

A LOZENGE

FIELD OF THE INVENTION

The invention relates generally to the field of pharmaceutical lozenges. More particularly,
5 the invention relates to a lozenge comprising bupivacaine or a salt thereof. The lozenge is suitable for use in the treatment or alleviation of pain, such as pain in the oral cavity (mouth and/or pharynx) in patients who have, e.g., oral mucositis (OM) following cancer treatment.

10 BACKGROUND OF THE INVENTION

Pain has for many years been treated with opioids, which has caused suffering to a lot of people as well as terrible addiction to the opioids. There is a need for analgesic or anaesthetic medications that are less addictive for the person in need of pain relief and still powerful enough to help alleviate the pain.

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Mucositis is a painful inflammation and ulceration of the mucous membranes lining the gastrointestinal tract, the GI tract, though the term mucositis mainly refers to the inflammation and ulceration that occurs in the oral cavity (mouth). Often mucositis is caused by cancer treatment and is very painful for the patient, severely impacting their
20 quality of life and ability to eat, speak and sleep. Mucositis can be mitigated by, for example, opioids and to a lesser degree morphine mouthwash.

There is a need for new improved medications to help patients suffering from pain in the oral cavity such as from oral mucositis (OM).

25 Bupivacaine hydrochloride is an amide based local anesthetic and is a well established active ingredient. Bupivacaine has been used for more than 20 years in daily clinical practice as a local anesthetic, for both surgery and postoperative pain treatment. The IUPAC name of bupivacaine is 1-butyl-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (formula: C₁₈H₂₈N₂O).

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EP3284459 discloses a sustained release composition for local administration of bupivacaine for the alleviation of pain in the mouth or pharynx.

However, there is still a need for new improved compositions, preferably giving both a fast and an extended relief of pain in the oral cavity, for example, in a patient suffering from oral mucositis.

5 SUMMARY OF THE INVENTION

The invention relates to a lozenge comprising a core and a first coat, wherein: the core comprises bupivacaine or a salt thereof, and at least one excipient; and the first coat comprises bupivacaine or a salt thereof, at least one film-forming agent, and optionally an excipient.

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The first coat is a coating layer covering and enclosing the core of the lozenge. The coat is referred to as a first coat, since it is contemplated that the lozenge may contain further coating layers, e.g. a further coat external to the first coat.

15 Preferably, the lozenge is substantially free from oxidizing agents, such as e.g. peroxides.

Generally, in the preparation of a conventional lozenge, one or more of the excipients may contain small amounts of oxidizing agents, which normally do not give rise to oxidation of the active pharmaceutical ingredient (API). Bupivacaine is known to be a reactive API

20 upon coming in contact, with for example peroxides, wherein bupivacaine oxidizes to bupivacaine N-oxide, thus there are regulations from the authorities that the level of N-oxide should be low. The limit of N-oxide in the different products depends on the formulation and administration route. However, preferably no oxidizing agents should be present in the product to ensure that the API is stable during storage. To ensure that a
25 major part of bupivacaine remains unaffected, excipients used in the production of the compressed lozenge of the present invention should be substantially free from oxidizing agents and more preferably the ingredients should be validated before use for the absence of oxidizing agents.

30 In a lozenge according to the invention, preferably containing essentially no oxidizing agents, bupivacaine remains stable during storage, with essentially no oxidation to N-oxide.

The lozenge of the present invention comprises a compressed core. Preferably, the bupivacaine used to prepare the core is in the form of particles, e.g. micronized particles, having a homogenous particle size, e.g. a particle size of less than 250 μm (i.e., 0.25 mm). Suitably, such a core will provide a lozenge having a linear release of bupivacaine from the
5 core over an extended period of time, to give a prolonged relief of pain.

The core of the inventive lozenge is coated by a coat comprising bupivacaine or a salt thereof, at least one film-forming agent, and optionally excipient, e.g. at least one excipient. This coat may be referred to herein as the first coat. Suitably, the first coat
10 provides a rapid release of bupivacaine, which gives a fast relief of pain.

In addition, the lozenge may contain a second coat, containing a film-forming agent, and optionally one or more further excipients, such as a coloring agent or a flavor. The second coat may assist to further protect bupivacaine from contact with the environmental oxygen
15 and humidity. Film forming agents and excipients used in the second coat may be selected from, for example, those indicated herein. For the avoidance of doubt, it is pointed out that a lozenge of the invention may include more than one "second" coat or may be free from a second coat altogether. In some embodiments, the lozenge contains a first inner coat, adjacent to the core, and a second outer coat.

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The first coat and the optional second coat comprising film forming agents give a smooth and soft feeling to the lozenge in the mouth compared to a lozenge without such a coat which will give a rough feeling causing further pain to the patient already suffering from pain in the mouth. Additionally, the initial release of bupivacaine from the first coat
25 reduces pain prior to the exposure of the compressed core and therefore, very advantageously, will provide a first pain relief to a patient suffering from pain in the mouth or throat, such as a patient suffering from OM.

The invention also relates to the use of the lozenge of the invention for the treatment or
30 alleviation of pain or burning sensation of the oral cavity, such as in oral mucositis, or other oral pain stemming from other indications such as chronic pain, post operative pain, Burning Mouth Syndrome, or for use in the treatment or alleviation of oral mucositis.

Thus, also provided herein is a method for the treatment or alleviation and/or a burning sensation in the oral cavity of a mammal (e.g. a human) in need thereof, by administering a lozenge as described herein to said mammal. The mammal may, for example, be a patient suffering from oral mucositis.

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DESCRIPTION OF THE DRAWINGS

Fig. 1 shows dissolution profiles (over a time period of 5 minutes) of bupivacaine containing lozenges. "Original" is an uncoated lozenge containing 25 mg of bupivacaine. The "20/20" to "80/20" are lozenge placebo cores coated with different ratios of Opadry II clear/bupivacaine, obtained by keeping the concentration of bupivacaine constant in the
10 coating suspension at 10 mg and increasing the amount of coating suspension.

Fig. 2 shows dissolution profiles of bupivacaine containing lozenges obtained using three different coating polymers, viz. Opadry II clear (a polyvinyl alcohol), Kollicoat IR (a
15 macrogol poly(vinyl alcohol) grafted copolymer) and Methocel E3 (Hydroxypropyl methyl cellulose), respectively, each containing 10 mg bupivacaine, on 25 mg lozenge cores.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

20 Unless indicated otherwise, all technical and scientific terms used herein will have their common meaning as understood by one of ordinary skill in the art to which this invention pertains.

The term "lozenge" or, alternatively, "compressed lozenge" means preparations that are
25 solid, containing one or more active substances intended for administration to the oral cavity and/or the throat to obtain a local or systemic effect. The lozenge should dissolve in the oral cavity, wherein the active substance is released and can give an effect. As used herein, the term "lozenge" refers to a "compressed lozenge".

30 Furthermore, it is noted that, as used herein, the term "compressed lozenge" refers to a lozenge having a compressed lozenge core, covered by a coat.

The term "substantially free from" (or "essentially free from") is intended to mean that the ingredients are substantially free from any oxidizing agents, such as peroxides which

minimizes the risk that bupivacaine converts to N-oxide during storage. Measurements can be performed using the FOX2 reagent kit which measures the peroxides by a series of oxidation reactions, further analyzed at a wavelength of 560 nm "Pierce™ Quantitative Peroxides Assay Kits" from Thermo Scientific, well known for a person skilled in the art.

- 5 Preferably the peroxides levels should be sufficiently low below the limits stipulated by the authorities, such as below 500 $\mu\text{mol/l}$, for example below 400 $\mu\text{mol/l}$, 300 $\mu\text{mol/l}$, 200 $\mu\text{mol/l}$, such as below 150 $\mu\text{mol/l}$, 100 $\mu\text{mol/l}$, 50 $\mu\text{mol/l}$ or even below the measuring limit by the FOX2 reagent kit "Pierce™ Quantitative Peroxide Assay Kits".
- 10 By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, e.g., the material may be incorporated into a dosage form of the invention without interacting in a deleterious manner with any of the other components of the dosage form formulation. When the term "pharmaceutically acceptable" is used to refer to a pharmaceutical excipient, it is implied that the excipient has met the required standards of
- 15 toxicological and manufacturing testing and/or that it is included in the Inactive Ingredient Guide prepared by the U.S. Food and Drug Administration or European Pharmacopoeia (Ph. Eur.).

- For the avoidance of doubt, it is pointed out that any ingredient of the lozenge of the
- 20 invention, for example, any salt of bupivacaine or any excipient or film-forming agent, is selected from pharmaceutically acceptable ingredients.

- The terms "treating" and "treatment" as used herein refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of
- 25 the occurrence of symptoms and/or their underlying cause, and improvement or remediation of an undesirable condition. Thus, for example, "treating" a patient involves prevention of an adverse condition in a susceptible individual as well as treatment of a clinically symptomatic individual by inhibiting or causing regression of the condition.

- 30 By an "effective" amount of a local anaesthetic is meant a nontoxic but sufficient amount of the agent to provide the desired effect. The amount of beneficial agent that is "effective" will vary from subject to subject, depending on the age and general condition of the individual, the particular active agent or agents, and the like. Thus, it is not always possible to specify an exact "effective amount." However, an appropriate "effective" amount in any

individual case may be determined by one of ordinary skill in the art using routine experimentation.

The term “mammal” as used herein includes a human as well as a non-human mammal,
5 such as a mammal selected from primates, domesticated animals such as farm animals, e.g. cattle, sheep, pigs, horses and the like, as well as pet animals, such as dogs and cats, and the like. Preferably, the mammal is a human.

As used herein, the expression “salt of bupivacaine” refers to any pharmaceutically
10 acceptable salt of bupivacaine, e.g. an acid addition salt, such as a salt with a strong mineral acid, for example a hydrohalic acid, such as HCl.

The teaching of any patent or non-patent prior art publication as referred to herein is incorporated herein by reference.

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The lozenge

In a first aspect, the invention relates to a lozenge, comprising a core covered by a coat (the first coat), wherein:

the core comprises bupivacaine or a pharmaceutically acceptable salt thereof and at least
20 one excipient; and

the coat covering the core comprises bupivacaine or a pharmaceutically acceptable salt thereof, at least one film-forming agent, and optionally an excipient (e.g. at least one excipient).

25 Preferably, the lozenge is substantially free from oxidizing agents, such as peroxides.

The one or more excipients may include, for example, a binding agent, such as a binding agent selected from the group consisting of starch, mannitol, copovidone, kollidone, hydroxypropyl methyl cellulose (HPMC), microcrystalline cellulose and methyl cellulose
30 (Methocel E3), sodium carboxymethyl cellulose (CMC), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), DC lactose and sodium alginate. One specific suitable binding agent is methyl cellulose.

Bupivacaine or a salt thereof is preferably micronized, i.e., milled and filtered through for example a mesh to ensure a small and homogenous particle size, e.g. a particle size less than 250 μm . The size reduction of bupivacaine provides a homogeneous blend suitable for direct compression, resulting in lozenge cores with acceptable content uniformity. Thus, a
5 homogenous compressed core is obtained, and a controlled release of bupivacaine obtained, which alleviates the pain symptoms of a patient over a prolonged time.

In some embodiments, bupivacaine is present in the core in an amount of 5 to 25 mg, such as 5-20 mg such as 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg. The core is
10 preferably dissolved by the saliva within about 30 minutes, such as within about 10, 20 or 30 minutes whereby the patient is relieved from pain. How fast the core is dissolved is dependent on the saliva as well as the intensity of sucking the lozenge.

Bupivacaine is preferably present in the first coat in an in an amount of 1 to 10 mg such as
15 5 to 10 mg, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg. The first coat is preferably dissolved in the saliva within about 5 minutes, such as within 1, 2, 3, 4 or 5 minutes.

In some embodiments, bupivacaine is present in an amount of 5 to 20 mg in the core and 5
20 to 10 mg in the first coat. In some embodiments, bupivacaine is present in an amount of 9 mg or 15 mg in the core and 6 mg or 10 mg in the first coat.

In some embodiments, bupivacaine is present in an amount of 15 mg in the core and 10 mg
in the first coat. In some embodiments, bupivacaine is present in an amount of 9 mg in the core and 6 mg in the first coat.

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In some embodiments, the ratio of the amount of bupivacaine present in the core to bupivacaine present in the coat is in the range of about 4:1 to 1:1, e.g. about 3:1 to 1:1, such as about 2:1 to 1:1 by weight. In some of these embodiments, the ratio is at least 1.2:1, at least 1.3:1, at least 1.4:1 or at least 1.5:1 by weight. In some embodiments, the
30 ratio of the amount of bupivacaine present in the core to bupivacaine present in the coat is about 1.5:1 by weight.

Examples of excipients include fillers, glidants, lubricants, sweeteners, flavors/taste masking agents coloring agents, and mixtures thereof.

Suitable lubricants include long chain fatty acids and their salts, such as magnesium
5 stearate and stearic acid, talc, glycerides waxes, and mixtures thereof.

Suitable glidants include colloidal silicon dioxide.

Examples of sweeteners include, synthetic or natural sugars; artificial sweeteners such as
10 saccharin, sodium saccharin, aspartame, neotame, acesulfame, thaumatin, glycyrrhizin, sucralose, cyclamate, dihydrochalcone, alitame, miraculin and monellin; sugar alcohols such as sorbitol, mannitol, glycerol, lactitol, maltitol, and xylitol; sugars extracted from sugar cane and sugar beet (sucrose), dextrose (also called glucose), fructose (also called laevulose), and lactose (also called milk sugar); isomalt, stevia, and mixtures thereof.

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Examples of flavors/taste masking agents include fruit and berry flavors such as lime, orange, lemon, black current, blood orange, cranberry, cloudberry, goji berry, raspberry, strawberry, wild strawberry, sea buckthorn, cherry, melon, kiwi, papaya, pineapple, passion fruit, coconut, and other flavors such as honey, water grass, lemon grass,
20 cacao/cocoa, vanilla or mixtures thereof. The flavors/taste masking agent may be natural extracts as well as synthetic versions. Bupivacaine has a bitter taste thus it is important to include a flavor/taste masking agent that covers the bitter taste of bupivacaine until the mucus is stunned, which occurs during the dissolution of the first coat. In addition, for example in a patient suffering from OM, it is highly important that the flavor/taste masking
25 agent is mild to the mucus of the patient. There is no need to have a flavor/taste masking agent in the core.

Examples of coloring agents include lakes and dyes being approved as a food and/or pharmaceutical additive.

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Examples of fillers that may be used include maltitol, xylitol, sorbitol, mannitol, lactose, dextrose, saccharose or fructose, or any mixture thereof. One example is mannitol.

In one embodiment the core comprising at least one excipient selected from the list consisting of sweeteners, glidant, lubricating agent and sugar alcohols/filling agents.

The first coat ensures that the core is protected from oxidation as well as delivering a fast
5 release of bupivacaine upon being dissolved.

In another embodiment the first coat is covered by a second coat to further reduce the risk of contact with environmental oxygen and humidity, to further reduce the risk of oxidation of bupivacaine. The compressed lozenge may as well be packed in a package that protects
10 the lozenge from getting in contact with any environmental oxygen or humidity.

The thickness of the first coat has an influence on the degree of reduction of pain that the patient suffers from and that influences the acceptance of the product. The first coat may have an average thickness from 10 to 500 μm , more preferably from 20 to 250 μm , such as
15 from 30 to 150 μm . The film thickness may be measured using different methods known in the art such as SEM (Scanning Electron Microscopy), X-ray microtomography, terahertz pulsed imaging etc. See further e.g. Quantitative Analysis of Film First coating in a Pan First coater Based on In-Line Sensor Measurements, Jose D. Perez-Ramos et al, AAPS PharmSciTech 2005; 6 (1) Article 20, Nondestructive analysis of tablet first coating
20 thicknesses using terahertz pulsed imaging. J Pharm Sci. 2005; 94:177Y183. Fitzgerald A J, Cole B E, Taday P F., Hancock B, Mullarney M P. X-ray microtomography of solid dosage forms. Pharm Technol. 2005; 29:92Y100.

The film-forming agents (or film-forming polymers) may be chosen from cellulose ethers
25 e.g. hydroxy propyl methyl cellulose (HPMC), methyl hydroxy ethyl cellulose (MHEC), hydroxy propyl cellulose (HPC), hydroxyethyl cellulose (HEC), ethyl hydroxyl ethyl cellulose (EHEC), and other film forming polymers such as methacrylic acid copolymer-type C sodium carboxy methyl cellulose, polydextrose, polyethylene glycols, acrylate polymers (e.g. poly vinyl acrylate (PVA)), polyvinyl alcohol-polyethylene glycol graft
30 copolymers, complex of polyvinylpyrrolidone (PVP), such as povidone, polyvinyl alcohol, microcrystalline cellulose, carrageenan, pregelatinized starch, polyethylene glycol, and combinations thereof. Typically, the molecular weight (weight average and/or number average) of the polymer is from 1,000 to 10,000,000 g/mol, preferably from 10,000 to

1,000,000 g/mol, as measured by e.g., gel permeation chromatography. In one embodiment the film-forming polymer is polyvinyl alcohol.

In another embodiment the first coat comprises at least one excipient selected from the
5 group consisting of sweeteners, and flavor/taste masking agents.

The lozenges of the invention may be prepared by way of a variety of routine techniques, and using standard equipment, known to the skilled person (see, for example, Lachman et al, "The Theory and Practice of Industrial Pharmacy", Lea & Febiger, 3rd edition (1986)
10 and "Remington: The Science and Practice of Pharmacy", Gennaro (ed.), Philadelphia College of Pharmacy & Sciences, 19th edition (1995)). In one embodiment, a core comprising bupivacaine is first produced using known tableting techniques, and is subsequently coated with a solution containing a film-forming polymer.

15 Standard mixing equipment may be used for mixing together ingredients of compositions of the invention. The mixing time is likely to vary according to the equipment used, and the skilled person will have no difficulty in determining by routine experimentation a suitable mixing time for a given combination of ingredient(s). One way of producing the lozenges of the invention is found in the examples. The manufacturing process may
20 comprise additional steps of granulation, drying and milling and/or sieving to obtain a compressed lozenge. Depending on the release profile of the API the hardness of the compression varies.

In another embodiment the lozenge has
25 a core comprising:
9 mg bupivacaine or the equivalent amount of a salt thereof (e.g., 10.7 mg of bupivacaine HCl monohydrate),
40 mg of binding agent,
697 mg of filling agent,
30 8 mg of lubricant,
40 mg of glidant, and
4.2 mg of sweetener (e.g., aspartame); and
a first coat comprising:

- 6 mg bupivacaine or the equivalent amount of a salt thereof (e.g. 7.2 mg bupivacaine HCl monohydrate),
3 mg of sweetener (e.g., aspartame),
4.2 mg of flavor, and
5 35.6 mg of film forming polymer.

In another embodiment the lozenge has
a core comprising:

- 15 mg of bupivacaine or the corresponding amount of a salt thereof (e.g., 17.8 mg of
10 bupivacaine HCl monohydrate),
40 mg of binding agent,
687.2 mg of filling agent,
8 mg of lubricant,
40 mg of glidant, and
15 7 mg of sweetener (e.g., aspartame); and
a first coat comprising:
10 mg of bupivacaine or the corresponding amount of a salt thereof (e.g., 11.87 mg of
bupivacaine HCl monohydrate),
5 mg of sweetener (aspartame),
20 7 mg of flavor, and
35.6 mg of film forming polymer.

Use of the lozenge

- In a further aspect the invention relates to the use of the lozenge for the treatment or
25 alleviation of pain, burning of the oral cavity, the mouth and the pharynx. One specific
example being oral mucositis often following cancer treatment. Other examples of suitable
disorders or diseases to be treated include Suttons disease (aphthous stomatitis), oral lichen
planus, viral infections of the oral mucosa e.g. herpes simplex and Behcet's disease.

30 EXAMPLES

The invention will be further illustrated by the following non-limiting examples.

EXAMPLE 1

Lozenge containing 15 mg of bupivacaine

The amounts of the ingredients used in Example 1 are as indicated in Tables 1 and 2.

(a) Preparation of cores

Mixing of core material

- 5 The humidity in the manufacturing room was adjusted to <40% RH. Micronized bupivacaine HCl, monohydrate and all the excipients were sieved through a 1 mm screen. Pearlitol was weighed into a 5 L Turbula vessel. Micronized bupivacaine HCl, monohydrate was added to a stainless-steel bowl followed by the addition of an equivalent amount of Pearlitol from the 5 L Turbula vessel to the bupivacaine and manually mixing.
- 10 The bupivacaine/Pearlitol mix was transferred into a 250 ml Duran bottle and further mixed in a Turbula T2F for 5 min at 32 rpm. Aspartame was weighed into a stainless-steel bowl and mixed manually with an equivalent amount of Pearlitol from the 5 L turbula vessel and thereafter added back to the 5 L turbula vessel through a 1 mm sieve. Talc was weighed into a stainless-steel bowl and mixed manually with an equivalent amount of
- 15 Pearlitol from the 5 L turbula vessel. The mix was added back to the 5 L turbula vessel through a 1 mm sieve. Methocel E3 was weighed and sieved through a 1 mm screen into the 5 L Turbula vessel. The Bupivacaine/Pearlitol mix was added from the 250 ml Duran bottle to the 5 L Turbula vessel through a 1 mm sieve. The container was attached to the Turbula T10B and mixing was performed for 8 minutes at 32 rpm. To a weighed amount
- 20 of magnesium stearate was added an equal amount of the mix from the Turbula followed by manual mixing. The mix was added back to the 5 L Turbula vessel through a 1 mm sieve. The container was attached to the Turbula T10B and mixing was performed for an additional 2 minutes at 23 rpm.

25 *Tableting*

The humidity in the manufacturing room was adjusted to <40% RH. The following conditions were selected:

Core weight	800 mg
Compaction force	22-24 kN
30 Core thickness	6.5 mm
Resistance to crushing/breaking force	>190 N
Friability	≤ 1.0 %

The core material mix was added to a rotary tablet machine and compressing was started.

(b) Coating of the cores

The humidity in the manufacturing room was adjusted to <40% RH.

5 *Preparation of coating solution*

Purified water was weighed into a 1 L glass beaker and stirring was started with a propeller stirrer. Aspartame was weighed and added to the 1 L glass beaker followed by mixing until all was dissolved. Orange Flavor was weighed and added to the 1 L glass beaker followed by mixing until all was dissolved. Bupivacaine was weighed and added to the 1 L glass
10 beaker followed by mixing until all was dissolved. Opadry Clear II powder was weighed and slowly added during stirring to the 1 L glass beaker. When all Opadry Clear II powder had been added mixing was continued for at least 45 minutes. The stirring speed was reduced to nearly eliminating the vortex. The finished suspension was sieved through a 0.25 mm sieve into a new 1 L beaker and a magnetic bar was added. The 1 L beaker was
15 put on a magnetic stirrer and mixing was continued during coating.

Coating

600 g of compressed cores were weighed and added to an O'Hara Labcoat M10 perforated pan coater. The coater was started and the coating process was initiated when an outlet bed
20 temperature higher than 46°C was reached. Coating was started with an addition of 5 g of coating material/min and with an increase of 1 g of coating material/min every 5 minutes. The outlet temperature was kept below 47.5 °C by lowering the inlet temperature over time.

25 *Process parameters*

Spray Gun	Schlick model 951/7-1-S24 Nano ABC
Nozzle diameter	0.5 mm
Tubing wall thickness	1.6 mm
Atomizing Air Pressure	1.2 bar
30 Pattern Air Pressure	1.4 bar
Airflow	150 m ³ /h
Inlet Air Temperature	60°C
Pan speed	13 rpm
Spray rate	7 g/min

The coating suspension to be added was calculated on a theoretical weight gain of 7.8%. Thus, for a batch size of 600 g of tablet cores the theoretical coating suspension to add was 556 g when compensated for an efficiency of 80%.

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After terminating the coating, the lozenges were dried for 10 minutes with heater on, to provide lozenges containing 9 mg of bupivacaine in the core and 6 mg of bupivacaine in the coat. The obtained lozenges weighed about 849.9 g/lozenge.

10 TABLE 1 Ingredients for compressed core containing 9 mg of bupivacaine

Ingredient	mg/core	Amount (%)	Function
Pearlitol 200 SD (Mannitol)	697.0	87.13	Filler
Mg stearate	8	1.0	Lubricant
Talc	40	5.0	Glidant
Methocel E3	40	5.0	Binder
Aspartame	4.2	0.53	Sweetener
Bupivacaine HCl, monohydrate	10.7	1.34	API
Sum	800	100	-

*10.7 mg of bupivacaine HCl monohydrate correspond to 9.0 mg of bupivacaine

TABLE 2 Ingredients for lozenge having a coated core (6 mg of bupivacaine in coat)

Ingredient	mg/lozenge	Amount (%)	Function
Compressed core	800	94.1	Core
Bupivacaine HCl monohydrate*	7.12	0.84	API
Aspartame	3	0.35	Sweetener
Deionized water**	-	-	Solvent
Orange Flavor PHS-140155	4.2	0.49	Flavor
Opadry II Clear	35.6	4.19	Film coat
Sum	849.9	100	-

*7.12 mg of bupivacaine HCl monohydrate correspond to 6 mg of bupivacaine

15 **Evaporates during coating

EXAMPLE 2Lozenge containing 25 mg of bupivacaine

The procedure of Example 1 was repeated, using the ingredients in amounts as indicated in Tables 3 and 4 respectively.

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TABLE 3 Ingredients for compressed core containing 15 mg of bupivacaine

Ingredient	mg/core	Amount (%)	Function
Pearlitol 200 SD (Mannitol)	687.2	85.9	Filler
Mg stearate	8	1.0	Lubricant
Talc	40	5.0	Glidant
Methocel E3	40	5.0	Binder
Aspartame	7	0.88	Sweetener
Bupivacaine HCl, monohydrate*	17.8	2.22	API
Sum	800	100	-

* 17.8 mg of bupivacaine HCl monohydrate correspond to 15 mg of bupivacaine

TABLE 4 Ingredients for lozenge having a coated core (10 mg of bupivacaine in coat)

Ingredient	mg/lozenge	Amount (%)	Function
Compressed core	800	93.1	Core
Bupivacaine HCl monohydrate*	11.87	1.38	API
Aspartame	5.0	0.58	Sweetener
Deionized water**	-	-	Solvent
Orange Flavor PHS-140155	7.0	0.81	Flavor
Opadry II Clear	35.6	4.14	Film coat
Sum	859.5	100	-

10 *11.87 mg of bupivacaine HCl monohydrate correspond to 10 mg of bupivacaine

**Evaporates during coating

CLAIMS

1. A lozenge comprising a core and a first coat, wherein:
the core comprises bupivacaine or a salt thereof, and at least one excipient; and
the first coat comprises bupivacaine or a salt thereof, at least one film-forming agent, and
5 optionally an excipient.
2. The lozenge according to claim 1, wherein the first coat has a dissolution time in saliva
of at most 5 minutes.
- 10 3. The lozenge according to claim 1 or claim 2, wherein the core has a dissolution time in
saliva of at most 30 minutes.
4. The lozenge according to any one of claims 1 to 3, wherein at least one excipient is a
binding agent selected from the group consisting of starch, mannitol, copovidone,
15 hydroxypropyl methyl cellulose (HPMC), Kollidone, microcrystalline cellulose and methyl
cellulose (Methocel E3), sodium carboxymethyl cellulose (CMC), polyvinylpyrrolidone
(PVP), polyethylene glycol (PEG), DC lactose and sodium alginate
5. The lozenge according to claim 4, wherein the binding agent is methyl cellulose.
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6. The lozenge according to any one of claims 1 to 5, wherein bupivacaine or a salt thereof
of the compressed core has a particle size of less than 250 μm .
7. The lozenge according to any one of claims 1 to 6, wherein bupivacaine is present in an
25 amount of 5 to 20 mg in the core and 5 to 10 mg in the first coat.
8. The lozenge according to claim 7, wherein the bupivacaine is present in an amount of 9
mg or 15 mg in the core and 6 mg or 10 mg in the first coat.
- 30 9. The lozenge according to any one of claims 1 to 8, wherein the lozenge comprises at
least one excipient selected from the group consisting of sweeteners, flavor/taste masking
agent, lubricating agent and sugar alcohols/filling agents.

10. The lozenge according to claim 9, wherein the flavor/taste masking agent is selected from the group consisting of honey, orange, banana, chocolate and berry flavor.
11. The lozenge according to claim 9 or 10, wherein the sugar alcohols are selected from
5 the group consisting of sorbitol, mannitol, glycerol, lactitol, maltitol, and xylitol, and mixtures thereof.
12. The lozenge according to any one of claims 1 to 11, wherein the core is free from flavor/taste masking agent.
- 10 13. The lozenge according to any one of claims 1 to 12, wherein the first coat is covered by a second coat.
14. The lozenge according to any one of claims 1 to 13, wherein the lozenge is
15 substantially free from oxidizing agent.
15. The lozenge according to claim 14, wherein the oxidizing agent is peroxide.
16. The lozenge according to any one of claims 1 to 15, for use in the treatment or
20 alleviation of pain and burning sensation in the oral cavity.
17. The lozenge according to any one of claims 1 to 16, for use in the treatment or alleviation of oral mucositis.
- 25 18. Use of the lozenge according to any one of claims 1 to 15, for the treatment or alleviation of pain and burning sensation in the oral cavity.
19. Use of the lozenge according to any one of claims 1 to 15 or use according to claim 18,
for the treatment or alleviation of oral mucositis.
- 30 20. A method for the treatment or alleviation of pain and burning sensation in the oral cavity of a mammal in need thereof, by administering a lozenge according to any one of claims 1 to 15 to said mammal.

21. The method according to claim 20, for the treatment or alleviation of oral mucositis.