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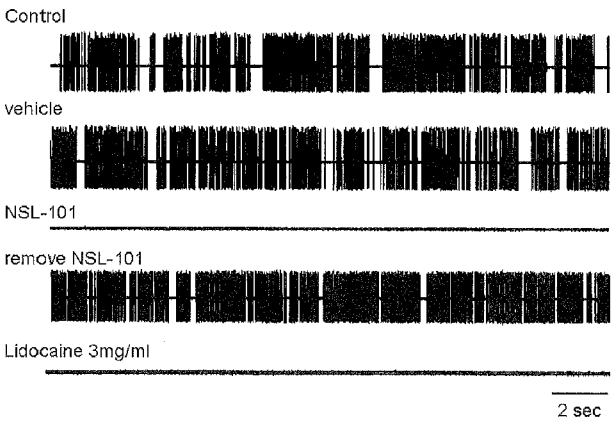
(54) **Title**: LOCAL PHARMACEUTICAL COMPOSITIONS

Figure 2



(57) **Abstract**: The present invention provides a composition adapted to supply locally to the site of need in a patient in need thereof a compound having a pharmaceutical activity, wherein the active agent of said composition comprises an extract of *Spilanthes oleracea*. The composition is of particular use, for example, as an analgesic in providing rapid treatment of neuropathic pain and as a long-lasting anaesthetic. Compositions of the invention for buccal admininistration can preferably be in the form of lozenges, tablets or mucoadhesive gels.

LOCAL PHARMACEUTICAL COMPOSITIONS

Field of the invention

The invention relates to a composition adapted to supply locally to a patient in need thereof a compound having a pharmaceutical activity, wherein the active agent of said composition comprises an extract of *Spilanthes oleracea.*

Aspects of the invention relate to buccal and topical formulations of the said extract including immediate and sustained release formulations.

Background of the invention

Spilanthes oleracea is a native South American herbaceous plant, which has been used for human consumption since pre-Hispanic times, both as food and for its medicinal effects without any known adverse effect. Its medicinal use is featured by its effect as a local anaesthetic (known colloquially as the toothache plant), an anti-bacterial and an anti-fungal agent.

Spilanthes oleracea is a flowering herb in the plant family Asteraceae. It is also known as "toothache plant" or "paracress" as the leaves and flower heads contain an analgesic agent spilanthol as well as other chemical identities including alkaloids.

The active agent has been used in documented empirical form for more than five centuries as a dental analgesic in Peru, with anti-inflammatory and disinfectant effects, in chewed form, with or without other meals.

Traditionally, *Spilanthes oleracea* is used to treat headaches, infections of the throat and gums, and for toothache. Typically it is mixed in equal proportions with conventional additives to form a topical or intradermal injection form. The compositions have been used as topical, ointment or spray forms.

US Patent 6264926 discloses that extracts of *Spilanthes calva* can be used in a natural herbal tooth powder as a synergistic composition with zanthoxylum. *Spilanthes calva* flowers are made into paste in formulation useful as a natural herbal tooth powder and for toothache.

Formulations comprising *Spilanthes oleracea* have also been used against toothache and gum disease and are moderately effective as a local anaesthetic for a duration of 5 to 20 minutes.

Dental procedures and dental surgery are a source of pain for many people worldwide. The pain associated with the extraction of a wisdom tooth is well-known. On average, after surgical extraction, 60% of patients experience moderate pain and 40% experience severe pain before asking for an analgesic drug. The non-steroidal anti-inflammatory drugs (NSAIDs) are used extensively for the control of pain after minor surgery or other dental procedures and are effective for acute and chronic pain but unwanted side effects such as gastrointestinal intolerance can often appear.

None of the prior art formulations has successfully used extracts of *Spilanthes oleracea* to obtain an effective local analgesic effect, nor have any of the existing formulations had anything other than a short-term anaesthetic effect. We have now found that by providing extracts of *Spilanthes oleracea* in a form that enables the active agent to be delivered locally to the site to be treated, these objectives have been achieved.

Summary of the invention

In accordance with the present invention, in a first aspect there is provided:

(1) A pharmaceutically active extract of a plant of the genus *Spilanthes*, wherein said extract is obtainable through:

(i) washing and maceration of the said *Spilanthes* plant material with a mixture of water and alcohol followed by filteration to give a first alcoholic extract;

(ii) removal of the alcohol from the said first extract under reduced pressure to give a second extract; and

(iii) freeze-drying of said second extract to give the desired pharmaceutically active extract of a plant of the genus *Spilanthes*.

(2) a composition adapted to supply locally to the site of need in a patient in need thereof a compound having a pharmaceutical activity, wherein the active agent of said composition comprises an extract of a plant of the genus *Spilanthes* .

(3) A composition according to (1) and (2), wherein the said extract is of *Spilanthes oleracea.*

(4) A composition according to (3), wherein the said extract is characterised by the UV chromatographic profile shown in Figure 3a or Figure 3b.

(5) In a first preferred embodiment of the invention, the active agent has an analgesic activity.

Preferred compositions according to the invention include:

(6) a composition according to any of (1) to (5), wherein said extract is an aqueous extract, an alcoholic extract or an extract obtained by freeze-drying;

(7) a composition according to any one of (1) to (6), wherein said composition is adapted to be delivered bucally;

(8) a composition according to (7), wherein said buccal composition is selected from the group consisting of lozenges, tablets, solutions, suppositories, gels and gelfoams;

(9) a composition according to (8), wherein said buccal composition is in the form of a lozenge;

(10) a composition according to (9), wherein said buccal composition is a lozenge wherein an alcoholic extract of *Spilanthes oleracea* is formulated with sucrose, lactose, a binder and a filling agent;

(11) a composition according to (8), wherein said buccal composition is in the form of a tablet;

(12) a composition according to (11), wherein the tablet is a non-dissolving matrix tablet;

(13) a composition according to (12), wherein the non-dissolving matrix is prepared from a mucoadhesive polymer;

(14) a composition according to (13), wherein the mucoadhesive polymer is selected from the group consisting of one or more of hydroxypropylmethylcellulose (HPMC), polycarbophil, sodium alginate, polyvinyl alcohol, acacia, chitosan, carrageenan, tragacanth and polyoxyethylene;

(15) a composition according to (11), wherein said buccal composition is a tablet wherein an alcoholic extract of *Spilanthes oleracea* is formulated with a mucoadhesive polymer, lactose and a filling agent;

(16) a composition according to (11), wherein said buccal composition is a tablet, wherein an alcoholic extract of *Spilanthes oleracea* is formulated with an emulsifier, a mucoadhesive polymer, and a filling agent;

(17) a composition according to (11), wherein said buccal composition is a tablet, wherein an alcoholic extract of *Spilanthes oleracea* is formulated with a mucoadhesive polymer, a binder, water and a filling agent;

(18) a composition according to (8), wherein the buccal composition is in the form of a gel;

(19) a composition according to (18), wherein the gel is a mucoadhesive gel;

(20) a composition according to (18), wherein said buccal composition is a gel wherein an alcoholic extract of *Spilanthes oleracea* is formulated with xanthan gum, buffering agent, a preservative and water;

(21) a composition according to (18), wherein said buccal composition is a gel wherein an alcoholic extract of *Spilanthes oleracea* is formulated with a mucoadhesive polymer, buffering agent, a preservative and water;

(22) a composition according to (8), wherein said buccal composition is in the form of a gelfoam;

(23) a composition according to (22), wherein the gelfoam comprises a piece of gelfoam saturated with a concentrated solution of *Spilanthes oleracea*;

In a further preferred embodiment of the present invention, there is provided:

(24) a composition according to (2) adapted to supply locally to the site of need in a patient in need thereof a compound having a wound treating activity, wherein the active agent of said composition comprises an extract of *Spilanthes oleracea*.

Further aspects of the present invention include:

(25) use of a composition according to (24) for the manufacture of a medicament for the treatment of wounds;

(26) a composition as defined in (1) to (2) and (5) to (23) for use in the treatment of inflammatory pain, neuropathic pain and nociceptive pain;

(27) use of a composition according to (1) to (2) and (5) to (23) for the manufacture of a medicament for the treatment of inflammatory pain, neuropathic pain and nociceptive pain;

(28) a composition as defined in (1) to (2) and (5) to (23) for use as an anti-inflammatory agent;

(29) use of a composition according to (1) to (2) and (5) to (23) for the manufacture of a medicament for the treatment of inflammation;

(30) a composition as defined in (1) to (2) and (5) to (23) for use as an analgesic or anaesthetic;

(31) use of a composition according to (1) to (2) and (5) to (23) for the manufacture of a medicament for use as an analgesic or anaesthetic;

(32) a composition as defined in (1) to (2) and (5) to (23) for use in the treatment of vulvodynia;

(33) use of a composition according to (1) to (2) and (5) to (23) for the manufacture of a medicament for the treatment of vulvodynia;

(34) a composition as defined in (1) to (2) and (5) to (23) for use in the treatment of periodontitis;

(35) use of a composition according to (1) to (2) and (5) to (23) for the manufacture of a medicament for the treatment of periodontitis;

(36) a composition as defined in (1) to (2) and (5) to (23) for use in the treatment of allodynia;

(37) use of a composition according to (1) to (2) and (5) to (23) for the manufacture of a medicament for the treatment of allodynia;

(38) a composition as defined in (1) to (2) and (5) to (23) for use in the treatment of mouth ulcers;

(39) use of a composition according to (1) to (2) and (5) to (23) for the manufacture of a medicament for the treatment of mouth ulcers;

(40) a composition as defined in (1) to (2) and (5) to (23) for use in the treatment of irritable bowel syndrome (IBS); and

(41) use of a composition according to (1) to (2) and (5) to (23) for the manufacture of a medicament for the treatment of IBS.

(42) a method for the prophylaxis or treatment of a disease or condition selected from the group consisting of wounds, inflammatory pain, neuropathic pain, nociceptive pain, inflammation, vulvodynia, periodontitis, alloydnia, mouth ulcers and irritable bowel syndrome, which comprises administering to a mammal in need thereof an effective amount of a composition according to (1) to (2) and (5) to (24).

(43) A method for the prophylaxis or treatment of analgesia or anaesthesia which comprises administering to a mammal in need thereof an effective amount of a composition according to (1) to (2) and (5) to (24).

In another preferred embodiment of the invention, there is provided a formulation containing an extract of *Spilanthes oleracea*, where biological activity following local application is sustained for 4-6 hours.

Extracts of *Spilanthes oleracea* used in the example of preparation of NSL-101 in the present application originate from the same plot and are obtained using the same process. Extracts were collected at different times of the year and, as such, the yields are subject to seasonal variation. Lot 1 corresponds to extracts collected in February and Lot 2 corresponds to extracts collected in May. Figures 3a and 3b show the chromatographic profile of Lots 1 and 2 recorded at 230 nm and the UV spectra of the peaks corresponding to spilanthol.

Figure 3a shows the chromatographic profile at 230 nm of the *Spilanthes* extract corresponding to Lot 1. The peak with a retention time of 30.646 minutes corresponds

to alkylamides, as shown by the UV spectrum with an absorption peak at approximately 228 nm.

Figure 3b shows the chromatographic profile at 230 nm of the *Spilanthes* extract corresponding to Lot 2. The peaks with retention times of 30.675 and 33.046 minutes correspond to alkylamides, as shown by the UV spectra with an absorption peak at approximately 228 nm.

Both Lots 1 and 2 are used in the preparation of NSL-101. It can be seen that Lot 2 corresponding to the extract in May has a higher concentration of alkylamides present than the extract obtained in February (Lot 1). However, both are suitable for preparation of NSL-101 (see below in the Examples regarding the extraction procedure).

Detailed Description of the Invention

One problem to be addressed by the present invention was to produce formulations that had a rapid local analgesic effect. Also, another problem was to produce formulations having a reasonably long lasting local anaesthetic effect. These problems have been overcome by the present inventors by providing a composition adapted to supply locally to the site of need in a patient in need thereof a compound having a pharmaceutical activity, wherein the active agent of said composition comprises an extract of *Spilanthes oleracea*.

The key feature is that the compositions are adapted so that the extract of *Spilanthes oleracea* is delivered locally to the site of need in the patient in need thereof. By this, we mean that the compositions are adapted so that they are suitably conformed to be in direct or close contact with the site of treatment or prophylaxis (e.g. topical application). As a result, the present inventors have found that using these compositions the active agents in the extract of *Spilanthes oleracea* are rapidly delivered to the site of need. In patients suffering from neuropathic pain, these local compositions give a rapid analgesic effect not previously achieved and this can last for several hours. They can also be adapted to provide a rapid anaesthetic affect that can last for several hours. Other conditions can also be treated, as explained below.

The active agent is obtainable from the plant of the genus Spilanthes. In a preferred embodiment, the active agent is an extract from *Spilanthes oleracea* and contains spilanthol. Suitable extraction techniques to obtain the active agent are detailed in the examples, but the active extract can be obtained using aqueous, alcoholic and dry extraction techniques, for example.

In another preferred embodiment it will have an activity selected from analgesic activity, wound treatment activity, neuropathic pain treatment activity, anti-inflammatory activity, anaesthetic activity, activity in the treatment of vulvodynia, activity in the treatment of irritable bowel syndrome, activity in the treatment of periodontitis, activity in the treatment of allodynia and activity in the treatment of mouth ulcers.

As noted above, a main aspect of the invention the composition is that the local composition of the invention can be adapted to be delivered bucally. A number of delivery systems were found to be suitable for the proposed indications and mechanisms of action of the product. Preferred formulations of the present invention include lozenges, mucoadhesive tablets, mucoadhesive gels and gelfoams as the means for buccal/local delivery. Delivery systems such as suppositories or pessaries are preferred formulations for the localised and systemic treatment of IBS and vulvodynia.

Lozenges according to the invention typically comprise a *Spilanthes oleracea* extract, an excipient, a binder, a sweetening agent and a filling agent.

Examples of an excipient suitable for use include organic excipients such as sugar derivatives, e.g. lactose, sucrose, glucose, mannitol or sorbitol, starch derivatives, e.g. corn starch, potato starch, α-starch, dextrin or carboxymethyl starch, cellulose derivatives, e.g. crystalline cellulose, low substituted hydroxypropyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, calcium carboxymethyl cellulose or internally crosslinked sodium carboxymethyl cellulose, and gum Arabic, dextran or pullulan; and, inorganic excipients such as silicate derivatives, e.g. light anhydrous silicic acid, synthetic aluminium silicate or magnesium aluminium

metasilicate, phosphates, e.g. calcium phosphate, carbonates, e.g. calcium carbonate, or sulfates, e.g. calcium sulfate. Lactose and sucrose are preferred.

Examples of binders include polyvinylpyrrolidone, Macrogol and compounds similar to the aforementioned excipients, of which polyvinylpyrrolidone resins are preferred.

Examples of the filling agents include stearic acid, metal stearates such as calcium stearate and magnesium stearate; talc; colloidal silica; wax such as beeswax and spermaceti; boric acid; adipic acid; sulfates such as sodium sulfate; glycol; fumaric acid; sodium benzoate; DL-leucine; fatty acid sodium salts; lauryl sulfates such as sodium lauryl sulfate and magnesium lauryl sulfate; silicic acids such as silicic anhydride and silicic acid hydrate; and said starch derivatives. Of these, metal stearates such as magnesium stearate are preferred.

Tablets containing an extract of *Spilanthes oleracea* are also suitable formulations for buccal delivery. The preferred form is a non-dissolving matrix tablet, wherein the said non-dissolving matrix is prepared using a mucoadhesive polymer. Mucoadhesive polymers have been utilised in many different dosage forms in efforts to achieve systemic delivery of drugs through the different mucosae. These dosage forms include tablets, patches, tapes, films, and powders.

Mucoadhesive tablets according to the invention typically comprise a *Spilanthes oleracea* extract, an exipient, a filling agent and a mucoadhesive polymer.

Non-disintegrating tablets were prepared from a range of mucoadhesive polymers. Examples of a mucoadhesive polymer suitable for use include hydroxypropylmethlycellulose (HPMC), polycarbophil, sodium alginate, polyvinyl alcohol, acacia, chitosan, carrageenan, tragacanth and polyoxyethylene. Polycarbophil, polyvinyl alcohol, chitosan, polyox and carrageenan are preferred.

Examples of an excipient include those listed above for use in the preparation of lozenges. Polyvinylpyrrolidone resins or lactose are preferred.

Examples of the filling agents include those listed above for use in the preparation of

lozenges. Again metal stearates such as magnesium stearate are preferred.

In another aspect of the invention, suitable candidates for buccal delivery include gels, wherein the gel is a mucoadhesive gel.

Mucoadhesive gels/pastes according to the invention typically comprise a *Spilanthes oleracea* extract, a mucoadhesive polymer, a buffering agent, a preservative and water.

Examples of suitable buffering agents include acetic acid, potassium hydroxide, sodium hydroxide, citric acid, hydrochloric acid, lime, magnesium oxide, and sodium carbonate.

Common preservatives suitable for use include metal sorbates, such as sodium sorbate, potassium sorbate, calcium sorbate, benzoic acid, sodium benzoate, potassium benzoate, calcium benzoate, ethyl p-hydroxybenzoate, sodium ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sodium propyl p-hydroxybenzoate, methyl p-hydroxybenzoate, sodium methyl p-hydroxybenzoate, sulphites such as sodium sulphite, sodium hydrogen sulphite, sodium metabisulphite, potassium metabisulphite, potassium sulphite, calcium sulphite, calcium hydrogen sulphite, potassium hydrogen sulphite, formates including formic acid, sodium formate, calcium formate, metal nitrites and metal nitrates e.g. potassium nitrite, sodium nitrite, sodium nitrate, potassium nitrate, acetates including acetic acid, potassium acetate, sodium acetate, sodium diacetate, calcium acetate, ammonium acetate, metal propionates such as sodium propionate, calcium propionate, potassium propionate, and malic acid, lactic acid, propionic acid and fumaric acid. Of these, hydroxybenzoate derivates are preferred.

Examples of a mucoadhesive polymer suitable for use include hydroxypropylmethlycellulose (HPMC), polycarbophil, sodium alginate, xanthan gum, polyvinyl alcohol, acacia, chitosan, carrageenan, tragacanth and polyoxyethylene. Preferred mucoahdehesive polymers for use in the preparation of gels of the invention include sodium alginate, Xanthan gum, chitosan and hydroxypropylmethylcellulose.

Gelfoams according to the invention typically comprise a piece of precut gelfoam saturated with a concentrated solution of *Spilanthes oleracea*. The precut gelfoam is saturated with a solution obtained by the procedure as described earlier. Preferably between 1 and 5 ml of the *Spilanthes oleracea* solution is used to saturate a precut piece of gelfoam. More preferably 2.5 ml of the solution is placed in a 5 ml sterile corning, with a piece of precut gelfoam between 1 and 4 cm^2. Most preferably a 1.5cm^2 precut piece of gelfoam is saturated with 2.5 ml of the *Spilanthes oleracea* solution. This mixture is left for approximately fifteen minutes or until complete saturation has occurred.

Suppositories and pessaries are also suitable formulations for buccal delivery of *Spilanthes oleracea.*

Suppositories can take the form of capsules or molds which contain the active product either solely or with suitable exipients dissolved in a greasy base such as cocoa butter, other vegetable fats or oils, biocompatible polymers, gels or aqueous solutions. Pessaries and urethal suppositories combine the active ingredient with exicpients in a water-soluble base, such as polyethylene glycol, geletine, or glycerinated geletin.

Such formulations can be designed to release the active product within 30 minutes of administration or can be designed to maximise the duration of exposure. These formulations are preferred for the treatment of IBS and vulvodynia, providing immediate or slow (or intermediaries thereof) release of the active ingredient.

The present invention may be further understood by consideration of the following Examples and Test Example that refer to the following figures:

Figure 1 is a plot of the paw withdrawal threshold (PWT) against time for CCI rats before and after oral dosing with either aqueous extract of *Spilanthes oleracea* or saline; and

Figure 2 shows discharges for CCI rats with exposed sciatic nerve on application of control, vehicle, aqueous extract of *Spilanthes oleracea*, removal of aqueous extract of *Spilanthes oleracea* and application of lidocaine.

Figure 3a shows the chromatographic profile at 230 nm of the *Spilanthes* extract corresponding to Lot 1.

Figure 3b shows the chromatographic profile at 230 nm of the *Spilanthes* extract corresponding to Lot 2.

Figure 4 shows the number of patients needing medication during the post-SRP observation period was 6% in the NSL-101 group and 14% of patients in the 5% lidocaine group.

Figure 5 shows the least square mean pain intensity difference and 95% CI at each evaluation time.

Figure 6 demonstrates the differences between the NSL-101 and 5% lidocaine groups, showing that the weighted summed pain intensity difference is larger in the 5% lidocaine group.

Figure 7a shows the comparison of the gingival inflammation at baseline and post-SRP.

Figure 7b shows that 98% of patients presented moderate inflammation whilst only 2% presented severe inflammation.

Examples

Example 1: Extraction of active agent

(a) Alcoholic extraction

The *Spilanthes oleracea* plant material was washed in distilled water. The washed plant material was macerated with a solution of 3:7 ethanol:distilled water solution for 48 hours in a sterile environment. The solution was filtered to give extract 1.

The residual materials were macerated and further filtered with progressive filters to give extract 2. Extracts 1 and 2 were separated, and each solvated in distilled water (1/5 parts) to obtain two separate solutions of *Spilanthes olaracea*. Both solutions were filtered.

(b) Aqueous extraction

The ethanol was removed from both solutions by steam extraction under reduced pressure. The resulting aqueous solutions 1 and 2 were filtered, bottled and refrigerated.

(c) Dried extraction

Solution 1 obtained from steam extraction was freeze-dried. The resulting freeze-dried extract was used for the formulation of the gelfoam and 5% gel dose.

Example 2: Preparation of a Gelfoam

The freeze-dried extract was combined with solution 2 and re-filtered to obtain a final concentrated solution for use in the formulation of the gelfoam.

The precut gelfoam is saturated with a solution obtained by the procedure as described above. Typically 2.5 ml of the *Spilanthes oleracea* solution is placed in a sterile 5ml corning containing typically 1.5 cm^2 gelfoam. This mixture is left for approximately fifteen minutes or until complete saturation has occurred.

Example 3: Preparation of a Lozenge

Ingredient	**Quantity per Lozenge**
Alcoholic extract of *Spilanthes oleracea*	50 mg*
Sucrose	250 mg
Lactose	50 mg
Povidone K30	10 mg
Ethanol	A sufficient amount; removed from the formulation by drying
Lemon flavour	10mg
Magnesium stearate	10 mg

* equivalent dry weight of *Spilanthes oleracea* plant material

The povidone K30 was dissolved in the alcoholic extract of *Spilanthes oleracea*. The sucrose and lactose were granulated in a suitable mixer using the povidone solution containing the extract of *Spilanthes oleracea* together with an appropriate amount of ethanol, and dried in an air oven. The dried product was milled, sieved, and blended with the magnesium using a tumbling blender. Tablets were compressed using a tablet machine to produce tablets with a breaking strength of at least 10 kg.

Following dental extraction, a lozenge would be placed in the mouth on the source of the pain and retained there until the lozenge dissolved. We believe on the basis of the Test Examples below that pain relief will be rapid and last for several hours. Continued use of the product afterwards (e.g. twice daily for up to seven days) would be possible.

Example 4: Preparation of a Tablet

Ingredient	**Quantity per tablet**
Alcoholic extract of *Spilanthes oleracea*	50 mg*
Polycarbophil	300 mg
Lactose	50 mg
Magnesium stearate	10 mg

* equivalent dry weight

The ingredients (except the magnesium stearate) were mixed together, dried in an air oven, and sieved through a 1 mm sieve. The sieved material was mixed with the magnesium stearate in a tumbling blender, and compressed into tablets with a hardness of 10kg.

Following dental extraction, a tablet would be placed in the mouth on the source of the pain. It is anticipated on the basis of the Test Examples below that pain relief will be rapid and last for several hours.

Example 5: Preparation of a Tablet

Ingredient	**Quantity per tablet**
Alcoholic extract of *Spilanthes oleracea*	50 mg*
Sodium alginate	300 mg
Polyvinyl alcohol	50 mg
Ethanol	A sufficient amount; removed from the formulation by drying
Magnesium stearate	10 mg

*equivalent dry weight

The polyvinyl alcohol was dissolved in the alcoholic extract of *Spilanthes oleracea*. All of the ingredients except the magnesium stearate were thoroughly mixed together, dried in an air oven, and sieved through a 1 mm sieve. The sieved material was mixed with the magnesium stearate in a tumbling blender, and compressed into tablets with a hardness of 10kg.

Example 6: Preparation of a Tablet

Ingredient	**Quantity per tablet**
Dried extract of *Spilanthes oleracea*	50 mg
Polyox	300 mg
Magnesium stearate	10 mg

The ingredients were mixed in a tumbling blender, and compressed into tablets with a hardness of 10kg.

Example 7: Preparation of a Tablet

Ingredient	**Quantity per tablet**
Aqueous extract of *Spilanthes oleracea*	50 mg*
Chitosan	300 mg
Povidone K30	30 mg
Water	A sufficient amount; removed from the formulation by drying
Magnesium stearate	10 mg

*equivalent dry weight

All of the ingredients except the magnesium stearate were thoroughly mixed together, and granulated by the addition of a sufficient amount of water. The wet mass was sieved through a 1mm sieve, dried in an air oven, and sieved through a 1 mm sieve. The sieved material was mixed with the magnesium stearate in a tumbling blender, and compressed into tablets with a hardness of 10kg.

Example 8: Preparation of a Tablet

Ingredient	**Quantity per tablet**
Aqueous extract of *Spilanthes oleracea*	50 mg*
Carrageenan	300 mg
Povidone K90	30 mg

Water	A sufficient amount; removed from the formulation by drying
Magnesium stearate	10 mg
*equivalent dry weight	

All of the ingredients except the magnesium stearate were thoroughly mixed together, and granulated by the addition of a sufficient amount of water. The wet mass was sieved through a 1mm sieve, dried in an air oven, and sieved through a 1 mm sieve. The sieved material was mixed with the magnesium stearate in a tumbling blender, and compressed into tablets with a hardness of 10kg.

Example 9: Preparation of a Gel

The freeze-dried extract was combined with solution 2 and a support gel comprising Polyethylene Glycol 4000 and Polyethylene Glycol 400.

Typically, 5mg of the freeze-dried extract of *Spilanthes oleracea* was used per 100g of gel to produce a 5% gel dose.

Ingredient	**Quantity per gel**
Aqueous extract of *Spilanthes oleracea*	1 g*
HPMC E4M	2.5 g
Buffering agent	a sufficient amount
Hydroxybenzoate	
Preservative	0.5%
Water	to 100g

The HPMC was dispersed in approximately half of the water and allowed to dissolve. The aqueous extract was added, and the pH of the solution adjusted to pH 4-8. The solution was then made up to volume while taking care to avoid the incorporation of air bubbles.

Following dental extraction, gel would be placed in the mouth on the source of the pain using the finger. It is anticipated on the basis of the Test Examples below that pain relief will be rapid and last for several hours.

Example 10: Preparation of a Gel

Ingredient	**Quantity per gel**
Aqueous extract of *Spilanthes oleracea*	1 g*
Xanthan gum	4.0 g
Buffering agent	a sufficient amount
Hydroxybenzoate	
Preservative	0.5%
Water	to 100g

The xanthan gum was dispersed in approximately half of the water and allowed to dissolve. The aqueous extract was added, and the pH of the solution adjusted to pH 4-8. The solution was then made up to volume while taking care to avoid the incorporation of air bubbles.

Example 11: Preparation of a Gel

Ingredient	**Quantity per gel**
Aqueous extract of *Spilanthes oleracea*	1 g*
Sodium alginate	10g
Buffering agent	a sufficient amount
Hydroxybenzoate	
Preservative	0.5%
Water	to 100g

The sodium alginate was dispersed in approximately half of the water and allowed to dissolve. The aqueous extract was added, and the pH of the solution adjusted to pH 4-8. The solution was then made up to volume while taking care to avoid the incorporation of air bubbles.

Example 12: Preparation of a Gel

Ingredient	**Quantity per gel**
Aqueous extract of *Spilanthes oleracea*	1 g*
Chitosan	5.0 g
Buffering agent	a sufficient amount
Hydroxybenzoate	
Preservative	0.5%
Water	to 100g

The chitosan was dispersed in approximately half of the water and allowed to dissolve. The aqueous extract was added, and the pH of the solution adjusted to pH 4-8. The solution was then made up to volume while taking care to avoid the incorporation of air bubbles.

Example 13: Preparation of a Gel

Ingredient	**Quantity per gel**
Aqueous extract of *Spilanthes oleracea*	1 g*
Chitosan	2.0 g
HPMC (E4M)	2.0 g
Buffering agent	a sufficient amount
Hydroxybenzoate	
Preservative	0.5%
Water	to 100g

The chitosan was dispersed approximately half of the water and allowed to dissolve. The aqueous extract was added, and the pH of the solution adjusted to the required pH 4-8 The solution was then made up to volume while taking care to avoid the incorporation of air bubbles.

Example 14: Preparation of a Gel

The freeze-dried extract was combined with solution 2 and a support gel comprising Polyethylene Glycol 4000 and Polyethylene Glycol 400.

Ingredient	**Quantity per gel**
Freeze-dried extract of *Spilanthes oleracea*	5mg
Strawberry essence	1 drop

Test Example

The efficacy of local action of extracts of *Spilanthes oleracea* was tested using a rat model, as described below. For the purposes of the tests, the extracts of *Spilanthes oleracea* were prepared as an aqueous extract as follows.

2 g of pulverised dried flower buds and leaves were placed in a sterile 20 ml plastic tube. To this 20 ml of sterile 0.9% saline was added. The suspension was incubated for 12 hours at 4°C. Whatman filter paper was used for the initial coarse filtering of the plant extract. The solution was then further filtered using a sterile 0.22μm filter to give the final aqueous extract of *Spilanthes oleracea* to be used in Test Examples 1 and 2 (referred to below as NSL-101).

Pre-clinical efficacy data generated for the aqueous *Spilanthes oleracea* extract

Animal model: A chronic constriction injury (CCI) model of rat was employed. The rats were made neuropathic by placing four ligatures on the left sciatic nerve under pentobarbitone anaesthesia. 14 days after surgery, the animals showed typical phenomenon of neuropathic pain: their paw withdrawal threshold (PWT) in response to mechanical stimulation (von Frey hairs) significantly decreased (≤4 gram compared to the normal level of 10-15 gram). Only the animals showing mechanical allodynia were selected for behavioural and electrophysiological experiments.

(a) Behavioural test: the rats were left in a plastic chamber individually on a lifted mesh for at least 30 min before the test. The PWT was assessed before and after oral

dosing of the aqueous *Spilanthes oleracea* extract (NSL-101) or saline at 0.5, 1, 2 and 3 hours. NSL-101 was dosed at 2 ml per rat orally. The results are shown in Figure 1. It can be seen that aqueous *Spilanthes oleracea* extract significantly increased the PWT at 0.5 and 1 hour after dosing in CCI rats, thus providing clear proof that application of *Spilanthes oleracea* extract gives rapid relief from neuropathic pain that lasts for a significant time.

(b) Electrophysiological experiments: the CCI rats were anaesthetised with pentobarbitone. The ligated area of sciatic nerve was exposed and the ligatures and connective tissue around the ligated nerve were removed thoroughly under microscope. The exposed nerve was covered with saline soaked cotton. An oil pool was formed to expose sciatic nerve at the part proximal to the ligated area. The nerve were teased repetitively and examined for spontaneous ectopic discharge. When a fiber with stable ectopic activity was found, the activity was recorded for 5 -10 min as control and then the cotton covering the ligated area was removed and for applying either saline or the aqueous *Spilanthes oleracea* extract (NSL-101) (1 ml) applied directly to the exposed nerve. The results showed that NSL-101 completely blocked the ectopic discharge for the time the solution was in the place. Figure 2 is a typical experiment testing saline, NSL-101 and lidocaine (3mg/ml). The results for the locally applied the aqueous *Spilanthes oleracea* extract are remarkable, showing that they completely blocked the ectopic discharge while in place, having a similar efficacy to lidocaine. This provides clear proof of the remarkable effectiveness of compositions of the present invention adapted to provide *Spilanthes oleracea* extract directly to the site of neuropathic pain in order to provide a rapid analgesic effect.

Double blind randomized trial to evaluate the analgesic and anti-inflammatory efficacy and the safety of NSL-101 gel, compared to Lidocaine 5% gel, applied on scaling and root planing, carried out in a single research centre (Lima Peru).

The aim of this study was to evaluate the analgesic efficacy, anti-inflammatory action and safety of the dental NSL-101 gel, in comparison with 5% lidocaine, during dental root scaling and planing procedures (SRP) as a non-surgical treatment for periodontitis.

A total of 50 patients entered the study (22 women and 28 men), with an age range between 18 and 77, minimum and maximum respectively. The quadrants for application of one of the two treatments were selected randomly. All the selected patients completed the study, in total performing 100 clinical tests, 50 corresponding to the dental gel NSL-101 and 50 to the 5% lidocaine treatment. The NSL-101 gel was prepared as described in Example 14 previously.

Table 1: Initial clinical evaluation

	Anaesthetic Gel	
	NSL-101	**5% lidocaine**
	(n= 50)	(n= 50)
	Median (range)	Median (range)
Individual mean PD (mm)*	3.8 (3.0 – 5.5)	3.8 (3.2 – 6.0)
Individual mean deepest PD (mm)*	5.0 (4.0 – 8.0)	5.0 (4.0 – 9.0)
Individual percent of bleeding pockets*	60.7 (0 - 100)	60.7 (0 - 100)
*For each patient, the mean probing depth (PD, 6 sites per tooth), mean deepest probing depth (using only the deepest site of each tooth), percentage of bleeding pockets were calculated.		
The median and ranges of these individual values are provided above.		

The mean probing depth of the treated quadrants (evaluated at baseline) was similar for both the NSL-101 treated group (3.8 (3.0 – 5.5) mm and (3.8 (3.2 – 6.0) mm). The percentage of bleeding pockets on probing was also similar for both groups (60.7%).

Table 2: Baseline clinical characteristics for NSL-101 and 5% lidocaine

	NSL-101	5% lidocaine
Characteristics	**(n=50)**	**(n=50)**
Quadrant treated, n (%)*		
Right maxilla	9 (18.0)	17 (34.0)
Left maxilla	17 (34.0)	9 (18.0)
Right mandible	12 (24.0)	12 (24.0)
Left mandible	12 (24.0)	12 (24.0)
Number of teeth treated according quadrants*		
2 teeth	1 (0.6)	0 (0.0)
3 teeth	1 (1.0)	1 (1.0)
4 teeth	4 (5.20)	5 (6.70)
5 teeth	9 (14.40)	10 (16.70)
6 teeth	8 (15.30)	15 (30.0)
7 teeth	17 (38.0)	15 (35.0)
8 teeth	10 (25.50)	4 (10.6)
Total teeth treated, n (%)	313 (51.0)	300 (49.0)
Duration of treatment, M (SD)		
Minutes	68.98 (18.59)	66.72 (17.29)

In the right superior maxilla (quadrant I), the contents of 9 syringes containing NSL-101 and 17 syringes containing 5% lidocaine were randomly placed inside the periodontal pockets (total number of syringes deposited 26). On the contra-lateral side (quadrant II), the contents of 9 syringes were used containing 5% lidocaine and 17 containing NSL-101. A total of 26 blunt syringes were used in the maxilla. In the right mandible (quadrant IV) 12 syringes of NSL-101 and 12 of 5% lidocaine were used, with an equal number of syringes in the contra-lateral side (quadrant III). The total number of blunt syringes used in the mandible was 24.

Out of the total number of teeth (613) undergoing scaling and planing, 51% were anaesthetised with NSL-101 gel and 49% with 5% lidocaine. The average duration of SRP was similar for both treatments (NSL-101 gel 68.98 ±18.59 minutes, 5% lidocaine group 66.72 ± 17.29 minutes).

Seventeen quadrants (38%) received NSL-101 treatment, with an average of 7 teeth, and 15 quadrants (35%) received 5% lidocaine treatment for an equal number of teeth.

Table 3: Analgesic efficacy for NSL-101 and 5% lidocaine during SRP

Efficacy Parameter	NSL-101 (n=50)	5% lidocaine (n=50)
Patients needed reinforcement anesthesia n (%) during and post-SRP	12 (24,0)	11 (22,0)
Patients needed rescue anesthesia n (%) during and post-SRP	0 (0,0)	0 (0,0)
Patients needed medication post-SRP n (%)	3 (6,0)	7 (14,0)
Adverse effects n (%) during and post-SRP	0 (0,0)	0 (0,0)
Duration of analgesic effect (time needed to use medication over 90 minutes) Median (95%CI), minutes[a]	>89,4 (88,5; >90,3)	>87,6 (85,2; >90,0)
[a] Kaplan-Meier estimator was used, adjusting for number of teeth		

The number of patients requiring re-enforcement anaesthesia was similar in both groups (26% in NSL-101 group compared to 20% in the 5% lidocaine group). For patients with a diagnosis of periodontitis it is sometimes justified to use re-enforcement anaesthesia, due to the lack of efficacy of the local anaesthetic in inflamed areas. Figure 4 shows the number of patients needing medication during the post-SRP observation period was 6% in the NSL-101 group and 14% of patients in the 5% lidocaine group.

During SRP and during the observation period no patients from either group mentioned being in pain sufficiently strong to need the use of rescue anaesthetic, including the follow-up period post SRP and the period up to a week after treatment. There were no adverse events, either during the SRP, during the post-SRP follow up period or during the follow up week after treatment. Both products were very well tolerated by the patients.

The duration of the analgesic effect during the observation period post-SRP was prolonged after the SRP for both groups.

Table 4: Analgesic efficacy post-SRP for NSL-101 and 5% lidocaine

PEfficacy Parameter	NSL-101 (n=50)		5% lidocaine (n=50)		p value
Summed Pain Intensity Difference (SPID) LSM (SEM)[a]	-0.12	(0.34)	-0.30	(0.34)	0.106
Weighted Summed Pain Intensity Difference (WSPID) LSM (SEM)[a]	-0.13	(1.16)	-0.29	(2.09)	0.232
Pain Intensity Difference (PID) at each evaluation time					
15 min, LSM (SEM)b	0.0	(0.0)	0.0	(0.0)	
30 min, LSM (SEM)b	0.0	(0.0)	0.0	(0.0)	
45 min, LSM (SEM)b	0.0	(0.0)	0.0	(0.14)	0.283
60 min, LSM (SEM)b	0.0	(0.0)	0.0	(0.20)	0.161
75 min, LSM (SEM)b	0.0	(0.20)	-0.10	(0.30)	0.202
90 min, LSM (SEM)b	-0.08	(0.30)	-0.14	(0.35)	0.392
[a] Least Square Mean (LSM) obtained from ANCOVA , adjusting for number of teeth					
[b] LSM obtained from Repeated Measures ANCOVA, adjusting for number of teeth					

It can be seen that NSL-101 (compared to 5% lidocaine) has a longer anaesthetic effect and delayed appearance of pain for approximately 75 minutes post-SRP.

The primary efficacy variable was the summed pain intensity difference (weighted in time) between the baseline evaluation time and 90 minutes after the application of the product (WSPI). The secondary variables included the pain intensity difference (PID) at each evaluation time and the summed pain intensity difference (SPID).

With regards to analgesic efficacy, both treatments provided similar levels of analgesia and they both improved the SPID score at the 90 minutes evaluation time. Pain was first apparent after 60 minutes in the NSL-101 group, and after 30 minutes in the 5% lidocaine group.

Figure 5 shows the least square mean pain intensity difference and 95% CI at each evaluation time. The summed PID shows significant difference between the NSL-101 and the 5% lidocane group, between the values obtained at time 0 (baseline) and 90 minutes.

Figure 6 demonstrates the differences between the NSL-101 and 5% lidocaine groups, showing that the weighted summed pain intensity difference is larger in the 5% lidocaine group.

Table 5: Evaluation of the gingival inflammation at the beginning and post-SRP

Index Gingival			Mild		Moderate		Severe		p value[a]
	Mean	SD	n	(%)	n	%	n	%	0.012
Basal	1.81	(0.17)	0	(0.0)	49	(98.0)	1	(2.0)	
Post SRP	1.29	(0.16)	7	(14.0)	43	(86.0)	0	(0.0)	
Variation	0.51	(0.13)							
[a] Fisher's exact test was used									

Gingival inflammation was evaluated in the quadrants treated with either NSL-101 or 5% lidocaine. Figure 7a shows that the percentage of patients that presented moderate inflammation at baseline was reduced from 98% to 86%. Figure 7b shows that 98% of patients presented moderate inflammation whilst only 2% presented severe inflammation.

Neither of the treatments (NSL-101 or 5% lidocaine) resulted in adverse events in patients, during SRP, during the post-SRP follow up period or during the follow up week after treatment.

The results demonstrate that sub-gingival application of NSL-101 gel as an anaesthetic, provides additional advantages compared to conventional anaesthetic (nerve block or infiltration) for periodontal treatment. None of the treated patients required rescue anaesthesia to complete SRP treatment. A decrease in the degree of gingival inflammation was also observed. No adverse effects were reported, demonstrating that this product has a good safety profile and the patients were able to continue with their daily activities immediately after the observation period post-SRP.

The NSL-101 anaesthetic gel was as efficacious as the 5% lidocaine gel at reducing pain during SRP. The analgesic efficacy of the NSL-101 gel lasts for approximately 75 minutes after termination of treatment, compared to 45 minutes for the 5% lidocaine gel. The patients reported no feeling of anaesthesia on tissues surrounding the treatment area, such as lips, tongue or cheeks; they behaved in a relaxed manner

throughout the periodontal procedure and were pleased to return for the second treatment appointment, if it would include the use of anaesthetic gel.

Claims

1. A pharmaceutically active extract of a plant of the genus *Spilanthes*, wherein said extract is obtainable through:

   (i) washing and maceration of the said *Spilanthes* plant material with a mixture of water and alcohol followed by filtration to give a first alcoholic extract;

   (ii) removal of the alcohol from the said first extract under reduced pressure to give a second extract; and

   (iii) freeze-drying of said second extract to give the desired pharmaceutically active extract of a plant of the genus *Spilanthes*.

2. A composition adapted to supply locally to the site of need in a patient in need thereof a compound having a pharmaceutical activity, wherein the active agent of said composition comprises an extract of a plant of the genus *Spilanthes*.

3. A composition according to claim 1 or claim 2, wherein the said extract is of *Spilanthes oleracea.*

4. A composition according to claim 3, wherein the said extract is characterised by the UV chromatographic profile according to Figure 3a or Figure 3b.

5. A composition according to claims 1 to 4, wherein the active agent has an analgesic activity.

6. A composition according to claims 1 to 5, wherein said extract of *Spilanthes oleracea* contains spilanthol.

7. A composition according to any one of claims 1 to 6, wherein said composition is adapted to be delivered bucally.

8. A composition according to claim 7, wherein said buccal composition is selected from the group consisting of lozenges, tablets, suppositories, gels and gelfoams.

9. A composition according to claim 8, wherein said buccal composition is in the form of a lozenge.

10. A composition according to claim 9, wherein said buccal composition is a lozenge wherein an alcoholic extract of *Spilanthes oleracea* is formulated with sucrose, lactose, a binder and a filling agent.

11. A composition according to claim 8, wherein said buccal composition is in the form of a tablet.

12. A composition according to claim 11, wherein the tablet is a non-dissolving matrix tablet.

13. A composition according to claim 12, wherein the non-dissolving matrix is prepared from a mucoadhesive polymer.

14. A composition according to claim 13, wherein the mucoadhesive polymer is selected from the group consisting of one or more of hydroxypropylmethylcellulose (HPMC), polycarbophil, sodium alginate, polyvinyl alcohol, acacia, chitosan, carrageenan, tragacanth and polyoxyethylene.

15. A composition according to claim 11, wherein said buccal composition is a tablet wherein an alcoholic extract of *Spilanthes olacera* is formulated with a mucoadhesive polymer, lactose and a filling agent.

16. A composition according to claim 11, wherein said buccal composition is a tablet, wherein an alcoholic extract of *Spilanthes olacera* is formulated with an emulsifier, a mucoadhesive polymer, and a filling agent.

17. A composition according to claim 11, wherein said buccal composition is a tablet, wherein an alcoholic extract of *Spilanthes olacera* is formulated with a mucoadhesive polymer, a binder, water and a filling agent.

18. A composition according to claim 8, wherein the buccal composition is in the form of a gel.

19. A composition according to claim 18, wherein the gel is a mucoadhesive gel.

20. A composition according to claim 19, wherein a dried extract of *Spilanthes olacera* is dissolved in an aqueous extract of *Spilanthes olacera* and combined with a support gel.

21. A composition according to claim 18, wherein said buccal composition is a gel wherein an alcoholic extract of *Spilanthes olacera* is formulated with xanthan gum, buffering agent, a preservative and water.

22. A composition according to claim 18, wherein said buccal composition is a gel wherein an alcoholic extract of *Spilanthes olacera* is formulated with a mucoadhesive polymer, buffering agent, a preservative and water

23. A composition according to claim 8, wherein said buccal composition is in the form of a gelfoam.

24. A composition according to claim 23, wherein the gelfoam comprises a piece of gelfoam saturated with a concentrated solution of *Spilanthes oleracea.*

25. A composition according to claim 2 adapted to supply locally to the site of need in a patient in need thereof a compound having a wound treating activity, wherein the active agent of said composition comprises an extract of *Spilanthes oleracea.*

26. Use of a composition according to claim 25 for the manufacture of a medicament for the treatment of wounds.

27. A composition as defined in claims 1 to 2 and claims 5 to 24 for use in the treatment of inflammatory pain, neuropathic pain and nociceptive pain.

28. Use of a composition according to claims 1 to 2 and claims 5 to 24 for the manufacture of a medicament for the treatment of inflammatory pain, neuropathic pain and nociceptive pain.

29. A composition as defined in claims 1 to 2 and claims 5 to 24 for use as an anti-inflammatory agent.

30. Use of a composition according to claims 1 to 2 and claims 5 to 24 for the manufacture of a medicament for the treatment of inflammation.

31. A composition as defined in claims 1 to 2 and claims 5 to 24 for use as an anaesthetic.

32. Use of a composition according to claims 1 to 2 and claims 5 to 24 for the manufacture of a medicament for use as an anaesthetic.

33. A composition as defined in claims 1 to 2 and claims 5 to 24 for use as an analgesic.

34. Use of a composition according to claims 1 to 2 and claims 5 to 24 for the manufacture of a medicament for use as an analgesic.

35. A composition as defined in claims 1 to 2 and claims 5 to 23 for use in the treatment of vulvodynia.

36. Use of a composition according to claims 1 to 2 and claims 5 to 24 for the manufacture of a medicament for the treatment of vulvodynia.

37. A composition as defined in claims 1 to 2 and claims 5 to 24 for use in the treatment of periodontitis.

38. Use of a composition according to claims 1 to 2 and claims 5 to 24 for the manufacture of a medicament for the treatment of periodontitis.

39. A composition as defined in claims 1 to 2 and claims 5 to 24 for use in the treatment of allodynia.

40. Use of a composition according to claims 1 to 2 and claims 5 to 24 for the manufacture of a medicament for the treatment of allodynia.

41. A composition as defined in claims 1 to 2 and claims 5 to 24 for use in the treatment of mouth ulcers.

42. Use of a composition according to claims 1 to 2 and claims 5 to 24 for the manufacture of a medicament for the treatment of mouth ulcers.

43. A composition as defined in claims 1 to 2 and claims 5 to 24 for use in the treatment of irritable bowel syndrome.

44. Use of a composition according to claims 1 to 2 and claims 5 to 24 for the manufacture of a medicament for the treatment of irritable bowel syndrome.

43. A method for the prophylaxis or treatment of a disease or condition selected from the group consisting of wounds, inflammatory pain, neuropathic pain, nociceptive pain, inflammation, vulvodynia, periodontitis, alloydnia, mouth ulcers and irritable bowel syndrome, which comprises administering to a mammal in need thereof an effective amount of a composition according to (1) to (2) and (5) to (24).

44. A method for the prophylaxis or treatment of analgesia or anaesthesia which comprises administering to a mammal in need thereof an effective amount of a composition according to (1) to (2) and (5) to (24).

45. A formulation containing an extract of *Spilanthes oleracea* according to any one of claims 1 to 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, wherein 50% of the active agent is released over a period of 4-6 hours.

Figure 1

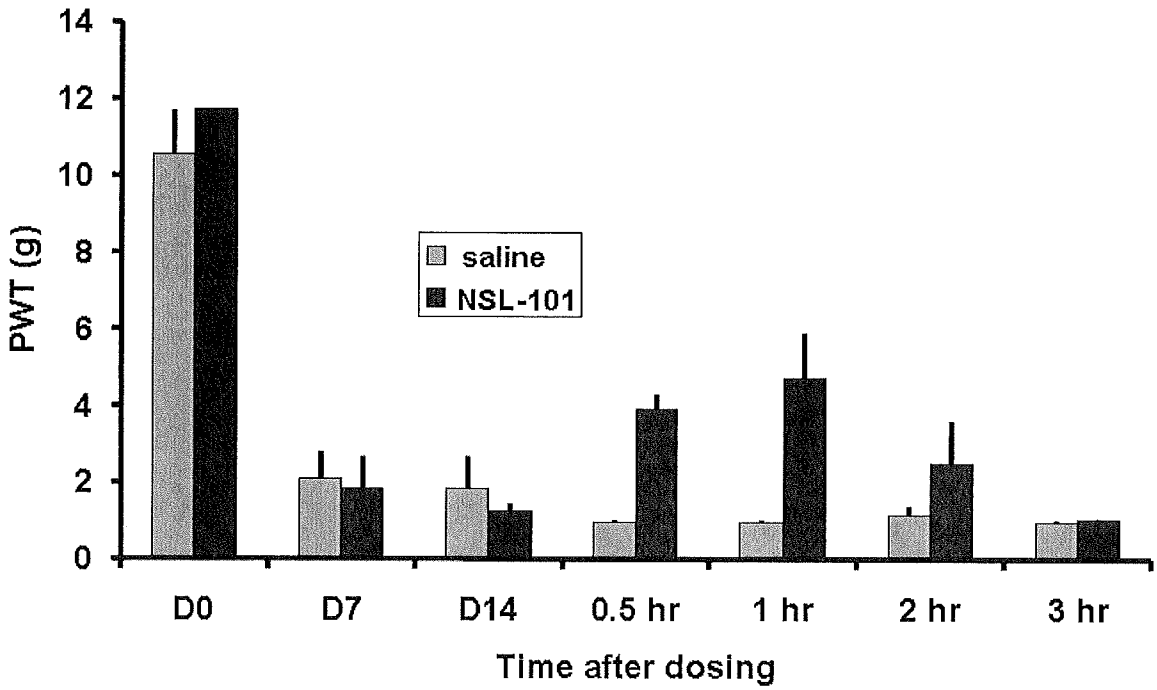

14
12
10
8
6
4
2
0
PWT (g)
saline
NSL-101
D0
D7
D14
0.5 hr
1 hr
2 hr
3 hr
Time after dosing

Figure 2

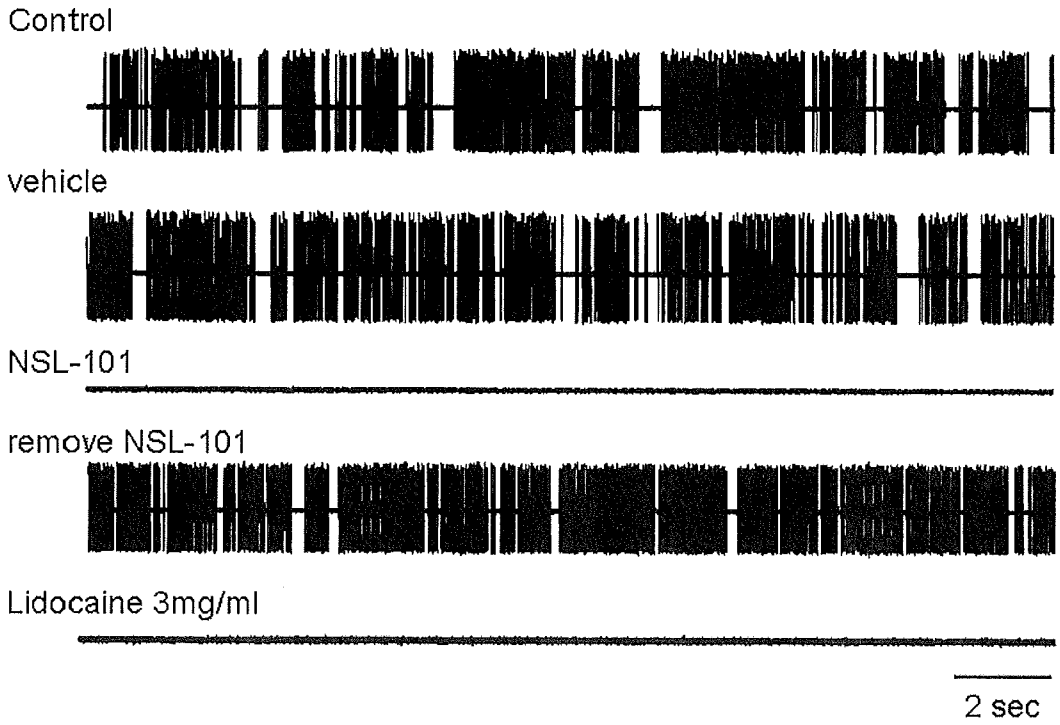

Control
vehicle
NSL-101
remove NSL-101
Lidocaine 3mg/ml
2 sec

Figure 3a

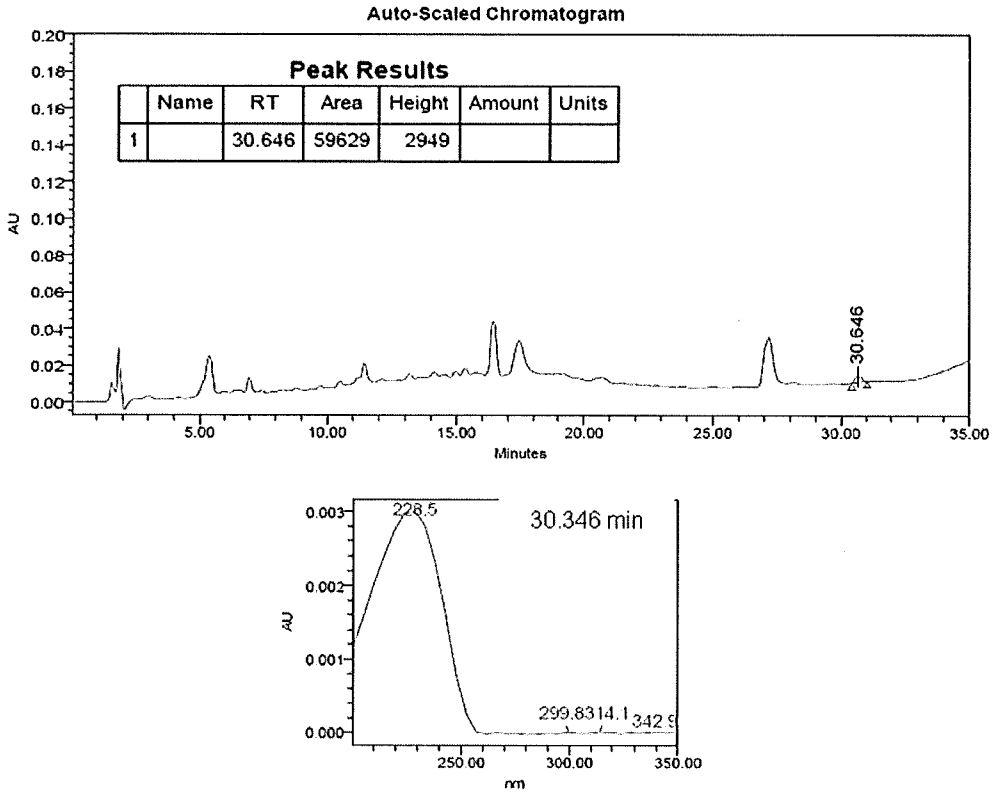


Figure 3b

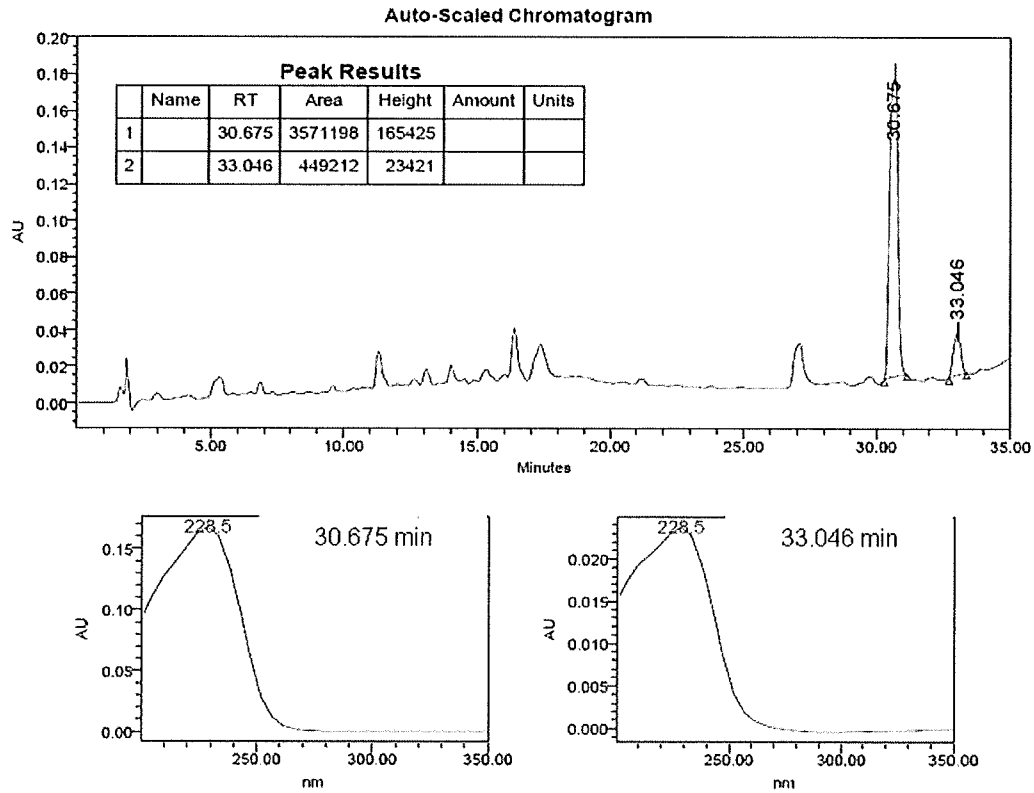


Figure 4

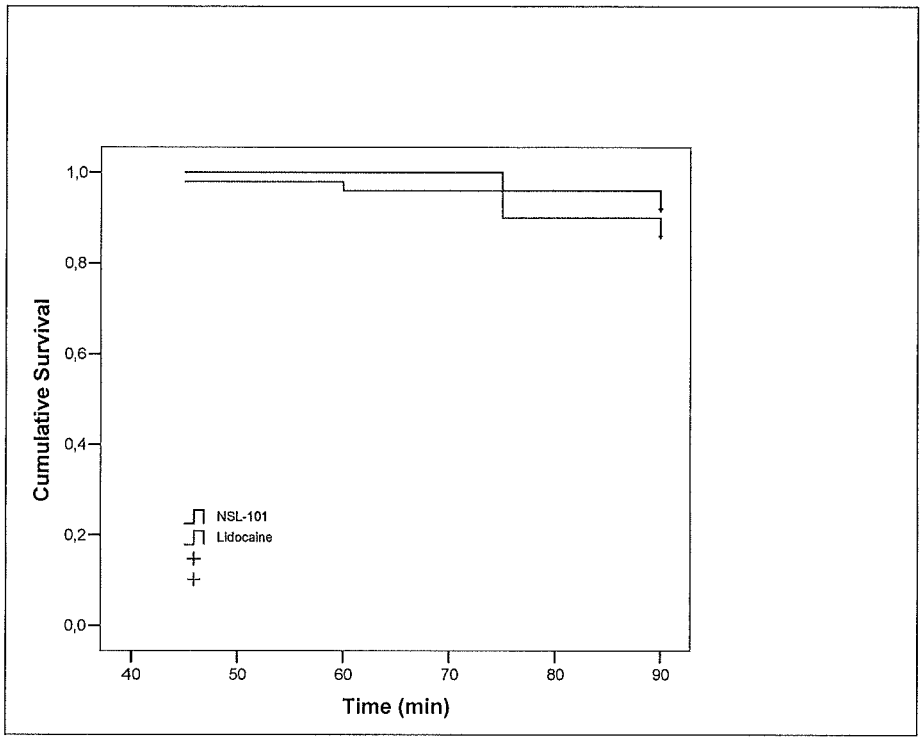


Figure 5

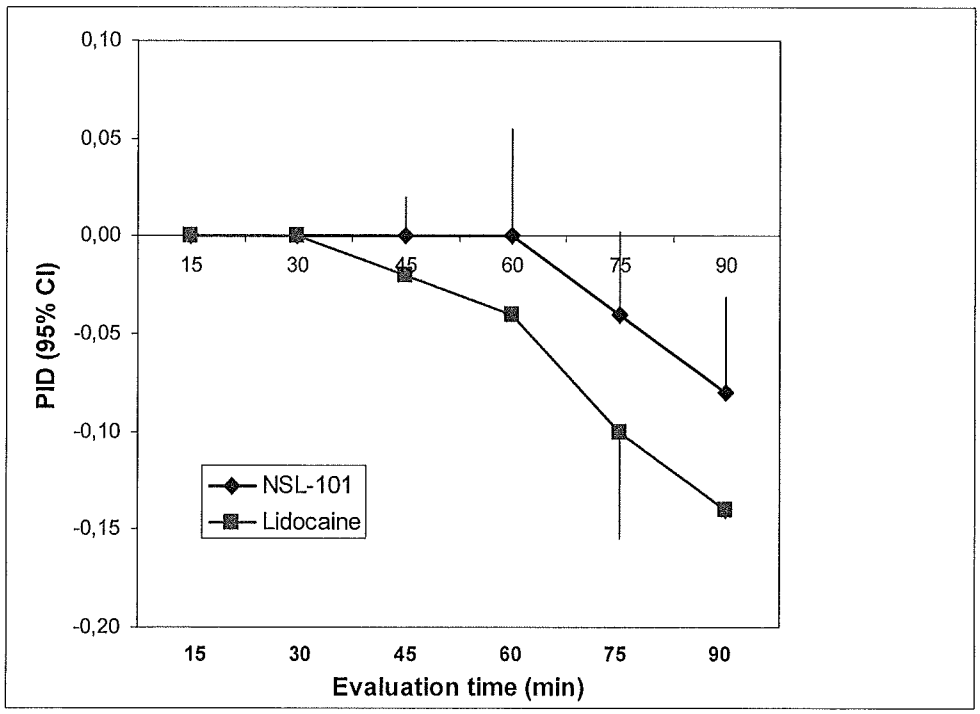


Figure 6

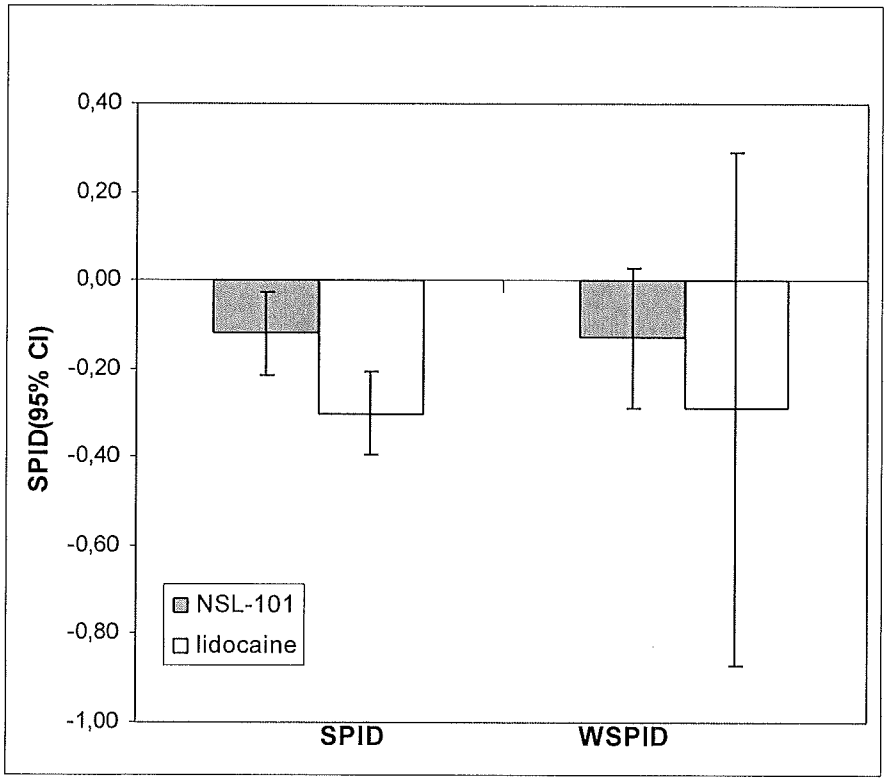


Figure 7a

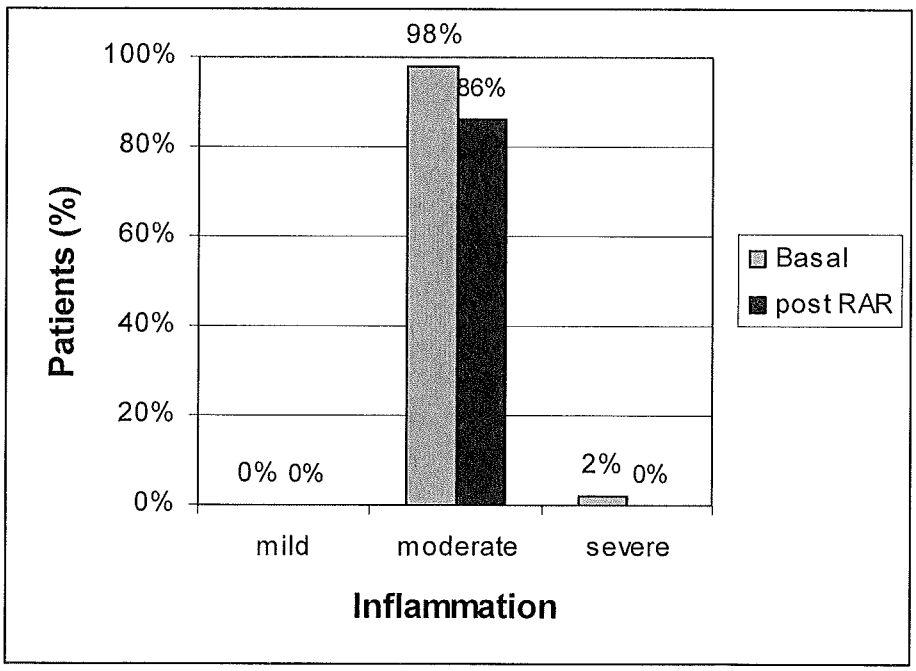
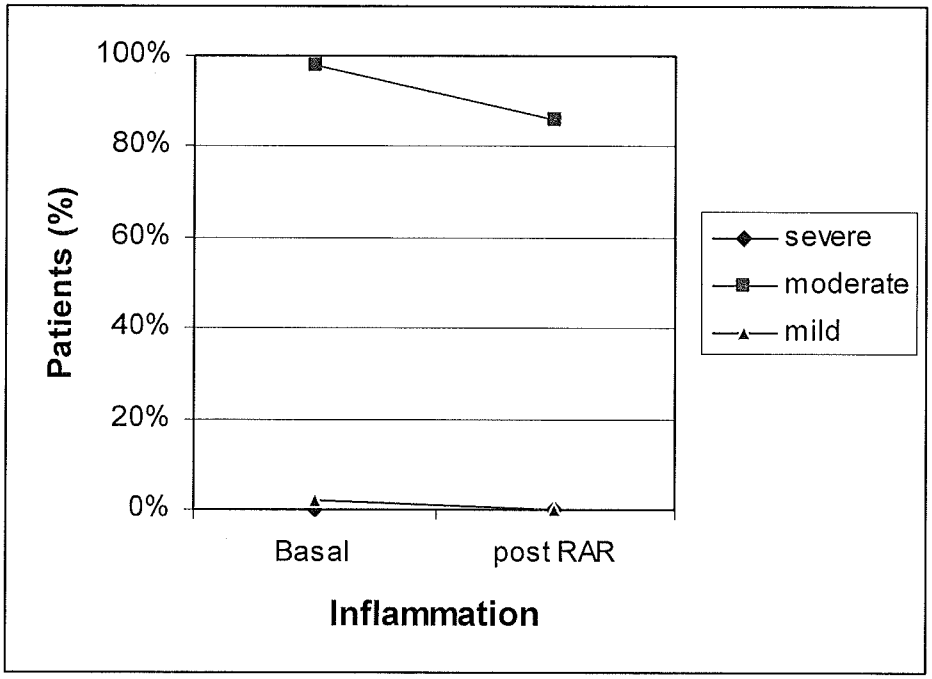


Figure 7b


100%
80%
60%
40%
20%
0%
Patients (%)
Basal
post RAR
Inflammation
severe
moderate
mild