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(54) Title: NEW PHARMACEUTICAL COMPOSITION WITH ANAESTHETIC EFFECT

(57) **Abrégé/Abstract:**

The invention is directed to a novel pharmaceutical composition comprising one or more local anaesthetics in oil form, one or more surfactants, water and optionally a taste masking agent. The novel composition is advantageously used as a local anaesthetic for pain relief within the oral cavity.

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/SE97/00566 <b>(22) International Filing Date:</b> 1 April 1997 (01.04.97)  <b>(30) Priority Data:</b> 9601421-2                      12 April 1996 (12.04.96)                      SE  <b>(71) Applicant (for all designated States except US):</b> ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BRODIN, Arne [SE/SE]; Kämpevägen 24, S-151 54 Södertälje (SE). FYNES, Ray- mond [CA/CA]; 1540 Troika Court, Mississauga, On- tario L5J 4O4 (CA). HEIJL, Lars [SE/SE]; Hammarströms Tappa 5 B, S-443 39 Lerum (SE). NYQVIST-MAYER, Adela [SE/SE]; Eklidsvägen 20, S-146 40 Tullinge (SE). SCHERLUND, Marie [SE/SE]; Tackjärnsvägen 12, S-161 31 Bromma (SE).  <b>(74) Agent:</b> ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> NEW PHARMACEUTICAL COMPOSITION WITH ANAESTHETIC EFFECT  <b>(57) Abstract</b>  The invention is directed to a novel pharmaceutical composition comprising one or more local anaesthetics in oil form, one or more surfactants, water and optionally a taste masking agent. The novel composition is advantageously used as a local anaesthetic for pain relief within the oral cavity.		

## NEW PHARMACEUTICAL COMPOSITION WITH ANAESTHETIC EFFECT

The field of the invention

5 The present invention is directed to a new pharmaceutical composition and its use in therapy, particularly as an anaesthetic for use on mucous membranes and particularly within the oral cavity.

10 Background and prior art

It is estimated that approximately 10-13 % of the population suffers from periodontal diseases with pathological periodontal pockets. In order to eliminate or control the disease and arrest further periodontal tissue destruction, periodontal pockets need repeated  
15 subgingival mechanical debridement/cleansing. The number of periodontal pockets in a patient may vary as can the pocket depth measurement. Approximately 40 % of all periodontal scaling procedures performed involve some kind of anaesthesia.

Accumulation of bacterial plaque on teeth and in the gingival sulcus elicits an inflammatory  
20 response in the marginal gingiva which may spread in an apical direction and result in loss of tooth support with the formation of periodontal pockets. The object of mechanical debridement of periodontal pockets is to control and arrest further destruction of tooth support by removal of plaque and calculus from within the pockets.

25 The majority of the scaling procedures are performed by hygienists. The main use of anaesthesia techniques used in conjunction with periodontal scaling is either a nerve block or infiltration. Infiltration anaesthesia is either carried out alone or in combination with topical anaesthesia, mainly jelly, ointment or spray. However, the problem with existing  
topical products are lack of efficacy due to inadequate depth of penetration, too short  
30 duration and difficulties in administration due to spread, taste etc.



EP 244 118 discloses a controlled release drug delivery system for placement in the periodontal pocket, having a plurality of discrete microparticles consisting of a rate-controlling polymer matrix having a drug dispersed therein, said microparticles being in the range of 10-500  $\mu\text{m}$ . EP 241 178 also discloses a controlled release drug delivery system  
5 for placement in the periodontal pocket, which composition comprises solid particles having an average size of 1-500  $\mu\text{m}$ . However, the drug delivery systems disclosed in both these prior art patents are devised for administration of a medicament for a longer period of time. Thus the drug delivery systems of EP 244 118 and EP 241 178 are not suitable for use in pain management in conjunction with minor surgical procedures, where a fast onset of  
10 action and relatively short duration is required.

Thus, the problem underlying the present invention is to provide a pharmaceutical composition which would provide effective pain relief in conjunction with periodontal scaling and root planing following local administration. In other words, the object of the  
15 invention is to provide a local anaesthetic that can be applied in a facile manner in the oral cavity, and more precisely within periodontal pockets. A further object of the invention is to provide a pharmaceutical composition having a short onset time and an adequate duration for the intended procedure, with no inconvenient anaesthesia.

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Outline of the invention

The problem identified above has now been solved by providing a new pharmaceutical composition which preferably is in form of an emulsion, more preferably in  
5 form of a microemulsion, comprising the following ingredients:

(i) one or more local anaesthetics in oil form in the final composition;

(ii) one or more surfactants, together present in  
10 an amount effective to produce a homogenous formulation; and

(iii) water up to 100% by weight, based on the total weight of the composition.

According to one aspect of the present invention, there is provided a pharmaceutical composition comprising  
15 (i) one or more surfactants, together present in an amount effective to produce a homogenous formulation, wherein, if more than one surfactant is present in the composition, at least one of the surfactants has thermoreversible gelling properties, and if only one surfactant is present in the  
20 composition, the surfactant acts as a thickening agent with thermoreversible gelling properties, as a solubilizer and as an emulsifier; (ii) one or more local anaesthetics in oil form in the final composition; and (iii) water up to 100% by weight, based on the total weight of the composition;  
25 wherein the pharmaceutical composition is in the form of an emulsion or microemulsion.

The local anaesthetic in the final composition is one or more local anaesthetics in oil form as such, or a eutectic mixture formed by two or more local anaesthetics.

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The amount of the local anaesthetic in the oil phase depends on the pH-value of the formulation.

In a particularly preferred embodiment of the invention the local anaesthetic is a eutectic mixture of  
5 lidocaine base and prilocaine base.

In a further embodiment of the invention a eutectic mixture may also be formed by two or more substances, where at least one of these substances is a local anaesthetic.

10 The amount of the local anaesthetic or mixture of local anaesthetics is preferably in the range 0.5 - 20% by weight, more preferably in the range 2-7% by weight, based on the total weight of the composition.

The local anaesthetic(s) in the final composition  
15 are present in a non-solid form.



By the wording "surfactant" we mean any agent that acts as a solubilizer and/or as an emulsifier and/or as a thickening agent with thermoreversible gelling properties. The wording surfactant is also intended to include thickening agents without thermoreversible properties. If only one surfactant is used in the composition, it must be selected with care and in suitable amounts so that it acts both as a solubilizer and/or as an emulsifier, as well as a thickening agent with thermoreversible gelling properties. If more than one surfactant is present in the composition, at least one of the surfactants should have thermoreversible gelling properties. The total amount of the surfactant(s) should be present in an amount effective to produce a homogenous formulation.

The surfactants are preferably selected from non-ionic surfactants, more preferably from any non-ionic poloxamer known in the art.

Poloxamers are synthetic block copolymers of hydrophilic ethylene oxide chains and hydrophobic propylene oxide chains, having the general formula

$\text{HO}-[\text{C}_2\text{H}_4\text{O}]_a-[\text{C}_3\text{H}_6\text{O}]_b-[\text{C}_2\text{H}_4\text{O}]_a-\text{H}$ , a and b representing the number of the hydrophilic and hydrophobic chains respectively.

By choosing the surfactant(s) having hydrophobic and hydrophilic domains in appropriate amounts, in combination with an appropriate amount of the local anaesthetic or mixture of local anaesthetics, it is possible to achieve a composition having suitable thermoreversible gelling properties, i.e. the system remains less viscous at room temperature, and upon application into a periodontal pocket the viscosity of the composition is increased. In other words, the pharmaceutical composition according to the present invention is less viscous at room temperature. Above this temperature the composition is more viscous, providing the advantage of remaining in the periodontal pockets for the time necessary to induce local anaesthesia. The change in viscosity is reversible with temperature.

In a particularly preferred embodiment of the invention the surfactant is one or more of Lutrol F68<sup>®</sup>, which also has the name poloxamer 188 and wherein a= 80 and b=27, and Lutrol F127<sup>®</sup>, which also has the name poloxamer 407 and wherein a=101 and b=56, the definitions being in accordance with USP (1995) NF18, p. 2279. Lutrol F68<sup>®</sup> and Lutrol F127<sup>®</sup> are commercially available from BASF.

In a further preferred embodiment of the invention the surfactant Arlatone 289<sup>®</sup> is used, which also has the name polyoxyethylene hydrogenated castor oil, as well as Adinol CT95<sup>®</sup> which is sodium N-methyl N-cocoyl taurate.

The total amount of surfactant(s) is preferably present in an amount of up to 50 % by weight, based on the total weight of the composition.

The pH-value of the pharmaceutical composition is adjusted with suitable acid or base in such a way that the final pH-value for the composition is:

(A)  $\text{pH} \geq [\text{pK}_a (\text{local anaesthetic}) - 1.0]$  if the composition comprises one local anaesthetic; or

(B)  $\text{pH} \geq [\text{pK}_a (\text{local anaesthetic with the lowest pK}_a \text{ value}) - 1.0]$  if the composition comprises two or more local anaesthetics.

Preferably the pH is over 7.5.

Since local anaesthetics by nature have an unpleasant bitter taste, one or more taste masking agents may optionally be added to the pharmaceutical composition. The choice of taste masking agents will be appreciated by a person skilled in the art, but as an example any fruit flavours may be mentioned.



By topical application within the periodontal pocket, local anaesthesia is achieved in a very localised area, without causing the often extensive soft tissues such as the tongue, cheek and lips, to get anaesthetized which is often the case with infiltration anaesthesia. Preferably  
5 the composition is applied into a periodontal pocket by means of a blunt needle, thereby facilitating the administration of the anaesthetic and giving an increased patient comfort.

The pharmaceutical composition of the present invention has a fast onset of action being from seconds and up to approximately 5-15 minutes. The onset time is most preferably  
10 from seconds and up to approximately 5 minutes.

For the definition of emulsions, we refer to *Pharmaceutics, The Science of Dosage Form Design*, 1988, p. 109-110, by ME Aulton.

15 The pharmaceutical composition according to the present invention is preferably a microemulsion. By microemulsion we mean a formulation that consists of water, oil and amphiphile(s) which constitute a single optically isotropic and thermodynamically stable liquid solution (*I. Danielsson and B Lindman, Colloids Surf. 3:391, (1981)*).

This provides a suitable amount of the local anaesthetic in the oil phase, which in turn  
20 confers a fast onset of action. No separate oil needs to be added to the composition, since the oil is already present by the active component(s) as such. A further advantage is that a thermodynamically stable composition is achieved in a temperature range of 5-40 °C.

The pharmaceutical composition according to the present invention may advantageously  
25 also be used as a local anaesthetic on other surfaces and/or cavities than in the oral cavity. The composition may thus also be used vaginally, genitally and rectally.

The local anaesthetic(s) used for preparing a pharmaceutical composition according to the present invention may be selected from any local anaesthetic. Preferably the local  
30 anaesthetic as the starting material is in a non-ionized form.

In the final composition a fraction of the local anaesthetic or mixture of local anaesthetics are present in oil form. The size of this fraction, local anaesthetics in oil form, depends on the pH of the composition.

- 5 The best mode of performing the invention known at present, is to use the composition according to Example 1.

#### Methods of preparation

10

The pharmaceutical composition according to the present invention may be prepared by the following steps:

- 15 (i) the local anaesthetic(s) and the surfactant with the lowest molecular weight if more than one surfactant is used, are melted together;

(ii) a part of the water is slowly added to the melt (i) during homogenization, forming an emulsion concentrate;

- 20 (iii) if more than one surfactant is used, the surfactant with the higher molecular weight is dispersed in water;

(iv) the emulsion concentrate of step (ii) and part of the surfactant solution of step (iii) are thoroughly mixed;

25

(v) the pH-value is adjusted by the addition of a suitable acid or base;

(vi) the weight is adjusted with water to the final weight of the composition.

- 30 The composition is preferably kept at 5 °C until a homogenous composition is obtained.

Detailed description of the invention

The invention will now be described in more detail by the following examples, which are not to be construed as limiting the invention.

5

<u>Example 1</u>	<u>[% by weight]</u>
Lidocaine	2.50
Prilocaine	2.50
10 Lutrol F68 <sup>®</sup>	5.50
Lutrol F127 <sup>®</sup>	15.50

purified water up to a total weight of 100 %.

15 The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

<u>Example 2</u>	<u>[% by weight]</u>
Lidocaine	2.50
Prilocaine	2.50
20 Lutrol F68 <sup>®</sup>	5.00
Lutrol F127 <sup>®</sup>	16.25

purified water up to a total weight of 100 %.

25 The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.



<u>Example 3</u>	<u>[% by weight]</u>
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Lidocaine	2.25
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Prilocaine	2.25
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5 Lutrol F68 <sup>®</sup>	3.5
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Lutrol F127 <sup>®</sup>	14.0
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purified water up to a total weight of 100 %.

10 The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

<u>Example 4</u>	<u>[% by weight]</u>
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Lidocaine	2.25
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Prilocaine	2.25
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15 Arlatone 289 <sup>®</sup>	1.90
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Adinol CT95 <sup>®</sup>	0.07
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Lutrol F127	14.00
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purified water up to a total weight of 100 %.

20 The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

	<u>Example 5</u>	<u>[% by weight]</u>
	Lidocaine	2.25
	Prilocaine	2.25
5	Arlatone 289 <sup>®</sup>	1.90
	Adinol CT95 <sup>®</sup>	0.16
	Lutrol F127	14.00

purified water up to a total weight of 100 %.

- 10 The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

	<u>Example 6</u>	<u>[% by weight]</u>
15	Lidocaine	2.25
	Prilocaine	2.25
	Arlatone 289 <sup>®</sup>	1.90
	Adinol CT95 <sup>®</sup>	0.28
	Lutrol F127	14.00

- 20 purified water up to a total weight of 100 %.

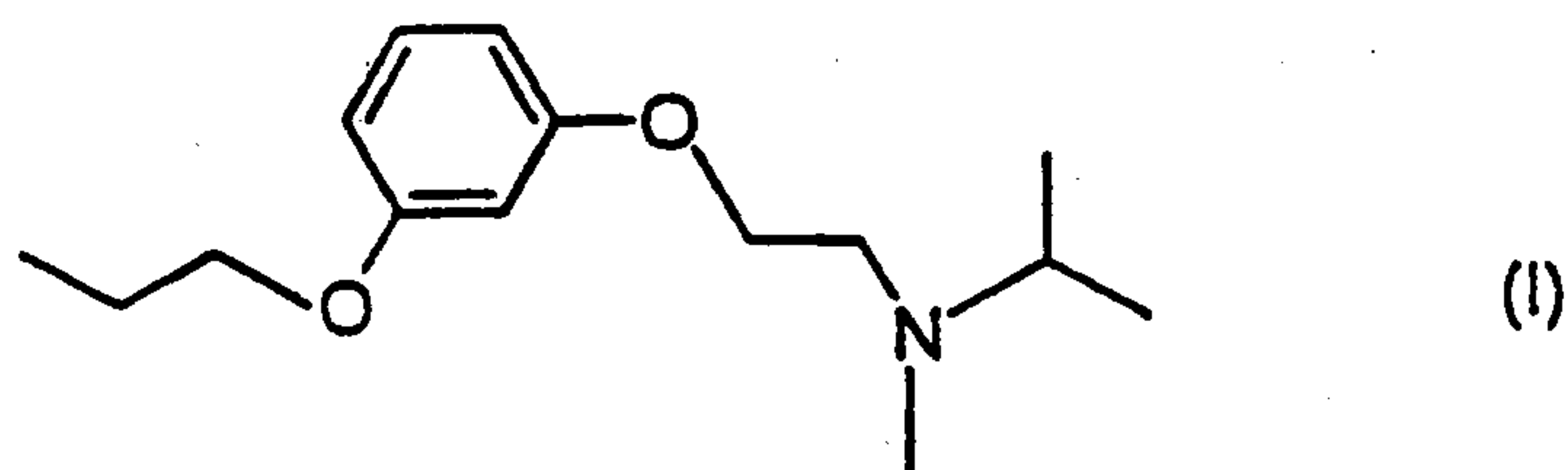
The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

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**Example 7 and 8**

In Examples 7 and 8, a local anaesthetic of the formula (I) was used as the active ingredient.



This compound is disclosed in the International Patent Publication No. WO 97/15548.

The following pharmaceutical compositions were prepared.

<u>Example 7</u>	<u>[% by weight]</u>
Compound (I)	2.5
Lutrol F127 <sup>®</sup>	17.0
Lutrol F68 <sup>®</sup>	5.5

purified water up to a total weight of 100 %.

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

<u>Example 8</u>	<u>[% by weight]</u>
Compound (I)	2.5
Lutrol F127 <sup>®</sup>	20.0
Lutrol F68 <sup>®</sup>	5.5

purified water up to a total weight of 100 %.



The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

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### Biological studies

A pharmaceutical composition according to Example 1 was applied to a human periodontal pocket with a blunt end needle. After an onset time of 30 - 45 seconds, a satisfactory anaesthetic effect had been achieved in order that periodontal scaling could be performed. The scaling was initiated, and the time taken to scale the tooth was noted. At the end of the scaling, the intensity of pain was measured by means of a visual analogue scale (VAS). The duration of the anaesthetic effect was 10-20 minutes.

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CLAIMS:

1. A pharmaceutical composition comprising

(i) one or more surfactants, together present in an amount effective to produce a homogenous formulation, wherein, if more than one surfactant is present in the composition, at least one of the surfactants has thermoreversible gelling properties, and if only one surfactant is present in the composition, the surfactant acts as a thickening agent with thermoreversible gelling properties, as a solubilizer and as an emulsifier;

(ii) one or more local anaesthetics in oil form in the final composition; and

(iii) water up to 100% by weight, based on the total weight of the composition; wherein the pharmaceutical composition is in the form of an emulsion or a microemulsion.

2. A pharmaceutical composition according to claim 1, further comprising one or more taste masking agents.

3. A pharmaceutical composition according to claim 1 or 2, wherein the one or more local anaesthetics are present in an amount of 0.5 - 20% by weight based on the total weight of the composition.

4. A pharmaceutical composition according to claim 3, wherein the one or more local anaesthetics are present in an amount of 2-7% by weight based on the total weight of the composition.

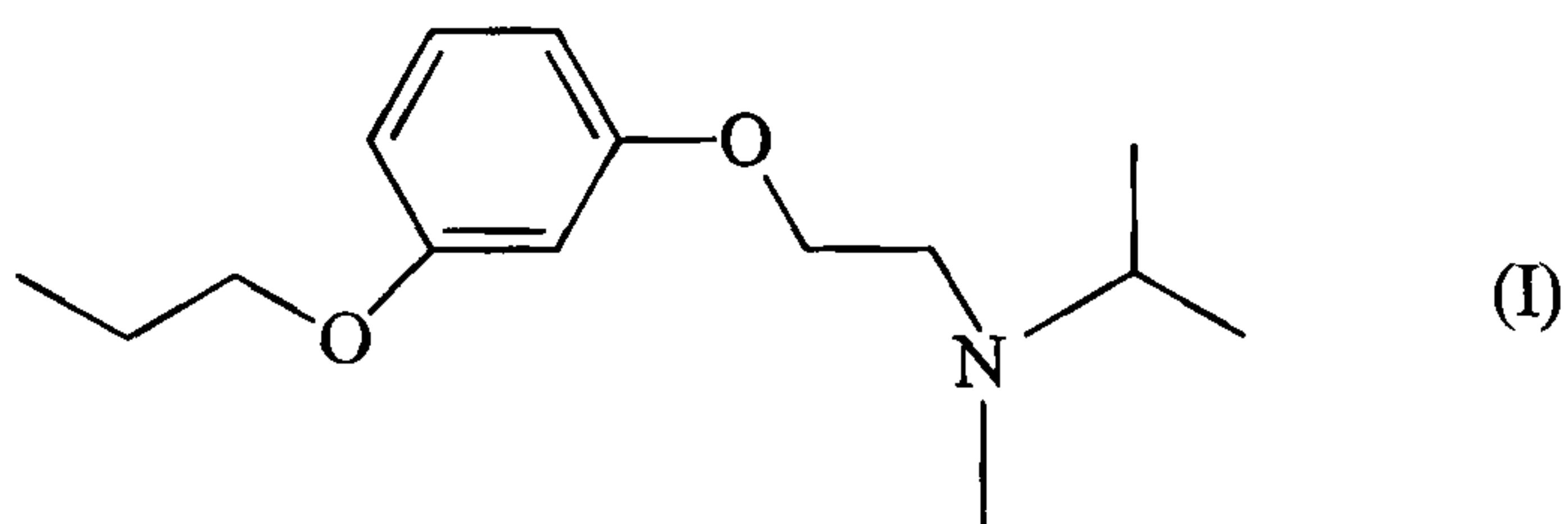
5. A pharmaceutical composition according to any one of claims 1 to 4, wherein the one or more local anaesthetics is a eutectic mixture of local anaesthetics.

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6. A pharmaceutical composition according to claim 5, wherein the one or more local anaesthetics is a eutectic mixture of lidocaine and prilocaine.

7. A pharmaceutical composition according to claim 1,  
5 wherein the one or more local anaesthetics is



10 8. A pharmaceutical composition according to any one of claims 1 to 7, wherein the total amount of the one or more surfactants is up to 50% by weight based on the total weight of the composition.

9. A pharmaceutical composition according to any one  
15 of claims 1 to 8, wherein the one or more surfactants comprise a non-ionic surfactant.

10. A pharmaceutical composition according to claim 9, wherein the non-ionic surfactant is a poloxamer.

11. A pharmaceutical composition according to any one  
20 of claims 1 to 10, wherein the one or more surfactants comprise Lutrol F68® and Lutrol F127®.

12. A pharmaceutical composition according to any one of claims 1 to 11 for locally anaesthetising mucosa of the oral cavity.

25 13. Use of components (i), (ii) and (iii), as defined in any one of claims 1 and 3 to 11 in manufacture of a



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pharmaceutical composition for locally anaesthetising mucosa of the oral cavity.

14. Use of a pharmaceutical composition according to any one of claims 1 to 11 for locally anaesthetising mucosa  
5 of the oral cavity.

15. A pharmaceutical composition according to any one of claims 1 to 11 for pain relief during periodontal scaling.

16. Use of components (i), (ii) and (iii), as defined  
10 in any one of claims 1 and 3 to 11, in manufacture of a medicament for pain relief during periodontal scaling.

17. A use of a pharmaceutical composition according to any one of claims 1 to 11 for pain relief during periodontal scaling, in a patient in need thereof.

15 18. A process for the manufacture of a pharmaceutical composition according to claim 1, whereby

(i) the one or more local anaesthetics and the surfactant with the lowest molecular weight, if more than one surfactant is used, are melted together;

20 (ii) a part of the water is slowly added to the melt (i) during homogenization, forming an emulsion concentrate;

(iii) if more than one surfactant is used, the surfactant with the higher molecular weight is dispersed in  
25 water;

(iv) the emulsion concentrate of step (ii) and part of the surfactant solution of step (iii) are thoroughly mixed;

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(v) the pH-value is adjusted by the addition of a suitable acid or base;

(vi) the weight is adjusted with water to the final weight of the composition.

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