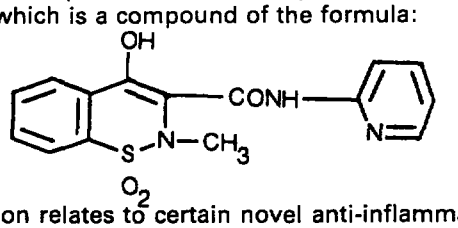
Description

This invention relates to new and useful anti-inflammatory compositions for topical administration containing as an active ingredient, piroxicam, viz., N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide, 1,1-dioxide, which is a compound of the formula:



More particularly, this invention relates to certain novel anti-inflammatory pharmaceutical compositions for external use comprising an effective anti-inflammatory amount of piroxicam, nontoxic bases for topical formulation and appropriate solvents therefor.

Piroxicam is a nonsteroidal anti-inflammatory agent described and claimed under its chemical name by J. G. Lombardino in U.S. Patent No. 3,591,584 and it is highly effective in therapy when administered to mammalian subjects suffering from chronic arthritic rheumatism, arthritis deformans, low back pain, shoulder pain, cerrico-omo-brachial syndrome, trauma or the pain caused by tooth extraction. Piroxicam is sold in capsule form world-wide and it is recognized to be a potent long-acting drug that ensures an effective piroxicam blood level when administerd orally once a day.

Some of the above diseases require a relatively long period of treatment in order to avoid or minimize side effects, and it would be desirable that the oral administration be replaced by the topical administration as the disease reaches a recuperative stage. Furthermore, the topical administration is suitable for a mild case or a case where the lesion is localized.

This invention is meant to provide anti-inflammatory compositions suitable for topical administration: these compositions are characterized in that they comprise an effective anti-inflammatory amount of piroxicam, nontoxic bases for topical formulation and solvents.

Piroxicam is very active as an anti-inflammatory agent, but it is sparingly soluble in water and is not liposoluble. When piroxicam is simply compounded in suspension with conventional bases for ointment or cream, it is poorly absorbed through skin and does not afford expected therapeutical effects. Additionally, the formulation so produced is very sticky and unpleasant to apply to a wide area of the skin. The active ingredients in the formulation may also be lost easily when in contact with clothing. In this connection, it seems possible to apply piroxicam in the form of a tincture after dissolving same in an alcoholic solvent such as ethanol. However, piroxicam will precipitate on the skin due to the evaporation of the solvent and will not be absorbed through the skin.

A gel ointment is prepared by adding a polymer to a lower alkanol-water system. It is generally a preferred form for topical administration because it is refreshing and not sticky. Unfortunately, the gel ointment cannot be formulated with piroxicam according to the standard techniques since piroxicam is sparingly soluble in water or any other solvent. Piroxicam, in the presence of moisture, turns into a hydrate thereof which is less soluble than piroxicam itself and this hydrate crystallizes out gradually. This not only reduces the absorbability of piroxicam through skin, but also impairs the coating and stability of the gel ointment.

A further problem arises when the gel ointment is applied to the skin in that dermal salt causes crystallization of piroxicam. This hydrate forms a yellow deposit on the skin. The hydrate will also come off when in contact with clothing or other material.

A similar problem arises when the gel ointment is applied directly to sweating skin, viz., a polymer gel-forming agent in the ointment is salted out and, as a result, the ointment agglomerates on the skin instead of forming a film layer. This affords unpleasantness to the user and the active ingredient is lost, whereby poor therapeutic effects are obtained.

In accordance with the present invention, there has now been developed a novel anti-inflammatory composition for external use that has excellent skin-permeability and none of the defects described above. It has thus been surprisingly found that by combining and blending an effective anti-inflammatory amount of piroxicam with water-soluble bases, solvents, gel-forming agents and, if necessary, an appropriate amount of film-forming agents, one can obtain an anti-inflammatory composition for external use that has an unexpectedly high degree of therapeutic efficacy and good stability. It is, in addition, pleasant to use.

Thus, according to the present invention there is provided a topical anti-inflammatory composition in gel ointment form in an aqueous system characterised in that it comprises an effective anti-inflammatory amount of piroxicam; from 10% to 50% by weight of a lower alkanol having from one to four carbon atoms; a gel-forming amount of carboxyvinyl polymer; from 5% to 40% by weight of at least one polyhydric alcohol selected from the lower alkylene glycols having from two to six carbon atoms, glycerine and polyethylene glycols having an average molecular weight of from 200 to 2,000; and a piroxicam-solubilizing amount of at least one alkanolamine selected from the monoalkanolamines having from one to four carbon atoms, dialkanolamines having from two to eight carbon atoms and trialkanolamines having from three to twelve carbon atoms, and sufficient water to total 100%, said composition having a pH range of from 6.5 to 9.0.

Also encompassed by this invention is an anti-inflammatory composition for external use which contains in addition to the above-stated ingredients, an effective amount of a film-forming agent selected from carboxymethyl cellulose, hydroxyethyl cellulose and polyvinylpyrrolidone, said composition having a pH range of from 6.5 to 9.0.

An effective anti-inflammatory amount of piroxicam in the composition is preferably from 0.3% to 2.0% by weight, of the total composition. Use of a lower piroxicam level affords unsatisfactory anti-inflammatory effects but, on the other hand, use of higher levels is not preferred for economic reasons.

The lower alkanols used in this invention are, for example, methanol, ethanol, isopropanol and butanol. A preferred amount of the lower alkanol is from 10% to 50% by weight of the composition.

A preferred amount of water is from 30% to 60% by weight of the composition.

The lower alkylene glycol having from two to six carbons which can be used includes ethylene glycol, propylene glycol and butylene glycol.

Glycerine or polyethylene glycol having an average molecualr weight of from 200 to 2000 can also be used in place of glycol. It is possible to use only one kind of such polyhydric alcohol, but more than one kind may also be used. A preferred amount of the polyhydric alcohol is from 5% to 40% by weight of the composition. Use of the polyhydric alcohol level greater than 40% is not preferred, since the formulation gives unpleasant feelings such as stickiness after use. Although these polyhydric alcohols are known to dissolve active ingredients in bases, it is a particularly surprising feature of this invention that the polyhydric alcohols in combination with the above-mentioned alkanolamines prevent the conversion of piroxicam into its hydrate, thereby precluding the formation of the previously-mentioned yellow deposit on the skin.

As Table 1 below indicates, it will be understood that when the polyhydric alcohols are not present in the composition, piroxicam crystallizes out as a yellow deposit on the skin:

TABLE 1
Formation of Yellow Deposit (piroxicam hydrate)

Formulation	A	B	C	D
Polyhydric alcohol	Polyethylene glycol	Polyethylene glycol	Polyethylene glycol and propylene glycol	None
Concn. level	20 w/w %	30 w/w %	25 w/w %	
Yellow deposit	No	No	No	Yes

This invention employs a solubilizing agent to dissolve piroxicam in bases for formulation; the piroxicam-solublizing agent is an alkanolamine. It has been discovered that monoalkanolamine, dialkanolamine and trialkanolamine are highly effective for increasing the solubility of piroxicam in the composition, as well as enchancing the skin-permeability of piroxicam. The monoalkanolamines have from one to four carbon atoms and include methanolamine, ethanolamine, propanolamine and butanolamine. The dialkanolamines have from two to eight carbon atoms and include dimethanolamine, diethanolamine, dipropanolamine and dibutanolamine. The trialkanolamines have from three to twelve carbon atoms and include trimethanolamine, triethanolamine, tripropanolamine and tributanolamine.

The marked solubilizing powr of these alkanolamines has been demonstrated by reference to testing results where the ability of these amines to dissolve piroxicam is compared with that of other solubilizers listed in the table below (Table 2):

TABLE 2
Piroxicam Solubilizers

Solubilizers	Amount added	solvent:water Solubility of Piroxicam (mg./g.)
Ethanolamine	10%	392
Diethanolamine	10%	204
Di-isopropanolamine	10%	195
Di-isopropyl adipate	10%	1.2*
Diethyl sebacate	10%	2.0*
N-Ethyl-*o*-crotonotoluidide	10%	1.8*
Isopropyl myristate	10%	0.4*
Ammonia	10%	60.0
Control (none)	0	0.01

* solvent: 1:1 water-ethanol

It is possible to use only one kind of the alkanolamines, but more than one kind may also be used. A preferred amount of the alkanolamines is up to 3% by weight of the composition: this amount is sufficient to dissolve piroxicam in the ointment bases, but levels of the alkanolamines are not limited to this range.

In accordance with this invention, carboxyvinyl polymers are used as gel-forming agents. Carboxyvinyl polymers are hydrophilic polymers and prepared by polymerizing monomers principally consisting of acrylic acid. They are commercially available from Goodrich Chemicals, U.S.A., under the trade name of Carbopole 934, 940 or 941 and also from Wako Pure Chemicals, Japan under the trade name of HIVISWAKO 103, 104 or 105.

An aqueous solution containing the carboxyvinyl polymer is acidic, since the polymer has free carboxylic acid residues. Neutralization of the aqueous solution with an appropriate base furnishes a viscous gel with desired viscosity. The appropriate bases which can be used are the aforementioned alkanolamines, inorganic bases such as sodium hydroxide, potassium hydroxide and potassium carbonate and organic bases such as alkylamine, dialkylamine and trialkylamine. A preferred amount of the gel-forming agent is from 0.2% to 2.0% by weight of the composition.

A gel ointment formulation containing carboxyvinyl polymer is generally stable. It has a constant viscosity with very little variation due to temperature or time. However, as previously described herein, several problems arise when the compositions of this invention containing carboxyvinyl polymer are applied to the skin. It sometimes happens that the polymer is salted out by the salt contained in sweat and forms soft agglomerates which disintegrate easily. In such a case, the active ingredient may be lost before it is absorbed through skin and the formulation affords an unpleasant feeling on administration.

Accordingly, the formulation must be administered after the area of application is wiped and cleaned. It has been discovered that if certain hydrophilic polymers are incorporated in the formulation, the ointment can be administered topically even on the sweating skin to form a suitable film without the above problems.

Japanese Published Patent Application No. 55—40,604 describes a similar phenomenon and teaches a method for preventing the same with the use of hydroxypropyl cellulose. Hydroxypropyl cellulose has, however, turned out to be ineffective when combined with the compositions of this invention. For the purpose of this invention, polyvinylpyrrolidone, carboxymethyl cellulose and hydroxyethyl cellulose are satisfactory. The film-forming ability of these hydrophilic polymers has been illustrated in the test results of Table 3, as shown below, where the use of film-forming polymers in the compositions of this invention are observed to afford very favorable effects:

TABLE 3
Film-forming Ability of Piroxicam Ointment[1]

Film-forming agent	Applied to the normal skin	Applied to the skin with brine
Polyvinylpyrrolidone (1.0% added)	good film	good film
Carboxymethyl cellulose (1.0% added)	good film	good film
Hydroxyethyl cellulose (1.0% added)	good film	good film
Hydroxyethyl cellulose (0.5% added)	good film	good film
Control (None)	a small amount of soft agglomerates	soft agglomerates disintegrate

[1] The above formulation contains the following ingredients (Table 4):

TABLE 4
Piroxicam Ointment (1%)

Ingredient	Percent by weight
Piroxicam	1.0
Carboxyvinyl polymer 940	1.0
Ethanol	30.0
Propylene glycol	20.0
Ethylene glycol	10.0
Diethanolamine	1.5
Distilled water	remaining part

It is possible to use only one kind of the film-forming agents, but more than one kind may also be used. A preferred amount of the film-forming agents is from 0.2% to 2.0% by weight of the total.

In addition to the above-mentioned film-forming agents, various other ingredients can be incorporated into the anti-inflammatory compositions of this invention to improve their therapeutic efficacy and stability. These include antiseptics such as benzyl alchol, corneous tissue-dissolving agents such as urea and suitable skin-permeation enchancing adjuvants, like diethyl sebacate, which are well-known to those skilled in the art.

The anti-inflammatory compositions of this invention have a pH range of from 6.5 to 9.0, and preferably from 6.5 to 8.0. In general, it is believed that the percutaneous absorptiion or skin-penetration of a given drug is dependent upon the ratio of lipophilicity to water solubility (partition coefficient) and that a high ratio is preferred, but too high a ratio adversely decreases the absorption and skin-penetration. Piroxicam has a pKa value of from 1.5 to 5.1. A preferrred pH range for the compositions of this invention is from 6.5 to 8.0, since it is in this range that piroxicam is present partially in a dissociated form and the alkanolamines can also be used. At a higher pH than 9.0, piroxicam is chemically unstable and may even decompose or deteriorate in quality.

Accordingly, the compositions of this invention can be prepared in the manner described below:

1. dispersing carboxyvinyl polymer and, if desired, a film-forming agent in distilled water;
2. blending the above with lower alkanols, glycols, glycerine or polyethlene glycols uniformly;
3. independently dissolving piroxicam in an aqueous solution of alkanolamine until it is completely dissolved and, if necessary adding a neutralizing agent thereto; and
4. adding the resulting mixture of step 3 to the mixture obtained in step 2 and mixing under constant agitation to form a gel ointment.

The compositions of this invention so produced are stable even after storage for a prolonged period of time and exhibit excellent anti-inflammatory activity, as is evident from the following examples. These examples further illustrate this invention, but are not to be construed as limiting the same.

Example 1

The following ingredients were combined and blended uniformly together to produce an ointment formulation having a pH of 7.9:

	Percent by weight
Piroxicam	1.0
Carboxyvinyl polymer 940	1.0
Ethanol	30.0
Propylene glycol	30.0
Diethanolamine	1.5
Hydroxyethyl cellulose	0.5
Polyvinylpyrrolidone K-30	0.5
Distilled water	remaining part

Example 2

The following ingredients were combined and blended uniformly together to produce an ointment formulation having a pH of 7.8:

	Percent by weight
Piroxicam	1.0
Carboxyvinyl polymer 940	1.0
Ethanol	30.0
Glycerine	20.0
Polyethylene glycol 300	10.0
Diisopropanolamine	1.7
Distilled water	remaining part

Example 3

The following ingredients were combined and blended uniformly together produce an ointment formulation having a pH of 8.0:

	Percent by weight
Piroxicam	1.0
Carboxyvinyl polymer 940	1.0
Ethanol	30.0
Propylene glycol	10.0
Glycerine	10.0
Diisopropanolamine	1.8
Hydroxyethyl cellulose	1.0
Distilled water	remaining part

(13)

Example 4

The following ingredients were combined and blended uniformly together to produce an ointment formulation having a pH of 7.3:

	Percent by weight
Piroxicam	1.0
Carboxyvinyl polymer 940	1.0
Ethanol	30.0
Glycerine	30.0
Diethanolamine	1.3
Distilled water	remaining part

Example 5

The following ingredients were combined and blended uniformly together to produce an ointment formulation having a pH of 7.7:

	Percent by weight
Piroxicam	1.0
Carboxyvinyl polymer 940	1.0
Ethanol	30.0
Propylene glycol	10.0
Polyethylene glycol 300	10.0
Diethanolamine	1.7
Carboxymethyl cellulose	1.0
Distilled water	remaining part

Example 6

The following ingredients were combined and blended uniformly together to produce an ointment formulation having a pH of 8.2:

	Percent by weight
Piroxicam	1.0
Carboxyvinyl polymer 940	1.0
Ethanol	30.0
Glycerine	20.0
Diethanolamine	1.3
Triethylamine	q.s.
Hydroxyethyl cellulose	0.5
Distilled water	remaining part

Example 7

The following ingredients were combined and blended uniformly together to produce an ointment formulation having a pH of 7.6:

	Percent by weight
Piroxicam	1.0
Carboxyvinyl polymer 940	0.7
Ethanol	35.0
Propylene glycol	20.0
Polyethylene glycol 300	10.0
Diisopropanolamine	1.5
Distilled water	remaining part

Example 8

The following ingredients were combined and blended uniformly together to produce an ointment formulation having a pH of 6.7:

	Percent by weight
Piroxicam	1.0
Carboxyvinyl polymer 940	1.0
Ethanol	40.0
Polyethylene glycol 300	20.0
Diisopropanolamine	1.0
Triethylamine	q.s.
Distilled water	remaining part

Example 9

The following ingredients were combined and blended uniformly together to produce an ointment formulation having a pH of 7.7:

	Percent by weight
Piroxicam	0.5
Carboxyvinyl polymer 940	0.7
Ethanol	25.0
Propylene glycol	20.0
Benzyl alcohol	1.0
Hydroxyethyl cellulose	0.4
Diisopropanolamine	1.2
Water	51.2

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Example 10

The following ingredients were combined and blended uniformly together to produce an ointment formulation having a pH of 7.8:

	Percent by weight
Piroxicam	1.0
Carboxyvinyl polymer 940	0.9
Ethanol	30.0
Propylene glycol	7.5
Polyethylene glycol 300	7.5
Benzyl alcohol	1.0
Hydroxyethyl cellulose	0.5
Diisopropanolamine	1.7
Water	49.9

Example 11

Analgesic Testing

Piroxicam ointment (1%), prepared according to Example 10 at a dose level of 100 mg per mouse was administered topically to a group of ten mice on the paw of their hind legs in order to determine the effects of the compositions of this invention on adjuvant induced pain in the joints. Pain threshold values were measured five hours later by means of an Analgesy-meter (UGO BASILE) and the results obtained are shown below in the following table (Table 5):

TABLE 5

Drug	Pain threshold value (g) Before administration	Five hours later
Control (non-drug)	46.7 ± 3.3	46.7 ± 2.0
1% Piroxicam ointment	42.2 ± 3.2	105.6 ± 17.5

The above test results indicate that the compositions of this invention are active analgesics against adjuvant induced joint paint.

Example 12

Anti-inflammatory Activity

The anti-inflammatory activity of the compositions of this invention was determined using the standard carragenin-induced rat foot edema test. [C.A. Winter et al., *Proceedings of the Society for Experimental Biology and Medicine*, Vol. 111, p.544 (1962)]. Piroxicam ointment (1%), prepared according to Example 10, was administered topically at a dose level of 100 mg. per rat. The results obtained are presented in the table below (Table 6) in terms of the percent inhibition of edema formation, as compared to the non-drug treated control and the oral administration of piroxicam (1 mg./kg.):

TABLE 6

Drug	% Inhibition of edema
1% Piroxicam ointment	41.6
Oral administration	39.6
Control	—

The above test results indicate that the compositions of this invention inhibit the edema formation significantly and they are as effective as the oral route of piroxicam administration.

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Claims for the Contracting States: BE CH DE FR GB IT LI NL SE

1. A topical anti-inflammatory composition in gel ointment form in an aqueous system characterised in that it comprises an effective anti-inflammatory amount of piroxicam; from 10% to 50% by weight of a lower alkanol having from one to four carbon atoms; a gel-forming amount of carboxyvinyl polymer; from 5% to 40% by weight of at least one polyhydric alcohol selected from the lower alkylene glycols having from two to six carbon atoms, glycerine and the polyethylene glycols having an average molecular weight of from 200 to 2,000; and a piroxicam-solubilizing amount of at least one alkanolamine selected from the monoalkanolamines having from one to four carbon atoms, the dialkanolamines having from two to eight carbon atoms and the trialkanolamines having from three to twelve carbon atoms, and sufficient water to total 100%, said composition having a pH range of from 6.5 to 9.0.

2. A composition as claimed in claim 1 wherein piroxicam is present at a concentration level of 0.3% to 2.0% by weight of the composition.

3. A composition as claimed in claim 1 or claim 2 wherein the carboxyvinyl polymer is present at a concentration level of 0.2% to 2.0% by weight of the composition.

4. A composition as claimed in any preceding claim wherein said alkanolamine is present at a concentration level of up to 3.0% by weight of the composition.

5. A composition as claimed in any preceding claim wherein water is present at a concentration level of 30% to 60% by weight of the composition.

6. A composition as claimed in any preceding claim which also comprises a film-forming amount of at least one film-forming agent selected from carboxymethyl cellulose, hydroxyethyl cellulose and polyvinylpyrrolidone.

7. A composition as claimed in claim 6 wherein said film-forming agent is present at a concentration level of 0.2% to 2.0% by weight of the composition.

Claims for the Contracting State: AT

1. A process for preparing a topical anti-inflammatory composition in gel ointment form in an aqueous system characterised by the steps of:

(a) dispersing a carboxyvinyl polymer in water;

(b) blending the resulting aqueous dispersion with a lower alkanol having from one to four carbon atoms and at least one polyhydric alcohol selected from the lower alkylene glycols having from two to six carbon atoms, glycerine and the polyethylene glycols having an average molecular weight of from 200 to 2,000;

(c) dissolving piroxicam in an aqueous solution of a piroxicam-solubilizing amount of at least one alkanolamine selected from the monoalkanolamines having from one to four carbon atoms, the dialkanolamines having from two to eight carbon atoms and the trialkanolamines having from three to twelve carbon atoms;

(d) combining the aqueous solution obtained in step (c) and the alcoholic mixture obtained in step (b) and thereafter subjecting the resulting mixture to constant agitation to form a gel ointment; the amounts of the ingredients being such as to provide in the gel ointment so formed a gel-forming amount of carboxyvinyl polymer, from 10% to 50% of lower alkanol, from 5% to 40% by by weight of polyhydric alcohol, an effective anti-inflammatory amount of piroxicam, sufficient water to total 100%, and a pH in the range from 6.5 to 9.0.

2. A process as claimed in claim 1, wherein the piroxicam is present at a concentration level of 0.3% to 2.0% by weight of the composition.

3. A process as claimed in claim 1 or claim 2, wherein the carboxyvinyl polymer is present at a concentration level of 0.2% to 2.0% by weight of the composition.

4. A process as claimed in any preceding claim, wherein the alkanolamine is present at a concentration level of up to 3.0% by weight of the composition.

5. A process as claimed in any preceding claim, wherein the water is present at a concentration level of 30% to 60% by weight of the composition.

6. A process as claimed in any preceding claim, wherein a film-forming amount of at least one film-forming agent selected from carboxymethyl cellulose, hydroxyethyl cellulose and polyvinylpyrrolidone is dispersed in the water with the carboxyvinyl polymer in step (a).

7. A process as claimed in claim 6, wherein the film-forming agent is present at a concentration level of 0.2% to 2.0% by weight of the composition.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI NL SE

1. Topisches, entzündungshemmendes Mittel in Gelsalbenform in einem wäßrigen System, dadurch gekennzeichnet, daß es eine wirksame, entzündungshemmende Menge Piroxicam, 10 Gew.-% bis 50 Gew.-% eines niederen Alkanols mit ein bis vier Kohlenstoffatomen, eine gelbildende Menge an Carboxyvinylpolymerem, 5 Gew.-% bis 40 Gew.-% wenigstens eines mehrwertigen Alkohols, ausgewählt unter den niederen Alkylenglycolen mit zwei bis sechs Kohlenstoffatomen, Glycerin und den Polyethylenglycolen mit

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einem durchschnittlichen Molekulargewicht von 200 bis 2000, und eine Piroxicam löslich machende Menge wenigstens eines Alkanolamins, ausgewählt unter den Monoalkanolaminen mit ein bis vier Kohlenstoffatomen, den Dialkanolaminen mit zwei bis acht Kohlenstoffatomen und den Trialkanolaminen mit drei bis zwölf Kohlenstoffatmen, und ausreichend Wasser bis zur Summe von 100% enthält, wobei das Mittel einen pH-Bereich von 6,5 bis 9,0 hat.

2. Mittel nach Anspruch 1, worin Piroxicam in einer Konzentration von 0,3 Gew.-% bis 2,0 Gew.-% des Mittels vorliegt.

3. Mittel nach Anspruch 1 oder 2, worin das Carboxyvinylpolymere in einer Konzentration von 0,2 Gew.-% bis 2,0 Gew.-% des Mittels vorliegt.

4. Mittel nach einem beliebigen der voranstehenden Ansprüche, worin das Alkanolamin in einer Konzentration von bis zu 3,0 Gew.-% des Mittels vorliegt.

5. Mittel nach einem beliebigen der voranstehenden Ansprüche, worin Wasser in einer Konzentration von 30 Gew.-% bis 60 Gew.-% des Mittels vorliegt.

6. Mittel nach einem beliebigen der voranstehenden Ansprüche, welches außerdem eine filmbildende Menge wenigstens eines filmbildenden Mittels, ausgewählt unter Carboxymethylcellulose, Hydroxyethylcellulose und Polyvinylpyrrolidon, enthält.

7. Mittel nach Anspruch 6, worin das filmbildende Mittel in einer Konzentration von 0,2 Gew.-% bis 2,0.-% des Mittels vorliegt.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellen eines topischen, entzündungshemmenden Mittels in Gelsalbenform in einem wäßrigen System, gekennzeichnet durch die Schritte:

(a) Dispergieren eines Carboxyvinylpolymeren in Wasser,

(b) Mischen der anfallenden wäßrigen Dispersion mit einem niederen Alkanol mit ein bis vier Kohlenstoffatomen und wenigstens einem mehrwertigen Alkohol, ausgewählt unter den niederen Alkylenglycolen mit zwei bis sechs Kohlenstoffatomen, Glycerin und den Polyethylenglycolen mit einem durchschnittlichen Molekulargewicht von 200 bis 2000,

(c) Lösen des Piroxicams in einer waßrigen Lösung einer Piroxicam löslich machenden Menge von wenigstens einem Alkanolamin, ausgewählt unter den Monoalkanolamin mit einem bis vier Kohlenstoffatomen, den Dialkanolaminen mit zwei bis acht Kohlenstoffatomen und den Trialkanolaminen mit drei bis zwölf Kohlenstoffatomen,

(d) Kombinieren der wäßrigen, in Stufe (c) erhaltenen Lösung und des in Stufe (b) erhaltenen, alkoholischen Gemischs und anschließendes gleichmäßiges Bewegen der entstandenen Mischung, um eine Gelsalbe zu bilden, wobei die Mengen der Bestandeteile so gewählt sind, daß in der so gebildeten Gelsalbe eine gelbildende Menge an Carboxyvinylpolymerem, 10 Gew.-% bis 50 Gew.-% niederes Alkanol, 5 Gew.-% bis 40 Gew.-% mehrwertiger Alkohol, eine wirksame, entzündungshemmende Menge Piroxicam, ausreichend Wasser bis zur Summe von 100% und ein pH im Bereich von 6,5 bis 9,0 bereitgestellt wird.

2. Verfahren nach Anspruch 1, worin das Piroxicam in einer Konzentration von 0,3 Gew.-% bis 2,0 Gew.-% des Mittels vorliegt.

3. Verfahren nach Anspruch 1 oder 2, worin das Carboxyvinylpolymere in einer Konzentration von 0,2 Gew.-% bis 2,0 Gew.-% des Mittels vorliegt.

4. Verfahren nach einem beliebigen der voranstehenden Ansprüche, worin das Alkanolamin in einer Konzentration von bis zu 3,0 Gew.-% des Mittels vorliegt.

5. Verfahren nach einem beliebigen der voranstehenden Ansprüche, worin das Wasser in einer Konzentration von 30 Gew.-% bis 60 Gew.-% des Mittels vorliegt.

6. Verfahren nach einem beliebigen der voranstehenden Ansprüche, worin eine filmbildende Menge wengistens eines filmbildenden Mittels, ausgewählt unter Carboxymethylcellulose, Hydroxyethylcellulose und Polyvinylpyrrolidon, in Schritt (a) in dem Wasser mit dem Carboxyvinylpolymeren dispergiert wird.

7. Verfahren nach Anspruch 6, worin das filmbildende Mittel in einer Konzentration von 0,2 Gew.-% bis 2,0 Gew.-% des Mittels vorliegt.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI NL SE

1. Composition topique anti-inflammatoire sous forme de gel en milieu aqueux, caractérisée en ce qu'elle comprend une quantité efficace du point de vue anti-inflammatoire de piroxicam; 10% à 50% en poids d'un alcanol inférieur ayant un à quatre atomes de carbone; une quantité, apte à former un gel, de polymère carboxyvinylique; 5% à 40% en poids d'au moins un alcool polyhydroxylique choisi entre les alkylèneglycols inférieurs ayant deux à six atomes de carbone, le glycérol et les polyéthylèneglycols ayant un poids moléculaire moyen de 200 à 2000; et une quantité, propre à la solubilisation du piroxicam, d'au moins une alcanolamine choisie entre les monoalcanolamines ayant un à quatre atomes de carbone, les dialcanolamines ayant deux à huit atomes de carbone et les trialcanolamines ayant trois à douze atomes de

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carbone, et une quantité d'eau suffisante pour atteindre un total de 100%, ladite composition ayant un pH compris dans l'intervalle de 6,5 à 9,0.

2. Composition suivant la revendication 1, dans laquelle le piroxicam est présent à une concentration de 0,3% à 2,0% en poids de la composition.

3. Composition suivant la revendication 1 ou la revendication 2, dans laquelle le polymère carboxyvinylique est présent à une concentration de 0,2% à 2,0% en poids de la composition.

4. Composition suivant l'une quelconque des revendications précédentes, dans laquelle l'alcanolamine est présente à une concentration allant jusqu'à 3,0% en poids de la composition.

5. Composition suivant l'une quelconque des revendications précédentes, dans laquelle l'eau est présente à une concentration de 30% à 60% en poids de la composition.

6. Composition suivant l'une quelconque des revendications précédentes, qui comprend également une quantité, apte à former un film, d'au moins un agent filmogène choisi entre la carboxyméthylcellulose, l'hydroxyéthylcellulose et la polyvinylpyrrolidone.

7. Composition suivant la revendication 6, dans laquelle l'agent filmogène est présent à une concentration de 0,2% à 2,0% en poids de la composition.

Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'une compositiuon topique anti-inflammatoire sous forme de gel en milieu aqueux, caractérisé en ce qu'il comprend les étapes consistant:

(a) à disperser un polymère carboxyvinylique dans de l'eau;

(b) à mélanger la dispersion aqueuse résultante à un alcanol inférieur ayant un à quatre atomes de carbone et à au moins un alcool polyhydroxylique choisi entre les alkylèneglycols inférieurs ayant deux à six atomes de carbone, le glycérol et les polyéthylèneglycols ayant un poids moléculaire moyen de 200 à 2000;

(c) à dissoudre du piroxicam dans une solution aqueuse d'une quantité, propre à la solubilisation du piroxicam, d'au moins une alcanolamine choisie entre les monoalcanolamines ayant un à quatre atomes de carbone, les dialcanolamines ayant deux à huit atomes de carbone et les trialcanolamines ayant trois à douze atomes de carbone;

(d) à rassembler la solution aqueuse obtenue dans l'étape (c) et le mélange alcoolilque obtenu dans l'étape (b), puis à sommetre le mélange résultant à une agitation constante pour former un gel; les quantités des ingrédients étant choisies de manière à obtenir dans le gel ainsi formé une quantité, apte à former un gel, de polymère carboxyvinylique, 10% à 50% d'alcanol inférieur, 5% à 40% en poids d'alcool polyhydroxylique, une quantité efficace du point de vue anti-inflammatoire de piroxicam, une quantité d'eau suffisante pour atteindre un total de 100%, et un pH compris dans l'intervalle de 6,5 à 9,0.

2. Procédé suivant la revendication 1, dans lequel le piroxicam est présent à une concentration de 0,3% à 2,0% en poids de la composition.

3. Procédé suivant la revendication 1 ou la revendication 2, dans lequel le polymère carboxyvinylique est présent à une concentration de 0,2% à 2,0% en poids de la composition.

4. Procédé suivant l'une quelconque des revendications précédentes, dans lequel l'alcanolamine est présente à une concentration allant jusqu'à 3,0% en poids de la composition.

5. Procédé suivant l'une quelconque des revendications précédentes, dans lequel l'eau est présente à une concentration de 30% à 60% en poids de la composition.

6. Procédé suivant l'une quelconque des revendications précédentes, dans lequel une quantité, apte à former un gel, d'au moins un agent filmogène, choisi entre la carboxyméthylcellulose, l'hydroxyéthylcellulose et la polyvinylpyrrolidone, est dispersée dans l'eau avec le polymère carboxyvinylique dans l'étape (a).

7. Procédé suivant la revendication 6, dans lequel l'agent filmogène est présent à une concentration de 0,2% à 2,0% en poids de la composition.