mu\text{g}/\text{cm}^2/\text{h}$

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