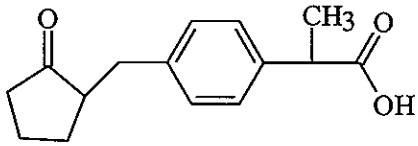
PHARMACEUTICAL COMPOSITION FOR INTRAMUSCULAR INJECTION CONTAINING LOXOPROFEN

TECHNICAL FIELD

The present invention relates to a novel pharmaceutical formulation containing loxoprofen. In particular, the invention relates to the formulation for intramuscular injection containing loxoprofen or a pharmaceutically acceptable salt thereof, which has an excellent anti-inflammatory analgesic effect, as the active ingredient.

BACKGROUND ART

Loxoprofen (chemical name: 2-[4-(2-oxocyclopentyl)phenyl]propionic acid) is a nonsteroidal anti-inflammatory drug (NSAID) of propionic acid type and is represented by the following formula:



The above drug is usually used in the form of a sodium salt, that is, as loxoprofen sodium.

Loxoprofen sodium is effective for the treatment of rheumatoid arthritis, deformant arthritis, lumbosacral strain, adhesive capsulitis and shoulder-arm-neck syndrome. The drug is also known to be effective for relief of post-operative or post-traumatic pains, or for pain relief after tooth extraction. Currently, it is widely used in an oral tablet.

The above drug causes relatively less gastroenteric disorders than any other

propionic acid-type NSAIDs, but still causes such side effects as gastroenteric disorders and peptic ulcer upon a long-term administration. Therefore, several studies have been recently carried out to develop transdermal formulations thereof such as sustained release adhesive preparations [PCT/JP1997/02936, Korean Patent Application No 98-41351 (October 1, 1998), US Patent No. 4,740,374 (April 26, 1988), PCT/WO95/16440 (June 22, 1995), Korean Patent Application No. 96-38430 (September 5, 1996)]. Such transdermal formulations have the advantage that they can alleviate side effects or uneasiness from administration of oral formulations for patients having difficulty in oral absorption or requiring a long-term administration. However, the above formulations must also comprise polymers in the same manner as the previously developed adhesive preparations and thus, may cause skin eruptions due to long-term adhesion or skin allergies such as itching, *etc.* They also cause other side effect such as discomfort in motions of patients. Further, even though the absorption rate of a drug through the skin can be controlled, it takes a long time to obtain the desired therapeutic effect due to difference in the percutaneous absorption rate or absorption amount, depending on a part of pain and physical constitution of each individual. Thus, the transdermal formulations have a drawback that they cannot be used in such emergent cases as suffering from severe pains.

Loxoprofen sodium has a different reaction mechanism from ketoprofen and ibuprofen, generally known propionic acid-type NSAIDs. It has an excellent anti-inflammatory analgesic effect by the inhibitory action on the biosynthesis of prostaglandin, a causative agent of inflammation and pain. That is, this drug is a pro-drug, which is converted into a trans-OH metabolite, *i.e.* 2-[para-(trans-2-hydroxycyclopentyl) phenyl]propionic acid *in vivo* through the metabolism by a ketone reductase upon oral administration. The above metabolite exhibits an excellent anti-inflammatory analgesic effect by the inhibitory action on cyclooxygenase, a prostaglandin synthetase [Matsuda *et al.*, Japanese Journal of Inflammation, Vol. 2, No. 3, Summer, pp263-266 (1983)]. The ketone reductase is mainly distributed in liver or kidney [Tanaka *et al.*, Japanese Journal of Inflammation, Vol. 3, No. 2, Spring, pp151-155 (1983)]. The enzyme metabolizes loxoprofen sodium into the trans-OH metabolite to exhibit the strong anti-inflammatory

analgesic effect. This enzyme is also known to exist on the surface of the skin to exhibit the equivalent pharmacological effect [US Patent No. 4,740,374 (April 26, 1988)]. For the above reason, oral formulations such as tablets containing loxoprofen or a pharmaceutically acceptable salt thereof as an active ingredient are widely commercialized (Loxonin or Loxfen). Also, external formulations such as adhesive preparations and patches have been recently studied. By contrast, no intramuscular injection of this drug has been reported.

As previously described, it is difficult to administer oral formulations of loxoprofen, which have been developed hitherto, in serious cases with difficulty in the oral absorption or cases with gastroenteric disorders. However, patches under extensive studies have not yet been developed completely. Also, the transdermal formulation of loxoprofen must contain many auxiliary agents such as penetration enhancing agents and thus, may cause side effects such as skin eruptions. Moreover, they may cause such discomforts as restricting motions due to the long-term adhesion onto a particular part of the body. Particularly, since inflammation or pain is likely to occur in a joint, patches for percutaneous absorption are likely to have many problems in continuously providing the desired pharmacological effects, for example, because they are easily detached from the skin by motions of a joint.

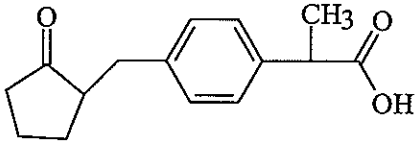
Therefore, it has been needed to develop a novel formulation of loxoprofen, which can also be applied to patients with difficulty in the oral absorption and can solve all the drawbacks due to the transdermal administration.

DISCLOSURE OF THE INVENTION

The present inventors performed extensive studies to develop a novel formulation of loxoprofen. As a result, the inventors found that loxoprofen sodium can provide an excellent anti-inflammatory analgesic effect not only on the skin but also in the muscle through the conversion into the trans-OH metabolite by the ketone reductase. Based on

the above, the inventors identified that an intramuscular injection of loxoprofen is also applicable to patients having difficulty in the oral absorption. Moreover, it was found that as compared with the oral formulations, it has an equivalent or higher anti-inflammatory analgesic effect even in smaller quantities and has a fast action without any side effect in the oral formulations. Accordingly, the following present invention was completed.

The present invention relates to a pharmaceutical composition for intramuscular



injection containing loxoprofen of the following formula:

, or a pharmaceutically acceptable salt thereof as the active ingredient.

In a preferable embodiment, the pharmaceutically acceptable salt of loxoprofen is loxoprofen sodium.

Hereinafter, the present invention will be explained in more detail. As described above, loxoprofen or a pharmaceutically acceptable salt thereof is absorbed into the gastrointestinal tract in inactivated forms upon oral administration. Then, it is converted into trans-OH metabolites by action of ketone reductases in the liver or kidney to provide an excellent anti-inflammatory analgesic effect. It is also converted into trans-OH metabolites by action of ketone reductases on the skin to show the same effect. However, the present inventors identified that in the muscle, they are also convertible into trans-OH metabolites by ketone reductases to have the similar effect, particularly, an equivalent or higher effect even in 1/2 to 2/3 of the tablet quantities. In addition, it is generally the first requirement for treating patients suffering from pains to obtain an anti-inflammatory analgesic effect. The present intramuscular injection also provides the fast action satisfying the above requirement.

The invention provides an intramuscularly injectable formulation of loxoprofen, which can solve side effects of oral formulations such as tablets, *e.g.* limitation in use for patients having difficulty in the oral absorption or having gastroenteric disorders upon long-term administration. The formulation simultaneously solves side effects of formulations for external use, *e.g.* discomfort in use, skin allergies and the like. Particularly, it can be conveniently used for patients in need of the fast pharmacological effect.

The formulation of the present invention may be properly prescribed. In order to keep the storage stability, an acidic aqueous solution or a buffer such as a phosphate buffer, which is injectable, may be used to adjust its pH thereby to give the injection excellent physical and chemical stability.

More specifically, the present formulation may be prepared by dissolving loxoprofen or a pharmaceutically acceptable salt in the water for injection in combination with a stabilizing agent or a solubilizing aid and sterilizing the obtained solution, for example, at a high temperature under vacuum or by aseptic filtration. The water for injection may be the distilled water or a buffer, for example, a phosphate buffer or a sodium dihydrogen phosphate (NaH_2PO_4)-citric acid buffer having the pH in the range of 3.5 to 7.5. The phosphate may be in the form of sodium or potassium salt, or anhydrous or hydrate, and the citric acid may be in the form of anhydrous or hydrate. The stabilizing agent, which can be used in the present invention, may be sodium pyrosulfite, sodium bisulfite ($NaHSO_3$), sodium metabisulfite ($Na_2S_2O_3$), or ethylene diamine tetraacetic acid. The solubilizing aid may be a base such as sodium hydroxide (NaOH), sodium bicarbonate ($NaHCO_3$), sodium carbonate (Na_2CO_3) and potassium hydroxide (KOH), or an acid such as hydrochloric acid (HCl) or acetic acid (CH_3COOH).

The formulation of the present invention is preferably a solution having the pH in range of 3.5 to 7.5, or a powder prepared by sterilization and freeze-drying. The

concentration of the active ingredient is preferably in the range of 2 to 20%.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a comparative distribution curve of the drug plasma concentrations of loxoprofen between tablet and intramuscular injection.

BEST MODE FOR CARRYING OUT THE INVENTION

This invention will be better understood from the following examples. However, one skilled in the art will readily appreciate the specific materials and results described are merely illustrative of, and are not intended to, nor should be intended to, limit the invention as described more fully in the claims which follows thereafter.

Preparation of Injectable Solution

Example 1:

Loxoprofen sodium and sodium pyrosulfite were dissolved in the distilled water for injection. The solution was sterilized at a high temperature under vacuum and filled into a 1 ml ampule to give an intramuscular injection (Table 1).

Table 1: Composition of the 1 ml intramuscular injection of loxoprofen

Ingredients	Contents
Loxoprofen sodium	6.81%(w/v)
Sodium pyrosulfite	0.2%(w/v)
d.w. for injection	ad 1 ml

Example 2:

Loxoprofen sodium and sodium pyrosulfite were dissolved in the distilled water

for injection. Thereto was added dilute hydrochloric acid to adjust the pH to 6. The resulting solution was sterilized at a high temperature under vacuum, or by aseptic filtration, and filled into a 1 ml ampule to give an intramuscular injection (Table 2).

Table 2: Composition of the 1 ml intramuscular injection of loxoprofen

Ingredients	Contents
Loxoprofen sodium	6.81%(w/v)
Sodium pyrosulfite	0.1%(w/v)
d.w. for injection	ad 1 ml
Dilute hydrochloric acid	q.s. (pH 6)

Example 3:

Loxoprofen sodium and sodium pyrosulfite were dissolved in the distilled water for injection. Thereto was added dilute hydrochloric acid to adjust the pH to 5. The resulting solution was sterilized at a high temperature under vacuum, or by aseptic filtration, and filled into a 1 ml ampule to give an intramuscular injection (Table 3).

Table 3: Composition of the 1 ml intramuscular injection of loxoprofen

Ingredients	Contents
Loxoprofen sodium	6.81%(w/v)
Sodium pyrosulfite	0.1%(w/v)
d.w. for injection	ad 1 ml
Dilute hydrochloric acid	q.s. (pH 5)

Example 4:

Loxoprofen sodium and sodium metabisulfite were dissolved in the distilled water for injection. Thereto was added dilute hydrochloric acid to adjust the pH to 4. The resulting solution was sterilized at a high temperature under vacuum, or by aseptic filtration, and filled into a 1 ml ampule to give an intramuscular injection (Table 4).

Table 4: Composition of the 1 ml intramuscular injection of loxoprofen

Ingredients	Contents
Loxoprofen sodium	6.81%(w/v)
Sodium metabisulfite ($Na_2S_2O_5$)	0.2%(w/v)
d.w. for injection	ad 1 ml
Dilute hydrochloric acid	q.s. (pH 4)

Example 5:

Potassium dihydrogen phosphate and sodium hydroxide were dissolved in the distilled water for injection to prepare a phosphate buffer solution of pH 6.5. To the prepared buffer solution were dissolved loxoprofen sodium and sodium pyrosulfite. The resulting solution was sterilized at a high temperature under vacuum, or by aseptic filtration, and filled into a 1 ml ampule to give an intramuscular injection (Table 5).

Table 5: Composition of the 1 ml intramuscular injection of loxoprofen

Ingredients	Contents
Loxoprofen sodium	6.81%(w/v)
Sodium pyrosulfite	0.2%(w/v)
Potassium dihydrogen phosphate (KH_2PO_4)	0.68%(w/v)
Sodium hydroxide (NaOH)	0.06%(w/v)
d.w. for injection	ad 1 ml

Example 6:

Sodium dihydrogen phosphate·dodecahydrate and citric acid were dissolved in the distilled water for injection to prepare a sodium dihydrogen phosphate-citric acid buffer solution of pH 5.4. To the prepared buffer solution were dissolved loxoprofen sodium and sodium pyrosulfite. The resulting solution was sterilized at a high temperature under vacuum, or by aseptic filtration, and filled into a 1 ml ampule to give an intramuscular injection (Table 6).

Table 6: Composition of the 1 ml intramuscular injection of loxoprofen

Ingredients	Contents
Loxoprofen sodium	6.81%(w/v)
Sodium pyrosulfite	0.2%(w/v)

Sodium dihydrogen phosphate·dodecahydrate ($NaH_2PO_4 \cdot 12H_2O$)	1.45%(w/v)
Citric acid	0.53%(w/v)
d.w. for injection	Ad 1 ml

Example 7:

Potassium dihydrogen phosphate and anhydrous sodium monohydrogen phosphate were dissolved in the distilled water for injection to prepare phosphate buffer solution of pH 6.8. To the prepared buffer solution were dissolved loxoprofen sodium and sodium pyrosulfite. The resulting solution was sterilized at a high temperature under vacuum, and filled into a 1 ml ampule to give an intramuscular injection (Table 7).

Table 7: Composition of the 1 ml intramuscular injection of loxoprofen

Ingredients	Contents
Loxoprofen sodium	6.81%(w/v)
Sodium pyrosulfite	0.2%(w/v)
Potassium dihydrogen phosphate (KH_2PO_4)	0.34%(w/v)
Anhydrous sodium monohydrogen phosphate (Na_2HPO_4)	0.34%(w/v)
d.w. for injection	Ad 1 ml

Example 8:

Potassium dihydrogen phosphate and sodium hydroxide were dissolved in the distilled water for injection to prepare a phosphate buffer solution of pH 7.0. To the prepared buffer solution were dissolved loxoprofen sodium and sodium pyrosulfite. The resulting solution was sterilized at a high temperature under vacuum, and filled into a 1 ml ampule to give an intramuscular injection (Table 8).

Table 8: Composition of the 1 ml intramuscular injection of loxoprofen

Ingredients	Contents
Loxoprofen sodium	6.81%(w/v)
Sodium pyrosulfite	0.2%(w/v)
Potassium dihydrogen phosphate (KH_2PO_4)	0.68%(w/v)
Sodium hydroxide (NaOH)	0.12%(w/v)
d.w. for injection	ad 1 ml

Example 9:

Potassium dihydrogen phosphate and sodium hydroxide were dissolved in the distilled water for injection to prepare a phosphate buffer solution of pH 7.4. To the prepared buffer solution were dissolved loxoprofen sodium and sodium pyrosulfite. The resulting solution was sterilized at a high temperature under vacuum, and filled into a 1 ml ampule to give an intramuscular injection (Table 9).

Table 9: Composition of the 1 ml intramuscular injection of loxoprofen

Ingredients	Contents
Loxoprofen sodium	6.81%(w/v)
Sodium pyrosulfite	0.4%(w/v)
Potassium dihydrogen phosphate (KH_2PO_4)	0.68%(w/v)
Sodium hydroxide (NaOH)	0.16%(w/v)
d.w. for injection	ad 1 ml

Example 10:

Loxoprofen sodium, sodium pyrosulfite and mannitol were dissolved in the distilled water for injection. The solution was sterilized at a high temperature under vacuum, and filled into a 1 ml ampule to give an intramuscular injection (Table 10).

Table 10: Composition of the 1 ml intramuscular injection of loxoprofen

Ingredients	Contents
Loxoprofen sodium	6.81%(w/v)
Sodium pyrosulfite	0.4%(w/v)
Mannitol	5.0%(w/v)
d.w. for injection	ad 1 ml

Preparation of Injectable Powder

Example 11:

Loxoprofen sodium and mannitol were dissolved in the distilled water for injection. The solution was aseptically filtered and then, introduced into a vial. The vial was freeze-dried to prepare a dry powdered product. Before the use, to the vial was added 1 ml of the distilled water, which was packaged separately from the vial, and stirred to the complete dissolution to give an intramuscular injection (Table 11).

Table 11: Composition of the 1 ml intramuscular injection of loxoprofen

Ingredients	Contents
Loxoprofen sodium	6.81%(w/v)
Sodium pyrosulfite	0.4%(w/v)
Mannitol	20.0%(w/v)
d.w. for injection	ad 1 ml

Example 12:

Potassium dihydrogen phosphate and sodium hydroxide were dissolved in the distilled water for injection to prepare a phosphate buffer solution of pH 6.5. To the prepared buffer solution were completely dissolved mannitol, loxoprofen sodium and sodium pyrosulfite. The resulting solution was aseptically filtered and introduced into a vial. The vial was freeze-dried to prepare a dry powdered product. Before the use, to the vial was added 1 ml of the distilled water, which was packaged separately from the vial, and stirred to the complete dissolution to give an intramuscular injection (Table 12).

Table 12: Composition of the 1 ml intramuscular injection of loxoprofen

Ingredients	Contents
Loxoprofen sodium	6.81%(w/v)
Sodium pyrosulfite	0.4%(w/v)
Potassium dihydrogen phosphate (KH_2PO_4)	20.0%(w/v)
Sodium hydroxide (NaOH)	0.06%(w/v)
Mannitol	25.0%(w/v)
d.w. for injection	ad 1 ml

Example 13:

Loxoprofen and sodium bicarbonate were dissolved in the distilled water to prepare a solution of 1 ml. To this solution was added sodium pyrosulfite and the mixture was stirred to the complete dissolution. The resulting solution was aseptically filtered and introduced into a vial. The vial was freeze-dried to prepare a dry powdered product. Before the use, to the vial was added 1 ml of the distilled water, which was packaged separately from the vial, and stirred to the complete dissolution to give an intramuscular injection (Table 13).

Table 13: Composition of the 1 ml intramuscular injection of loxoprofen

Ingredients	Contents
Loxoprofen	6.25%(w/v)
Sodium pyrosulfite	0.4%(w/v)
Sodium bicarbonate ($NaHCO_3$)	2.13%(w/v)
d.w. for injection	ad 1 ml

Example 14:

Loxoprofen and sodium hydroxide were dissolved in the distilled water to prepare a solution of 1 ml. To this solution was added sodium pyrosulfite and the mixture was stirred to the complete dissolution. The resulting solution was aseptically filtered and introduced into a vial. The vial was freeze-dried to prepare a dry powdered product. Before the use, to the vial was added 1 ml of the distilled water, which was packaged separately from the vial. The mixture was stirred to the complete dissolution to give an intramuscular injection (Table 13).

Table 14: Composition of the 1 ml intramuscular injection of loxoprofen

Ingredients	Contents
Loxoprofen	6.25%(w/v)
Sodium pyrosulfite	0.4%(w/v)
Sodium hydroxide (NaOH)	2.13%(w/v)
d.w. for injection	ad 1 ml

Experiment 1: Comparison of the drug plasma concentrations of loxoprofen between

tablet and intramuscular injection in rats

The plasma concentration of loxoprofen in the intramuscular injection obtained from Example 1 was evaluated and compared with the commercially available loxoprofen tablet (Loxonin: control) in male SD rats of 6 weeks old free from specific pathogens.

In the control group, the formulation was orally administered to the rats with a single dose of 10 mg/kg. In the experimental group, the formulation was intramuscularly injected to the rats with a single dose of 5 mg/kg. The blood gathered from the rats at 2, 5, 10, 20, 30, 60, 120 and 180 minutes after the administration and pretreated. Then, the drug plasma concentrations were analyzed. The following results are the plasma concentration of loxoprofen (μg/ml) vs. time (min).

Table 15: Comparison of the drug plasma concentrations of loxoprofen between tablet and intramuscular injection

Time (min)	Drug plasma concentration (μg/ml) of intramuscular injection	Drug plasma concentration (μg/ml) of tablet
2	4.0	4.1
5	4.5	5.5
10	5.6	5.8
20	6.5	7.4
60	5.4	6.5
120	4.1	5.0
180	2.8	3.7

As shown in the above Table 15, because the intramuscular injection was administered at the amount of 50% of the tablet, the drug plasma concentration thereof was shown to be slightly lower than that of the tablet. However, the curves of the drug plasma concentration change between the experimental and the control group were shown to be similar (Fig. 1)

Experiment 2: Stability test of intramuscular injection

Samples were taken from the intramuscular injection of loxoprofen obtained from Example 1 stored at the room temperature, 50 °C and 60 °C, for 1, 3 and 4 weeks, respectively. Subsequently, the drug content and variation in the pH were measured. The results are shown in the following Table 16.

Table 16a: Variation in the drug content of loxoprofen intramuscular injection

Storage temperature	0 week	1 week	3 weeks	4 weeks
R.T.	100.1%	99.8%	99.7%	99.9%
50 °C	99.6%	98.6%	99.5%	99.8%
60 °C	99.6%	100.1%	99.3%	98.9%

Table 16b: Variation in the pH of loxoprofen intramuscular injection

Storage temperature	0 week	1 week	3 weeks	4 weeks
R.T.	6.46	6.43	6.43	6.42
50 °C	6.44	6.44	6.44	6.44
60 °C	6.44	6.44	6.44	6.45

As shown in the above Table 16, both of the drug content and the pH in the loxoprofen intramuscular injection were stably maintained without significant variation.

Experiment 3: Comparison of foot edemas of loxoprofen between tablet and intramuscular injection in rats

1) Experimental animal: Male SD rats over 6 weeks old free from specific pathogens

2) Test material and administration dosage: An edema inducing agent, 1% carageenan lambda type IV (Sigma Co.), was subcutaneously injected into the bottom of the paw in the rat to induce the foot edema. Loxoprofen sodium was formulated into 5 mg/2 ml and 10 mg/10 ml solutions for an intramuscular injection using phosphate buffer according to the method in Example 5. The obtained formulations were intramuscularly injected with the dose of 5 mg/2 ml/kg, and orally administered with the dose of 10 mg/ml/kg, respectively.

3) Test method and calculation formula: A standard point was marked in the joint region of the ankle in the left hind paw of the rat and then, the volume of the foot before the administration was measured by plethysmometer (Hugo Sacks & Coulbourn). Test formulations were intramuscularly injected or orally administered to the rats. After 20 minutes, 1% carageenan was subcutaneously injected to the left hind paw of the rats with the dose of 0.1 ml per animal. After 2 hours and 30 minutes, the volume of the foot was measured, and the edema rate and the inhibition rate of edema were calculated by the following formulae:

Edema rate (%) = [(foot edema after injection of the edema inducing agent – foot edema before injection of the edema inducing agent) / foot edema before injection of the edema inducing agent]×100

Inhibition rate of edema (%) = 100 – [average edema rate of the test material-administered group / average edema rate of the non treatment group×100]

4) Evaluation: The significance of the difference in an edema inhibition rate of the experimental group and the control group was verified according to ANOVA. It was concluded that the edema was inhibited in the level of $p<0.05$.

5) Rate of edema and inhibition rate of edema: The results are shown in the following Table 17.

Table 17: Comparison of foot edemas after the administration of loxoprofen between tablet and intramuscular injection

Experimental group	Administration route	Dose per body weight	# of rats	Edema rate (%)	Inhibition rate of edema (%)
Control	Non treatment	-	4	133.2±8.3	-
Injection	Intramuscular injection	5 mg/kg	4	36.0±18.8*	73.0
Tablet	Oral	10 mg/kg	4	31.7±19.0*	76.2

	administration				

*: P<0.05 vs. control group

(The edema rate was expressed in Mean±Standard Deviation)

As shown in the above Table 17, in case of the intramuscular injection of loxoprofen sodium with the dose of 5 mg/kg, the inhibition rate of edema was 73.0%. On the other hand, in case of the oral administration of loxoprofen sodium with the dose of 10 mg/kg, the inhibition rate of edema was 76.2%. Accordingly, the equivalent inhibition rate could be obtained by an intramuscular injection of only 50% dose of the drug compared with the oral administration.

Experiment 4: Comparison of analgesic effects of loxoprofen between tablet and intramuscular injection in rats

1) Experimental animal: Male ICR mice of 5 weeks old free from specific pathogens

2) Test material and administration dosage: Loxoprofen sodium was formulated into solutions of 5 mg/2 ml and 10 mg/10 ml using the phosphate buffer according to the method in Example 5. The solutions were intramuscularly injected with a dose of 5 mg/2 ml/kg, and orally administered with a dose of 10 mg/10 ml/kg, respectively. At 20 minutes after the administration, a pain inducing agent, 0.7% acetic acid in D.W., was intraperitoneally injected with a dose of 10 ml/kg to induce pain. Then, the number of writhing was measured from 5 minutes after inducing pain for 10 minutes.

3) Comparison of analgesic effects: The results are shown in the following Table 18.

Table 18: Comparison of analgesic effect of loxoprofen between tablet and intramuscular injection

Experimental group	Administration route	Dose per body weight	# of mice	# of writhing	Inhibition rate of pain (%)
Control	Non treatment	-	18	35.6± 10.8	-
Injection	Intramuscular injection	5 mg/kg	13	16.5± 10.4*	53.7
Tablet	Oral administration	10 mg/kg	15	17.7± 8.0*	64.0

*: P<0.05 vs. control group

(The number of writhing was expressed in Mean±Standard Deviation)

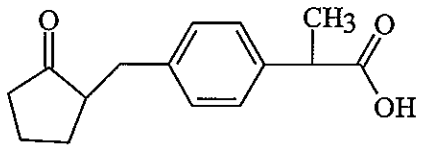
As shown in the above Table 18, in case of the intramuscular injection of loxoprofen sodium with the dose of 5 mg/kg, the inhibition rate of pain was 53.7%. On the other hand, in case of the oral administration of loxoprofen sodium with the dose of 10 mg/kg, the inhibition rate of edema was 64.0%. Accordingly, the dominant inhibition rate of pain could be obtained by an intramuscular injection of only 50% dose of the drug compared with an oral administration.

INDUSTRIAL APPLICABILITY

The intramuscular injection of the present invention can be applied to patients with difficulty in oral absorption, and can also obtain an equivalent or higher anti-inflammatory analgesic effect even in smaller quantities, compared with the oral formulations. Further, it can exhibit the fast action without side effects due to the percutaneous absorption.

Claims

1. A pharmaceutical composition for intramuscular injection containing loxoprofen of the following formula:



or a pharmaceutically acceptable salt thereof, as an active ingredient, wherein the composition is prepared by the process comprising the steps of dissolving loxoprofen or the pharmaceutically acceptable salt thereof in the water for injection in combination with a stabilizing agent or a solubilizing aid followed by sterilizing the obtained solution.

2. The composition according to Claim 1, wherein the pharmaceutically acceptable salt of loxoprofen is loxoprofen sodium.

3. The composition according to Claim 1 sterilized by the treatment at a high temperature under vacuum or by aseptic filtration.

4. The composition according to Claim 1, wherein the water for injection is the distilled water for injection or a buffer solution for injection.

5. The composition according to Claim 4, wherein the buffer solution for injection is a phosphate buffer or a sodium dihydrogen phosphate (NaH_2PO_4)-citric acid buffer solution having the pH in the range of 3.5 to 7.5.

6. The composition according to Claim 5, wherein the phosphate is in the form of sodium or potassium salt, or of anhydrate or hydrate, and the citric acid is in the form of anhydrous or hydrate.

7. The composition according to Claim 1, wherein the stabilizing agent is selected from the group consisting of sodium pyrosulfite, sodium bisulfite ($NaHSO_3$), sodium metabisulfite ($Na_2S_2O_3$) and ethylene diamine tetraacetic acid.

8. The composition according to Claim 1, wherein the solubilizing aid is selected from the group consisting of sodium hydroxide (NaOH), sodium bicarbonate ($NaHCO_3$), sodium carbonate (Na_2CO_3), potassium hydroxide (KOH), hydrochloric acid (HCl) and acetic acid (CH_3COOH).

9. The composition according to Claim 1, which is a solution having the pH in the range of 3.5 to 7.5.

10. The composition according to Claim 1, which is a powder prepared by sterilization followed by freeze-drying.