Description

Field of the Art:

The present invention relates to pharmaceutical plasters which can be used in the treatment of a variety of diseases.

Background of the Art:

As the administration routes of medicines, ointments or the like have been frequently used as a local administration in addition to conventional ones such as oral, injection or rectal administrations. Further in recent years, the technical development has made steady progress in transdermal application of systemically acting drugs and several kinds of drugs have come to be clinically used in practice.

Since the transdermal administration of drugs enables them to avoid the first-pass effect which they would suffer in liver, if they were orally given, drug concentration in blood is far more stable than in the case of oral or injection administration, and many advantages also can be obtained, for example longer effective time, easier removal of the drug by detaching the preparation in case of serious side-effects, and the like.

These merits have received much attention and changes of from conventional oral route preparations to transdermal ones have been investigated for a variety of drugs.

As the clinical application of transdermal preparations has advanced, however, the difficulties and problems in the transdermal route have become clear.

Several of them are as follows:

(1) One of the most serious problems with transdermal preparations is the outbreak of local irritation and skin rash or contact dermatitis. According to statistics, the incidence of rash is 20 to 50 % with transdermal preparations of a typical occlusive type tape.

In many cases, however, the patients must use such preparations for their merits, even when the application of such preparations results in rash development.

Further, many of the drugs used clinically today are generally resistant to transdermal absorption and, even in the drugs which are transdermally absorbable, the absorption of the clinically effective amount needs enlarged application areas and a combination of additives such as an absorption-promoting agent.

The enlarged application areas and the use of absorption-promoting agent and the like frequently bring about increased areas and aggravation of skin rash.

Thus, a transdermally applicable preparation which enables the absorption of a clinically effective dose of the drug with skin rash eruption inhibited is desired.

(2) In addition, when a transdermal preparation is applied for a long time, the preparation becomes stained or peelable with time; bathing especially accelerates the removability.

It is troublesome, however, to apply a new plaster every time the old one peels off. Moreover, the dose control becomes difficult, satisfactory efficacy cannot be attained and problems remain in appearance and hygiene.

Thus, a transdermal preparation which is resistant to staining and peeling, are desired even after prolonged application, is desired.

(3) Usually, a transdermal preparation is of the sustained release type and particularly effective for chronic diseases or diseases requiring long-term treatment. And the patients with such diseases are older people, of advanced age in many cases. Generally, however, older people are not good at handling things which require complicated operation.

Thus, a transdermal preparation is desired which is easy to handle for the patients, in addition to being pharmaceutically satisfactory in its high absorption and the like.

Conventionally, as a plaster aiming at absorption of a clinically effective amount of a drug with inhibition of skin rash, for example, there are known plasters of the present inventors which bear a knitted fabric of microporous hollow fibers as a constituent (WO 87/00046, W087/04343 and W090/09784).

Such plasters have been satisfactory for skin rash reduction and absorption of a clinically effective amount of a drug, but other more excellent plasters which cause no skin rash and resist peeling, even when applied for a more prolonged time, thus revealing sufficient efficacy with no problem of appearance, are still desired.

In other words, an object of the present invention is to provide a pharmaceutical plaster which can enable the absorption of a clinically effective amount of a drug, with extremely reduced skin rash, no

breakage and, because of its satisfactory stretchability, enough to follow skin contraction and expansion, no peeling from the skin.

Another object of the present invention is to provide such a pharmaceutical plaster which has excellent handleability.

Further, another object of the present invention is to provide a pharmaceutical plaster which can expect to develop sufficient clinical efficacy with a reduced content of a drug, when an expensive drug such as buprenorphine or buprenorphine hydrochloride or a drug where it is desired to reduce the amount remaining after application according to the legislation on psychopharmaceuticals handling, is employed.

DISCLOSURE OF THE INVENTION

The present inventors have made intensified studies with a view to providing plasters which can utilise the advantages of conventional transdermal preparations with skin rash decreased, enable the absorption of a clinically effective amount of as many kinds of drugs as possible even if they are resistant to transdermal absorption, and have excellent handleability, and attained the present invention.

In one aspect the present invention is a plaster comprising

(1) a film layer which is composed of a polyester film having a thickness of 0.5 to 4.9 μm, strengths of 8 to 85 g/mm respectively in the two directions intersecting substantially at right angles, elongations of 30 to 150% respectively in the two directions intersecting substantially at right angles, and an elongation ratio of 1.0 to 5.0 (wherein the smaller elongation is used as the denominator when the elongations in the two directions are different), said polyester film containing 0.01 to 1.0% by weight, based on the total weight of said polyester film, of solid fine particles in which

1) the average particle size is 0.001 to 3.0 μm and

2) the average particle size substantially does not exceed 1.5 times the thickness of said polyester film,

(2) an adhesive layer (a) having a thickness of 2 to 60 μm, which is composed of an adhesive containing a transdermally-absorbable drug and is laminated to said film layer, and (3) a release liner removably laminated to the adhesive layer (a).

In a second aspect the present invention provides a plaster comprising

(1) a film layer which is composed of a polyester film having a thickness of 0.5 to 4.9 μm, strengths of 8 to 85 g/mm respectively in the two directions intersecting substantially at right angles, elongations of 30 to 150% respectively in the two directions intersecting substantially at right angles, and an elongation ratio of 1.0 to 5.0 (wherein the smaller elongation is used as the denominator when the elongations in the two directions are different), said polyester film containing 0.01 to 1.0% by weight, based on the total weight of said polyester film, of solid fine particles in which

1) the average particle size is 0.001 to 3.0 μm and

2) the average particle size substantially does not exceed 1.5 times the thickness of said polyester film,

(2) an adhesive layer (a) having a thickness of 2 to 60 μm, which contains a transdermally-absorbable drug and is laminated to one surface of said film layer, and

(3) a backing sheet which is partially or entirely adhered, with an adhesive force of at least 3 g/12 mm, through an adhesive layer (b) of thickness 2 to 100 μm, to the surface of the film layer remote from that to which the adhesive layer (a) is laminated.

In a further aspect the present invention is a plaster comprising

(1) a film layer (a) which is composed of a polyester film having a thickness of 0.5 to 4.9 μm, strengths of 8 to 85 g/mm respectively in the two directions intersecting substantially at right angles, elongations of 30 to 150% respectively in the two directions intersecting substantially at right angles, and an elongation ratio of 1.0 to 5.0 (wherein the smaller elongation is used as the denominator when the ratios of the elongations in the two directions are different), said polyester film containing 0.01 to 1.0% by weight, based on the total weight of said polyester film, of solid fine particles in which

1) the average particle size is 0.001 to 3.0 μm and

2) the average particle size substantially does not exceed 1.5 times the thickness of said polyester film,

(2) an adhesive layer (a) having a thickness of 2 to 60 μm, which contains a transdermally-absorbable drug and is laminated to one surface of said film layer,

(3) a backing sheet which is partially or entirely adhered, with an adhesive force (a1) of over 20 g/12 mm, through an adhesive layer (b1) to the surface of the film layer (a) remote from that to which the adhesive layer (a) is laminated, and

(4) a film layer (b) which is composed of a film having a thickness of 0.5 to 4.9 μm, strengths of 8 to 85 g/mm respectively in the two directions intersecting substantially at right angles, elongations of 30 to 150% respectively in the two directions intersecting substantially at right angles, and an elongation ratio of 1.0 to 5.0 (wherein the smaller elongation is used as the denominator when the elongations in the two directions are different), and is laminated with an adhesive force (b1) of at least 3 g/12 mm, through an adhesive layer (b2) partially or entirely to said backing sheet on the surface thereof not bonded to the adhesive layer (b1).

Brief Description of Figures:

Fig. 1 depicts the cross section of the plaster which has been prepared in Example 1 of the present invention. In the figure, 1 means the backing sheet (hollow fiber sample); 2, the adhesive layer (b); 3, the film layer (polyethylene terephthalate film); 4, the adhesive layer (a) (the progesterone-containing layer); and 5, a release liner (it can be peeled off, when the plaster is applied).

Fig. 2 depicts the cross section of the plaster which has been prepared in Example 4 of the present invention. In the figure, 1 is the film layer (polyethylene terephthalate film); 2, the adhesive layer (a) (progesterone-containing layer); and 3, a release liner.

Fig. 3 depicts the cross section of the plaster which has been produced in Example 22 of the invention. In the figure, 1 means the film layer (b) (polyethylene terephthalate film); 2, the adhesive layer (b2); 3, the backing sheet (hollow fiber sample); 4, the adhesive layer (b1); 5, the film layer (a); 6, the adhesive layer (a) (estradiol-containing layer) and 7, the release liner.

Best Embodiment of the Present Invention:

The plasters according to the present invention have a film layer which is composed of a film of 0.5 to 4.9 μm thickness, 8 to 85 g/mm strengths and 30 to 150 % elongations in the two directions intersecting substantially at right angle, respectively, and a 1.0 to 5.0 elongation ratio (wherein smaller elongation is used as the denominator, when the elongation ratio is different in the two directions). In order to reduce skin rash, it is important, first of all, to reduce the physical stimulation caused by the plaster preparations. Thus, the film thickness is preferably decreased to less than 4.9 μm, preferably less than 4.0 μm, because skin stimulation is weakened, as the film becomes thin. Particularly, less than 3.5 μm is preferred, since this tendency becomes pronounced. At present, plasters are used by applying them to human skins and requiring them to follow the expansion and contraction of the skins in body actions to some extent. The films may be often broken, when they are extremely thin, while the skin stimulation becomes severe when they hardly follow the skin stretching. It was found that the physical stimulation scarcely changed, even when the thickness was reduced to less than 0.5 μm, in addition, the production of the plaster became troublesome.

The purposes of using the film layer as a substrate are to increase the seal tightness at the plaster application sites and promote the transdermal absorption, to cover the adhesion surface with the film and prevent the adhesive from sticking to clothes or other skin areas, and the like. As the film becomes thin, the seal tightness lowers, less than 5 μm reveals a tendency to decrease the tightness and less than 1 μm, particularly less than 0.5 μm becomes difficult to ensure the satisfactory seal tightness as a plaster.

As for the film strength, higher than 85 g/mm, respectively, in the two directions intersecting substantially at right angle cannot reduce the physical stimulation sufficiently, however the film thickness is thin, while less than 8 g/mm is apt to cause breakage of the plasters on or during the application and they cannot be used with high reliability.

As for the film elongation, over 150%, respectively, in the two directions intersecting substantially at right angle give the handleability damage, while less than 30% increases the physical stimulation and raises the frequency in film breakage on application.

Further, according to the investigation results by the present inventors, a film having an elongation ratio of 1.0 to 5.0 in said two directions (wherein the smaller elongation is used as the denominator, when the elongations are different in the two directions), preferably of 1.0 to 3.0, is preferably used to improve the application feeling. The films of over 5.0 ratio, namely of extremely low elongation in one direction, cannot follow the expansion and contraction of the skin satisfactorily and cause several problems or troubles, for example, making the application feeling unpleasant because of skin stretched, making the film easier peelable and damageable, thus being concluded to be unsuitable.

Accordingly, the film of the invention has 0.5 to 4.9 μm thickness, 8 to 85 g/mm strengths, respectively, in the two directions intersecting substantially at right angle, 30 to 150 % elongations, respectively, in the

two substantially rectangular directions, and 1.0 to 5.0 elongation ratio in said two directions (wherein the smaller elongation is used as the denominator, when the ratios of the elongations in the two directions are different). Particularly, the film is preferred, which has less than 3.5 μm, more preferably 0.5 to 2.0 μm thickness, 8 to 85 g/mm strength, 45 to 150 % elongations and 1.0 to 3.0 elongation ratio.

The strength in the present invention shows a value which is obtained by measuring the maximum load at break of a film according to the measurement of tensile strength of plasters in Japanese Pharmacopoeia and turning the result into the load per unit length (g/mm) and the elongation means the elongation at break (%). The two directions intersecting substantially at right angle means so-called lengthwise direction and widthwise direction.

In the present invention, said film is preferably desired to have good stability with the passage of time and high safety such as resisting allergic reactions, when applied. Such films include polyolefins, for example polyethylene or polypropylene; polyesters, for example polyethylene terephthalate or polyethylene naphthalate; polyamides, for example nylon 6 or nylon 66; ethylene-vinyl acetate copolymer and the like. They can be used alone or may be used in a composite or laminated form.

Among these films, polyester films are preferred. Polyester films have generally high stability to heat and light, low drug absorption, poor interaction with drugs and high safety to humans. In addition, the film of the thickness specified above is preferred, because it has a proper level of seal tightness to moderate the moisture permeability, thus holding the moisture content in the corneal layer at a level enough to help the transdermal absorption of the drug at the plaster application site.

Polyethylene terephthalate films are preferred among polyester films.

Especially, when an ultrathin film of less than 3.5 μm thickness, 8 to 85 g/mm strength and 45 to 150 % elongation is used, stabilized plastering is possible for a prolonged time, even when the adhesive layer (a) is less than 30 μm thick.

Further, it is surprising that, when a more ultra thin film of 0.5 to 2.0 μm thickness, 8 to 85 g/mm strength and 45 to 150 % elongation is used, the plaster can be applied to human skin with satisfactory stability, even when the adhesive layer (a) is 2 to 15 μ thick, particularly less than 10 μm.

It is possible to prepare a plaster having a, for example, 10 μm thick adhesive layer on a 5 to 20 μm thick film (of usual thickness). But, surprisingly this case is quite different from the plaster of the present invention, having a 10 μm thick adhesive layer on a 0.5 to 4.9 μm, particularly 0.5 to 2.0 μm thick film, in the adhesion to human skin and its stability, and an ultra thin film is markedly superior. One of the reasons is probably because human skins have microscopic unevenness, and the films of usual thickness cannot follow the unevenness, while the film according to the invention can do and sufficient adhesion is attained even with an extremely small amount of the adhesive layer.

In other words, the present invention can produce a plaster which has high stability, a reduced dose of a drug and minimized skin rash, differing from the conventional plasters by laminating a thin adhesive layer containing the drug on an ultra thin film of specified strength and elongation.

In the present invention, a polyester film is preferably used as the above-stated film layer. Usually, polyester films include a small portion of solid fine particles for improving the slipperiness. But, there was not sufficient information as to what influence such solid particles will exert on plasters, for example, of the present invention.

The present inventors have energetically investigated these subjects and found that 0.01 to 1 wt.% solid fine particle content in the polyester film, 0.01 to 3.0 μm average particle size and the average particle size of less than 1.5 time film thickness are especially important to reduce skin rash, as the absorption of a clinically effective amount of a drug is maintained.

Such solid fine particles include inorganic or organic fine particles of, for example, (1) silicon dioxide, (2) alumina, (3) silicate salts or aluminosilicate compounds containing more than 30 wt.% of silicon dioxide components, (4) one or more oxides of metals selected from magnesium, zinc, zirconium and titanium, (5) one or more sulfates of metals selected from calcium and barium, (6) one or more phosphates of metals selected from lithium, sodium and calcium, (7) one or more terephthalate salts of metals selected from calcium, barium, zinc and manganese, (8) one or more titanate salts of metals selected from magnesium calcium, barium, iron, cobalt, manganese and nickel, (9) a metal selected from calcium and magnesium, (11) carbon, (12) glass and (13) cross-linked polystyrene. As a matter of course, they may be in a single form or in a mixed form of 2 or more different kinds of particle.

Less than 0.01 wt.% solid fine particle content is not desired because the prevention of skin rash oftentimes becomes insufficient, and over 1 wt.% is also undesirable as a pharmaceutical preparation because the transdermal absorption of the drug sometimes becomes difficult to reach a sufficiently satisfactory level. Further, less than 0.01 μm average particle size sometimes causes insufficient film slipperiness, resulting in unsatisfactory film handleability and sometimes in insufficient prevention of skin

rash. Average particle size more than 3.0 μm or more than 1.5 time film thickness causes unsatisfactory transdermal drug absorption in some cases. In such cases, it is presumed that moisture transpiration and permeability become too large due to the voids around the solid fine particles in the film layer.

This film layer plays a role of a substrate (backing) layer for the adhesive layer, as preventing the skin from erupting rash, when the plaster is composed of the film layer and the adhesive layer (a). Further, in the case where the plaster of the invention comprises this film layer, the adhesive layers (a) and (b) and a plane substrate, this film can be used as the backing sheet, too, and, in this case, the film layer used as the backing sheet has the role to improve the handleability. When the plaster of the invention comprises the film layer (a) and the film layer (b), the former film plays a role of backing the adhesive layer (a), as preventing the skin from erupting rash, while the latter improves the handleability.

The plaster according to the present invention has the adhesive layer (a) which is composed of an adhesive containing transdermally absorbable drugs and is spread on one surface of the above-stated film layer in 2 to 60 μm thickness.

Generally, the adhesive layer plays a role of retaining a needed amount of the principal ingredient, namely transdermally absorbable drugs, and stabilizing the application of the plaster to the skin, but a various kinds of solvents remaining in the adhesive layer after the layer formation become one of the major causes of rash eruption. Accordingly, if the adhesive layer can play these roles satisfactorily, its layer thickness is preferably as thin as possible because of easy removal of the remaining solvents and economic reasons.

In the present invention, because the above-stated specific films are used as the film layer, the thickness of the adhesive layer more than 2 μm can extremely reduce the peeling of the plaster during the application, and less than 60 μm, preferably less than 30 μm, can reduce skin rash caused by the remaining solvents because the remaining solvents themselves can be reduced to less than 100 ppm, more preferably less than 50 ppm as required, and stabilize the application with a needed amount of the drug retained.

As the adhesive including the drugs used in the present invention, a usual adhesive is used and can be selected from, for example, a rubber viscous composition such as silicone rubber, polyisoprene rubber, styrene-butadiene copolymer rubber, acryl rubber or natural rubber; a vinyl viscous composition such as a polyvinyl alcohol (PVA) or an ethylene-vinyl acetate copolymer; a viscous composition mainly containing, for example, a silicone adhesive, a polyurethane elastomer, polyester elastomer or polybutadiene elastomer; acrylic resin and the like. Particularly an acrylic resin is preferably used and, from the view points of more reduced skin irritation, proper tackiness and adhesion, high cohesion and high solvent resistance, an acrylic resin which is prepared by copolymerization of (1) at least 80 to 98 mole % of an alkyl (meth)acrylate in which the alkyl is of 4 or more carbon atoms and (2) 2 to 20 mole % of acrylic acid and/or methacrylic acid. The examples of alkyl (meth)acrylate whose alkyl group is of 4 or more carbon atoms are butyl (meth)-acrylate, amyl (meth)acrylate, hexyl (meth)acrylate, heptyl (meth)acrylate, octyl (meth)acrylate, nonyl (meth)acrylate, decyl (meth)acrylate, 2-ethylhexyl (meth)acrylate and the like. These adhesives may be used alone or in 2 or more combination.

As stated above, the plaster comprising the film layer specified in the present invention and the adhesive layer of a specified thickness containing transdermally absorbable drugs is an extremely thin laminated product and desires careful handling in some cases so that film damage, blocking between the adhesive layers (a) and (a) or the like may not occur.

In the plaster of the present invention, a backing sheet can be laminated via the adhesive layer (b) onto said film layer by adhering the sheet partially or entirely to the one face of the film layer opposite to the other surface on which the adhesive layer (a) is laminated, with an adhesion force of higher than 3 g/12 mm.

Such backing sheet may be left on the plaster as it is, but can be also used for leaving the film layer and the adhesive layer (a) on human skin by applying the plaster, then removing the sheet therefrom.

The lamination of such a backing sheet decreases the curling of the plaster and the damages and facilitates the application by patients themselves.

The backing sheet which can be used in the present invention is films, nonwoven fabrics, paper-like substance and/or cloth such as woven or knitted fabrics or their combination. In the case where the backing sheet of the present invention is removed after application of the plaster, there is no specific limitation to these materials, but in the case where the material remains laminated after application, the sheet is preferably flexible and suitably stretchable without disturbance of moisture permeation of the film layer so that the plaster can prevent skin rash and follow the expansion and contraction of the skin.

When the backing sheet of the present invention is film, the base material for such film are, for example, polyolefins such as polyethylene or polypropylene; polyesters such as polyethylene terephthalate

or polyethylene naphthalate; polyamides such as nylon 6 or nylon 66; ethylene-vinyl acetate copolymer, polyvinyl alcohol and the like. Among the backing sheet materials made of these films, microporous films are preferred because the moisture permeability of the film layer of the invention is not disturbed.

Particularly, the films having the thickness, strength and elongation which are specified in the present invention are preferred, further the polyester films containing the above-defined amount of solid fine particles of the above-defined particle sizes are more particularly preferred.

When the backing sheet is cloth such as nonwoven fabric, paper-like substance or woven or knitted fabric, yarns made of synthetic fiber base materials such as nylon, polyester, acrylic or urethane fibers or natural or regenerated fibers such as cotton, rayon, acetate or the like can be used in the single form or in combination.

Among these nonwoven fabrics, paper-like substances, woven or knitted fabrics, knitted fabrics are preferred as a backing sheet, because they little irritate skins.

Particularly, the knitted fabrics of 10 to 300 g/m^2 can be cited. Such fabrics scarcely cause skin irritation and exert very little influence on the moisture permeability of the film layer. Further, the fabrics hardly lose their flexibility, even when the knitted fabric is laminated to the film layer. This is presumably because the allowance in the delicate fiber structure of the knit can absorb the external stress. Moreover, it is very surprising that both the tackiness of the plaster to the human skin and the adhesion of the knitted fabric to the film layer are stabilized despite that a backing sheet made of a markedly heavy and voluminous knitted fabric is bonded via a very thin adhesive layer to the human skin with a relatively small tackiness. Thus, the use of the adhesive layer (a) and the film layer can be decided independently from the backing sheet. When the unit area weight of the fabric is less than 10 g/m^2, the handleability is little improved, while more than 300 g/m^2 leads to so high bulkiness that bad appearance comes about undesirably. Additionally, too high bulkiness frequently causes the plaster to be involuntarily peeled off because the hand often hits the plaster, when it wanders near.

Such knitted fabrics give desirable results, particularly when they are made from hollow fibers having through-holes radially extending toward the outer periphery.

The hollow fibers having through-holes radially extending toward the outer periphery are preferably the hollow fibers having fine pores which distribute all over the cross section and are arranged in the fiber-axis direction, and at least a part of which connect through to the hollow part.

The cross section of the periphery and the hollow of the hollow fiber according to the invention may be of any shape. There may be cases, for example, where both the periphery and the hollow section are round, or one of them is round, while the other is modified, or both are modified similarly or dissimilarly. Further, there is in no need of special limitation to the outer size of fibers.

The outer size (filament thickness) of such hollow fibers is preferably 4 to 45 μm diameter. More than 45 μm size causes too high skin irritation. Less than 4 μm is accompanied by poor handleability.

The percentage of hollowness of the fibers in the present invention is optional but more than 5 % is preferred, and the area proportion of the through-holes extending toward the outer periphery to the fiber cross section is preferably 0.01 to 70 %, particularly preferably 0.01 to 50 %, more preferably 1 to 50 % based on the cross section area after the hollow part is subtracted.

Such knitted fabrics are satisfied, if they are mainly made of the above-stated hollow fibers and fibers other than hollow fibers may be partially mixed as long as the effect which the invention aims at is not affected.

The material which constitutes the hollow fibers is particularly preferably polyethylene terephthalate which does not interact with drugs with high stability and high safety.

The polyethylene terephthalate hollow fibers to be used in the present invention can be produced by the methods described in, for example, Japanese Patent Laid-open No.56-20612 (1981), Japanese Patent Laid-open No. 56-20613 (1981), Japanese Patent Laid-open No. 43420 (1981) and the like.

This backing sheet and the film layer are laminated with the adhesive layer (b). The adhesive which can be used as the adhesive layer (b) are, in addition to a variety of usual pressure-sensitive adhesives exemplified as an adhefor the adhesive layer (a), other adhesives such as polyvinyl acetate adhesive, for example, ethylene-vinyl acetate copolymer, polyvinyl pyrrolidone, sorbitol, starch and the like.

An acrylic resin is preferred as an adhesive for the adhesive layer (b), particularly an acrylic resin which is produced by copolymerization of (1) at least 80 to 98 mole % of an alkyl (meth)acrylate wherein the alkyl is of 4 or more carbon atoms and (2) 2 to 20 mole % of acrylic and/or methacrylic acid from the view points of reduced skin irritation, adequate tackiness or adhesion, high cohesion and excellent solvent resistance. The alkyl (meth)acrylates wherein the alkyl is of 4 or more carbon atoms is, for example, butyl (meth)-acrylate, amyl (meth)acrylate, hexyl (meth)acrylate, heptyl (meth)acrylate, octyl (meth)acrylate, nonyl (meth)acrylate, decyl (meth)acrylate, 2-ethylhexyl (meth)acrylate and so on. These adhesives may be

combined.

Or, in the cases where the backing sheet is removed after application of the plaster, as an adhesive for adhesive layer (b), PVA (polyvinyl alcohol), ethylene-vinyl acetate copolymer, polyvinyl pyrrolidone, sorbitol, starch or above-stated vinyl acetate adhesive can be cited.

When PVA or polyvinyl acetate is used as an adhesive for adhesive layer (b), PVA of 100 to 2,000 average polymerization degree and 3 to 20 % concentration and polyvinyl acetate of 100 to 1,000 average polymerization degree and 3 to 20 % concentration can be cited.

Particularly, good results will be readily obtained, when woven or knitted fabrics are used as the backing sheet and PVA or the like is used as the adhesive.

In other words, the backing sheet is adhered to the film layer during the plaster handling, then can be removed if needed, after application to human skin. But, the plaster is kept in an air-tightly sealed aluminum foil-laminated pouch before use and, if the solvents such as methanol, ethyl acetate or water remains in the adhesive layer after lamination of the sheet to the film layer, they tend to move and diffuse into the adhesive layer (a) containing the drugs during storage. Thus, skin rash may develop and deterioration of the drug occurs with the passage of time in some cases.

In order to remove such troubles or inconveniences, the solvents used in lamination of the sheet and the film layer should be completely removed, but it is difficult, when the sheet is made of a film layer, and special ideas or techniques are needed in the production process. In this case, the plaster of the present invention employs a specific film as a backing and the reduction in production efficiency tends to occur due to film breakage, wrinkling and the like, if complicated processes are included in the production. On the contrary, the backing sheet of woven or knitted fabric can easily release the vapor of solvents through the meshes, thus preferred embodiments of complete solvent withdrawal can be realized.

Particularly, the backing sheet of woven or knitted fabric and a film are put together, an adhesive solution is applied from over the fabric, and they are heated, thus sufficient adhesion can be effected without any anxiety of solvent remaining. Or an adhesive is applied to the sheet of woven or knitted fabric and dried beforehand, then the material is laminated on the film layer directly as it is or after heating or air-drying to remove the remaining solvents, when needed. The adhesive layer containing the drug can be laminated either before or after the lamination of the sheet, but preliminary lamination between the film layer and the sheet is preferred as drugs are generally unstable to heat.

In the present invention, the backing sheet may be partially or entirely adhered to the surface of the film layer, but troubles such as peeling off of the extremely thin film tend to happen, when only the sheet is removed after plaster application to human skin, even when the adhesion between the sheet and the film layer is small. In order to prevent this, it is a preferred embodiment to provide the only overlapping but not adhered parts so that the entire surface of the film layer does not always stick to the sheet. The patients can peel off the sheet much more easily from the non-adhered part. It is a useful technique to place a film, paper, cloth or the like of 5 to 100 μm thickness between both of the surfaces for providing the surface having parts where the sheet is not adhered to the film layer.

It has been found that the patient can peel off the sheet with extreme ease, when the non-adhered part is near the edge of the plaster. Moreover, since the patient peels off only the sheet from the edge by pulling it, for example, in 90° or 180° direction, the peeling off of the plaster from human skin and the breakage of the film layer are also reduced. It is particularly preferred, when the plaster is prepared from an extremely thin and skin irritation-reduced, thus strength-lowered film and the thin adhesive layer according to the present invention.

The film layer and the backing sheet are laminated, for example, by dissolving such an adhesive in a solvent, forming the adhesive layer (b) on the film layer in a 2 to 100 μm thickness, then pressing the backing sheet thereto. Or the adhesive layer (b) of 2 to 100 μm thickness is prepared beforehand and the layer is pressed on to one surface of the sheet and/or on to one surface of the film layer, then the sheet and the film layer are adhered via the adhesive layer (b) to each other by pressing. The film layer and the sheet can be adhered via the adhesive layer in part only of these surfaces or can be adhered entirely all over the surfaces. Above all, in the case where the sheet is not removed after application of the plaster, it is preferred to adhere them to each other through a part of these surfaces in a range where the sheet can be stably stuck to for a long period of time, because there happens no reduction in moisture permeability of the film layer. As an embodiment such as partial adhesion, is cited, for example, scattering spots of the adhesive layer (b) measuring 0.5 to 100 mm^2 sizes and 2 to 100 μm thickness or stripes of the adhesive layer (b) measuring 1 to 20 mm width and 2 to 100 μm thickness. Such partial adhesion can additionally relieve the skin irritation by the sheet with plaster handleability improved.

The thickness of the adhesive layer (b) is 2 to 100 μm, preferably 5 to 20 μm.

In the present invention, the adhesion strength between the backing sheet and the film layer is greater than 3 g/12 mm, and such strength is preferred because even patients of advanced age can easily apply the plaster to the affected part without curling or breakage of the plaster.

The adhesion strength in the present invention is defined as the load (in grams) for peeling off the sheet or the film from a 12 mm wide laminate comprising the film layer and the sheet at a rate of 30 cm/minute in the 90° direction. When the laminate is partially adhered with spots or stripes of adhesive, the load (in gram) for peeling off the adhered part is measured and the value is converted to the one corresponding to 12 mm width (g/mm).

The adhesion strength can be suitably varied depending on the cases where the sheet is removed after application of the plaster to the affected part or not, or on the correlation of the adhesion strength of the film layer via the adhesive layer (a) to the skin. For example, if the adhesion strength between the sheet and the film layer is over 20 g/12 mm, the breakage of the film layer may possibly happen, when the backing sheet is removed from the film layer. Theoretically, the adhesion strength exceeds 20 g/12 mm, when the film strength is 8 to 85 g/mm, and it is thought that the film will not break even, for example, at 24 g/12 mm (2 g/mm). In the actual plasters, however, over 20 g/12 mm adhesion strength sometimes causes film breakage or the peeling of the plaster from the human skin. Less than 3 g/12 mm may cause delamination between the sheet and the film layer during the production, storage or handling. Accordingly, in the case where the backing sheet is removed after application of the plaster to the affected part, the adhesion strength preferably ranges from 3 g/12 mm to 20 g/12 mm, while in the case not to be removed, it can exceed 20 g/12 mm.

When the backing sheet is removed after application of the plaster to the affected site, the film layer manifests its merits fully during the application to attain the objects such as reduction in skin rash or the like.

Other measures for the same objects are disclosed in, for example, Japanese Patent Laid-open No. H1-51260 (1989). But, it did not make detail investigation on the structure of plaster as done in the present invention.

In the present invention, more desired plasters can be produced by controlling the "KOSHI" (a Japanese technical term on cloth touch or handle showing physical properties including flexural rigidity, compression modulus and instantaneous bouncing properties). The KOSHI of the backing sheet can be represented by a stiffness ($cm^3/100$) determined, for example, according to JIS P-8143, Stiffness Test, and the stiffness is preferably more than 0.08, particularly preferably more than 0.27.

Further, in the plaster comprising the above-stated film layer and the adhesive layer (a) according to the invention, a backing sheet can be partially or entirely laminated through the adhesive layer (b1) to film layer (a) on the other side surface of that to which the adhesive layer (a) is adhered, with an adhesion force higher than 20 g/12 mm, and another film layer (b) can be laminated partially or entirely through the adhesive layer (b2) to the backing sheet on the other side surface of that to which said adhesive layer b1 is laminated, with an adhesion force (b1) higher than 3 g/12 mm wherein the film (b) has 0.5 to 4.9 μm thickness, 8 to 85 g/mm strength, 30 to 150 % elongations, respectively, in the two directions intersecting substantially at right angle and 1.0 to 5.0 ratio of the elongations in the two directions (wherein the smaller elongation is used as the denominator, when the ratios of the elongations in the two directions are different).

As the backing sheet for the plaster, can be cited moisture-permeating ones selected from the films, nonwoven fabrics, paper-like substances and cloth of woven or knitted fabrics which have been exemplified previously. In the present invention, the term, moisture-permeating sheets, means the sheets having a moisture permeability higher than 10 mg/day • cm^2, when the permeation is evaluated according to the method shown in the example (vi) of the present invention.

Among them, knitted fabrics are preferred and knitted fabrics of polyethylene terephthalate hollow fibers having 10 to 300 g/cm^2 unit area weight and through-hole pores extending radially toward the outer periphery, exemplified in the preferred embodiment of the backing sheet.

In other words, a plaster is desired to have adequately high transdermal absorption of the drug in addition to high flexibility, reduced skin rash and satisfactory handleability, and a proper level of tight seal is important for this purpose. In this case, it is preferred that a backing sheet made of a knitted fabric is laminated between adhesive layers (b1) and (b2), then film layer (b) is arranged on the outermost surface of the adhesive layer (b2) rather than a plaster coated with film layer (a) is simply laminated on adhesive layer (a). At this time, the knitted fabric not only plays a role of an interlayer for laminating the film layer (b) to make up for the lack of tight-sealing effect of the film layer (a), but also contributes significantly to the improvement in handleability of the plaster, further concerns the moisture retention, too. In addition, the knitted fabric is 10 to 300 g/m^2 in its unit area weight, thus having flexibility in the structure itself, and can delicately follow the contraction and expansion of skins to which the plaster is applied to decrease skin rash

because of reduced physical stimulation to the affected site.

As a film for the film layer (b), are preferably cited similar base materials to those for the film layer (a).

Such a backing sheet and the film layer (b) are laminated via the adhesive layers (b1) and (b2) to the film layer (a), respectively, in the same manner as the backing sheet is laminated by pressing a part only of the surface or the entire surface of the backing sheet to the film layer, by pressing the film layer (a) to a part or all of the backing sheet, and by pressing the backing sheet to a part or all of the film layer (b). The lamination can be conducted, as the backing sheet is laminated to the film layer (a) by pressing, by preparing the adhesive layers (b1) and (b2) separately and pressing them in turns, when needed, with heat, or by preparing separately laminate 1 of a backing sheet and the adhesive layer (b1), laminate 2 of the film layer (b) and the adhesive layer (b2) and laminate 3 of the film layer (a) and the adhesive layer (a) and then laminating free surface of the adhesive layer (b2) of the laminate 2 on the free surface of the backing sheet of the laminate 1, and then laminating free surface of the adhesive layer(b) on free surface of film layer (a) of the laminate 3.

In the particularly preferable process, the free surface of the adhesive layer (b) of the laminate 2 is laminated on the backing sheet, thus obtaining the laminate 4, then in turns, the free surface of the backing sheet of this laminate 4 is laminated on the adhesive layer (b1) followed by lamination of film layer (a), thus obtaining the laminate 5 which comprises, from top to down, film layer (b), adhesion layer (b2), backing sheet, adhesion layer (b1), and film layer (a). Then, free surface of the film layer (a) of the laminate 5 is laminated on the adhesive layer (a), or adhesive layer (a) is formed on the free surface of the film layer (a). In other words, any of the constituents of the plaster according to the present invention, namely film layer (b), adhesive layer (b2), backing sheet, adhesive layer (b1), and film layer (a), are thin and flexible, thus each of them desires handling with special caution, but such sequential lamination can facilitate the production. Especially the lamination process of adhesive layer (a) containing a drug is one of the most important stage influencing the content and the cost of the plaster of the present invention, and the use of laminate 5 as stated above enables stabilized production of plasters of uniform quality.

As an adhesive for the adhesive layers (b1) and (b2) used here, can be cited the same base material as of the above-stated adhesive (b). Particularly, the above-stated acrylic resins and the like are preferred. The thickness of these adhesive layers (b1) and (b2) is 2 to 100 μm.

Less than 2 μm thickness of the adhesive layer weakens the adhesion to the backing sheet to cause peeling of the backing sheet during application in some cases. More than 100 μm thickness tends to squeeze out the adhesive from the side face during plaster cutting or application, thus causing sometimes process difficulties and contamination.

The particularly preferable thickness of adhesive layer (b2) ranges from 5 to 20 μm, while adhesive layer (b1), from 10 to 50 μm. The thickness of adhesive layer (b1) relates to the adhesion force of the plaster and extremely thinness is unsuitable.

In the plasters according to present invention, when the backing sheet and the film layer (b) are additionally laminated, the adhesion force is higher than 20 g/12 mm between the backing sheet and the film layer (a) and the film layer (b) is laminated to the backing sheet with 3 g/12 mm and higher adhesion force.

The plasters according to the invention have preferably more than 10 mg/day • cm^2 transpiration rate. Less than 10 mg/day • cm^2 tends to increase stuffiness, thus causing skin rash in some cases. On the contrary, there is a tendency to lower the transdermal absorption of the drug, when the moisture transpiration rate increases more than 80 mg/day • cm^2, and the transpiration rate ranges preferably from 10 to 80 mg/day • m^2.

The plasters of the present invention are connected partially or entirely through the adhesive layer (b), the adhesive layers (b1) and (b2) or the adhesive layer (c). The thickness of these adhesive layers is preferably as thin as possible, unless any hindrance or trouble occurs in the adhesion force, since the total thickness of the plaster can be reduced and peeling due to touching or hitting can be prevented. In many cases, generally it is enough with less than 20 μm, preferably less than 10 μm thickness.

The thickness of the adhesive layer (b1) is preferably 10 to 50 μm because the adhesion force to human skin tends to weaken as the thickness lessens.

In the meantime, the adhesive layer (a) is also desirably as thin as possible unless any trouble happens in adhesion, but the correlation of the compatibility between the drug and the adhesive with the dose also should be taken into consideration.

Generally, it has been known that the adhesion force of the plaster increases as the thickness becomes larger until it reaches about 50 μm and adhesive layers of 30 to 100 μm thickness are usually employed because stabilized adhesion force is realized. In the present invention, the use of ultra thin film layer (a) has improved the adhesion to human skin, thus the range from 5 to 30 μm can be adopted as a preferable

thickness of adhesive layer (a).

As for the size of the plaster, namely the application area, the solubility and transdermal absorption change depending on the kinds of drugs and the sort of adhesives and some cases require expanded application areas in order to secure adequate transdermal absorption. As a matter of course, however, there is area limitation in human bodies to which the plaster is applicable, and area increase means dose increase, thus the area should be minimized as needed. Usually, about 5 to 200 cm^2 is preferred for good handleability.

The drugs used in the present invention are, for example, isosorbide dinitrate, nitroglycerin, buprenorphine (BN) hydrochloride, morphine, estradiol, progesterone, ketotifen, vinpocetine, nicotine and their derivatives and other known transdermally absorbable drugs and they can be used in a single form or in combination in 0.1 to 20 % concentration in the adhesive.

The present invention is very desirable because an extremely thin adhesive layer can be provided to lower the dose of the drug largely, when the drug is expensive or overdose causes any skin damage or abnormal transdermal absorption. Such drugs are, for example, narcotic analgesics such as buprenorphine hydrochloride or morphine and hormone preparations such as estradiol or progesterone derivatives.

The plasters of the present invention may include solubilizers, diffusion auxiliaries, fillers and the like, when needed.

As a diffusion auxiliary used in the present invention, are cited, for example, alcohols such as glycerol, diethylene glycol, polyethylene glycol, higher fatty acid alcohols; dimethyl sulfoxide and its alkylmethyl derivatives; salicylic acid, urea, dimethylacetamide, dimethylformamide, lanolin, allantoin, squalene, carbopol, diisopropyl adipate, lauryl pyroglutamate, ethyl laurate, methyl nicotate, sorbitol and pyrrolidone derivatives such as dodecylpyrrolidone or methylpyrrolidone; olive oil, castor oil, fluid paraffin and camphor.

The filler is, for example, water, titanium oxide, calcium carbonate, gypsum, calcium silicate, aluminum silicate, kieselguhr, carbon black, Indian red, a variety of face cleaners, lactose, perfumes, deodorants and powders or formed products of synthetic resins such as polyethylene, polypropylene, polyester or polystyrene.

Examples

The present invention will be illustrated in more detail using examples and comparative examples. The parts in the examples mean parts by weight and the properties in the examples were measured by the following procedures:

(i) Water absorption rate (based on JIS-L 1018)

The fibers are knitted and the knitted fabric is washed prescribed times in a domestic washing machine with 0.3 % aqueous solution of an anionic detergent (ZABU produced by KAO) at 40 °C for 30 minutes, then dried. The sample is extended horizontally and a drop of water (0.04 cc) is allowed to fall from the height of 1 cm and the time is measured until the water is completely absorbed and the reflection light cannot be noticed.

(ii) Water absorption percentage

The sample obtained by drying the knitted fabric is dipped in water longer than 30 minutes, then dehydrated for 5 minutes with the centrifuge in the domestic washing machine. The water absorption percentage is calculated from the dry weight of the sample and the wet weight after centrifugation according the equation given below:

$$\text{Water absorption \%} = (\text{the wet weight} - \text{the dry weight})/\text{the dry weight} \times 100$$

(iii) Serum concentration of isosorbide dinitrate

Serum is separated from 3 ml of blood sample, extracted with 4 ml n-hexane, concentrated, combined with ethyl acetate to adjust the volume 100 µl and isosorbide dinitrate was determined by means of GC-ECD technique.

(iv) Serum concentration of BN

Serum is separated from 1 ml blood sample and BN is determined by the GC-MS technique according to the description in Journal of Chromatography, 338, 89 - 98 (1985).

(v) Serum concentration of progesterone

Serum is separated from 1 ml blood sample and progesterone was determined by the radioimmunoassay technique.

(vi) moisture transpiration

A cavity (for example, a round well of 4 cm diameter and 0.6 cm depth) is formed at the center of a thick glass plate and 3 ml water is poured into the well. A plaster (5 cm x 5 cm) having a sufficient margin to paste up is stuck to the thick glass plate so that the well comes to the center of the plaster. They are allowed to stand under air-flowing conditions at 37 °C for 1 day and the moisture transpiration is calculated by dividing the weight reduction per day with the area of the plaster over the well (12.56 cm^2 in the above-stated well).

Reference examples

The hollow fiber sample (knitted fabric) and the adhesive solution were prepared by the following procedures:

(1) Hollow fiber sample (knitted fabric)

Dimethyl terephthalate (297 parts), ethylene glycol (265 parts), sodium 3,5-di(carbomethoxy)-benzenesulfonate (11.7 mole % based on dimethyl terephthalate), manganese acetate tetrahydrate (0.084 part) and sodium acetate trihydrate (1.22 part) were charged into a glass flask equipped with a rectification column and ester interchange was effected according to the usual method. After distillation of the theoretical amount of methanol, the reaction mixture was transferred into a polycondensation flask equipped with a rectification column, combined with 0.090 part of 56 % orthophosphoric acid solution in water as a stabilizer and 0.135 part of antimony trioxide as a polymerization catalyst, and they were allowed to react at 275 °C under normal pressure for 20 minutes, under reduced pressure of 4000 Pa (30 mmHg) for 15 minutes, then under high vacuum for 100 minutes. The final inner pressure was 52 Pa (0.39 mmHg) and the resultant copolymer had 0.402 intrinsic viscosity, 200 °C softening point. After completion of the reaction the copolymer was made into chips according to a usual process.

The copolymer chips (15 parts) and polyethylene terephthalate chips of 0.640 intrinsic viscosity were mixed in a Nauter mixer (produced by Hosokawa Iron Works) for 5 minutes, dried at 110 °C in a nitrogen stream for 2 hours, then at 150 °C for 7 hours, and melt-kneaded and extruded through a twin screw extruder at 285 °C into chips. The chips had 0.535 intrinsic viscosity and 261 °C softening point.

The chips were dried in a usual manner, melt-spun through a spinneret having arc-shaped openings formed by clotting 2 places of each circular slit of 0.05 mm width and 0.6 mm diameter in a usual manner to form hollow fibers of 2 : 1 ratio of the outer diameter to the inner diameter (25 % hollowness). This yarn is composed of 300 deniers/24 filaments and drawn at a ratio of 4.2 in a usual manner to give a multifilament yarn of 71 deniers/24 filaments. The multifilament yarn was knitted and the fabric was scoured, dried, treated with 1 % caustic soda aqueous solution at the boiling point for 2 hours to give a knitted fabric of 15 % alkali weight reduction, 3 seconds water absorption and 80 % water absorption. The knitted fabric was thermoset at 100 °C for one minute after stretching 1.5 time longitudinally to form a knitted fabric of 38 g/m^2 unit area weight.

The resultant hollow fibers of the knitted fabric were observed to have fine pores which distribute all over the cross section with orientation along the fiber-extending direction and at least a part of which pass through to the hollow part.

(2) The adhesive solution

2-Ethylhexyl acrylate (97.4 parts), methacrylic acid (2.5 parts), polyethylene glycol (polymerization degree: 14) dimethacrylate (0.1 part), benzoyl peroxide (1.0 part) and ethyl acetate (100 parts) were

charged in a reaction vessel equipped with a reflux condenser and a mechanical stirrer and polymerization was continued for 9 hours with slow stirring at 60 to 70°C in a nitrogen atmosphere. The polymer conversion was 99.5 to 99.9 %.

The resultant polymer solution was combined with ethyl acetate (500 parts) to adjust the solid content to about 20 %.

Example 1

Example 8 of the published application was repeated except that the PET film was replaced with a PET film which had 1.3 µm thickness, 22 and 32 g/mm and 75 to 35 % strengths and elongations in the two rectangular cross directions, respectively, and contains, in the film as solid fine particles, 0.08 % by weight, based on the film total weight, of synthetic silica of 0.70 µm average particle size, to prepare a laminate.

The adhesive force between the film and the woven fabric was 5 g/12 mm. The stiffness was 4.8 $cm^3/100$. The adhesive layer (a) of 15 µm thickness, containing 1.3 g/m^2 of progesterone was press-bonded to the free surface of the film layer of the laminate.

The plaster sheet was cut into pieces of 3 cm × 3 cm and the pieces were applied to shaved backs of rats weighing about 180 g, then the woven fabric as a backing sheet was peeled off. There was substantially no PVA remaining on the surface of the film. Then, blood was sampled at the times prescribed in Table 1 and serum progesterone was determined by the RIA technique and the rat skins were observed 24 hours after applications. The results are given in Table 1.

Examples 2 through 4 and comparative examples 1 and 2

The films described in Table 1 were used to prepare progesterone plasters in the same manner as in Example 1. The plasters were applied to rat backs and the results are shown in Table 1.

Table 1

Serum concentration of progesterone

Preparations	Film layer					Solid fine particles (substance) Amount (wt%)/ average size (μm)	Progesterone concentration (n=3, ng/ml)				Skin 24 hours after application
	Thickness (μm)	Strength (g/mm)		Elongation (%)		Elongation ratio	Application hours				
		A	B	A	B		0	2	8	24	
Example 1	1.3	22	32	75	35	2.1	synthetic silica 0.08/0.70	0.5	7.6	7.9	6.5	No change substantially
Example 2	1.8	36	48	77	75	1.9	synthetic silica 0.1/0.45	0.5	7.3	6.8	6.1	No change substantially
Example 3	3.5	72	59	91	120	1.3	talc	0.5	9.3	10.4	7.3	Practically no change
Example 4	1.8	25	33	40	30	1.3	synthetic silica 2.0/0.45	0.2	2.1	2.4	2.0	Serum concentration was relatively low
Comparative exaple 1	6.0	104	120	96	70	1.4	talc 0.1/0.75	0.5	8.8	7.7	7.6	Erythema was seen
Comparative example 2	1.3	29	55	26	5	5.2	synthetic silica 0.08/0.70	0.5	4.2	3.9	2.3	No change at all but removal of plaster was difficult due to film breakage

Note: A and B indicate 2 substantially rectangular directions.

Example 5

Example 1 was repeated except that progesterone was replaced with buprenorphine hydrochloride and the adhesive layer (a) containing buprenorphine hydrochloride was set 7 μm thick after drying to prepare a

plaster containing 0.56 g/m^2 buprenorphine hydrochloride. The plaster was cut into pieces measuring 3 cm x 3 cm and they were applied to shaved backs of rats (n = 3). Blood was sampled before application, 2, 8 and 24 hours after application to determine serum buprenorphine and the results were 0, 4.3, 6.0 and 5.8 (ng/ml) with good analgesic effect. There was found no skin rash on the plaster application sites after the plaster pieces were removed.

Moreover, regardless of using an extremely thin adhesive layer of 7 µm thickness which was not seen in existing plasters, the plaster had sufficient adhesion force to the skin and the amount of expensive buprenorphine hydrochloride could be largely reduced.

Test Example 1

Placebo preparations in Example 11 of the published application and Example 5 were cut into pieces measuring 7.1 cm^2 and applied to human right chests of 5 persons each placebo preparation for 48 hours. Skin stimulation was observed 1 hour after removal of the preparations to evaluate the skin stimulation. As for the rashes, no reaction was judged to be 0; very slight erythema, 0.5; well defined erythema, 1.0; erythema and edema 2 and erythema, edema and papule, 3 and the groups were compared with the sum-ups of individual values in each group. As a result, the placebo in Example 11 was 2.0 point, while that in Example 5 was 1.0 and Example 5 was judged to be less stimulant.

Example 6

Example 5 was repeated except that the buprenorphine hydrochloride was replaced with nicotine to prepare a plaster. The plaster was applied to rat backs to confirm no skin rash.

Example 7

Example 5 was repeated except that the buprenorphine hydrochloride was replaced with estradiol to prepare a plaster. The plaster was applied to rat backs to confirm no skin rash.

Example 8 and comparative example 3

The plaster was composed of the first 1.8 µm thick PET film as the backing sheet, the second 1.3 µm thick PET film which is the same one as used in Example 1 as the film layer, and the adhesive layer (a) of 10 µm thickness, containing 1.3 g/m^2 progesterone and the backing sheet was press-bonded to the film layer all over the surface through the adhesive layer (b) of 10 µm thickness, which was prepared from the adhesive solution in reference example (2).

The PET films used in the laminate included 0.08 % by weight of synthetic silica of 0.7 µm average particle size as the solid fine particles. The plaster sheet (Example 7) was measured on its moisture evaporation and found to be 12.7 mg/day • cm^2.

Further, a polyester film of 12 µm thickness was laminated with the adhesive layer of 10 µm thickness same as in Example 8, containing progesterone were laminated for comparison (comparative example 3).

The resultant plaster showed only 7.3 mg/day • cm^2 moisture evaporation.

Example 9

As the backing sheet, a knitted fabric of finely pored polyester hollow fibers used as the backing sheet in Example 1 of the published application was inserted between the film used as the backing sheet in Example 7 (the film layer (b)) and the film layer (a) and these 3 layers were laminated with acrylic adhesive layers (b1 and b2) of 10 µm thickness. Then, the adhesive layer (a) containing the drug, which was used in Example 7, was press-bonded on the film layer (a) of the laminate.

The plaster sheet showed a moisture evaporation of 19.4 mg/day • cm^2.

Comparative example 4

Example 5 of the published application was repeated except that a polyethylene film of 7 µm thickness, 20 g/mm strength and 276 % elongation in one direction was used instead of a PET film of 1.3 µm thickness to produce a plaster containing 0.56 g/m^2 of buprenorphine hydrochloride. The plaster was cut into pieces measuring 3 cm x 3 cm, applied as in the said Example 5 and found to show serum

concentrations, 0, 0.5, 1.2 and 3.8 ng/ml before application, 2, 8 and 24 hours after application, respectively. There was no skin rash on the application site of the skin after removal of the plaster.

The moisture permeability of the plaster was 133 g/day • cm^2.

Test example 2

The plaster sheets prepared in Examples 8, 9 and Comparative examples 3 and 4 were cut into pieces of 7.1 cm^2 and the pieces of each plaster were applied to right chests of 2 humans for 48 hours and the states were observed 1 hour after removal of the plaster. The results are shown in Table 2.

Table 2

	Observation 1 hour after removal
Example 8	Substantially no change in both
Example 9	Substantially no change in both
Comparative example 3	Erythema was noticed in both
Comparative example 4	Substantially no change in both

The plasters according to the present invention were proved to be excellent because the skins showed substantially no change before and after application.

Example 10

The adhesive layer (b2) which was obtained by coating the adhesive solution shown in Reference example in 15 μm thickness was laminated onto the 1.3 μm thick PET film (b) used in Example 1, then a backing sheet of hollow fiber-knitted fabric (38 g/m^2 unit area weight) and the adhesive (b1) which was prepared by coating the adhesive solution shown in the Reference example in 40 μm thickness were contact-bonded thereto, and finally the 1.3 μm thick PET film used in Example 1 was contact-bonded to the free surface of the adhesive layer (b1).

Meanwhile, an adhesive layer of 10 μm thickness containing 1.13 g/m^2 buprenorphine hydrochloride, which was obtained as in Example 1 of the published application, was laminated onto the surface of the PET film (a) in the above-stated laminate, thus a plaster containing 2.8 mg buprenorphine hydrochloride per 5 cm x 5 cm area was obtained. The plaster was cut into pieces of 4.5 cm^2 and applied to the shaved necks of rats weighing 150 grams on the average (n = 5) to determine the serum concentration of buprenorphine hydrochloride by sampling blood before application, 2, 8 and 24 hours after application. The results were 0, 1.9, 2.7 and 3.4 ng/ml, respectively and showed good analgesic effect.

This plaster had good handleability and no change was observed in the skin after removal of the plaster, proving reduced skin stimulation.

Possibility of industrial utility

The plasters according to the present invention can be utilized in the clinical field of the medical treatment as a plaster for transdermal absorption of a clinically effective amount of drugs with skin rashes reduced and high peeling resistance.

Particularly, the plasters of the present invention, combined with the backing sheet and the sheet-like body are improved in their handleability and can be easily and simply applied even by aged patients.

Claims

1. A plaster comprising

(1) a film layer which is composed of a polyester film having a thickness of 0.5 to 4.9 μm, strengths of 8 to 85 g/mm respectively in the two directions intersecting substantially at right angles, elongations of 30 to 150% respectively in the two directions intersecting substantially at right angles, and an elongation ratio of 1.0 to 5.0 (wherein the smaller elongation is used as the denominator when the elongations in the two directions are different), said polyester film containing 0.01 to 1.0%

concentrations, 0, 0.5, 1.2 and 3.8 ng/ml before application, 2, 8 and 24 hours after application, respectively. There was no skin rash on the application site of the skin after removal of the plaster.

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by weight, based on the total weight of said polyester film, of solid fine particles in which
1) the average particle size is 0.001 to 3.0 μm and
2) the average particle size substantially does not exceed 1.5 times the thickness of said polyester film,
(2) an adhesive layer (a) having a thickness of 2 to 60 μm, which is composed of an adhesive containing a transdermally-absorbable drug and is laminated to said film layer, and
(3) a release liner removably laminated to the adhesive layer (a).

2. A plaster comprising
(1) a film layer which is composed of a polyester film having a thickness of 0.5 to 4.9 μm, strengths of 8 to 85 g/mm respectively in the two directions intersecting substantially at right angles, elongations of 30 to 150% respectively in the two directions intersecting substantially at right angles, and an elongation ratio of 1.0 to 5.0 (wherein the smaller elongation is used as the denominator when the elongations in the two directions are different), said polyester film containing 0.01 to 1.0% by weight, based on the total weight of said polyester film, of solid fine particles in which
1) the average particle size is 0.001 to 3.0 μm and
2) the average particle size substantially does not exceed 1.5 times the thickness of said polyester film,
(2) an adhesive layer (a) having a thickness of 2 to 60 μm, which contains a transdermally-absorbable drug and is laminated to one surface of said film layer, and
(3) a backing sheet which is partially or entirely adhered, with an adhesive force of at least 3 g/12 mm, through an adhesive layer (b) of thickness 2 to 100 μm, to the surface of the film layer remote from that to which the adhesive layer (a) is laminated.

3. A plaster comprising
(1) a film layer (a) which is composed of a polyester film having a thickness of 0.5 to 4.9 μm, strengths of 8 to 85 g/mm respectively in the two directions intersecting substantially at right angles, elongations of 30 to 150% respectively in the two directions intersecting substantially at right angles, and an elongation ratio of 1.0 to 5.0 (wherein the smaller elongation is used as the denominator when the ratios of the elongations in the two directions are different), said polyester film containing 0.01 to 1.0% by weight, based on the total weight of said polyester film, of solid fine particles in which
1) the average particle size is 0.001 to 3.0 μm and
2) the average particle size substantially does not exceed 1.5 times the thickness of said polyester film,
(2) an adhesive layer (a) having a thickness of 2 to 60 μm, which contains a transdermally-absorbable drug and is laminated to one surface of said film layer,
(3) a backing sheet which is partially or entirely adhered, with an adhesive force (a1) of over 20 g/12 mm, through an adhesive layer (b1) to the surface of the film layer (a) remote from that to which the adhesive layer (a) is laminated, and
(4) a film layer (b) which is composed of a film having a thickness of 0.5 to 4.9 μm, strengths of 8 to 85 g/mm respectively in the two directions intersecting substantially at right angles, elongations of 30 to 150% respectively in the two directions intersecting substantially at right angles, and an elongation ratio of 1.0 to 5.0 (wherein the smaller elongation is used as the denominator when the elongations in the two directions are different), and is laminated with an adhesive force (b1) of at least 3 g/12 mm, through an adhesive layer (b2) partially or entirely to said backing sheet on the surface thereof not bonded to the adhesive layer (b1).

4. A plaster according to any of claims 1 to 3 wherein said adhesive is an acrylic resin adhesive.

5. A plaster according to any of claims 1 to 4 wherein said elongation ratio is 1.0 to 3.0.

6. A plaster according to any of claims 1 to 5 wherein the drug comprises one or more of isosorbide dinitrates, nitroglycerin, buprenorphine, estradiol, progesterone, ketotifen, vinpocetine, nicotine and their derivatives.

7. A plaster according to claim 2 wherein said adhesive force ranges from 3 g/12 mm to 20 g/12 mm.

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8. A plaster according to claim 2 wherein said adhesive force is over 20 g/12 mm.

9. A plaster according to claim 7 or claim 8 wherein said adhesive force is smaller than that between said film layer and said adhesive layer (a).

10. A plaster according to claim 3 wherein said adhesive force (b1) ranges from 3 g/12 mm to 20 g/12 mm.

11. A plaster according to claim 2 or 3 wherein said backing sheet is a film, non-woven fabric, paper-like substance, and/or a kind of cloth selected from woven and knitted fabrics and their combination.

12. A plaster according to claim 11 wherein said backing sheet is a microporous film or a woven or knitted fabric of 10 to 300 g/cm^2 unit area weight.

13. A plaster according to claim 12 wherein said knitted fabric is made from hollow filaments which have through-holes radially extending toward the outer periphery and a filament thickness of 4 to 45 µm.

14. A plaster according to claim 2 wherein said adhesive layer (b) is composed of an adhesive containing polyvinyl alcohol and/or vinyl acetate polymer as a major component.

15. A plaster according to claim 2 or 3 wherein said adhesive layer (b,b1) is composed of an acrylic resin adhesive.

16. A plaster according to claim 14 or 15 wherein said adhesive layer (b,b1) is 2 to 100 µm thick.

17. A plaster according to claim 2 having a backing sheet which is adhered with an adhesive force ranging from 3 g/12 mm to 20 g/12mm, through an adhesive layer (c) partially or entirely to said backing sheet on the surface thereof not bonded to the film layer.

18. A plaster according to claim 3 having a plane backing body which is adhered with an adhesive force ranging from 3 g/12 mm to 20 g/12 mm, through an adhesive layer (c) partially or entirely to said film layer (b) on the surface thereof not bonded to said backing sheet.

19. A plaster according to claim 3 wherein said adhesive force (b1) is smaller than the adhesive force (a1).

20. A plaster according to any preceding claim whose moisture transpiration rate is from 10 to 80n mg/day/cm^2.

Patentansprüche

1. Pflaster umfassend
   (1) eine Filmschicht, welche aus einem Polyesterfilm besteht, welcher eine Dicke von 0,5 bis 4,9 µm, Festigkeiten von 8 bis 85 g/mm in den zwei Richtungen, welche sich im wesentlichen in rechten Winkeln schneiden, Dehnungen von 30 bis 150 % in den zwei Richtungen, welche sich im wesentlichen in rechten Winkeln schneiden, und ein Dehnungsverhältnis von 1,0 bis 5,0 (worin die geringere Dehnung als der Nenner verwendet wird, wenn die Dehnungen in den zwei Richtungen unterschiedlich sind) aufweist, welcher Polyesterfilm 0,01 bis 1,0 Gew.-%, basierend auf dem Gesamtgewicht des Polyesterfilms, an festen, feinen Teilchen enthält, in welchen
      1) die mittlere Teilchengröße 0,001 bis 3,0 µm ist und
      2) die mittlere Teilchengröße im wesentlichen nicht 1,5 mal die Dicke des Polyesterfilms übersteigt,
   (2) eine Klebeschicht (a), welche eine Dicke von 2 bis 60 µm aufweist, welche aus einem Kleber enthaltend einen transdermal absorbierbaren Wirkstoff zusammengesetzt ist und an die Filmschicht laminiert ist, und
   (3) eine abziehbare Unterlage, welche entfernbar an die Klebeschicht (a) laminiert ist.

2. Pflaster umfassend
   (1) eine Filmschicht, welche aus einem Polyesterfilm besteht, welcher eine Dicke von 0,5 bis 4,9 µm, Festigkeiten von 8 bis 85 g/mm in den zwei Richtungen, welche sich im wesentlichen in rechten

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Winkeln schneiden, Dehnungen von 30 bis 150 % in den zwei Richtungen, welche sich im wesentlichen in rechten Winkeln schneiden, und ein Dehnungsverhältnis von 1,0 bis 5,0 (worin die geringere Dehnung als der Nenner verwendet wird, wenn die Dehnungen in den zwei Richtungen unterschiedlich sind) aufweist, welcher Polyesterfilm 0,01 bis 1,0 Gew.-%, basierend auf dem Gesamtgewicht des Polyesterfilms, an festen, feinen Teilchen enthält, in welchen

1) die mittlere Teilchengröße 0,001 bis 3,0 µm ist und

2) die mittlere Teilchengröße im wesentlichen nicht 1,5 mal die Dicke des Polyesterfilms übersteigt,

(2) eine Klebeschicht (a), welche eine Dicke von 2 bis 60 µm aufweist, welche einen transdermal absorbierbaren Wirkstoff enthält und an eine Oberfläche der Filmschicht laminiert ist, und

(3) ein Unterlageblatt, welches teilweise oder vollständig mit einer Klebekraft von wenigstens 3 g/12 mm mittels einer Klebeschicht (b) mit einer Dicke von 2 bis 100 µm an der Oberfläche der Filmschicht anhaftet, welche von jener abgewandt angeordnet ist, an welche die Klebeschicht (a) laminiert ist.

3. Pflaster umfassend

(1) eine Filmschicht (a), welche aus einem Polyesterfilm, welcher eine Dicke von 0,5 bis 4,9 µm, Festigkeiten von 8 bis 85 g/mm in den zwei Richtungen, welche sich im wesentlichen in rechten Winkeln schneiden, Dehnungen von 30 bis 150 % in den zwei Richtungen, welche sich im wesentlichen in rechten Winkeln schneiden, und ein Dehnungsverhältnis von 1,0 bis 5,0 (worin die geringere Dehnung als der Nenner verwendet wird, wenn die Dehnungen in den zwei Richtungen unterschiedlich sind) aufweist, welcher Polyesterfilm 0,01 bis 1,0 Gew.-%, basierend auf dem Gesamtgewicht des Polyesterfilms, an festen, feinen Teilchen enthält, in welchen

1) die mittlere Teilchengröße 0,001 bis 3,0 µm ist und

2) die mittlere Teilchengröße im wesentlichen nicht 1,5 mal die Dicke des Polyesterfilms übersteigt,

(2) eine Klebeschicht (a), welche eine Dicke von 2 bis 60 µm aufweist, welche einen transdermal absorbierbaren Wirkstoff enthält und an eine Oberfläche der Filmschicht laminiert ist,

(3) ein Unterlageblatt, welches teilweise oder vollständig mit einer Klebekraft (a1) von mehr als 20 g/12 mm durch eine Klebeschicht (b1) an der Oberfläche der Filmschicht (a) anhaftet, welche von jener abgewandt ist, an welche die Klebeschicht (a) laminiert ist, und

(4) eine Filmschicht (b), welche aus einem Film besteht, welcher eine Dicke von 0,5 bis 4,9 µm, Festigkeiten von 8 bis 85 g/mm in den zwei Richtungen, welche sich im wesentlichen in rechten Winkeln schneiden, Dehnungen von 30 bis 150 % in den zwei Richtungen, welche sich im wesentlichen in rechten Winkeln schneiden, und ein Dehnungsverhältnis von 1,0 bis 5,0 (worin die geringere Dehnung als der Nenner verwendet wird, wenn die Dehnungen in den zwei Richtungen unterschiedlich sind) aufweist, und mit einer Klebekraft (b1) von wenigstens 3 g/12 mm durch eine Klebeschicht (b2) teilweise oder vollständig an das Unterlageblatt auf der Oberfläche desselben, welche nicht an die Klebeschicht (b1) gebunden ist, laminiert ist.

4. Pflaster nach einem der Ansprüche 1 bis 3, worin der Kleber ein Acrylharzkleber ist.

5. Pflaster nach einem der Ansprüche 1 bis 4, worin das Dehnungsverhältnis 1,0 bis 3,0 ist.

6. Pflaster nach einem der Ansprüche 1 bis 5, worin der Wirkstoff einen oder mehrere aus Isosorbiddinitraten, Nitroglycerin, Buprenorphin, Östradiol, Progesteron, Ketotifen, Vinpocetin, Nikotin und ihrer Derivate umfaßt.

7. Pflaster nach Anspruch 2, worin die Klebekraft von 3 g/12 mm bis 20 g/12 mm beträgt.

8. Pflaster nach Anspruch 2, worin die Klebekraft über 20 g/12 mm ist.

9. Pflaster nach Anspruch 7 oder 8, worin die Klebekraft kleiner als jene zwischen der Filmschicht und der Klebeschicht (a) ist.

10. Pflaster nach Anspruch 3, worin die Klebekraft (b1) von 3 g/12 mm bis 20 g/12 mm beträgt.

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11. Pflaster nach Anspruch 2 oder 3, worin das Unterlageblatt ein Film, ein nicht-gewebtes Textilmaterial, eine papierartige Substanz und/oder eine Art Stoff, gewählt aus gewebten oder gewirkten Textilien und ihrer Kombination, ist.

12. Pflaster nach Anspruch 11, worin das Unterlageblatt ein mikroporöser Film oder ein gewebtes oder gewirktes Textilmaterial von 10 bis 300 g/cm^2 Flächengewicht ist.

13. Pflaster nach Anspruch 12, worin das gewirkte Textilmaterial aus Hohlfäden besteht, welche durchgehende Löcher aufweisen, welche sich radial nach außen in Richtung zum äußeren Rand erstrecken, und eine Fadendicke von 4 bis 45 µm aufweist.

14. Pflaster nach Anspruch 2, worin die Klebeschicht (b) aus einem Kleber enthaltend Polyvinylalkohol und/oder Vinylacetatpolymer als eine Hauptkomponente zusammengesetzt ist.

15. Pflaster nach Anspruch 2 oder 3, worin die Klebeschicht (b, b1) aus einem Acrylharzkleber zusammengesetzt ist.

16. Pflaster nach Anspruch 14 oder 15, worin die Klebeschicht (b, b1) 2 bis 100 µm dick ist.

17. Pflaster nach Anspruch 2, welches ein Unterlageblatt aufweist, welches mit einer Klebekraft im Bereich von 3 g/12 mm bis 20 g/12 mm durch eine Haftschicht (c) teilweise oder vollständig an dem Unterlageblatt an der Oberfläche desselben, welche nicht an die Filmschicht gebunden ist, anhaftet.

18. Pflaster nach Anspruch 3, welches einen ebenen Unterlagekörper aufweist, welcher mit einer Klebekraft im Bereich von 3 g /12 mm bis 20 g/12 mm durch eine Haftschicht (c) teilweise oder vollständig an der Filmschicht (b) an der Oberfläche derselben, welche nicht an das Unterlageblatt gebunden ist, anhaftet.

19. Pflaster nach Anspruch 3, worin die Klebekraft (b1) kleiner als die Klebekraft (a1) ist.

20. Pflaster nach einem der vorhergehenden Ansprüche, dessen Feuchtigkeits-Transpirationsrate von 10 bis 80 mg/Tag/cm^2 ist.

Revendications

1. Emplâtre comprenant :
   (1) une couche pelliculaire, qui est constituée d'un film de polyester ayant une épaisseur de 0,5 à 4,9 µm, une résistance mécanique de 8 à 85 g/mm respectivement dans les deux directions se coupant essentiellement à angle droit, un allongement de 30 à 150 % respectivement dans les deux directions se coupant essentiellement à angle droit, et un rapport d'allongement de 1,0 à 5,0 (où on utilise le plus petit allongement comme dénominateur quand les allongements dans les deux directions sont différents), ledit film de polyester contenant de 0,01 à 1,0 % en poids, par rapport au poids total dudit film de polyester, de particules solides fines, dont :
      1) la granulométrie moyenne est de 0,001 à 3,0 µm, et
      2) la granulométrie moyenne ne dépasse essentiellement pas 1,5 fois l'épaisseur dudit film de polyester,
   (2) une couche adhésive (a) ayant une épaisseur de 2 à 60 µm, constituée d'un adhésif contenant un médicament pouvant être absorbé par absorption transdermique, et est contrecollée sur ladite couche pelliculaire, et
   (3) un support anti-adhésif, contrecollé à la couche adhésive (a), et pouvant en être enlevé.

2. Emplâtre comprenant :
   (1) une couche pelliculaire, qui est constituée d'un film de polyester ayant une épaisseur de 0,5 à 4,9 µm, une résistance mécanique de 8 à 85 g/mm respectivement dans les deux directions se coupant essentiellement à angle droit, un allongement de 30 à 150 % respectivement dans les deux directions se coupant essentiellement à angle droit, et un rapport d'allongement de 1,0 à 5,0 (où on utilise le plus petit allongement comme dénominateur quand les allongements dans les deux directions sont différents), ledit film de polyester contenant de 0,01 à 1,0 % en poids, par rapport au poids total dudit film de polyester, de particules solides fines, dont :

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1) la granulométrie moyenne est de 0,001 à 3,0 µm, et

2) la granulométrie moyenne ne dépasse essentiellement pas 1,5 fois l'épaisseur dudit film de polyester,

(2) une couche adhésive (a) ayant une épaisseur de 2 à 60 µm, qui contient un médicament pouvant être absorbé par absorption transdermique, et est contrecollée sur une surface de ladite couche pelliculaire, et

(3) une couche d'envers, qui adhère en totalité ou en partie, avec une force d'adhérence d'au moins 3 g/12 mm, par l'intermédiaire d'une couche adhésive (b) de 2 à 100 µm d'épaisseur, à la surface de la couche pelliculaire éloignée de celle sur laquelle est contrecollée la couche adhésive (a).

3. Emplâtre comprenant :

(1) une couche pelliculaire (a), qui est constituée d'un film de polyester ayant une épaisseur de 0,5 à 4,9 µm, une résistance mécanique de 8 à 85 g/mm respectivement dans les deux directions se coupant essentiellement à angle droit, un allongement de 30 à 150 % respectivement dans les deux directions se coupant essentiellement à angle droit, et un rapport d'allongement de 1,0 à 5,0 (où on utilise le plus petit allongement comme dénominateur quand les rapports des allongements dans les deux directions sont différents), ledit film de polyester contenant de 0,01 à 1,0 % en poids, par rapport au poids total dudit film de polyester, de particules solides fines, dont :

1) la granulométrie moyenne est de 0,001 à 3,0 µm, et

2) la granulométrie moyenne ne dépasse essentiellement pas 1,5 fois l'épaisseur dudit film de polyester,

(2) une couche adhésive (a) ayant une épaisseur de 2 à 60 µm, qui contient un médicament pouvant être absorbé par absorption transdermique et contrecollée à une surface de ladite couche pelliculaire,

(3) une couche d'envers qui adhère en totalité ou en partie, avec une force d'adhérence (a1) supérieure à 20 g/12 mm, par l'intermédiaire d'une couche adhésive (b1), à la surface de la couche pelliculaire (a) éloignée de celle à laquelle est contrecollée la couche adhésive (a), et

(4) une couche pelliculaire (b), qui est constituée d'un film ayant une épaisseur de 0,5 à 4,9 µm, une résistance mécanique de 8 à 85 g/mm respectivement dans les deux directions se coupant essentiellement à angle droit, un allongement de 30 à 150 % respectivement dans les deux directions se coupant essentiellement à angle droit, et un rapport d'allongement de 1,0 à 5,0 (où on utilise le plus petit allongement comme dénominateur quand les allongements dans les deux directions sont différents), et est contrecollée en totalité ou en partie, avec une force d'adhérence (b1) d'au moins 3 g/12 mm, par l'intermédiaire d'une couche adhésive (b2), à ladite feuille d'envers, sur la surface de cette dernière qui n'est pas liée à la couche adhésive (b1).

4. Emplâtre selon l'une quelconque des revendications 1 à 3, dans lequel ledit adhésif est un adhésif à base d'une résine acrylique.

5. Emplâtre selon l'une quelconque des revendications 1 à 4, dans lequel ledit rapport d'allongement est de 1,0 à 3,0.

6. Emplâtre selon l'une quelconque des revendications 1 à 5, dans lequel ledit médicament comprend un ou plusieurs des médicaments suivants : dinitrates d'isosorbide, nitroglycérine, buprénorphine, oestradiol, progestérone, kétotifène, vinpocétine, nicotine et leurs dérivés.

7. Emplâtre selon la revendication 2, dans lequel la force adhésive est comprise entre 3 g/12 mm et 20 g/12 mm.

8. Emplâtre selon la revendication 2, dans lequel ladite force adhésive est supérieure à 20 g/12 mm.

9. Emplâtre selon la revendication 7 ou la revendication 8, dans lequel ladite force adhésive est inférieure à celle qui existe entre ladite couche pelliculaire et ladite couche adhésive (a).

10. Emplâtre selon la revendication 3, dans lequel ladite force adhésive (b1) est comprise entre 3 g/12 mm et 20 g/12 mm.

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11. Emplâtre selon la revendication 2 ou 3, dans lequel ladite feuille d'envers est un film, un tissu non tissé, une substance de type papier et/ou un type de tissu choisi parmi les tissus tissés et les tissus tricotés et leurs combinaisons.

12. Emplâtre selon la revendication 11, dans lequel ladite feuille d'envers est un film microporeux ou un tissu tissé ou tricoté ayant une masse surfacique de 10 à 300 g/cm^2.

13. Emplâtre selon la revendication 12, dans lequel ledit tissu tricoté est fabriqué à partir de filaments creux, qui possèdent des trous traversants s'étendant radialement vers la périphérie extérieure, et une épaisseur de filament de 4 à 45 µm.

14. Emplâtre selon la revendication 2, dans lequel ladite couche adhésive (b) est constituée d'un adhésif contenant comme constituant principal du poly(alcool vinylique) et/ou un polymère d'acétate de vinyle.

15. Emplâtre selon la revendication 2 ou 3, dans lequel ladite couche adhésive (b, b1) est constituée d'un adhésif à base d'une résine acrylique.

16. Emplâtre selon la revendication 14 ou 15, dans lequel ladite couche adhésive (b, b1) a une épaisseur de 2 à 100 µm.

17. Emplâtre selon la revendication 2, ayant une feuille d'envers qui adhère en totalité ou en partie, avec une force d'adhérence de 3 g/12 mm à 20 g/12 mm, par l'intermédiaire d'une couche adhésive (c), à ladite feuille d'envers, sur sa surface qui n'est pas liée à la couche pelliculaire.

18. Emplâtre selon la revendication 3, possédant un corps d'envers plan, qui, en totalité ou en partie, adhère avec une force d'adhérence comprise entre 3 g/12 mm et 20 g/12 mm, par l'intermédiaire d'une couche adhésive (c), à ladite couche pelliculaire (b), sur la surface de cette dernière non collée à ladite couche d'envers.

19. Emplâtre selon la revendication 3, dans lequel ladite force d'adhérence (b1) est inférieure à la force d'adhérence (a1).

20. Emplâtre selon l'une quelconque des revendications précédentes, dont le taux de transpiration de l'humidité est de 10 à 80 mg/jour/cm^2.