Title: ORAL PATCH WITH SALT OF GLYCERYRRHETINIC ACID WATER SOLUBLE AT HUMAN MOUTH TEMPERATURES

Abstract: A dissolving oral patch with a form a glycyrrhetinic acid that is soluble in water at human mouth temperatures. For higher levels of absorption into local tissues and therefore greater effectiveness for the level of drug used (to minimize risks of side effects) it is preferable to use a water soluble salt of glycyrrhetinic licorice extract (Soluble Glyceric Extract, "SGE"). SGE comprises a group of chemical salts of glycyrrhetinic acid that are soluble in water at human mouth temperatures, including potassium salt of glycyrrhetinic acid and other alkali metal salts of glycyrrhetinic acid.
ORAL PATCH WITH SALT OF GLYCRRHETINIC ACID
WATER SOLUBLE AT HUMAN MOUTH TEMPERATURES

This application claims priority from US provisional application
60/792,121 (agent reference 0795-022-02) filed 13 April 13, 2006.

BACKGROUND

To deliver a medication in the mouth over time for treatment of
health problems in the mouth or throat, oral patches have been developed.

As used herein, the word "patch" does not include preparations that
move about the mouth rather than adhering in one place, such as cough drops or
throat lozenges, and therefore do not maintain a high concentration of released
medication in the desired spot. Nor does it include preparations that do not hold
together as a single item when held in the mouth such as preparations of powder,
liquid, paste, viscous liquid gel, or a tablet or troche that crumbles into a powder or
paste when chewed or placed in saliva. Conversely, it does include an adherent
preparation formed of a hydrocolloid that holds together as a single item when
held in the mouth, such as the adherent, soluble oral patch disclosed by the same
inventor in US patent application serial number 10/287,843 filed 5 November
2002.

The most significant differences between an oral patch as used
herein and other forms of medicinal preparations is that an oral patch is designed
to release medication into the mouth over a relatively long period of time, such as
30 minutes or more, and be adherent to stay in one place so that the medication
can reach high concentrations along side the patch, and remain in the mouth as a
single item that will not spread to be in a plurality of locations in the mouth at one time.

Licorice extract which includes glycyrrhizic acid relieves pain from canker sores without numbing surrounding tissues and promotes healing, although strong enough concentrations to be as effective as desired have an unacceptably strong flavor. An enzyme in saliva, glucuronidase, breaks the glycyrrhizic acid molecule from licorice extract into glucuronic acid plus glycyrrhetinic acid (GTA) and the later acts as an anti-inflammatory.

SUMMARY OF THE INVENTION

Through trials, the inventor has discovered that, directly placing glycyrrhetinic acid ("GTA") which may be extracted from licorice root (glycyrrhiza) in an adhesive oral patch for treatment of ordinary mouth ulcers (also called denture sores, canker sores and aphthous ulcers) is effective for relieving pain and speeding of healing. When GTA is held on a canker sore with an oral patch for longer than 15 minutes, the canker sore pain is significantly reduced and there is no numbing of surrounding tissues. The pain relief continues while eating long enough to complete a meal with reduced pain. The patch with GTA also speeds healing.

GTA base may be used in the oral patch. However, for higher levels of absorption into local tissues and therefore greater effectiveness for the level of drug used (to minimize risks of side effects) it is preferable to use a salt of glycyrrhetinic licorice extract that is water soluble at human mouth temperatures (Soluble Glycyrrhetinic Extract, "SGE"). SGE comprises a group of chemical salts of glycyrrhetinic acid that are soluble in water at human mouth temperatures,
including potassium salt of glycyrrhetinic acid and other alkali metal salts of glycyrrhetinic acid.

In one aspect, the invention is a method for treating canker sores by providing patches which, when exposed to saliva in a human mouth, release GTA over more than 30 minutes, and instructing people to hold the patches in their mouths on or near the canker sore for at least 2 or more hours per day. The patch may include a binder ingredient to hold and release the medication.

The binder ingredients may be a combination of gums that dissolve in saliva, such as gum Arabic (acacia gum), carrageenan, xanthan gum, konjac gum, agar, or locust bean gum and non-dissolving food fibers. If the binders are xanthan gum, konjac gum, and cellulose fiber, effective dry weight formulations have between 1% and 10% SGE, such as potassium salt of GTA, between 20% and 55% food grade gelatin, and between 20% and 75% other binders. Another effective formula has 2-4% SGE with about 5-7% benzocaine and 50 - 93% gelatin, with acacia gum added on a side intended to be more adherent.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1a shows a side view of an oral patch that completely dissolves (erodes).

Figure 1b shows a top view of the same oral patch.

Figure 2 shows a layered oral patch covering a canker sore.

Figure 3 shows a domed oral patch with a dimple made by pressing powders.
DETAILED DESCRIPTION

Figure 1 shows an adhesive oral patch that completely dissolves (more precisely, erodes as the molecules become hydrated). In the mouth, it has a feel and texture like hard gummy candies. It is made with slowly dissolving hydrocolloids so that that it typically lasts in the mouth for at least one to six hours. The patch can be formed in the shape of a tablet or a lozenge or a wafer or any other desired shape. A preferred shape is a thin lentil which may be nearly flat on one side as shown in Figure 1a.

Another preferred shape for adhering to a tooth or braces that caused a cut that has become or is likely to become an ulcer is a dimpled dome - that is, convex on one side and concave on the other side. An example is shown in cross-section in Figure 3. The dimple may be a slight concavity. Nine millimeters diameter is a preferred size for such a dimpled dome made by pressing powders, with 0.5 to 1.5 millimeters for the depth of the dimple. For adhering to a bracket of orthodontic braces, such a dimple will allow greater contact with the bracket and wires for better adhesion. For adhering to a tooth, the concave dimple will allow the patch to adhere to a convex tooth surface at the periphery of the patch with multiple points of contact rather than with essentially a single point of contact near the center of a flat or convex patch surface.

A detailed description of a deposited patch and how to make it are disclosed by the same inventor in US patent application serial number 10/287,843 filed 5 November 5 2002 and published by the US Patent Office. A detailed description of a pressed powders patch made with mucoadhesive hydrocolloids pressed in two layers, one quite adhesive, entitled "Xylitol troches and methods of
use” is disclosed by the same inventor in US patent application serial number 60/879,846 filed 11 January 2007 (agent reference 0795-037-02(2)).

To cause the patch to dissolve (erode) very slowly in saliva, a binder that dissolves slowly in saliva is incorporated. Binders that have been tested and found to work well include gelatin, carrageenan (preferably kappa), xanthan gum, konjac gum, agar, gum arabic, and pectin. Other gums similar to those listed, such as locust bean gum which has properties similar to konjac gum, and guar gum should also work.

In addition to causing the patch to erode very slowly in the mouth, the binder also moderates any strong flavors by spreading out over a long period of time the release of that flavor. Consequently, sweeteners and other products to mask strong flavors are not required, although some users prefer a small amount of sweetener and some also prefer the addition of other flavors.

A method of manufacturing the patches of Figure 1 is to use gum drop manufacturing equipment, squirting a hydrated mixture heated above the gel melting temperature through nozzles onto a sheet of plastic or mold, allowing the patches to cool and gel, and drying the patches. The patches are preferably dried until the water activity level is lower than 0.8 so that the patches will not grow mold or other organisms. The patches are packaged with a hermetic seal to prevent absorption of water moisture from air. The resulting patches are at least 5 mm in each of at least two dimensions, preferably 8-18 mm.

The mixture may be deposited as an array of hot, viscous drops onto a sheet of high temperature plastic or coated paper. The drops are allowed to cool and then the sheets of plastic or coated paper with the drops on them are
dried in a drying room. The product is sold still adhered to the plastic or paper and the user pulls it off the plastic or paper.

Figure 2 shows a bi-layer oral patch comprising a permeable layer 1 and a non-permeable smooth outer layer 2. The oral patch is covering a canker sore 3 in a human cheek 4. The outer layer 2 is preferably smooth to minimize dislodging of the patch. Medication is held in the permeable layer 1 either by using a high viscosity liquid medication that slowly oozes out of the layer or by binding the medication to the layer with slowly dissolving binders such as any of the gums described above, including gelatin. A preferred size for the patch is 18 millimeters, and one or both layers of the patch may include a red pigment to color it like the inside of the mouth.

Alternatively, any of the other oral patches known in the art may be used, such as patches made by heat a thermo gel mixture, extruding a flat sheet, and die cutting.

For higher levels of absorption into local tissues and therefore greater effectiveness for the level of drug used (to minimize risks of side effects) it is preferable to use a water soluble salt of glycyrrhetinic licorice extract (Soluble Glycyrrhetinic Extract, "SGE"). This avoids a drop in pH that would be caused by using pure glycyrrhetic acid. SGE comprises a group of chemical salts of glycyrrhetic acid that are soluble in water at human mouth temperatures, including potassium salt of glycyrrhetic acid and other alkali metal salts of glycyrrhetic acid.

A preferred quantity of SGE in each patch that lasts 20 minutes to 6 hours is 1% to 10% of the non-water ingredients, most preferably 2-6%. For
patches of .1 to .2 grams dry weight, this is 2 - 12 mg of SGE, such as potassium salt of glycyrrhetinic acid. For an oral patch made by a tablet pressing process, the preferred size is about 100 to 150 milligrams for total tablet weight and the preferred quantity of SGE is 2.5 - 4 milligrams.

Glycyrrhetinic acid (GTA) is a mer component of glycyrrhizic acid, which is the negative part of the salt glycyrrhizin, which is a major ingredient in simple water extract of licorice root. When dissolved in water, the glycyrrhizic acid becomes bio-available from the glycyrrhizin. Aided by the enzyme glucuronidase which is in all body fluids including saliva, this component hydrolyzes to release the glycyrrhetinic acid which causes undesirable side effects when taken in too large a quantity. However, in moderate quantities, the anti-inflammatory effect of glycyrrhetinic acid is desirable for reducing pain and speeding healing of ulcers because the quantities required are far below the side effect threshold, especially when a water soluble form of GTA (SGE) is used so that the GTA leaches well out of the patch and passes easily into the epithelium.

The preferred patch formulation is made by combining the GTA extract with collagen and with binder ingredients. Collagen, which is the organic molecule that makes up skin and the lining of the mouth (a form of skin), tends to adhere very well to itself, making it glutinous, and therefore adheres very well to the lining of the mouth. An effective and cost effective form of collagen is food grade gelatin which is made from animal skins. As the collagen molecules slough off the patch while it slowly dissolves (erodes), they tend to adhere to the nearby mouth lining, forming a film. This film significantly reduces the sensitivity of the ulcer, both to touch and to chemical irritants.
Testing shows that, if the binders are xanthan gum, konjac gum, and cellulose fiber, effective dry weight formulations have between 1% and 10% GTA, between 20% and 99% food grade gelatin, between 0% and 75% other binders.

Presented below are conclusions from testing on 49 subjects of the adherent, soluble oral patches with about 7-9% GTA:

**Pain relief:** Using a patch for 10-15 minutes before a meal reduces pain of the canker sore, and, if used up to commencement of a meal, the pain relief lasts through a typical meal. There is no numbing effect on surrounding tissues.

**Catching it early:** If the user catches the canker sore early, shorter treatment is required. The sore will often start in a small cut. Some users report that if they apply one patch to a cut for 1-4 hours before there is any sensation of a canker sore, then they will not get a canker sore from the cut. Other times, the sore starts with a feeling that the mucous layer is becoming too thin in a spot before it becomes painful. Some users report that if they apply one patch to that spot, no canker sore develops. Users report that if they begin applying the patch when the canker sore is very small and barely painful, the patches control the pain to the extent that there is no significant pain and healing is accelerated.

**Treatment of the tongue:** For treatment of the tongue, most users stick a patch (which releases extract on both sides) to the closest tooth. This works particularly well at night.

**Braces:** Users with braces apply the patch to the braces opposite the canker sore so that the patch is touching the canker sore most of the time and is stuck to the teeth and braces. As it softens, the patch settles into the braces. It will completely dissolve out of the braces in 3 - 9 hours. All this time it supplies GTA to the sore.
While particular embodiments of the invention have been described above the scope of the invention should not be limited by the above descriptions but rather limited only by the following claims.
Claims

1. A method for treating mouth ulcers, comprising:
   (a) providing adhesive oral patches, each at least 5 millimeters by 5 millimeters, comprising a salt of glycyrrhetinic acid that is water soluble at human mouth temperatures which patch, when exposed to saliva in a human mouth, releases glycyrrhetinic acid; and
   (b) instructing recipients of the patches to hold the patches in their mouths on or near an ulcer to treat mouth ulcers.

2. The method of claim 2 where the salt is an alkali metal salt of glycyrrhetinic acid.

3. The method of claim 2 where the salt is potassium salt of glycyrrhetinic acid.

4. The method of claim 1 wherein the patch includes a gum that dissolves or erodes in saliva.

5. The method of claim 4 where the gum is xanthan gum.

6. The method of claim 4 where the gum is konjac gum.

7. The method of claim 4 where the gum is gelatin.

8. The method of claim 4 where the gum is locust bean gum.

9. The method of claim 4 where the gum is acacia gum.

10. An adherent patch, at least 5 millimeters by 5 millimeters, that, when held in a human mouth, remains in the mouth as a single item that will not spread to be in a plurality of locations in the mouth at one time and slowly erodes, thereby releasing over time glycyrrhetinic acid, consisting essentially of, by dry weight:

   (a) between 1% and 10% salt glycyrrhetinic acid that is water soluble at human mouth temperatures; and
   (b) between 50% and 99% binder ingredients.
11. The patch of claim 10 where the salt is an alkali metal salt of glycyrrhetinic acid.
12. The patch of claim 11 where the salt is potassium salt of glycyrrhetinic acid.
13. The patch of claim 10 where the glycyrrhetinic acid is between 2 and 6 percent.
14. A dimpled adhering troche for adhering to teeth or orthodontic braces, comprising:
   a. a troche, having a convex surface of at least 5 millimeters in at least two dimensions and a concave surface opposite the convex surface;
   b. the concave surface comprising an adhesive.
15. The troche of claim 14 wherein the troche erodes when held in a human mouth.
16. The troche of claim 14 wherein the troche releases glycyrrhetinic acid.
17. The troche of claim 14 wherein the troche releases benzocaine.
18. The troche of claim 14 wherein the troche releases collagen.
19. The troche of claim 14 wherein the concave surface has a depth of at least 0.5 millimeters.
20. The troche of claim 14 wherein the adhesive comprises acacia gum.
21. The troche of claim 14 wherein the adhesive comprises collagen.
INTERNATIONAL SEARCH REPORT
WO 2007/120768

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/19(2006.01)i, A61K 31/215(2006.01)i, A61K 9/70(2006.01)i, A61P 1/02(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC8 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKIPASS, STN(Caplas), Pubmed

* Key words: glyceryrrhetic acid, patch, oral, inflammatory, transdermal, troche, xanthan gum, gelatin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>US 4,406,882 B (BIOREX LABORATORIES LIMITED) 27 September 1983</td>
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<td>See the column 2, line 42 - column 3, line 33, and claims.</td>
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<td>US 6,197,331 B1 (PERIO PRODUCTS LTD.) 06 March 2001</td>
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed
  "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  "&" document member of the same patent family

Date of the actual completion of the international search
06 SEPTEMBER 2007 (06.09.2007)

Date of mailing of the international search report
07 SEPTEMBER 2007 (07.09.2007)

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
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Facsimile No. 82-42-472-7140

Authorized officer
LEE, SUN HWA
Telephone No. 82-42-481-5606

Form PCT/ISA/210 (second sheet) (April 2007)
### Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos 1-9 because they relate to subject matter not required to be searched by this Authority, namely Claims 1-9 are directed to a method of treatment of the human body by therapy and thus relate to a subject matter under Rule 39 l(iv) of PCT. Nevertheless, a search has been performed based on the oral patch or composition for treating mouth ulcers.

2. [ ] Claims Nos because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically.

3. [ ] Claims Nos because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a).

### Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims. It is covered by claims Nos.

### Remark on Protest

- [ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- [ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- [ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2007)
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<tr>
<td></td>
<td></td>
<td>AU 7999782 A1</td>
<td>12.08.1982</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BE 891987 A1</td>
<td>27.05.1982</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 1171784 A1</td>
<td>31.07.1984</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 3203310 A1</td>
<td>02.12.1982</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 3203310 C2</td>
<td>18.03.1993</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2499407 A1</td>
<td>13.08.1982</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2499407 B1</td>
<td>15.05.1987</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GB 2092442 B2</td>
<td>08.02.1984</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GB 2092442 A1</td>
<td>18.08.1982</td>
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<tr>
<td></td>
<td></td>
<td>HK 32085 A</td>
<td>03.05.1985</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IT 1151953 A</td>
<td>24.12.1986</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IT 8219482 A0</td>
<td>05.02.1982</td>
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<tr>
<td></td>
<td></td>
<td>JP 3010608 B4</td>
<td>14.02.1991</td>
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<td></td>
<td></td>
<td>MY 3186 A</td>
<td>31.12.1986</td>
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<tr>
<td></td>
<td></td>
<td>ZA 8200361 A</td>
<td>29.12.1982</td>
</tr>
<tr>
<td>US 06197331 B1</td>
<td>06.03.2001</td>
<td>US 2001024657 AA</td>
<td>27.09.2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>KR 10-2005-055858 A</td>
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