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# DESCRIPTION

## FIELD OF THE INVENTION

**[0001]** The invention relates to a lozenge comprising micronized Benzocaine, at least one dissolution enhancer wherein the dissolution enhancer is PEG, and one or more excipients, wherein the micronized Benzocaine have a mass median particle size of 7 to 18 µm, as well as the lozenge for use in the treatment of sore throat.

## BACKGROUND OF THE INVENTION

**[0002]** Sore throat is generally treated using lozenges containing a therapeutically effective amount of an Active Pharmaceutical Ingredient (API). Suitably, the lozenge is dissolved slowly in the mouth and the API released in the oral cavity and delivered to the surface of the sore throat (i.e. mucous membrane).

**[0003]** Benzocaine is a local anesthetic agent commonly used as a topical pain reliever in topical products, cough drops or hard boiled candies. Topically administered Benzocaine is used to reduce pain or discomfort caused by minor skin irritations, sore throat, sunburn, teething pain, vaginal or rectal irritation, ingrown toenails, hemorrhoids, and many other sources of minor pain on a surface of the body. Benzocaine is also used to numb the skin or surfaces topically inside the mouth, nose, throat, vagina, or rectum to lessen the pain of inserting a medical instrument such as a tube or speculum. Benzocaine is the active ingredient in many pharmaceutical over-the-counter products.

**[0004]** EP2170275 relates to a dosage form having both a disintegrative portion and a hard candy portion, wherein the disintegrative portion should dissolve in preferably less than about 15 seconds, which is much too fast to be able to give an effect.

**[0005]** US3511914 relates to a flavored medicated lozenge capable of dissolving slowly and uniformly in the mouth comprising a major amount of polyethylene glycol and having a medicament.

**[0006]** US2005152972 relates to an oral anaesthetic based on a soft chewable lozenge which disintegrates and dissolves slowly in the mouth to sooth an irritated area.

**[0007]** US2016 relates to a solid pharmaceutical dosage form intended for release of one or more Active Pharmaceutical ingredients (API) in the oral cavity, wherein the API is taste masked due to bad taste.

**[0008]** Kristoffersson, et al., "Xylitol as an excipient in oral lozenges", Acta Pharmaceutica

Fennica, vol. 87, no. 2, pages 61 - 73 (1978), relates to the suitability of xylitol for use as an excipient in tablets and describes tablets containing xylitol, PEG 6000 and benzocaine.

**[0009]** US 2010/0010101 A1 describes a rapid-melt pharmaceutical composition, a rapid-melt bead composition and a chew tablet composition, each comprising a binder, an emulsifer, a diluent or bulking material, and an active ingredient.

**[0010]** The most efficient Benzocaine products available on the market today for treatment of pain caused by sore throat comprise Benzocaine in hard boiled candy lozenges. Hard boiled candy lozenges are large in size which is not pleasant for most of the consumers. In hard boiled candies Benzocaine resides in the amorphous phase and it will be very fast dissolved thus giving the consumer a fast pain relief. However, imperfections, of the surface of the lozenge caused by incorporation of air bubbles in the viscous melt mass before cooling may damage the mucous membranes in the oral cavity while the lozenge is dissolving.

## SUMMARY OF THE INVENTION

**[0011]** The invention relates to a compressed lozenge comprising micronized Benzocaine, at least one dissolution enhancer wherein the dissolution enhancer is PEG, and one or more excipients, wherein the micronized Benzocaine have a mass median particle size of 7 to 18 µm.

**[0012]** Benzocaine in the crystalline phase provides a slow dissolution compared to Benzocaine in the amorphous phase. Thus, the problem to be solved was to develop a lozenge comprising Benzocaine in the crystalline phase having about the same dissolution profile as Benzocaine in the amorphous phase, i.e., being bioequivalent with the hard boiled candies comprising Benzocaine in the amorphous phase and present on the market for the treatment of sore throat.

**[0013]** In addition to the same dissolution rate the lozenge should be small, i.e., mouth friendly and give rise to a smooth mouth feeling.

**[0014]** The invented lozenge is suitable for the treatment of sore throat.

**[0015]** The dissolution problem was solved by using micronized Benzocaine together with specific dissolution enhancers that surprisingly showed similar dissolution profiles compared to the amorphous Benzocaine products.

## DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

**Definitions:**

**[0016]** The term "dissolution enhancer" is intended to mean an agent that increases the dissolution of the active ingredient, i.e., benzocaine.

**[0017]** The term "lozenge" means preparations that are 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.

**LOZENGE**

**[0018]** In a first aspect, the invention relates to a lozenge, which might be direct compressed or granulated and compressed, comprising micronized Benzocaine, at least one dissolution enhancer wherein the dissolution enhancer is PEG, and one or more excipients, wherein the micronized Benzocaine have a mass median particle size of 7 to 18 µm.

**[0019]** The dissolution enhancer may be selected from the group consisting of polyethylene glycol (PEG), sodium dodecylsulphate (SDS) and poloxamer or a mixture thereof. In the present invention the dissolution enhancer is PEG or mixtures of different PEGs. Examples of different PEGs are PEG 4000 to PEG 6000, PEG 6000 or mixtures thereof. The particle size range of PEG may influence the dissolution rate. Different grades of PEG may be used as well.

**[0020]** The micronized Benzocaine present in the lozenge has a mass median particle size of about 7 to about 18 µm, about 10 to about 18 µm, about 12 to about 18 µm, or about 14 to about 18 µm.

**[0021]** Benzocaine may be present in an amount of from about 2 to about 15 mg, about 8 to about 15, about 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3 or 2 mg per unit dose.

**[0022]** The dissolution enhancers may be present in an amount of from about 1 to about 30 mg, about 4 to about 17 mg per unit dose. When the dissolution enhancer is PEG 6000 it is present in an amount of about 5 to about 25, such as about 10 mg per unit dose.

**[0023]** Examples of excipients include fillers, glidants, lubricants, sweeteners, flavors, coloring agents, binding/gelling agents and mixtures thereof.

**[0024]** Suitable lubricants include long chain fatty acids and their salts, such as magnesium stearate and stearic acid, talc, glycerides waxes, and mixtures thereof.

**[0025]** Suitable glidant is colloidal silicon dioxide.

**[0026]** Examples of sweeteners include, synthetic or natural sugars; artificial sweeteners such as saccharin, sodium saccharin, aspartame, 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.

**[0027]** Examples of flavoring agents/flavors 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, herbs, the, anise, water grass, lemon grass, cooling agent ginger, coffe, eucalyptus, mangostan, peppermint, spearmint, wintergreen, cinnamon, cacao/cocoa, vanilla, liquorice, salt, pepper, chili, menthol, aniseeds, mint or mixtures thereof. The flavoring agents/flavors may be natural extracts as well as synthetic versions.

**[0028]** Examples of coloring agents include lakes and dyes being approved as a food additive.

**[0029]** 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.

**[0030]** Examples of biding/gelling agents include but are not limited to xanthan gum, alginate, locust bean gum and guar gum as well as mixtures thereof. One example is xanthan gum.

**[0031]** In one example the filler is mannitol, the binding/gelling agent is xanthan gum and the lubricant is magnesium stearate.

**[0032]** The lozenge may be coated with a film coating agent, such as one or more fil-forming polymers. The thickness of the film coating has an influence on the degree of reduction of the organoleptically disturbing sensations. The film coating may have an average thickness from 10 to 500 microns, more preferably from 20 to 250 microns, such as from 30 to 150 microns. The film thickness may be measured using different methods known in the art such as SEM (Scanning Electron Microscopy), digital micrometer, X-ray microtomography, terahertz pulsed imaging etc. See further e g Quantitative Analysis of Film Coating in a Pan Coater Based on In-Line Sensor Measurements, Jose D. Perez-Ramos et al, AAPS PharmSciTech 2005; 6 (1) Article 20, Nondestructive analysis of tablet coating 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.

**[0033]** The film-forming polymers may be chosen among cellulose ethers 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 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, preferably from 10,000 to 1,000,000, as measured by e.g. gel permeation chromatography. In one embodiment the film-forming polymers are selected among cellulose ethers e g hydroxy propyl methyl cellulose (HPMC), methyl hydroxy ethyl cellulose (MHEC), hydroxy propyl cellulose (HPC), hydroxyethyl cellulose (HEC), ethyl hydroxyl ethyl cellulose (EHEC).

**[0034]** In addition the film coating may contain one or more plasticizer may be added to the film-forming polymer to facilitate the spreading and film forming capability. Examples on useful plasticizers are glycerol, propylene glycol, polyethylene glycol (PEG 200-6000), organic esters e g triacetin (glyceryl triacetate), triethyl citrate, diethyl phtalate, dibutyl phtalate, dibutyl sebacete, acetyltriethyl citrate, acethyltributyl citrate, tributyl citrate, and oils/glycerides such as fractionated coconut oil, castor oil and distilled acetylated monoglycerides. Additionally, or alternatively, surfactants may be included to facilitate the incorporation of flavors and to improve penetration and spreading properties of the coating liquid. Non-limiting examples of surfactant are polysorbates derived from PEG-ylated sorbitan esterified with fatty acids such as Polysorbate 20 (Polyoxyethylene (20) sorbitan monolaurate), Polysorbate 40 (Polyoxyethylene (20) sorbitan monopalmitate), Polysorbate 60 (Polyoxyethylene (20) sorbitan monostearate), Polysorbate 80 (Polyoxyethylene (20) sorbitan monooleate) (e g Tween 80, Tween 40, Tween 20), sodium lauryl sulphate (SLS), poloxamer surfactants i.e. surfactants based on ethylene oxide-propylene oxide block copolymers and other surfactants with high HLB-value.

**[0035]** Other components may be included in the composition of the film such as coloring agents, opacifiers, glossing agents, pore forming agents, excipient stabilizers.

**[0036]** The dosage forms 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, 3.sup.rd edition (1986) and "Remington: The Science and Practice of Pharmacy", Gennaro (ed.), Philadelphia College of Pharmacy & Sciences, 19.sup.th edition (1995)). In one embodiment, a core comprising Benzocaine is first produced using known tableting techniques, which is then coated with a solution containing a film-forming polymer.

**[0037]** Standard mixing equipment may be used for mixing together components of compositions of the invention. The mixing time period 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 is found in the examples. The manufacturing process may as well comprise additional steps of granulation, drying and milling and/or sieving to obtain a lozenge.

**USE OF THE LOZENGE**

**[0038]** In a final aspect the invention relates to the lozenge for use in the treatment of sore throat.

**EXAMPLES**

**EXAMPLE 1**

**PRODUCTION OF THE CORE**

**[0039]** All ingredients were purchased in pharmaceutical quality except for the flavoring agents that were of food grade.

**[0040]** The ingredients shown in table 1 were sieved through a 1mm mesh and blended.

**[0041]** The blending times were optimized to obtain a homogenous powder mixture obvious for a person skilled in the art.

**[0042]** The lozenges were produced by direct compression of the powder mix.

**[0043]** The lozenge shape was oblong with targeted lozenge weight of 600 mg.

**[0044]** The manufacturing was performed in manufacturing area with controlled temperature and humidity.

**[0045]** Table 1 and 2 shows the amounts of the different ingredients present in the core of the lozenges.

Table 1

| Ingredients | Amount mg/lozenge |
|---|---|
| Benzocaine | 15,0 |
| Mannitol | 533,5 |
| Xanthan gum | 12,0 |
| PEG 6000 | 10,0 |
| Poloxamer | 4,0 |
| SDS | 2,0 |
| Magnesiumstearate | 12,0 |
| Mint flavour | 10,00 |
| Sucralose | 1,00 |

| Ingredients | Amount mg/lozenge |
|---|---|
| Acesulfame K | 0,50 |

Table 2

| Ingredients | Amount mg/lozenge |
|---|---|
| Benzocaine | 15,0 |
| Mannitol | 537,5 |
| Xanthan gum | 12,0 |
| PEG 4000 | 12,0 |
| Magnesiumstearate | 12,0 |
| Mint flavour | 10,00 |
| Sucralose | 1,00 |
| Acesulfame K | 0,50 |

**EXAMPLE 2**

**COATING OF THE LOZENGE**

**[0046]** All ingredients were purchased in pharmaceutical quality except for the flavoring agents that were of food grade.

**[0047]** The lozenges produced in Example 1 were film coated according to the method disclosed below.

**[0048]** The coating polymer was dispersed in warm water and then cooled down. The other raw materials were added into the coating solution.

**[0049]** The coating solution was homogenized.

**[0050]** The cores were then spray coated and the spray coating was controlled on the outlet air temperature of 45°C.

**[0051]** Table 3 shows the ingredients and the amount of a film coating that could be used for specific embodiments of the invention.

Table 3

| Ingredients | Amount/lozenge (mg) |
|---|---|
| HPMC | 16,8 |
| Titanium dioxide | 2,5 |

| Ingredients | Amount/lozenge (mg) |
|---|---|
| Mint flavour | 2,5 |
| PEG 400 | 1,5 |
| Sucralose | 0,8 |
| Acesulfame K | 0,4 |
| Polysorbate | 0,1 |
| Aqua purificata | q.s |

**EXAMPLE 3**

**[0052]** The dissolution rate was analyzed using the method USP paddle 2 using Liquid Chromatography (LC).

**Example: Dissolution profiles**

**[0053]**

| % Benzocaine dissolved for lozenges with different mass median particle size range of PEG 6000 at given dissolution times | | | |
|---|---|---|---|
| Dissolution time (min) | No PEG | Standard PEG 10mg | Fine Powder PEG 10mg |
| 3 | 4,7 | 3,9 | 16,4 |
| 5 | 20,7 | 24,2 | 30,9 |

| % Benzocaine dissolved for lozenges with different amounts of PEG 6000 at given dissolution times | | | | |
|---|---|---|---|---|
| Dissolution time (min) | 0mgPEG | 5mg PEG | 10mg PEG | 60mg PEG |
| 3 | 4,7 | 14,3 | 17,5 | 11,4 |
| 5 | 20,7 | 37,2 | 41,1 | 30,9 |
| 10 | 54,3 | 72,3 | 74,4 | 62,8 |

| % Benzocaine dissolved for lozenges with different mass median particle size of Benzocaine at given dissolution times (only samples with a mass median particle size of 7-18 µm are within the scope of the claims) | | | |
|---|---|---|---|
| Dissolution time (min) | *≤207 µm | *≤7 | *≤3 |
| 10 | 25,7 | 44,8 | 38,5 |
| 15 | 43,1 | 80,0 | 63,4 |
| 20 | 53,3 | 85,6 | 79,0 |

| * Mass median particle size |
|---|

**Example 4: Products for comparison**

**[0054]**

| % Benozocaine dissolved for lozenges at given dissolution times | | | |
|---|---|---|---|
| Dissolution time (min) | Anaesthesin 8mg | Neo Angin 8mg | Lozenge produced according to Example 1* |
| 5 | 15,4 | 34,5 | 41,1 |
| 10 | 31,4 | 64,5 | 74,4 |
| 15 | 45,0 | 85,3 | 90,6 |
| *The lozenge produced according to Example 1 having 8 mg of Benzocaine. | | | |

# REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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**Patentkrav**

**1.** Pastil omfattende

a. mikroniseret benzocain

b. mindst en opløsningsforstærker hvor opløsningsforstærkeren er PEG, og

c. et eller flere hjælpestoffer,

hvor den mikroniserede benzocain har en massemedian partikelstørrelse på 7 til 18 µm.

**2.** Pastillen ifølge krav 1, hvor PEG'en er polyethylenglycol 4000 til 6000 (PEG).

**3.** Pastillen ifølge krav 2, hvor PEG er PEG 6000.

**4.** Pastillen ifølge et hvilket som helst foregående krav, hvor benzocain er til stede i en mængde fra 2 til 15 mg.

**5.** Pastillen ifølge krav 4, hvor benzocain er til stede i en mængde på 8 mg.

**6.** Pastillen ifølge et hvilket som helst foregående krav, hvor opløsnings-forstærkeren er til stede i en mængde fra 1 til 30 mg.

**7.** Pastillen ifølge krav 6, hvor opløsningsforstærkeren er PEG, og PEG er til stede i en mængde på 5 til 25 mg.

**8.** Pastillen ifølge et hvilket som helst foregående krav, hvor hjælpestoffet er mindst et sødestof.

**9.** Pastillen ifølge krav 8, hvor sødestoffet er valgt fra gruppen bestående af syntetiske eller naturlige sukre; kunstige sødestoffer inklusive saccharin, natriumsaccharin, aspartam, acesulfam, thaumatin, glycyrrhizin, sucralose, cyclamat, dihydrochalcon, alitam, miraculin og monellin; sukkeralkoholer inklusive sorbitol, mannitol, glycerol, lactitol, maltitol og xylitol; sakkarose, dextrose, fructose og lactose; isomalt, stevia og blandinger deraf.

**10.** Pastillen ifølge et hvilket som helst foregående krav, hvor hjælpestoffet er mindst et aromastof.

**11.** Pastillen ifølge krav 10, hvor aromastoffet er valgt fra gruppen bestående af lime, appelsin, citron, solbær, blodappelsin, tranebær, multebær, gojibær, hindbær, jordbær, skovjordbær, havtorn, kirsebær, melon, kiwi, papaja, ananas, passionsfrugt, kokosnød og andre aromastoffer såsom honning, urter, te, anis, vandgræs, citrongræs, kølemiddel ingefær, kaffe, eukalyptus, mangostan, pebermynte, grøn mynte, bjergte, kanel, kakao, vanilje, lakrids, salt, peber, chili, mentol, anisfrø, mynte, naturlige eller syntetiske versioner og blandinger deraf.

**12.** Pastillen ifølge et hvilket som helst foregående krav, omfattende mindst følgende hjælpestoffer; et fyldstof, et binde-/gelatineringsmiddel og et smøremiddel.

**13.** Pastillen ifølge krav 12, hvor fyldstoffet er mannitol, binde-/gelatineringsmidlet er xanthangummi, sødestoffet, smagsstofferne og smøremidlet er magnesiumstearat.

**14.** Pastillen ifølge et hvilket som helst foregående krav, hvor nævnte pastil er overtrukket med en filmdanner.

**15.** Pastillen ifølge krav 14, hvor nævnte pastil er overtrukket med en celluloseether-filmdanner.

**16.** Pastillen ifølge krav 15, hvor celluloseether-filmdanneren er valgt fra gruppen bestående af hydroxypropylmethylcellulose (HPMC), methylhydroxy-ethylcellulose (MHEC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), ethylhydroxylethylcellulose (EHEC).

**17.** Pastillen ifølge et hvilket som helst foregående krav, hvor pastillen er direkte komprimeret eller granuleret og komprimeret.

**18.** Pastillen ifølge et hvilket som helst af kravene 1-17 til anvendelse til behandling af en halsbetændelse.