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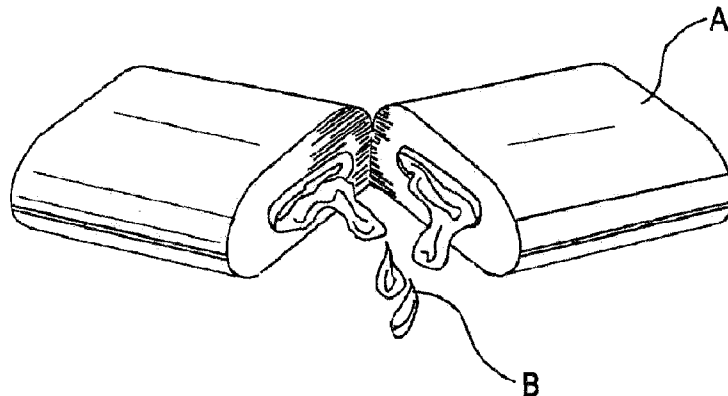


Fig. 1

(57) **Abstract:** A method for delivering nitric oxide therapy to a subject can include administering a composition including a nitric-oxide releasing agent and silica to the subject and releasing a therapeutic amount of nitric oxide from the composition.

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NITRIC OXIDE THERAPIES**CLAIM OF PRIORITY**

[0001] This application claims the benefit of prior U.S. Provisional Application No.
5 61/219,200, filed on June 22, 2009, which is incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] This description relates to methods of treatment.

BACKGROUND

[0003] The inhalation or topical exposure of nitric oxide gas to a subject can be
10 beneficial in promoting healing of a wound, preparing a wound bed for further recovery,
reducing infection and inflammation, and treating pulmonary disorders. However, typical
nitric oxide (NO) therapies include compositions that may be toxic to a subject and can be
difficult to administer.

SUMMARY

[0004] In general, a method for delivering nitric oxide therapy to a subject an include
15 administering a composition including a nitric-oxide releasing agent and silica to the
subject and releasing a therapeutic amount of nitric oxide from the composition. In certain
circumstances, silica gel can prevent toxic compounds from entering the subject. In other
circumstances, the composition further includes an antioxidant. The antioxidant can be
20 ascorbic acid, alpha tocopherol, or gamma tocopherol.

[0005] In certain circumstances the composition can be in the form of an ointment. In
other circumstances, the composition can be incorporated into an adhesive strip. The
adhesive strip can optionally include a foil backing to prevent nitric oxide from being
released into an external environment. In some circumstances, the adhesive strip can
25 have a calibrated scale on one surface thereof for accurate measurement of an ointment
dosage.

[0006] In certain circumstances, a composition can be in the form of a gum or
lozenge. In other circumstances, the composition can be incorporated into a gas delivery
device such as an inhaler or nasal cartridge.

[0007] In some circumstances, a therapeutic amount of nitric oxide is at least 1 ppm, at least 100 ppm, at least 200, or at least 300 ppm.

[0008] A composition for delivering nitric oxide therapy to a subject can include silica and a nitric oxide -releasing agent. The agent can be a polymeric composition having a polymer and at least one nitric oxide releasing N_2O_2 functional group. The agent can also be selected from the group consisting of $X\{N(O)NO\}$ and $[N(O)NO]X$.

[0009] A method for manufacturing a nitric oxide therapy to a subject can include incorporating a therapeutic amount of a nitric oxide-releasing agent into a silica composition into a delivery device. The delivery device can be an inhaler, an adhesive strip, an ointment, a gum, or a lozenge.

[0009a] Definitions of specific embodiments of the invention as claimed herein follow.

[0009b] According to a first embodiment of the invention, there is provided a method of delivering nitric oxide therapy to a subject, said method comprising:

exposing a composition including a nitric-oxide releasing agent, silica and an antioxidant to water in a chamber of a gas delivery device that includes an inlet, an outlet, a particle filter at the outlet and the chamber, wherein the nitric-oxide releasing agent is polymeric composition including a polymer and at least one nitric oxide releasing N_2O_2 functional group;

administering the gas delivery device to the subject;

generating an air flow through the inlet, the composition in the chamber and the outlet by subject inhalation; and

releasing a therapeutic amount of nitric oxide from the composition.

[0009c] According to a second embodiment of the invention, there is provided a composition when used for delivering nitric oxide therapy to a subject in a gas delivery device, said composition comprising:

silica, an antioxidant and a nitric oxide-releasing agent.

[0009d] According to a third embodiment of the invention, there is provided a method of manufacturing a nitric oxide therapy for a subject, said method comprising:

incorporating an antioxidant and a therapeutic amount of a nitric oxide-releasing agent into a silica composition into a gas delivery device,

wherein the nitric-oxide releasing agent is polymeric composition including a polymer and at least one nitric oxide releasing $N_2O_2^-$ functional group.

[0009e] The term “comprise” and variants of the term such as “comprises” or “comprising” are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

[0009f] Any reference to publications cited in this specification is not an admission that the disclosures constitute common general knowledge in Australia.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. 1 illustrates a gum or lozenge containing a composition a nitric-oxide releasing agent and silica.

[0011] FIG. 1A illustrates one embodiment of a conversion cartridge 104 that generates NO from NO_2 .

[0012] FIGS. 2 and 3 illustrate an inhaler or nasal plug that contains a nitric-oxide releasing agent and silica.

[0013] FIG. 4 illustrates an adhesive strip containing composition that includes a nitric-oxide releasing agent and silica.

[0014] FIG. 5 illustrates an adhesive strip containing composition that includes a nitric-oxide releasing agent and silica.

DETAILED DESCRIPTION

[0015] Various embodiments are directed to methods, compositions and devices for nitric oxide (NO) therapies. Generally, nitric oxide (NO) is topically applied, inhaled, or otherwise delivered to the individual's lungs. Providing a therapeutic dose of NO can provide several benefits including reducing microbial infection, reducing inflammation, regulating the formation of collagen, and treating pulmonary disorders. In addition, a therapeutic dose of NO can be used to supplement or minimize the need for oxygen therapy or rapid descent to lower elevations to treat symptoms of high-altitude sickness. A therapeutic dose of NO may be used without inducing toxicity to a subject. For

example a concentration greater than 1 ppm, greater than 100 ppm, or greater than 200 ppm can be used.

[0016] FIG. 1 illustrates a shell A, such as a gum or lozenge, the shell containing a therapeutic amount of a composition B, wherein the composition a nitric-oxide releasing agent and silica. The composition can be contained in the shell as shown, or alternatively,
5 incorporated into the shell itself.

[0017] FIG. 1A illustrates one embodiment of a conversion cartridge 104 that generates NO from NO₂. The conversion cartridge 104 also may be referred to as a NO generation cartridge, a GENO cartridge, or a GENO cylinder. The conversion cartridge
10 104 includes an inlet 105 and an outlet 110. In one embodiment a particle filter 115 are located at both the inlet 105 and the outlet 110, and the remainder of the cartridge 104 is filled with a surface-active material 120 that is soaked with a saturated solution of antioxidant in water to coat the surface-active material. In another embodiment, the
15 particulate filter 115 may be in the form of two concentric annular filters with the surface-active material 120 placed between the two annular filters. In this embodiment the gas flows from the inside of the annulus to the outside, or vice versa. In another embodiment, the surface-active material 120 and the filter material 115 are cast into one solid matrix as a sintered tube. In the example of FIG. 1A, the antioxidant is ascorbic acid.

[0018] FIGS. 2 and 3 illustrate an inhaler or nasal plug that contains a nitric-oxide releasing agent and silica. The composition can be contained in the inhaler or nasal plug,
20 or alternatively, incorporated into the inhaler or nasal plug itself.

[0019] FIG. 4 illustrates an adhesive strip 10 containing composition that includes a nitric-oxide releasing agent and silica. The composition can be an ointment or salve embedded into a pocket 12 on a surface 11 of the adhesive strip. The adhesive strip can
25 include calibrations 16 and 17 that can be used to select or indicate the amount of ointment administered. The pocket can be a distance 21 from the perimeter of the adhesive strip.

[0020] FIG. 5 illustrates an adhesive strip wherein a composition such as an ointment or salve is embedded into a pocket 12 of the adhesive strip, the adhesive strip having
30 calibrations 16 and 17 that can be used to select or indicate the amount of ointment 18 administered. The adhesive strip can include a foil backing 12A, that can prevent NO or NO₂ from being released into an external environment.

[0021] NO can be created from different processes and releasing compositions that are discussed, for example in U.S. Patent Application No. 11/206,305, which is incorporated by reference herein. Referring to FIG. 1A, in a general process for converting NO₂ to NO, an air flow having NO₂ is received through the inlet 105 and the
5 air flow is fluidly communicated to the outlet 110 through the surface-active material 120 coated with the aqueous antioxidant. As long as the surface-active material remains moist and the antioxidant has not been used up in the conversion, the general process is effective at converting NO₂ to NO at ambient temperatures.

[0022] The inlet 105 may receive the air flow having NO₂, for example, from a
10 pressurized bottle of NO₂, which also may be referred to as a tank of NO₂. The inlet 105 also may receive an air flow with NO₂ in nitrogen (N₂), air, or oxygen (O₂). The inlet 105 may also receive the air flow having NO₂ from an air pump that fluidly communicates an air flow over a permeation tube 235 containing liquid N₂O₄. The conversion occurs over a wide concentration range. Experiments have been carried out at concentrations in air of
15 from about 0.2 ppm NO₂ to about 100 ppm NO₂, and even to over 1000 ppm NO₂.

[0023] In one example, a cartridge that was approximately 5 inches long and had a diameter of 0.8-inches was packed with silica gel that had first been soaked in a saturated aqueous solution of ascorbic acid. Other sizes of the cartridge are also possible. The moist silica gel was prepared using ascorbic acid (i.e., vitamin C) designated as A.C.S
20 reagent grade 99.1% pure from Aldrich Chemical Company and silica gel from Fischer Scientific International, Inc., designated as S8 32-1, 40 of Grade of 35 to 70 sized mesh. Other similar sizes of silica gel also are effective, provided that the particle size and the pore size within the particles are similar.

[0024] The silica gel was moistened with a saturated solution of ascorbic acid that
25 had been prepared by mixing up to 35% by weight ascorbic acid in water, stirring, and straining the water/ascorbic acid mixture through the silica gel, followed by draining. It has been found that the conversion of NO₂ to NO proceeds well when the silica gel coated with ascorbic acid is moist. The conversion of NO₂ to NO does not proceed well in an aqueous solution of ascorbic acid alone.

[0025] The cartridge filled with the wet silica gel/ascorbic acid was able to convert
30 1000 ppm of NO₂ in air to NO at a flow rate of 150 ml per minute, quantitatively, non-stop for over 12 days. A wide variety of flow rates and NO₂ concentrations have been

successfully tested, ranging from only a few ml per minute to flow rates of up to 5,000 ml per minute. Using an annular cartridge, flow rates of up to 60,000 ml per minute have been used. The reaction also proceeds using other common antioxidants, such as variants of vitamin E (e.g., alpha tocopherol and gamma tocopherol).

- 5 **[0026]** The antioxidant/surface-active material GENO cartridge may be used for various therapies. In one such example, the GENO cartridge may be used as a NO₂ scrubber for NO inhalation therapy that delivers NO from a pressurized bottle source. The GENO cartridge not only scrubs the NO₂ but converts the NO₂ back into NO gas, which is then inhaled by the patient. This cartridge is also referred to as a recuperator.
- 10 This GENO cartridge may be used to help ensure that no harmful levels of NO₂ are inadvertently inhaled by the patient. Additionally, the GENO cartridge ensures that the patient is receiving the entire NO dose as NO gas and not as the toxic form, NO₂.

- [0027]** According to one embodiment, a therapeutic composition is a mixture of a surface-activated material such as, but not limited to, silica gel and one or more suitable
- 15 thermoplastic resins that are sintered at high temperatures to form a porous solid matrix. The polymers include, but are not limited to, polyethylene, polypropylene or any thermoplastic resin that can be ground into a fine powder and the poured into a mold and sintered at high temperature to form a porous solid matrix. The thermoplastic resin, when cured, provides a rigid porous structure with the surface-activated material embedded in
- 20 the pores. Additionally, the polymer may be shaped or molded into any form.

- [0028]** According to one embodiment, the porous solid matrix is composed of at least 20% silica gel. In another embodiment, the porous solid matrix includes approximately 20% to approximately 60% silica gel. In yet another embodiment, the porous solid matrix is composed of 50% silica gel. As those skilled in the art will appreciate, any ratio of
- 25 silica gel to thermoplastic resin is contemplated so long as the mechanical and structural strength of the porous solid matrix is maintained. In one embodiment, the densities of the silica gel and the polymer are generally similar in order to achieve a uniform mixture and, ultimately, a uniform porous solid matrix.

- [0029]** According to one method, the solid matrix is formed by mixing silica gel with
- 30 a thermoplastic resin. The mixture is then sintered at a high temperature to form a porous solid matrix and allowed to cool. After the porous solid matrix is formed, the porous solid matrix is flushed with an antioxidant solution. In one embodiment, the antioxidant

solution is approximately 20% ascorbic acid in water. Alternatively, ascorbic acid may be substituted with other antioxidants such as, but not limited to, alpha tocopherol or gamma tocopherol. In other embodiments, the antioxidant solution may have varying antioxidant concentrations. Dissolved gases (e.g., oxygen and air) are excluded from the antioxidant solution in order to prevent the formation of microscopic gas bubbles around the solid polymer/silica gel matrix. The gas bubbles would alter the surface chemistry and would prevent NO₂ from interacting with the antioxidant liquid inside the silica gel.

[0030] Once the solid matrix has been flushed, the excess antioxidant solution that is not bound by the silica gel may be rinsed off in order to minimize the precipitation of excess antioxidant solution during the drying step. According to one embodiment, the porous solid matrix is vacuum dried until the moisture content is reduced to approximately 30%. In alternate embodiments, the solid matrix may be dried to have any moisture content ranging from approximately 1% to approximately 99%. During the drying process, precautions need to be taken to ensure that oxygen is excluded. The dried, solid matrix is assembled into the body and flushed with inert gas before and during the sealing process. Oxygen is excluded from the manufacturing process and during storage in order to prevent the ascorbic acid (or other antioxidants) from slowly oxidizing to dehydro-ascorbic acid and other oxidation products during long-term storage. In another embodiment, the cartridge is dried until there is no detectable water present, and the cartridge is then sealed and packaged dry in a moisture-proof container. The dried cartridge is reconstituted into an active cartridge by exposing the cartridge to water prior to use.

[0031] Compositions capable of releasing NO are taught, for example in U.S. Patent Nos. 7,425,218; 6,397,660; 6,200,558; 5,632,981; 5,525,357; and 5,405,919, which are incorporated by reference herein.

[0032] NO can be released from certain devices, such as those taught in U.S. Application No. 61/090,617, which is incorporated by reference herein. For example, a light, portable device for delivering NO with air has the potential to improve a patient's quality of life. The device may be powered by a small, battery-driven pump or by patient inhalation (using an inhaler used in a manner similar to smoking a cigar). Additionally, a treatment providing NO (e.g., converting N₂O₄ into NO) would be more cost effective than oxygen therapy.

[0033] Currently, approved devices and methods for delivering inhaled NO gas require complex and heavy equipment. NO gas is stored in heavy gas bottles with nitrogen and no traces of oxygen. The NO gas is mixed with air or oxygen with specialized injectors and complex ventilators, and the mixing process is monitored with
5 equipment having sensitive microprocessors and electronics. All this equipment is required in order to ensure that NO is not oxidized into nitrogen dioxide (NO₂) during the mixing process since NO₂ is highly toxic. However, this equipment is not conducive to use in a non-medical facility setting (e.g., combat operations or remote wilderness) since the size, cost, complexity, and safety issues restrict the operation of this equipment to
10 highly-trained professionals in a medical facility.

[0034] In contrast, the delivery devices disclosed herein are self-contained, portable systems that do not require heavy gas bottles, sophisticated electronics, or monitoring equipment. Additionally, the delivery devices are easy to use and do not require any specialized training. Moreover, the delivery devices allow an individual to self-
15 administer a NO treatment. The delivery devices are also lightweight, compact, and portable. According to one embodiment, the NO delivery device is the size of a cigar or a conventional inhaler for one-time use or short-term treatments. Alternatively, the NO delivery device is a larger device, yet portable device that can deliver NO for longer periods of time.

[0035] Useful pharmacological agents can be provided by incorporating nitric oxide-releasing N₂O₂- functional groups into a biopolymer. Accordingly, the N₂O₂- functional group is "bound to the polymer" as that term has been defined herein. The term NONOate is used herein as a shorthand to refer to the nitric oxide-releasing N₂O₂- group. It has been discovered that incorporation of a NONOate into a biopolymer provides a
25 biopolymer-bound NONOate composition that can be applied with specificity to a biological site of interest. Site specific application of the biopolymer-bound NONOate enhances the selectivity of action of the nitric oxide-releasing NONOate. If N₂O₂ functional groups attached to the biopolymer are necessarily localized, then the effect of their nitric oxide release will be concentrated in the tissues with which they are in contact.
30 If the biopolymer is soluble, selectivity of action can still be arranged, for example, by attachment to or derivatization of an antibody specific to the target tissue. Similarly, attachment of N₂O₂ groups to small peptides that mimic the recognition sequences of ligands for important receptors provides localized concentrated effect of nitric oxide

release, as would attachment to oligonucleotides capable of site-specific interactions with target sequences in a nucleic acid. Other proteins, peptides, polypeptides, nucleic acids and polysaccharides, including hormones and motility, chemotactic and extravasating factors or agents, can be similarly utilized.

5 **[0036]** By way of illustration, a piperazine monoNONOate derivative can be covalently attached to a polypeptide containing the IKVAV recognition sequence important in tumor cell chemotaxis. Through retention of both the capacity to regenerate NO as an antichemotactic agent and the affinity of the IKVAV sequence for tumor cells and/or sites in the vascular and lymphatic systems where the tumor cells tend to attach,
10 metastasis can be reduced or even prevented.

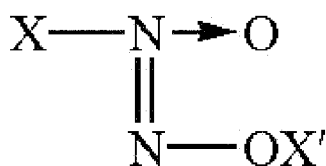
[0037] It is believed that longevity of nitric oxide release in the biopolymer-bound NONOate compositions of the present invention is to be attributed both to the physical structure of the composition and to electrostatic effects. Thus, it is believed that if the biopolymer is an insoluble solid, $N_2O_2^-$ groups near the surface of the particle should be
15 available for rapid release while those that are more deeply imbedded are sterically shielded, requiring more time and/or energy for the nitric oxide to work its way into the medium. Unexpectedly, it has been found that increasing positive charge in the vicinity of an $N_2O_2^-$ -functional group also tends to increase the half-life of nitric oxide generation. The mechanism of this rate retardation may be attributable simply to repulsive
20 electrostatic interactions, i.e., increasing the number of H^+ positive charges in the vicinity of the $N_2O_2^-$ groups inhibits attack of positively charged H^+ ions on the $N_2O_2^-$ functional group and slows the rate of its H^+ catalyzed decomposition. For example, by attaching amino groups to the polymeric support that are capable of forming the nitric oxide-releasing $N_2O_2^-$ functional group on reaction with nitric oxide, partially converted
25 structures can be produced on less-than-exhaustive treatment with nitric oxide that after exposure to water contain a large number of positively charged ammonium centers surrounding the $N_2O_2^-$ group that electrostatically inhibit the approach of H^+ ions capable of initiating nitric oxide loss from the nitric oxide-releasing $N_2O_2^-$ -functional group.

[0038] The nitric oxide-releasing $N_2O_2^-$ functional groups that are bound to the
30 biopolymer generally are capable of releasing nitric oxide in an aqueous environment spontaneously upon contacting an aqueous environment, i.e., they do not require activation through a redox reaction or electron transfer such as is required for glyceryl trinitrate and sodium nitroprusside. Some of the nitric oxide/nucleophile complexes

useful in the context of the present invention do require activation by particular means, but only as necessary to free the nitric oxide-releasing X[N(O)NO] group in the vicinity of the particular cells of interest. As an example, covalent attachment of a protecting group to the anionic [N(O)NO]⁻ function provides a means of postponing nitric oxide
 5 release until the molecule reaches an organ capable of metabolically removing the protecting group. By choosing a protecting group that is selectively cleaved by enzymes specific to a tumor, biological disorder, cell, or tissue of interest, for example, the action of the nitric oxide/nucleophile complex can be targeted to maximize the desired effect. While the biopolymer-bound NONOate compositions of the present invention are capable
 10 of releasing nitric oxide in an aqueous solution, such a compound preferably releases nitric oxide under physiological conditions.

[0039] For example, a NONOate functionality can be attached to a tumor-specific antibody or other protein which has one or more lysine side chain amino groups that are unnecessary to the function of the protein by reacting said lysine group(s) with a
 15 derivatizing agent capable of covalently attaching first to the lysine amino nitrogen then in a subsequent step to the sulfur atom of an O-functionalized NONOate containing a free thiol grouping elsewhere in the molecule. Once such a protein arrives at the desired target tissue after systemic application, enzymatic or hydrolytic removal of the substituent bound to oxygen frees the anionic NONOate function to concentrate NO release at that
 20 site.

[0040] The preferred nitric oxide-releasing N₂O₂⁻ functional group which is used to form the biopolymer-bound NONOates of the present invention is defined by the formula:



wherein X is an organic or inorganic moiety and X' is an organic or inorganic substituent,
 25 a pharmaceutically acceptable metal center, a pharmaceutically acceptable cation, or the like. The N₂O₂⁻ group is bonded to the biopolymer through either or both the linking groups X and X'. The nitric oxide-releasing N₂O₂⁻ functional group is preferably a nitric

oxide/nucleophile adduct, e.g., a complex of nitric oxide and a nucleophile most preferably a nitric oxide/nucleophile complex which contains the anionic moiety $X[N(O)NO]^-$, where X is any suitable nucleophile residue. The nucleophile residue is preferably that of a primary amine (e.g., $X=(CH_3)_2CHNH$, as in $(CH_3)_2CHNH[N(O)NO]Na$), a secondary amine (e.g., $X=(CH_3CH_2)_2N$, as in $(CH_3CH_2)_2N[N(O)NO]Na$), a polyamine (e.g., X=spermine, as in the zwitterion $H_2N(CH_2)_3NH_2^+(CH_2)_4N[N(O)NO]^- (CH_2)_3NH_2$, X=2-(ethylamino)ethylamine, as in the zwitterion $CH_3CH_2N[N(O)NO]^-CH_2CH_2NH_3^+$, or X=3-(n-propylamino)propylamine, as in the zwitterion $CH_3CH_2CH_2N[N(O)NO]^-CH_2CH_2CH_2NH_3^+$), or oxide (i.e., $X=O^-$, as in $NaO[N(O)NO]Na$), or a derivative thereof. Such nitric oxide/nucleophile complexes are capable of delivering nitric oxide in a biologically usable form as a predictable rate.

[0041] The various embodiments described above are provided by way of illustration only and should not be construed to limit the claimed invention. Those skilled in the art will readily recognize various modifications and changes that may be made to the claimed invention without following the example embodiments and applications illustrated and described herein, and without departing from the true spirit and scope of the claimed invention, which is set forth in the following claims.

CLAIMS

1. A method of delivering nitric oxide therapy to a subject, said method comprising:
exposing a composition including a nitric-oxide releasing agent, silica and an antioxidant to water in a chamber of a gas delivery device that includes an inlet, an outlet, a particle filter at the outlet and the chamber, wherein the nitric-oxide releasing agent is polymeric composition including a polymer and at least one nitric oxide releasing N_2O_2^- functional group;
administering the gas delivery device to the subject;
generating an air flow through the inlet, the composition in the chamber and the outlet by subject inhalation; and
releasing a therapeutic amount of nitric oxide from the composition.
2. The method of claim 1, wherein the silica prevents toxic compounds from entering the subject.
3. The method of claim 1 or claim 2, wherein the antioxidant is ascorbic acid, alpha tocopherol or gamma tocopherol.
4. The method of any one of claims 1 to 3, wherein the composition is incorporated into the gas delivery device.
5. The method of any one of claims 1 to 4, wherein the gas delivery device is an inhaler or a nasal cartridge.
6. The method of any one of claims 1 to 5, wherein the therapeutic amount of nitric oxide is at least 1 ppm.
7. The method of any one of claims 1 to 6, wherein the therapeutic amount of nitric oxide is at least 100 ppm.
8. The method of any one of claims 1 to 7, wherein the therapeutic amount of nitric oxide is at least 200 ppm.
9. The method of any one of claims 1 to 8, wherein the therapeutic amount of nitric oxide is at least 300 ppm.

10. A composition when used for delivering nitric oxide therapy to a subject in a gas delivery device, said composition comprising:
silica, an antioxidant and a nitric oxide-releasing agent.
11. The composition of claim 10, wherein the agent is a polymeric composition having a polymer and at least one nitric oxide releasing $N_2O_2^-$ functional group.
12. The composition of claim 10 or claim 11, wherein the agent is selected from the group consisting of $X\{N(O)NO\}$ and $[N(O)NO]X$.
13. A method of manufacturing a nitric oxide therapy for a subject, said method comprising:
incorporating an antioxidant and a therapeutic amount of a nitric oxide-releasing agent into a silica composition into a gas delivery device,
wherein the nitric-oxide releasing agent is polymeric composition including a polymer and at least one nitric oxide releasing $N_2O_2^-$ functional group.
14. The method of claim 13, wherein the delivery device is an inhaler.

Date: 10 December 2015

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Fig. 1

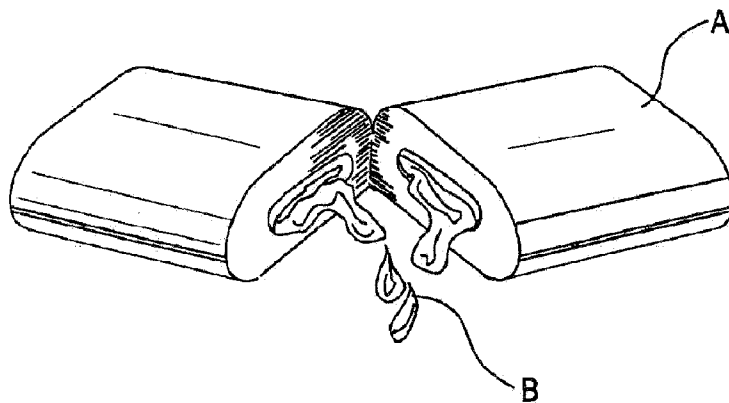
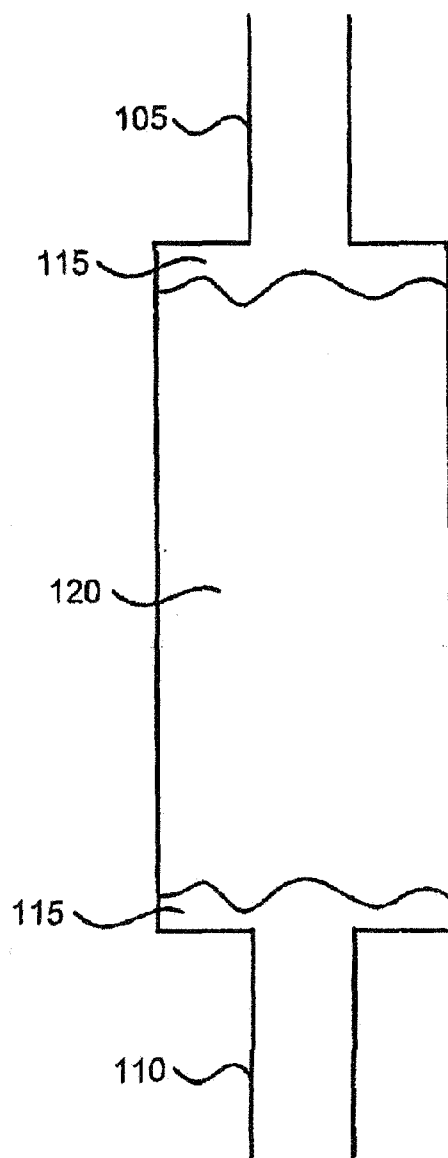


Fig. 1A



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Fig. 2

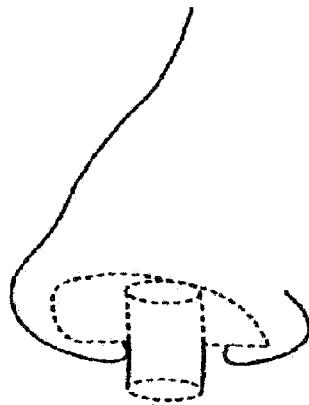
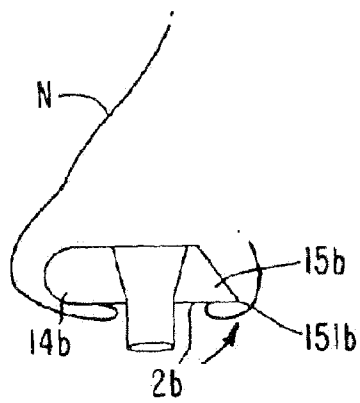


Fig. 3



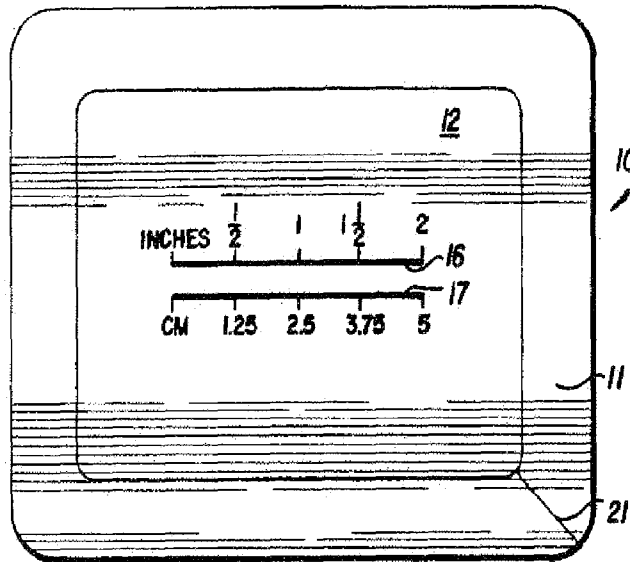


FIG. 4

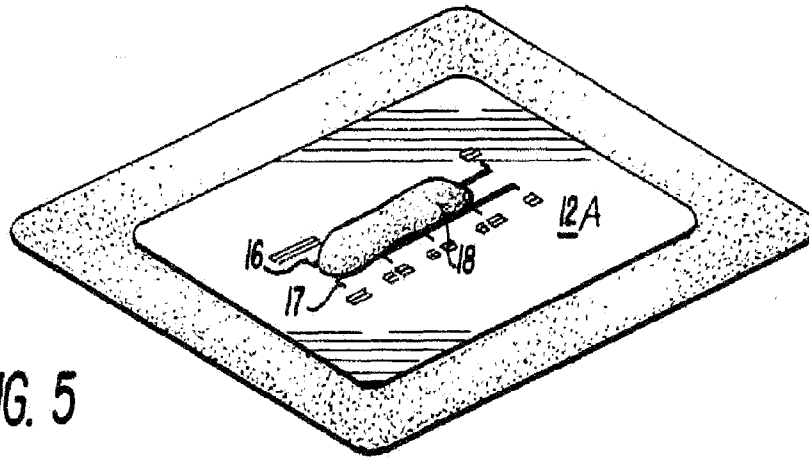


FIG. 5