(54) Title: COMPOUNDS AND METHOD FOR THE TOPICAL TREATMENT OF INFLAMMATION AND PAIN

(57) Abstract

Esters of methyl salicylate with certain non-steroidal antiinflammatory drugs (NSAID's) can be used for topical administration to mammals, to elicit a response which combines the antiinflammatory and analgesic effects of the NSAID and the counterirritant effect of the methyl salicylate. Typical NSAID's which can be used in this way are aspirin (acetylsalicylic acid), ibuprofen and indomethacin. Advantageously, the NSAID-methyl salicylate ester is administered in the form of a pharmaceutical composition, such as an ointment, gel, lotion, cream or the like.
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COMPOUNDS AND METHOD FOR THE TOPICAL
TREATMENT OF INFLAMMATION AND PAIN

Technical Field

This invention relates to the treatment of inflammation and pain in mammalian subjects by topical administration of certain chemical substances.

Musculo-skeletal inflammation and pain are common afflictions of mammals. They often appear as a manifestation of a chronic, inflammatory disease state, such as one of the arthritides, but they also appear as acute conditions in which case they can be triggered by a variety of causative factors. Such factors include bacteria, radiation and hypersensitivity to one or more chemical agents. However, a common cause of acute inflammation and pain in humans is simple over-exertion, leading to sprains, strains, muscle spasms, muscle tension, and the like.

Background Art

Inflammation, both chronic and acute, can be treated by the use of steroids, and the narcotic analgesics are often used to alleviate pain. However, steroidal drugs can produce undesirable side-effects, such as fluid retention, and narcotic analgesics suffer from their high addictive potential. On the other hand, there are a variety of agents commonly used in medical practice which are non-narcotic and non-steroidal, but which nevertheless can be used to combat both inflammation and pain. These agents, which are often termed non-steroidal antiinflammatory drugs (NSAID's), are typified by aspirin (acetylsalicylic acid) and related salicylates, but there are now a variety of newer drugs available. Although the
chemical structures of these newer agents vary quite widely, a common structural feature of many of these compounds is the presence of a carboxylic acid group (COOH). For example, one group of NSAID's consists of propionic acid derivatives (the so-called "profens," e.g., ibuprofen), and another group of NSAID's consists of acetic acid derivatives (e.g., indomethacin).

NSAID's, and various salts thereof, are commonly administered orally, thereby achieving systemic levels of the drug entity. On the other hand, in many situations, particularly when acute therapy is desired, a more convenient mode of treatment involves topical administration directly to the inflamed and/or painful situs. However, NSAID's are often not well-absorbed when administered topically.

In addition, acute inflammation and pain are often treated by the topical administration of a counter-irritant. In this regard, a widely-used agent is methyl salicylate, which is often applied to the skin in the form of an ointment or cream and which elicits a soothing, mildly-analgesic effect. However, methyl salicylate suffers from the disadvantage that it possesses an odor, which under certain circumstances, and to certain individuals, can be regarded as unpleasant.

The ester of aspirin with methyl salicylate has been described by Reepmeyer, Journal of Pharmaceutical Sciences, 72, 322 (1983), but no utility was reported for this compound.

Disclosure of Invention

Accordingly, it is an object of this invention to provide a method for the treatment of inflammation and/or pain in a mammalian subject, by topical administration of a chemical substance.

Thus, in its broadest sense, this invention
relates to the use of compounds of the formula

\[
\text{CH}_3\text{O-CO} \quad \text{(I)}
\]

\[
\text{Z-CO-O}
\]

for the topical treatment of inflammation and/or pain
associated with musculo-skeletal disorders in mammals,
especially humans. In compounds of the formula I, the
5 grouping Z-CO- represents an acyl radical of a
carboxylic acid of the formula Z-CO-OH, wherein Z-CO-OH
is a carboxy group-containing, non-steroidal
antiinflammatory drug (NSAID). After application to
10 the skin of a mammalian subject at an inflamed and/or
painful situs, a compound of the formula I is absorbed,
and then it breaks down by ester cleavage to give the
NSAID of the formula Z-CO-OH and methyl salicylate.
This results in concurrent delivery of the NSAID (which
15 exerts an antiinflammatory and/or analgesic effect) and
methyl salicylate (which exerts a soothing, counter-
irritant effect). This coherent therapy with two
complementary drug entities provides fast, effective
relief, and has advantages of use in that:
(i) absorption of the two components is converged,
20 thereby delivering both components to the site of
action at the same time; (ii) the odor of methyl
salicylate is not observed because it is liberated only
beneath the surface of the skin; and (iii) improved
levels of absorption of the NSAID are achieved,
25 compared to conventional formulations.

Further, this invention provides a pharmaceutical
composition which comprises a topically-acceptable
pharmaceutical carrier and an antiinflammatory and
analgesic response eliciting amount of a phenolic ester
30 of methyl salicylate of the formula I, wherein Z is as
defined above.
Moreover, the compounds of the formula I above are novel compositions of matter, except in the case in which the NSAID component is derived from aspirin. Thus, this invention also provides a new genus of chemical compounds which can be represented by the following chemical formula

\[
\begin{align*}
\text{CH}_3\text{O-CO} & \\
\text{Z}^1\text{-CO-O} & 
\end{align*}
\]

in which the grouping \(Z^1\text{-CO-}\) represents an acyl radical of a carboxylic acid of the formula \(Z^1\text{-CO-OH}\), wherein \(Z^1\text{-CO-OH}\) is a carboxy group-containing NSAID other than aspirin.

A wide variety of NSAID's can be used as the NSAID component of a compound of the formula I. However, among the various carboxy group-containing compounds of the formula \(Z\text{-CO-OH}\) which can be used, four sub-classes of NSAID's are particularly effective. There are:

(a) the salicylates;
(b) the propionic acids, or profens;
(c) the acetic acids; and
(d) the biphenylcarboxylic acids.

Typical examples of NSAID's of the above four types are: (a) aspirin; (b) carprofen, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, pranoprofen and suprofen; (c) diclofenac, etodolac, ibufenac, indomethacin, sulindac, tolmetin and zomepirac; and (d) diflunisal and flufenisal. However, the preferred compounds of the formula I are those in which the acyl group \(Z\text{-CO-}\) is derived from aspirin, ibuprofen or indomethacin. Consequently, preferred groups for \(Z^1\text{-CO-}\) in compounds of the formula II are the acyl groups derived from ibuprofen and indomethacin.
Detailed Description

The compounds of the formula I can be prepared directly from the appropriate NSAID and methyl salicylate, viz:

\[
\begin{array}{c}
\text{CH}_3\text{O-CO} \\
\text{Z-CO-OH} + \\
\text{HO} \\
\rightarrow I
\end{array}
\]

This is a classical esterification reaction, and it can be carried out by standard methods for this type of transformation. For example, it can be carried out by activation of the carboxy group of the NSAID (such as by acid chloride formation), followed by reaction with one molar equivalent of methyl salicylate, in an inert solvent, in the presence of one to four molar equivalents of a tertiary amine catalyst.

In a typical procedure for acid chloride formation, the acid of the formula Z-COOH is reacted with from one to four molar equivalents of thionyl chloride, in an inert solvent such as carbon tetrachloride or chloroform, at a temperature from about 40 to about 80°C. The reaction proceeds quite quickly, and conversion into acid chloride is usually substantially complete within about 12 hours. At that point, the volatile materials are removed by evaporation \textit{in vacuo} to give the crude acid chloride. Although the crude acid chloride can be purified if desired, it is usually pure enough in the crude state for conversion into a compound of the formula I.

During acid chloride formation, a small amount of aluminum trichloride can be added if desired.

In a typical procedure for conversion of the acid chloride Z-CO-Cl into a compound of the formula I, substantially equimolar quantities of the acid chloride and methyl salicylate are dissolved in a suitable,
reaction-inert, organic solvent and the solution is treated cautiously with from about one to about four molar equivalents of a tertiary amine. Convenient reaction-inert solvents are ethers, such as diethyl ether, tetrahydrofuran and 1,2-dimethoxyethane, and chlorinated hydrocarbons, such as chloroform and dichloromethane. Convenient tertiary amines are pyridine, triethylamine and N,N-dimethylaniline. The reagents are usually combined at or about room temperature, but it is then common to heat the reaction mixture at a temperature from about 30 to about 80°C., preferably about 40°C., for several hours to complete the reaction. The product can be isolated by standard procedures. For example, when a water-immiscible reaction solvent has been used, the reaction mixture can be washed with dilute hydrochloric acid, followed by dilute sodium bicarbonate solution. Evaporation of the dried organic solvent then affords the crude product of formula I. The product can be purified by conventional methods, such as recrystallization and/or chromatography.

If the Z grouping of the NSAID of the formula Z-CO-OH contains a functional group which can react with an acid chloride (e.g., OH, NH₂, etc), it is usually advantageous to protect this functional group prior to acid chloride formation. The protecting group is then removed after reaction with the methyl salicylate. Conventional protecting groups can be used for this purpose. Selection of an appropriate group, and methods for its attachment and removal, will be achieved readily by one skilled in the art.

An alternate method for the synthesis of the compound of the formula I, wherein Z-CO- is derived from aspirin is taught by Reepmeyer, Journal of Pharmaceutical Sciences, 72, 322 (1983).
As indicated hereinbefore the aforementioned compounds of the formula I are useful for topical administration to a mammalian subject, especially a human subject, for the treatment of inflammation and/or pain, both chronic and acute. Chronic conditions which can be treated using a compound of the formula I include rheumatoid arthritis, osteoarthritis, bursitis and the like; and acute conditions include sprains and strains, muscle tension, urticaria, eczema, dermatoses, insect bites and the like.

Advantageously, a compound of the formula I will be administered in combination with a topically-acceptable pharmaceutical carrier, in a pharmaceutical composition. Said pharmaceutical composition will be prepared according to standard pharmaceutical practice for a composition intended for topical use. For example, the pharmaceutical composition will be in the form of an ointment, gel, lotion or cream.

In the case of ointments, a compound of the formula I can be formulated with waxes, such as white wax or lanolin, and paraffins such as petrolatum. Emulsifying agents, such as sodium lauryl sulfate and stearyl alcohol, can also be added.

In the case of gels, a compound of the formula I can be formulated by adding a gelling agent to a solution or partial solution of the active ingredient in a suitable organic solvent, such as ethyl alcohol, propyl alcohol, propylene glycol, glycerol or mixtures thereof. Typical gelling agents which can be used are polyoxyethylated amines (e.g., PEG-15 cocamine) and carboxymethyl celluloses.

In the case of lotions and creams, a compound of the formula I can be formulated in aqueous propylene glycol containing various emulsifying agents and emollients. Typical emulsifying agents are glyceryl
stearate, sorbitan monostearate, sorbitan mono-oleate, and the like; typical emollients are waxes and paraffins, such as lanolin or light mineral oil.

A pharmaceutical composition containing a compound of the formula I can also contain other additives conventionally used for topical pharmaceuticals, such as stabilizers, preservatives and antioxidants, and penetration enhancers, such as dimethyl sulfoxide and N-methylpyrrolidone. Conventional coloring and odor-enhancing substances can also be added.

In a pharmaceutical composition comprising a compound of the formula I, the ratio of pharmaceutical carrier to active ingredient will vary according to a variety of factors, such as the precise nature of the composition, the site of intended use and the dosage contemplated. However, in general, the weight ratio of carrier to active ingredient will normally be in the range from 1:1 to 10:1, preferably 1:2 to 2:1.

When a pharmaceutical composition comprising a compound of the formula I is used for topical treatment of a human subject, the dosage to be used will vary according to factors such as the severity of the symptom's being treated, the response of the individual patient, the frequency of administration and the antiinflammatory and/or analgesic potency of the NSAID component of the compound of the formula I. However, having full regard for these factors, administration of an antiinflammatory and analgesic response eliciting amount of a compound of a formula I will require topical administration of a pharmaceutical composition containing a compound of the formula I such that the subject being treated receives from 0.1 to 10 mg/cm² of said compound of formula I. This dosage may be repeated at intervals, as necessary; for example, every 4, 6 or 12 hours. The existence of only minor symptoms
of inflammation and/or pain, and the use of a compound of the formula I in which the NSAID component is of relatively high potency, are factors which indicate that dosages towards the lower end of the above range will be preferred. Conversely, the existence of more severe inflammation and/or pain, and the use of a compound of the formula I in which the NSAID component is of relatively low potency, are factors which indicate that dosages towards the upper end of the above range will be preferred.

The following examples are being provided solely for further illustration. The term "flash chromatography" refers to the procedure described by Still et al., Journal of Organic Chemistry, 43, 2923 (1978).
EXAMPLE 1

Ester of Aspirin with Methyl Salicylate

To 10.0 g of aspirin (acetylsalicylic acid) in 50 ml of carbon tetrachloride was added 0.5 g of aluminum trichloride, with stirring, and the mixture was stirred at 60°C for 1 hour. Thionyl chloride (15 ml) was added and stirring was continued at 60°C for 14 hours. The solvent was removed by evaporation to give the acid chloride of aspirin as a reddish liquid.

The above acid chloride was dissolved in 20 ml of diethyl ether and 7.66 g of methyl salicylate was added, with stirring. After 10 minutes, 3.98 g of pyridine was added, dropwise, with stirring, during 30 minutes, and stirring was continued for 2 hours. The reaction mixture was then filtered, and the filtrate was washed with dilute hydrochloric acid, followed by 5% sodium bicarbonate solution, followed by water. The resulting organic solution was dried (MgSO₄) and evaporated in vacuo. To the residue was added a small amount of toluene and the solid which did not dissolve was removed by filtration. The toluene solution was evaporated in vacuo and the residue was flash chromatographed on silica gel, eluting with 95:5 chloroform/ethyl acetate. Evaporation of the solvent from the product-containing fractions afforded a 30% yield of the title ester.

The $^1$H nuclear magnetic resonance spectrum (CDCl₃; 280 MHz) of the product showed absorptions at 2.3 (singlet, 3H), 3.8 (singlet, 3H) and 7.2-8.5 (multiplet, 8H) ppm downfield from internal tetramethylsilane.

The infrared spectrum of the product (KBr disc) showed prominent absorptions at 3200-2950, 1770, 1725, 1610, 1220-1190 and 1165 cm$^{-1}$. 
The mass spectrum of the product showed major peaks at mass-to-charge ratios (m/e) of 314.1, 282.9, 163.3, 151.9, 134.9 and 120.9.

Analysis: Calcd. for \( \text{C}_{17}\text{H}_{14}\text{O}_{6} \): C, 64.97; H 4.46%.

Found: C, 64.63; H, 4.32%.

**EXAMPLE 2**

**Ester of Ibuprofen with Methyl Salicylate**

To a stirred mixture of 10.0 g of ibuprofen and 30 ml of carbon tetrachloride was added 8.0 g of thionyl chloride. The resulting mixture was stirred at room temperature for 1 hour and then at 60°C overnight. The volatile components were removed by evaporation in vacuo, leaving the acid chloride of ibuprofen as a dark colored liquid.

The above acid chloride and 6.1 g of methyl salicylate were dissolved in 30 ml of diethyl ether, and 3.8 g of pyridine was added dropwise, with stirring. The resulting mixture was heated under reflux for 24 hours, and then it was cooled and filtered. The filtrate was washed with dilute hydrochloric acid, followed by 5% sodium bicarbonate, followed by water. The organic solution was dried (MgSO\(_4\)) and evaporated in vacuo to give a brown oil, which was flash chromatographed on silica gel, eluting with dichloromethane as solvent. Evaporation of the appropriate fractions afforded the title ester.

The \( ^1\text{H} \) nuclear magnetic resonance spectrum (CDCl\(_3\); 280 MHz) of the product showed absorptions at 0.9 (doublet, 6H), 1.65 (doublet, 3H), 1.8 (multiplet, 1H), 2.5 (doublet, 2H), 3.7 (singlet, 3H), 4.1 (quartet, 8H) ppm downfield from internal tetramethylsilane.

The infrared spectrum of the product (KBr disc) showed prominent absorptions at 3100-2850, 1765, 1730, 1610, 1300, 1140 and 1080 cm\(^{-1}\).
The mass spectrum of the product showed major peaks at mass-to-charge ratios (m/e) of 341.0, 309.0, 188.2, 161.0, 145.0, 118.0 and 57.0.

**EXAMPLE 3**

Ester of Indomethacin with Methyl Salicylate

The title compound can be prepared by conversion of indomethacin into its acid chloride, followed by reaction with methyl salicylate, using the procedure of Example 2.

**EXAMPLE 4**

Topical Formulations of the Ester of Aspirin with Methyl Salicylate

**OINTMENT NO. 1**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (Parts by Weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lanolin, anhydrous</td>
<td>3</td>
</tr>
<tr>
<td>2. Aspirin-Methyl Salicylate ester</td>
<td>3-6</td>
</tr>
<tr>
<td>3. Propylene glycol</td>
<td>1</td>
</tr>
<tr>
<td>4. White wax</td>
<td>1</td>
</tr>
<tr>
<td>5. Lanolin</td>
<td>2</td>
</tr>
</tbody>
</table>

Ingredients 1 and 2 are blended until homogeneous at a suitable temperature, not to exceed 80°C, such that a molten mixture is obtained (Mixture A).

Ingredients 3, 4 and 5 are blended until homogeneous at a suitable temperature, not to exceed 80°C, such that a molten mixture is obtained (Mixture B).

Mixtures A and B are combined while still molten and blended until homogeneous. The resulting mixture is allowed to cool to room temperature with slow stirring.
### OINTMENT NO. 2

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (Parts by Weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Stearyl alcohol</td>
<td>1</td>
</tr>
<tr>
<td>2. Petrolatum</td>
<td>2</td>
</tr>
<tr>
<td>3. Aspirin-Methyl Salicylate ester</td>
<td>3-6</td>
</tr>
<tr>
<td>4. Water</td>
<td>2</td>
</tr>
<tr>
<td>5. Propylene glycol</td>
<td>2</td>
</tr>
<tr>
<td>6. Sodium lauryl sulfate</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Ingredients 1, 2 and 3 are blended until homogeneous at a suitable temperature, not to exceed 80°C., such that a molten mixture is obtained (Mixture A).

Ingredients 4, 5 and 6 are blended until homogeneous at a suitable temperature, not to exceed 80°C., such that a molten mixture is obtained (Mixture B).

Mixtures A and B are adjusted to the same temperature, mixed, and blended until homogeneous. The resulting mixture is allowed to cool to room temperature with slow stirring.

### GEL

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (Parts by Weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ethyl alcohol, denatured</td>
<td>4.3</td>
</tr>
<tr>
<td>2. Propylene glycol</td>
<td>2.5</td>
</tr>
<tr>
<td>3. Carbomer(^1)</td>
<td>0.1</td>
</tr>
<tr>
<td>4. Aspirin-Methyl Salicylate ester</td>
<td>3-6</td>
</tr>
<tr>
<td>5. PEG-15 cocamine(^2)</td>
<td>0.1</td>
</tr>
</tbody>
</table>
1 A cross-linked polyacrylic acid
2 A polyoxyethylated derivative of the coconut amine

Ingredients 1, 2, 3 and 4 are blended until homogeneous at a temperature between 22 and 30°C., to produce a molten mixture. Ingredient 5 is added slowly, with gentle mixing, until a gel forms. Mixing is continued until a uniform blend is obtained.

**LOTION**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Glyceryl stearate</td>
<td>4</td>
</tr>
<tr>
<td>2. Lanolin</td>
<td>4</td>
</tr>
<tr>
<td>3. Mineral oil, light</td>
<td>4</td>
</tr>
<tr>
<td>4. Aspirin-Methyl Salicylate ester</td>
<td>25-50</td>
</tr>
<tr>
<td>5. Propylene glycol</td>
<td>15</td>
</tr>
<tr>
<td>6. Water</td>
<td>30</td>
</tr>
<tr>
<td>7. Carbomer1</td>
<td>0.5</td>
</tr>
<tr>
<td>8. Water</td>
<td>10</td>
</tr>
<tr>
<td>9. Potassium hydroxide</td>
<td>0.2</td>
</tr>
</tbody>
</table>

1 A cross-linked polyacrylic acid

Ingredients 1, 2, 3, 4 and 5 are blended until homogeneous at a suitable temperature, not to exceed 80°C., such that a molten mixture is obtained (Mixture A).

Ingredient 7 is dispersed in ingredient 6 and heated to 60°C with agitation (Mixture B).

Mixture A is blended into Mixture B at 60°C and stirred until uniform and then the mixture is cooled to 50°C (Mixture C).
A solution of ingredient 9 in ingredient 8 is heated to 50°C. This solution is added to Mixture C with gentle stirring and gradual cooling during the addition.

EXAMPLE 5
Topical Formulations of the Ester of Ibuprofen with Methyl Salicylate

GEL

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount (Parts by Weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Water</td>
<td>2</td>
</tr>
<tr>
<td>2. Glycerol</td>
<td>2</td>
</tr>
<tr>
<td>3. Ethyl alcohol</td>
<td>3</td>
</tr>
<tr>
<td>4. Ibuprofen-Methyl salicylate ester</td>
<td>3-6</td>
</tr>
<tr>
<td>5. Carbomer&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.1</td>
</tr>
<tr>
<td>6. PEG-15 cocamine&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.1</td>
</tr>
</tbody>
</table>

<sup>1</sup> A cross-linked polyacrylic acid
<sup>2</sup> A polyoxyethylated derivative of the coconut amine

Ingredients 3 and 4 are blended until homogeneous, and then a mixture of ingredients 1 and 2 is added. Blending is continued until homogeneous. The PEG-15 cocamine is added and blending is continued until a gel forms.

CREAM

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount (Parts by Weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Stearic acid</td>
<td>10</td>
</tr>
<tr>
<td>2. Glycereryl stearate</td>
<td>7</td>
</tr>
<tr>
<td>3. Lanolin</td>
<td>2</td>
</tr>
<tr>
<td>4. Polysorbate 85</td>
<td>2</td>
</tr>
<tr>
<td>5. Sorbitan tristearate</td>
<td>1</td>
</tr>
</tbody>
</table>
## CREAM

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount (Parts by Weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Ibuprofen-Methyl Salicylate ester</td>
<td>25-50</td>
</tr>
<tr>
<td>7. Water</td>
<td>40</td>
</tr>
<tr>
<td>8. Triethanolamine</td>
<td>1</td>
</tr>
</tbody>
</table>

Ingredients 1-6 are blended until homogeneous at a suitable temperature, not to exceed 60°C., such that a molten mixture is obtained (Mixture A). A solution of the triethanolamine in the water is heated to the same temperature as Mixture A. Mixture A is added to the aqueous triethanolamine with vigorous agitation and cooling. As a cream forms, the rate of agitation is slowed, and a smooth, white product develops.

## OINTMENT

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount (Parts by Weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lanolin</td>
<td>4</td>
</tr>
<tr>
<td>2. White wax</td>
<td>1</td>
</tr>
<tr>
<td>3. Ibuprofen-Methyl Salicylate ester</td>
<td>3-6</td>
</tr>
<tr>
<td>4. Water</td>
<td>1</td>
</tr>
</tbody>
</table>

Ingredients 1, 2 and 3 are blended until homogeneous at a temperature which is just sufficient to give a molten mixture. The water is then added, with mixing, and mixing is continued until a homogeneous ointment is obtained. The ointment is cooled to room temperature.
**LOTION**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount (Parts by Weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Propylene glycol stearate</td>
<td>3</td>
</tr>
<tr>
<td>2. Lanolin oil</td>
<td>4</td>
</tr>
<tr>
<td>3. Mineral oil, light</td>
<td>8</td>
</tr>
<tr>
<td>4. Ibuprofen-Methyl Salicylate ester</td>
<td>25-50</td>
</tr>
<tr>
<td>5. Water</td>
<td>30</td>
</tr>
<tr>
<td>6. Carbomer&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.5</td>
</tr>
<tr>
<td>7. Potassium hydroxide</td>
<td>0.2</td>
</tr>
<tr>
<td>8. Water</td>
<td>20</td>
</tr>
</tbody>
</table>

<sup>1</sup> A cross-linked polyacrylic acid

Ingredients 1, 2, 3 and 4 are blended until homogeneous at a suitable temperature, not to exceed 80°C., such that a molten mixture is obtained (Mixture A).

Ingredient 6 is dispersed in ingredient 5 and heated to 60°C with agitation (Mixture B).

Mixture A is blended into Mixture B at 60°C and stirred until uniform and then the mixture is cooled to 50°C (Mixture C).

A solution of ingredient 8 in ingredient 7 is heated to 50°C. This solution is added to Mixture C with gentle stirring and gradual cooling during the addition.
CLAIMS

1. A method of eliciting an antiinflammatory and/or an analgesic response in a mammalian subject, which comprises topically administering to said subject an antiinflammatory and analgesic response eliciting amount of a phenolic ester of methyl salicylate of the formula

\[
\begin{array}{c}
\text{CH}_3\text{O-CO} \\
\text{Z-CO-O}
\end{array}
\]

in which the grouping Z-CO- represents an acyl radical derived from a carboxylic acid of the formula Z-CO-OH, wherein Z-CO-OH is selected from the group consisting of aspirin, ibuprofen and indomethacin.

2. The method according to claim 1, wherein Z-CO-OH is aspirin.

3. The method according to claim 1 wherein Z-CO-OH is ibuprofen.

4. A pharmaceutical composition, suitable for topical administration to a mammalian subject to elicit an antiinflammatory or analgesic response, which comprises a topically-acceptable pharmaceutical carrier and an antiinflammatory and analgesic response eliciting amount of a phenolic ester of methyl salicylate of the formula

\[
\begin{array}{c}
\text{CH}_3\text{O-CO} \\
\text{Z-CO-O}
\end{array}
\]

in which the grouping Z-CO- represents an acyl radical derived from a carboxylic acid of the formula Z-CO-OH, wherein Z-CO-OH is selected from the group consisting
of aspirin, ibuprofen and indomethacin.

5. A composition according to claim 4, wherein the weight ratio of the carrier to the methyl salicylate ester is in the range from 1:1 to 10:1.

6. A composition according to claim 5, wherein the composition is in the form of a cream, oil, gel or lotion.

7. A phenolic ester of methyl salicylate of the formula

\[
\text{CH}_3\text{O-CO} \quad \text{Z}^1\text{-CO-O} \\
\]

in which the grouping \(Z^1\text{-CO-}\) represents an acyl radical derived from a carboxylic acid of the formula \(Z^1\text{-CO-OH}\), wherein \(Z^1\text{-CO-OH}\) is selected from the group consisting of ibuprofen and indomethacin.

8. The compound of the formula

\[
\text{CH}_3\text{O-CO} \\
\text{CH}_3 \\
\text{CH-CO-O} \\
(\text{CH}_3)_2\text{CH-CH}_2
\]

the compound of claim 7, wherein \(Z^1\text{-CO-OH}\) is ibuprofen.
9. The compound of the formula

the compound of claim 7, wherein \( Z^1 \)-CO-OH is indomethacin.
# INTERNATIONAL SEARCH REPORT

## I. CLASSIFICATION OF SUBJECT MATTER

<table>
<thead>
<tr>
<th>Classification System</th>
<th>Classification Symbols</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.</td>
<td>514/159 514/947</td>
</tr>
</tbody>
</table>

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

**INT. CL. A61K 31/235**

**U.S. CL. 514/159 514/947**

## II. FIELDS SEARCHED

**Minimum Documentation Searched**

- U.S. 514/159 514/947

**Documentation Searched other than Minimum Documentation**

- to the extent that such documents are included in the fields searched

## III. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of Document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to Claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>DE, C, 236,196, Published 1 July 1911 See page 1, Column 2, lines 47-52</td>
<td>1, 2 + 4-6</td>
</tr>
<tr>
<td>A</td>
<td>DE, C, 211,403, Published 25 June 1909 See page 1, column 2, line 55 to page 2, column 1, line 45</td>
<td>1,2 + 4-6</td>
</tr>
<tr>
<td>X</td>
<td>Reepmeyer et al, J. of Pharm. Sci., 72, (1983) pages 322 &amp; 323</td>
<td>1,2 + 4-6</td>
</tr>
<tr>
<td>X</td>
<td>Merck Index 9th Ed. (1976) Merck &amp; Co., U.S.A., Pages 1080 and 1081</td>
<td>1,2 + 4-6</td>
</tr>
</tbody>
</table>

### Notes:

- *: Special categories of cited documents:
  - **A**: document defining the general state of the art which is not considered to be of particular relevance
  - **B**: earlier document but published on or after the international filing date
  - **L**: document which may throw doubts on priority claim(s) or which 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.
  - **A**: document member of the same patent family

- **IV. CERTIFICATION**

  **Date of the Actual Completion of the International Search**: 16 January 1986
  **Date of Mailing of this International Search Report**: 30 JAN 1986
  **International Searching Authority**: ISA/US
  **Signature of Authorized Official**: David B. Springer

Form PCT/ISA/210 (second sheet) (October 1981)
FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

VI. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 10

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 11 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 12, specifically:

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 13

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

I. Claims 1, 2 and 4-6 in 514/159
II. Claims 1 and 3-6 in 514/159 and 7 and 8 in 560/066
III. Claims 1 and 4-6 in 514/420 and 7 and 9 in 548/500

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:

1, 2 & 4-6

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.