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(54) Title: THERAPEUTIC COMPOSITIONS AND METHODS OF USE THEREOF

(57) Abstract: A therapeutic composition and a method of using the composition are provided. The composition includes an osmotic agent and an active agent. The osmotic agent improves the delivery of the active agent to the targeted tissue site.

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1 THERAPEUTIC COMPOSITIONS AND METHODS OF USE THEREOF

2
3 BACKGROUND

4
5 Cross Reference to Related Applications

6 This application is a continuation-in-part under 35 U.S.C. § 120 to commonly
7 owned and co-pending U.S. Patent Application Serial No. 09/633,424, filed on
8 August 7, 2000, which is a continuation-in-part under 35 U.S.C. § 120 to commonly
9 owned and U.S. Patent 6,099,868, filed November 12, 1999.

10
11 Field of the Invention

12 The present application is directed to therapeutic compositions including an
13 osmotic agent and an active agent and, in particular, to compositions including
14 dimethyl isosorbide as the osmotic agent.

15
16 Related Art

17 The inventor of the present invention has done extensive research into the
18 cause of pain, particularly in the area of oral and dental surgery. In this research, it
19 has been discovered that potassium is effective for desensitizing hypersensitive teeth
20 (U.S. Patent No. 3,863,006), for treating canker sores (U.S. Patent No. 4,191,750), for
21 preserving dental pulp (U.S. Patent Nos. 4,343,608 and 4,407,675), for treating
22 gingival and periodontal tissues (U.S. Patent No. 4,400,373), for treating post-
23 restoration dental pain (U.S. Patent No. 5,153,006), and for anesthetizing teeth (U.S.
24 Patent No. 5,522,726), all of which patents are incorporated herein by reference.

25 Accordingly, the present invention is a result of the continued research of the
26 inventor, which research has determined that potassium nitrate, in combination with
27 other compounds, can be used for the reduction of pain associated with a variety of
28 procedures and conditions. Accordingly, the present invention includes the
29 combination of potassium nitrate and dimethyl isosorbide, for the treatment of

1 ulcerative lesions of the skin and mucous membranes, for improved tooth
2 desensitization of hypersensitive teeth, the use of potassium nitrate, EGTA, citric acid,
3 and EDTA, wherein the EDTA, EGTA, citric acid, etc. removes the smear layer from
4 the teeth first to allow the potassium nitrate next to better penetrate to the nerves of
5 the tooth, as set forth in the '726 patent, and the combination of potassium nitrate and
6 various potent topical anesthetics to simultaneously anesthetize the a tooth and the
7 surrounding gum tissue to provide pain-free periodontal and hygienist scaling and
8 maintenance visits. This same combination of substances can be applied locally for
9 effective post-operative and restorative pain control, post-periodontal and other post-
10 surgery comfort while healing is taking place. This diminishes the need to use
11 ingested and/or injected analgesics or narcotics for pain control.

12 Cells and other membranous tissues contain and are surrounded by various
13 fluids that contain electrolytes. The difference in the type and concentration of the
14 electrolytes contained in the cells and membranous tissues may in some instances
15 polarize, or provide an electrical potential across the membrane. For example, in
16 general, the electrolytic fluid contained in the interior of a cell contains more
17 negatively charged ions than the electrolytic fluid surrounding the exterior of the cells,
18 which contains positively charged ions. Thus, it can be seen that the normal state of
19 cells is one in which the electrical charge of the fluids contained in and surround a cell
20 are not balanced. The normal charge difference across the membrane creates an
21 electrical potential which is known as the resting threshold potential. For a nerve to
22 conduct a pain impulse, it must be at its resting threshold potential.

23 With respect to nerve cells, the electrolytic fluid in the interior of a nerve cell
24 at rest has a resting threshold potential of about -85 millivolts with respect to the
25 electrolytic fluid surrounding the nerve cell. Pain is felt by a subject when an irritant
26 to the nerve cell occurs, causing sodium channels in the nerve cell membrane to open
27 for a brief period of time (on the order of milliseconds), allowing sodium ions
28 contained in the fluid surrounding the nerve cells to move into the fluid contained in

1 the interior of the nerve cells, after which conduction along the nerve takes place,
2 leading to a complete action potential and pain emission.

3 One example of such a mechanism involves the pulpal nerves. The electrolytic
4 fluid in the interior of the pulpal nerves has a resting threshold potential of about -85
5 millivolts with respect to the electrolytic fluid surrounding the pulpal nerve cell.
6 When an irritant of about +15 millivolts occurs, sodium ions in the fluid surrounding
7 the pulpal nerve move across the pulpal nerve membrane to the interior of the pulpal
8 nerve and conduction takes place, leading to a complete action potential and pain
9 emission.

10 One known mechanism for preventing pain in pulpal nerves is to increase the
11 concentration of potassium ions in the electrolytic fluid surrounding the pulpal nerves.
12 Surrounding the pulpal nerves with a high concentration of potassium ions causes the
13 nerve to depolarize. "Depolarization" occurs when the resting threshold potential is
14 increased. In the present instance, the resting threshold potential is increased from -85
15 millivolts to zero or a positive value. When the resting threshold potential is zero, or
16 a positive value, the nerve cannot initiate a pain impulse. Thus, it is known that if the
17 resting threshold potential of a nerve is increased, it is possible to prevent an action
18 potential from taking place, the nerve will be unable to conduct an impulse, and the
19 subject will not feel pain.

20 In theory, pain inhibition in the pulpal nerves may be accomplished by a
21 variety of mechanisms. However, in practice, anatomical constrictions, irregularities,
22 and other resistances found in the dentinal tubules sometimes minimize or prevent
23 potassium ions from reaching the electrolytic fluid surrounding the nerve cell.

24 Any mechanism for changing the resting threshold potential of nerves is
25 desirable for interfering with its ability to illicit pain.

26
27 SUMMARY

28 According to a first embodiment of the invention, a method of anesthetizing
29 a tooth requiring tooth preparation, caries removal or manual manipulation thereof is

1 disclosed. The method comprises the step of applying a composition having a high
2 concentration of potassium to the tooth requiring tooth preparation, caries removal or
3 manual manipulation, the composition being adapted to anesthetize the tooth so that
4 the tooth may be drilled or manually manipulated, whereby the potassium enters the
5 dentinal tubules and odontoblastic fibrils and penetrates the pulpal tissues of the tooth
6 for anesthetizing the tooth. The improvement consists essentially of applying a
7 solution of EDTA, EGTA, and citric acid to the tooth before the application of the
8 potassium composition, the solution of EDTA, EGTA, and citric acid effectively and
9 safely removing a smear layer from the tooth so as to facilitate the penetration of the
10 potassium solution through the dentinal tubules and odontoblastic fibrils.

11 According to another embodiment of the invention, a method of anesthetizing
12 a tooth requiring tooth preparation, caries removal or manual manipulation thereof is
13 disclosed. The method comprises the step of applying a composition having a high
14 concentration of potassium to the tooth requiring tooth preparation, caries removal or
15 manual manipulation, the composition being adapted to anesthetize the tooth so that
16 the tooth may be drilled or manually manipulated, whereby the potassium enters the
17 dentinal tubules and odontoblastic fibrils and penetrates the pulpal tissues of the tooth
18 for anesthetizing the tooth. The improvement consists essentially of including a
19 topical anesthetic in the potassium solution to enable the solution to anesthetize the
20 tooth and the gingivae and other soft tissues surrounding the tooth.

21 According to yet another embodiment of the invention, a method of
22 anesthetizing a tooth requiring tooth preparation, caries removal or manual
23 manipulation thereof is disclosed. The method comprises the step of applying a
24 composition having a high concentration of potassium to the tooth requiring tooth
25 preparation, caries removal or manual manipulation, the composition being adapted
26 to anesthetize the tooth so that the tooth may be drilled or manually manipulated,
27 whereby the potassium enters the dentinal tubules and odontoblastic fibrils and
28 penetrates the pulpal tissues of the tooth for anesthetizing the tooth. The improvement
29 consists essentially of including a concentration of dimethyl isosorbide in the

1 potassium solution, whereby the concentration of dimethyl isosorbide acts to increase
2 the ability of the potassium to penetrate in increased amounts through the dentinal
3 tubules and odontoblastic fibrils and to better penetrate the pulpal tissues of the tooth
4 for anesthetizing the tooth.

5 By employing an enhancer, such as Dimethyl Isosorbide or phospholipids, we
6 are able to improve the desensitizing of hypersensitive teeth, since Dimethyl
7 Isosorbide enhances the penetration of potassium ions (whatever the source of
8 potassium-refer to U.S. Patent No. 5,522,726) through the tooth and dentinal tubules
9 into the pulpal tissues. The effect is to provide faster, more complete, longer lasting
10 (duration) desensitization. Another application is to use potent topical anesthetics in
11 combination with high concentration potassium compounds (e.g., potassium nitrate,
12 potassium citrate, potassium chloride-refer to U.S. Patent No. 5,522,726) for
13 providing pain-free comfort during periodontal and/or hygienist scaling, maintenance,
14 and other manipulative procedures. We use saturated KNO_3 , 20 percent
15 benzocaine, 10 percent tetracaine for controlling both tooth and gingival pain. It
16 controls pain with such hygienic procedures, periodontal treatments, papillectomy.
17 Since the gingival and other soft oral tissues do not have dentinal tubules, the soft
18 tissue anesthesia is accomplished by potent topical anesthetics. Some are benadryl,
19 lidocaine, tetracaine, benzocaine, cetracaine, etc.

20 According to yet another embodiment of the invention, a method for reducing
21 pain and shortening the healing period of in aphthous ulcers is disclosed. The method
22 includes the step of applying a solution of potassium (2 percent - 35 percent) and
23 dimethyl isosorbide to the site of the ulcer, whereby the solution acts on nerve endings
24 within the ulcer to reduce inflammation and prevent the induction of pain within the
25 ulcer while promoting faster healing of the ulcer. Dimethyl isosorbide enhances the
26 effect of the potassium ion by aiding its penetration into the affected tissue. Any
27 source of potassium can be utilized for this purpose. Examples are KNO_3 , KCl ,
28 KCO_3 , KPO_4 , etc. (refer to issued U.S. Patent No. 5,522,726). This is an improvement
29 over the use of potassium nitrate to treat canker sores (U.S. Patent No. 4,191,750).

1 According to another embodiment, the invention is directed to a method of
2 decreasing the volume of a cell having a membrane and an electrical potential across
3 the membrane that is substantially equal to a resting threshold potential. The method
4 involves the steps of topically applying a composition containing an osmotic agent,
5 increasing the electrical potential across the cell membrane to a level greater than the
6 resting threshold potential, and decreasing the electrical potential across the cell
7 membrane to a level less than the resting threshold potential.

8 In another embodiment, the invention is directed to a therapeutic composition.
9 The therapeutic composition includes dimethyl isosorbide and an active agent.

10 Another embodiment of the present invention is directed to a method of
11 treating a subject. The method involves topically applying an effective amount of a
12 composition containing an osmotic agent and an active agent to an area to be treated.

13 Another embodiment of the present invention is directed to a method of
14 treating a subject. The method involves topically applying an effective amount of a
15 composition containing dimethyl isosorbide and an active agent to an area to be
16 treated.

17 18 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

19 In general, human nerve cells have a low threshold of excitation. Stimuli for
20 exciting nerve cells may be electrical, chemical, or mechanical. A stimulus creates
21 a physicochemical disturbance or impulse which is transmitted by conduction along
22 the nerve axon to its termination. Nerves do not transmit impulse passively (as do
23 telephone wires) and conduction of nerve impulses, although rapid, is much slower
24 than that of electricity. Conduction is an active self-propagating process which
25 requires expenditure of energy by the nerve at a constant amplitude and velocity.

26 For more than one hundred years it has been known that there are electrical
27 potential changes in a nerve when it conducts impulses. There is a constant potential
28 difference between the inside and the outside of the nerve cell at rest. The magnitude
29 of this potential in most neurons (otherwise referred to as "Resting Membrane

1 Potential") is approximately seventy-eight millivolts (MV) and is expressed as a
2 negative potential (i.e., -70-80 MV) because the inside of the cell is negatively
3 charged relative to the positively charged exterior of the cell. If the nerve axon is
4 stimulated and a conducted impulse occurs, a characteristic series of potential changes
5 is observed.

6 The first manifestation of the approaching impulse is a beginning
7 depolarization of the membrane. The potential changes are small, being measured in
8 millivolts. After an initial fifteen millivolts of depolarization of the membrane, the
9 rate of depolarization increases. The point at which this change in rate occurs is
10 termed the "firing level." Thereafter it rapidly reaches and overshoots the iso-
11 potential (zero potential) line to approximately thirty-five millivolts positive. It then
12 reverses and falls rapidly towards a resting level. When re-polarization is about
13 seventy percent completed, the rate of re-polarization decreases approaching the
14 resting level more slowly. The sharp rise and rapid fall are the spike potential of the
15 nerve axon, and the slower fall at the end of the process is the after-depolarization.
16 The whole sequence of potential changes is called the "action potential." Once the
17 minimal intensity of stimulating current (threshold intensity which will just produce
18 an impulse) is reached, a full fledged action potential is produced.

19 Further increases in the intensity of a stimulus produce no increment or other
20 change in the action potential. The action potential fails to occur if the stimulus is
21 subthreshold in magnitude, and it occurs with a constant amplitude and form
22 regardless of the strength of the stimulus if the stimulus is at or above the threshold
23 intensity. The action potential is therefore all or none. The depolarizing forces must
24 be stronger than the re-polarizing forces in order to overwhelm the re-polarizing
25 process (i.e., fifteen millivolts) and an action potential results. At this level of
26 depolarization some fundamental change in the nerve leads to runaway depolarization
27 in the membrane.

28 At rest, the nerve cell membrane is polarized with positive charges lined up
29 along the outside of the membrane and negative charges along the inside of the

1 membrane. During the action potential this polarity is abolished and for a brief period
2 of time it is actually reversed. Positive charges from the membrane ahead of and
3 behind the action potential flow into the area of negativity. By drawing off positive
4 charges, this flow decreases the polarity of the membrane ahead of the action
5 potential. Electronic depolarization initiates a local response, and when the firing
6 level is reached a propagated response occurs which in turn electronically depolarizes
7 the membrane in front of it. This sequence of events moves regularly along an
8 unmyelinated nerve axon (i.e., a nerve axon lacking a myelin sheath) to its end. The
9 self-propagating nature of the nerve impulse is due to circular current flow and
10 successive electronic depolarization to the fire level of the membrane ahead of the
11 axon potential. Once initiated, a mixing impulse does not depolarize the area behind
12 it to the firing level because the area is refractory.

13 The action potentials produced at synaptic junctions also depend on electronic
14 depolarization of the nerve cell membrane to the firing level. Conduction in
15 myelinated axons depends on a similar pattern of current flow, but myelin is a relative
16 effective insulator, and current flow through it is negligible. Instead, depolarization
17 in myelinated axons jumps from one node of Ranvier to the next, with the current sink
18 at the active node serving to electronically depolarize to the firing level. The jumping
19 of depolarization from node to node is called saltatory conduction. Myelinated axons
20 conduct up to fifty times faster than unmyelinated axons.

21 The innervation of the tooth pulp includes both afferent neurons which conduct
22 sensory impulses, and autonomic fibers which provide neurogenic modulation of the
23 microcirculatory system and perhaps regulate dentinogenesis as well. Most of the
24 nerves of the pulp fall into two categories: A fibers and C fibers. The A fibers are
25 myelinated and the C fibers are unmyelinated. In addition to sensory nerves,
26 sympathetic fibers from the cervical sympathetic ganglion appear with blood vessels.
27 All of the fibers enter the tooth through the apical foramen. The A fibers are enclosed
28 within sheath formed by the Schwann cells. The myelinated A fibers are grouped in
29 bundles in the central region of the apical pulp. Most of the unmyelinated C fibers

1 entering the pulp are located with the fiber bundles in the central region of the apical
2 pulp and are situated toward the periphery of the pulp. Approximately eighty percent
3 of the nerves of the pulp are C fibers. The nerves from the coronal pulp divide and
4 send branches towards the peripheral pulp where a parietal layer of both myelinated
5 and unmyelinated nerve axon form the plexus of Raschkow beneath the cell rich zone.
6 The A fibers of the parietal layer emerge from their myelin sheaths and Schwann cell
7 coverings to ramify into eight to ten unmyelinated branches forming a network under
8 the dentin. Terminal axons exit their Schwann cell investiture and pass between the
9 odontoblast with some fibers actually entering the dentinal tubules lying in close
10 association with the odontoblastic processes.

11 A nerve axon can conduct in either direction. If an action potential is initiated
12 in the middle of the axon, two impulses traveling in opposite directions are set up by
13 electronic depolarization on either side of the current sink. In humans, impulses
14 normally pass from synaptic junction or receptors along axons to their termination.
15 Such conduction is called "orthodromic" and conduction in the opposite direction is
16 called "antidromic". Synapses, unlike axons, permit conduction in one direction only.

17 It has been discovered that a tooth subject to hypersensitivity can be
18 desensitized by applying a composition saturated with a potassium containing
19 compound thereto. It has been further discovered that highly concentrated potassium
20 ions and cations, when exposed to the dentinal tubules and odontoblastic processes,
21 penetrate the pulpal tissues of the tooth for desensitizing the tooth. When applied to
22 the tooth, potassium polarizes the pulpal nervous tissues of the tooth thereby rendering
23 these sensory nerves inactive and unable to depolarize for a significant time period
24 until the potassium dissipates. This process, sometimes referred to as
25 "hyperpolarization," allows no stimulus, no matter how strong, to excite the pulpal
26 nervous tissue.

27 More specifically, in nerve cells, as in other tissues, sodium is actively
28 transported out of the cell and a small amount of potassium is actively transported into
29 the cell. Potassium diffuses back out of the cell down its concentration gradient, and

1 sodium diffuses back into the cell; however, since the permeability of the membrane
2 to potassium is much greater than it is to sodium at rest, the passive potassium efflux
3 is much greater than the passive sodium influx. Since the membrane is impermeable
4 to most of the anions in the cell, the potassium efflux is not accompanied by an equal
5 flux of anions and the membrane is maintained in a polarized state with the outside
6 of the membrane being positive and the inside of the membrane being negative.

7 A slight decrease in resting membrane potential leads to increased movement
8 of potassium out of and chlorine into the cell, thereby restoring the resting membrane
9 potential. In the case of nerve cells, there is a unique change in the cell membrane
10 when depolarization exceeds seven millivolts. This change is a voltage dependent
11 increase in membrane permeability to sodium so that the closer the membrane
12 potential is to the firing level the greater the sodium permeability. The electrical and
13 concentration gradients for sodium are both directed inwardly. During a typical
14 injected local response, sodium permeability is slightly increased, but potassium
15 efflux is able to restore the potential to the resting value. When the firing level is
16 reached, permeability is significant enough so that sodium influx further lowers
17 membrane potential and sodium permeability is further increased.

18 The consequent sodium influx swamps the re-polarizing processes, and
19 runaway depolarization results, producing the spike potential. With the increase in
20 sodium permeability at the start of the action potential, the membrane potential
21 approaches sixty millivolts positive. The membrane potential fails to reach this mark;
22 primarily because the change in sodium permeability is short lived. Sodium
23 permeability starts to return to the resting value during the rising phase of spike
24 potential and sodium conductance is decreased during re-polarization. Additionally,
25 the direction of the electrical gradient for sodium is reversed during the overshoot
26 because the membrane potential is reversed. These factors limit sodium influx and
27 help bring about re-polarization.

28 Another important factor producing re-polarization of the nerve membrane is
29 the increase in potassium permeability that accompanies sodium permeability. The

1 change in potassium permeability starts more slowly and reaches a peak during the
2 falling phase of the action potential. The increase in permeability decreases the barrier
3 to potassium diffusion, and potassium consequently leaves the cell. The resulting net
4 transfer of positive charge out of the cell serves to complete re-polarization.

5 The changes in sodium and potassium conductance of an ion is the reciprocal
6 of its electrical resistance in a membrane and is a measure of membrane permeability
7 to that ion. The ionic hypothesis as the basis of action potential is provided by the
8 observation that decreasing the external sodium concentration decreases the size of the
9 action potential, but has little effect on the resting membrane potential since the
10 permeability of the membrane to sodium is very low. Conversely, increasing the
11 external potassium in the tooth, decreases the resting membrane potential. This
12 renders the nerve unable to develop an action potential, and causes the nerve to fail
13 to fire when stimulated.

14 In this way the potassium applied to the tooth desensitizes the tooth directly
15 in that potassium flows through the vast network of dentinal tubules. The potassium
16 traverses the 30,000 - 59,000 dentinal tubules per square millimeter of dentin and
17 flows over and through the dentinal tubules and odontoblastic fibrils to the
18 odontoblast and into the pulp increasing the external potassium about the nerve. This
19 interruption of neuron function is caused by the actual bathing of nerve tissue with an
20 abundant source of potassium. This process of hyperpolarizing elevates the membrane
21 potentials as they would be in the absolute refractory period allowing no stimulus, no
22 matter how strong, to excite the nerve. As the potassium bathing the nerve dissipates,
23 the membrane threshold is again decreased as it would be after repolarization. At this
24 point, the patient may begin to feel some pain and concentrated potassium gel is
25 applied again in order to re-anesthetize the tooth and eliminate pain caused by the drill
26 etc.

27 In cavity preparation, it is important to adhere to basic principles when using
28 a drill, i.e, minimize heat production, use copious water spray to avoid overheating the
29 pulp, and use a light, painting, or wiping motion when drilling. These techniques

1 lessen the feeling in the tooth experienced by the patient. This is important especially
2 as the clinician enters and passes through the enamel to reach the dentinal tubules.
3 When the dentinal tubules are reached, the selected potassium composition is
4 reapplied. This allows the potassium composition to enter into the exposed dentinal
5 tubules.

6 The potassium composition of the subject invention may be in the form of a
7 liquid, although for greater efficacy the composition preferably comprises a viscous
8 liquid composition, such as a gel. Ointments, pastes and creams have also proven to
9 be very acceptable. In order to properly apply the composition, a liberal amount of
10 it should be applied to the patient's teeth which are subject to hypersensitivity.
11 Preferably, the composition is applied over the tooth for a time period of greater than
12 one minute, at least twice a day, every day. When in the form of a gel, the
13 composition can be applied with a cotton swab or the like. When in the form of a
14 paste, the composition can be brushed onto the patient's teeth with a toothbrush.

15 As previously stated, the composition comprising potassium is preferable in
16 a viscous form, such as a liquid gel or paste, so that when applied liberally to the
17 tooth, the composition tends to remain in place and is not washed away quickly. It has
18 been found that a viscous liquid gel or paste composition comprising a compound of
19 potassium nitrate at saturation level is especially effective in achieving the objectives
20 of this invention. Contrary to the teachings of the above-noted Patent No. 3,863,006,
21 it should be pointed out that the potassium containing compound should exceed
22 twenty percent by weight of the overall composition. Preferably, in order to reach
23 saturation level, the composition comprises approximately 35 percent (35%) by
24 weight potassium nitrate and 65 percent (65%) by weight hydroxyethylcellulose and
25 water. Compositions comprising compounds other than potassium nitrate may also
26 be applied; such compounds include potassium bicarbonate, potassium biphthalate,
27 potassium bromide, potassium chromate, potassium acetate, potassium dichromate,
28 potassium phosphate, potassium sulfate, potassium chromium sulfate, potassium
29 citrate, potassium thiocyanate, potassium alum, potassium bitartrate, potassium

1 bromate, potassium carbonate, potassium chlorate, potassium chloroglatinate,
2 potassium chloride, potassium hydroxide, potassium perchlorate, potassium
3 persulfate, potassium oxalate, potassium azide, potassium fluoride, potassium
4 hydrogen sulfate, potassium iodate, potassium sodium tartrate, potassium fluoride,
5 tartrate, etc. However, it has been determined that potassium nitrate produces the best
6 result.

7 Further experimentation has shown that substances on the tooth can reduce the
8 effectiveness of the potassium solution. These substances include the smear layer of
9 the tooth, which consists of organic and inorganic materials including heat coagulated
10 proteins such as gelatin, which are derived from heat denaturation of collagen under
11 the effects of cutting temperatures. The smear layer may also include saliva, blood
12 and microorganisms.

13 In order to remove the smear layer before the application of the potassium
14 nitrate anesthetic, a solution of 50% EDTA disodium salt solution 0.02 normal
15 and 50% citric acid is applied to the cemento-enamel junction of the tooth and to other
16 areas of the dentin as tooth preparation and caries removal progresses. The
17 EDTA/citric acid solution effectively removes the smear layer mucopolysaccharide
18 coating and peritubular dentin, thereby exposing the orifices of the dentinal tubules
19 for better penetration of the potassium ions.

20 With this preparation, the potassium ions enter the exposed dentinal tubules
21 more readily and mingle with their contained fluid (lymph) which occupies about 22%
22 of the tooth's fluid volume flowing through the tubules over the odontoplastic
23 processes and inward to the pulpal nerves, thereby anesthetizing the tooth by this
24 direct path. The solution may also be added to the enamel of the tooth to increase the
25 porosity of the tooth, thereby allowing the potassium ions to penetrate through the
26 enamel into the underlying dentin more readily.

27 Other smear layer-removing substances that may be used include other acids
28 such as ascorbic acid, phosphoric and lactic acid, gluconic acid salt, polyacrylic acid,
29 tartoric acid, acetic acid, hydrochloric acid, ethylene glycol Bis (2-aminoethyl ether)

1 tetracetic acid (ETGA), and edtate sodium. Smear layers are also removed by sodium
2 hypochlorate with sodium hydroxide or EDTA, formulation based phenol sulfonate,
3 aqueous hydrohide peroxide, and other compounds known in the art.

4 Another embodiment of the invention includes the addition of a topical
5 anesthetic, such as benzocaine, tetracaine, lidocaine benadryl, etc., with the potassium
6 solution. This solution effectively anesthetizes the tooth and the gingivae or other soft
7 tissues surrounding the tooth. The potassium solution provides direct pulpal
8 anesthesia, as described above. Since the gingivae and other soft oral tissues do not
9 have dentinal tubule which could allow potassium ions to enter their structure as do
10 teeth, the topical anesthetics are combined with the potassium solution to topically
11 anesthetize the tooth's pulp. This combination provides excellent pain control for
12 periodontal and hygienist procedures for treatment and maintenance visits.

13 A preferred solution includes the following approximate concentrations of
14 elements:

15

16	Potassium Nitrate	35% by wt.
17	Benzocaine	20% by wt.
18	Tetracaine	10% by wt.
19	Hydroethylcellulose	15% by wt.
20	Water	15% by wt.
21	Dimethyl Isosorbate	10 drops per oz. of the total solution

22 It will be understood, however, that other known topical anesthetics may be
23 substituted for the benzocaine and tetracaine in the above solution. Suitable topical
24 anesthetics include lidocaine, phenol benadryl, cetracaine, and others known in the art.

25 According to another embodiment of the invention, it has been found that,
26 while potassium ions are an excellent anesthetic for use on teeth, which have dentinal
27 tubules for transporting the potassium ions to the nerves of the teeth, it is not as
28 effective as an anesthetic for other tissues of the body. Since these other tissues do not
29 have the tubules which transport the potassium ions to the nerves, another means for

1 transporting the potassium ions to the nerves of the tissue must be used. The skin
2 serves as a protective barrier which limits ionic penetration elements. Therefore, an
3 enhancer is required to bring the potassium ions in quantity to the desired tissue site.
4 The rationale for nerve inactivation is the same wherever nerves are involved. If skin,
5 mucous membranes, muscles, tendons and other tissues can be penetrated by a high
6 gradient of potassium ions which can be brought to surround the nerves in sufficient
7 quantities, then the action potential can be inhibited.

8 In connection with this, it has been discovered that dimethyl isosorbide is an
9 excellent enhancer of potassium ions for the purpose of delivering the potassium ions
10 to the nerves of the treatment site. The dimethyl isosorbide is mixed as a gel solution
11 which preferably includes the following:

13	Potassium Nitrate	3.4% by wt.
14	Hydroethylcellulose	3.4% by wt.
15	dimethyl isosorbide	1.9% by wt.
16	water	91% by wt.

17
18 This solution has been found to be effective for the reduction of pain
19 associated with aphthous ulcers (canker sores) and other ulcer-producing illnesses,
20 such as herpes and shingles. Furthermore, the solution has been found effective in the
21 reduction of inflammation associated with inflammatory lesions and localized injuries.
22 When the gel solution is applied to the area to be treated, the dimethyl isosorbide
23 facilitates the penetration of the potassium ions to the nerves which are being
24 stimulated and are therefore causing the patient pain. It has been found that the
25 potassium ions not only exert their pain-inhibiting effects on central nervous system
26 nerves, they also have a remarkable effect on the autonomic nerves by minimizing
27 inflammatory stimulation. Accordingly, the dimethyl isosorbide/ KNO_3 solution can
28 be used as a pain reducer and anti-inflammatory agent.

1 Thus, in other embodiments, the present invention is directed to therapeutic
2 compositions containing at least one osmotic agent and at least one active agent. The
3 compositions may be used topically by subjects to treat, relieve, or treat and relieve,
4 the symptoms of various conditions and disorders, by providing improved delivery of
5 the active agent contained in the composition to the region of interest. The amount
6 of the osmotic agent, the amount of the active agent, or the amount of both the
7 osmotic agent and the active agent contained in the present compositions may be
8 varied in order to achieve the desired therapeutic results. This may be easily
9 accomplished by those of skill in the art using routine experimentation and traditional
10 techniques.

11 In practice, anatomical constrictions, irregularities, and resistances may
12 sometimes minimize or prevent active agents from reaching a targeted site selected
13 for therapeutic treatment. "Osmotic agent," as used herein, means any agent that
14 raises the osmotic pressure of fluid on one side of a membranous structure drawing
15 water across the membrane, causing the structure to shrink in volume. Using the
16 example of a cell, an osmotic agent according to the present compositions may draw
17 water from the interior of the cell such that the volume of the cell is reduced. When
18 cells in a targeted region are reduced in volume, the intercellular spaces are increased.
19 Thus, the osmotic agents of the present compositions increase the amount of space
20 available between cells, allowing the electrolytic fluid surrounding the cells to move
21 more freely and quickly between the cells.

22 In addition to increasing the intercellular volume, the reduction in cell volume
23 resulting from the osmotic agents disturbs the normal function of the cells, i.e., the cell
24 with reduced volume is unable to function normally. The functions of nerves that may
25 be disturbed as a result of the cell volume reduction may include the ability to
26 stimulate an inflammatory response and the ability to illicit pain, depending on
27 whether the nerves are from the central nervous system or the autonomic nervous
28 system.

1 The present compositions unexpectedly allow active agents to be delivered
2 directly to deeper targeted sites, eliminating the need for injections, or systemic (oral)
3 medications that may present safety concerns. The present compositions have the
4 capability to readily penetrate into and through the skin, and in some instances into the
5 underlying tissue. In this manner, the osmotic agent of the present compositions
6 increases the absorption and penetration depth of the active agents into, for example,
7 the skin and underlying tissues, the mucosae, and teeth. Thus, the therapeutic
8 effectiveness of the active agent may be increased for its desired purpose. The
9 increased therapeutic effectiveness of active agents in the present compositions,
10 without untoward side effects, is unexpected.

11 As a result, many otherwise suitable active agents may be made therapeutically
12 effective by the addition of an osmotic agent to a composition containing an active
13 agent. For example, many active agents have been used to treat diseases or conditions
14 unsuccessfully. In some instances, they have been unsuccessful because the delivery
15 agent involves other tissues and systems (digestive, absorptive, vascular) that are not
16 affected by the disease or conditions, which is generally undesirable. Thus, the active
17 agents are made therapeutically effective with the addition of osmotic agent (tissue
18 healing, pain elimination, etc.) because other systems are not involved and it targets
19 the affected tissues, penetrating them directly.

20 It is thought that the beneficial effects and therapeutic effectiveness of many
21 active agents are enhanced by the addition of the osmotic agent apparently without
22 entering the deeper pharmacokinetic pathways, such as the vascular system, the gastro-
23 intestinal system, or the endocrine system. Therefore, treatment with the present
24 compositions does not involve healthy tissue and eliminates the possibility of side
25 effects, making each substance more effective as a disease fighter, without hazards
26 and side effects.

27 Suitable osmotic agents that may be used in the present compositions include
28 any agent that raises the osmotic pressure of fluid on one side of a membranous
29 structure and draws water across the membrane, causing the structure giving up the

1 water to shrink in volume. One preferred osmotic agent is dimethyl isosorbide (DMI).
2 While not wishing to be bound to any theory, it is thought that the methyl groups of
3 DMI make it more lipid soluble and increases its capability of being able to pass
4 through membranes in comparison to isosorbide, allowing DMI to cross barriers such
5 as skin or tissue membranes more easily and quickly, much like DMSO. DMI's ability
6 to penetrate barriers provides enhanced penetration and/or absorption of the active
7 agents to the targeted treatment site. Thus, DMI acts as a delivery vehicle for active
8 agents that might otherwise require injection, and this is accomplished without
9 involving other tissues or systems.

10 The possibilities are enormous as differing beneficial agents for varying
11 treatment regimes can be delivered into targeted sites attacking the problem directly.
12 DMI by virtue of its osmotic penetrating synergizing quality opens a direct route of
13 drug administration enabling targeted therapy that is non-invasive. It encourages
14 patient compliance, and is well tolerated. "Active agent," as used herein, means any
15 beneficial substance including medications, minerals, potassium compounds,
16 corticosteroid, antibiotics, antihistamines, anti-inflammatories, ansaids, nutrients,
17 chemotherapeutic agents, vitamins, and combinations thereof.

18 Suitable active agents that may be responsive to the synergistic effect of
19 osmotic agent include anti-inflammatories; dentifrices; desensitizing agents; pain
20 relievers; anti-fungal agents; topical anesthetics, e.g: benzocaine, tetracaine, benadryl,
21 etc.; moisturizers; humectants; anti-wrinkle or anti-aging preparations; skin pigment
22 removers; skin cleansers (colds creams); skin peels (e.g.. Alpha hydroxy, citric acids,
23 ascorbic acid, retinyl palmitate); antibacterials, e.g.: chlorhexadine, etc., for oral rinses
24 and dermatological usage. The may also be used to treat and prevent periodontal
25 disease being brought by the osmotic into the gingival tissues; sun tanning and
26 blocking preparations (e.g. PABA); sterilizing agents (e.g. alcohol); anti-itch
27 preparations (calamine lotion); topical antibiotics (e.g. Bacitracin, Neosporin);
28 nutrients; preparations that contain sunflower seed oil, nutrients and other agents (e.g.
29 mucopolysaccharides, wheat protein, wheat amino acids, yeast extract, cysteine,

1 methionine, glutamine, biotin, niacin, tocopherol, lineic acid, arachidonic acid, saw
2 palmetto extract, methyl nicotinate, ginseng extract, inositol, tetrasodium EDTA);
3 agents that improve hair health and growth; balms used to relieve muscle pain (e.g.
4 camphor, menthol, salicylate (menthol, trolamine), capsaicin); and, pain relieving
5 hemorrhoid preparations (e.g. Preparation-H), antihistamines, anesthetic agents,
6 chemotherapeutic agents, vitamins, corticosteroid, antibiotics, potassium compounds,
7 minerals, and other beneficial substances.

8 Thus, the present compositions containing osmotic agent and an active agent
9 have increased therapeutic effectiveness in comparison to compositions without the
10 osmotic agent.

11 Increasing the concentration of the osmotic agent in the electrolytic fluid
12 surrounding a cell increases the osmotic pressure of the electrolytic fluid surrounding
13 the cell. An increase in the osmotic pressure in the electrolytic fluid surrounding the
14 cell causes water to be drawn from the interior of the cell, resulting in a reduction in
15 cell volume (cell shrinkage).

16 In order to regain equilibrium, the cell must restore its lost volume. Potassium
17 ion influx is necessary to restore cell volume. Cell and membranous tissue shrinkage
18 provides a strong stimulus for the uptake of potassium across the cell membrane, into
19 the interior of the nerve cell, resulting in an increased concentration of potassium ions
20 in the electrolytic fluid contained in the cell.

21 In order to regain equilibrium, the potassium ions contained in the electrolytic
22 fluid contained in the interior of the cell will escape and cross the cell membrane into
23 the electrolytic fluid surrounding the cell. When this occurs, the electrical potential
24 across the cell membrane is increased, resulting in a potential that is more highly
25 negative than the resting threshold potential, typically on the order of about -110
26 millivolts. Because a nerve cell must be at its resting threshold potential in order to
27 form an action potential for the conduction of pain, the increased negative potential
28 (hyperpolarity) across the cell membrane prevents this from occurring. Moreover, the
29 potassium ions in the electrolytic fluid that surrounds the nerve cell slows the escape

1 of potassium ions from the electrolytic fluid contained within the cell, further delaying
2 the cell's return to its normal volume and normal resting threshold potential (-85 mvs.)
3 To conduct an impulse, the nerve must be at the normal resting threshold potential.
4 Thus, the nerve cannot conduct an impulse.

5 The compositions described above are administered in effective amounts. An
6 effective amount is a dosage of the composition sufficient to provide a medically
7 desirably result. The effective amount will vary with the particular condition being
8 treated, the age and physical condition of the subject being treated, the severity of the
9 condition, the duration of the treatment, the nature of the concurrent therapy (if any),
10 the specific route of administration and like factors within the knowledge and
11 expertise of the health practitioner. For example, an effective amount for treating
12 psoriasis would be an amount sufficient to slow or halt the development or further
13 progression of psoriatic lesions. It is preferred generally that a maximum dose be
14 used, that is, the highest safe dose according to sound medical judgment.

15 It is expected that the compositions may be applied in one or several
16 administrations per day, preferably topically. In the event that a response in the
17 subject is insufficient at the initial doses applied, higher doses (or effectively higher
18 doses by a different, more localized delivery route) may be employed to the extent that
19 patient tolerance permits. Multiple doses per day are contemplated to achieve
20 appropriate systemic levels of compounds.

21 When administered, the pharmaceutical preparations of the invention are
22 applied in pharmaceutically-acceptable amounts and in pharmaceutically-acceptably
23 compositions. Such preparations may routinely contain salt, buffering agents,
24 preservatives, compatible carriers, and optionally other therapeutic agents. When used
25 in medicine, the salts should be pharmaceutically acceptable, but non-
26 pharmaceutically acceptable salts may conveniently be used to prepare
27 pharmaceutically-acceptable salts thereof and are not excluded from the scope of the
28 invention. Such pharmacologically and pharmaceutically-acceptable salts include, but
29 are not limited to, those prepared from the following acids: hydrochloric,

1 hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, citric, formic,
2 malonic, succinic, and the like. Also, pharmaceutically-acceptable salts can be
3 prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or
4 calcium salts.

5 The compositions may be combined, optionally, with a pharmaceutically-
6 acceptable carrier. The term "pharmaceutically-acceptable carrier" as used herein
7 means one or more compatible solid or liquid filler, diluents or encapsulating
8 substances which are suitable for administration into a human or other animal. The
9 term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with
10 which the active agent is combined to facilitate the application. The components of
11 the osmotic agents and the active agents also are capable of being co-mingled with
12 such carriers, other additives, and with each other, in a manner such that there is no
13 interaction which would substantially impair the desired pharmaceutical efficacy.

14 The pharmaceutical compositions may contain suitable buffering agents,
15 including: acetic acid in a salt; citric acid in a salt; boric acid in a salt; and phosphoric
16 acid in a salt. The pharmaceutical compositions also may contain, optionally, suitable
17 preservatives, such as: benzalkonium chloride; chlorobutanol; parabens and
18 thimerosal. The compositions may also include a variety of other materials such
19 as solvents, surfactants, thickeners, colorants, flavorants, and the like.

20 A variety of administration routes are available. The particular mode selected
21 will depend of course, upon the particular active agent selected, the severity of the
22 condition being treated and the dosage required for therapeutic efficacy. The methods
23 of the invention, generally speaking, may be practiced using any mode of
24 administration that is medically acceptable, meaning any mode that produces effective
25 levels of the active agents without causing clinically unacceptable adverse effects.
26 According to one particular characteristic of the invention, these products are used for
27 the preparation of a pharmaceutical composition intended for local topical application,
28 and may be in any suitable form including liquids, pastes, creams, ointments, gels,
29 lotions, chewing gum, or any other form desired. The pharmaceutical composition

1 may also be in the form of a liquid, soft capsules, solution, or transdermal patches
2 containing the active agent. Such modes of administration include topical routes.

3 The pharmaceutical compositions may conveniently be presented in unit
4 dosage form and may be prepared by any of the methods well known in the art of
5 pharmacy. All methods may include the step of bringing the active agents and
6 osmotic agents into association with a carrier which constitutes one or more accessory
7 ingredients. In general, the compositions may be prepared by uniformly and
8 intimately bringing the active agents into association with a liquid carrier, a finely
9 divided solid carrier, or both, and then, if necessary, shaping the product.

10 Compositions suitable for oral administration may be presented as discrete
11 units, such as capsules, tablets, lozenges, each containing a predetermined amount of
12 the active agents. Other compositions include suspensions in aqueous liquids or non-
13 aqueous liquids such as a syrup, elixir or an emulsion.

14 Other delivery systems can include time-release, delayed release or sustained
15 release delivery systems. Such systems can avoid repeated administrations of the
16 active agents described above, increasing convenience to the subject and the
17 physician. Many types of release delivery systems are available and known to those
18 of ordinary skill in the art. They include polymer base systems such as poly(lactide-
19 glycolide), copolyoxalates, polycaprolactones, polyesteramides, polyorthoesters,
20 polyhydroxybutyric acid, and polyanhydrides. Microcapsules of the foregoing
21 polymers containing drugs are described in, for example, U.S. Patent 5,075,109.
22 Delivery systems also include non-polymer systems that are: lipids including sterols
23 such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono- di-
24 and tri- glycerides; hydrogel release systems; sylastic systems; peptide based systems;
25 wax coatings; compressed tablets using conventional binders and excipients; partially
26 fused implants; and the like.

27 Use of a long-term sustained release implant may be particularly suitable for
28 treatment of chronic conditions. Long-term release, as used herein, means that the
29 implant is constructed and arranged to deliver therapeutic levels of the active agent for

1 at least 30 days, and preferably 60 days. Long-term sustained release implants are
2 well-known to those of ordinary skill in the art and include some of the release
3 systems described above.

4 In some embodiments of the present composition, the active agent may be a
5 pain reliever or desensitizer. "Pain reliever," as used herein, means an active agent
6 that reduces or eliminates a subject's pain. "Desensitizer," as used herein, means an
7 active agent that reduces or eliminates a subject's sensitivity to a sensitizing agent or
8 to a sensitive area of the subject's body. One preferred composition includes
9 potassium ions, from potassium nitrate, as a pain reliever and/or a desensitizer.
10 Potassium ions from a potassium nitrate source are known to desensitize
11 hypersensitive teeth by nerve depolarization. Potassium nitrate travels through the
12 dentinal tubules and causes the pulpal nerves to depolarize by bathing them with
13 potassium ions. The relatively high concentration of potassium ions contained in the
14 electrolytic fluid surrounding the pulpal nerves changes the resting threshold potential
15 of the pulpal nerve from -85 millivolts to zero or a positive value and prevents
16 initiation of an action potential. This inhibits nerve conductance and pain emission,
17 and in this way it desensitizes hypersensitive teeth.

18 A composition containing an osmotic agent and potassium nitrate is able to
19 reduce the cell volume, increase the intercellular openings and increase the amount of
20 potassium ions that may be delivered to the pulpal nerve in comparison to a
21 composition without the osmotic agent.

22 The increased intercellular volume resulting from the osmotic agent allows the
23 composition including potassium nitrate to overcome the resistant factors of the
24 dentin/pulp barriers and to more rapidly reach the pulpal nerves, blood vessels, and
25 embryonic connection tissues. It overcomes the tubular constrictions, irregularities,
26 man-made tubular obliterations, dentinal sclerosis, odontoblast processes, fluid with
27 contained minerals and immunoglobulins, tubule contained bacteria, antibiotics, anti-
28 microbial agents, odontoblasts, odontoblast junctions (tight, intermediate, and gap),
29 and intercellular bridges that restrict and slow the penetration of potassium ions into

1 pulpal tissues. As the osmotic agent advances through the dentinal tubules, it
2 encounters the previously mentioned structures. Due to its osmotic qualities, the
3 osmotic agent opens intercellular spaces between cells as well as spaces through cells.
4 The intercellular bridges connecting cells (odontoblasts) serve as permeability barriers.

5 The present compositions can then flow through the bridge spaces, junctions,
6 and enlarged openings between the shrunken odontoblasts processes and odontoblasts,
7 enhancing the permeability of the dentin/pulp. The fluid containing the potassium
8 ions then flows more rapidly and easily through the newly created spaces to reach the
9 pulpal nerves and blood vessels.

10 In a similar manner, pulpal nerves lose water and shrink significantly due to
11 the increased osmotic pressure caused by the surrounding fluid containing potassium
12 nitrate and osmotic agent. When cells and membranous structures are caused to shrink
13 osmotically, potassium located outside the nerves' membrane, as well as potassium
14 from the high potassium gradient obtained from the potassium nitrate desensitizer,
15 flows into these nerve cells in quantity. Osmotic cell shrinkage is a strong stimulus
16 for the uptake of potassium. As the captured potassium leaves the inside of nerves,
17 it escapes, leaving a strongly negative hyperpolarized nerve that cannot form an action
18 potential. This dynamic process inhibits pain production and conduction.

19 Thus, desensitization of hypersensitive teeth may be accomplished by
20 simultaneously depolarizing and hyperpolarizing the pulpal nerves. The osmotic agent
21 DMI works with KNO_3 to disturb the functions of the nerve cell simultaneously
22 depolarizing and hyperpolarizing it. These agents antagonize the recovery process to
23 the resting potential. Potassium positioned on the outside of the nerve keeps it
24 depolarized. This slows the escape of the potassium held between the nerve's
25 membranes and makes it more difficult for the nerve to recover volume after
26 shrinking. A lot of potassium outside the nerve keeps the cell shrunken and the nerve
27 so shrunken, is not going to work well. This keeps the nerves inactive longer and
28 causes a faster, more complete, and longer lasting desensitization to take place than
29 potassium nitrate alone that bathes the outside of the pulpal nerves only.

1 An application of potassium nitrate/osmotic agent desensitizer continues to
2 desensitize for hours after its initial application because the composition
3 accomplishes desensitization without obliterating or diminishing the radii of the
4 dentinal tubules. The dentin/pulp circulation and mineral defense system remains
5 functionally intact, flowing, and even improved, which is important for the long term
6 health and longevity of the dentition. It may be helped by the nitrate ion, since nitrate
7 salts tend to increase circulation by being converted to nitric oxide. This is very
8 important for long term vitality and longevity of the dentition as the dentin/pulp's
9 afferent/efferent circulatory system is an extension of the pulp and its long term health
10 is dependent on its remaining functional and flowing. It serves to replenish the
11 dentin's mineral loss and as a barrier to combat the penetration of noxious substances
12 and bacteria as well as a warning system for untoward changes that could make the
13 pulp unhealthy. It may help also to accommodate for barometric and atmospheric
14 changes such as is seen with deep sea diving, or air and space travel.

15 It takes usually 2-4 weeks for the potassium ions to penetrate through the
16 structures described above, and into the pulp surrounding the nerves in sufficient
17 numbers to desensitize a hypersensitive tooth. The addition of osmotic agent to
18 compositions containing potassium increases the flow of potassium ions, nitrate ions,
19 and fluoride through the dentin, quickly reaching the pulp in sufficient quantities to
20 effect more complete, more rapid, and more lasting desensitization of supersensitive
21 teeth.

22 Suitable potassium containing compounds include any of the afore-mentioned
23 potassium containing compounds. Preferred potassium sources include potassium
24 nitrate, potassium acetate, potassium chloride, potassium citrate, potassium phosphate,
25 potassium carbonate. Potassium nitrate is especially preferred because it can penetrate
26 membranes readily, the nitrate yields nitric oxide, a blood vessel dilator, and it
27 clinically works well to desensitize teeth.

28 Potassium is also known to be useful to treat ulcerative lesions of an oral and
29 dermatologic nature. The present compositions containing potassium have been found

1 to reduce or eliminate the pain associated with ulcers, especially aphthous ulcers, as
2 well as herpes and Herpes Labialis. Some of the oral ulcerative lesions are acute
3 necrotizing ulcerative gingivitis (ANUG), bullous ulcers, aphthous and herpetic
4 lesions, traumatic ulcers, pemphigus, AIDS related ulcers, bullous Lichen Planus, oral
5 shingles and others. Many of these ulcers are oral manifestations of dermatologic
6 illnesses. Aphthous (Behcets), traumatic ulcers, Lichen Planus, Pemphigus, Lupus,
7 are some of these diseases. Another of these ulcerative oral ulcers are seen as a
8 sequelae to chemotherapy and radiation therapy. Shingles often exhibits dermatologic
9 ulcers.

10 In both labial herpes and shingles the potassium ion if it was to help this
11 condition would have to penetrate the skin and surround the involved nerve thus
12 changing the nerve's threshold potential from about -80 to -90 millivolts to a zero or
13 positive value. Potassium gels without dimethyl isosorbide are moderately helpful.
14 A potassium nitrate gel with DMI increases the amount and speed of penetration of
15 the ionic potassium. A high gradient of potassium is able to surround the nerves
16 (central nervous system nerves and automatic system nerves) changing the threshold
17 potential and preventing an action potential from taking place, and initiating pain
18 or/and failing to allow the automatic nerves to signal for an inflammatory response.
19 This makes the nerve unable to conduct an impulse thus eliminating the pain of these
20 disease entities and hastening healing. For the treatment of ulcers, viscous
21 preparations such as creams or gels are preferable because when applied liberally to
22 the ulcers, they remain on the lesions and continually feed potassium into them, which
23 reduces pain and hastens healing by reducing the inflammatory response. Suitable
24 potassium containing compounds include those previously mentioned.

25 In one embodiment of the present composition, the active agent may be a
26 topical corticosteroid. Topical corticosteroids may be absorbed from normal intact
27 skin. When combined with DMI, the absorption of topical corticosteroids by the
28 lesion is improved. As topical corticosteroids are absorbed through the skin, they
29 enter pharmacokinetic pathways similar to systemically administered corticosteroids.

1 Topical corticosteroids are generally used for the treatment of swelling, inflammation,
2 itching, and combinations thereof. Thus, topical corticosteroids are effective in the
3 treatment of corticosteroid-responsive dermatoses primarily because of the anti-
4 inflammatory, antipruritic and vasoconstrictive actions. Such symptoms may be
5 caused by any number of skin conditions including eczema, dermatitis, rashes, insect
6 bites, poison ivy, poison sumac, soaps, detergents, cosmetics, jewelry, Seborrheic
7 Dermatitis, psoriasis, external anal and genital itching.

8 The extent of percutaneous absorption of topical corticosteroids is determined
9 by many factors including the delivery vehicle, the integrity of the epidermal barrier,
10 and the use of occlusive dressings. Inflammation and/or other disease processes in the
11 skin may increase percutaneous absorption. Occlusive dressings substantially increase
12 the percutaneous absorption of topical corticosteroids. Examples of topical
13 corticosteroids include betamethasone, clobetasol, diisopropionate, dipropionate,
14 hydrocortisone, propionate, and combinations thereof.

15 A preferred composition includes the topical corticosteroid betamethasone an
16 active agent. The composition may be effective for treating, among other things,
17 psoriasis, as betamethasone is often used to reduce inflammation of the skin of
18 subjects with psoriasis. Psoriasis may be characterized by increased cell proliferation
19 and increased skin thickening. The skin of subjects with psoriasis acts as a barrier to
20 the absorption of corticosteroids and even percutaneous absorptive medications do not
21 have the ability to fully penetrate to and below the basal membranes to reduce or arrest
22 the proliferation and skin thickening seen in conditions such as psoriasis. The
23 addition of osmotic agent to corticosteroids (or vitamin D) used to treat psoriasis
24 enhances the absorption amount and penetration depth of the corticosteroid into the
25 very proliferative skin layers of the psoriatic skin lesions, increasing the anti-
26 inflammatory effect of the corticosteroid.

27 In another embodiment of the present composition, the active agent may be
28 an anti-inflammatory drug. The osmotic agent enhances the passage of various
29 molecules through the skin to the underlying tissues. One preferred embodiment of

1 a composition includes the non-steroidal anti-inflammatory drug (NSAID), and viox, and the like which is an effective oral therapy for pain and inflammatory conditions. Such topical compositions, viox, and others may provide distinct advantages compared to oral usage. Thus, arthritis and other painful, inflammatory conditions may be treated while eliminating many of the safety issues associated with the oral use.

2 In another embodiment of the present composition, the active agent may be an anti-viral substances such as acetosalicylic acid, which is commonly used for the removal of warts. Osmotic agent increases the penetration and absorption of the acetosalicylic acid into and through the wart(s) thickness increasing the effectiveness of the active agent. The composition improves the penetration of the acetosalicylic acid into the basal layers of the wart to achieve increased effectiveness and efficacy of the active agent. Thus, healing of the wart lesions take place more quickly and completely than the preparation containing only acetosalicylic acid as an active agent. The composition may be effective for the treatment of all types of warts.

3 Other embodiments of the present composition may include anti-fungal substances such as amorolfine, ciclopirox, oxiconazole, and nystatin which are typically used to treat fungal infections of the nail (onychomycoses), which can occur in, around, or under the nail plate. Such infections are common and are reported in 2% to 14% of the population, but the actual incidence is probably much higher. The microorganisms involved are usually molds such as trichophyton rubrum, or yeasts, such as candida. Clinical investigations have demonstrated that it is feasible to treat fungal infections of the nail through the topical delivery of these antifungal agents. However, onset of visible cure is slow, treatment is usually long-term, and re-infection often occurs. The lack of a rapid visible onset of cure is a major reason for lack of patient compliance during therapy. By combining such substances with osmotic agent, the rate and extent of delivery of the aforementioned active agents through the nail plate to the nail bed is increased. Thus, therapeutically effective

1 levels of the antifungal active agent within and below the nail are rapidly achieved,
2 increasing the onset of the visible cure of fungal infections of nails.

3 In another embodiment of the composition the active agent may be a caries
4 fighting substance. Most commercial dentifrices contain at least one caries fighting
5 substance. "Dentifrice," as used herein, means a powder, paste, gel, or liquid for
6 cleaning the teeth. Osmotic agent increases the penetration of caries fighting
7 substances into tooth matter (enamel and dentin). For example, osmotic agent
8 enhances the penetration of the fluoride ion into the tooth enamel and the 30,000 -
9 59,000/mm² dentinal tubules by with brushing with a dentifrice that contains fluoride
10 and osmotic agent. The resistance of enamel and dentin to fluoride penetration is
11 overcome and the fluoride ions penetrate in larger quantities and penetrate the tubular
12 system in greater numbers enhancing the ability of fluoride to be a caries (including
13 root caries) fighter. This is of major importance as fluoride is a major element
14 involved in caries prevention, and when its effectiveness is enhanced and improved
15 the battle against caries becomes more successful.

16 Suitable sources of fluoride include stannous fluoride, sodium fluoride, sodium
17 monofluorophosphate, potassium fluoride, and the like. However, any source of
18 fluoride may be used, as they all result in the release of fluoride ions into the saliva.

19 Potassium from any of the previously mentioned sources and fluoride from any
20 of the previously mentioned sources may be incorporated into chewing gums and
21 chewed to supply potassium ions for desensitizing/anesthetizing, as disclosed in U.S.
22 Patent Application No. 5,522,726, to treat ulcers, and to fight caries with fluoride ions
23 to the saliva and into tooth structure. Osmotic agent may also be combined with the
24 chewing gums to enhance the penetration of such substances into the ulcers and tooth
25 enamel and dentin (dentinal tubules), resulting in improved desensitization, protection
26 from caries, or both. Upon being chewed, such a chewing gum releases the
27 desensitizers directly into the saliva, allowing the active agents to enter the ulcers and
28 the dentinal tubules and pass into the pulp. Such chewing gums also release the caries
29 fighting substances directly into the saliva and then into tooth structure to prevent

1 tooth decay. This effectively increases the desensitizing effect of potassium and
2 allows the method of these ingredients being incorporated into chewing gum to be
3 very effective for fighting caries and treating dentinal hypersensitivity (pain from
4 thermal (hot, cold) chemical (sweet, sour, salt, acid etc.), and tactile (touch, brushing).

5 In another embodiment, the active agent may be a formulation for the
6 treatment of erectile dysfunction, such as alprostadil. In the present embodiment, the
7 composition is preferably formulated as a cream or ointment, and is applied locally on
8 the glans (the head) of the penis. Thus, the side effects of delivery by injection or
9 orally (e.g. with Viagra), such as heart attacks, possibly hitting a blood vessel during
10 injection, and hematoma may be avoided. This approach to the treatment of
11 impotence has important advantages.

12 Another embodiment involves the addition of an osmotic agent to a dental
13 cement, which are especially effective when used as a liner and/or pulp capping
14 material. Dental cements that have been found suitable include polycarboxylate, glass
15 ionomer, resin reinforced glass ionomer, zinc oxyphosphate, zinc, oxide-eugenol,
16 methacrylate, dimethacrylate, and composite. Dental cements including potassium
17 nitrate and an osmotic agent such as DMI prevented the untoward sequelae of pulpal
18 pressure atrophy from occurring and causing the pulp to be devitalized, necrotic and
19 abscessed by minimizing the pulpal inflammatory response. The present
20 compositions of dental cement allow the pulpal connective tissues to remain healthy
21 and to heal pulpal connective tissues in the same manner as do inflamed connective
22 tissues of other parts of the body. Uniquely, the present dental cement prevents or
23 relieves pulpal edema by inactivating the teeth's autonomic nerves, keeping them from
24 calling forth and maintaining pulpal inflammation, thereby preventing the build-up of
25 intrapulpal pressure and subsequent pulpal atrophy. The dental cement keeps the
26 dentinal pulpal/tubular circulation intact, flowing and healthy. Potassium nitrate in
27 a polycarboxalate cement alone is less predictable and less efficient as the present
28 dental cements which enhance the potassium penetration travel through the dentinal
29 tubules while the osmotic activity causes nerve cell shrinkage with a resultant negative

1 hyperpolarization of the pulpal and dentinal nerves. This places these nerves in a
2 depolarized/hyperpolarized state. In this way the potassium nitrate works predictably
3 faster and more profoundly as a tooth desensitizer, and the vitality of teeth is
4 maintained with KNO_3 /DMI in a superior manner than with KNO_3 alone, in teeth with
5 deep caries and/or nerve exposures. Vital nerve exposed pulpal connective tissues are
6 able to heal and do not require pulp extirpation and associated endodontic therapy, by
7 simply incorporating KNO_3 /DMI into dental cement and applying it as a liner or pulp
8 capping cement. Thus, the present dental cements are especially effective when used
9 as a liner and/or pulp capping material as it continues to release KNO_3 /DMI into tooth
10 structure over time.

11 Another embodiment involves the addition of an active agent and an osmotic
12 agent to dental bleaching products to prevent post-bleaching pain (hypersensitivity).
13 The present compositions are effective for preventing post bleaching pain while
14 maintaining the effectiveness of tooth bleaching. Normally, there is a high incidence of
15 severe or very severe post bleaching pain induced by peroxide bleaching preparations.
16 As the percentage used of peroxide is increased (say to 35%) the incidence of post
17 restoration pain is increased even more. The present bleaching compositions reduce
18 or eliminate post-bleaching pain. KNO_3 /DMI is a superior desensitizer and is much
19 more health promoting than when KNO_3 was used without DMI. The use of KNO_3
20 (without DMI) diminishes the incidence of post bleaching pain. Its effect is not as
21 predictably successful as when DMI is added to the KNO_3 . KNO_3 /DMI beneficial
22 qualities are reproducible and predictable.

23 The present invention will be further illustrated by the following examples,
24 which are intended to be illustrative in nature and are not to be considered as limiting
25 the scope of the invention.

26 WORKING EXAMPLES

The following examples were performed to evaluate the effectiveness of osmotic agents, (e.g., DMI) for enhancing the therapeutic effectiveness of a various active agents.

EXAMPLE 1

Two compositions were formed, one containing DMI, and betamethasone, and the other containing hydrocortisone and DMI About 20-50 drops of DMI was added to 35 grams of Diprolene cream (augmented betamethasone), which is a commercially available cream containing about 0.05% betamethasone as well as 1% hydrocortisone cream.

The composition was used by a subject with psoriatic lesions of a rather extensive nature on the left and right elbows, right dorsal metacarpal (knuckle), and legs and buttocks. The left elbow had multiple markedly raised, red, hyperkeratotic lesions ranging from a 4 inch area to one-half inches. The knuckle had a circular lesion of about one inch long by 1/2 inch wide.

The lesions were previously treated over a 30+ year period using Diprolene cream two to four times daily. The Diprolene cream did not heal the psoriatic lesions, but it did keep them from exacerbating out of control.

The composition was applied directly to the aforementioned-mentioned psoriatic lesions 3-4 times per day. Within a week, the psoriatic lesions began to shrink, flatten, and became less red and raised. The hyperkeratotic character lessened. The lesions began to regress, fade, and shrink and were about 45-60% healed within about one week.

Treatment was continued for about 30 days. After 30 days, the lesions were improved, being smaller and flatter, but they failed to completely disappear.

EXAMPLE 2

A composition for the treatment of pain was formed.

About 1-60 drops of osmotic agent were added to a commercial preparation containing 1% hydrocortisone. A male subject having an exquisitely painful ankle applied the composition directly to his ankle. The subject suffered from fasciitis and felt pain when walking.

Within five minutes after application of the composition, the subject's pain was reduced by about 80%. The subject was able to touch his ankle without as much pain and was able to walk with better vigor.

The DMI apparently synergized the hydrocortisone to penetrate to the source of the pain and diminished the pain by its anti-inflammatory action. The DMI enhanced the penetration of hydrocortisone into the affected areas, which could not be fully penetrated by the surface cortisone without DMI.

EXAMPLE 3

A mixture of an osmotic agent and the topical corticosteroid betamethasone was prepared.

A patient having classically damaged nails from a fungal infection applied the composition directly to the nails and nail beds 4 times per day for a period of four months.

At the end of the four month period, the classically damaged nails were moderately improved, but the nails were not replaced with healthy new nails.

EXAMPLE 4

A composition for the treatment of warts was formed.

DMI was combined with a commercial preparation containing acetosalicylic acid which was used to treat warts (plantar, palmar, and other dermatological warts).

The resulting composition is shown below in Table 1.

TABLE 1

Function	Compound	Wt %
Active Agent	Salicylic acid	17.0

Osmotic Agent	DMI	3.0
	alcohol	
	camphor	
	castor oil	
	colloidon 63/6 ether	
	ethylcellulose	
	hypophosphorous acid	
	menthol	
	Polporbate 80	

The composition increased the absorption and penetration of the acetosalicylic acid into the wart lesions, providing faster removal.

EXAMPLE 5

A composition for the treatment of Herpes virus was formed by adding about 35-50 drops of osmotic agent to a gel preparation containing about 30 grams of potassium nitrate, about 17 grams of hydroxyethylcellulose, and about 28.35 grams of water.

EXAMPLE 5A

Several subjects with Herpetic lip lesions applied the composition directly to the lesions three to four times per day. Herpetic lip lesions usually require about two to four weeks to heal.

The pain associated with the lesions was quickly alleviated, and pain relief remained for several hours without the need for a second application. Subjects were able to eat and speak comfortably. In all cases treated healing was reduced to about one week. In several cases when the subjects felt the lesions developing and immediately applied the gel, the lesions failed to form.

1 Thus, the composition provided good to excellent comfort and reduced healing
2 time to at least one half the usual healing time.

3

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EXAMPLE 5B

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Several subjects with shingles applied the composition directly to the Shingles lesions. Shingles is a condition which follows a single nerve. Shingles is usually a protracted and difficult to heal disease characterized by very painful lesions.

The subjects experienced good to excellent pain relief from the lesions when the composition was applied three to four to five times per day. In addition, healing of the lesions was hastened.

EXAMPLE 6

A commercially available dentifrice was combined with DMI to provide the following composition:

TABLE 2

Material	Wt %
Glycerine	12.55
Sodium Carboxymethyl Cellulose	0.92
Xantham Gum	0.38
Sodium Saccharin	0.23
Methylparaben	0.06
Propylparaben	0.02
Sorbitol Solution (70%w/v)	9.00
Potassium Nitrate	5.00
Sodium Laurel Sulfate	2.10
Colloidal Silica	1.00
Calcium Carbonate	30.00
Flavoring	1.35
Sodium Monflouroposphate	0.81
DMI	2-50 drops/ounce

I used this formula with six patients with 10 moderate to severe hypersensitive teeth. I applied it to the hypersensitive teeth in the office and gave some to the patients to apply at home. Two patients with 3 teeth had immediate relief as a result of the office application. The other four patients with 7 hypersensitive teeth brushed their teeth three times per day for at least a minute for each brushing, and the teeth all returned to normal within two to four days. All six patients (10 teeth) remained free of pain for three months of the study.

EXAMPLE 7

A composition for the treatment of hypersensitive teeth, ulcers (oral and dermatologic), and herpetic lesions was formed as shown below in Table 4.

TABLE 3

Function	Compound	Wt %
Base Gel	Glycerol	60% - 75% by wt.
Active Agent	potassium (from potassium nitrate)	from 1/2% wt % to about 35 wt % (Saturation)
Osmotic Agent	DMI	1/2% - 40% by wt.

EXAMPLE 8

Several compositions for the treatment of oral and dermatological ulcers were formed. The active agents were various potassium compounds, which have been found effective sources of potassium for the treatment of oral and dermatological ulcers. The concentrations of the various ingredients may be adjusted with commensurate adjustment of water to attain the desired percentage of these ingredients.

EXAMPLE 8A

A composition for the treatment of oral and dermatological ulcers was formed as shown below in Table 5. The active agent was potassium nitrate, from a potassium nitrate source.

TABLE 4

Function	Compound	Wt %
Solvent	Water	86.5
Active Agent	Potassium, from potassium nitrate	11.5
Osmotic Agent	DMI	1/2% - 40% by wt.
Thickener	Hydroxyethyl cellulose	1.8
Colorant		1.0

EXAMPLE 8B

A composition for the treatment of oral and dermatological ulcers was formed as shown below in Table 6. The active agent was potassium, from a potassium chloride source.

TABLE 5

Function	Compound	Wt %
Solvent	Water	77.2
Active Agent	potassium, from potassium chloride	21.0
Osmotic Agent	DMI	0.5 - 40
Thickener	Hydroxyethyl cellulose	1.8
Colorant		0.1-0.2

EXAMPLE 8C

A composition for the treatment of oral and dermatological ulcers was formed as shown below in Table 7. The active agent was potassium, from a potassium acetate source.

TABLE 6

Function	Compound	Wt %
Solvent	Water	30.4
Active Agent	Potassium acetate	11.5
Osmotic Agent	DMI	0.5 - 35
Thickener	Hydroxyethyl cellulose	0.1-0.2
Colorant		0.1-0.2

The potassium acetate can be altered from 1/2% to saturation in the same manner as with DMI and water.

EXAMPLE 8C

A composition for the treatment of oral and dermatological ulcers was formed as shown below in Table 8. The active agent was potassium, from a potassium acetate source.

TABLE 7

Function	Compound	Wt %
Solvent	Water	30.3
Source of Potassium	Potassium acetate	67.3
Osmotic Agent	DMI	0.5 - 50
Thickener	Hydroxyethyl cellulose	1.8
Colorant		0.1-0.2
	Titanium Dioxide	0.6

EXAMPLE 9C

A composition for the treatment of oral and dermatological ulcers was formed as shown below in Table 8. The active agent was potassium, from a potassium acetate source.

TABLE 8

Function	Compound	Wt %
Solvent	Water	30.3
Source of Active Agent	Potassium acetate	67.3
Osmotic Agent	DMI	0.5 - 50
Thickener	Hydroxyethyl cellulose	1.8
Colorant		0.1-0.2
	Titanium Dioxide	0.6
Thickener	Methyl Cellulose	

EXAMPLE 10

A chewing gum for the prevention of caries and/or the desensitization of sensitive teeth was formed as shown below in Table 9.

TABLE 9

Function	Material
Base	Gum Base
Active Agent	Desensitizer, any source of Potassium
Sweetener	Sugar, Aspartame, Saccharin
Flavoring	Any
Caries Fighter	Fluoride
Osmotic Agent	DMI

EXAMPLE 11

Several compositions for the treatment of tooth sensitivity were prepared by adding from one (1) to forty (40) drops of osmotic agent to a variety commercially available dentifrices, per ounce of dentifrice, as shown below in Table 10. The dentifrice and DMI were mixed thoroughly. Each dentifrice contained at least 5% potassium nitrate, as well as various amounts of humectants, surfactants, fluorides, abrasives, and/or binders. The osmotic agent combined well with the ingredients used in commercially sold dentifrices.

TABLE 10

Dentifrice	DMI
Sensodyne	1-40 drops
Aquafresh Sensitive	1-40 drops
Crest Sensitive	1-40 drops
Oral B Sensitive	1-40 drops
Butler Sensitive	1-40 drops

1 teeth had notable pain reduction with an office gel application (going from severe pain
2 to slight pain), and with two self applications of gel during the same day, the teeth
3 became normal. All of the 19 patients (55 hypersensitive teeth) were normal
4 within 2 - 4 days of treatment. The gel and toothpaste appeared to be equally effective
5 with the patients all experiencing rapid (even immediate in some cases) pain relief
6 from their hypersensitive teeth. The resultant comfort was profound, complete, more
7 rapid, and lasting than with the use of 5% potassium nitrate dentifrices or gels without
8 DMI.

9 DMI overcomes the resistance factors of dentin/pulp by enhancing potassium
10 ion penetration through the dentin/pulp barriers. Genuine patient comfort was
11 achieved, often within a couple of days and in all instances by four days of
12 desensitizer usage. The patients were given only two ounces of dentifrice or gel, and
13 they reported no recurrences in up to three months follow-up. No untoward or
14 deleterious reactions were seen in the oral tissues or the teeth. There were no visible
15 red or white lesions, irritations, ulcerations, or constitutional effects observed or
16 reported. Its effectiveness, amazingly, increases between applications of the
17 desensitizing dentifrice or gel, as it continues to more profoundly desensitize the teeth
18 hours after its application to the teeth, which is very important for the health and
19 longevity of the dentition. DMI increases the efficiency and therapeutic effectiveness
20 of potassium while allowing the tooth with its pulp and extended dentinal tubular
21 circulatory defense system to remain intact and fully functional, which may allow the
22 continued return to normalcy between the applications of the desensitizing dentifrice
23 or gel.

24 DMI/ KNO_3 desensitizes hypersensitive teeth more efficaciously than KNO_3
25 alone. DMI readily penetrates the dentinal tubule orifices and travels rapidly through
26 the pulpal tissues. DMI enhances KNO_3 's effectiveness, causing it to work by a
27 different mode of action than occurs when used alone. KNO_3 used in a desensitizing
28 dentifrice or other preparation without DMI also travels through the dentinal tubules,
29 but at a slower rate. It causes the pulpal nerves to depolarize by bathing them with

1 potassium ions. It changes the minus 85 millivolt resting threshold potential to a zero
2 or a positive value preventing an action potential from forming. This inhibits nerve
3 conductance and pain emission. In this way it desensitizes hypersensitive teeth.

4 The addition of DMI to KNO_3 dynamically potentiates the desensitizing effects
5 of KNO_3 due to its strong osmotic qualities. As it travels towards the pulp via the
6 dentinal tubule conduit it overcomes the resistant factors of the dentin/pulp barriers.
7 DMI helps KNO_3 to more rapidly reach the all important pulpal nerves, blood vessels
8 and embryonic connective tissues. It overcomes the tubular constrictions,
9 irregularities, man-made tubular obliterations, dentinal sclerosis, odontoblast
10 processes, fluid with contained minerals and immunoglobulins, tubule contained
11 bacteria, antibiotics, antimicrobial agents, odontoblasts, odontoblast junctions (tight,
12 intermediate and gap), and intercellular bridges that join cells. These structures
13 restrict and slow the penetration of potassium into pulpal tissues. As DMI/ KNO_3
14 advances through the dentinal tubules it encounters the structures cited. Due to DMI's
15 osmotic properties, it opens intercellular spaces between cells as well as space through
16 cells. The intercellular bridges connecting cells (such as odontoblasts) serve as
17 permeability barriers. DMI raises the osmotic pressure of fluid surrounding cells and
18 other membranous structures shrinking them in size. The fluid containing KNO_3 /DMI
19 flows through the widened bridge spaces, junctions, and enlarged openings between
20 the shrunken osteoblasts processes and osteoblasts enhancing and enabling potassium
21 dentin/pulp permeability. The KNO_3 /DMI fluid flows more rapidly and easily
22 through these newly created spaces to reach pulpal nerves and blood vessels. In the
23 same way as described pulpal nerves lose water and shrink significantly due to the
24 increased osmotic pressure caused by the surrounding solution. When cells and
25 membranous structures are caused to shrink osmotically by DMI, potassium located
26 outside the nerve's membrane, as well as potassium from the high potassium gradient
27 obtained from the KNO_3 /osmotic agent desensitizer, flows rapidly into these nerve
28 cells in quantity. Osmotic cell shrinkage is a strong stimulus for the uptake of
29 potassium. As the captured cellular potassium leaves the inside of nerves it escapes

1 leaving strongly negative hyperpolarized nerves that can not form an action potential.
2 This dynamic process inhibits pain production and nerve conduction. Desensitization
3 of hypersensitive teeth is accomplished in this way. It takes place faster, more
4 completely and lasts longer than with just the use of KNO_3 to bathe teeth. This is due
5 to the way DMI works osmotically. The teeth desensitize faster than with KNO_3 alone
6 as the KNO_3 /DMI penetrate through the dentinal tubules at a more rapid rate for the
7 reasons described. However, a major reason for the increased speed of tooth
8 desensitization is that hyperpolarization is a result of DMI's osmotic ability to cause
9 cell shrinkage. It takes place immediately while KNO_3 depolarizes the nerve and this
10 takes longer to accomplish. The reason for this is that water moves faster than
11 potassium. KNO_3 /DMI accomplishes desensitization without obliterating or
12 diminishing the radius of the dentinal tubules. The dentin/pulp circulation and natural
13 dentin and pulp defense system remains functionally intact, flowing, and even
14 improved. It may be helped by the nitrate ion, since nitrate salts tend to increase
15 circulation by being converted to nitric oxide. This is very important for long term
16 vitality and longevity of the dentition as the dentin/pulp's afferent/efferent circulatory
17 system is an extension of the pulp and its long term health is dependant on its
18 remaining functional and flowing. It serves to replenish mineral loss and as a barrier
19 to combat the penetration of noxious substances and bacteria as well as a warning
20 system for untoward changes that could make the pulp unhealthy. It may help also
21 to accommodate for barometric and atmospheric changes such as is seen with deep sea
22 diving, or air and space travel.

23 The osmotic agent DMI works with the active agent to disturb the functions
24 of the nerve cell simultaneously depolarizing and hyperpolarizing it. These agents
25 antagonize the recovery process to the resting potential. Potassium positioned on the
26 outside of the nerve keeps it depolarized. This slows the escape of the potassium held
27 within the nerve's membrane and makes it more difficult for the nerve to recover
28 volume after shrinking. A lot of potassium outside the nerve keeps the cell shrunken,
29 and if the nerve is shrunken, it is not going to work well. This keeps the nerves

1 inactive longer. Desensitization of hypersensitive teeth by the combinations of DMI
2 and potassium nitrate is more effective and efficient than when KNO_3 is used alone.
3 They work to desensitize hypersensitive teeth at a higher, quicker, more profound and
4 lasting level.

6 EXAMPLE 13

7 A composition for the treatment of calluses and rough skin was formed by
8 combining osmotic agent and petroleum jelly. The composition was applied to
9 calluses on sole and heel areas of the feet of a subject that had existed for many years.
10 The composition was applied twice daily. White socks were placed on the feet of the
11 subject after applying the composition at night. An immediate improvement was seen.
12 The callus had markedly diminished and softened and an obvious improvement
13 occurred. The more the composition was applied, the more the calluses were reduced
14 and the smoother and softer the feet became. The soft calluses were also more easily
15 trimmed once they had softened. The composition was surprisingly effective for areas
16 of hyperkeratosis (calluses) on the hands and feet or other frictional surfaces. The
17 DMI enhanced the beneficial effects of petroleum jelly by enhancing its penetration
18 within the deeper skin layers.

20 EXAMPLE 14

21 A composition of DMI and Calcipotriene (a synthetic Vitamin D_3 derivative)
22 was formed. Calcipotriene is contained in Dovonex, which is an ointment for topical
23 dermatological use. The composition was formed by dissolving the DMI in
24 petrolatum, followed by adding Dovonex ointment to the DMI/Dovonex mixture.
25 DMI does not directly dissolve in Dovonex. DMI remains in solution with Dovonex
26 when mixed in this manner.

27 Chemically, Calcipotriene is (5Z, 7E, 22E, 24S)-24 cyclopropyl-9, 10-
28 secochola-5, 7 (19) 22 tetraene 1X, 3B, 24 triol with the empirical formula $\text{C}_{27}\text{H}_{40}\text{O}_3$,

1 and a molecular weight of 412.6. Calcipotriene is a white or off-white crystalline
2 substance.

3 Dovonex contains Calcipotriene 50 mg/g in an ointment base of dibasic
4 sodium phosphate, edate disodium, mineral glycerin, oil, petrolatum, propylene
5 glycol, tocopherol, and water.

6 In humans, the natural supply of Vitamin D depends mainly on exposure to the
7 ultraviolet rays of the sun for conversion of 7-dehydrocholesterol to Vitamin D
8 (cholecalciferol) in the skin. Calcipotriene is a synthetic analog of Vitamin D₃.
9 Clinical studies with radiolabeled Calcipotriene ointment indicate that
10 approximately 6% of the applied dose of Calcipotriene is absorbed systemically when
11 the ointment is applied topically to psoriasis plaques or 5% active when applied to
12 normal skin, and much of the absorbed active is converted to inactive metabolites
13 within 24 hours of application.

14 Vitamin D and the metabolites are transported in the blood, bound to specific
15 plasma proteins. The active form of the vitamin, 1, 25-dihydroxy vitamin D₃ (calcitrol)
16 is known to be recycled via the liver and excreted in the bile. Calcipotriene
17 metabolism following systemic uptake is rapid and occurs via a similar pathway to the
18 natural hormone.

19 Adequate and well controlled trials of patients treated with Dovonex ointment
20 (twice daily) have demonstrated improvement usually beginning after two weeks of
21 therapy. This improvement continued with approximately 50% of patients showing
22 at least marked improvement in the signs and symptoms of psoriasis after eight weeks
23 of therapy, but only approximately 4% showed complete clearing.

24 Although the precise mechanism of Calcipotriene's anti-psoriatic action is not
25 understood, in vitro evidence suggest that Calcipotriene is roughly equipotent to the
26 natural vitamin in its effects on proliferation and differentiation of a variety of cell
27 types. Calcipotriene has also been shown in animal studies to be 100 to 200 times less
28 potent in its effects on calcium utilization than the natural hormones.

1 Clinical studies with radiolabeled Calcipotriene solution indicate that less
2 than 1% of the applied dose of Calcipotriene is absorbed through the scalp when the
3 solution (2.0 ml) is applied topically to normal skin or psoriasis plaques (160 cm²)
4 for 12 hours and that much of the absorbed Calcipotriene is converted to inactive
5 metabolites within 24 hours of application.

6 DMI, when added to Dovonex, enhances the beneficial effects of
7 Calcipotriene, apparently increasing the absorption into and below the psoriasis
8 plaques, causing them to start to soften and flatten overnight. By applying the
9 DMI/Dovonex ointment twice a day, they continue to disappear. Within a week, the
10 lesions are almost cleared; and with continued applications of the DMI/Dovonex
11 ointment b.i.d. for a second week, or third week, complete clearing of the psoriasis
12 plaques usually takes place with the skin appearing normal. The DMI enhances the
13 Dovonex, causing this commercial preparation (prescription) to become an effective
14 treatment for clearing psoriasis plaques.

15 The DMI/Dovonex composition was used on a male subject with seven
16 psoriatic areas on his body which were calcitrant to all topical medications, including
17 Dovonex, for 35 years. Using DMI/Dovonex b.i.d., in two weeks all seven areas were
18 clear of psoriasis plaques. DMI/Calcipotriene in a vehicle (Dovonex) apparently
19 inhibited undesirable proliferation of certain cells and abnormal cell differentiation far
20 better than with Calcipotriene alone.

21 The composition was also applied to the male subject's psoriatic nails. It takes
22 time for nails to grow, but the results (improvement) have been remarkable so far.
23 In ten days of b.i.d. application of Dovonex/DMI gel application, the subject's nails
24 have shown remarkable improvement.

25 EXAMPLE 15

26 A dental cement was formed using 2% KNO₃ with 10 drops of DMI added to
27 20 gms of polycarboxylate liquid. The cement was used as a liner in 28 deep
28 multisurface cavities, with 1mm or less of dentin covering the pulp. This potassium/
29

1 polycarboxylate cement was also used with 12 carious exposed teeth as a pulp-capping
2 agent. The exposures ranged from pinpoint to two mms in size. The exposures were
3 capped with a thin layer of KNO_3 /DMI polycarboxylate cement and allowed to
4 harden. The teeth were then restored with either large amalgams or composite
5 restorations. In the case of composites, the hardened polycarboxylate liners and teeth
6 were etched with 37% phosphoric acid gel and restored with light bond composite.
7 There were no untoward sequelae with any of the 28 deep carious teeth or the 12 pulp
8 capped exposures. There were no failures clinically or by x-ray. In no case was post
9 restoration pain, swelling or infection encountered. No systemic complications were
10 observed or reported. Six-month post restoration x-rays were taken and no periapical
11 pathology was observed.

12 Twelve (12) volunteer patients, each with one deep carious lesion (1mm or less
13 of dentin overlying the pulp) had KNO_3 /polycarboxylate cement liners, which were
14 restored with either amalgam or light bond composite restorations. Ten volunteer
15 patients each with one pulp exposure which ranged from pinpoint to 1 ½ mm in
16 diameter were capped with KNO_3 /Polycarboxylate cement. When hardened, the teeth
17 were restored with amalgam or composite. The deeply carious and pulp exposed teeth
18 restorations usually involved multiple surfaces. Polycarboxylate (with KNO_3 /DMI)
19 is especially applicable as it readily and steadily releases potassium ions into the
20 dentinal tubules and pulpal tissues. It has a very thin film thickness and it bonds
21 firmly to tooth structure. For this reason, the lining and pulp capping cements remain
22 where placed, strong and capable of resisting the overlying pressure of the restoration
23 without cracking or breaking up. When composites are used to restore teeth,
24 polycarboxylate cement can be safely etched with 37% phosphoric acid.

25 Twenty-eight (28) teeth (28 cavities) with deep caries that were lined with
26 KNO_3 /DMI/Polycarboxylate liners exhibited no untoward sequelae. They were
27 completely free of post-restoration pain and the six month post-operative x-ray
28 examination showed no evidence of periapical pathology. There was no swelling or
29 sensitivity to percussion or other untoward sequelae observed or reported. The 12

1 patients with 12 pulp exposures capped with KNO₃/DMI/Polycarboxylate cement
2 were remarkably totally asymptotic and free of pain clinically. None of the pulp
3 capped or deeply carious teeth had pain from hot, cold, touch, sweet, or sour. In none
4 of the cases was there sensitivity to percussion or was swelling or infection
5 encountered. Six month post-operative x-ray examination revealed no periapical
6 pathology.

7 Twelve (12) teeth (12 cavities) with deep caries lined with
8 KNO₃/Polycarboxayate (no DMI) cement, six teeth were either free of pain or had
9 very slight pain for 1-3 days. Four teeth exhibited moderate post-restoration pain
10 for 7-14 days, and two teeth had persistent intermittent lingering pain of a spontaneous
11 nature along with cold sensitivity. Three month post-operative evaluation revealed
12 that pulp extirpation and root canal therapy was indicated.

13 With the 10 pulp capping patients using KNO₃/Polycarboxylate cement, 6 of
14 all the pulp exposed teeth were asymptotic for the 6 months of this study and four
15 teeth exhibited periapical pathology and clinical symptomology of pain with
16 percussion, spontaneous pain, pain to heat, and in some cases swelling. These four
17 teeth had pulp extirpation and root canal therapy by 3 months post restoration of the
18 teeth.

19 All pulp exposed teeth capped with KNO₃/DMI/Polycarboxylate cement
20 remained asymptomatic and appeared healthy clinically free of pain and periapical
21 pathology by x-ray examination for the six months of this study.

22

23 EXAMPLE 17

24 With the advent of the more popular use of composite restorations instead of
25 amalgam alloys, there has been a significant rise in post composite restoration pain
26 (hypersensitivity). This is due partly to the need to etch enamel and dentin with 37%
27 phosphoric acid (or other acid). However, the composite itself sometimes contributes
28 to causing post restoration pain.

The use of a thin liner of KNO_3 /DMI/Polycarboxylate or other cement eliminates most of the post restoration pain. Thus, a KNO_3 /DMI liquid was mixed with the composite (light bond) and performed 50 restorations. 25 were done with a KNO_3 /DMI/polycarboxylate lining and 25 were inserted without a base. The restorations were performed on volunteer patients and they were 50% anterior and 50% posterior restorations of both upper and lower jaws. In both cases, with and without KNO_3 /DMI/Polycarboxylate lining there was no post restoration pain, indicating that the KNO_3 /DMI in the cement lining and in the composite were both contributing to keep the teeth from becoming hypersensitive post restoration. KNO_3 /DMI tends to promote pulpal health. As with the KNO_3 cement and KNO_3 teeth bleaching agents, KNO_3 helps to minimize the post treatment pain. It is known that composite restorations with KNO_3 helps in this regard, but its success in preventing post restoration pain is not absolute and is not routinely effective, which is not so for KNO_3 /DMI/ Composite. In all cases where KNO_3 /DMI was incorporated into composite it completely, predictably, and routinely eliminated the post restoration pain seen with composites. It did this even without a liner of KNO_3 /DMI/Polycarboxylate cement being in place. KNO_3 /DMI composite is significantly superior to KNO_3 composite for restorations.

20 EXAMPLE 18

The same principles and modes of action are involved with KNO_3/DMI when it is incorporated into peroxide (carbamide peroxide) tooth bleaching products to prevent post-bleaching pain (hypersensitivity). I tested 5% KNO_3/DMI in the Confidential bleach (10% carbamide peroxide) in 13 patients and it prevented post bleaching pain from occurring in all cases while tooth bleaching effectiveness was maintained. A custom tray was 1/3 filled with the KNO_3/DMI 10% carbamide peroxide bleach, and worn by the patients for 1 hour per day for 10 days. There was no x-ray or clinically observable damage to the pulps, and bleaching was effective.

1 As a control 5% KNO₃ (without DMI) was added to bleach and given to and
2 used by 13 patients. The bleach contained 10% carbamide peroxide and glycerin.
3 Seven patients exhibited moderate post bleaching pain that lasted for 1-3 weeks and
4 then disappeared and became normal. Four patients had severe post bleaching pain,
5 which gradually subsided over a 3-month period by the use of a 5% KNO₃
6 desensitizing dentrifice. Two patients did not have post bleaching pain.

7 5% KNO₃ was added to the bleach and 25 drops of DMI was added to each
8 ounce of bleach. Each patient was given a soft custom tray made on the omnivac
9 vacuum machine and told to fill the tray 1/3 with bleach. They kept the KNO₃/DMI
10 bleach in the tray and over the teeth for 1 hour each day for two weeks. The teeth
11 were void of pain and felt normal with all 12 patients. The use of KNO₃ (without
12 DMI) diminishes the incidence of post bleaching pain. Its effect is not as predictably
13 successful as when DMI is added to the KNO₃. KNO₃/DMI beneficial qualities are
14 reproducible and predictable.

15 Although particular embodiments of the invention have been described in
16 detail for purposes of illustration, various changes and modifications may be made
17 without departing from the scope and spirit of the invention. All combinations and
18 permutations of the compositions and methods are available for practice in various
19 applications as the need arises. For example, the compositions and methods of the
20 invention may be applied to processes that are presently not practically feasible.
21 Accordingly, the invention is not to be limited except as by the appended claims.

CLAIMS

What is claimed is:

1 1. A method of decreasing the volume of a cell having a membrane and
2 an electrical potential across the membrane that is substantially equal to a resting
3 threshold potential, comprising the step of:

4 topically applying a composition containing an osmotic agent;
5 increasing the electrical potential across the cell membrane to a level greater
6 than the resting threshold potential; and
7 decreasing the electrical potential across the cell membrane to a level less than
8 the resting threshold potential.

1 2. The method of claim 1, wherein the composition further includes an
2 active agent.

1 3. The method of claim 2, wherein the osmotic agent is dimethyl
2 isosorbide.

1 4. The method of claim 3, wherein the active agent is an anti-
2 inflammatory compound.

1 5. The method of claim 3, wherein the active agent is a desensitizing
2 agent.

1 6. The method of claim 3, wherein the active agent is a caries fighting
2 substance.

1 7. The method of claim 3, wherein the active agent is a pain reliever.

- 1 8. The method of claim 3, wherein the active agent is a skin treatment.
- 1 9. The method of claim 1, wherein the active agent is calcipotriene.
- 1 10. The method of claim 4, wherein the anti-inflammatory agent is a
2 topical corticosteroid.
- 1 11. The method of claim 10, wherein the topical corticosteroid is selected
2 from the group consisting of clobetasol, propionate, hydrocortisone, betamethasone,
3 dipropionate, and combinations thereof.
- 1 12. The method of claim 11, wherein the topical corticosteroid is
2 betamethasone.
- 1 13. The method of claim 5, wherein the desensitizing agent is a source of
2 potassium.
- 1 14. The method of claim 13, wherein the source of potassium is selected
2 from the group consisting of potassium bicarbonate, potassium biphthalate, potassium
3 bromide, potassium acetate, potassium chloride, potassium phosphate, potassium
4 carbonate, potassium chromate, potassium dichromate, potassium sulfate, potassium
5 chromium sulfate, potassium thiocyanate, potassium bitartrate, potassium alum,
6 potassium bromate, potassium fluoride, potassium hydrogen sulfate, potassium iodate,
7 potassium tartrate, and combinations thereof.
- 1 15. The method of claim 14, wherein the source of potassium is potassium
2 nitrate.

1 16. The method of claim 6, wherein the caries fighting substance is
2 selected from the group consisting of potassium, fluoride, and combinations thereof.

1 17. The method of claim 16, wherein the caries fighting substance is
2 fluoride.

1 18. The method of claim 7, wherein the pain reliever is selected from the
2 group consisting of viox, ibuprofen, acetaminophen, and combinations thereof.

1 19. The method of claim 8, wherein the skin treatment is selected from the
2 group consisting of a moisturizer, a humectant, an exfoliant, and combinations thereof.

1 20. The method of claim 1, wherein the membrane is the membrane of a
2 nerve cell.

1 21. The method of claim 1, wherein the membrane is the membrane of a
2 tumor cell.

1 22. A therapeutic composition, comprising:
2 dimethyl isosorbide; and
3 an active agent.

1 23. The therapeutic composition of claim 22, wherein the active agent is
2 an anti-inflammatory compound.

1 24. The therapeutic composition of claim 22, wherein the active agent is
2 a desensitizing agent.

1 25. The therapeutic composition of claim 22, wherein the active agent is
2 a caries fighting substance.

1 26. The therapeutic composition of claim 22, wherein the active agent is
2 a pain reliever.

1 27. The therapeutic composition of claim 22, wherein the active agent is
2 a skin treatment.

1 28. The therapeutic composition of claim 23, wherein the anti-
2 inflammatory agent is a topical corticosteroid.

1 29. The therapeutic composition of claim 28, wherein the topical
2 corticosteroid is selected from the group consisting of clobetasol, propionate,
3 hydrocortisone, betamethasone, dipropionate, and combinations thereof.

1 30. The therapeutic composition of claim 29, wherein the topical
2 corticosteroid is betamethasone.

1 31. The therapeutic composition of claim 24, wherein the desensitizing
2 agent is a source of potassium.

1 32. The therapeutic composition of claim 31, wherein the source of
2 potassium is selected from the group consisting of potassium bicarbonate, potassium
3 biphthalate, potassium acetate, potassium carbonate, potassium chloride, potassium
4 phosphate, potassium bromide, potassium chromate, potassium dichromate, potassium
5 sulfate, potassium chromium sulfate, potassium thiocyanate, potassium bitartrate,
6 potassium alum, potassium bromate, potassium fluoride, potassium hydrogen sulfate,
7 potassium iodate, potassium tartrate, and combinations thereof.

1 33. The therapeutic composition of claim 32, wherein the source of
2 potassium is potassium nitrate.

1 34. The therapeutic composition of claim 25, wherein the caries fighting
2 substance is selected from the group consisting of potassium, fluoride, and
3 combinations thereof.

1 35. The therapeutic composition of claim 34, wherein the caries fighting
2 substance is fluoride.

1 36. The therapeutic composition of claim 23, wherein the active agent is
2 a pain reliever.

1 37. The composition of claim 22, wherein the active agent is calcipotriene.

1 38. The therapeutic composition of claim 36, wherein the pain reliever is
2 selected from the group consisting of viox, ibuprofen, acetaminophen, and
3 combinations thereof.

1 39. The method of claim 27, wherein the skin treatment is selected from
2 the group consisting of a moisturizer, a humectant, an exfoliant, and combinations
3 thereof.

1 40. A method of treating a subject, comprising:
2 topically applying an effective amount of a composition containing an osmotic
3 agent and an active agent to an area to be treated.

1 41. A method of treating a subject, comprising:
2 topically applying an effective amount of a composition containing dimethyl
3 isosorbide and an active agent to an area to be treated.

1 42. A method of treating a subject, comprising:
2 topically applying an effective amount of a composition containing dimethyl
3 isosorbide and potassium to an area to be treated.

1 43. A method of treating a subject, comprising:
2 topically applying an effective amount of a composition containing dimethyl
3 isosorbide and calcipotriene to an area to be treated.

1 44. A method of treating a subject, comprising:
2 topically applying an effective amount of a composition containing dimethyl
3 isosorbide and a skin treatment.

1 45. A dental cement, comprising:
2 a potassium-containing compound, a dental cement, and an osmotic agent.

1 46. The dental cement of claim 45, wherein the osmotic agent is dimethyl
2 isosorbide.

1 47. In a method of anesthetizing a tooth requiring tooth preparation, caries
2 removal or manual manipulation thereof, said method comprising the step of applying
3 a composition having a high concentration of potassium to said tooth, the composition
4 being adapted to anesthetize the tooth so that the tooth may be drilled or manually
5 manipulated, whereby said potassium enters the dentinal tubules and odontoblastic
6 fibrils and penetrates the pulpal tissues of the tooth for anesthetizing the tooth, the
7 improvement consisting essentially of applying a solution comprising EDTA, EGTA,

8 or citric acid to the tooth before the application of the potassium composition, said
9 solution effectively removing any smear layer that may exist on the tooth so as to
10 facilitate the penetration of the potassium composition through the enamel, dentinal
11 tubules and odontoblastic fibrils.

1 48. In a method of anesthetizing a tooth requiring tooth preparation, caries
2 removal or manual manipulation thereof, said method comprising the step of applying
3 a composition having a high concentration of potassium to said tooth, the composition
4 being adapted to anesthetize the tooth so that the tooth may be drilled or manually
5 manipulated, whereby said potassium enters the dentinal tubules and odontoblastic
6 fibrils and penetrates the pulpal tissues of the tooth for anesthetizing the tooth, the
7 improvement consisting essentially of combining a topical anesthetic with the
8 potassium composition to enable the composition to anesthetize the tooth and the
9 gingivae and other soft tissues surrounding the tooth for pain control during post
10 surgical, periodontal, and hygienist procedures.

1 49. In a method of anesthetizing a tooth requiring tooth preparation, caries
2 removal or manual manipulation thereof, said method comprising the step of applying
3 a composition having a high concentration of potassium to said tooth, the composition
4 being adapted to anesthetize the tooth so that the tooth may be drilled or manually
5 manipulated, whereby said potassium enters the dentinal tubules and odontoblastic
6 fibrils and penetrates the pulpal tissues of the tooth for anesthetizing the tooth, the
7 improvement consisting essentially of combining a concentration of dimethyl
8 isosorbide with the potassium composition, whereby said concentration of dimethyl
9 isosorbide acts to increase the penetration of the potassium through the dentinal
10 tubules and odontoblastic fibrils so as to achieve better penetration of the pulpal
11 tissues of the tooth for more effective anesthetization of the tooth.

1 50. The method of claim 49 used for the desensitizing of hypersensitive
2 teeth.

1 51. A method for reducing pain in ulcers comprising the step of applying
2 a solution comprising potassium and dimethyl isosorbide to the site of the ulcer,
3 whereby said solution acts on nerve endings within the ulcer to prevent the induction
4 of pain and inflammation within the ulcer and to diminish the inflammatory response
5 and thus promote faster, better healing.

1 52. The method of claim 51, wherein said solution comprises concentrated
2 potassium nitrate, dimethyl isosorbide, benzocaine, and tetracaine.

1 53. A method for treating inflammation that may exist anywhere on the
2 body of a living being comprising the steps of applying a solution comprising
3 potassium and dimethyl isosorbide to the site of the inflammation, whereby said
4 solution prevents the induction of pain within the inflammation, and diminishes the
5 inflammatory response to promote faster, better, healing.

1 54. The method of claim 53, wherein said solution comprises concentrate
2 potassium nitrate, dimethyl isosorbide, benzocaine and tetracaine.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/31086

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 33/00, 31/34, 31/24, 31/19, 31/195

US CL : 424/600; 514/470, 535, 557, 561

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)

U.S. : 424/600; 514/470, 535, 557, 561

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 4,082,881 A (CHEN et al.) 04 April 1978 (04.04.78), see the abstract, column 1, lines 36-54, column 2, lines 13, 22-26 and 33-63 and column 7, line 36 - column 8, line 39.	22, 23, 27, 28, 39-41 and 44 ----- 22, 23, 27-30, 39-41 and 44
X -- Y	US 4,228,162 A (LUZZI et al.) 14 October 1980 (14.10.80), see the abstract, column 8, lines 37-39 and column 12, lines 6-17.	22-24 and 36 ----- 22-24, 36, 40 and 41
X	US 4,711,904 A (LUZZI et al.) 08 December 1987, (08.12.87), see column 2, lines 14-68.	22, 27, 39-41 and 44

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
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"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"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	

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01 JANUARY 2001

Date of mailing of the international search report

19 MAR 2001

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