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ANTI-INFLAMMATORY ANALGESIC PLASTER

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(57) Claim

1. An antiphlogistic analgesic plaster which comprises as essential ingredients:

(a) at least one nonsteroidal antiphlogistic analgesic drug selected from the group consisting of ketoprofen, flurbiprofen, loxoprofen, ketorolac and ester derivatives or salts thereof,

(b) a solubilizer comprising a combination of a rosin ester derivative with ℓ-menthol,

(c) a styrene/isoprene/styrene block copolymer employed as a base polymer,

(d) a softener, and

(e) a backing comprising a polyester cloth,

the nonsteroidal antiphlogistic analgesic drug, rosin ester derivative, ℓ-menthol, styrene/isoprene/styrene block copolymer and softener are present in respective mixing ratios by weight of

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from 0.5 to 10.0%, from 5.0 to 70.0%, from 0.5 to 15.0%, from 5.0 to 40.0% and from 10.0 to 75.0% in this order, the amounts of all said ingredients totalling 100% by weight,

the nonsteroidal antiphlogistic analgesic drug, rosin ester derivative and ℓ-menthol are present in a mixing ratio of 1.0 : 3.0 - 11.0 : 1.0 - 4.0.

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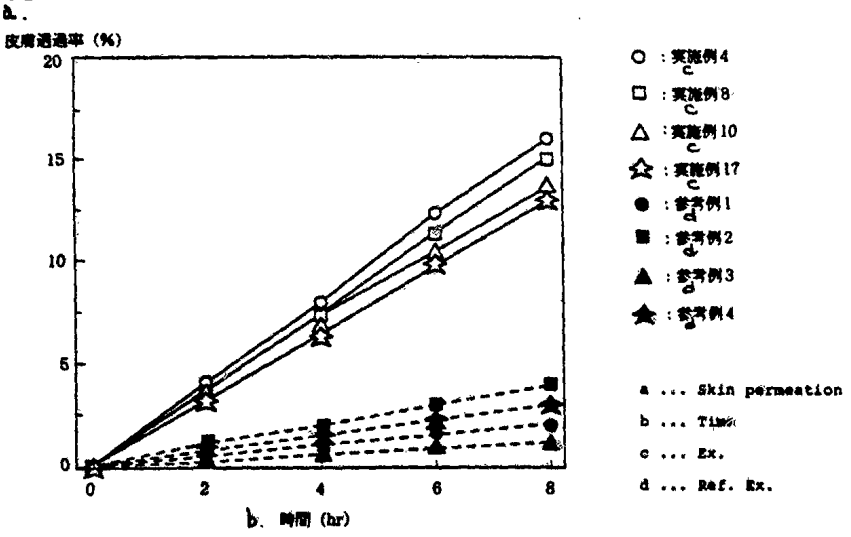


(57) Abstract

An anti-inflammatory analgesic plaster containing the following components as the essential ingredients: (a) a nonsteroidal anti-inflammatory analgesic comprising at least one member selected from the group consisting of ketoprofen, flurbiprofen, loxoprofen, ketorolac, and ester derivatives and salts thereof; (b) a solvent comprising both of a rosin ester derivative and *l*-methol; (c) a styrene/isoprene/styrene block copolymer as the base polymer; (d) an emollient; and (e) a support made of polyester fabric.

(57) 要約

1．下記の成分

(a) ケトプロフェン、フルルビプロフェン、ロキソプロフェン、ケトロラク、およびそのエステル誘導体または塩より選ばれる少なくとも一種である非ステロイド消炎鎮痛薬、

(b) ロジンエステル誘導体およびl－メントールを併用してなる溶解剤、

(c) ベースポリマーとしてスチレン－イソプレン－スチレンブロック共重合体、

(d) 軟化剤、

(e) ポリエステル布よりなる支持体、

を必須成分とする消炎鎮痛貼付剤。

SPECIFICATION

ANTIPHLOGISTIC ANALGESIC PLASTER

[Technical Field]

This invention relates to a novel antiphlogistic analgesic plaster for therapeutic use which contains at least one nonsteroidal antiphlogistic analgesic drug selected from among ketoprofen, flurbiprofen, loxoprofen, ketorolac and esters or salts thereof and a rosin ester derivative and ℓ-menthol employed as a solvent and has a polyester cloth employed as a backing.

[Background Art]

Attempts have been widely made to apply so-called tapes comprising a nonsteroidal antiphlogistic (or anti-inflammatory) analgesic drug contained in an oily pressure-sensitive adhesive to therapeutic uses. For example, Japanese Patent Laid-Open Gazette No. 227819/1984 has disclosed an attempt to administer a nonsteroidal antiphlogistic analgesic drug which is contained in an acrylic pressure-sensitive adhesive located on a composite backing consisting of a nonwoven fabric and a film. Further, Japanese Patent Laid-Open Gazette No.139615/1985 has disclosed an attempt to administer ketoprofen which is contained in a pressure-sensitive adhesive comprising polyisobutylene/paraffin/rosin-modified glycerol ester, to allow the ketoprofen to be percutaneously

absorbed. Japanese Patent Laid-Open Gazette No. 227524/1988 has disclosed an attempt to administer flurbiprofen together with an oily base. Furthermore, Japanese Patent Laid-Open No. 40420/1989 has disclosed an attempt to administer, together with an oily base, a nonsteroidal antiphlogistic analgesic drug having a carboxyl group.

However, none of these attempts are satisfactory in drug-release characteristics or percutaneous absorption characteristics. It is therefore urgently required to develop a preparation having more excellent.

It is an object of the present invention to provide an antiphlogistic analgesic plaster having characteristics remarkably improved in the following points:

(1) improvement in percutaneous absorption (improvements in the solubility and releasability of a nonsteroidal antiphlogistic analgesic drug in a base),

(2) improvement in drug-releasability (selection of a backing adsorbing no nonsteroidal antiphlogistic analgesic drug),

(3) relief from side effects including skin rash caused by repeated plastering (utilization of a safe base and search for not adhesion but stickiness

through the establishment of an appropriate compositional ratio of the base), and

(4) convenient usability in the remedial field (impartment of such strechability as to enable the stickiness to a flexional part).

[Disclosure of the Invention]

In order to achieve the above-mentioned object, the present inventors have conducted extensive studies on ketoprofen, flurbiprofen, loxoprofen and ketorolac, which are nonsteroidal antiphlogistic analgesic drugs involved in the category of carboxylic acid, and ester derivatives or salts thereof. As a result of their studies, they have successfully completed the development of an antiphlogistic analgesic plaster according to present invention which is characterized by comprising the following ingredients (a) to (e) as essential ingredients. Accordingly, the antiphlogistic analgesic plaster of this invention comprises as essential ingredients:

(a) at least one nonsteroidal antiphlogistic analgesic drug selected from among ketoprofen, flurbiprofen, loxoprofen, ketorolac and ester derivatives or salts thereof;

(b) a solubilizer comprising a combination of a rosin ester derivative with ℓ-menthol;

(c) a styrene/isoprene/styrene block copolymer employed as a base polymer;

(d) a softener; and

(e) a backing comprising a polyester cloth.

As the backing to be used in the present invention, polyester clothes exerting no effect on the release of the nonsteroidal antiphlogistic analgesic drug are selected. Among others, a cloth made from PET (polyethylene terephthalate) or PBT (polybutylene terephthalate) is preferable. In order to achieve excellent release of the nonsteroidal antiphlogistic analgesic drug, it is essentially required that the backing undergoes no interaction with the nonsteroidal antiphlogistic analgesic drug, namely, never adsorbs the drug. As the result of the examination of backings of various compositions, the present inventors have found out that PET or PBT is the most suitable polymer composition for the backing. By using a backing comprising PET or PBT, excellent release can be achieved without causing any adsorption of the drug on the backing.

The antiphlogistic analgesic plaster of the present invention is endowed with such a strechability having an average stress of 0.3 kg/cm or below when it is 50% elongated in the longitudinal or lateral direction as to enable the antiphlogistic analgesic plaster to be applied even to a flexional part. This strechability makes it possible not only to conveniently use the antiphlogistic analgesic plaster

of the present invention but also to reduce the friction and oppression at the time of application of the plaster owing to the fact that the plaster follows the movement of the skin to thereby reduce a side effect (a skin rash).

The present invention is particularly characterized by finding that when compounded with ℓ-menthol in a specified ratio, a rosin ester derivative which has been known as a tackiness-providing resin to those skilled in the art, will serve as a solubilizar for the nonsteroidal antiphlogistic analgesic drug. It has been further found that the rosin ester derivative so compounded will greatly improve the release of the nonsteroidal antiphlogistic analgesic drug. In order to satisfactorily dissolve the nonsteroidal antiphlogistic analgesic drug and release the same, it is preferable that the nonsteroidal antiphlogistic analgesic drug, rosin ester derivative and ℓ-menthol be mixed together in ratio by weight of 1.0 : 3.0 - 11.0 : 1.0 - 4.0. Within the range of said ratios, the nonsteroidal antiphlogistic analgesic drug will exhibit satisfactory solubility and releasability.

The rosin ester derivative as used herein refers to those obtained by esterifying various rosins followed by the hydrogenation or purification of the same so esterified. Depending on the type of the

ester, methyl esters, glycerol esters, pentaerythritol esters, etc., may be cited. Particular examples thereof include Ester Gums A, AA-G, H and HP (tradenames, mfd. by Arakawa Kagaku K.K.), Hariesters L, S and P (tradenames, mfd. by Harima Chemicals, Inc.), Superester A-75 (tradename, mfd. by Arakawa Kagaku, K.K.), KE-311 (tradename, mfd. by Arakawa Kagaku K.K.), Hercolyn D (tradename, mfd. by Hercules) and Forals 85 and 105 (tradenames, mfd. by Hercules).

Next, the base polymer of the present invention may be appropriately selected from among known ones in view of its safety for the skin, drug-releasability and stickiness to the skin. In view of the releasability of the nonsteroidal antiphlogistic analgesic drug, it is particularly preferable to use a styrene/isoprene/styrene block copolymer having low polarity as the base polymer. Particular examples of said block copolymer include Cariflexes TR-1107, TR-1111, TR-1112 and TR-1117 (tradenames, mfd. by Shell Chemical) and Solprene 428 (tradename, mfd. by Phillips Petroleum). A styrene/isoprene/styrene block copolymer is used in the present invention as a base polymer as described above, and, furthermore, other polymers such as polyisobutylene may be used together with it.

A softener is a substance which plasticizes and softens the styrene/isoprene/styrene block

copolymer employed as a base polymer to thereby contribute to the maintenance of a suitable stickiness of the block copolymer to the skin. The softener includes almond oil, olive oil, camellia oil, persic oil, peanut oil, olefinic acids or liquid paraffin. The softener is preferably used in a mixing ratio of from 150 to 350 parts by weight per 100 parts by weight of the styrene/isoprene/styrene block copolymer.

Although the content of the nonsteroidal antiphlogistic analgesic drug in the plaster is not particularly restricted, it preferably ranges from 100 to 430 $\mu g/cm^2$ from the viewpoints of the release and usability of the drug in such an amount as to effectively contribute to the treatment and the bioavailability.

In the plaster preparation as a whole, the nonsteroidal antiphlogistic analgesic drug, the rosin ester derivative, ℓ-menthol, the styrene/isoprene/styrene block copolymer and the softener may be preferably used each in such an amount as specified below:

nonsteroidal antiphlogistic analgesic drug	0.5-10.0% by weight
rosin ester derivative	5.0-70.0% by weight
ℓ-menthol	0.5-15.0% by weight
styrene/isoprene/styrene block copolymer	5.0-40.0% by weight

softener 10.0-75.0% by weight

It is needless to say that the antiphlogistic analgesic plaster according to the present invention may contain additional ingredients such as inorganic fillers, antioxidants, UV absorbers, antihistamines, antibacterial agents and perfumes which have been publicly known in the art without any restriction, if required.

The antiphlogistic analgesic plaster of the present invention can be easily produced by a conventional method. For example, the styrene/isoprene/styrene block copolymer is heated and mixed with the softener and the rosin ester derivative in a mixing device such as a kneader or a mixer at a temperature of 120 to 160°C to obtain a mixture. Then the nonsteroidal antiphlogistic analgesic drug and ℓ-menthol are added to the mixture and mixed to obtain a preparation. Next, the obtained preparation is directly applied onto a polyester cloth or a nonwoven fabric. Alternatively, the preparation is temporarily spread on a paper or film previously subjected to a mold-release treatment, covered with a desired backing and then pressed to effect the transfer of the spread preparation onto the backing.

As will be described in the Examples and Test Examples hereinafter, the antiphlogistic analgesic plaster of the present invention thus obtained is

surely an ideal one having the following properties and being highly useful in the industrial field:

(1) improved percutaneous absorptivity,

(2) improved drug-releasability,

(3) reduction in side effects including skin rash caused by repeated plastering, and

(4) convenient use in the field of remedy (impartment of such a strechability as to enable the plaster to stick to a flexional part).

[Brief Description of the Drawing]

Fig. 1 is a graph which shows the results of a skin penetration test on hairless mice.

[Best Mode for Carrying out the Invention]

To further illustrate the present invention in greater detail, the following Examples, Test Examples, etc., will be given. In these Examples, Comparative Examples and Referential Examples, all parts are by weight unless otherwise specified.

Example 1

styrene/isoprene/styrene block copolymer (tradename: Cariflex TR-1107)	25.0 parts
liquid paraffin	68.0 parts
rosin ester derivative (tradename: Ester Gum AA-G)	5.0 parts
ℓ-menthol	1.5 parts
ketoprofen	0.5 parts

In accordance with this formulation, a plaster was produced by the above-mentioned method. Namely, the styrene/isoprene/styrene block copolymer was heated and mixed with the softener and the rosin ester derivative in a kneader employed as a mixing device at a temperature of 120 to 160°C to obtain a mixture. Subsequently, the nonsteroidal antiphlogistic analgesic drug (ketoprofen) and ℓ-menthol were added to the thus obtained mixture and mixed to obtain a preparation. The obtained preparation was spread directly on a polyester cloth (PET) and then cut into pieces of a desired size.

Example 2

styrene/isoprene/styrene block copolymer (tradename: Cariflex TR-1107)	20.0 parts
liquid paraffin	43.5 parts
butylhydroxytoluene	2.0 parts
rosin ester derivative (tradename: KE-311)	28.5 parts
ℓ-menthol	3.0 parts
ketoprofen	3.0 parts

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 3

styrene/isoprene/styrene block copolymer (tradename: Cariflex TR-1107)	21.0 parts

liquid paraffin	63.0 parts
butylhydroxytoluene	2.0 parts
rosin ester derivative	
(tradename: KE-311)	8.0 parts
ℓ-menthol	4.0 parts
ketoprofen	2.0 parts

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 4

styrene/isoprene/styrene block copolymer	
(tradename: Cariflex TR-1111)	30.0 parts
liquid paraffin	57.0 parts
butylhydroxytoluene	2.0 parts
rosin ester derivative	
(tradename: Ester Gum H)	7.0 parts
ℓ-menthol	3.0 parts
ketoprofen	1.0 part.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 5

Styrene/isoprene/styrene block copolymer	
(tradename: Cariflex TR-1111)	15.0 parts
polyisobutylene (mfd. by Exxon Co.)	5.0 parts
liquid paraffin	23.0 parts
butylhydroxytoluene	2.0 parts

rosin ester derivative

(tradename: Ester Gum H) 40.0 parts

ℓ-menthol 10.0 parts

ketoprofen 5.0 parts.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 6

Styrene/isoprene/styrene block copolymer

(tradename: Cariflex TR-1112) 18.0 parts

liquid paraffin 54.5 parts

butylhydroxytoluene 2.0 parts

rosin ester derivative

(tradename: Foral 105) 16.5 parts

ℓ-menthol 6.0 parts

ketoprofen ethyl ester 3.0 parts.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 7

Styrene/isoprene/styrene block copolymer

(tradename: Solprene 418) 28.0 parts

polybutene 5.0 parts

liquid paraffin 57.7 parts

butylhydroxytoluene 2.0 parts

rosin ester derivative

(tradename: KE-311) 5.0 parts

ℓ-menthol	1.8 parts
flurbiprofen	0.5 parts.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 8

Styrene/isoprene/styrene block copolymer (tradename: Cariflex TR-1107)	21.0 parts
liquid paraffin	66.8 parts
butylhydroxytoluene	2.0 parts
rosin ester derivative (tradename: KE-311)	8.0 parts
ℓ-menthol	1.2 parts
flurbiprofen	1.0 part.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 9

Styrene/isoprene/styrene block copolymer (tradename: Cariflex TR-1107)	11.0 parts
Styrene/isoprene/styrene block copolymer (tradename: Cariflex TR-1111)	11.0 parts
liquid paraffin	44.0 parts
butylhydroxytoluene	2.0 parts
rosin ester derivative (tradename: Ester Gum AA-G)	20.0 parts
ℓ-menthol	7.0 parts

flurbiprofen 5.0 parts.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 10

Styrene/isoprene/styrene block copolymer

(tradename: Cariflex TR-1107) 30.0 parts

liquid paraffin 56.0 parts

butylhydroxytoluene 2.0 parts

rosin ester derivative

(tradename: KE-311) 8.0 parts

ℓ-menthol 3.0 parts

loxoprofen 1.0 part.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 11

Styrene/isoprene/styrene block copolymer

(tradename: Cariflex TR-1111) 12.0 parts

liquid paraffin 26.0 parts

butylhydroxytoluene 2.0 parts

rosin ester derivative

(tradename: Ester Gum H) 40.0 parts

ℓ-menthol 12.0 parts

loxoprofen 8.0 parts.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 12

Styrene/isoprene/styrene block copolymer (tradename: Cariflex TR-1112)	21.0 parts
liquid paraffin	50.0 parts
butylhydroxytoluene	2.0 parts
rosin ester derivative (tradename: Ester Gum H)	20.5 parts
ℓ-menthol	3.5 parts
loxoprofen	3.0 parts.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 13

Styrene/isoprene/styrene block copolymer (tradename: Cariflex TR-1111)	5.0 parts
liquid paraffin	11.0 parts
butylhydroxytoluene	2.0 parts
rosin ester derivative (tradename: KE-311)	65.0 parts
ℓ-menthol	10.0 parts
loxoprofen sodium	7.0 parts.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 14

Styrene/isoprene/styrene block copolymer

(tradename: Cariflex TR-1107)	20.0 parts
liquid paraffin	45.0 parts
butylhydroxytoluene	2.0 parts
rosin ester derivative	
(tradename: Ester Gum H)	21.0 parts
ℓ-menthol	9.0 parts
loxoprofen sodium	3.0 parts.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 15

Styrene/isoprene/styrene block copolymer

(tradename: Cariflex TR-1107)	22.0 parts
polyisobutylene (mfd. by Exxon Co.)	5.0 parts
liquid paraffin	52.0 parts
butylhydroxytoluene	2.0 parts
rosin ester derivative	
(tradename: Hercolyn D)	10.0 parts
ℓ-menthol	7.0 parts
loxoprofen	2.0 parts.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 16

Styrene/isoprene/styrene block copolymer

(tradename: Cariflex TR-1107)	20.0 parts
liquid paraffin	38.0 parts
butylhydroxytoluene	2.0 parts
rosin ester derivative	
(tradename: KE-311)	28.0 parts
ℓ-menthol	8.0 parts
ketorolac	4.0 parts.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 17

Styrene/isoprene/styrene block copolymer

(tradename: Cariflex TR-1107)	28.0 parts
liquid paraffin	57.5 parts
butylhydroxytoluene	2.0 parts
rosin ester derivative	
(tradename: Ester Gum H)	9.0 parts
ℓ-menthol	2.5 parts
ketorolac	1.0 part.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 18

Styrene/isoprene/styrene block copolymer

(tradename: Cariflex TR-1112)	21.0 parts
liquid paraffin	59.0 parts
butylhydroxytoluene	2.0 parts

rosin ester derivative

(tradename: Ester Gum H) 10.0 parts

Ω-menthol 6.0 parts

ketorolac tromethamine 2.0 parts.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 19

Styrene/isoprene/styrene block copolymer

(tradename: Cariflex TR-1111) 33.0 parts

liquid paraffin 58.0 parts

butylhydroxytoluene 2.0 parts

rosin ester derivative

(tradename: Foral 105) 5.0 parts

Ω-menthol 1.5 parts

ketorolac 0.5 parts.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 20

Styrene/isoprene/styrene block copolymer

(tradename: Cariflex TR-1111) 20.0 parts

polyisobutylene (mfd. by Exxon Co.) 5.0 parts

liquid paraffin 58.0 parts

butylhydroxytoluene 2.0 parts

rosin ester derivative

(tradename: KE-311) 10.0 parts

ℓ-menthol	3.0 parts
ketoprofen	2.0 parts.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 21

Styrene/isoprene/styrene block copolymer (tradename: Cariflex TR-1111)	15.0 parts
polyisobutylene (mfd. by Exxon Co.)	14.0 parts
liquid paraffin	36.0 parts
butylhydroxytoluene	2.0 parts
rosin ester derivative (tradename: KE-311)	25.0 parts
ℓ-menthol	5.0 parts
ketoprofen	3.0 parts.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 22

Styrene/isoprene/styrene block copolymer (tradename: Cariflex TR-1111)	22.0 parts
polyisobutylene (mfd. by Exxon Co.)	8.0 parts
liquid paraffin	50.0 parts
butylhydroxytoluene	1.0 part
rosin ester derivative (tradename: KE-311)	14.0 parts
ℓ-menthol	3.0 parts

ketorolac	2.0 parts.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Example 23

Styrene/isoprene/styrene block copolymer (tradename: Cariflex TR-1111)	15.0 parts
polyisobutylene (mfd. by Exxon Co.)	12.0 parts
liquid paraffin	25.0 parts
butylhydroxytoluene	2.0 parts
rosin ester derivative (tradename: KE-311)	38.0 parts
ℓ-menthol	4.0 parts
ketorolac	4.0 parts.

In accordance with this formulation, a plaster was produced by the same method as described in the above Example 1.

Comparative Example 1

A plaster was produced by using the same composition and the same production method as described in the above Example 4 except that no rosin ester derivative (Ester Gum H) was added.

Comparative Example 2

A plaster was produced by using the same composition and production method as described in the above Example 4 except that no ℓ-menthol was added.

Comparative Example 3

A plaster was produced by using the same composition and production method as described in the above Example 8 except that no rosin ester derivative (KE-311) was added.

Comparative Example 4

A plaster was produced by using the same composition and production method as described in the above Example 8 except that no ℓ-menthol was added.

Comparative Example 5

A plaster was produced by using the same composition and production method as described in the above Example 10 except that no rosin ester derivative (KE-311) was added.

Comparative Example 6

A plaster was produced by using the same composition and production method as described in the above Example 10 except that no ℓ-menthol was added.

Comparative Example 7

A plaster was produced by using the same composition and production method as described in the above Example 17 except that no rosin ester derivative (Ester Gum H) was added.

Comparative Example 8

A plaster was produced by using the same composition and production method as described in the above Example 17 except that no ℓ-menthol was added.

Comparative Example 9

A plaster was produced by using the same composition and production method as described in the above Example 4 except that the polyester cloth (PET cloth) employed as the backing was replaced by a polyurethane cloth.

Comparative Example 10

A plaster was produced by using the same composition and production method as described in the above Example 8 except that the polyester cloth (PET cloth) employed as the backing was replaced by a polyurethane cloth.

Comparative Example 11

A plaster was produced by using the same composition and production method as described in the above Example 10 except that the polyester cloth (PET cloth) employed as the backing was replaced by a polyurethane cloth.

Comparative Example 12

A plaster was produced by using the same composition and production method as described in the above Example 17 except that the polyester cloth (PET cloth) employed as the backing was replaced by a polyurethane cloth.

Comparative Example 13

A plaster was produced by using the same composition and production method as described in the above Example 4 except that the polyester cloth (PET

cloth) employed as the backing was replaced by a PVC film.

Comparative Example 14

A plaster was produced by using the same composition and production method as described in the above Example 8 except that the polyester cloth (PET cloth) employed as the backing was replaced by a PVC film.

Comparative Example 15

A plaster was produced by using the same composition and production method as described in the above Example 10 except that the polyester cloth (PET cloth) employed as the backing was replaced by a PCV film.

Comparative Example 16

A plaster was produced by using the same composition and production method as described in the above Example 17 except that the polyester cloth (PET cloth) employed as the backing was replaced by a PCV film.

Referential Example 1

96 parts of an acrylic pressure-sensitive adhesive Nissetsu PE-300 (tradename, mfd. by Nippon Carbide Industries Co., Ltd.) were mixed with 4 parts of ketoprofen. The resulting mixture was spread on a polyester film which had been subjected to a mold-release treatment and then a polyester cloth was

pressed onto the spread mixture to effect transfer of the mixture, after which the product obtained was cut into pieces of a desired size to thereby give plasters.

Referential Example 2

A plaster was produced by using the same composition and production method as described in the above Referential Example 1 except that the ketoprofen was replaced by flurbiprofen.

Referential Example 3

A plaster was produced by using the same composition and production method as described in the above Referential Example 1 except that the ketoprofen was replaced by loxoprofen.

Referential Example 4

A plaster was produced by using the same composition and production method as described in the above Referential Example 1 except that the ketoprofen was replaced by ketorolac.

Test Example 1 (Dissolution-stability test)

Using the plasters of Examples 4, 8, 10 and 17 and Comparative Examples 1 to 8, a stability test was effected by storing said plasters for one month at 5°C. Table 1 summarizes the results.

TABLE 1

Ex. No.	5°C, 1 month	Conditions after the test
Ex. 4	○	no change
Ex. 8	○	do.
Ex. 10	○	do.
Ex. 17	○	do.
Comp. Ex. 1	×	crystallization
Comp. Ex. 2	×	do.
Comp. Ex. 3	×	do.
Comp. Ex. 4	×	do.
Comp. Ex. 5	×	do.
Comp. Ex. 6	×	do.
Comp. Ex. 7	×	do.
Comp. Ex. 8	×	do.

Test Example 2 (Drug-release test 1)

Using the plasters of Examples 4, 8, 10 and 17 and Comparative Examples 1 to 8, a test on the release of the drug into water was effected to determine the ratio of drug release from each plaster. Table 2 summarizes the results.

TABLE 2

Ex. No.	Drug release ratio after 4 hrs. (%)
Ex. 4	53.10±2.89
Ex. 8	46.77±3.14
Ex. 10	48.82±2.55
Ex. 17	40.92±3.66
Comp. Ex. 1	21.60±1.07
Comp. Ex. 2	27.72±2.32
Comp. Ex. 3	24.13±1.98
Comp. Ex. 4	26.95±1.91
Comp. Ex. 5	19.97±1.84
Comp. Ex. 6	25.98±2.83
Comp. Ex. 7	20.12±2.80
Comp. Ex. 8	19.92±2.66

The results given in the above Tables 1 and 2 clearly reveal that the combined use of a rosin ester derivative with ℓ-menthol is essential for the preparation of the plasters of the present invention.

Test Example 3 (Drug-release test 2)

Using the plasters of Comparative Examples 9 to 12, a test on the release of the drug into water was effected in the same manner as the one employed in the above Test Example 2 to determine the ratio of the drug release from each plaster. Table 3 summarizes the results. For comparison, the data for the

plasters of Examples 4, 8, 10 and 17 obtained in Test Example 2 are also listed.

TABLE 3

Ex. No.	Drug release ratio after 4 hrs. (%)
Ex. 4	53.10±2.89
Ex. 8	46.77±3.14
Ex. 10	48.82±2.55
Ex. 17	40.92±3.66
Comp. Ex. 9	15.21±2.00
Comp. Ex. 10	13.19±0.98
Comp. Ex. 11	13.57±1.69
Comp. Ex. 12	19.26±2.94

The results given in the above Table 3 clearly reveal that the drug releasability is obviously improved when a polyester cloth (PET cloth) is used as the backing. When a PBT cloth is used as the polyester cloth, similar results are obtained.

Test Example 4 (Skin penetration test on hairless mice)

Using the plasters of Examples 4, 8, 10 and 17 and Referential Examples 1 to 4, a skin penetration test on hairless mice was effected. Fig. 1 shows the results.

As Fig. 1 shows, the plasters of Examples 4, 8, 10 and 17 are obviously superior to those of Referential Examples 1 to 4 in drug release ratio and bioavailability (skin penetration ratio).

Test Example 5 (Sticking test)

The plasters of Example 4 and Comparative Example 13 were stuck to the elbows of 30 healthy male human subjects for 8 hours. Table 4 shows the results.

TABLE 4

Ex. No.	Stickiness	Fitness feeling
Ex. 4	○	○
Comp. Ex. 13	×	×

○: good, ×: poor,

Also, the plasters of Examples 8, 10 and 17 and Comparative Examples 14 to 16 were tested in the same manner as above. Consequently, the results achieved by using the plasters of Examples 8, 10 and 17 were almost the same as that of Example 4, while the results of the plasters of Comparative Examples 14 to 16 were also the same as that of Comparative Example 13.

Test Example 6 (Skin safety test)

The plasters of Examples 2 and 4, Comparative Example 10 and Referential Example 1 and an adhesive

plaster of The Pharmacopoeia of Japan were stuck to the upper dorsal parts of 30 healthy male human subjects for 8 hours per day for 7 days. Table 5 summarizes the results. The post-test conditions were evaluated according to the following criteria:

±: slight rubefaction,

+: obvious rubefaction,

++: severe rash.

TABLE 5

Ex. No.	No. of subjects ++	+	±	Positive ratio (%) + or above	± or above
Ex. 2	0	0	1	0	3.3
Ex. 4	0	0	2	0	6.7
Comp. Ex. 10	0	2	3	6.7	16.7
Ref. Ex. 1	1	3	6	13.3	33.3
Adhesive plaster of JP	2	4	6	20.0	40.0

As the results given in the above Tables 4 and 5 clearly show that the antiphlogistic analgesic plaster of the present invention is a product which is excellent in convenient use thereof and has a high safety.

[Industrial Applicability]

As described above, the solubility and release characteristics of a nonsteroidal

antiphlogistic analgesic drug are enhanced by the practice of the present invention, thereby to make it possible to achieve a high drug efficacy and furthermore to remarkably relieve skin rash. Thus, the antiphlogistic analgesic plaster of the present invention is one which can also be conveniently used and is highly useful in the industrial field.

ANNEX

CLAIMS

1. An antiphlogistic analgesic plaster which comprises as essential ingredients:

(a) at least one nonsteroidal antiphlogistic analgesic drug selected from the group consisting of ketoprofen, flurbiprofen, loxoprofen, ketorolac and ester derivatives or salts thereof,

(b) a solubilizer comprising a combination of a rosin ester derivative with ℓ-menthol,

(c) a styrene/isopreñe/styrene block copolymer employed as a base polymer,

(d) a softener, and

(e) a backing comprising a polyester cloth,

the nonsteroidal antiphlogistic analgesic drug, rosin ester derivative, ℓ-menthol, styrene/isoprene/styrene block copolymer and softener are present in respective mixing ratios by weight of from 0.5 to 10.0%, from 5.0 to 70.0%, from 0.5 to 15.0%, from 5.0 to 40.0% and from 10.0 to 75.0% in this order, the amounts of all said ingredients totalling 100% by weight,

the nonsteroidal antiphlogistic analgesic drug, rosin ester derivative and ℓ-menthol are present in a mixing ratio of 1.0 : 3.0 - 11.0 : 1.0 - 4.0.

2. (deleted)

3. (deleted)

ABSTRACT

An antiphlogistic analgesic plaster which comprises as essential ingredients:

(a) at least one nonsteroidal antiphlogistic analgesic drug selected from among ketoprofen, flurbiprofen, loxoprofen, ketorolac and ester derivatives or salts thereof,

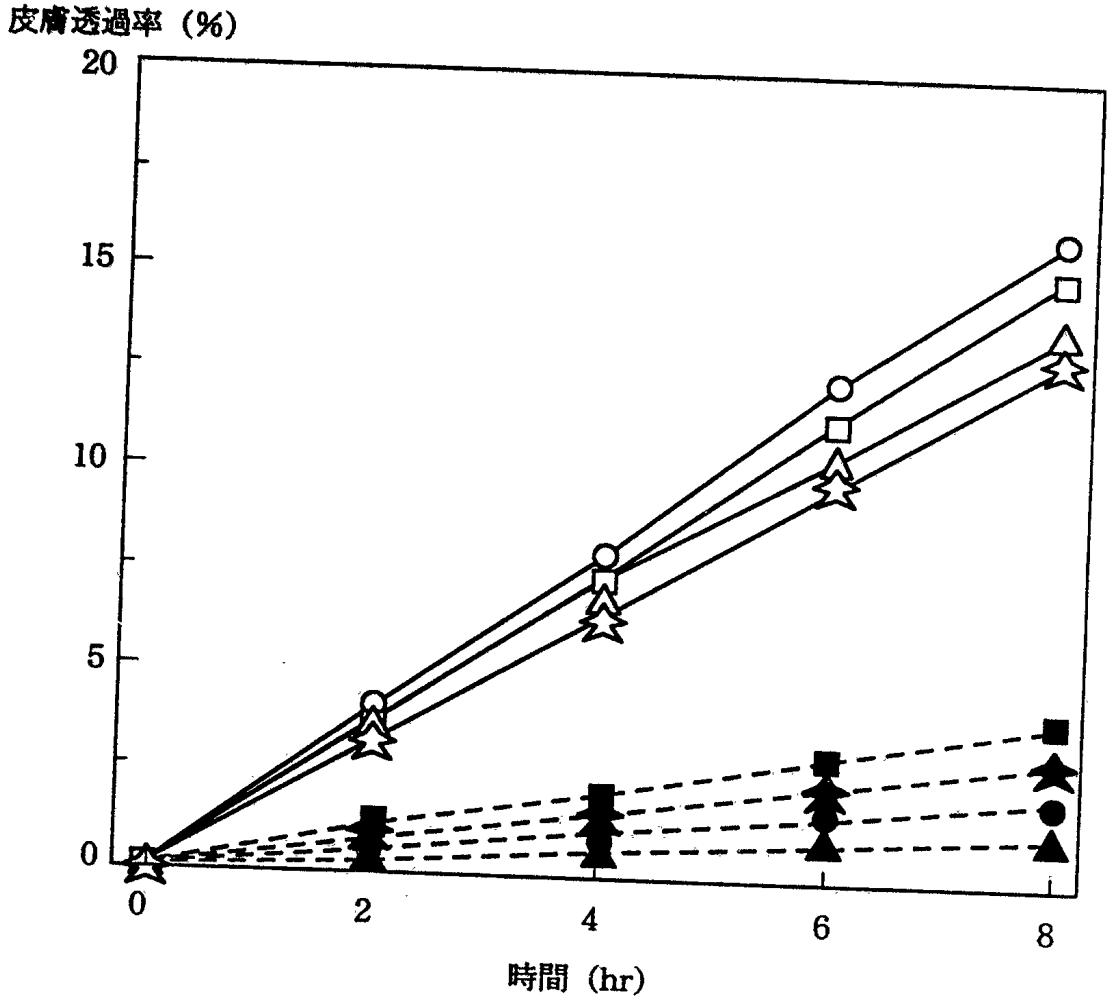
(b) a solubilizer comprising a combination of a rosin ester derivative with ℓ-menthol,

(c) a styrene/isoprene/styrene block copolymer employed as a base polymer,

(d) a softener, and

(e) a backing comprising a polyester cloth.

図 1


皮膚透過率（%）
20
15
10
5
0
0
2
4
6
8
時間（hr）
○：実施例4
□：実施例8
△：実施例10
☆：実施例17
●：参考例1
■：参考例2
▲：参考例3
★：参考例4

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP92/01022

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl[5] A61K31/19, A61K31/215, A61K9/70

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC	A61K31/19, A61K31/215, A61K9/70

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	JP, A, 63-246327 (Teikoku Seiyaku K.K.), October 13, 1988 (13. 10. 88), & EP, A, 285181 & US, A, 4963361	1-3
Y	JP, A, 64-40420 (Hisamitsu Pharmaceutical Co., Ltd.), February 10, 1989 (10. 02. 89), (Family: none)	1-3
Y	JP, A, 60-152413 (American Home Products Corp.), August 10, 1985 (10. 08. 85), & EP, A, 147146 & US, A, 4931283	1-3
Y	JP, A, 59-227819 (Nitto Denko K.K.), December 21, 1984 (21. 12. 84), (Family: none)	1-3
Y	JP, A, 56-20515 (Suzuki Nippondo K.K.), February 26, 1981 (26. 02. 81), (Family: none)	1-3

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
October 5, 1992 (05. 10. 92)	October 27, 1992 (27. 10. 92)
International Searching Authority	**Signature of Authorized Officer**
Japanese Patent Office	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

Y	JP, A, 55-133310 (Hisamitsu Pharmaceutical Co., Ltd.), October 17, 1980 (17. 10. 80), DE, A, 3007368 & GB, A, 2045618 & FR, A, 2452935 & US, A, 4455146	1-3

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers .... , because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

国際調査報告

国際出願番号PCT/JP92/01022

I. 発明の属する分野の分類

国際特許分類 (IPC) Int. Cl[5]
A61K31/19, A61K31/215, A61K9/70

II. 国際調査を行った分野

調査を行った最小限資料

分類体系	分類記号
IPC	A61K31/19, A61K31/215, A61K9/70

最小限資料以外の資料で調査を行ったもの

III. 関連する技術に関する文献

引用文献のカテゴリー※	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	請求の範囲の番号
Y	JP, A, 63-246327 (帝国製薬株式会社), 13. 10月. 1988 (13. 10. 88), &EP, A, 285181&US, A, 4963361	1-3
Y	JP, A, 64-40420 (久光製薬株式会社), 10. 2月. 1989 (10. 02. 89), (ファミリーなし)	1-3
Y	JP, A, 60-152413 (アメリカン・ホーム・プロダクツ・コーポレイション), 10. 8月. 1985 (10. 08. 85), &EP, A, 147146&US, A, 4931283	1-3
Y	JP, A, 59-227819 (日東電工株式会社), 21. 12月. 1984 (21. 12. 84), (ファミリーなし)	1-3
Y	JP, A, 56-20515 (株式会社 鈴木日本堂),	1-3

※引用文献のカテゴリー
「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」先行文献ではあるが、国際出願日以後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「T」国際出願日又は優先日の後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリーの文献

IV. 認証

国際調査を完了した日	国際調査報告の発送日
05. 10. 92	27.10.92
国際調査機関	権限のある職員
日本国特許庁 (ISA/JP)	4C8413 特許庁審査官 穴吹智子

様式PCT/ISA/210(第2ページ) (1981年10月)

第2ページから続く情報

	(III欄の続き) 26. 2月. 1981 (26. 02. 81), (ファミリーなし) JP, A, 55-133310 (久光製薬株式会社), 17. 10月. 1980 (17. 10. 80), DE, A, 3007368&GB, A, 2045618 &FR, A, 2452935&US, A, 4455146	
Y		1-3

V. ☐ 一部の請求の範囲について国際調査を行わないときの意見

次の請求の範囲については特許協力条約に基づく国際出願等に関する法律第8条第3項の規定によりこの国際調査報告を作成しない。その理由は、次のとおりである。

1. ☐ 請求の範囲_____は、国際調査をすることを要しない事項を内容とするものである。

2. ☐ 請求の範囲_____は、有効な国際調査をすることができる程度にまで所定の要件を満たしていない国際出願の部分に係るものである。

3. ☐ 請求の範囲_____は、従属請求の範囲でありかつPCT規則6.4(a)第2文の規定に従って起草されていない。

VI. ☐ 発明の単一性の要件を満たしていないときの意見

次に述べるようにこの国際出願には二以上の発明が含まれている。

1. ☐ 追加して納付すべき手数料が指定した期間内に納付されたので、この国際調査報告は、国際出願のすべての調査可能な請求の範囲について作成した。
2. ☐ 追加して納付すべき手数料が指定した期間内に一部分しか納付されなかったので、この国際調査報告は、手数料の納付があった発明に係る次の請求の範囲について作成した。
   請求の範囲_____
3. ☐ 追加して納付すべき手数料が指定した期間内に納付されなかったので、この国際調査報告は、請求の範囲に最初に記載された発明に係る次の請求の範囲について作成した。
   請求の範囲_____
4. ☐ 追加して納付すべき手数料を要求するまでもなく、すべての調査可能な請求の範囲について調査することができたので、追加して納付すべき手数料の納付を命じなかった。

追加手数料異議の申立てに関する注意

☐ 追加して納付すべき手数料の納付と同時に、追加手数料異議の申立てがされた。
☐ 追加して納付すべき手数料の納付に際し、追加手数料異議の申立てがされなかった。