Title: Zinc lactate lozenges and uses thereof

Abstract: A lozenge, for release of zinc 2+ ions in the oral cavity of a human comprises 0.5 to 5% by wt of zinc lactate in combination with a pharmaceutically acceptable carrier or sugar. In the presence of human saliva, said lozenge releases at least 0.2 mg of zinc 2+ ions per ml of saliva with a pleasant taste and aftertaste. The lozenges may be used as medicaments or nutritional supplements for reducing the symptoms and/or duration of the common cold, rhinitis and/or sinusitis.
ZINC LACTATE LOZENGES AND USES THEREOF

FIELD OF INVENTION
The present invention relates to medicinal or nutritional lozenges comprising zinc lactate for oral absorption by humans. The present invention also relates to chemically, thermally and flavour stable lozenges comprising 0.5 to 5% by wt of zinc lactate and certain pharmaceutically acceptable carriers. In particular, the present invention relates to such lozenges which, when sucked, allow the absorption of zinc 2+ ions into the oral and oral pharyngeal tissues, and which thereby provide the particular benefits of reducing the duration and symptoms of complaints such as common colds.

PRIOR ART
The use of zinc gluconate or zinc acetate lozenges for treating the common cold has now become well established in the USA, mainly as a result of positive evidence of safety and efficacy in several properly controlled clinical trials. Such trials are described by Eby et al ("Reduction in duration of common cold symptoms by zinc gluconate lozenges in a double blind study." Antimicrobial Agents and Chemotherapy. 1984;25: 20-24); Al-Nakib et al ("Prophylaxis and treatment of rhinovirus colds with zinc gluconate lozenges." Journal of Antimicrobial Chemotherapy. 1987;20:893-901); Godfrey et al ("Zinc gluconate and the common cold; a controlled clinical study." The Journal of International Medical Research. 1992; 20:234-246); and Mossad et al ("Zinc gluconate Lozenge for Treating the Common Cold - A randomized, double-blind, placebo-controlled study." Annals of Internal Medicine. 1996; 125: 81-88).

Further, it has been recognised that for zinc to act effectively, it must be delivered in a form that guarantees release of zinc 2+ ions locally in the vicinity of the pharyngeal mucosa. This generally occurs under the following conditions:-
(i) The zinc salt used releases free zinc 2+ ions at physiological pH.

(ii) The zinc salt used is not formulated together with substances that neutralize the zinc 2+ ions or chelate the zinc. This has precluded the use of many formulation additives, including citric acid, ascorbic acid and tartaric acid, as described by Zarembo et al ("Zinc(II) in saliva: determination of concentrations produced by different formulations of zinc gluconate lozenges containing common excipients." J Pharm Sci. 1992; 81: 128-130).

(iii) The composition comprising the zinc salt is sucked slowly and not chewed or swallowed rapidly. This ensures that a sufficiently high concentration of zinc 2+ ions are available locally.

Since most zinc salts have a generally objectional taste, it is vital for compliance that a formulation be used that not only fulfils the above conditions, but also provides a pleasant tasting composition. Formulations that achieve this generally contain sugars for sweetening or masking flavours that do not rely on citric acid.

Despite prior description of flavour stable masking agents (see US Patent Number 5,002,970), compositions used previously were generally limited in the amount of zinc that they could contain, because of the unpleasant zinc aftertaste at levels higher than 13 mg of elemental zinc per 4g of composition.

Moreover, US Patent Number 5,002,970 teaches that hard candy lozenges made using zinc gluconate in a sucrose/glucose base are objectionable in taste and that a sucrose/fructose base is required to enable successful flavour masking. Furthermore, as taught in US patent No 4,684,528, when using zinc gluconate, it was necessary to use glycine as a sweetener in order to achieve a palatable lozenge that contained sufficient zinc to be effective in the treatment of the common cold. Further, in the case of zinc acetate, it has been described (see US patent No
5,095,035, p5, line 12) that this substance has a "vile taste completely offensive by any standard" that can only be useful as a treatment for the common cold by way of masking with sweeteners and flavours free of acids

Although the role of free zinc 2+ ions in reducing the severity and shortening the duration of common colds has been described, it is claimed that only zinc salts with a stability constant of less than \( K_1 = 1.70 \) at pH 7.4, such as zinc gluconate and zinc acetate, have any utility in this regard. In contrast, zinc lactate has generally been dismissed by previous inventors as a useful treatment for colds, because it was assumed to fall into the category of substances unable to release sufficient zinc 2+ ions in saliva when made into a lozenge. Indeed, in 1994 it was stated (Eby GA, Handbook for curing the common cold. 1994; Pub by George Eby Research, Austin, Texas, USA) that the availability of \( \mathrm{Zn}^{3+} \) ions from zinc sulfate, lactate, malate, maleate, tartrate, and succinate (log \( K_1 = 1.8 \) to 2.8) ranges in effect from being less than desirable to being useless for treating colds.

WO98/37859 discloses an oral composition comprising a zinc salt and at least one taste masking salt that is suitable for use in oral hygiene and dental care. Although the composition may be in the form of a lozenge, the preferred content of zinc salt is relatively low. The preferred amount of zinc ions released into the mouth is thus only 0.01 to 0.06 mg per mil of saliva, with such a low level of zinc ion release having the disadvantage that the composition is ineffectual as a medicament for the treatment of colds, rhinitis and/or sinusitis. By contrast, the present invention provides a novel selection of a composition that is not specifically disclosed by WO98/37859, the composition providing sufficient release of zinc ions into saliva, so as to allow it to be useful as a medicament for the treatment of colds and so forth.

It is therefore one aim of the present invention to provide a lozenge comprising a substantial
amount of zinc lactate that is nevertheless pleasant in taste and aftertaste and that, when sucked, releases sufficient $\text{Zn}^{2+}$ ions to reduce the duration and/or symptoms of the common cold, rhinitis and/or sinusitis.

**SUMMARY OF INVENTION**

Thus, according to a first aspect, the present invention provides a lozenge for release of zinc $2^+$ ions in the oral cavity of a human comprising 0.5 to 5% by wt of zinc lactate in combination with a pharmaceutically acceptable carrier, wherein, in the presence of human saliva, said lozenge releases at least 0.2 mg of zinc $2^+$ ions per ml of saliva.

The term "releases" is generally defined as being release under conditions of body temperature.

The present invention, in a second aspect, provides a lozenges as described above for use as a medicament or nutritional supplement for reducing the symptoms and/or duration of the common cold, rhinitis and/or sinusitis.

In a third aspect, the present invention provides for the use of a lozenge as described above for the manufacture of a medicament or nutritional supplement for reducing the symptoms and/or duration of the common cold, rhinitis and/or sinusitis.

Further, in a fourth aspect, the present invention provides for the use of a pharmaceutically acceptable carrier or sugar in a lozenge comprising 0.5 to 5% wt of zinc lactate to allow release, in the presence of human saliva, of zinc $2^+$ ions into the oral cavity.

In a fifth aspect, the present invention provides a process for forming a hard-boiled
lozenge comprising: heating a sugar-containing solution to form a syrup, cooling the syrup, adding zinc lactate, and forming the resultant mixture into a lozenge.

Additional features of the invention will be evident from the dependent claims, as well as the rest of the description below.

The present invention allows the preparation (see below) of lozenges containing zinc lactate, based on a sucrose/glucose base or on a sucrose-free base composed of polyols, that surprisingly and unexpectedly are both palatable and show a high level of zinc $^{2+}$ ion release in the presence of human saliva.

Moreover, the novel zinc lactate lozenges, although producing the astringency normally associated with effective zinc ion-releasing lozenges, do not produce an unpleasant aftertaste, even at high levels of zinc (for example even at levels as high as 19 mg zinc per 5g lozenge).

Further, the new zinc lactate lozenges of the present invention, contrary to previous teaching, are effective in reducing symptoms of rhinitis, whether from a rhinoviral infection or from an allergic response and also reduce symptoms of a sore throat and sinusitis.

The present invention will now be described in further detail with reference to the following non-limiting embodiments and examples.

**BEST MODE OF THE INVENTION**

The compositions of the invention typically comprise 0.5 to 5% by wt of zinc lactate in combination with a sugar or a pharmaceutically acceptable carrier. The pharmaceutically
acceptable carrier itself may also comprise sugars.

Examples of such sugars include:

- hexo-sugars, for example glucose and fructose;
- di-saccharides, for example lactose and sucrose;
- oligo and polysaccharides, for example maltodextrins;
- polyols, for example sugar alcohols, such as maltitol, mannitol, sorbitol, xylitol and lactitol; and
- honey;
- or mixtures thereof.

Typically, the specific sugar(s) chosen should not cause any significant chelation of the zinc. Preferred polyols are maltitol and lactitol.

The lozenges of the present invention should preferably be retained in the oral cavity and slowly sucked for at least 15 minutes.

In the presence of human saliva, said lozenges typically release at least 0.2 mg zinc 2+ ions per ml saliva, and preferably release at least 0.5 mg of zinc 2+ ions per ml of saliva.

The lozenge preferably comprises between 0.7% and 2.5% by weight, preferably 1% and 2% by weight of zinc lactate.

The lozenge typically comprises between 80% and 99 % by weight, preferably between 90 and 99 % by weight, more preferably 97% and 99 % by weight of the
pharmaceutically acceptable carrier or sugar.

The composition is most practicably made in the form of a hard boiled lozenge.

The lozenge may also comprise optional additional additives such as flavours, medicinal agents, pharmaceutical excipients and so forth.

Examples of flavours or flavour enhancers that may be present include peppermint or spearmint, menthol, eucalyptus oil, stevia, liquorice, honey, butterscotch and a range of fruit flavours such as lemon, lime, orange, cherry, tropical fruits, provided that they do not chelate zinc ions.

Examples of medicinal agents that may be present include anaesthetics, antiseptics, antibiotics, decongestants, antiviral agents, antihistamines, antipyretics, anti-inflammatory agents, antifungal agents, cough relievers, and other medicinal and nutritional supplements such vitamins and minerals other than zinc provided that they do not chelate zinc ions.

An example of a suitable anaesthetic is benzocaine; examples of antiseptics include cetylpyridinium chloride and chlorohexidine gluconate; however both anaesthetics and antiseptics should be used in such a way that they do not cause chelation of zinc.

Examples of other natural herbal or complementary medicines helpful for colds, rhinitis or other conditions, that may be present include echinacea, ginger, ginseng, gingko biloba, propolis and St John's Wort.

Examples of pharmaceutical excipients that may be present include tablet binders, lubricants,
glidants, and stabilisers.

Lozenges according to the present invention may be manufactured as described in the following examples:-

Example 1
To make a 15 mg zinc hard-boiled sugar-based, zinc lactate lozenge with peppermint flavouring and containing 15 mg zinc, sucrose (60%) and glucose (40%) were mixed and heated to 139°C with a small quantity of water to produce a thick syrup. The syrup was cooled to a temperature of 122 °C and 10 kg of this syrup was mixed with 140 g of zinc lactate powder and 40 g of peppermint oil. While cooling further, the mixture was passed into a lozenge die machine which produced lozenges of approximately 4.7g. Such a composition has a pleasant taste, an astringency associated with zinc ion release and no unpleasant aftertaste.

Example 2
To make a 19 mg zinc hard-boiled honey-based zinc lactate lozenge, flavoured with menthol and eucalyptus, sucrose (60%) and glucose (40%) were mixed and heated first to 122 °C with a small quantity of water to produce a thick syrup. Then honey (10%) was added and the mixture temperature was raised to 139°C in order to drive off excess water. The resulting honey-based syrup was cooled to 122 °C and to 10 kg of this mixture was added 180 g of zinc lactate powder followed by 8 g of menthol and 24 ml of eucalyptus oil. While cooling, the mixture was passed into a lozenge die machine which produced lozenges of approximately 4.7g. Such a composition has a pleasant taste, an astringency associated with zinc ion release and no unpleasant aftertaste.

Example 3
To make a sucrose-free hard-boiled 15 mg zinc lactate lozenge, flavoured with tropical fruit and
peppermint, lactitol (75%) and maltitol (25%) were mixed and heated to 169 °C with a small quantity of water to produce a thick syrup. The syrup was cooled to 122 °C and 10 kg of this syrup was mixed with 140 g of zinc lactate powder and 35g of tropical fruit flavouring and 10g of peppermint oil. While cooling further, the mixture was passed into a lozenge die machine, which produced lozenges of approximately 4.7g. Such a composition has a pleasant taste, an astringency associated with zinc ion release and no unpleasant aftertaste.

The lozenges of the present invention were tested to determine the levels of release of zinc 2+ ions in saliva according to the following protocol:

1) Saliva was collected during the dissolution of single lozenges in the mouth, care being taken to avoid swallowing. Once the saliva samples were collected (30 to 40 ml) they were diluted to 60 ml with distilled water and divided into three equal aliquots of 20 ml each. Each aliquot was then treated as follows:

Aliquot A):- 5ml of distilled water added
Aliquot B):- 5ml of distilled water added
Aliquot C):- 5ml of sodium sulphide solution (1.1mg per ml) added with stirring.

2) Samples from A & C were then subjected to membrane filtration at 0.1 micron and a portion of filtrate collected and diluted in distilled water for elemental zinc analysis by atomic absorption (AA) spectroscopy. A sample of B) (unfiltered) was diluted with an equal volume of aqua regia and then further diluted in distilled water for elemental zinc analysis by atomic absorption spectroscopy.

Whilst, the zinc content of B) reveals the total quantity of zinc in the saliva sample, that of C) shows how much zinc remains after divalent ionic zinc has reacted with sodium sulphide to form
insoluble zinc sulphide which is removed by filtration. Some Zn 2+ also reacts with salivary proteins to form insoluble complexes which are removed by filtration and this is revealed by the zinc content of A).

(3) From the values determined above, a value for percentage of Zn 2+ ions present in the saliva samples can be calculated by taking the appropriate difference.

The following four saliva samples were subjected to the above-described test:

**Sample 1**
Saliva was collected while sucking a control lozenge without zinc, but containing citric acid (76mg per 6 gram lozenge). To the saliva, was added a solution of zinc acetate to give a final zinc concentration of approximately 0.167 mg per ml, equivalent to sucking one 10 mg zinc lozenge.

**Sample 2**
As for sample 1 but using zinc lactate solution instead of zinc acetate

**Sample 3**
Saliva was collected while sucking a 10 mg zinc acetate lozenge

**Sample 4**
Saliva was collected while sucking a 15 mg zinc lactate lozenge.
After AA analysis the calculations revealed the following:

Sample 1) Zn acetate added to saliva with citrated control lozenge

<table>
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<tr>
<th>Code</th>
<th>Zinc (mg)</th>
<th>%age of theor</th>
<th>%age of actual</th>
<th>Zn ion %age</th>
<th>pH</th>
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<tbody>
<tr>
<td>Theoretical total</td>
<td>N/A</td>
<td>10.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovered total</td>
<td>1B</td>
<td>10.17</td>
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<td>After filtration 1A</td>
<td>7.04</td>
<td>70.35</td>
<td>69.17</td>
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<td>(filtrate)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After sulphide 1C</td>
<td>4.35</td>
<td>43.50</td>
<td>42.77</td>
<td>57.23</td>
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<td>(filtrate)</td>
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</table>

Sample 2) Zn lactate added to saliva with citrated control lozenge

<table>
<thead>
<tr>
<th>Code</th>
<th>Zinc (mg)</th>
<th>%age of theor</th>
<th>%age of actual</th>
<th>Zn ion %age</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theoretical total</td>
<td>N/A</td>
<td>10.00</td>
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<td></td>
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<tr>
<td>Recovered total</td>
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<td>8.90</td>
<td>89.00</td>
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<td>6.0</td>
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<td>After filtration 2A</td>
<td>5.73</td>
<td>57.30</td>
<td>64.38</td>
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<td>6.0</td>
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<tr>
<td>(filtrate)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After sulphide 2C</td>
<td>2.63</td>
<td>26.30</td>
<td>29.55</td>
<td>70.45</td>
<td>6.0</td>
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<td>(filtrate)</td>
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</table>
Sample 3) Zinc acetate lozenges

<table>
<thead>
<tr>
<th>Code</th>
<th>Zinc (mg)</th>
<th>%age of theor.</th>
<th>%age of actual</th>
<th>Zn ion %age</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theoretical total</td>
<td>N/A</td>
<td>11.86</td>
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</tr>
<tr>
<td>Recovered total</td>
<td>3B</td>
<td>9.44</td>
<td>79.57</td>
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<td>6.2</td>
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<tr>
<td>After filtration 3A</td>
<td>0.23</td>
<td>1.94</td>
<td>2.43</td>
<td></td>
<td>6.1</td>
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<tr>
<td>(filtrate)</td>
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<td></td>
<td></td>
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<tr>
<td>After sulphide 3C</td>
<td>0.10</td>
<td>0.85</td>
<td>1.07</td>
<td>98.93</td>
<td>6.2</td>
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Sample 4) Zinc lactate lozenges

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<th>Code</th>
<th>Zinc (mg)</th>
<th>%age of theor.</th>
<th>%age of actual</th>
<th>Zn ion %age</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theoretical total</td>
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<td>15.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovered total</td>
<td>4B</td>
<td>11.60</td>
<td>75.64</td>
<td></td>
<td>6.0</td>
</tr>
<tr>
<td>After filtration 4A</td>
<td>0.87</td>
<td>5.65</td>
<td>7.47</td>
<td></td>
<td>6.1</td>
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<tr>
<td>(filtrate)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After sulphide 4C</td>
<td>0.08</td>
<td>0.53</td>
<td>0.71</td>
<td>99.29</td>
<td>6.2</td>
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<tr>
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</tbody>
</table>

The results show that zinc acetate lozenges release a high percentage (98.93%) of Zn $^{2+}$ ions and that, in the presence of citrate from a control lozenge, Zn $^{2+}$ ion release is reduced (to 57.23% under the conditions of this test). Surprisingly, and contrary to previous teaching, the zinc lactate lozenges release at least as good a level (99.29%) of zinc $^{2+}$ ions, as do the zinc acetate lozenges.
Zinc lactate added to the saliva containing control lozenge material is also less affected by citrate than acetate, which is an important advantage, since citrate is often also taken by patients when they treat their colds. These unexpected findings indicate that such zinc lactate lozenges can release high levels of zinc 2+ ions in saliva during sucking, and hence have utility in treatment of the symptoms of the common cold, contrary to previous teaching (see Eby, 1994, mentioned above).

In addition, lozenges with compositions of all the above examples, when sucked by sufferers of symptoms of rhinitis (sneezing, running nose), resulted in the rapid cessation of symptoms for periods of up to 2 hours. The alleviation of symptoms was associated with an oral astringency which faded before symptoms returned. Lozenges of these compositions when sucked, also relieved sore throats and cleared blocked sinus passages.

Further, sufferers of colds found that sucking lozenges of the compositions described in the above examples relieved symptoms and shortened the duration of their colds. Of particular importance was the observation that once the cold disappeared, little or no residual sinus problems remained.

Thus, in the present invention, 0.5 to 5% by wt of zinc lactate has been successfully formulated in lozenge form as a medicinal or nutritional agent for reducing the symptoms and the duration of complaints, such as the common cold, for the first time. Surprisingly, and contrary to teaching, such levels of zinc lactate have been formulated as a soluble salt that is virtually tasteless.

Indeed, when formulated as a hard-boiled candy lozenge with pharmaceutically acceptable carriers or sugars the zinc lactate imparts astringency to the mouth, demonstrating release of zinc 2+ ions. It does not, however, leave a vile aftertaste, but merely a dry-mouth effect that is generally acceptable to the majority of patients, despite the level of zinc per lozenge being high.
CLAIMS:

1. A lozenge for release of zinc 2+ ions in the oral cavity of a human comprising 0.5 to 5% by wt of zinc lactate in combination with a pharmaceutically acceptable carrier, wherein, in the presence of human saliva, said lozenge releases at least 0.2 mg of zinc 2+ ions per ml of saliva.

2. A lozenge as claimed in claim 1, wherein the pharmaceutically acceptable carrier comprises a sugar.

3. A lozenge as claimed in claim 2, wherein the sugar is selected from:—
   - hexo-sugars, for example glucose and fructose;
   - di-saccharides, for example lactose and sucrose;
   - oligo and polysaccharides, for example maltodextrins;
   - polyols, for example sugar alcohols, such as maltitol, mannitol, sorbitol, xylitol and lactitol; and
   - honey;
   - or mixtures thereof.

4. A lozenge as claimed in any preceding claim, wherein the lozenge comprises between 0.7% and 2.5% by weight, preferably 1% and 2% by weight of zinc lactate.

5. A lozenge as claimed in any preceding claim, wherein the lozenge comprises between 80% and 99% by weight, preferably between 90 and 99% by weight, more preferably 97% and 99% by weight of the pharmaceutically acceptable carrier or
sugar.

6 A lozenge as claimed in any preceding claim, wherein, in the presence of human saliva, said composition or matrix releases at least 0.3 mg of zinc 2+ ions per ml of saliva.

7 A lozenge as claimed in any preceding claim, wherein said lozenge is hard-boiled.

8 A lozenge as claimed in any preceding claim for use as a medicament or nutritional supplement for reducing the symptoms and/or duration of the common cold, rhinitis and/or sinusitis.

9 Use of a lozenge as claimed in any one of claims 1 to 8 for the manufacture of a medicament or nutritional supplement for reducing the symptoms and/or duration of the common cold, rhinitis and/or sinusitis.

10 Use of a pharmaceutically acceptable carrier or sugar in a lozenge comprising 0.5 to 5% by wt of zinc lactate to allow release, in the presence of human saliva, of zinc 2+ ions into the oral cavity.

11 A process for forming a hard-boiled lozenge comprising: heating a sugar-containing solution to form a syrup, cooling the syrup, adding zinc lactate, and forming the resultant mixture into a lozenge.
12 A lozenge, use of such a lozenge, or process for forming such a lozenge, substantially as hereinbefore described.