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71 **Full name(s) of applicant(s):**

LTS Lohmann Therapie-Systeme AG

72 **Full name(s) of inventor(s)**

BRACHT, Stefan

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54 **Title of invention**

MEDICAL ACTIVE AGENT PATCH OPTICALLY LESS VISIBLE ON SKIN

57 **Abstract**

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ADDRESS FOR SERVICE:
DR GERNTHOLTZ INC
PATENT AND TRADE MARK ATTORNEYS
P O BOX 8 CAPE TOWN 8000 SOUTH AFRICA
30 UNION ROAD MILNERTON 7441
TELEPHONE: +27 21 551 2650
TELEFAX: +27 21 551 2960

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(71) Anmelder (*für alle Bestimmungsstaaten mit Ausnahme von US*): **LTS LOHMANN THERAPIE-SYSTEME AG** [DE/DE]; Lohmannstrasse 2, 56626 Andernach (DE).

(72) Erfinder; und

(75) Erfinder/Anmelder (*nur für US*): **BRACHT, Stefan** [DE/DE]; Meisenweg 16, 07751 Cospeda (DE).

(74) Anwalt: **FLACCUS, Rolf-Dieter**; Bussardweg 10, 50389 Wesseling (DE).

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[Fortsetzung auf der nächsten Seite]

(54) Title: MEDICAL ACTIVE AGENT PATCH OPTICALLY LESS VISIBLE ON SKIN

(54) Bezeichnung: MEDIZINISCHE WIRKSTOFFPFLASTER MIT VERRINGERTER OPTISCHER AUFFÄLLIGKEIT AUF DER HAUT

(57) Abstract: The invention relates to a medical active agent patch consisting of a single-layer or multilayer matrix provided with at least one layer containing an active agent and one support layer connected thereto. Said patch is characterised in that it is transparent or at least translucent, when it is applied to the skin of a first person it has a brightness-colour value L_1 ranging between 50% and 200% of the brightness-colour value L_2, which is a brightness value of the surrounding cutaneous area of the same person and in that said patch fits to the skin of a second person or any other person in so far as L_2 of said persons ranges from 5° and 100°, in particular from 20° to 90°.

(57) Zusammenfassung: Ein medizinisches Wirkstoffpflaster, das eine ein- oder mehrschichtig aufgebaute Matrix mit mindestens einer wirkstoffhaltigen Schicht sowie eine mit dieser Matrix verbundene Rückschicht aufweist, ist dadurch gekennzeichnet, dass es transparent oder zumindest transluzent ist, und dass es im Zustand der Applikation auf der Haut einer ersten Person an einer mit dem Pflaster bedeckten Hautstelle einen Helligkeits-Farbwert L_1 aufweist, der nicht weniger als 50 % und nicht mehr als 200 % eines Helligkeits-Farbwertes L_2 beträgt, wobei L_2 der Helligkeitswert an der das applizierte Pflaster umgebenden Hautregion derselben Person ist, und dass dasselbe in Bezug auf die Haut einer zweiten oder einer jeden weiteren Person gilt, sofern L_2 bei allen genannten Personen im Bereich von 5° und 100°, insbesondere im Bereich von 20° und 90°, liegt.

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Medical active substance patch with reduced optical conspicuousness on the skin

The present invention relates to medical active substance patches, particularly to transdermal therapeutic systems, comprising a monolayer or multilayer, active substance-containing matrix and a backing layer connected with said matrix, said active substance patches being distinguished by an improved optical appearance when being worn on the skin.
The invention further encompasses processes enabling the production of such active substance patches.

Many of the active substances or auxiliary agents suitable for use in the manufacture of active substance patches or TTSs show a tendency to discolour, for example to yellow. Such adverse changes may also occur during the application period. It is known, for instance, that nicotine patches gradually turn yellow.

The aforementioned changes are in most cases due to oxidative decomposition processes which progress upon contact with atmospheric oxygen and moisture especially during storage of the active substance patch or when it is being worn on the skin and which are promoted by action of light. Particularly affected by such processes are pharmaceutical active substances, antioxidants, various enhancers (i.e. substances promoting or accelerating transdermal active substance absorption), as well as oxidation-sensitive components of the pressure-sensitive adhesive that is present in the active substance patch, such as resin adhesives, for example.

The extent of active substance decomposition does not necessarily have an adverse effect on the pharmaceutical quality of the products, for instance if the resulting decomposition products amount to only fractions of a weight percent of the starting composition and if these decomposition products are toxicologically acceptable. Thus, discolouration often already affects a product cosmetically whereas the pharmaceutical quality is still unimpaired. Frequently, users or patients especially in the case of medicaments associate such disadvantageous changes in the optical appearance of the active substance patches with defectiveness or deterioration, which causes a feeling of insecurity in those patients.
Often these changes are yellow, brown or red discolourations as typically appear in chemical decomposition. Even slight changes in colour may be interpreted by the users or patients as indicative of a deterioration of the quality of the medicament.

The problem of discolouration occurs particularly if the product, in fresh condition after manufacture, initially appears colourless or white to the human eye and the abovementioned discolouration occurs only after a certain period of storage or while the patch is being worn on the skin. This is perceived by the users to be even more critical and potentially dangerous than a discolouration which has been there from the start and only becomes more intense during storage.

In the field of medical active substance patches, transparent and colourless patches represent the ideal case in respect of cosmetics since the user himself or other persons regard them as inconspicuous when applied to the user's skin. Users of medicinal patches generally prefer patches

with such inconspicuous properties because they reduce the risk of other people becoming aware of the user's need for treatment and possibly finding out about his illness.

If for reasons of cosmetics a transparent design of an active substance patch does not make sense, for example because the ingredients are coloured or because of discolouration occurring during storage, it is possible to equip the patch with a non-transparent backing layer. During the application period this backing layer then prevents that the colour or discolouration is optically perceived.

In the latter case, it is disadvantageous, however, that patches or TTSs equipped with a nontransparent backing layer are much more conspicuous at the site of application, that is, on the patient's skin, than transparent or colourless patches. A measure known from the state of the art and frequently applied consists in applying a skin-coloured lacquer to the nontransparent backing layer. This, however, leads to a further problem since it proves extremely difficult to find a skin tone that in equal measure suits a larger number of users of different skin colour tone and is cosmetically acceptable. Taking into consideration all of the skin types of the world population, it is entirely impossible to determine a unitary, opaque skin colour tone that would be suitable as the colour tone for a non-transparent backing layer. This problem could be solved, it is true, by producing otherwise identical active substance patches having differently coloured backing layers that match the different skin colour tones of the world population, but this is out of the question because of the complex manufacturing and distribution logistics, and ultimately for reasons of cost.

The object of the present invention was therefore to provide active substance patches which despite colourations that are already existent or occurring over time ensure an optically inconspicuous appearance of the patch especially when the patch is located at the application site. The intention here is to preferably find a uniform solution which is suitable for the most different skin colour tones of the world population.
A further object of the invention was to indicate processes by means of which such active substance patches can be obtained.

These objects are achieved by means of medical active substance patches according to claim 1 and by means of processes of production according to claim 13, as well as by means of the embodiments described in the dependent claims.

Thus, the above-mentioned disadvantages do not occur or only occur in attenuated form in the medical active substance patches described in the introductory part of claim 1 if the active substance patch is transparent or at least translucent and if - in the state of having been applied to a person's skin - said patch, in an area of the skin covered with the patch, has a lightness colour value L_1 which is not less than 50% and not more than 200% of a lightness colour value L_2, L_2 being the lightness value of the region of the skin of the same person which surrounds the applied patch, and if the same is true in respect of the skin of a second or any other person, provided that L_2, for all the persons mentioned, is in a range from 5° to 100°, especially in a range from 20° to 90°. The aforementioned differences between the lightness values L_1, L_2 can be determined by measurements in representative spot checks of people of the respective skin type.

The colour value of the lightness L, designated as "lightness colour value" is a colorimetric characteristic value which, in conjunction with other characteristics, is used in engineering for the non-ambiguous characterisation of colours. The lightness colour value is indicated in degrees and can be determined by colour measuring instruments. The values of colour lightness indicated herein were determined by means of a "tristimulus colorimeter CP-320" of the firm of Techkon GmbH (DE-61462 Königstein).

Surprisingly, it emerged that active substance patches having the aforementioned features of the invention were of inconspicuous appearance at the place of application, i.e. on the skin, and that such active substance patches are optically inconspicuous on the most different skin colour types of the world population. For example, an active substance patch of the invention has an equally inconspicuous optical appearance when applied to the skin of a user of Caucasian, light skin colour or to the skin of a user of dark, Negroid skin colour. For this reason, according to a preferred embodiment an active substance patch of the invention is characterized in that the lightness colour value L_2 of the said first person, measured in the area of the skin not covered by the patch, is the lightness colour value of a person of light, Caucasian skin colour, and that the lightness colour value L_2 of the said second person is the lightness colour value of a person of dark, negroid skin colour, or vice versa.

The manufacture of active substance patches having the features of the introductory part of claim 1 and the substances suitable for said manufacture are in principle known to those skilled in the art. Substances which may be used to produce the matrix layer(s) are, for instance, from the group of the polyacrylates, poly(meth)acrylates, adhe-

sive resins, cellulose derivatives, polyisobutylenes, styrene-isoprene-styrene block copolymers, styrene-butadiene-styrene block copolymers, polydimethyl siloxane, ethylene vinyl acetate copolymers and vinyl acetate, optionally with addition of auxiliary substances known to the skilled artisan. At least one of the matrix layers contains an active substance, the term active substance referring, in particular, to a pharmaceutical active substance or a plurality of such substances.

The active substance patches of the invention, which are composed of a matrix and a superimposed backing layer, are substantially transparent or at least translucent (i.e. transmitting light but not transparent) and in any case not opaque. Thus, the backing layer is also substantially transparent or translucent.

Suitable as a backing layer are, first of all, polyesters, such as polyethylene terephthalate (PET) and polybutylene terephthalate, but also almost any other skin-compatible plastics, such as polyvinyl chloride, ethylene vinyl acetate, vinyl acetate, polyethylene, polypropylene, cellulose derivatives and many others.

According to a preferred embodiment, the active substance patches of the invention contain one or more substances from the group of the dyes and pigments in at least one of their layers. In combination with the transparent or translucent properties of the patch it is thereby achieved that a colouration of the matrix ingredient(s) which has been existing from the start or a discolouration of said ingredients which has begun and intensifies only after the patch has been manufactured is optically masked. At the same time, the colour is thereby sufficiently adapted to the skin tone of the application site so that the patch will be

inconspicuous on the most different skin colour types. Preferably the substance(s) used for optical masking, which are selected from the group of the dyes and pigments, are contained in the matrix layer or in at least one of the matrix layers of a multilayer patch.

According to a further, particularly preferred embodiment, optical masking is achieved by providing the transparent or translucent backing layer with a content of at least one substance selected from the group of the dyes and pigments. This can be accomplished, in particular, by coating the backing layer of the patch on its outer side, that is, on the side averted from the skin, with a coating or a lacquer which contains at least one dye or/and at least one pigment. This variant has the additional advantage that the dye(s) or pigment(s) cannot come into contact with the active substance-containing matrix.

It may further be of advantage for both the matrix layer(s) and the backing layer to contain a dye or dyes and/or a pigment or pigments.

It has, surprisingly, emerged that it is not so much the adaptation of the dyes or pigments to the respective skin tone which is decisive, rather this effect is essentially determined by the concentration(s) of the dyes or/and pigments utilised. The optical conspicuousness of an active substance patch is substantially determined by the concentrations of the dyes and pigments contained therein. In addition, the layer thickness of the patch must be taken into consideration in this connection. In order for the patch to be inconspicuous to the eye of a beholder, certain concentrations of the dyes or/and pigments (inclusive of the coloured or discoloured ingredients, in particular active sub-

stances) must not be exceeded. These concentrations can be determined by means of the conditions mentioned in claim 1.

At low concentrations of the coloured or discoloured ingredients comprised in the matrix, even such dyes or pigments can still be optically inconspicuous as clearly deviate from the colour tone of the underlying skin at the place of application. The same applies if the patch is of a small layer thickness. The low concentration and/or the small layer thickness results in a scope for the concentration or in corresponding possibilities of varying the layer thickness, thus fulfilling the requirements for optical masking of discolourations of ingredients of active substance patches by admixing dyes or/and pigments.

A further improvement of the optical appearance of active substance patches applied to the skin can be achieved, according to a particularly preferred embodiment, by providing at least that surface of the backing layer which is averted from the skin with reduced reflection properties. This can either be accomplished by means of physical methods or by applying an antireflection layer or antireflection coating. Such a layer or coating preferably contains an optical dulling agent or a combination of at least two dulling agents. This antireflection layer may at the same time contain a dye or dyes or/and a pigment or pigments to mask the ingredients of the patch, as described above.

In addition, it is possible by matting to eliminate or reduce that cause of optical conspicuousness of an active substance patch which is due to light reflection. Such light reflection frequently occurs in active substance patches which are provided with a transparent backing layer of smooth surface structure. The reflection properties of these backing layer materials differ greatly from the re-

flection properties of human skin, which is why such plasters are visually very conspicuous on the skin.

The active substance patches of the present invention are particularly advantageous if at least one layer of the matrix comprises one or more coloured ingredient(s). This may, in particular, be a substance or substances which is/are colourless in its/their initial state and which has/have a tendency to discolour or which discolour during storage or during the application period. Particularly preferred are active substance patches which contain one or more pharmaceutically active substances as coloured ingredients or as ingredients which have a tendency to discolour, with particular preference for nicotine.

Preferably, the active substance patches mentioned are transdermal therapeutic systems. These are distinguished by enabling a constant delivery of active substances via the skin for a determined period of time. The structure and manufacture of such systems are in principle known to those skilled in the art.

The invention further encompasses processes for the production of the above-described active substance patches. These processes comprise the following steps:

a) producing a system comprising a mono- or multilayer active substance-containing matrix and a backing layer connected therewith, wherein the matrix is produced by using (a) matrix polymer(s), (an) active substance(s) and auxiliary agents, and wherein one or more substance(s) selected from the group of the dyes and pigments is/are admixed to the matrix or/and the backing layer;

b) producing at least one further system according to step (a), this system being different in terms of the

concentration of the dyes or/and pigments, and/or in terms of the type of the dyes or/and pigments used;

c) producing surface sections or punched pieces from the systems obtained in steps (a) and (b);

d) producing or providing colour charts with lightness colour values L_2 in the range from 5° to 100°, particularly in the range from 20° to 90°,

e) applying or affixing the sections or systems obtained in step (c) to the colour charts mentioned in (d);

f) measuring the colour values of the lightness L_1 of the systems located on the colour charts and determining the difference between L_2 and L_1 in each particular case;

g) selecting those systems with a colour value of the lightness L_1 which is not less than 50% and not more than 200% of the lightness colour value L_2.

Through the teaching of the present invention it is made possible to produce active substance patches which despite containing coloured or discolouring ingredients are not easily perceivable to an observer and are optically inconspicuous when being worn on the skin, independently of whether the patch is attached to the skin of a light-skinned or dark-skinned person.

The invention will be illustrated in greater detail by means of the following examples.

Examples

1. Preparation of backing layers of different pigment concentrations

Coating compounds were prepared from ethyl cellulose and different portions of a pigment mixture (see Table 1) and

these compounds were coated by means of a doctor knife to a PET film of 15 µm thickness (weight per unit area 7-10 g/m²).

Table 1:

No.	Ethyl cellulose [%-wt.]	Pigment mixture [%-wt.]
1	99.75	0.25
2	99.5	0.5
3	99.0	1.0
4	98.0	2.0
5	96.0	4.0

Pigment mixture:

50.0%-wt. of Naturell BB Plv Pigment
50.0%-wt. of Naturell Pulver Pigment
(from Cosnaderm Chemische Rohstoffe GmbH, D-68526 Ladenburg)

Used as control examples were:

(6) PET film, aluminised und nicotine-resistant (nontranslucent)
(7) PET film, 15 µm, transparent
(8) Scotchpak 1006

2. Preparation of skin patches

Skin patches were produced using the backing layers prepared under 1. To this end, Durotak® 2052 (National Starch & Chemical B.V.) was spread at a weight per unit area of 80 g/m² and in each case covered with one of the backing lay-

ers mentioned under 1. Subsequently, individual patches, each patch of a size of 1 cm^2, were punched out.

3. Preparing colour charts corresponding to the human skin colours

By means of the software "PowerPoint" (Microsoft) and a colour printer (HP-C LaserJet 4500; Hewlett-Packard) eight colour charts were established representing the various skin colour tones of the world population.

The colour tones of the colour charts are characterized in "PowerPoint" by the six parameters colour tone, red, green, blue, saturation, intensity as listed below, and can be reproduced by means of these parameters:

Table 2:

Colour chart No.	Colour tone	Red	Green	Blue	Saturation	Intensity
A	16	255	215	191	255	223
B	21	50	25	0	255	25
C	21	80	40	0	255	40
D	21	255	236	217	255	236
E	21	197	137	77	130	137
F	21	72	36	0	255	36
G	21	117	78	39	128	78
H	25	255	226	183	255	219

The colour charts Nos. A-H were measured using a "tristimulus colorimeter CP-320" of the firm of Techkon GmbH (DE-61462 Königstein). The values (in degrees) for the lightness L, the red-green axis a, and the yellow-blue axis b

were determined. For each colour chart, 10 measurements were made and the mean values determined. The mean values are represented in the following Table 3.

Table 3:

Colour chart No.	L Value (L_2)	a Value	b Value
A	82.464	10.986	13.634
B	21.791	-3.203	8.877
C	25.776	5.905	14.758
D	88.086	4.945	9.572
E	50.596	10.893	36.304
F	25.811	3.747	12.968
G	32.562	5.519	21.015
H	83.228	6.712	24.95
Mean value*	51.289	5.688	17.758

* These are the respective mean values determined using the values of the 8 colour charts.

As can be seen, the colour value of the lightness L varies most, whereas the a value differs only slightly.

The range of the skin colours for which the principle of the present invention can be advantageously employed, according to the above-described "L,a,B" system particularly comprises the range of "5,8,60" up to "100,4,0".

4. Determining the differences in lightness value

The punched skin patches described under 2. were adhered to the colour charts described under 3. Subsequently, the lightness colour values L_1 of the affixed patches were determined using the measuring method described under 3. From the measurement values L_1 obtained, the difference to the lightness value L_2 of the respective background (i.e. the colour chart) was determined in each case. The percentage differences between the lightness colour values L_1 of the patch types (Nos. 1 to 5 and controls Nos. 6 to 8) affixed to the colour charts A to H on the one hand and the lightness values L_2 of the respective colour charts A to H on the other hand are represented in Table 4.

It is evident therefrom that on all the colour charts the transparent PET film (7) shows the smallest deviations in respect of the lightness value (positive control). Conversely, the largest deviations were found in the control examples (6) and (8).

5. Visual Evaluation

Since it is known that the colour perception of humans can deviate from the colorimetrically determined data, a visual assessment of the test patches affixed to the colour charts A to H, inclusive of the comparison examples 6 to 8, was carried out by test subjects.

To this end, a certain number (e.g. 10) of each of the test patches (1 to 8) was affixed to the colour charts A to H. These colour charts were presented to a group of test subjects under standardized conditions (lighting, distance, time for observing). The number of the patches that were not detected by the probands was used - after statistical

evaluation of the data - as a measure for the optical inconspicuousness and thereby the effectiveness of the optical masking of a patch.
In Figure 1 the individual test patches Nos. 1-8 are represented in the form of a bar chart in the order of their visual inconspicuousness (vertical axis). Patch No. 1 and control patch No. 7 were not perceivable or hardly perceivable on most of the colour charts.

Table 4

15 µm trsp. (No. 7)

	L
A	2.733
B	13.735
C	3.236
D	5.244
E	1.435
F	12.254
G	1.388
H	5.022

nontransparent PET film 15 µm, alum.

	L
A	1.42
B	273
C	215
D	7.89
E	60.3
F	215
G	150
H	2.65

Scotchpak 1006 (No. 8)

	L
A	2.903
B	267.078
C	210.289
D	9.157
E	58.254
F	209.79
G	144.61
H	4.059

0.25 % Pigment (No. 1)

	L
A	6.5
B	25.5
C	12.6
D	8.13
E	6.35
F	17.8
G	7.07
H	7.51

0.50 % Pigment (No. 2)

	L
A	6.978
B	22.133
C	7.294
D	5.325
E	4.577
F	17.144
G	4.53
H	3.189

1.00 % Pigment (No. 3)

	L
A	9.94
B	7.81
C	1.51
D	10.6
E	6.4
F	10.8
G	3.19
H	10.2

2.00 % Pigment (No. 4)

	L
A	14.387
B	1.647
C	4.058
D	8.295
E	33.528
F	1.794
G	2.709
H	13.731

4.00 % Pigment (No. 5)

	L
A	9.29
B	54.5
C	19.2
D	21.6
E	4.53
F	28.4
G	17.9
H	20

CLAIMS

1. Medical active substance patch comprising a matrix of monolayer or multilayer configuration as well as a backing layer connected with said matrix, wherein at least one layer of the matrix contains active substance, and wherein said active substance patch is characterized in that

- it is transparent or at least translucent, and
- in the state of having been applied to a first person's skin the said patch, at a place of the skin covered with the patch, has a lightness colour value L_1 which is not less than 50% and not more than 200% of a lightness colour value L_2, with L_2 being the lightness value of the region of the skin of the same person which surrounds the applied patch, and
- that the same applies in respect of the skin of a second or any other person, provided that L_2 is in the range from 5° to 100°, especially in the range from 20° to 90°.

2. Active substance patch according to claim 1, characterized in that the lightness colour value L_2 of the said first person is the lightness colour value of a person of light, Caucasian skin colour, and that the lightness colour value L_2 of the said second person is the lightness colour value of a person of dark, Negroid skin colour, or vice versa.

3. Active substance patch according to claim 1 or 2, characterized in that it contains one or more substances selected from the group of the dyes and pigments in at least one of the layers mentioned, preferably in the matrix layer or in at least one of the matrix layers.

4. Active substance patch according to any one of the preceding claims, characterized in that on the side averted from the skin the backing layer of the patch is covered with a coating, in particular a lacquer, containing a dye or dyes or/and a pigment or pigments.

5. Active substance patch according to any one of the preceding claims, characterized in that at least that surface of the backing layer which is averted from the skin has reduced reflection properties.

6. Active substance patch according to claim 5, characterized in that the reduction in reflection properties is accomplished by means of physical methods.

7. Active substance patch according to any one of the preceding claims, characterized in that on the side of the backing layer which is averted from the skin there is applied an antireflection layer which preferably contains an optical dulling agent or a combination of at least two optical dulling agents.

8. Active substance patch according to claim 7, characterized in that said antireflection layer additionally contains at least one substance selected from the group of the dyes and pigments.

9. Active substance patch according to any one of the preceding claims, characterized in that at least one layer of the matrix comprises one or more coloured ingredient(s).

10. Active substance patch according to any one of the preceding claims, characterized in that at least one layer of the matrix contains one or more ingredient(s) which is/are colourless in its/their initial state and which

has/have a tendency to discolour or which discolour during storage or during the application period.

11. Active substance patch according to claim 10, characterized in that the said ingredient is a pharmaceutical active substance, particularly nicotine.

12. Active substance patch according to any one of the preceding claims, characterized in that it is a transdermal therapeutic system.

13. Process for the production of an active substance patch according to any one of the preceding claims, characterized in that said process comprises the following steps:

a) producing a system comprising a mono- or multilayer active substance-containing matrix and a backing layer connected therewith, wherein the matrix is produced using a matrix polymer or matrix polymers, an active substance or active substances and auxiliary agents, and wherein one or more substance(s) selected from the group of the dyes and pigments is/are incorporated into the matrix or/and the backing layer;

b) producing at least one further system according to step (a), this system being different in terms of the concentration of the dyes or/and pigments, and/or in terms of the type of the dyes or/and pigments used;

c) producing surface sections or punched pieces from the systems obtained in steps (a) and (b);

d) producing or providing colour charts having lightness colour values L_2 in the range from 5° to 100°, particularly in the range from 20° to 90°,

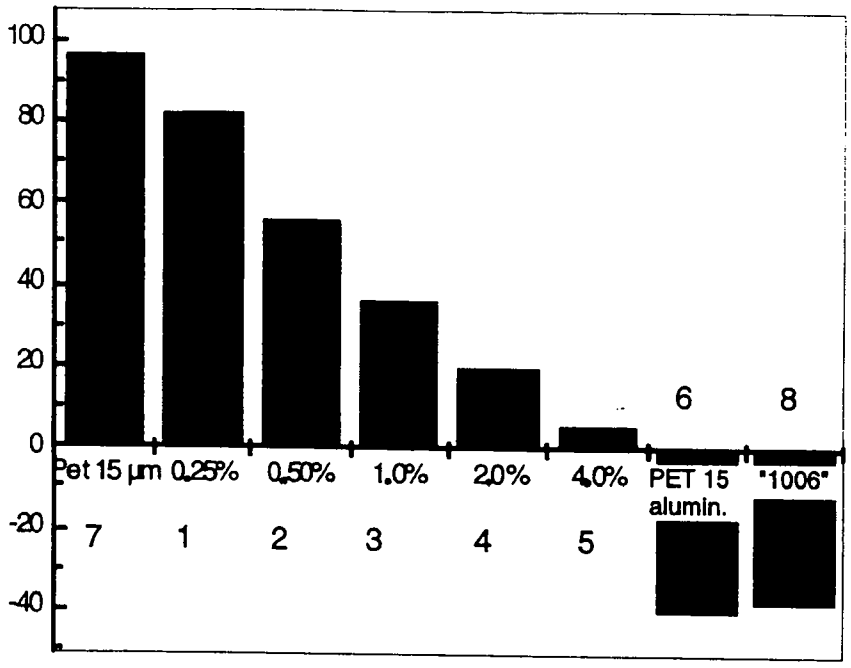
e) applying or affixing the sections or systems obtained in step (c) to the colour charts mentioned in (d);

f) measuring the colour values of the lightness L_1 of the systems located on the colour charts and determining

the difference between L_2 and L_1 in each particular case;

g) selecting those systems with a colour value of the lightness L_1 which is not less than 50% and not more than 200% of the lightness colour value L_2.

FIG. 1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0.50%
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