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(54) **TRANSDERMAL THERAPEUTIC SYSTEM**

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3,731,683 A	5/1973	Zaffaroni	424/434
3,797,494 A	3/1974	Zaffaroni	424/434
4,236,652 A	* 12/1980	Beguhn	222/92
4,286,592 A	9/1981	Chandrasekaran	424/448
4,314,557 A	2/1982	Chandrasekaran	424/449
3,598,122	11/1982	Zaffaroni	424/435
4,379,454 A	4/1983	Campbell et al.	604/897
4,435,180 A	3/1984	Leeper	424/402
4,597,961 A	7/1986	Etscorn	424/448
4,615,699 A	10/1986	Gale	424/448
4,690,683 A	9/1987	Chien	424/448

(List continued on next page.)

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **5,820,876**
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Appl. No.: **08/469,207**
Filed: **Jun. 6, 1995**

FOREIGN PATENT DOCUMENTS

AU	565178	7/1985
EP	A117027	1/1984
EP	0 416 842	3/1991
GB	A1 361 289	6/1971
WO	85/05036	4/1985

U.S. Applications:

(63) Continuation-in-part of application No. 08/341,844, filed on Nov. 18, 1994, now abandoned, which is a continuation of application No. 08/027,698, filed on May 17, 1993, now abandoned, which is a division of application No. 07/908,930, filed on Jul. 8, 1992, now abandoned, which is a continuation of application No. 07/597,102, filed on Oct. 12, 1990, now abandoned, which is a continuation of application No. 07/219,066, filed on Jun. 27, 1988, now abandoned.

OTHER PUBLICATIONS

Baker Dr., Richard., "Analysis of Transdermal Drug Delivery Patents, 1935 to 1984" (p. 7).

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(30) **Foreign Application Priority Data**

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Aug. 20, 1987 (WO) PCT/DE87/00372

(57) **ABSTRACT**

A therapeutic system for supplying active substances to the skin consists of a backing layer remote from the skin, with at least one active substance depot. The depot may consist of a fluid active substance or a fluid composition comprising an active substance delivery control matrix. There is also included an adhesive fixing device for fixing the therapeutic system on the skin. The therapeutic system is characterized in that the active substance depots (14) consist of at least one adjuvant having a supporting and distributing function by being provided with a planar textile material completely surrounded by matrix (12).

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(52) **U.S. Cl.** **424/449; 424/447; 424/448;**
206/440; 206/484; 428/34.3; 428/35.3;
428/35.4

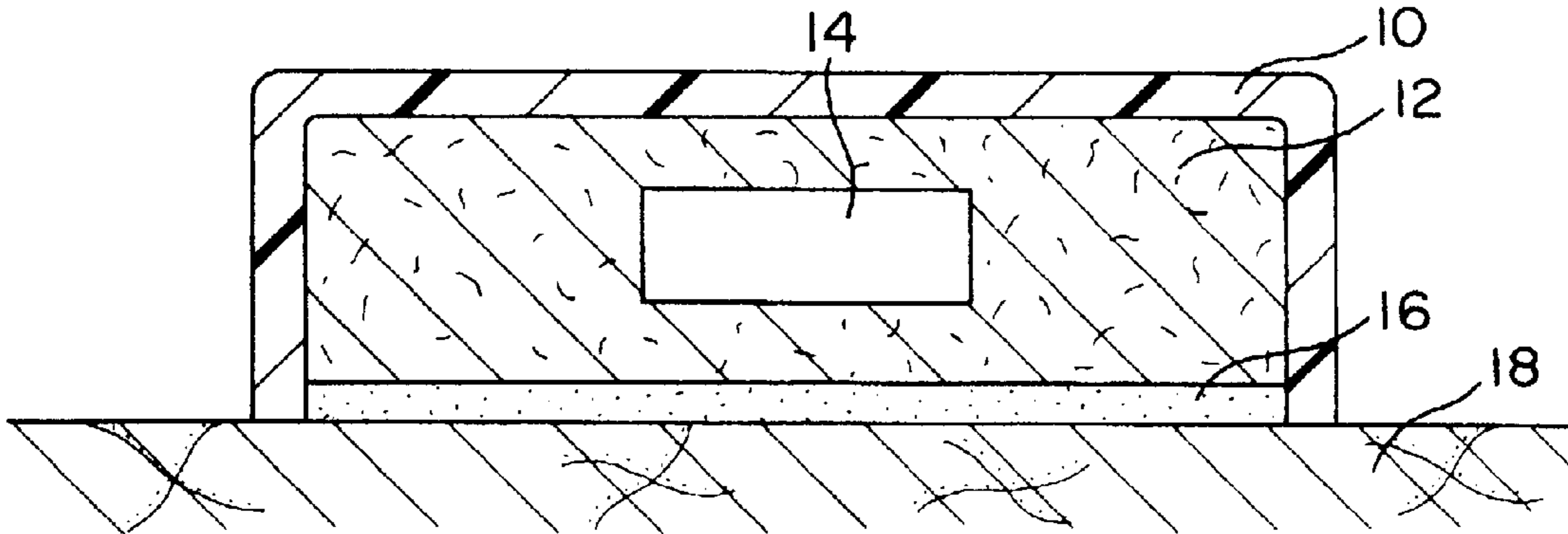
(58) **Field of Search** **424/447, 448,**
424/449; 206/440, 484; 428/34.3, 35.3,
35.4

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,598,123 A 8/1971 Zaffaroni 424/435

68 Claims, 2 Drawing Sheets



US RE37,934 E

Page 2

U.S. PATENT DOCUMENTS						
			4,933,184 A	6/1990	Tsuk	424/448
4,699,792 A	10/1987	Nick et al.	5,077,104 A	12/1991	Hunt et al.	428/343
4,719,226 A	1/1988	Otsuka et al.	5,268,209 A	12/1993	Hunt et al.	428/343
4,769,028 A	9/1988	Hoffman et al.	6,126,963 A	* 10/2000	Hoffmann	424/449
4,784,857 A	11/1988	Berry et al.				
4,915,950 A	4/1990	Miranda et al.				

* cited by examiner

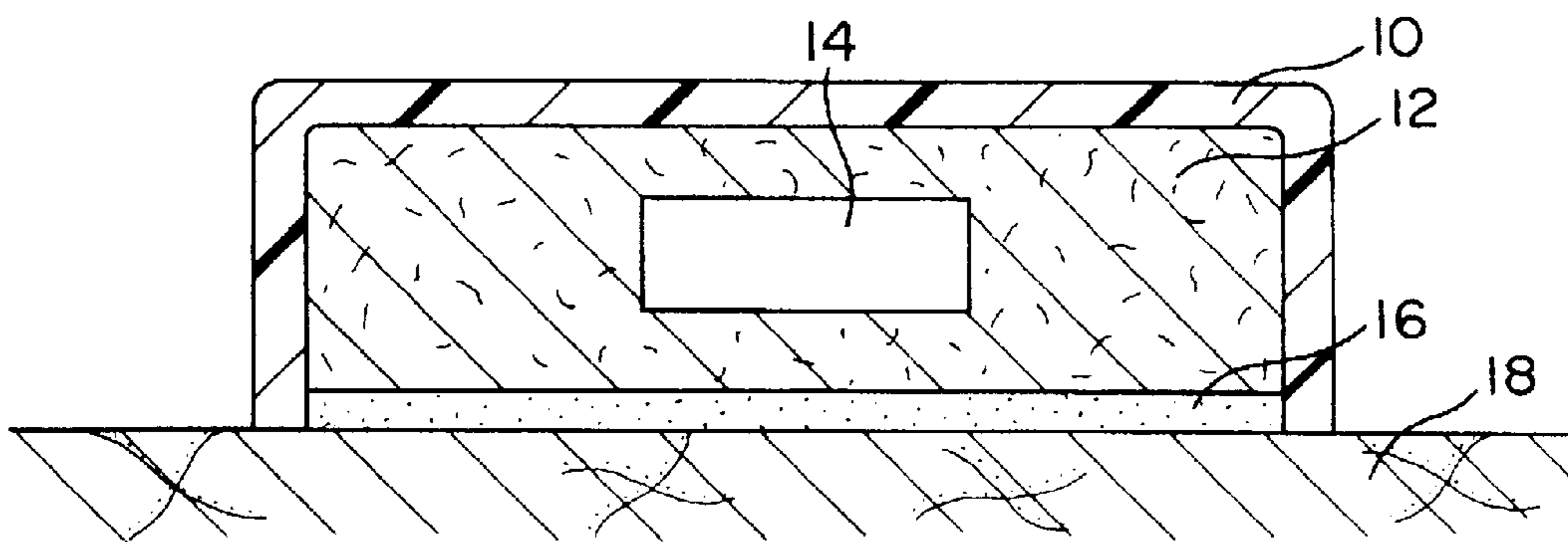


FIG. 1

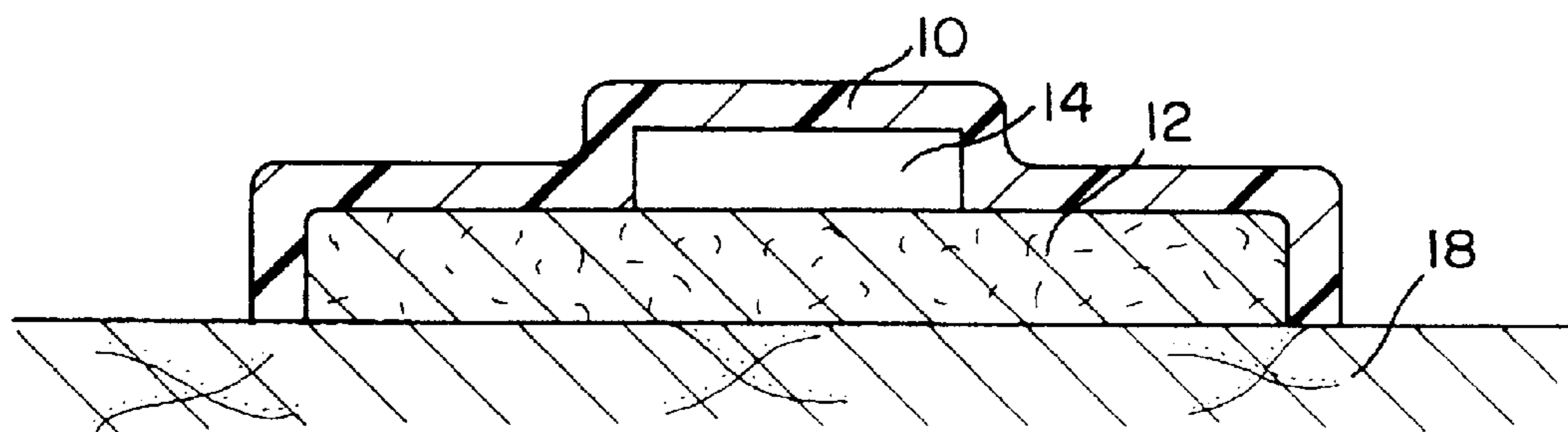


FIG. 2

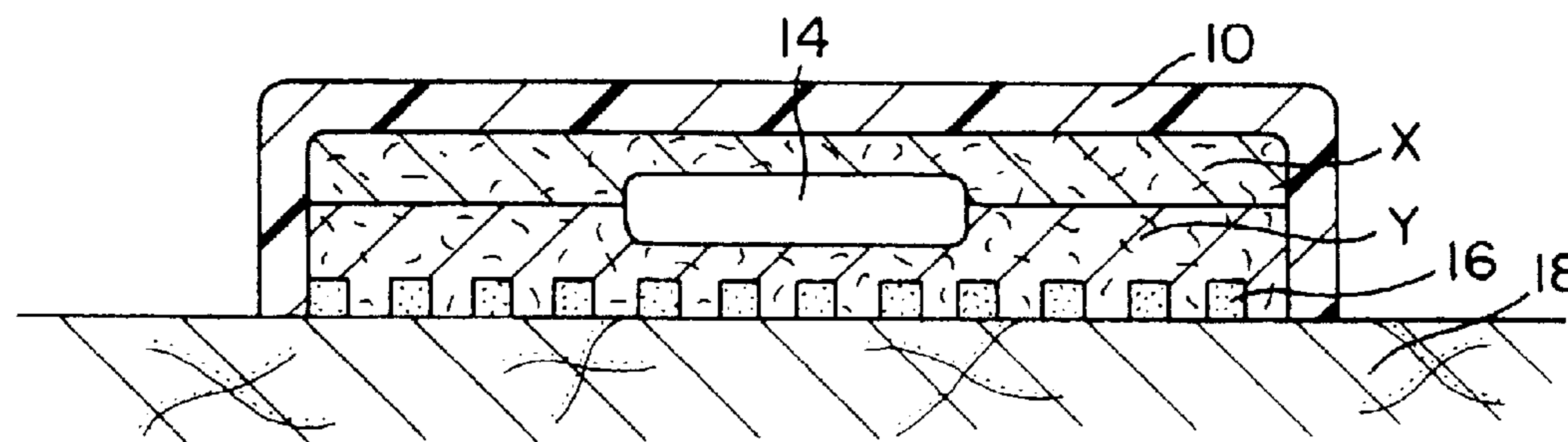


FIG. 3

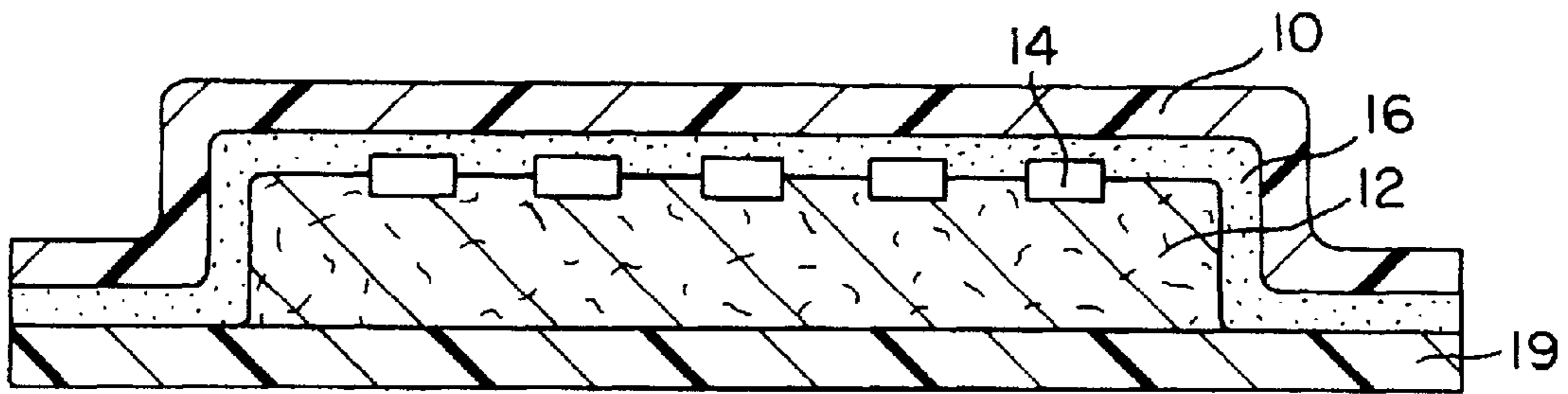


FIG. 4

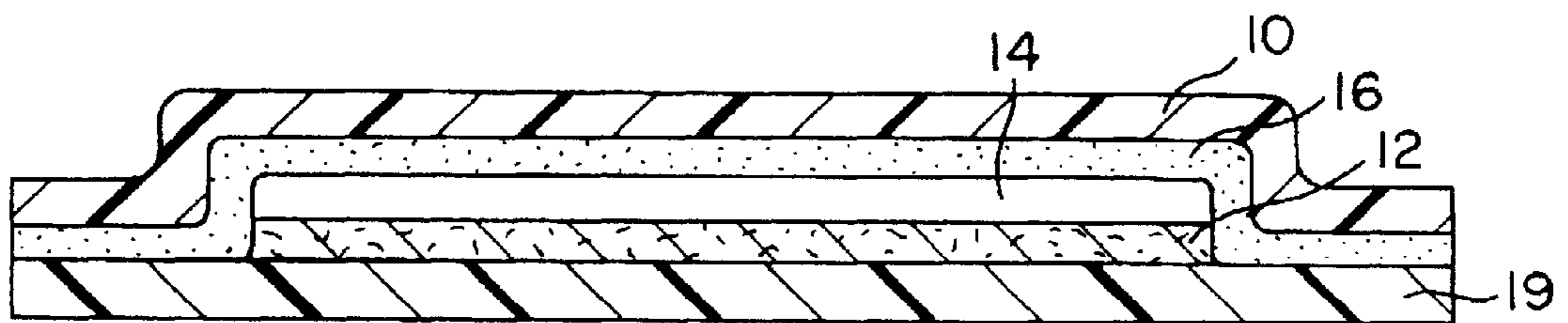


FIG. 5

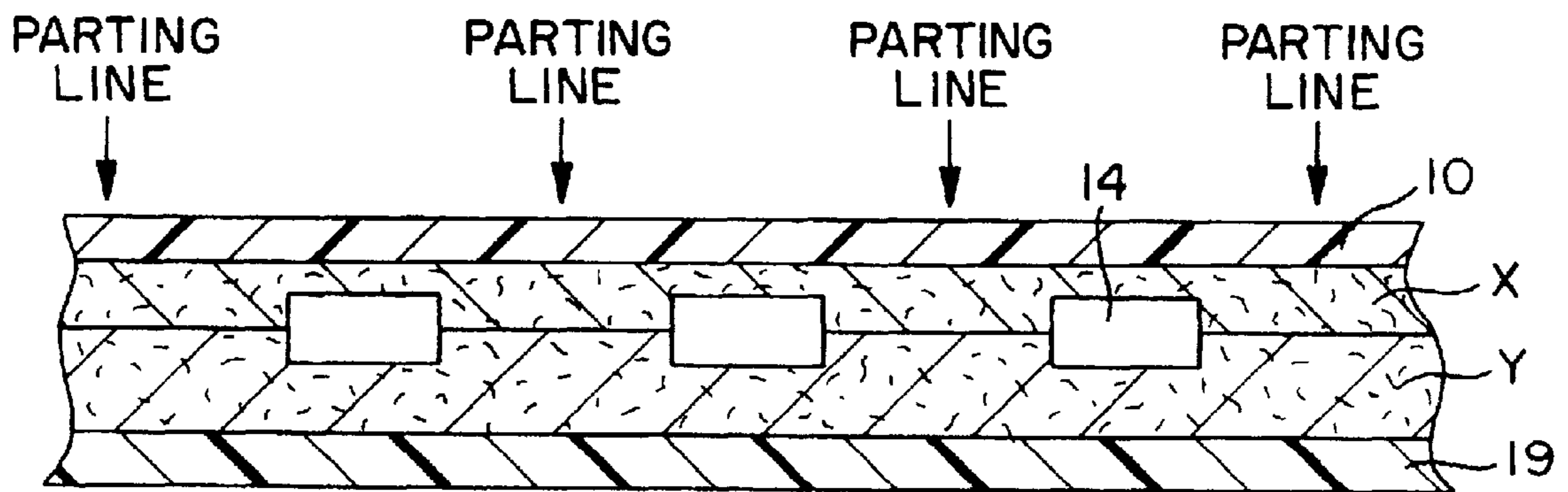


FIG. 6

TRANSDERMAL THERAPEUTIC SYSTEM

Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

[This] *This application is a Reissue of application Ser. No. 08/469,207, U.S. Pat. No. 5,820,876, which is a continuation-in-part of application Ser. No. 08/341,844, filed Nov. 18, 1994, now abandoned, which is a continuation of application Ser. No. 08/027,698, filed May 17, 1993, now abandoned, which is a division of application Ser. No. 07/908,930, filed Jul. 8, 1992, now abandoned, which is a continuation of application Ser. No. 07/597,102, filed Oct. 12, 1990, now abandoned, which is a continuation of application Ser. No. 07/219,066, filed Jun. 27, 1988, now abandoned, which claims priority of PCT application number DE87/00372, filed Aug. 20, 1987, which claims priority of German Patent Application P 36 29 304.0, filed Aug. 28, 1986.*

FIELD OF THE INVENTION

The invention relates to a therapeutic system for applying active substances to the skin, with a backing layer remote from the skin, at least one active substance depot, an active substance distribution device which is linked with the active substance depot, an active substance delivery control device controlling the delivery of the active substance through the system and a pressure sensitive adhesive fixing device for the therapeutic system on the skin, its use and process for the production thereof.

BACKGROUND OF THE INVENTION

Therapeutic systems for the transdermal administration of medicaments supply one or more active substances at a predetermined rate and in continuous manner over a fixed period to a given application point on the skin.

These systems are therapeutic precision instruments ensuring a continuous active substance release.

Such therapeutic systems can have both a topical and a systemic action and the large number of active substances which can be applied in this way and their different chemical, physical and pharmacological characteristics make ever new demands on the production of such systems.

Conventionally these transdermal systems have at least one active substance reservoir, where the active substance is present in solid, liquid or disperse molecular form and an adhesion layer through which the system is closely connected with the skin and through which active substance transfer takes place, a control membrane and protective/covering layers which are substantially impermeable for the active substance.

The known systems are difficult to manufacture and have a complicated structure.

One problem of conventional systems is that of being able to process readily volatile active substances, because the evaporation of the active substance is difficult to control during production.

Thermally sensitive active substances can only be used to a limited extent in the system in the case of matrices or therapeutic systems which have to be thermally treated and which are produced with heat treatment stages.

Attempts have already been made to introduce pure active substance in fine-crystalline form into a pressure sensitive adhesive polymer, so that the finely divided, fine-crystalline

active substance dissolves with time as depot crystals in the adhesive matrix layer (DE-OS 35 00 508=U.S. Pat. No. 4,719,226). This process is not suitable for volatile and thermally sensitive active substances, because it includes thermal treatment stages.

Another attempt to increase the capacity of such therapeutic systems comprises embedding in a pressure sensitive adhesive layer of such a system active substance depots in the form of microcapsules, which are surrounded by a control membrane (see U.S. Pat. Nos. 3,598,123 and 3,731,683). The production of such control membrane-surrounded microcapsules is extremely complicated and expensive and cannot be performed for many active substances. The mixing of the active substance-containing microcapsules under a reservoir material constitutes a further difficult process stage, during which the microcapsules can easily be damaged or destroyed, which can lead to an unsatisfactory constancy of the active substance content in the finished therapeutic system. The process of U.S. Pat. No. 3,598,123 is difficult to perform for liquid active substances, particularly if the liquid substance is present in readily volatile form.

German patent 3 424 837 discloses a depot plaster, which can be used for liquid materials and has a covering film, a liquid active substance in an outwardly bulging region of the covering film and a control membrane covering the active substance and permeable for the latter. Between the covering film and the control membrane is provided an active substance distribution device, namely a non-woven fabric, which uniformly distributes the active substance liquid on the control membrane and which is effective over a large surface area. In the case of the depot plaster of German patent 3 424 837 the covering film and the control membrane are welded together in their outer regions in order to prevent an outward flow of the liquid active substance.

However, the known depot plaster is disadvantageous in that the liquid therein flows freely and can easily run out if the adhesive or welded edges are damaged and also requires an expensive control membrane, which must be provided in addition to the active substance distribution device in order to kinetically control the delivery of the active substance.

The problem of the present invention is consequently to provide a novel therapeutic system with active substance depot for the administration of the active substance, which can be manufactured less expensively and more reliably than the prior art systems, which is also suitable for processing volatile and/or thermally unstable components.

SUMMARY OF THE INVENTION

According to the invention this problem is solved by a therapeutic system, which is characterized in that the active substance distribution device and the active substance delivery control device are a reservoir matrix having one or more discrete active substance depots arranged in a spatially defined manner with respect to one another and having a higher active substance concentration than in the reservoir matrix. During the production of the therapeutic system, the reservoir matrix can be free from active substances and is only enriched therewith over a period of time, i.e. during the storage of the system or, in the case of highly volatile substances, during the production of the system. Thus, it is an advantage of the invention that now active substances, which are thermally unstable and/or volatile can be introduced during manufacture into transdermal systems in the form of a depot and without any thermal stressing. There is no need for stages, such as the mixing of the reservoir matrix

material with the active substance, and instead said material becomes saturated with the active substance at room temperature during the storage of the therapeutic system. Production is simplified due to the omission of the production stages for the active substance-saturated matrix.

Due to the fact that here a reservoir matrix with its own control function is used, which is inter alia determined by the migration speed of the active substance through the matrix, there is no need to provide a control membrane, which requires additional process stages and membrane material during production. The depot can consist of pure active substance, which can be solid or fluid, but may contain also inert adjuvants. The term "inert" is here understood to mean that active substance and adjuvant do not react with one another. An "inert" adjuvant can also be a substance having physiological effects, such as e.g. dimethylsulfoxide (DMSO) or the like, which e.g. increases the permeability of the skin. Suitable adjuvants are also support materials which make the active substance depot insensitive with respect to pressure and tension application, as well as carriers. Thus, the support material may be an inert adjuvant of planar fabric material for providing and supporting a distributing function. For example, a non-woven fabric may serve as an inert adjuvant and as the supporting fabric and assist the uniform distribution of nicotine or any other active substance referred to hereafter. In other words, such fabric material will facilitate the processing of the active substance.

It is possible to use active substances which can be applied in transdermal manner and typical examples of these are given below.

Nicotine.

Corticosteroids: hydrocortisone, prednisolone, beclomethasone-propionate, flumethasone, triamcinolone, triamcinolone-acetonide, fluocinolon, fluocinolinacetonide, fluocinolon-acetonide acetate, clobetasolpropionate, etc.

Analgesics, anti-inflammatory agents: acetaminophen, mefenamic acid, flufenamic acid, diclofenac, diclofenac-sodium-alclofenac, oxyphenbutazone, phenylbutazone, ibuprofen, flurbiprofen, salicylic acid, 1-menthol, camphor, sulindac-tolmetin-sodium, naproxen, fenbufen, etc.

Hypnotically active sedatives: Phenobarbital, amobarbital, cyclobarbital, triazolam, nitrazepam, lorazepam, haloperidol, etc.

Tranquilizers: fluphenazine, thioridazine, lorazepam, flunitrazepam, chlorpromazine, etc.

Antihypertensives: pindolol, indenolol, nifedipin, lofexidin, nipradinol, bucumolol, etc.

Antihypertensively acting diuretics: hydrothiazide, bendroflumethiazide, cyclopentthiazide, etc.

Antibiotics: penicillin, tetracycline, oxytetracycline, fra-diomyacin sulfate, erythromycin, chloramphenicol, etc.

Anesthetics: lidocaine, benzocaine, ethylaminobenzoate, etc.

Antimicrobiological agents: benzalkonium chloride, nitrofurazone, nystatin, acetosulfamine, clotrimazole, etc.

Antifungal agents: pentamycin, amphotericin B, pyrrolnitrin, clotrimazole, etc.

Vitamins: vitamin A, ergocalciferol, cholecalciferol, octotiamine, riboflavin butyrate, etc.

Antiepileptics: nitrazepam, meprobamate, clonazepam, etc.

Coronary vasodilators: dipyridamole, erythritol tetranitrate, pentaerythritol tetranitrate, propatylnitrate, etc.

Antihistamines: diphenyl hydromine hydrochloride, chlorpheniramine, diphenylimidazole, etc.

Antitussives: dertromethorphan (hydrobromide), terbutaline (sulphate), ephedrine (hydrochloride), salbutanol (sulphate), isoproterenol (sulfate, hydrochloride), etc.

Sexual hormones: progesterone, etc.

Thymoleptics: doxepin, etc.

Further medicaments/pharmaceuticals: 5-fluorouracil, fentanyl, desmopressin, domperdon, scopolamine (hydrobromide), peptide, etc.

Obviously, this list is not exhaustive.

Advantageously the active substance reservoir matrix can be built up in layer form, the layers being the same or different. The reservoir matrix can be pressure sensitive adhesive and can e.g. be a rubber material, such as styrene/isoprene/styrene block copolymers, silicone rubber or synthetic resins, such as poly(meth)acrylate, polyurethane, polyvinylether, polyester, etc.—a list of suitable matrix materials appearing e.g. in DE-OS 35 00 508, corresponding to U.S. Pat. No. 4,719,226 the whole content of which is incorporated by reference. It can be advantageous if the reservoir matrix is pressure sensitive adhesive, because this can obviate the need for providing a separate pressure sensitive adhesive fixing device in the system. The use of such a pressure sensitive adhesive matrix is inter alia dependent on the compatibility of the matrix material with the active substance. Pressure sensitive adhesive matrix materials are known.

Preferred non-pressure sensitive adhesive matrix materials are polymers comprising poly(meth)acrylate, polyvinylpyrrolidone, ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulosephthalate, polyvinylalcohol or copolymers thereof with vinylaurate or maleic acid, vinylacetate or copolymers thereof with vinylaurate or maleic acid, polyvinylether, butylrubber and polycaprolactam.

For example, the active substance depot or depots can be introduced between a backing side reservoir matrix layer and a skin side reservoir matrix layer, the thickness ratio of the reservoir matrix layers preferably being between approximately X:Y=1:1 and 1:20 and in particularly preferred manner 1:1 and 1:5.

It can be appropriate in other cases if the reservoir matrix or reservoir matrix layers from which said matrix is formed, to be provided at least on one side with pressure sensitive adhesive coatings.

According to a further advantageous development of the inventive system, the active substance depot can be arranged between the reservoir matrix and the backing layer, which is e.g. suitable for solid active substances which may be applied in the form of a corpuscle.

In a preferred embodiment of the invention the fixing device can be formed by adhesive portions embedded in the reservoir matrix, such as e.g. an all-round adhesive edge or adhesion points.

In conventional manner, it is possible to provide a detachable protective layer for the surfaces of the therapeutic system facing the skin.

The sum of the active substance in the depot and reservoir matrix is advantageously up to 20 times the therapeutically necessary active substance quantity.

A particularly preferred process for producing such systems comprises the reservoir matrix being formed from two reservoir matrix layers, which can be the same or different, between which is introduced the active substance depot. The reservoir matrix layers can be joined together by the application of pressure and/or heat. The depot can also be

introduced into the reservoir matrix under pressure application, e.g. by injecting, for example, through a hypodermic syringe, a predetermined quantity or pressing in an active substance corpuscle into a soft matrix layer.

A further preferred process is forming at least part of the therapeutic system by strewing on particles.

It is also possible to produce a multilayer active substance matrix. The covering and reservoir matrix layer can also be joined by heat or pressure. The reservoir matrix layer or layers can at least partly be produced from liquid materials, e.g. from a dispersion, a melt or solutions.

The inventive therapeutic system is in particular suitable for local or systemic transdermal active substance application in human or veterinary medicine or can also be used in cosmetics.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is described in greater detail hereinafter relative to non-limitative embodiments of the inventive therapeutic system and the attached diagrammatic drawings, which show:

FIG. 1 is a section through a preferred embodiment of an inventive therapeutic system.

FIG. 2 is a section through a further preferred embodiment of a therapeutic system in which the active substance depot is located between the backing layer and the reservoir matrix.

FIG. 3 is a section through a further preferred embodiment of the inventive system, wherein the active substance reservoir is embedded between matrix layers.

FIG. 4 is a section through an inventive therapeutic system with several active substance depots arranged in one plane.

FIG. 5 is a section through an inventive therapeutic system with an active substance depot in layer form.

FIG. 6 is a section through a web-like semi-finished product according to the invention.

DETAILED DESCRIPTION OF THE INVENTION

FIG. 1 is a section through an inventive therapeutic system, which is fixed to the skin 18 by a fixing device 16, e.g. a porous pressure sensitive adhesive layer or the like. On fixing device 16 is located reservoir matrix 12 which, at the time of production, is preferably free from active substance (active substance saturation taking place during storage). In the reservoir matrix 12 is embedded a depot 14, which is represented here as a solid active substance which dissolves in the reservoir matrix material 12 and is supplied to the skin 18 by fixing device 16. The therapeutic system is sealed to the outside by a backing layer 10 which is impermeable for the active substance and preferably also moisture and simultaneously has a support function for the system.

FIG. 2 shows another variant of the inventive system, in which an active substance depot 14 is located on a reservoir matrix layer 12 and is covered by a backing layer 10. The fixing device is not shown in this drawing and can e.g. be a pressure sensitive adhesive border or edge or the like, which applies the skin contact surface of the therapeutic system closely to skin 18. This embodiment of the invention is advantageous in that its production is very simple. It is merely necessary to apply clearly defined quantities of active substance, in the form of a solid or a viscous liquid to the prefabricated matrix layer 12 and to seal or terminate the same by a backing layer 10.

The process for producing the system according to FIG. 2 is less expensive than for that according to FIG. 1. However, it can only be used if it is not absolutely necessary that active substance 14 is enclosed on all sides by matrix 12, e.g. due to the volatility of active substance 14 or due to a necessarily large contact surface between active substance 14 and reservoir matrix 12. It is e.g. advantageous for substances which very readily dissolve in active substance 14 reservoir and without difficulty diffuse in it, so that there is no need for a large contact surface between active substance 14 and active substance reservoir matrix 12.

FIG. 3 shows another preferred embodiment, in which an inventive therapeutic system is fixed to the skin 18 by means of adhesive particles or portions 16 embedded on the skin 18 side in the active substance reservoir matrix material. The active substance reservoir layer 12 here comprises an upper layer X and a lower layer Y, between which is introduced the active substance, which is e.g. here in liquid form. The provision of two reservoir matrix layers X, Y is advantageous if a system is being produced in such a way that firstly the lower active substance reservoir layer Y is provided, optionally with an already coated on covering film or the like and then in accordance with a predetermined pattern the active substance/material is applied, the next active substance reservoir layer X is superimposed, and finally in conventional manner the backing layer 10 or optionally various adhesive layers 16 are applied to complete the system. It may also be appropriate to firstly place the two active substance reservoir layers X, Y on top of one another, then inject a predetermined quantity of active substance between the two reservoir layers X, Y and in this way keep evaporation of the active substance 14 to a minimum.

FIG. 4 shows an embodiment of an inventive transdermal system with several active substance depots 14 arranged in one plane and placed between a pressure sensitive adhesive layer 16 and a reservoir matrix 12, layer 16 simultaneously fixing the backing layer 10 to the transdermal system. The transdermal system is sealed by a detachable protective layer 19.

FIG. 5 shows another embodiment of an inventive transdermal system, in which a backing layer 10 is coated on one side with an adhesive layer 16 and on it is located active substance 14, optionally with adjuvants, such as material for facilitating processing of active substance 14 (e.g. tableting aids) or carriers, like fabrics and the like. To the flat active substance depot 14 is applied a reservoir matrix 12 which is in turn covered by a detachable protective film.

FIG. 6 shows the precursor of an inventive transdermal system, such as is obtained during a preferred production process. A web-like protective coating material 19, such as e.g. waxed paper or the like is covered by a reservoir matrix layer Y, which is here constructed in pressure sensitive adhesive manner and on same are located in accordance with a predetermined pattern of active substance depot bodies 14. Matrix layer Y is covered by a second matrix layer X, which can e.g. comprise a material differing from that of layer Y. The second matrix layer X is sealed by a backing film 10. Along the arrows are located the parting or separating lines, along which the intermediate product is cut or punched during the production of the inventive transdermal systems and then prepared in the usual way.

Typical thicknesses for inventive transdermal systems are in the case of a total thickness of approximately 123 to 5550 μm , preferably 285 to 1550 μm ; thickness of the backing layer 8 to 150 μm and preferably 15 to 100 μm ; thickness of the reservoir 100 to 5000 μm , preferably 200 to 1330 μm ; thickness of the protective layer 15 to 400 μm , preferably 70 to 150 μm .

For special application it is also possible to market the "semifinished product" as such, so as to enable users to carry out the separation of the systems, so that the semifinished product acts in the manner of a "storage pack".

Preferred examples of the invention are described below.

EXAMPLE 1

PRODUCTION OF A NICOTINE PLASTER

Nicotine plasters, such as are used to stop people from smoking, are, according to the invention, produced as follows.

A pressure sensitive adhesive material comprising 2.0825 kg of a 40% solution of a self-crosslinking acrylate copolymer, e.g. of 2-ethyl-hexyl acrylate, vinyl acetate, acrylic acid and titanium chelate ester, or DUROTAC 280-2416 of the firm National Starch/Chemical B.V. in a mixture of ethyl acetate, ethanol, hexane and methanol, 147 g of an acrylic resin of dimethylaminoethylmethacrylate and neutral methacrylate (EUDRAGIT E 100 of the firm RÖHM PHARMA), and 20 g of a mixed acidic triglyceride of fractionated C₈-C₁₀ coconut fatty acids (Miglyol 812 of the firm Dynamit Nobel) are applied to a protective layer vapor-deposited with aluminum on one side and adhesively finished on both sides and the solvent is evaporated at 50° to 80° C. An approximately 300 g/m² layer is obtained. From the thus produced pressure sensitive adhesive layer are punched round discs with a diameter of 65 mm. The projecting edges are worked and central to the same is applied in each case one circular disc of a non-woven fabric e.g. fibrous mixture of viscose staple cotton fiber 50:50 with a substance weight of 80 g/m² and with a diameter of 40 mm. An example of such a product is PARATEX II/80, a product of LOHMANN GMBH & CO KG. PARATEX is a registered trademark of Lohmann GmbH & Co. KG. To this is applied nicotine as the active substance in solution (140 g nicotine in 100 g of an acrylic resin of dimethylaminoethylmethacrylate and neutral methacrylates (EUDRAGIT E 100 of the Firm RÖHM PHARMA) in 102 mg doses/disc. The thus produced patches are immediately laminated with a nicotine impermeable backing layer (a 15 μm thick polyester film on one side of which aluminum is vapor deposited) and sealed in four-edge sealing bags of a suitable packing material. The depot side of the backing layer may be layered with a layer of approximately 300 g/m² of the pressure sensitive adhesive layer, referred to above. The four-edge sealing bags may consist of a compound of paper (surface weight 50 g/m²), aluminum 9 μm and Barex (trademark of the firm Vistron Corp., Cleveland, Ohio, USA, for thermoplastic acrylonitrile-copolymers with negligible gas permeability and great resistance to solvents) with 26 g/m². Thus, those nitrile rubber modified acrylonitrile-methylacrylate copolymers serve as nicotine barrier layer, the aluminium as a nicotine degradation agent barrier, and the paper as a protective layer.

In the case of this example the non-woven fabric serves as the supporting fabric and to assist the uniform distribution of the nicotine as an inert adjuvant as defined hereinbefore.

The chemical composition of Barex has been known to the public, as is evident from the publication of M.TH. Schuler in "Kunststoffe-Plastics" 9/1974, pages 13-20. Particular reference is made to the title, page 13, left-hand column, lines 1 to 3 which both refer generally to "Barex-Harze", page 14/14-16, page 17, right-hand column, section "Untersuchungen an Barex zur Zulassung durch die FDA", lines 5-7 and page 18, column 2, paragraph 2 referring to the

approval of the US FDA and stating that Barex (without specific reference to Barex 210) is obtained by graft polymerisation (Pfropf-Polymerisation) of 73-77 parts of acrylonitrile and 23-27 parts of methyl acrylate in the presence of 8-10 parts butadiene-acrylonitrile copolymer of 70% of butadiene, the parts and percents always being by weight. Moreover, the fact that Barex is a thermoplastic copolymer which has negligible gas permeability and good resistance to solvents is, for example, evident from page 13, left-hand column, paragraph 1. Line 1 specifically recites thermoplastic, while the sentence starting in line 5 reads in translation as follows:

"As already the term "barring plastic" means, this novel material has very good barring properties against various gases such as oxygen, carbon dioxide (carbonic acid), nitrogen and also many chemical agents such as acids, alkalis and solvents".

The next sentence refers to the copolymerization of acrylonitrile with selected monomers. Lines 7 to 13 of paragraph 2 of left-hand column of page 13 read in translation:

"Its (i.e. of Barex 210) permeability for oxygen and carbon dioxide is about ten times smaller than that of other conventional bulk plastics. This modern plastic is particularly suitable for applications in which glass-like clarity, prevention of loss of flavor and gas-impermeability are required."

As used herein, the term "sealing bag" refers to a package or other container which is generally flexible and is sealed on at least one side. The sealing bags of this invention can comprise, for example, two sheets or lamina which have been joined along all edges; a single sheet or lamina which has been folded and sealed along all edges or along all non-folded edges; a pouch or pocket which is sealed along one or more edges; and the like.

The term "nicotine barrier" as used herein, implies that the barrier material is inert to nicotine and does not permit nicotine to migrate through the material over a nicotine barrier material is a metal film such as aluminum, which may be provided on one side with a protective layer, e.g. of paper.

The term "nicotine degradation agent barrier" refers to a barrier layer which is substantially impermeable to nicotine degradation agents, such as oxygen and water in liquid or vapor form, and light. The invention may also be defined as a nicotine containment sealing bag comprising:

- a) a nitrile rubber modified acrylonitrile-methyl acrylate copolymer nicotine barrier having a volume enclosed therein;
- b) a nicotine degradation agent barrier serving to prevent entry of nicotine degradation agents into said volume; and
- c) nicotine base within said volume.

Due to the fact that, according to the invention, an active substance solution can be rapidly applied to a matrix layer and is then covered by an active substance impermeable covering layer, it is possible for the first time to obtain in a satisfactory manner well dosed nicotine plasters.

NICOTINE RELEASE TEST (IN VITRO)

A nicotine plaster produced according to Example 1 after removing the protective layer is immersed in 80 ml of isotonic common salt solution at 37° C. and the released nicotine quantity is determined liquid chromatographically after predetermined intervals. The release medium volume was chosen in such a way that "sink" conditions are obtained over the entire test period. The following results were obtained:

Nicotine released in vitro per plaster:

after 2 hours: 23.90 mg/plaster

after 4 hours: 32.34 mg/plaster

after 8 hours: 41.50 mg/plaster

after 24 hours: 56.54 mg/plaster

EXAMPLE 2

PRODUCTION OF A NICOTINE PLASTER

Another nicotine plaster according to the invention may be inventively produced as follows:

A pressure sensitive adhesive material (adhesive 1) comprising 1.9758 kg of a 40% solution of a self-crosslinking acrylate copolymer (DUROTAC 280-2416 of the firm Delft National & Chemical B.V.) in a mixture of ethyl acetate, ethanol, heptane and methanol, 189.7 g of an acrylic resin of dimethylaminoethylmethacrylate and neutral methacrylate (EUDRAGIT E 100 of the firm RÖHM PHARMA), and 20 g of a mixed acidic triglyceride or fractionated C₈-C₁₀ coconut fatty acids (Miglyol 812 of the firm Dynamit Nobel) are applied to a protective layer vapor-deposited with aluminum on one side and abhesively finished on both sides and the solvent is evaporated at 50° to 80° C. An approximately 440 g/m² layer is obtained. From the thus produced pressure sensitive adhesive layer are punched round discs with a diameter of 51 mm. The projecting edges are worked and central to the same is applied in each case one circular disc of a non-woven fabric (fibrous mixture of viscose staple fibre/cotton 70:30 with a substance weight of 40 g/m²—PARATEX III/40 of LOHMANN GMBH & CO KG) and with a diameter of 42 mm. To this is applied nicotine as the active substance in solution (140 g nicotine in 100 g of an acrylic resin of dimethylaminoethylmethacrylate and neutral methacrylates—EUDRAGIT E 100 of the Firm RÖHM PHARMA) in 46 mg doses/disc. The thus produced patches are immediately laminated with a nicotine-impermeable backing layer (a 15 μm thick polyester film, on one side of which aluminum is vapor-deposited having an approximately 110 g/m² coating of adhesive 1), and sealed in four edge sealing bags of conventional suitable composite packing material.

In this case the non-woven fabric serves as the supporting fabric and to assist the uniform distribution of the nicotine as an inert adjuvant as defined hereinbefore.

Due to the fact that, according to the invention, an active substance solution can be rapidly applied to a matrix layer and is then covered by an active substance impermeable covering layer, it is possible for the first time to obtain in a satisfactory manner well dosed nicotine plasters.

NICOTINE RELEASE TEST (IN VITRO)

A nicotine plaster produced according to Example 2 after removing the protective layer is immersed in 80 ml of isotonic common salt solution at 37° C. and the released nicotine quantity is determined liquid chromatographically after predetermined intervals. The release medium volume was chosen in such a way that "sink" conditions are obtained over the entire test period. The following results were obtained:

after 2 hours: 5.1 mg/plaster

after 4 hours: 7.2 mg/plaster

after 8 hours: 10.1 mg/plaster

after 24 hours: 16.5 mg/plaster

It is to be understood that the invention is not limited to nicotine plasters and the production thereof with the claimed

build-up but that other substances as preferred substances are mentioned in the specification may be administered by this new therapeutic system.

What is claimed is:

- 5 1. A sealing bag containing a nicotine patch comprising:
 - a) a butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer layer, and
 - b) a composite layer comprising paper and, aluminum,
 - c) wherein the layers form a bag which is sealed on four edges, and
 - d) wherein a nicotine patch is contained within said bag.
- 10 2. A sealing bag according to claim 1, wherein the copolymer layer comprises a copolymer formed from about 73-77 parts by weight of acrylonitrile copolymerized with 23-27 parts by weight of methyl acrylate in the presence of 8-10 parts by weight of butadiene acrylonitrile copolymer containing about 70% by weight of polymer units derived from butadiene.
- 15 3. The sealing bag of claim 1 further comprising a protective layer forming the external surface of said sealing bag.
- 20 4. The sealing bag of claim 2 further comprising a protective layer forming the external surface of said sealing bag.
- 25 5. The sealing bag of claim 1 wherein said composite is disposed on the external surface of said copolymer layer.
- 30 6. The sealing bag of claim 2, wherein said composite is disposed on the external surface of said copolymer layer.
- 35 7. A sealing bag containing a nicotine patch comprising a four edged sealing bag made of a composite comprising paper, aluminum and a butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer, and wherein the nicotine patch is contained within said bag.
- 40 8. A sealing bag consisting of:
 - a) a thermoplastic butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer layer, and
 - b) a composite layer consisting of paper and aluminum,
 - c) wherein the layers form a bag which is sealed on four edges, and
 - d) wherein a nicotine patch is contained within said bag.
- 45 9. A sealing bag containing a nicotine patch comprising a four edged sealing bag made of a composite consisting of paper, aluminum and a thermoplastic butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer, and wherein the nicotine patch is contained within said bag.
- 50 10. A sealing bag according to claim 8, wherein the copolymer layer comprises a copolymer formed from about 73-77 parts by weight of acrylonitrile copolymerized with 23-27 parts by weight of methyl acrylate in the presence of 8-10 parts by weight of butadiene acrylonitrile copolymer containing about 70% by weight of polymer units derived from butadiene.
- 55 11. The sealing bag of claim 8, wherein said composite is disposed on the external surface of said copolymer layer.
- 60 12. The sealing bag of claim 10, wherein said composite is disposed on the external surface of said copolymer layer.
- 65 13. The sealing bag of claim 8 further comprising a protective layer forming the external surface of said sealing bag.
14. The sealing bag of claim 10 further comprising a protective layer forming the external surface of said sealing bag.
15. A sealing bag according to claim 7, wherein the copolymer layer comprises a copolymer formed from about 73-77 parts of acrylonitrile copolymerized with 23-27 parts by weight of methyl acrylate in the presence of 8-10 parts

by weight of butadiene acrylonitrile copolymer containing about 70% by weight of polymer units derived from butadiene.

16. The sealing bag of claim 7, wherein said composite is disposed on the external surface of said copolymer.

17. The sealing bag of claim 15, wherein said composite is disposed on the external surface of said copolymer layer.

18. The sealing bag of claim 7 further comprising a protective layer forming the external surface of said sealing bag.

19. The sealing bag of claim 15 further comprising a protective layer forming the external surface of said sealing bag.

20. A sealing bag according to claim 9, wherein the copolymer layer comprises a copolymer formed from about 73–77 parts by weight of acrylonitrile copolymerized with 23–27 parts by weight of methyl acrylate in the presence of 8–10 parts by weight of butadiene acrylonitrile copolymer containing about 70% by weight of polymer units derived from butadiene.

21. The sealing bag of claim 9, wherein said composite is disposed on the external surface of said copolymer layer.

22. The sealing bag of claim 20, wherein said composite is disposed on the external surface of said copolymer layer.

23. The sealing bag of claim 9 further comprising a protective layer forming the external surface of said sealing bag.

24. The sealing bag of claim 20 further comprising a protective layer forming the external surface of said sealing bag.

25. A sealing bag containing a nicotine patch comprising a combination of

a) a butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer layer, and

b) a layer comprising aluminum,

wherein the layers form a bag which is sealed on all edges and the nicotine patch is contained within said bag.

26. A sealing bag containing a nicotine patch comprising a bag sealed on all edges made of a composite comprising an aluminum layer and a butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer layer, wherein the nicotine patch is contained within said bag.

27. A sealing bag consisting of a combination of

a) a thermoplastic butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer layer, and

b) an aluminum layer,

wherein said layers form a bag which is sealed on all edges and a nicotine patch is contained within said bag.

28. A sealing bag containing a nicotine patch comprising a bag sealed on all edges comprising a composite consisting essentially of an aluminum layer and a thermoplastic butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer layer, wherein the nicotine patch is contained within said bag.

29. A sealing bag as claimed in claim 25, which is sealed on four edges.

30. A sealing bag as claimed in claim 26, which is a four edged sealing bag.

31. A sealing bag as claimed in claim 27, which is sealed of four edges.

32. A sealing bag as claimed in claim 28, which is a four edged sealing bag.

33. A sealing bag as claimed in claim 25, which further comprises a paper layer.

34. A sealing bag as claimed in claim 26, wherein the composite further comprises a paper layer.

35. A sealing bag as claimed in claim 27, wherein layer (b) further comprises a paper layer.

36. A sealing bag containing a nicotine patch comprising a bag sealed on all edges comprising a composite consisting essentially of a paper layer, an aluminum layer and a thermoplastic butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer layer, wherein the nicotine patch is contained within said bag.

37. A bag for a patch with an active substance comprising a sealing bag made of a composite comprising an aluminum layer and a butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer layer wherein the patch with the active substance is contained within said bag.

38. The bag according to claim 37, where the active substance is nicotine.

39. The bag according to claim 37, wherein the sealing bag is sealed on four edges.

40. The bag according to claim 37, wherein the composite further comprises a paper layer.

41. A bag for a patch with an active substance comprising a sealing bag made of a composite comprising a degradation agent barrier layer for said active substance and a butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer layer wherein said layers are in contact with each other and the active substance is contained in the patch within said bag.

42. The bag according to claim 41, wherein the sealing bag is sealed on four edges.

43. The bag according to claim 41, wherein the composite further comprises a protective layer.

44. The bag according to claim 43, wherein the protective layer is paper and the active substance is nicotine.

45. A sealing bag containing a nicotine patch comprising a bag sealed on all edges made of a composite comprising an aluminum layer and a butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer layer, wherein said layers are in contact with each other and the nicotine patch is contained within said bag.

46. A sealing bag consisting of a combination of

a) a thermoplastic butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer layer, and

b) an aluminum layer,

wherein the layers are in contact with each other and form a bag which is sealed on all edges and a nicotine patch is contained within said bag.

47. A sealing bag containing a nicotine patch comprising a bag sealed on all edges comprising a composite consisting essentially of an aluminum layer and a thermoplastic butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer layer, wherein said layers are in contact with each other and the nicotine patch is contained within said bag.

48. A sealing bag as claimed in claim 45, which is a four edged sealing bag.

49. A sealing bag as claimed in claim 46, which is sealed on four edges.

50. A sealing bag as claimed in claim 47, which is a four edged sealing bag.

51. A sealing bag as claimed in claim 45, wherein the composite further comprises a paper layer.

52. A sealing bag as claimed in claim 46, wherein layer (b) further comprises a paper layer.

53. A sealing bag containing a nicotine patch comprising a bag sealed on all edges comprising a composite consisting essentially of a paper layer, an aluminum layer and a thermoplastic butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer layer, wherein said layers are in

contact with each other and the nicotine patch is contained within said bag.

54. A bag for a nicotine patch comprising a sealing bag made of a composite comprising an aluminum layer and a butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer layer wherein said layers are in contact with each other and the nicotine patch is contained within said bag.

55. The bag according to claim 54, wherein the sealing bag is sealed on four edges.

56. The bag according to claim 54, wherein the composite further comprises a paper layer.

57. A bag for a nicotine patch comprising a sealing bag made of a composite comprising a degradation agent barrier layer for said nicotine patch and a butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer layer wherein said layers are in contact with each other and a nicotine patch is contained within said bag.

58. The bag according to claim 57, wherein the sealing bag is sealed on four edges.

59. The bag according to claim 57, wherein the composite further comprises a protective layer.

60. The bag according to claim 57, wherein the protective layer is paper.

61. A sealing bag for an active substance that can be applied in a transdermal manner comprising an acrylonitrile methyl acrylate copolymer containing medicament barrier layer and an aluminum-containing medicament-degradation agent barrier.

62. The sealing bag of claim 61, further including a paper protective layer.

63. The sealing bag of claim 61, wherein the transdermal substance is nicotine.

64. The sealing bag of claim 62, wherein the transdermal substance is nicotine.

65. The sealing bag of claim 61, wherein the active substance that can be applied in a transdermal manner is sealed within same sealing bag.

66. The sealing bag of claim 62, wherein the active substance that can be applied in a transdermal manner is sealed within same sealing bag.

67. The sealing bag of claim 65, wherein the active substance is nicotine that can be applied in a transdermal manner and is sealed within same sealing bag.

68. The sealing bag of claim 66, wherein the active substance is nicotine that can be applied in a transdermal manner and is sealed within same sealing bag.

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