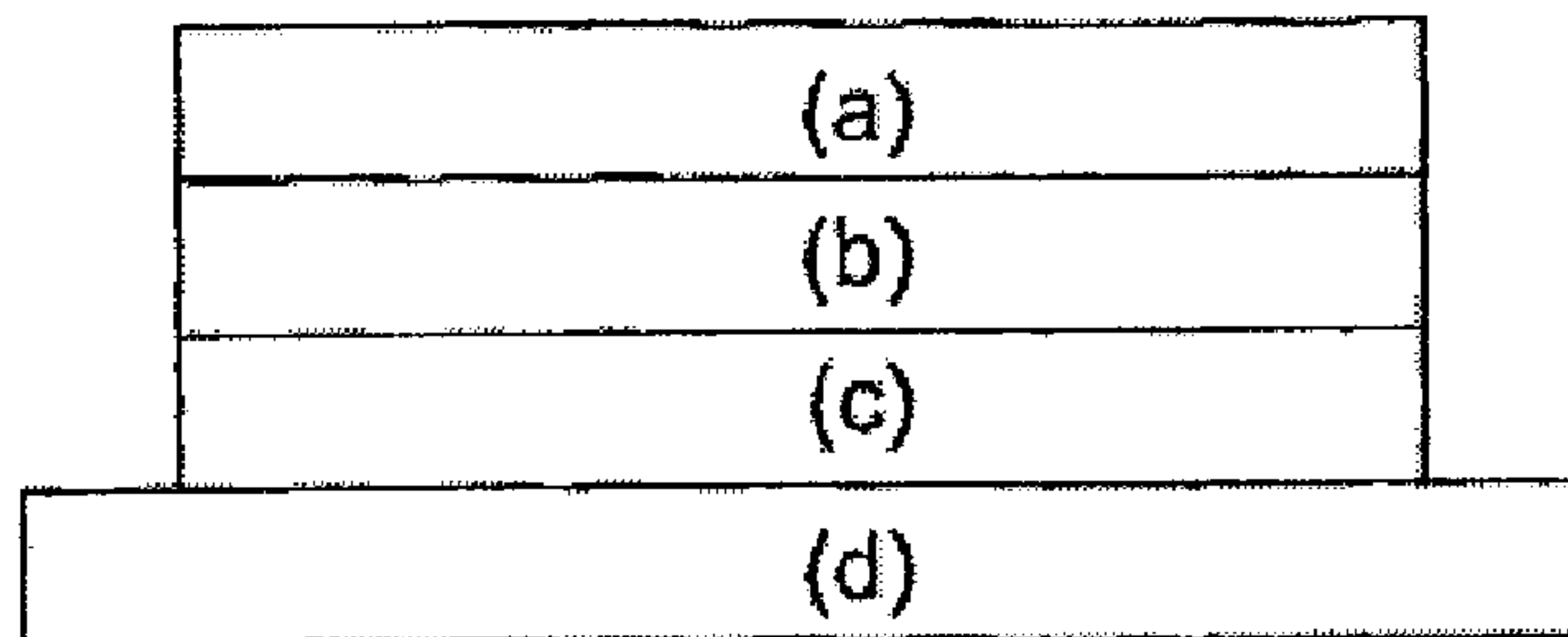




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(54) **Titre : PANSEMENT A ACTION MEDICALE LIBERANT UN COMPOSE ACTIF QUI EST LIQUIDE A LA TEMPERATURE AMBIANTE**  
 (54) **Title: MEDICALLY ACTIVE PLASTER FOR RELEASING AN ACTIVE COMPOUND THAT IS LIQUID AT ROOM TEMPERATURE**



(a) = top layer  
 (b) = adhesive layer  
 (c) = backing layer  
 (d) = peelable protective layer

(57) **Abrégé/Abstract:**

A medically active plaster for dispensing active pharmaceutical substances that are liquid at room temperature onto the skin, in particular for dispensing the antiphlogistic substance etofenamat, wherein this plaster has a structure according to Figure 1, in which the top layer (a) comprises an inert material, the backing layer (c) comprises a self-adhesive polysiloxane, in which the antiphlogistic substance, preferably etofenamat, possibly together with an agent promoting permeation through the skin, and possibly further additional substances, is incorporated in the form of a dispersion, wherein the backing layer (c) adheres directly to the top layer (a), or possibly is joined to it by means of the intermediate layer (b); and the peelable protective layer (d) comprises an inert material, adheres to the backing layer (c) and can be easily pulled off from the latter.

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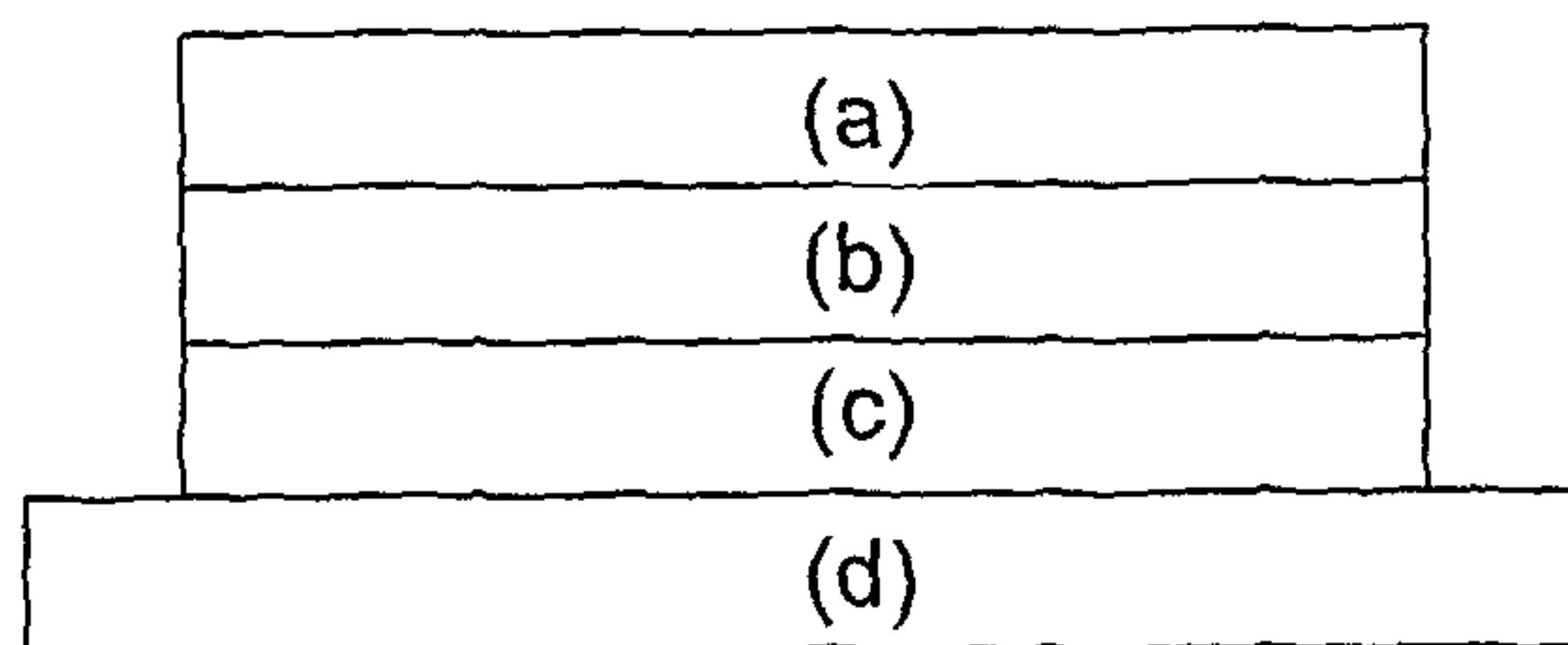
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(54) Title: MEDICALLY ACTIVE PLASTER

(54) Bezeichnung: MEDIZINISCH WIRKSAMES PFLASTER



(a) = Deckschicht

(b) = Klebeschicht

(c) = Trägerschicht

(d) = abziehbare Schutzschicht

(a) = top layer

(b) = adhesive layer

(c) = backing layer

(d) = peelable protective layer

(57) **Abstract:** A medically active plaster for dispensing active pharmaceutical substances that are liquid at room temperature onto the skin, in particular for dispensing the antiphlogistic substance etofenamat, wherein this plaster has a structure according to Figure 1, in which the top layer (a) comprises an inert material, the backing layer (c) comprises a self-adhesive polysiloxane, in which the antiphlogistic substance, preferably etofenamat, possibly together with an agent promoting permeation through the skin, and possibly further additional substances, is incorporated in the form of a dispersion, wherein the backing layer (c) adheres directly to the top layer (a), or possibly is joined to it by means of the intermediate layer (b); and the peelable protective layer (d) comprises an inert material, adheres to the backing layer (c) and can be easily pulled off from the latter.

(57) **Zusammenfassung:** Medizinisches Pflaster für die Abgabe von bei Raumtemperatur flüssigen pharmazeutischen Wirkstoffen an die Haut, insbesondere für die Abgabe des antiphlogistisch wirkenden Wirkstoffs Etofenamat, wobei dieses Pflaster einen Aufbau gemäss Figur 1 aufweist, worin die Deckschicht (a) aus einem inerten Material besteht, die Trägerschicht (c) aus einem selbstklebenden Polysiloxan besteht, in welchem der antiphlogistisch wirkende Wirkstoff, vorzugsweise Etofenamat, gegebenenfalls zusammen mit einem die Permeation durch die Haut fördernden Mittel und gegebenenfalls weiteren Zusatzstoffen, in Form einer Dispersion eingelagert ist, wobei die Trägerschicht (c) direkt an der Deckschicht (a) haftet, oder gegebenenfalls mit dieser über die Zwischenschicht (b) verbunden ist; und die abziehbare Schutzschicht (d) aus einem inerten Material besteht, an der Trägerschicht (c) haftet und von dieser leicht abziehbar ist.

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— *mit internationalem Recherchenbericht*

Medically Active Plaster for Releasing an Active  
Compound that is Liquid at Room Temperature

The present invention relates to a medically active plaster  
5 for releasing pharmaceutical active compounds which are  
liquid at room temperature to the skin, in particular for  
releasing the antiphlogistically active compound  
etofenamate.

10 Medically active plasters for releasing pharmaceutical  
active compounds to the skin are known per se. These  
plasters as a rule comprise a top layer, a backing layer  
containing the pharmaceutical active compound and a  
peelable protective layer. However, the production of such  
15 plasters is difficult since the backing layer in contact  
with the skin must ensure optimum passage of the active  
compound into the skin and at the same time adhere to the  
skin less firmly than to the top layer, so that the plaster  
can be removed easily and completely from the skin.

20

In this context, the backing layer should contain the  
highest possible concentration of the active compound so  
that this can be released from the plaster in a  
pharmaceutically active concentration over a comparatively  
25 long period of time. This is difficult to achieve for  
active compounds which are liquid at room temperature,  
since liquid active compounds must be embedded in the  
backing layer in a stable manner and must be compatible  
with the material of the backing layer. The active compound  
30 must also be released from the backing material at a  
sufficient rate over a relatively long period of time. In  
this context, not only the nature of the backing material  
but also the chemical structure of the active compound  
plays an important role.

It has now been found that the generally poorly soluble antiphlogistically active compound etofenamate surprisingly can be embedded in a pure and uniformly finely distributed form in a stable manner in a self-adhesive silicone matrix and forms a finely divided dispersion there, so that a matrix with very good adhesive properties which releases the active compound in an active concentration over a relatively long period of time and can be used according to the invention as the backing layer is obtained.

10 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an illustration showing the layers of a medical plaster according to one embodiment of the invention.

Figure 2 is an illustration showing the layers of a medical plaster according to another embodiment of the invention.

15 The present invention relates to a medical plaster for releasing pharmaceutical active compounds which are liquid at room temperature to the skin, in particular for releasing the antiphlogistically active compound etofenamate. In a particular embodiment, this plaster has a structure according to Figure 1,  
20 comprising the top layer (a), the backing layer (c), the peelable protective layer (d) and optionally an intermediate layer (b), characterized in that:

- the top layer (a) comprises an inert material,
- the backing layer (c) comprises a self-adhesive polysiloxane in which the antiphlogistically active compound, preferably etofenamate, optionally together with an agent which promotes permeation through the skin and optionally further additives, is embedded in the form of a dispersion, wherein
- 25
- 30 - the backing layer (c) adheres directly to the top layer (a) or is optionally joined to this via the intermediate layer (b); and

- the peelable protective layer (d) comprises an inert material, adheres to the backing layer (c) and can easily be peeled off from this.

5 A preferred medical plaster is that which has a structure according to Figure 2, comprising the top layer (a), the backing layer (c) and the peelable protective layer (d), characterized in that:

- the top layer (a) comprises an inert material,
- 10 - the backing layer (c) comprises a self-adhesive polysiloxane in which the antiphlogistically active compound, preferably etofenamate, optionally together with an agent which promotes permeation through the skin and optionally further additives, is embedded in
- 15 the form of a dispersion, and this backing layer (c) adheres directly to the top layer (a), and
- the peelable protective layer (d) comprises an inert material, adheres to the backing layer (c) and can easily be peeled off from this.

20

If an adhesive layer (b) is present as an intermediate layer between the top layer (a) and the backing layer (c), this adhesive layer (b) either contains no active compound or is optionally loaded with active compound in various

25 amounts and has a comparatively high adhesive strength, so that the adhesive layer (b) adheres firmly both to the top layer (a) and to the backing layer (c). In this context, the adhesive strength of the adhesive layer (b) is largely independent of the backing layer (c) containing the active

30 compound and higher than the adhesive strength of the backing layer (c). The adhesive strength of the backing

layer (c) is only so high for it to be possible to remove the plaster easily and completely from the skin.

If the adhesive layer (b) is loaded with active compound, the active compound is preferably present in the adhesive layer (b) in at least the same amount as the active compound is present in the backing layer (c). Preferably, the adhesive layer (b) is loaded with the active compound up to the saturation limit.

10

The present invention also relates to a process for the production of the plaster according to Figure 1 comprising an adhesive layer (b), characterized in that the constituents of the adhesive layer (b), in the liquefied state, i.e. as a "hot melt" without addition of a solvent, or as a solution in a suitable organic solvent, are applied to the top layer (a) and are then freed from the organic solvent which may be present, or dried; the constituents of the backing layer (c) are then applied in the liquefied state, i.e. as a "hot melt" without addition of a solvent, or as a solution in a suitable organic solvent, to the adhesive layer (b) and are then freed from the organic solvent which may be present, or dried; and the peelable protective layer (d) is applied to the dried backing layer (c). In this context, the adhesive layer (b), as described above, can in each case also optionally contain the active compound.

The present invention also relates to a process for the production of the plaster according to Figure 2, characterized in that the constituents of the backing layer (c) are applied in the liquefied state, i.e. as a "hot

30

melt" without addition of a solvent, or as a solution in a suitable organic solvent, to the top layer (a) and are then freed from the organic solvent which may be present, or dried; and the peelable protective layer (d) is applied to  
5 the dried layer (c).

The production of the plaster according to the invention can also be started from the peelable protective layer (d). The process for the production of the plaster, for example  
10 according to Figure 1, is then characterized in that the constituents of the backing layer (c), in the liquefied state, i.e. as a "hot melt" without addition of a solvent, or as a solution in a suitable organic solvent, are applied to the peelable protective layer (d) and are then freed  
15 from the organic solvent which may be present, or dried; in a separate step the constituents of the adhesive layer (b), in the liquefied state, i.e. as a "hot melt" without addition of a solvent, or as a solution in a suitable organic solvent, are applied to the top layer (a) and are  
20 then freed from the organic solvent which may be present, or dried; and the backing layer (c) is then laminated with the top layer (a), which already contains the adhesive layer (b).

25 Analogously, the process for the production of the plaster, for example according to Figure 2, is characterized in that the constituents of the backing layer (c), in the liquefied state, i.e. as a "hot melt" without addition of a solvent, or as a solution in a suitable organic solvent, are applied  
30 to the peelable protective layer (d) and are then freed from the organic solvent which may be present, or dried;

and the top layer (a) is applied to the dried backing layer (c).

Preferably, the adhesive layer (b) and the backing layer (c) are dried directly after the application if these contain solvents. However, it is also possible to apply all the layers in succession and to dry these only at the end.

Preferably, the backing layer is processed as a "hot melt". For this, the constituents of the backing layer (c) are mixed intensively in the liquefied state by employing the active compound without addition of a solvent, or as a solution in a suitable organic solvent, optionally together with an agent which promotes permeation through the skin and optionally further additives. In this context, the constituents are preferably mixed at a temperature in the range of 80°C - 190°C, preferably in the range of 140°C - 180°C and in particular in the range of 160°C - 180°C, until the desired dispersion of the active compound in the matrix has formed. The mixture is then allowed to cool to the laminating temperature, i.e. to a temperature in the range of 120°C - 140°C, preferably in the range of 80°C - 120°C and in particular to about 100°C, the dispersion being applied to or laminated on the desired substrate at this temperature in the form of a "hot melt" and processed to give the backing layer (c). At the laminating temperature the dispersion is preferably solvent-free, or is then freed, before or after the lamination, from the organic solvent which may still be present. Polysiloxanes which can be applied without a solvent and polysiloxanes which are preferably applied from a solvent with subsequent removal of the solvent are known per se.

The top layer (a) preferably comprises an elastic textile planar structure which is coated with a polymeric material. Textile material which is used is e.g. a textile planar structure which is produced, for example, from cotton and is coated with polyethylene terephthalate (PET). The textile planar structure can also comprise a synthetic textile fibre, such as, for example, PET, PVC, PU and further polymeric plastics, or be produced in non-woven form. Such materials are known per se and commercially obtainable.

The adhesive layer (b) comprises an organic polymer which is known per se, is preferably soluble in an organic solvent and has good adhesive properties. Suitable adhesive materials are, for example, polymers of isoprene or copolymers of isoprene with styrene, such as styrene/isoprene/styrene (SIS); polyalkyl acrylates, prepared from, for example, amyl, butyl, hexyl, heptyl, octyl, nonyl, 2-ethylhexyl or 2-methoxyethyl acrylate, or copolymers of such alkyl acrylates with acrylic acid, methacrylic acid, methyl or ethyl acrylate, hydroxyethyl acrylate or hydroxypropyl acrylate. Styrene/butadiene/styrene copolymers (SBS) or polyisobutylenes and copolymers thereof are also suitable.

Copolymers prepared from 2-ethylhexyl acrylate and methyl acrylate, such as, for example, from about 19.9 wt.% of 2-ethylhexyl acrylate and about 79.3 wt.% of methyl acrylate, with an average molecular weight in the range of from 350,000 to 550,000 dalton, preferably about 400,000 to 500,000 dalton, and polymerized e.g. in the presence of

azobisisobutyronitrile, are particularly preferred for the production of the adhesive layer (b).

The acrylate polymers mentioned are preferably also used in combination with SBS polymers, it being possible for the ratio to be optimized by the person skilled in the art. Thus, for example, the weight ratio of the acrylate polymer to SBS can be in the range of from 2:1 to 1:2, preferably in the range of from 5:3 to 3:5.

10

Styrene/butadiene/styrene block copolymers (SBS), styrene/butadiene block copolymers (SB) and mixtures of these copolymers with a glass transition temperature ( $T_g$ ) of preferably less than  $-22^\circ\text{C}$  [ $T_g < (-22^\circ\text{C})$ ] are also preferred for the production of the adhesive layer (b). These polymers can contain additives, such as e.g. the glycerol ester of hydrogenated colophony or polyterpenes. A preferred composition contains, for example, 17.0 wt.% of SB, 11.3 wt.% of SBS, 70.8 wt.% of colophony glycerol ester and 0.9 wt.% of an antioxidant. Preferred solvents for these adhesive materials are, for example, saturated and aromatic hydrocarbons, such as e.g. hexane, heptane, octane, benzene or toluene.

25 For the production of the adhesive layer (b), the polymers and/or copolymers are preferably dissolved in a suitable solvent. If the adhesive layer (b) contains the active compound, the active compound is preferably dissolved in the desired amount in a suitable solvent beforehand and mixed in the dissolved form with the polymer and/or copolymer of the adhesive layer (b). The solution of the adhesive layer (b) is applied to the top layer (a) and the

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solvent is removed. Suitable solvents are, for example, ethyl acetate, propyl acetate and saturated and aromatic hydrocarbons, such as e.g. hexane, heptane, octane, benzene or toluene.

5

Numerous polymers which are suitable for the production of the adhesive layer (b) can also be applied in the liquefied state without the addition of a solvent, as a "hot melt".

10 Such polymers and copolymers which can be used for the production of the adhesive layer (b) are known per se and commercially obtainable. Coated planar structures are obtainable, for example, as Scotchpak® from 3M. For example, the top layer is coated with about 40 g/m<sup>2</sup> of SBS  
15 (as the adhesive layer) in a first step. Scotchpak is used, for example, as the protective layer (e.g. Scotchpak 1022 from 3M). Whether the adhesive layer (b) is applied to the top layer (a) from a solvent or without a solvent is not essential according to the invention. Preferably, the  
20 plaster according to the invention comprises no adhesive layer (b).

According to the invention, the backing layer (c) comprises a self-adhesive polysiloxane. Self-adhesive polysiloxanes  
25 are known per se and are prepared in various compositions and marketed commercially, for example, by Dow Corning under the trade name BIO-PSA® Amine-Compatible Silicone Adhesives. Such silicone polymers can be used according to the invention. To optimize the adhesive properties, such  
30 silicone polymers can additionally contain additives known per se for modification of the adhesive properties, such as e.g. colophony compounds, such as e.g. dehydrogenated or

hydrogenated colophony, colophony glycerol ester, terpene resins, polyterpene resins from alpha- or beta-pinene, or low-viscosity silicones or polysiloxanes which contain terminal silanol groups, or polydimethylsiloxanes, such as  
5 e.g. dimethiconol.

Self-adhesive polysiloxanes which are suitable for the production of the backing layer (c) without addition of a solvent, as a "hot melt", are commercially obtainable, for  
10 example known as BIO-PSA® 7-4560 Silicone Adhesive from Dow Corning. Such siloxane compounds are known e.g. under CAS number 68440-70-0 and CAS number 63148-62-9, and mixtures thereof, e.g. compounds of CAS number 68440-70-0 in a concentration of at least 60 wt.% with compounds of CAS  
15 number 63148-62-9 in a concentration of from 10.0 to 30.0 wt.%.

Self-adhesive polysiloxanes which are suitable for the production of the backing layer (c) with the addition of a  
20 solvent are commercially obtainable, for example as BIO-PSA® 7-4603 or BIO-PSA® 7-4201 from Dow Corning. Suitable polysiloxanes for the production of the backing layer (c) can easily be chosen by the person skilled in the art.

25 Suitable self-adhesive polysiloxanes are obtained, for example, by condensation of a dimethylpolysiloxane containing silanol groups with a silicate resin which is soluble in organic solvents and subsequent reaction of the remaining silanol groups with a reactive trimethylsilyl  
30 compound. Such polysiloxanes are soluble in organic solvents, such as, for example, in ethyl acetate, propyl

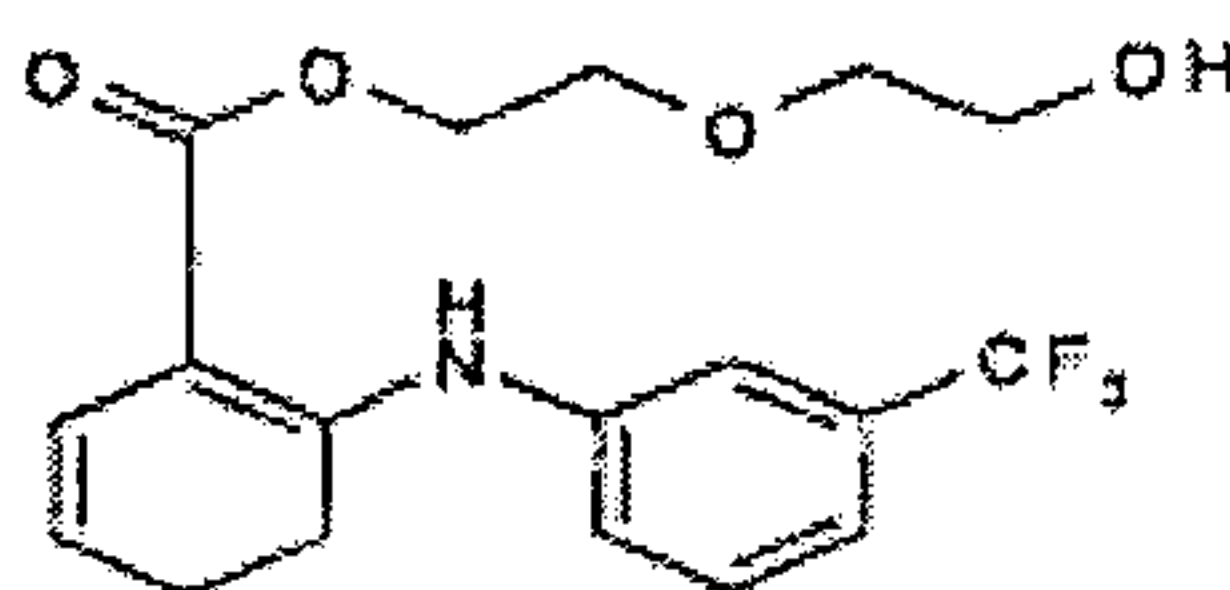
acetate and saturated and aromatic hydrocarbons, such as e.g. hexane, heptane, octane, benzene or toluene.

In a preferred embodiment, the self-adhesive polysiloxane  
5 of the backing layer (c) contains a compound or a mixture  
of compounds which lower the viscosity of the self-adhesive  
polysiloxane containing the active compound, without  
adversely influencing the other properties of the self-  
adhesive polysiloxane. Such compounds are preferably  
10 glycerol and/or ester compounds of a medium-chain fatty  
acid with a monohydric or polyhydric alcohol. Preferred  
ester compounds of a medium-chain fatty acid with a  
monohydric alcohol are, for example, esters of propyl  
alcohol, isopropyl alcohol, butyl alcohol or isopropyl  
15 alcohol with a (C<sub>10</sub>-C<sub>16</sub>)-fatty acid, preferably with medium-  
chain (C<sub>12</sub>-C<sub>16</sub>)-fatty acids, preferably with lauric acid,  
myristic acid or palmitic acid, such as, for example,  
isopropyl myristate. Ester compounds of medium-chain fatty  
acids with polyhydric alcohols are, for example, mono-, di-  
20 or triesters of glycerol with medium-chain (C<sub>10</sub>-C<sub>16</sub>)-fatty  
acids, preferably mono-, di or triesters of glycerol with  
medium-chain (C<sub>12</sub>-C<sub>16</sub>)-fatty acids, and also natural oils,  
preferably olive oil or castor oil. Compounds which can  
also be used as compounds which analogously lower the  
25 viscosity of the self-adhesive polysiloxane containing the  
active compound are liquid paraffin, polysorbates (i.e.  
polyoxyethylene sorbitan fatty acid ester compounds), such  
as, for example, Tween®60 (polyoxyethylene sorbitan  
monostearate) or Tween®80 (polyoxyethylene sorbitan  
30 monooleate), polyethylene glycols, such as e.g.  
polyethylene glycol 400, propylene glycol and polypropylene  
glycols, esters of polyhydric acids with alcohols, such as

triethyl citrate, and mixtures of these compounds. The self-adhesive polysiloxanes used according to the invention preferably contain about 2-15 wt.%, preferably about 5-10 wt.% of these compounds, based on the total weight of the backing layer (c). The compounds mentioned can occasionally also act as permeation accelerators.

- The backing layer (c) containing the active compound and also the adhesive layer (b) optionally containing the active compound contain the active compound optionally together with an agent which promotes permeation through the skin. However, the presence of an agent which promotes permeation through the skin is not critical. The active compound can additionally also be mixed with further active compounds and additionally contain e.g. stabilizers and odoriferous substances.

Etofenamate, corresponding to the chemical formula:



etofenamate

i.e. 2-(2-hydroxyethoxy)-ethyl ( $\alpha,\alpha,\alpha$ -trifluoro-m-tolyl)-anthranilate (etofenamate), is preferred.

The backing layer (c) contains the active compound, preferably etofenamate, preferably in a concentration in the range of from about 1.0 wt.% to about 25.0 wt.%, preferably 2.0 wt.% to 20 wt.% and preferably 2.5 wt.% to 15 wt.%, preferably in a concentration of from about 5 wt.%

to about 10 wt.%, calculated for the total weight of the backing layer.

A process for the preparation of the dispersion which can be used as the backing layer (c) containing at least one self-adhesive polysiloxane and the active compound, preferably etofenamate, optionally together with an agent which promotes permeation through the skin and optionally further additives, is characterized in that the self-adhesive polysiloxane which forms the backing layer (c) is heated together with the active compound, optionally together with an agent which promotes permeation through the skin and optionally further additives to a temperature in the range of 80°C - 200°C, preferably in the range of 140°C - 190°C and in particular in the range of 160°C - 190°C, with intensive stirring, until the desired dispersion has formed. This dispersion can be processed further without a solvent in the stated temperature range, but preferably in the range of 120°C - 140°C, preferably in the range of 80°C - 120°C and in particular at about 100°C, and applied as a thin layer in the desired amount to the envisaged substrate.

A further process for the preparation of the dispersion which can be used as the backing layer (c) containing at least one self-adhesive polysiloxane and the active compound, preferably etofenamate, optionally together with an agent which promotes permeation through the skin and optionally further additives, is characterized in that the self-adhesive polysiloxane which forms the backing layer (c) is heated together with the active compound, optionally together with an agent which promotes permeation through

the skin and optionally further additives in the presence of a solvent at elevated temperature, preferably in the range of 40°C - 90°C, preferably in the region of the boiling point of the solvent, with intensive stirring, until the desired dispersion has formed. Preferably, solvent is added in an amount such that the dispersion obtained can be processed to a plaster at room temperature, i.e. the dispersion obtained can be applied as a thin layer in the desired amount to the envisaged substrate at room temperature.

Alternatively, it is possible to remove the solvent substantially or completely from the dispersion formed [for formation of the backing layer (c)] and to further process the dispersion formed in this manner at elevated temperature substantially or completely without a solvent and to apply it as a thin layer in the desired amount to the envisaged substrate.

Solvents which are used are preferably an organic solvent, such as, for example, ethyl acetate, propyl acetate and saturated and/or aromatic hydrocarbons, such as e.g. hexane, heptane, octane, benzene or toluene. The solvent is preferably evaporated off at a temperature in the range of from 50°C to 90°C, depending on the boiling point of the solvent, preferably at a temperature of from about 60°C to 70°C, during a period of time of from about 30 minutes to 60 minutes, either from the dispersion obtained or from the layer applied in the plaster.

30

The backing layer (c) contains the active compound in highly disperse distribution with an average droplet size

in the range of from 0.1  $\mu\text{m}$  to 500  $\mu\text{m}$ , preferably from 1.0  $\mu\text{m}$  to 100  $\mu\text{m}$ . The covering of the surface for the adhesive layer (b) and the backing layer (c) is in each case in the range of from 30  $\text{g}/\text{m}^2$  to 300  $\text{g}/\text{m}^2$ , preferably in 5 the range of from about 40  $\text{g}/\text{m}^2$  to 200  $\text{g}/\text{m}^2$  and in particular in the range of from about 40  $\text{g}/\text{m}^2$  to 100  $\text{g}/\text{m}^2$ .

The adhesive strength of the adhesive layer (b) is preferably in the range of from 0.8 N/25 mm to 2.0 N/25 mm, 10 preferably in the range of from 0.9 N/25 mm to 1.7 N/25 mm. The adhesive strength of the backing layer (c) is preferably in the range of from 0.8 N/25 mm to 1.4 N/25 mm.

Compounds which promote permeation through the skin 15 (permeation enhancers) are additives which promote administration of the active compound to the skin or penetration of the stratum corneum. Such compounds are known per se and also for use in such plasters. Naturally occurring substances, such as natural oils and fats, or 20 fatty acids and higher fatty alcohols and esters thereof as well as glycerol and mixtures of these compounds are preferred. The weight ratio of active compound : permeation enhancer is preferably in the range of from 98 : 2 to 2 : 8, preferably in the range of from 9 : 1 to 3 : 7, 25 preferably about 1 : 2.

Natural oils and fats are, in particular, mono-, di- and triglycerides, which are glyceride esters with saturated and/or unsaturated fatty acids; for example esters of fatty 30 acids having preferably 4 to 22 carbon atoms. Such fatty acids are preferably butyric, caproic, capric, myristic, palmitic, stearic, arachic, palmitoleic, oleic, ricinoleic,

linoleic, linolenic or arachidonic acid. Such fatty acids having preferably 4 to 22 carbon atoms can also be employed as accelerators by themselves.

5 Alcohols are to be understood as meaning the corresponding alcohols and fatty alcohols having 4 to 22 carbon atoms, preferably n-, iso- and sec-butyl alcohol; n-, iso- and tert-amyl alcohol; n-hexyl alcohol, cyclohexyl alcohol; 10 octyl alcohol, capryl alcohol (2-octanol), n-decyl alcohol, lauryl alcohol, myristyl alcohol, cetyl alcohol and stearyl alcohol.

Synthetic fatty acid esters of the fatty acids mentioned with low or higher alcohols, such as, for example, ethyl 15 stearate, palmitic acid cetyl ester, isopropyl myristate, isopropyl palmitate or mixtures of such compounds, are also suitable. Isopropyl myristate is preferred.

Natural oils are also e.g. castor oil, olive oil, groundnut 20 oil, maize oil, hazelnut oil, jojoba oil and wheat germ oil.

The peelable protective layer (d) comprises an inert material which adheres to the backing layer (c) and can 25 easily be peeled off from this. Such materials are known in the form of thin films and are commercially obtainable, for example, from 3M under the brand name Scotchpak®. The following examples illustrate the invention without limiting this.

Example 1

5.0 parts of pure ethyl acetate are added to 5.0 parts of pure etofenamate in a glass round-bottomed flask and the substances are mixed intensively on a magnetic stirrer plate. 85 parts of a self-adhesive polysiloxane dissolved in ethyl acetate (BIO-PSA® 7-4603 or, respectively, BIO-PSA® 7-4560 from Dow Corning) are then added and the mixture is stirred intensively at room temperature for 2.5 hours. Where appropriate, 10 parts of isopropyl myristate (IPM) are added to the mixture. A laminate with a weight per unit area of 100 g/m<sup>2</sup>, 75 g/m<sup>2</sup> and 40 g/m<sup>2</sup> (= backing layer (c) on a peelable layer (d)] is produced from the resulting mixture using a coating unit, and is dried in a drying cabinet at a temperature of 60°C for 60 minutes, until all the solvents are removed. After the drying, the laminate obtained is laminated with a top layer (a) comprising PET fabric which is provided with an adhesive layer (b) (Duro-Tak® 87-6173 from National Starch), the adhesive layer having a weight per unit area of 40 g/m<sup>2</sup>. The additional examples of Table 1 were produced in an analogous manner.

Table 1

Etofenamate	Bio PSA 7-4603	IPM	Area mass
5 %	95 %	-	40 g/m <sup>2</sup>
5 %	95 %	-	75 g/m <sup>2</sup>
10 %	90 %	-	40 g/m <sup>2</sup>
10 %	90 %	-	75 g/m <sup>2</sup>
5 %	85 %	10 %	100 g/m <sup>2</sup>
10 %	80 %	10 %	100 g/m <sup>2</sup>

Example 2

5.0 parts of pure etofenamate are stirred intensively with 10 parts of isopropyl myristate (IPM) and 85 parts of a self-adhesive polysiloxane (BIO-PSA® 4650 from Dow Corning) in a high-speed mixer of the brand name Becomix at a temperature of 190°C for 2.5 hours. The mixture or dispersion obtained is allowed to cool and processed with a coating unit from Hofmann & Schwabe at a laminating temperature of 100°C to give a laminate with a weight per unit area of 100 g/m<sup>2</sup>, 75 g/m<sup>2</sup> and of 40 g/m<sup>2</sup> [= backing layer (c) on the top layer (a), comprising PET fabric], which is cooled to room temperature. The laminate obtained is then laminated with a protective layer (d) (Scotchpak®, a removable film from 3M coated with a fluoropolymer).

Claims

1. Medical plaster for releasing the pharmaceutically active compound etofenamate to the skin, wherein this plaster has a structure comprising the top layer (a), the backing layer (c), the peelable protective layer (d) and optionally an intermediate adhesive layer (b), wherein:
  - the top layer (a) comprises an inert material,
  - the backing layer (c) comprising a self-adhesive polysiloxane as a backing material which has been obtained by condensation of a dimethylpolysiloxane containing silanol groups with a silicate resin which is soluble in organic solvents and subsequent reaction of the remaining silanol groups with a reactive trimethylsilyl compound;
  - said backing layer (c) containing the pharmaceutically active compound etofenamate, optionally together with an agent which promotes permeation through the skin and optionally further additives, being embedded therein in the form of a dispersion, wherein
  - the adhesive strength of the backing layer (c) is in the range of from 0.8 N/25 mm to 1.4 N/25 mm;
  - the backing layer (c) contains the active compound etofenamate in a concentration in the range of from 1.0 wt.% to 25.0 wt.%, calculated for the total weight of the backing layer (c);
  - the backing layer (c) contains the active compound etofenamate in dispersed form with an average droplet size in the range of from 0.1  $\mu\text{m}$  to 500  $\mu\text{m}$ ;
  - the backing layer (c) adheres directly to the top layer (a) or is optionally joined to this via the intermediate layer (b); and
  - the peelable protective layer (d) comprises an inert material, adheres to the backing layer (c) and can easily be peeled off from the backing layer.
  
2. Plaster according to claim 1, comprising the top layer (a), the backing layer (c) and the peelable protective layer (d), wherein:
  - the top layer (a) comprises an inert material,
  - the backing layer (c) comprises a self-adhesive polysiloxane in which the pharmaceutically active compound etofenamate, optionally together with an agent which promotes permeation through the skin and optionally further additives, is embedded in the form of a dispersion, and this backing layer (c) adheres directly to the top layer (a), and
  - the peelable protective layer (d) comprises an inert material, adheres to the backing layer (c) and can easily be peeled off from the backing layer.

3. Plaster according to claim 1, wherein an intermediate layer (b) is present between the top layer (a) and the backing layer (c), this adhesive layer (b) either contains no active compound or is loaded with the active compound etofenamate in a varying amount, and the adhesive strength of the intermediate layer (b) is higher than the adhesive strength of the backing layer (c), the adhesive strength of the backing layer (c) being only so high for it to be possible to remove the plaster easily and completely from the skin.
4. Plaster according to claim 3, wherein the adhesive layer (b) is loaded with the active compound etofenamate and said active compound is present in the adhesive layer (b) in at least the same amount as said active compound is present in the backing layer (c), the intermediate layer (b) being loaded with said active compound up to the saturation limit.
5. Plaster according to any one of claims 1-4, wherein the top layer (a) comprises an elastic textile planar structure which is coated with a polymeric material.
6. Plaster according to any one of claims 1 or 3-5, wherein the adhesive layer (b) comprises an organic polymer which is soluble in an organic solvent and has good adhesive properties, wherein the organic polymer is 2-ethylhexyl acrylate, methyl acrylate, SBS polymers, styrene/-butadiene/styrene block copolymers (SBS), styrene/butadiene block copolymers (SB) or mixtures of these copolymers with a glass transition temperature ( $T_g$ ) of less than  $-22^\circ\text{C}$  [ $T_g < (-22^\circ\text{C})$ ], and these polymers optionally contain additives chosen from glycerol esters of hydrogenated colophony or polyterpenes.
7. Plaster according to claim 6, wherein the adhesive layer (b) comprises predominantly 2-ethylhexyl acrylate and methyl acrylate, in an amount of about 19.9 wt.% of 2-ethylhexyl acrylate and about 79.3 wt.% of methyl acrylate, with an average molecular weight in the range of from 350,000 to 550,000 dalton.
8. Plaster according to claim 6, wherein the adhesive layer (b) comprises 17.0 wt.% of SB, 11.3 wt.% of SBS, 70.8 wt.% of colophony glycerol ester and 0.9 wt.% of an antioxidant.
9. Plaster according to any one of claims 1-8, wherein the backing layer (c) comprises a self-adhesive polysiloxane which contains additives for modification of the adhesive properties wherein the additives are colophony compounds and wherein the colophony compounds are dehydrogenated or hydrogenated colophony, colophony glycerol ester, terpene resins, polyterpene resins from alpha-

or beta-pinene, or a mixture of these compounds, or low-viscosity silicones or polysiloxanes which contain terminal silanol groups.

10. Plaster according to any one of claims 1-9, wherein the self-adhesive polysiloxane of the backing layer (c) contains a compound or a mixture of compounds which lower the viscosity of the self-adhesive polysiloxane containing the active compound, wherein the compound is glycerol and/or an ester compound of a medium-chain fatty acid with a monohydric alcohol wherein about 2 - 15 wt.% of these compounds, based on the total weight of the backing layer (c), are present.

11. Plaster according to claim 10 wherein the ester compound is an ester of propyl alcohol, isopropyl alcohol, butyl alcohol or isopropyl alcohol with a (C<sub>10</sub>-C<sub>16</sub>)-fatty acid.

12. Plaster according to any one of claims 1-9, wherein the self-adhesive polysiloxane of the backing layer (c) contains a compound or a mixture of compounds which lower the viscosity of the self-adhesive polysiloxane containing the active compound, wherein the compound is an ester compound of a medium-chain fatty acid with a polyhydric alcohol, wherein the polyhydric alcohol is mono-, di or triesters of glycerol with medium-chain (C<sub>10</sub>-C<sub>16</sub>)-fatty acids, mono-, di- or triesters of glycerol with medium-chain (C<sub>12</sub>-C<sub>16</sub>)-fatty acids, and/or natural oils wherein the oil is olive oil or castor oil, wherein about 2-15 wt.%, of these compounds, based on the total weight of the backing layer (c), are present.

13. Plaster according to any one of claims 1-9, wherein the self-adhesive polysiloxane of the backing layer (c) contains a compound or a mixture of compounds which lower the viscosity of the self-adhesive polysiloxane containing the active compound, wherein the compound or mixture of compounds is liquid paraffin, polyoxyethylene sorbitan fatty acid ester compounds, wherein the polyoxyethylene sorbitan fatty acid ester compounds are polyoxyethylene sorbitan monostearate or polyoxyethylene sorbitan monooleate, polyethylene glycol, polyethylene glycol 400, propylene glycol, polypropylene glycol, esters of polybasic acids with alcohols, triethyl citrate, or mixtures of these compounds, wherein about 2 - 15 wt.% of these compounds, based on the total weight of the backing layer (c), are present.

14. Plaster according to any one of claims 1-13, wherein the backing layer (c) contains at least one compound which promotes permeation through the skin and optionally additionally stabilizers and odoriferous substances.

15. Plaster according to claim 14, wherein the compound which promotes permeation through the skin (permeation enhancer) is a natural oil or fat, fatty acid, higher fatty alcohol, or esters thereof or glycerol, or mixtures of these compounds, wherein the weight ratio of active compound : permeation enhancer is in the range of from 98 : 2 to 2 : 8.
16. Plaster according to any one of claims 1-15, wherein the backing layer (c) contains the active compound etofenamate in a concentration in the range of from 2.5 wt.% to 15 wt.%, calculated for the total weight of the backing layer (c).
17. Plaster according to any one of claims 1 - 16, wherein the backing layer (c) contains the active compound etofenamate in disperse form with an average droplet size in the range of from 1.0  $\mu\text{m}$  to 100  $\mu\text{m}$ .
18. Plaster according to any one of claims 1 - 17, wherein the covering of the surface for the backing layer (c) is in the range of from 30  $\text{g}/\text{m}^2$  to 300  $\text{g}/\text{m}^2$ .
19. Process for the preparation of the backing layer (c) in which the pharmaceutically active compound etofenamate is embedded in the form of a dispersion according to claim 1, wherein the self-adhesive polysiloxane which forms the backing layer (c) is mixed together with the active compound etofenamate, optionally together with an agent which promotes permeation through the skin and optionally further additives, at a temperature in the range of 80°C - 190°C, until the desired dispersion of the active compound in the matrix has formed, the mixture is then brought to a temperature in the range of 120°C - 140°C, the dispersion is applied to a top layer (a), an adhesive layer (b) or a peelable layer (d) at this temperature in the form of a "hot melt" and processed to give the backing layer (c), and any remaining organic solvent may be removed, before or after the lamination.
20. Process for the preparation of the backing layer (c) in which the pharmaceutically active compound etofenamate is embedded in the form of a dispersion according to claim 1, wherein the self-adhesive polysiloxane which forms the backing layer (c) is heated together with said active compound, optionally together with an agent which promotes permeation through the skin and optionally further additives, in the presence of sufficient solvent at elevated temperature in the range of 40°C - 90°C, with intensive stirring, until the desired dispersion has formed.

21. Process for the production of the plaster according to claim 1, wherein the constituents of the adhesive layer (b), in the liquefied state or as a solution in a suitable organic solvent, are applied to the top layer (a) and are then removed from the organic solvent which may be present, or dried to remove the organic solvent; the dispersion of the backing layer (c) made according to claim 19 or 20 is then applied to the adhesive layer (b) and is then removed from the organic solvent which may be present, or dried to remove the organic solvent; and the peelable protective layer (d) is applied to the dried backing layer (c).

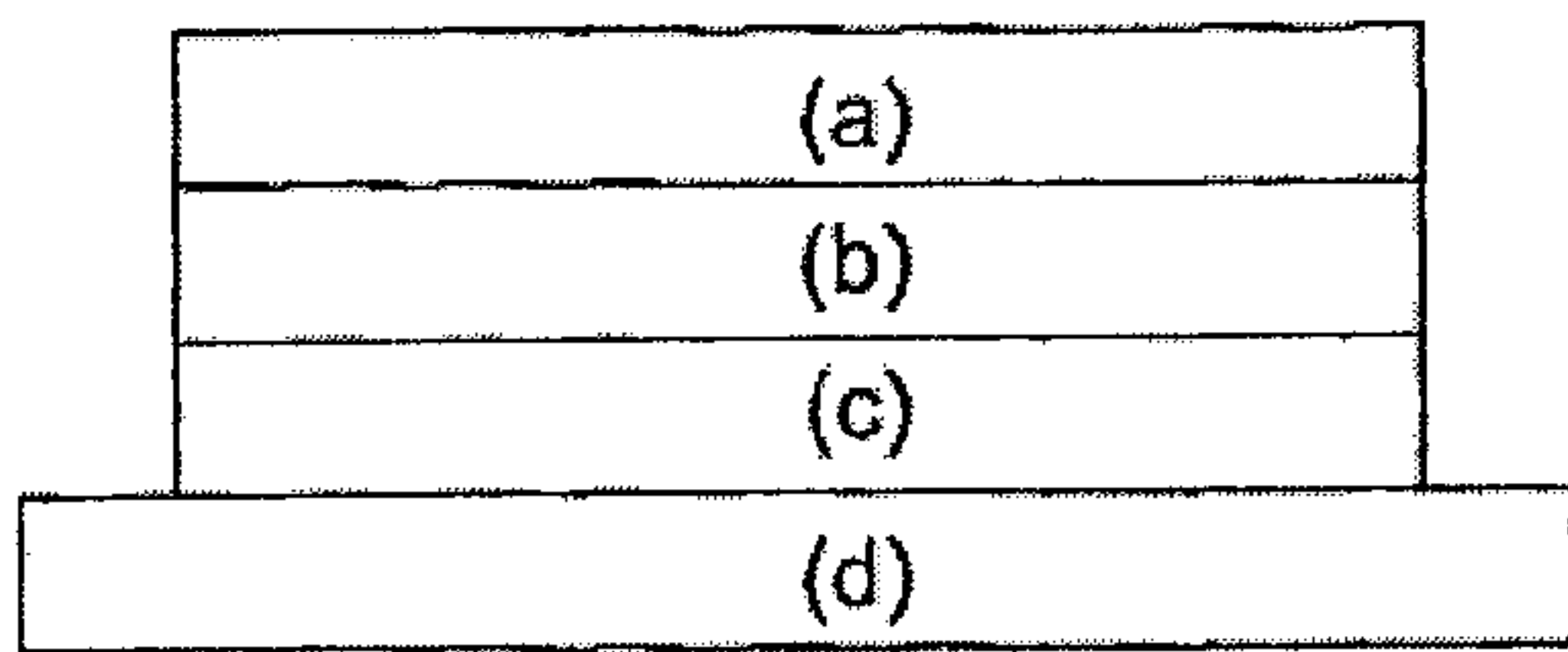
22. Process for the production of the plaster according to claim 2, wherein the dispersion of the backing layer (c) made according to claim 19 or 20 is applied to the top layer (a) and is then removed from the organic solvent which may be present, or dried to remove the organic solvent; and the peelable protective layer (d) is applied to the dried layer (c).

23. Process for the production of the plaster according to claim 1, wherein the dispersion of the backing layer (c) made according to claim 19 or 20, is applied to the peelable protective layer (d) and is then freed from the organic solvent which may be present, or dried to remove the organic solvent; in a separate step the constituents of the adhesive layer (b), in the liquefied state or as a solution in a suitable organic solvent, are applied to the top layer (a) and are then removed from the organic solvent which may be present, or dried to remove the organic solvent; and the backing layer (c) is then laminated with the top layer (a), which already contains the adhesive layer (b).

24. Process for the production of the plaster according to claim 2, wherein the dispersion of the backing layer (c) made according to claim 19 or 20 is applied to the peelable protective layer (d) and is then removed from the organic solvent which may be present, or dried to remove the organic solvent; and the top layer (a) is applied to the dried backing layer (c).

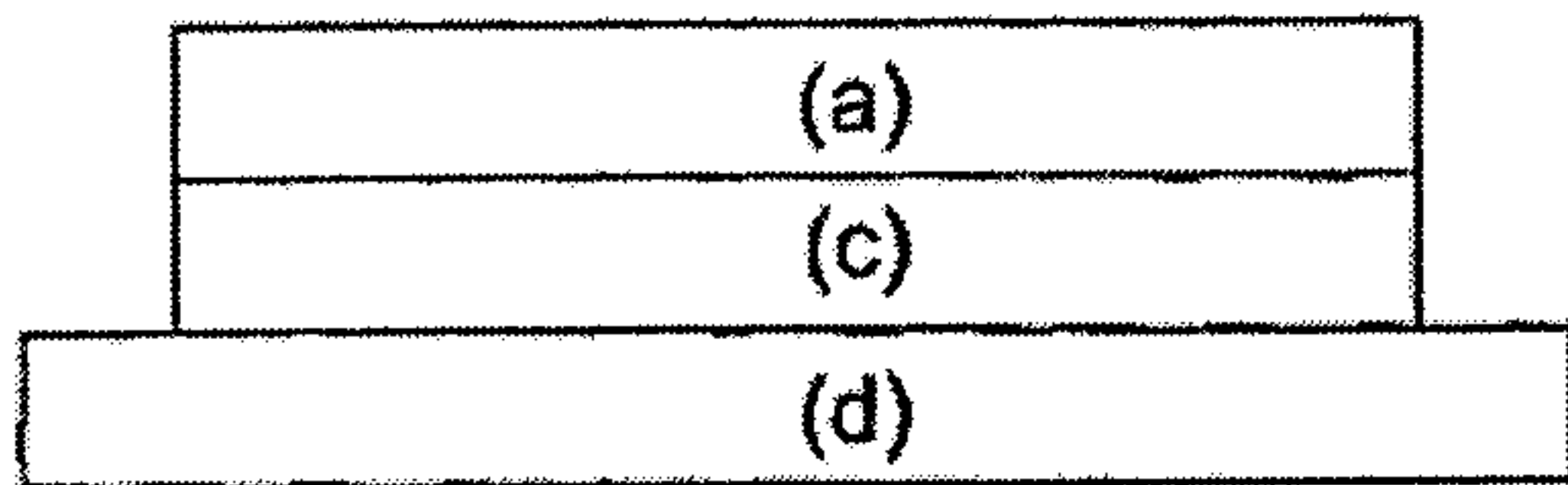
25. Process according to any one of claims 21-24, wherein the dispersion of the backing layer (c) is applied without a solvent at a temperature in the range of 120°C-140°C.

Figure 1

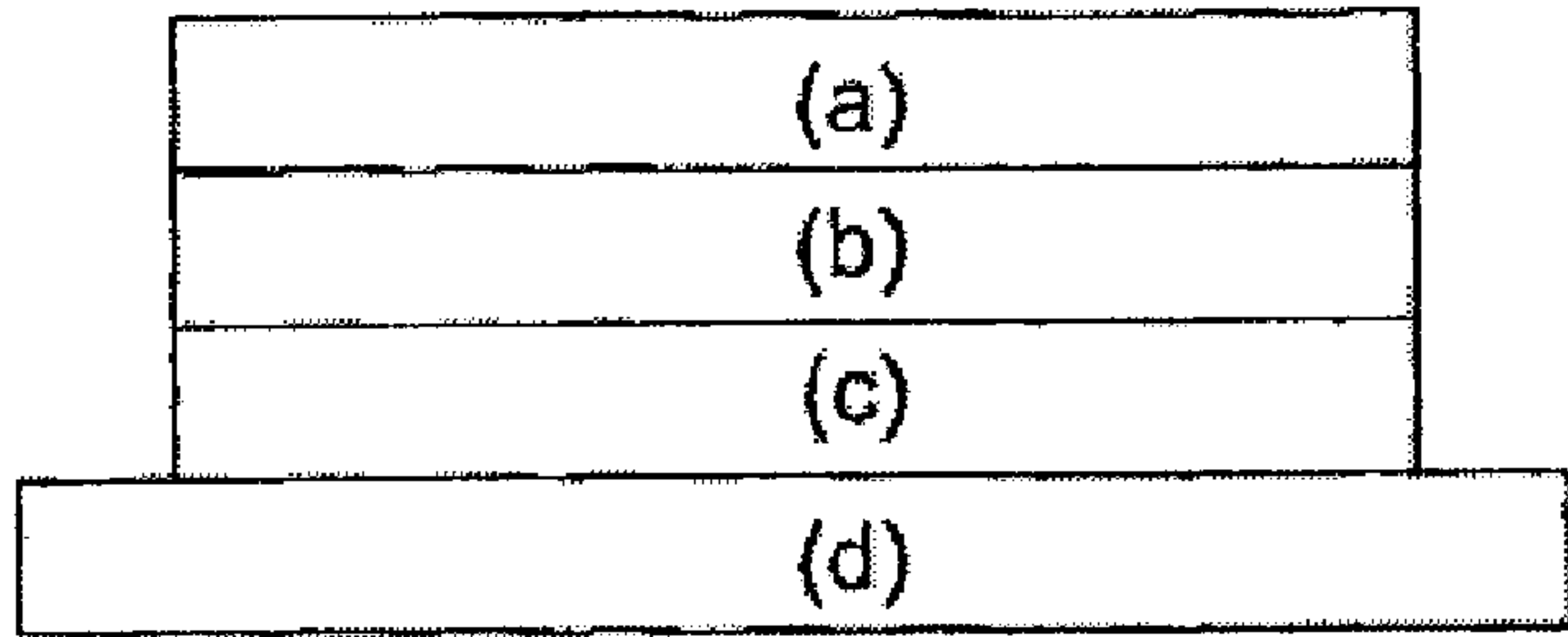


- (a) = top layer
- (b) = adhesive layer
- (c) = backing layer
- (d) = peelable protective layer

Figure 2



- (a) = top layer
- (c) = backing layer
- (d) = peelable protective layer



(a) = top layer

(b) = adhesive layer

(c) = backing layer

(d) = peelable protective layer