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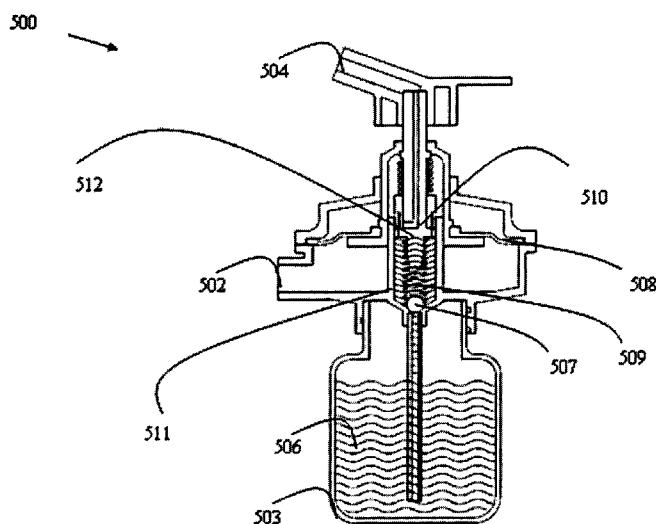
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(54) Title: A NASAL DELIVERY DEVICE

**Fig. 15**

(57) **Abstract:** It is one object of the present invention to provide an air-intake actuated device adapted for delivering a substance to a nasal cavity of a subject, comprising: a. a container for containing said substance; b. a nosepiece extending from said device for placement in proximity to a nose of said subject. c. a valve mechanically connectable to said container, characterized by an ACTIVE CONFIGURATION and an INACTIVE CONFIGURATION; and, d. a trigger mechanism adapted to reconfigure said valve from said ACTIVE CONFIGURATION to said INACTIVE CONFIGURATION, and vice versa; wherein said trigger mechanism is activated by means of said subject intaking air through said mouthpiece; further wherein said trigger mechanism is adapted to reconfigure said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION for a predetermined period of time in response to said subject intake of air.

A NASAL DELIVERY DEVICE

FIELD OF THE INVENTION

The present invention generally relates to a nasal substance delivery device, and more specifically, to a drinking/breathing -actuated device for delivering a substance to a nasal cavity of a subject in a variety of different delivery methods.

BACKGROUND OF THE INVENTION

Nasal delivery of a substance (e.g., a drug, a vaccine, etc.) can be useful both for treating diseases or disorders in the nasal passageways themselves and for treating other disorders or conditions through the systemic route (e.g., vaccine, neurological, etc.). The advantages of nasal delivery of a substance are among others the following:

(a) rich vascular plexus- direct route into the blood stream; (b) avoiding gastrointestinal destruction as drug degradation that is observed in the gastrointestinal tract is absent. (c) Hepatic first pass metabolism (destruction of drugs by liver enzymes) is absent; (d) rates of absorption and plasma concentrations are comparable to intravenous administration; (e) ease, convenience and safety; (f) rapidly achieve therapeutic brain and spinal cord (CNS) drug concentrations; (g) rapid drug absorption and quick onset of action can be achieved; (h) the bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approaches; (i) The nasal bioavailability for smaller drug molecules is good; (j) drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery; (k) based on published information, the nasal route was indicated as an alternate to parenteral route, especially, for protein and peptide drugs; (l) convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.

On the other hand, the limitations of nasal delivery of a substance are:

(a) the histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established; (b) relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation; (c) nasal cavity provides smaller absorption surface area when compared to (Gastro intestinal tract GIT).

Therapy through intranasal administration has been an accepted form of treatment in many countries. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. Advances in biotechnology have made available a

large number of protein and peptide drugs for the treatment of a variety of diseases. These drugs are unsuitable for oral administration because they are significantly degraded in the gastrointestinal tract or considerably metabolized by first pass effect in the liver. Also, the parenteral route is inconvenient for long term therapy. Of many alternate routes tried, intranasal drug delivery is found much promising for administration of such drugs.

There are many traditional devices that are adapted to supply substances to the nasal cavity. These devices include, for example, syringed nose drops, pump spray devices, and fluorinated propellant metered dose inhalers (MDI). These traditional devices have not generally been able to achieve the particle sizes necessary to maximize efficacy while helping mitigate undesired pulmonary absorption. For example, both eye dropper type devices and simple spray devices typically present medicament into the nasal cavity in a stream. The result is that much of the medicament simply runs out of the patient's nose, and only a small amount of the drug is absorbed, with even less of the drug reaching the nasal epithelia.

In the recent years a few companies have developed novel drug delivery devices which are activated when a subject exhales air from the lungs through the mouth. As a result of the air exhale, the soft palate is closed, and thereby operates to isolate the nasal passageways from the remainder of the pulmonary system. By that, the soft palate acts as a natural check valve preventing the flow of air between the lungs and the nasal cavity. Thus, in these air-exhale based devices, it is believed that nasal substance delivery can be improved if the patient is exhaling orally while the substance is being sprayed into the nasal passages. One nasal delivery device that takes advantage of this phenomenon is shown in US patent 6,715,485 to Optinose. This patent application discloses a delivery device for delivering a substance to the nasal airway of a subject, in particular the posterior region of the nasal airway, the delivery device comprising: a closure unit for causing the closure of the oropharyngeal velum of the subject, and a delivery unit for delivering a gas flow entraining a substance to one of the nostrils of the subject at such a driving pressure as to flow around the posterior margin of the nasal septum and out of the other nostril of the subject, wherein the delivery unit comprises a nosepiece which includes an outlet through which the gas flow in use is delivered to the one nostril and a sealing member for sealing the one nostril to the outlet such as in use to prevent the escape of the gas flow through the one nostril.

The present invention takes advantage of the normal swallowing mechanism in which the soft palate closes, in the delivery process of a substance to nose. In this mechanism the isolation of the nose passageways from the respiratory system is better than in the case of air exhalation (on which the nasal drug delivery devices known in the prior art is based). Furthermore, the present invention is able to deliver a desired amount of substance to the nasal epithelium while preventing entry into

the pulmonary tract and the lungs. This substance delivery device has to comply with the following key requirements: a. they have to be accurate in the doses of the substance they provide, b. good penetration to the nasal canals, c. painless, d. with minimal stomach deposition, e. with minimal lung deposition, f. easy to use, g. with improved patient compliance, h. washing of the drug flavor, i. suitable platform for various drugs and vaccines, j. and with subject-independent actuation. The present invention is intended to comply with all these requirements.

SUMMARY OF THE INVENTION

It is one object of the present invention to provide an air-intake actuated device adapted for delivering a substance to a nasal cavity of a subject, said device comprising:

- a. a container for containing said substance;
- b. a nosepiece extending from said device for placement in proximity to a nose of said subject, said nosepiece being in fluid communication with said container;
- c. a valve mechanically connectable to said container, characterized by at least two configurations: (i) an ACTIVE CONFIGURATION in which said valve enables delivery of predetermined amount of said substance from said container to said nasal cavity via said nosepiece; and, (ii) an INACTIVE CONFIGURATION, in which said valve prevents delivery of said predetermined amount of said substance from said container to said nasal cavity;
- d. a mouthpiece extending from said device for placement in a mouth of said subject; and,
- e. a trigger mechanism adapted to reconfigure said valve from said ACTIVE CONFIGURATION to said INACTIVE CONFIGURATION, and vice versa;

wherein said trigger mechanism is activated by means of said subject intaking air through said mouthpiece;

further wherein said trigger mechanism is adapted to reconfigure said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION for a predetermined period of time in response to said subject intake of air.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein said trigger mechanism is adapted to reconfigure said valve from said ACTIVE CONFIGURATION to said INACTIVE CONFIGURATION when said subject ceases said intake.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein said trigger mechanism comprises a flexible membrane; said membrane is in mechanical communication with said valve; such that when said subject intake air, said membrane is relocated from its initial position and said valve is opened.

It is another object of the present invention to provide the air-intake actuated device as defined above, additionally comprising an intermediate compartment adapted to be filled with predetermined amount of said substance; such that said delivery of said substance to said subject is from said intermediate compartment.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein the operation of said trigger mechanism is synchronized with said intake of air by said subject.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein said trigger mechanism comprises a pulsation mechanism adapted to reconfigure said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION and vice versa in sequence of pulses, each of which is characterized by a predetermined length of pulse, said valve adapted to release said predetermined amount of said substance according to said sequence of pulses.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein in each said pulse at least two doses of said predetermined amount of said substance are released.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein said nosepiece is in fluid communication with said valve by means of a spray nozzle.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein said spray nozzle is characterized by a diameter which influences on said predetermined period of time.

It is another object of the present invention to provide the air-intake actuated device as defined above, further comprising a cap adapted to cover at least a portion of the components of said device for sterilization/aseptic purposes.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein said cap comprises an opening.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein said container adapted to be connected to an external container, said external container adapted to fill said container with said substance.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein said external container adapted to fill said container with a predetermined dose of said substance.

It is another object of the present invention to provide the air-intake actuated device as defined above, further comprising indicating means adapted to indicate the amount of said substance within said container.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein said indicating means is a transparent window located on a side of said container.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein said substance is a drug selected from a group consisting of: Anti-Angiogenesis agents, Antisense, anti-ulcer, butorphanol, Calcitonin and analogs, COX-II inhibitors, desmopressin and analogs, dihydroergotamine, Dopamine agonists and antagonists, Enkephalins and other opioid peptides, Growth hormone and analogs, growth hormone releasing hormone, Growth hormone antagonists, IgE suppressors, Insulin, insulinotropin and analogs, Ketamine, Kytril, Leutenizing hormone releasing hormone and analogs, lidocaine, metoclopramide, Midazolam, Narcotic analgesics, neuraminidase inhibitors, nicotine, Non-steroid anti-inflammatory agents, Oligosaccharides, ondansetron, Parathyroid hormone and analogs, Parathyroid hormone antagonists, Prostaglandin antagonists, Prostaglandins, Recombinant soluble receptors, scopolamine, Serotonin agonists and antagonists, Sildenafil, Terbutaline, vasopressin, or any combination thereof.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein said substance is a vaccine with or without carriers and/or adjuvant selected from the group consisting of: Prophylactics and therapeutic antigens, subunit protein, peptide and polysaccharide, polysaccharide conjugates, toxoids, genetic based vaccines, live attenuated, reassortant, inactivated, whole cells, viral and bacterial vectors for the treatment of arthritis, *Lactobacillus* species: *Lactobacillus acetotolerans*, *Lactobacillus acidifarinae*, *Lactobacillus acidipiscis*, *Lactobacillus acidophilus* (Doderlein bacillus), *Lactobacillus agilis*, *Lactobacillus algidus*, *Lactobacillus alimentarius*, *Lactobacillus amylolyticus*, *Lactobacillus amylophilus*, *Lactobacillus amylotrophicus*, *Lactobacillus amylovorus*, *Lactobacillus animalis*, *Lactobacillus antri*, *Lactobacillus apodemi*, *Lactobacillus aviarius*, *Lactobacillus bif fermentans*, *Lactobacillus brevis*, *Lactobacillus buchneri*, *Lactobacillus camelliae*, *Lactobacillus casei*, *Lactobacillus*

cateniformis, *Lactobacillus ceti*, *Lactobacillus coleohominis*, *Lactobacillus collinoides*,
Lactobacillus composti, *Lactobacillus concavus*, *Lactobacillus coryniformis*, *Lactobacillus*
crispatus, *Lactobacillus crustorum*, *Lactobacillus curvatus*, *Lactobacillus delbrueckii*,
Lactobacillus delbrueckii subsp. Bulgaricus, *Lactobacillus delbrueckii subsp. Lactis*, *Lactobacillus*
diolivorans, *Lactobacillus equi*, *Lactobacillus equigenersi*, *Lactobacillus farraginis*, *Lactobacillus*
farciminis, *Lactobacillus fermentum*, *Lactobacillus fornicalis*, *Lactobacillus fructivorans*,
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secaliphilus, *Lactobacillus sharpeae*, *Lactobacillus siliginis*, *Lactobacillus spicheri*, *Lactobacillus*
suebicus, *Lactobacillus thailandensis*, *Lactobacillus ultunensis*, *Lactobacillus vaccino*
stercus, *Lactobacillus vaginalis*, *Lactobacillus versmoldensis*, *Lactobacillus vini*, *Lactobacillus vitulinus*,
Lactobacillus zae, *Lactobacillus zymae*, Probiotics selected from a group consisting of Lactic acid
bacteria (LAB) and bifidobacteria, or any combination thereof; said substance is used for the
treatment of at least one selected from a group consisting of cholera, moraxella catarrhali, cocaine
addiction, HIB, meningococcus, measles, mumps, rubella, varicella, yellow fever, Respiratory
syncytial virus, pneumococcus, streptococcus, typhoid, influenza, hepatitis, including hepatitis A,
B, C and F, polio, HIV, parainfluenza, rotavirus, CMV, chlamydia, non-typeable haemophilus,
moraxella catarrhalis, human papilloma virus, tuberculosis including BCG, gonorrhoea, asthma,
atherosclerosis, malaria, otitis media, E-coli, Alzheimers, H. Pylori, salmonella, diabetes, cancer
and herpes simplex, Staphylococcus aureus, Streptococcus, or any combination thereof.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein said substance is used for the treatment of at least one selected from a group consisting of cholera, moraxella catarrhali, cocaine addiction, HIB, meningococcus, measles, mumps, rubella, varicella, yellow fever, Respiratory syncytial virus, pneumococcus, streptococcus, typhoid, influenza, hepatitis, including hepatitis A, B, C and F, polio, HIV, parainfluenza, rotavirus, CMV, chlamydia, non-typeable haemophilus, moraxella catarrhalis, human papilloma virus, tuberculosis including BCG, gonorrhoea, asthma, atherosclerosis, malaria, otitis media, E-coli, Alzheimers, H. Pylori, salmonella, diabetes, cancer and herpes simplex, Staphylococcus aureus, Streptococcus, or any combination thereof.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein the substance is a peptide or protein therapeutic agent such as cytokines, hormones, clotting factors, vaccines, monoclonal antibody.

It is another object of the present invention to provide the air-intake actuated device as defined above, used for the treatment of CNS disorder, brain disorders such as: brain cancer, acute brain injury, spinal cord injury, Alzheimer disease, Neurogenesis, Parkinson's disease, depression, Epilepsy, schizophrenia by the delivery of substances such as: Neurotrophins, BDNF, GDNF, anti EGF receptor AB, Enzymes as Lysosomal enzyme, Neuregulin.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein said substance is a therapeutic substance selected from a group consisting of: agents for the common cold, Anti-addiction, anti-infectives, analgesics, anesthetics, anorexics, antiarthritics, anti-allergy agents, antiasthmatic agents, anticonvulsants, anti-depressants, antidiabetic agents, anti-depressants, anti-diuretics, anti-emetics, antihistamines, anti-inflammatory agents, antimigraine preparations, antiontension sickness preparations, antinauseants, antineoplastics, anti-obesity, antiosteoporotic, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, anticholinergics, benzodiazepine antagonists, bone stimulating agents, central nervous system stimulants, hormones, hypnotics, immunosuppressives, prostaglandins, proteins, peptides, polypeptides and other macromolecules, psychostimulants, rhinitis treatment, sedatives, sexual hypofunction, tranquilizers and vitamins including B12, probiotics, natural oils, natural ingredients, or any combination thereof.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein said substance may be delivered to said nasal cavity in a form selected from the group consisting of: a powder, a granule, a cachet, a capsule, a tablet, a paste, a cream, a gel, an ointment, a salve, a foam, a paste, a lotion, a cream, an oil suspension, a spray, a suspension, a

solution, an emulsion, a patch, a stick, a spray, preferably a nasal spray, or a buccal spray, a mouth wash, an aerosol, in a venture effect, a drink, and a solution.

It is another object of the present invention to provide the air-intake actuated device as defined above, wherein said substance is selected from a group consisting of natural oils; Mint oils, Peppermint oil, Spearmint oil, Menthol, Olive oil, Eucalyptus oil, Amino acids, fatty acids and any combination thereof.

It is another object of the present invention to a method for delivering a substance to a nasal cavity of a subject, said method comprising steps of:

- a. providing an air-intake actuated device adapted for delivering a substance to a nasal cavity of a subject, said device comprising: (i) a container for containing said substance; (ii) a nosepiece extending from said device for placement in proximity to a nose of said subject, said nosepiece being in fluid communication with said container; (iii) a valve mechanically connectable to said container, characterized by at least two configurations: (i) an ACTIVE CONFIGURATION in which said valve enables delivery of predetermined amount of said substance from said container to said nasal cavity via said nosepiece; and, (ii) an INACTIVE CONFIGURATION, in which said valve prevents delivery of said predetermined amount of said substance from said container to said nasal cavity; (iv) a mouthpiece extending from said device for placement in a mouth of said subject; and, a (v) trigger mechanism adapted to reconfigure said valve from said ACTIVE CONFIGURATION to said INACTIVE CONFIGURATION, and vice versa; wherein said trigger mechanism is activated by means of said subject intaking air through said mouthpiece; further wherein said trigger mechanism is adapted to reconfigure said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION for a predetermined period of time in response to said subject intake of air;
- b. placing said nosepiece in or around the nose of said subject;
- c. placing said mouthpiece in the mouth of said subject;
- d. inhaling air; thereby reconfiguring said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION for a predetermined period of time in response;
- e. releasing a predetermined amount of said substance from said container to said nosepiece;

It is another object of the present invention to provide the method as defined above, further comprising step of reconfiguring said valve via said trigger mechanism from said ACTIVE CONFIGURATION to said INACTIVE CONFIGURATION when said subject ceases said intake.

It is another object of the present invention to provide the method as defined above, additionally comprising step of providing said trigger mechanism with a flexible membrane; said membrane is in mechanical communication with said valve; such that when said subject intake air, said membrane is relocated from its initial position and said valve is opened.

It is another object of the present invention to provide the method as defined above, additionally comprising step of providing said device with an intermediate compartment adapted to be filled with predetermined amount of said substance; such that said delivery of said substance to said subject is from said intermediate compartment.

It is another object of the present invention to provide the method as defined above, further comprising step of synchronizing the operation of said trigger mechanism with said drinking of said fluid by said subject.

It is another object of the present invention to provide the method as defined above, further comprising step of providing said trigger mechanism with a pulsation mechanism adapted to reconfigure said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION and vice versa in sequence of pulses, each of which is characterized by a predetermined length of pulse, said valve adapted to release said predetermined amount of said substance according to said sequence of pulses.

It is another object of the present invention to provide the method as defined above, further comprising step of releasing in each said pulse at least two doses of said predetermined amount of said substance.

It is another object of the present invention to provide the method as defined above, wherein said nosepiece is in fluid communication with said valve by means of a spray nozzle.

It is another object of the present invention to provide the method as defined above, wherein said spray nozzle is characterized by a diameter which influences on said predetermined period of time.

It is another object of the present invention to provide the method as defined above, further comprising step of providing said device with a cap adapted to cover at least a portion of the components of said device for sterilization/ aseptic purposes.

It is another object of the present invention to provide the method as defined above, wherein said cap comprises an opening.

It is another object of the present invention to provide the method as defined above, wherein said container adapted to be connected to an external container, said external container adapted to fill said container with said substance.

It is another object of the present invention to provide the method as defined above, further comprising step of filling said container by said external container with a predetermined dose of said substance.

It is another object of the present invention to provide the method as defined above, further comprising step of providing said container with indicating means adapted to indicate the amount of said substance within said container.

It is another object of the present invention to provide the method as defined above, wherein said indicating means is a transparent window located on a side of said container.

It is another object of the present invention to provide the method as defined above, wherein said substance is a drug selected from a group consisting of: Anti-Angiogenesis agents, Antisense, anti-ulcer, butorphanol, Calcitonin and analogs, COX-II inhibitors, desmopressin and analogs, dihydroergotamine, Dopamine agonists and antagonists, Enkephalins and other opioid peptides, Growth hormone and analogs, growth hormone releasing hormone, Growth hormone antagonists, IgE suppressors, Insulin, insulinotropin and analogs, Ketamine, Kytril, Leutenizing hormone releasing hormone and analogs, lidocaine, metoclopramide, Midazolam, Narcotic analgesics, neuraminidase inhibitors, nicotine, Non-steroid anti-inflammatory agents, Oligosaccharides, ondansetron, Parathyroid hormone and analogs, Parathyroid hormone antagonists, Prostaglandin antagonists, Prostaglandins, Recombinant soluble receptors, scopolamine, Serotonin agonists and antagonists, Sildenafil, Terbutaline, vasopressin, or any combination thereof.

It is another object of the present invention to provide the method as defined above, additionally comprising step of selecting said substance from a vaccine with or without carriers and/or adjuvant selected from the group consisting of: Prophylactics and therapeutic antigens, subunit protein, peptide and polysaccharide, polysaccharide conjugates, toxoids, genetic based vaccines, live attenuated, reassortant, inactivated, whole cells, viral and bacterial vectors for the treatment of arthritis, *Lactobacillus* species: *Lactobacillus acetotolerans*, *Lactobacillus acidifarinae*, *Lactobacillus acidipiscis*, *Lactobacillus acidophilus* (*Doderlein bacillus*), *Lactobacillus agilis*, *Lactobacillus algidus*, *Lactobacillus alimentarius*, *Lactobacillus amylolyticus*, *Lactobacillus amylophilus*, *Lactobacillus amylophobicus*, *Lactobacillus amylovorus*, *Lactobacillus animalis*, *Lactobacillus antri*, *Lactobacillus apodemi*, *Lactobacillus aviarius*, *Lactobacillus bifementans*, *Lactobacillus brevis*, *Lactobacillus buchneri*, *Lactobacillus camelliae*, *Lactobacillus casei*, *Lactobacillus catenaformis*, *Lactobacillus ceti*, *Lactobacillus coleohominis*, *Lactobacillus*

collinoides, *Lactobacillus composti*, *Lactobacillus concavus*, *Lactobacillus coryniformis*, *Lactobacillus crispatus*, *Lactobacillus crustorum*, *Lactobacillus curvatus*, *Lactobacillus delbrueckii*, *Lactobacillus delbrueckii subsp. Bulgaricus*, *Lactobacillus delbrueckii subsp. Lactis*, *Lactobacillus diolivorans*, *Lactobacillus equi*, *Lactobacillus equigenerosi*, *Lactobacillus farraginis*, *Lactobacillus farciminis*, *Lactobacillus fermentum*, *Lactobacillus fornicalis*, *Lactobacillus fructivorans*, *Lactobacillus frumenti*, *Lactobacillus fuchuensis*, *Lactobacillus gallinarum*, *Lactobacillus gasseri*, *Lactobacillus gastricus*, *Lactobacillus ghanensis*, *Lactobacillus graminis*, *Lactobacillus hammesii*, *Lactobacillus hamsteri*, *Lactobacillus harbinensis*, *Lactobacillus hayakitensis*, *Lactobacillus helveticus*, *Lactobacillus hilgardii*, *Lactobacillus homohiochii*, *Lactobacillus iners*, *Lactobacillus ingluviei*, *Lactobacillus intestinalis*, *Lactobacillus jensenii*, *Lactobacillus johnsonii*, *Lactobacillus kalixensis*, *Lactobacillus kefiranoferens*, *Lactobacillus kefir*, *Lactobacillus kimchii*, *Lactobacillus kitasatonis*, *Lactobacillus kunkeei*, *Lactobacillus leichmannii*, *Lactobacillus lindneri*, *Lactobacillus malefermentans*, *Lactobacillus mali*, *Lactobacillus manihotivorans*, *Lactobacillus mindensis*, *Lactobacillus mucosae*, *Lactobacillus murinus*, *Lactobacillus nagelii*, *Lactobacillus namurensis*, *Lactobacillus nantensis*, *Lactobacillus oligofermentans*, *Lactobacillus oris*, *Lactobacillus panis*, *Lactobacillus pantheris*, *Lactobacillus parabrevis*, *Lactobacillus parabuchneri*, *Lactobacillus paracollinoides*, *Lactobacillus parafarraginis*, *Lactobacillus parakefiri*, *Lactobacillus paralimentarius*, *Lactobacillus paraplantarum*, *Lactobacillus pentosus*, *Lactobacillus perolens*, *Lactobacillus plantarum*, *Lactobacillus pontis*, *Lactobacillus psittaci*, *Lactobacillus rennini*, *Lactobacillus reuteri*, *Lactobacillus rhamnosus*, *Lactobacillus rimae*, *Lactobacillus rogosae*, *Lactobacillus rossiae*, *Lactobacillus ruminis*, *Lactobacillus saerimneri*, *Lactobacillus sakei*, *Lactobacillus salivarius*, *Lactobacillus sanfranciscensis*, *Lactobacillus satsumensis*, *Lactobacillus secaliphilus*, *Lactobacillus sharpeae*, *Lactobacillus siliginis*, *Lactobacillus spicheri*, *Lactobacillus suebicus*, *Lactobacillus thailandensis*, *Lactobacillus ultunensis*, *Lactobacillus vaccinoferens*, *Lactobacillus vaginalis*, *Lactobacillus versmoldensis*, *Lactobacillus vini*, *Lactobacillus vitulinus*, *Lactobacillus zaeae*, *Lactobacillus zymae*, Probiotics selected from a group consisting of Lactic acid bacteria (LAB) and bifidobacteria, or any combination thereof; said substance is used for the treatment of at least one selected from a group consisting of cholera, moraxella catarrhali, cocaine addiction, HIB, meningococcus, measles, mumps, rubella, varicella, yellow fever, Respiratory syncytial virus, pneumococcus, streptococcus, typhoid, influenza, hepatitis, including hepatitis A, B, C and F, polio, HIV, parainfluenza, rotavirus, CMV, chlamydia, non-typeable haemophilus, moraxella catarrhalis, human papilloma virus, tuberculosis including BCG, gonorrhoea, asthma, atherosclerosis, malaria, otitis media, E-coli, Alzheimers, H. Pylori, salmonella, diabetes, cancer and herpes simplex, , Staphylococcus aureus, Streptococcus, or any combination thereof.

It is another object of the present invention to provide the method as defined above, wherein said substance is used for the treatment of at least one selected from a group consisting of cholera, moraxella catarrhali, cocaine addiction, HIB, meningococcus, measles, mumps, rubella, varicella, yellow fever, Respiratory syncytial virus, pneumococcus, streptococcus, typhoid, influenza, hepatitis, including hepatitis A, B, C and F, polio, HIV, parainfluenza, rotavirus, CMV, chlamydia, non-typeable haemophilus, moraxella catarrhalis, human papilloma virus, tuberculosis including BCG, gonorrhoea, asthma, atherosclerosis, malaria, otitis media, E-coli, Alzheimers, H. Pylori, salmonella, diabetes, cancer and herpes simplex, Staphylococcus aureus, Streptococcus, or any combination thereof.

It is another object of the present invention to provide the method as defined above, wherein the substance is a peptide or protein therapeutic agent such as cytokines, hormones, clotting factors, vaccines, monoclonal antibody.

It is another object of the present invention to provide the method as defined above, used for the treatment of CNS disorder, brain disorders such as: brain cancer, acute brain injury, spinal cord injury, Alzheimer disease, Neurogenesis, Parkinson's disease, depression, Epilepsy, schizophrenia by the delivery of substances such as: Neurotrophins, BDNF, GDNF, anti EGF receptor AB, Enzymes as Lysosomal enzyme, Neuregulin.

It is another object of the present invention to provide the method as defined above, wherein said substance is a therapeutic substance selected from a group consisting of: Agents for the common cold, Anti-addiction, anti-infectives, analgesics, anesthetics, anorexics, antiarthritics, anti-allergy agents, antiasthmatic agents, anticonvulsants, anti-depressants, antidiabetic agents, anti-depressants, anti-diuretics, anti-emetics, antihistamines, anti-inflammatory agents, antimigraine preparations, antinausea preparations, antinauseants, antineoplastics, anti-obesity, antiosteoporotic, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, anticholinergics, benzodiazepine antagonists, bone stimulating agents, central nervous system stimulants, hormones, hypnotics, immunosuppressives, prostaglandins, proteins, peptides, polypeptides and other macromolecules, psychostimulants, rhinitis treatment, sedatives, sexual hypofunction, tranquilizers and vitamins including B12, probiotics, natural oils, natural ingredients, or any combination thereof.

It is another object of the present invention to provide the method as defined above, wherein said substance is delivered to said nasal cavity in a form selected from the group consisting of: a powder, a granule, a cachet, a capsule, a tablet, a paste, a cream, a gel, an ointment, a salve, a foam, a paste, a lotion, a cream, an oil suspension, a spray, a suspension, a solution, an emulsion, a patch, a stick, a spray, preferably a nasal spray, or a buccal spray, a mouth wash, an aerosol, in a ventouse effect, a drink, and a solution.

It is another object of the present invention to provide the method as defined above, additionally comprising step of selecting said substance from a group consisting of natural oils; Mint oils, Peppermint oil, Spearmint oil, Menthol, Olive oil, Eucalyptus oil, Amino acids, fatty acids and any combination thereof.

BRIEF DESCRIPTION OF THE FIGURES

For a better understanding of the invention and to show how the same may be carried into effect, reference will now be made, purely by way of example, to the accompanying drawings in which like numerals designate corresponding elements or sections throughout. In the accompanying drawings:

FIG. 1 is an illustration of the pattern of breathing while drinking according to a study of J. Smith et al.

FIGS. 2a-c is an illustration of the pattern of swallowing and breathing according to the study of J. Smith et al.

FIGS. 3a-f is a schematic illustration of the motor events of the swallowing reflex;

FIGS. 4a-h is a schematic illustration of the mechanism of a drinking-actuated substance delivery device of the present invention and the swallowing mechanism of a subject;

FIG. 5 is a schematic illustration of the drinking-actuated substance delivery device according to one embodiment of the present invention;

FIG. 6 is a schematic illustration of the a cross-section of the drinking-actuated substance delivery device according to another embodiment of the present invention;

FIG. 7 is a schematic illustration of the a cross-section of the drinking-actuated substance delivery device according to another embodiment of the present invention;

FIG. 8 is a schematic side-view illustration of the drinking-actuated substance delivery device according to another embodiment of the present invention;

FIG. 9 is a schematic illustration of the controlling member according to one embodiment of the present invention;

FIG. 10 is a schematic illustration of the specific elements of the drinking-actuated substance delivery device according to another embodiment of the present invention;

FIG. 11 is a schematic illustration of the drinking-actuated substance delivery device according to another embodiment of the present invention;

Fig. 12 illustrates another embodiment of the present invention in which an inhaling-actuating device 500 is presented.

Figs. 13-14 illustrates the basic concept behind the idea.

Figs. 15-19b illustrates a first specific mechanism of the inhaling-actuating device 500.

Figs. 18a-18b and 19a-19b provide a closer view of the actuation step of device 500.

Figs. 20-26e illustrates a second embodiment 600 of the present invention.

Figs. 27-28 illustrating another embodiment of the present invention.

Figs. 29-38 illustrating a third mechanism 700 based on the intake of air.

Figs. 38a-38b illustrate the top part 550 prior to and post loading of the medicament 560.

Figs. 39-41 illustrate a fourth embodiment of the inhaling-actuating device 800.

The drawings together with the description make apparent to those skilled in the art how the invention may be embodied in practice.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of the components set forth in the following description or illustrated in the drawings. The invention is applicable to other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting. The present invention discloses an intranasal substance delivery platform, giving synchronized delivery of drug and improving patient's compliance by eliminating bad flavor and insuring dose delivery.

The term '**substance**' refers hereinafter to any material which may be used for delivery to the nasal cavity of a subject for medical and alike purposed. According to different embodiments of the present invention, the substance may be delivered to the nasal cavity in a form of a powder, a granule, a cachet, a capsule, a tablet, a paste, a cream, a gel, an ointment, a salve, a foam, a paste, a lotion, a cream, an oil suspension, a spray, a suspension, a solution, an emulsion, a patch, a stick, a spray, preferably a nasal spray, or a buccal spray, a mouth wash, an aerosol, in a venture effect, or a drink or solution.

The term '**pressure gradient**' refers hereinafter to physical quantity that describes in which direction and/or at what rate the pressure changes the most rapidly around a particular location.

The term '**suction**' refers hereinafter to the flow of a fluid (e.g., air, liquid) into a partial vacuum, or region of low pressure. The pressure gradient between this region and the ambient pressure will propel matter toward the low pressure area.

The term '**drinking**' in the current invention is associated with the physiological process of swallowing in the human or animal body that makes something pass from the mouth, to the pharynx, into the esophagus, with the shutting of the epiglottis and closing the soft palate. According to the present invention, drinking is accompanied with suction of a fluid through a tubule.

The term '**nasal passageways**' refers hereinafter to the nasal passageways of a nose of a subject.

The term '**release**' refers hereinafter to extraction of substance in a manner which can be, for example, spraying, sprinkling, scattering, dispersing, etc.

The term '**predetermined amount of substance**' is a specific dose of a substance that can be regulated by the device.

The term '**coordination**' to a synchronized order of the following: mastication, deglutition and respiration in which an aspiration is prevented.

According to the study of J. Smith et al. (Coordination of Eating, Drinking and Breathing in Adults, John Smith, et. al., Chest, 1989, 96:33, 578-582), it was shown that swallowing occurred almost exclusively in expiration (in the study 271 patients were tested in which only two occurred in inspiration). This physiologic phenomenon is very important for a proper operation of the device provided by the present invention.

According to one embodiment of the present invention, a substance is released into the nasal passageways of a subject and does not reach the pulmonary region (which can occur while inspiration). According to J. Smith et al's research, there is a full coordination between drinking and breathing, such that when the subject is drinking a fluid, an inspiration is prevented, thus, at this stage, the substance can be safely released into the nasal passageways of the subject.

The present invention provides an air-intake actuated device adapted for delivering a substance to a nasal cavity of a subject, said device comprising (a) a container for containing said substance; (b) a nosepiece extending from said device for placement in proximity to a nose of said subject, said nosepiece being in fluid communication with said container; (c) a valve mechanically connectable to said container, characterized by at least two configurations: (i) an ACTIVE CONFIGURATION in which said valve enables delivery of predetermined amount of said substance from said container to said nasal cavity via said nosepiece; and, (ii) an INACTIVE CONFIGURATION, in which said valve prevents delivery of said predetermined amount of said substance from said container to said

nasal cavity; (d) a mouthpiece extending from said device for placement in a mouth of said subject; and, (e) a trigger mechanism adapted to reconfigure said valve from said ACTIVE CONFIGURATION to said INACTIVE CONFIGURATION, and vice versa; wherein said trigger mechanism is activated by means of said subject intaking air through said mouthpiece; further wherein said trigger mechanism is adapted to reconfigure said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION for a predetermined period of time in response to said subject intake of air.

The present invention further provides a drinking-actuated device adapted for delivering a substance to a nasal cavity of a subject; the device comprising: (a) a container for containing said substance; (b) a nosepiece extending from said device for placement in proximity to a nose of said subject, said nosepiece being in fluid communication with said container; (c) a valve mechanically connectable to said container, characterized by at least two configurations: (i) an ACTIVE CONFIGURATION in which said valve enables delivery of predetermined amount of said substance from said container to said nasal cavity via said nosepiece; and, (ii) an INACTIVE CONFIGURATION; (d) a mouthpiece extending from said device for placement in a mouth of said subject; and, (e) a trigger mechanism adapted to reconfigure said valve from said ACTIVE CONFIGURATION to said INACTIVE CONFIGURATION, and vice versa; wherein said mouthpiece is fluidly connectable by means of a tubule to a fluid reservoir containing a fluid, said fluid reservoir is adapted to supply said fluid to said mouth of said subject via said mouthpiece; further wherein said trigger mechanism is adapted to reconfigure said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION for a predetermined period of time in response to a pressure gradient generated by suction applied by said subject to said tubule for drinking said fluid through said tubule.

FIG. 1 illustrates the pattern of breathing while drinking according to the study of J. Smith et al. The top graph illustrates tidal breathing, and the bottom graph illustrates the submental EMG (Electromyography), both related to the swallowing process. The arrows presented in the figure indicate swallows. The figure demonstrates that during drinking (the bottom graph) there is no change in the breathing pattern (upper graph). Hence it can be concluded that there is no breathing while drinking.

The different patterns of swallowing and breathing were also studied by J. Smith et al., and are illustrated in FIGS. 2a-2c. As will be demonstrated, the inspiration is terminated while swallowing occurs. The top graphs illustrate the change in volume during tidal breathing, and the bottom graphs illustrate the submental EMG. In FIG. 2a, the swallow occurs at the beginning of expiration (end of inspiration). In the majority of swallows, as illustrated in FIG. 2b, the swallows occurred in the midexpiration and followed by expiration. Occasionally, as illustrated in FIG. 2c, the swallows

occurred CLOSED to end expiration, and was usually followed by a further expiration. In each of the cases illustrated in FIGS. **2a-2c**, the inspiration is terminated while swallowing occurs.

FIGS. **3a-3f** schematically illustrate the motor events of the swallowing reflex (e.g., while drinking), on which the device of the present invention is based on.

As was discussed above, there is ample evidence to suggest an important relationship between swallowing and breathing. Swallowing may be initiated by stimulation of many sites in the upper respiratory tract, though most studies suggest the epiglottis and larynx are the most sensitive areas for initiation of the swallowing reflex. FIG. **3a** illustrates the onset of the swallowing reflex when a subject **60** swallows bolus **61** (e.g., water, food, etc.).

Said figure illustrates the tip of the tongue **62** in contact with the anterior part of the palate **63**. The bolus **61** is pushed backward in groove between the tongue **62** and the palate **63**. As a result, the soft palate **64** is being drawn upward, such that the nasal passageways **65** and the respiratory system **66** are isolated from each other.

As can be seen in FIG. **3b**, the bolus **61** has reached the vallecula, the hyoid bone and the larynx **67** move upward and forward, the epiglottis **68** is tipped downward, and the contraction wave on posterior pharyngeal wall moves downward. As can be seen in FIG. **3c**, the soft palate **64** has been pulled down and has been approximated to the root of the tongue **62** by contraction of the pharyngopalatine muscles, and by pressure of a descending pharyngeal contraction wave.

Following that, the cricopharyngeus muscle is opened to permit entry of the bolus into the esophagus **69**, and the trickle of the bolus **61** enters also the laryngeal opening **70** but is prevented from going further by closure of the ventricular folds.

As can be seen in FIG. **3d**, the contraction wave has reached the vallecula and is pressing out the remains of the bolus **61**. Now the bolus has largely passed through the upper sphincter into esophagus **69**. As can be seen in FIG. **3e**, the contraction wave has passed the pharynx, the epiglottis **68** is beginning to turn up again as hyoid bone and the larynx descends. Now, the communication with the nasopharynx has been re-established.

In FIG. **3f**, all structures of the pharynx have returned to resting position.

As was disclosed above, the present invention takes advantage of the physiological process illustrated in FIG. **3a-3f**. When the soft palate is drawn upwardly and closes, a substance (e.g., a drug, a vaccine, etc.) can be delivered to the nasal passageways, without reaching the repository system and the lungs.

Reference is now made to Fig. **4a-4f** which schematically illustrate the mechanism of a drinking-actuated substance delivery device **10** of the present invention and the action of the swallowing mechanism of a subject **90** according to some embodiments of the invention.

According to FIG. **4a**, a nosepiece **11** of device **10** is inserted into the nose of subject **90**, and mouthpiece **12** is inserted into said subject's mouth **18**. According to said embodiments, device **10** is fluidly connected to fluid reservoir **50** (e.g., a bottle, a can, etc.) such that subject **90** drinks fluid **51** (e.g., water, a juice, a fluid medication, a cold fluid, a warm fluid etc.) through device **10**. In FIG **4a**, the soft palate **20** of subject **90** is opened, such that subject **90** is able to breath. FIG. **4b** illustrates the activation of device **10**. When subject **90** begins to drink fluid **51**, the swallowing reflex is activated, such that soft palate **20** is closed.

Simultaneously to the passage of fluid **51** within the throat of said subject, a predetermined amount of substance **15** is delivered from device **10** to nasal passageways **30** into the subject's nose.

As illustrated in FIG. **4c**, the subject had finished drinking said fluid and the substance **15** had been delivered to nasal passageways **30**.

According to FIG. **4d**, said fluid has been swallowed by subject **90**, substance **15** has been already diffused within nasal passageways **30** and the soft palate is opened again.

According to FIG. **4e**, a nosepiece of the device **10** is inserted into the nose of subject **90**, the mouthpiece is inserted into said subject's mouth, and the device is fluidly connected to the fluid reservoir (e.g., a bottle, a can, etc.) such that subject **90** is able to drink the fluid (e.g., water, a juice, a fluid medication, a cold fluid, a warm fluid etc.) through the device. In FIG **4e**, the soft palate **20** of subject **90** is opened, such that subject **90** is able to breath.

FIG. **4f** illustrates the activation of device **10**. When subject **90** begins to drink fluid **51**, the swallowing reflex is activated, such that soft palate **20** is closed.

As illustrated in FIG. **4g**, the subject is drinking said fluid and simultaneously a predetermined amount of substance **15** is delivered from device **10** to nasal passageways **30** into the subject's nose.

According to FIG. **4h**, said fluid has been swallowed by the subject, substance **15** is in the process of diffusion within the nasal passageways and the soft palate is opened again.

Fig. **5** schematically illustrates one embodiment of the drinking-actuated substance delivery device **200** for delivering a substance to a nasal cavity of a subject.

According to this figure, drinking-actuated device **200** comprises the following main element:

- a. A container **195** for containing said substance (not shown).

- b. A nosepiece **190** extending from drinking-actuated device **200** for placement in proximity to a nose of said subject. Nosepiece **190** is in fluid communication with container **195**. The substance is adapted to be administrated through nosepiece **190** to the nose of the subject.
- c. A valve **145** mechanically connectable to container **195**. Valve **145** is characterized by at least two configurations:
 - i. an ACTIVE CONFIGURATION in which valve enables the delivery of predetermined amount of substance from container **195** to the nasal cavity of the subject via nosepiece **190**; and,
 - ii. an INACTIVE CONFIGURATION in which the substance is not delivered to the nose of the subject.
- d. A mouthpiece **111** extending from device **200** for placement in a mouth of the subject.
- e. A trigger mechanism **120** adapted to reconfigure valve **145** from the ACTIVE CONFIGURATION to the INACTIVE CONFIGURATION, and vice versa.
- f. A tubule **110** fluidly connectable with mouthpiece **111** and a fluid reservoir **105** containing a fluid **107**. Fluid reservoir **105** is adapted to supply fluid **107** to the mouth of the subject via mouthpiece **111**.

According to some embodiments of the present invention, the trigger mechanism **120** which is adapted to reconfigure valve **145** from the INACTIVE CONFIGURATION to the ACTIVE CONFIGURATION for a predetermined period of time in response to a pressure gradient generated by suction applied to tubule **110** (through mouthpiece **111**) while the subject sucks and drinks fluid **107** through tubule **110**.

Trigger mechanism **120** is adapted to reconfigure valve **145** from the ACTIVE CONFIGURATION to the INACTIVE CONFIGURATION when the pressure gradient is absent.

According to some embodiments, valve **145** is reconfigurable from the INACTIVE CONFIGURATION to the ACTIVE CONFIGURATION when the pressure gradient applied is above a predetermined threshold.

According to the present invention, while using device **200**, the substance is delivered to the nose of the subject while the same drinks fluid **107**.

During the drinking of the fluid **107**, the swallowing reflex is activated, and as a result the soft palate of the subject is closed. During this process, the nasal cavity of the subject is substantially isolated from the remainder of the pulmonary system, so that the delivery of the substance to the nasal cavity may be performed safely.

According to some embodiments, the operation of nosepiece **90** and valve **145** is similar to an operation known in the art spray device which is able to generate a spray effect on the target tissue.

According to a specific embodiment of trigger mechanism **120** which is illustrated in Fig. **5**, trigger mechanism **120** comprises a controlling member **130** vertically positioned relatively to tubule **110**.

Controlling member **130** has three main portions: a first end **126** positioned within tubule **110**; a middle portion **127** in communication with a membrane **140**; and, a second end **128**.

As will be explained hereinafter, when second end **128** is in communication with valve **145**, the valve is in the INACTIVE CONFIGURATION; and, when second end **128** of the controlling member is not in communication with valve **145**, the valve **145** is reconfigured to the ACTIVE CONFIGURATION.

The connection of first end **126** of controlling member **130** and tubule **110** is performed through an aperture **133**. First end **126** is reciprocally movable within tubule **110** and second end **128** is reciprocally movable within valve **145** in response to the pressure gradient.

Controlling member **130** is having two configurations:

- i. a CLOSED CONFIGURATION (illustrated in Figs. **5** and **6**) in which fluid is not provided to the subject via tubule **110** and valve **145** is in the INACTIVE CONFIGURATION; and,
- ii. an OPENED CONFIGURATION (illustrated in Fig. **7**) in which the subject drinks fluid **107** through tubule **110** and valve **145** is in the ACTIVE CONFIGURATION.

According to different embodiments of the present invention, controlling member **130** may be positioned with respect to tubule **110** at any predetermined angle between about 5° and about 175° .

According to different embodiments of the present invention and the embodiment of Fig. **5**, trigger mechanism **120** comprises a pressure responsive cavity **124** mechanically connected to controlling member **130** in middle portion **127**.

Cavity **124** is a pressure responsive cavity which is adapted to reconfigure controlling member **130** from the CLOSED CONFIGURATION to the OPENED CONFIGURATION, and vice versa.

When pressure gradient is applied (i.e., when the subject sucks tubule **110** through mouthpiece **111**), the controlling member is reconfigured to the OPENED CONFIGURATION, and when the pressure gradient is absent, the controlling member is reconfigured to the CLOSED CONFIGURATION.

In the CLOSED CONFIGURATION, controlling member **130** is adapted to block the passage of fluid **107** from fluid reservoir **105** to **111** mouthpiece through tubule **110**.

The reconfiguration of connecting member **130** between the two configurations is performed via flexible membrane **140** which is an essential part of cavity **124**.

Flexible membrane **140** is mechanically connected to connecting member **130** by surrounding the same in middle portion **127**.

Flexible membrane **140** is adapted to change its shape (e.g, to an arched shape) in response to the pressure gradient in tubule **110**. As a result of this shape change, controlling member **130** will be dragged towards tubule **110** and reconfigured from the CLOSED CONFIGURATION to the OPENED CONFIGURATION.

Controlling member **130** comprises two apertures:

- (i) a first aperture **133** which is adapted to fluidly communicate between cavity **124** and mouthpiece **111** through at least a part of tubule **110**. First aperture **133** is extendable within controlling member **130** from the area of tubule **110** to the area of cavity **124**. First aperture **133** is adapted to 'transfer' the pressure gradient from said tubule **110** to cavity **124**, such that controlling member **130** is reconfigured from the CLOSED CONFIGURATION to the OPENED CONFIGURATION.
- (ii) A second aperture **134** adapted to facilitate passage of fluid **107** through controlling member **130** when controlling member **130** is in the OPENED CONFIGURATION. Second aperture **134** is in fluid communication with the upper part of first aperture **133**. While being in the OPENED CONFIGURATION, the passage of fluid **107** within second aperture **134** is adapted to preserve controlling member **130** in this configuration as fluid **107** passes through controlling member **130**.

According to the embodiment of Fig. 5, valve **145** comprises a spring **180** which is at least partially tensed in the INACTIVE CONFIGURATION of the valve, and at least partially released in the ACTIVE CONFIGURATION of the valve.

In the at least partially tensed position of spring **180**, more static energy is stored within the spring relatively to the at least partially released position of spring **180**.

According to this embodiment, valve **145** further comprises a piston **170** to which spring **180** being connected. Piston **170** is adapted to push via spring **180** container **195** towards a needle **160**. As result of this, the substance will be released to the patient through nosepiece **190**.

In said INACTIVE CONFIGURATION piston **170** is not pushing container **195**. Furthermore, in said ACTIVE CONFIGURATION, in which spring **180** is release, the static energy stored with the spring is converted to a pushing energy actuated on container **195** via piston **170**.

The reconfiguration of the valve from the INACTIVE CONFIGURATION to the ACTIVE CONFIGURATION is performed when second end **128** moved down as a result of the reconfiguration of connecting element **130** from the CLOSED CONFIGURATION to the OPENED CONFIGURATION.

According to other embodiments, valve **145** may comprise a spring which is at least partially released in the INACTIVE CONFIGURATION, and at least partially tensed in the ACTIVE CONFIGURATION.

According to some embodiments, tubule **110** is at least partially a straw. According to other embodiments, the device of the present invention may be connected to a straw which may be inserted within the fluid reservoir.

According to the embodiment of Fig. **5**, the operation of trigger mechanism **120** is synchronized with the drinking of fluid **107** by performed by the subject.

According to some embodiments, trigger mechanism **120** comprises a pulsation mechanism adapted to reconfigure valve **145** from the INACTIVE CONFIGURATION to the ACTIVE CONFIGURATION and vice versa in sequence of pulses, each of which is characterized by a predetermined length of pulse.

Valve **145** adapted to a release the predetermined amount of the substance according to the sequence of pulses. For example, in each pulse at least two doses of said predetermined amount of said substance are released.

According to some embodiments, nosepiece **190** may comprise a spray nozzle **191**. According to different embodiments, the spray nozzle may be characterized by a diameter which influences on said predetermined period of time.

Reference is now made to Fig. **6** which schematically illustrates a cross section of device **200**. According to this figure, controlling member **130** is in the CLOSED CONFIGURATION, and as a result of that, valve **145** is in the INACTIVE CONFIGURATION.

When a subject (not shown) drinks a fluid via tubule **110** and opening **113** and mouthpiece **111**, a pressure gradient is formed within said tubule. Such fluid may be stored within a fluid reservoir (not shown). The pressure gradient which is formed within part of tubule **110** is delivered also to cavity **124** through first aperture **133**.

Reference is now made to Fig. **7**. According to this figure, as a result of the pressure gradient which is formed within cavity **124**, flexible membrane **140** is moved downwards. As a result of that,

controlling member **130** is dragged (by means of said membrane **140**) to recess **138**, and thus reconfigured from the CLOSED CONFIGURATION to the OPENED CONFIGURATION.

In the OPENED CONFIGURATION, the following two features occur:

- 1) The fluid flows within tubule **110** through first end **126** of controlling member **130**.
- 2) As a result of the movement of the controlling member **130** and hence the second end **128** (e.g., a safety catch), the valve **145** is reconfigured from the INACTIVE CONFIGURATION to the ACTIVE CONFIGURATION. As a result of that, the substance is delivered from container **195** to the nasal cavity of the patient via nosepiece (not shown).

According to some embodiments, the substance may be stored within container **195** under a predetermined pressure. Therefore, when needle **160** contacts a specific point in container **195**, the substance may be released (e.g., as a spray).

According to some embodiments, valve **145** may comprise more than one element which reconfigures it to the ACTIVE CONFIGURATION.

According to other embodiments, container **195** is a syringe.

According to other embodiments, device **200** may further comprise a cap which is adapted to cover at least a portion of the components of said device for sterilization/ aseptic purposes. This cap may comprise an opening.

According to some embodiments, container **195** adapted to be connected to an external container (not shown). The external container is adapted to fill container **195** with a predetermined dose of a substance.

According to some embodiments, device **200** may further comprise indicating means adapted to indicate the amount of said substance within said container. The indicating means may be a transparent window located on a side of the container.

According to some embodiments, fluid **107** may be selected from a group consisting of: water, a juice, a fluid medication, a cold fluid, a warm fluid, or any combination thereof.

Reference is now made to Fig. **8** which schematically illustrates a specific embodiment of device **300** according to the present invention.

According to this figure, device **300** comprises a nosepiece **290**, a mouthpiece **211**, a tubule **210**, and a triggering mechanism **220**.

According to this embodiment, the device **300** comprises a recess **238** to which the controlling member (not shown) enters when it is reconfigured from the CLOSED CONFIGURATION to the

OPENED CONFIGURATION (so as to reconfigure the valve from the INACTIVE CONFIGURATION to the ACTIVE CONFIGURATION).

The edge **212** of tubule **210** may be inserted into a fluid reservoir (not shown).

Reference is now made to a specific embodiment of controlling member **130**.

According to this embodiment, controlling member **130** has three main portions: a first end **126**; a middle portion **127**; and, a second end **128**.

The first end **126** is adapted to be placed within tubule **110**. The middle portion **127** is adapted to be connected to membrane **140**. The second end **128** is adapted to be reversibly connected to valve **145**.

First end **126** is reciprocally movable within tubule **110** and second end **128** is reciprocally movable with respect to valve **145** in response to the pressure gradient generated within tubule **110**.

Fig. **9** provides a better view of the first aperture **133**, and the second aperture **134**.

First aperture **133** is adapted to be in fluid communication with the cavity **124** and the mouthpiece **111** through a portion of tubule **110**.

First aperture **133** is extending within controlling member **130** from the area of tubule **110** to the area of cavity **124**. First aperture **133** is adapted to transmit the pressure gradient from said tubule **110** to cavity **124** (once the user sucks/drinks the fluid), such that controlling member **130** is reconfigured from the CLOSED CONFIGURATION to the OPENED CONFIGURATION.

Second aperture **134** is adapted to facilitate passage of fluid **107** through controlling member **130** when controlling member **130** is in the OPENED CONFIGURATION.

Second aperture **134** is in fluid communication with the upper part of first aperture **133**. While the controlling member **130** is in the OPENED CONFIGURATION, the passage of fluid **107** through second aperture **134** is adapted to preserve and maintain the controlling member **130** in the OPENED CONFIGURATION.

Fig. **10** illustrates another embodiment of several parts of the device according to the present invention. In this figure the following components are illustrated: controlling member **130**, tubule **110**, and mouthpiece **111**.

Reference is now made to Fig. **11** which schematically illustrates another embodiment of the drinking-actuated substance delivery device **400**.

The drinking-actuated device **400** includes housing **310**, having a mouthpiece **320** which extends out from device **300**.

Mouthpiece **320** is adapted to be placed in a mouth of a subject. Housing **310** also contains container **330** which is adapted to contain substance **332** (e.g., a drug, a vaccine, etc.).

Container **330** is in a fluid communication with nosepiece **340** through valve **335**.

Nosepiece **340** is extending from device **400**, and is adapted to be placed in or around a nose of a subject.

Valve **335** is adapted to regulate passage of substance **332** from container **330** to nosepiece **340**. The operation of valve **335** is performed by trigger mechanism **337** which is adapted to transform valve **335** from an INACTIVE CONFIGURATION to an ACTIVE CONFIGURATION, and vice versa.

According to the present invention, device **400** is fluid-based actuated. I.e., while a subject drinks a fluid (e.g., juice, water, etc.) **355** through device **400**.

Fluid **355** is supplied from a fluid reservoir **350** (e.g., a bottle, a can, etc.) to mouthpiece **320**, which is fluidly connected to fluid reservoir **350** by means of tubule **360**.

While a subject (e.g., user, patient, etc.) drinks fluid **355**, the fluid flows in tubule **360**. Such flow creates pressure within said tubule.

Said pressure in tubule **360** actuates a trigger mechanism **337** in actuation point **359**, such that the actuated trigger mechanism **337** opens valve **335** to a predetermined period of time.

The result of that is the following: a predetermined amount of substance **332** is released from container **330** to nosepiece **340** when said pressure is greater than a predetermined pressure threshold.

The pressure threshold is the minimum pressure needed to activate trigger mechanism **337** and is in the range of between about 0.1 Pascal to about 30 Pascal.

According to some embodiments, trigger mechanism **337** is synchronized with the drinking of fluid **355** by the subject. According to the preferred embodiment of the invention, fluid **355** which is drunk by the subject activates its swallowing reflex that closes the soft palate to a specific period of time, such that the nasal passageways of said subject's nose are substantially isolated from the remainder of the pulmonary system. At this specific period of time, the substance is released from device to the nasal passageways. According to some embodiments, the release of said substance is simultaneous with the drinking and swallowing of said fluid.

According to some embodiments, trigger mechanism **337** is incorporated within valve **335**, such that there is one valve which is responsive to an external pressure of fluid and is responsive for releasing the substance to the nosepiece.

According to some embodiments, the actuation of the valve by the trigger mechanism is at least partially based on the Venturi effect. This effect is based on the Bernoulli equation which states that the sum of all forms of energy in a gas flowing along an enclosed path is the same at any two points in that path (or streamline). Its formulation in the simplistic hypothesis of incompressible flow (gas motion with negligible changes in density) is:

$$\frac{v^2}{2} + gh + \frac{p}{\rho} = \text{const.}$$

Where: v is the gas velocity along the streamline, g is the acceleration of gravity on Earth, h is the height, p is the pressure along the streamline, and ρ is the gas density. As a consequence of the Bernoulli law, a gas passing through smoothly varying constrictions is subjected to changes in velocity and pressure. A Venturi is a system for speeding the flow of the gas, by constricting it in a cone shape tube. In the restriction the fluid must increase its velocity reducing its pressure and producing a vacuum. As the gas leave the constriction, its pressure increase back to the ambient or pipe level.

The opening of valve **335** is also influenced by the amount of substance which is release, and the inspiratory force according to which the subject is drinking the fluid. According to the Venturi effect, the amount of substance and the inspiratory force, or at least part of them, create the predetermined pressure threshold mentioned above.

In order to reconfigure valve **335** to the ACTIVE CONFIGURATION, the pressure in tubule **360** has to be greater than this pressure threshold, such that trigger mechanism **337** is actuated and valve **335** is acutated to a predetermined period of time.

The drinking-actuated mechanism of the device of the present invention has the ability to eliminate bad flavor of the substance which is released into the subject's nose by combining the release of the substance in the nose with a "throat washing" effect by the fluid which is simultaneously drunk by the subject. According to some embodiments of the invention, tubule **360** can be at least partially a straw.

According to the preferred embodiment of the invention, tubule **360** is fluidly connected to an external straw **362**. According to some embodiments, straw **362** is insertable into fluid reservoir **350**.

According to some embodiments of the invention, container **330** of device **400** may comprise a piston **131** which is adapted to compress substance **332** within the container **330**. Such a compression creates pressure within container **330** and push said substance **332** forward. In the preferred embodiment of the invention, piston **331** is located in the back side of container **130**.

According to some embodiments, trigger mechanism **337** is adapted to reciprocally move piston **331** within container **330**, when it is actuated in response to the fluid **355** pressure within the tubule **360** while the subject drinks the fluid.

According to some embodiment of the invention, trigger mechanism **337** comprises a pulsation mechanism which is adapted to actuate valve **335** in a predetermined sequence of pulses.

Each pulse is characterized by a predetermined length of pulse (in time) in which a predetermined amount of said substance is released by said valve according to said sequence of pulses.

For example, the subject drinks the fluid so as to actuate the trigger mechanism for a total amount of 4 second.

In this case two doses of substance can be sprayed into the nose, the first dose between the first second and the second one, and the second dose between the third second and the fourth second.

According to some embodiments, nosepiece **340** is in fluid communication with valve **335** by means of a spray nozzle. In this case, the spray nozzle might be a known in the art spray nozzle which is able to release the substance by spaying it into the nose. According to these embodiments, the spray nozzle might be characterized by a diameter, which influences the predetermined period of time in which the substance released to the nose. According to some embodiments, container **330** is a syringe.

According to some embodiments, device **400** might comprise a cap which is adapted to cover at least a portion of the components of said device for sterilization/ aseptic purposes. For example, a cap that covers the nosepiece, and/or the mouthpiece. This cap might comprise an opening.

According to one embodiment of the present invention, the device **400** is utilized for a single use (namely a disposable device). According to another embodiment of the present invention, the device **400** is utilized for a multiple use.

According to a preferred embodiment of the invention, as illustrated in FIG. **11**, device **400** might be mechanically connected (e.g., by piercing means) to external container **390**. External container **390** is adapted to fill container **330** with substance **332**.

According to some embodiments, device **400** might comprises indicating means which is adapted to indicate the amount of substance within the container.

According to some embodiments, the substance implemented by the device of the present invention may be a drug selected from a group consisting of: Anti-Angiogenesis agents, Antisense, anti-ulcer, butorphanol, Calcitonin and analogs, COX-II inhibitors, desmopressin and analogs, dihydroergotamine, Dopamine agonists and antagonists, Enkephalins and other opioid peptides, Growth hormone and analogs, growth hormone releasing hormone, Growth hormone antagonists, IgE suppressors, Insulin, insulinotropin and analogs, Ketamine, Kytril, Leutenizing hormone releasing hormone and analogs, lidocaine, metoclopramide, Midazolam, Narcotic analgesics, neuraminidase inhibitors, nicotine, Non-steroid anti-inflammatory agents, Oligosaccharides, ondansetron, Parathyroid hormone and analogs, Parathyroid hormone antagonists, Prostaglandin antagonists, Prostaglandins, Recombinant soluble receptors, scopolamine, Serotonin agonists and antagonists, Sildenafil, Terbutaline, vasopressin, or any combination thereof.

According to some embodiments, the substance implemented by the device of the present invention may be a vaccine with or without carriers and/or adjuvants selected from the group consisting of: Prophylactics and therapeutic antigens, subunit protein, peptide and polysaccharide, polysaccharide conjugates, toxoids, genetic based vaccines, live attenuated, reassortant, inactivated, whole cells, viral and bacterial vectors for the treatment of arthritis, *Lactobacillus species*: *Lactobacillus acetotolerans*, *Lactobacillus acidifarinae*, *Lactobacillus acidipiscis*, *Lactobacillus acidophilus* (*Doderlein bacillus*), *Lactobacillus agilis*, *Lactobacillus algidus*, *Lactobacillus alimentarius*, *Lactobacillus amylolyticus*, *Lactobacillus amylophilus*, *Lactobacillus amylophobicus*, *Lactobacillus amylovorus*, *Lactobacillus animalis*, *Lactobacillus antri*, *Lactobacillus apodemi*, *Lactobacillus aviarius*, *Lactobacillus bifementans*, *Lactobacillus brevis*, *Lactobacillus buchneri*, *Lactobacillus camelliae*, *Lactobacillus casei*, *Lactobacillus catenaformis*, *Lactobacillus ceti*, *Lactobacillus coleohominis*, *Lactobacillus collinoides*, *Lactobacillus composti*, *Lactobacillus concavus*, *Lactobacillus coryniformis*, *Lactobacillus crispatus*, *Lactobacillus crustorum*, *Lactobacillus curvatus*, *Lactobacillus delbrueckii*, *Lactobacillus delbrueckii subsp. Bulgaricus*, *Lactobacillus delbrueckii subsp. Lactis*, *Lactobacillus diolivorans*, *Lactobacillus equi*,

Lactobacillus equigenersi, Lactobacillus farraginis, Lactobacillus farciminis, Lactobacillus fermentum, Lactobacillus fornicalis, Lactobacillus fructivorans, Lactobacillus frumenti, Lactobacillus fuchuensis, Lactobacillus gallinarum, Lactobacillus gasseri, Lactobacillus gastricus, Lactobacillus ghanensis, Lactobacillus graminis, Lactobacillus hammesii, Lactobacillus hamsteri, Lactobacillus harbinensis, Lactobacillus hayakitensis, Lactobacillus helveticus, Lactobacillus hilgardii, Lactobacillus homohiochii, Lactobacillus iners, Lactobacillus ingluviei, Lactobacillus intestinalis, Lactobacillus jensenii, Lactobacillus johnsonii, Lactobacillus kalixensis, Lactobacillus kefiranofaciens, Lactobacillus kefiri, Lactobacillus kimchii, Lactobacillus kitasatonis, Lactobacillus kunkeei, Lactobacillus leichmannii, Lactobacillus lindneri, Lactobacillus malefermentans, Lactobacillus mali, Lactobacillus manihotivorans, Lactobacillus mindensis, Lactobacillus mucosae, Lactobacillus murinus, Lactobacillus nagelii, Lactobacillus namurensis, Lactobacillus nantensis, Lactobacillus oligofermentans, Lactobacillus oris, Lactobacillus panis, Lactobacillus pantheris, Lactobacillus parabrevis, Lactobacillus parabuchneri, Lactobacillus paracollinoides, Lactobacillus parafarraginis, Lactobacillus parakefiri, Lactobacillus paralimentarius, Lactobacillus paraplantarum, Lactobacillus pentosus, Lactobacillus perolens, Lactobacillus plantarum, Lactobacillus pontis, Lactobacillus psittaci, Lactobacillus rennini, Lactobacillus reuteri, Lactobacillus rhamnosus, Lactobacillus rimae, Lactobacillus rogosae, Lactobacillus rossiae, Lactobacillus ruminis, Lactobacillus saerimneri, Lactobacillus sakei, Lactobacillus salivarius, Lactobacillus sanfranciscensis, Lactobacillus satsumensis, Lactobacillus secaliphilus, Lactobacillus sharpeae, Lactobacillus siliginis, Lactobacillus spicheri, Lactobacillus suebicus, Lactobacillus thailandensis, Lactobacillus ultunensis, Lactobacillus vaccinoesterus, Lactobacillus vaginalis, Lactobacillus versmoldensis, Lactobacillus vini, Lactobacillus vitulinus, Lactobacillus zeae, Lactobacillus zymae, Probiotics selected from a group consisting of Lactic acid bacteria (LAB) and bifidobacteria or any combination thereof; said substance is used for the treatment of at least one selected from a group consisting of cholera, moraxella catarrhali, cocaine addiction, HIB, meningococcus, measles, mumps, rubella, varicella, yellow fever, Respiratory syncytial virus, pneumococcus, streptococcus, typhoid, influenza, hepatitis, including hepatitis A, B, C and F, polio, HIV, parainfluenza, rotavirus, CMV, chlamydia, non-typeable haemophilus, moraxella catarrhalis, human papilloma virus, tuberculosis including BCG, gonorrhoea, asthma, atherosclerosis, malaria, otitis media, E-coli, Alzheimers, H. Pylori, salmonella, diabetes, cancer and herpes simplex, Staphylococcus aureus, Streptococcus, or any combination thereof.

According to some embodiments, the substance implemented by the device of the present invention is used for the treatment of at least one selected from a group consisting of cholera, moraxella catarrhali, cocaine addiction, HIB, meningococcus, measles, mumps, rubella, varicella, yellow fever, Respiratory syncytial virus, pneumococcus, streptococcus, typhoid, influenza, hepatitis,

including hepatitis A, B, C and F, polio, HIV, parainfluenza, rotavirus, CMV, chlamydia, non-typeable haemophilus, moraxella catarrhalis, human papilloma virus, tuberculosis including BCG, gonorrhoea, asthma, atherosclerosis, malaria, otitis media, E-coli, Alzheimers, H. Pylori, salmonella, diabetes, cancer and herpes simplex, Staphylococcus aureus, Streptococcus, or any combination thereof.

According to some embodiments, the substance is a peptide or protein therapeutic agent such as cytokines, hormones, clotting factors, vaccines, monoclonal antibody.

According to some embodiments, the device is used for the treatment of CNS disorder, brain disorders such as: brain cancer, acute brain injury, spinal cord injury, Alzheimer disease, Neurogenesis, Parkinson's disease, depression, Epilepsy, schizophrenia by the delivery of substances such as: Neurotrophins, BDNF, GDNF, anti EGF receptor AB, Enzymes as Lysosomal enzyme, Neuregulin.

According to some embodiments, the substance implemented by the device of the present invention is selected from a group consisting of natural oils; Mint oils, Peppermint oil, Spearmint oil, Menthol, Olive oil, Eucalyptus oil, Amino acids, fatty acids and any combination thereof.

According to some embodiments, the substance implemented by the device of the present invention may be a therapeutic substance selected from a group consisting of: Agents for the common cold, Anti-addiction, anti-infectives, analgesics, anesthetics, anorexics, antiarthritics, anti-allergy agents, antiasthmatic agents, anticonvulsants, anti-depressants, antidiabetic agents, anti-depressants, anti-diuretics, anti-emetics, antihistamines, anti-inflammatory agents, antimigraine preparations, antimoion sickness preparations, antinauseants, antineoplastics, anti-obesity, antiosteoporotic, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, anticholinergics, benzodiazepine antagonists, bone stimulating agents, central nervous system stimulants, hormones, hypnotics, immunosuppressives, prostaglandins, proteins, peptides, polypeptides and other macromolecules, psychostimulants, rhinitis treatment, sedatives, sexual hypofunction, tranquilizers and vitamins including B12, probiotics, natural oils, natural ingredients, or any combination thereof.

As mentioned above, the particle's or droplet's size has significant impact on absorption when administering substance via the nose and the nasal epithelia. According to another embodiment of the present invention the particle's or droplet's size is in the micro and nano size.

The above disclosure is based on the user sucking (and drinking) liquid (e.g., water, juice etc.).

According to another embodiment of the present invention, the mechanism is based on the user inhaling air (instead of in taking fluid). Reference is now being made to Figure 12 which generally illustrates the above principle.

Fig. 12 illustrates the inhaling-actuating device 500 for delivering a substance to a nasal cavity 501 of a subject. The device generally comprises a mouthpiece 502 (through which the patient inhales and thus activates the mechanism), a container 503 accommodating a medicament to be delivered to said patient and a nose piece 504 adapted to dispense the medicament to the nasal cavity of the patient.

Reference is now made to Figs. 13-14 which generally illustrates the basic concept behind the idea. Fig. 13 illustrates the mouth piece 502 of the inhaling-actuating device 500 being place within the mouth of the patient and the nose piece 504 being place within the nose of the patient.

Fig. 14 illustrates the inhaling-actuating device 500 once the same is activated. Namely, once the patient intake (or sucks) air. As will be described hereinafter, once the patient intake air 505 the inhaling-actuating device 500 is activated and the medicament 506 is being release to the nose 501 of the patient.

Reference is now being made to Figs. 15-19b, illustrating a first specific mechanism of the inhaling-actuating device 500 as described above.

Fig. 15 illustrates the inhaling-actuating device 500 prior to the activation of the same (i.e., the air inhaling)

As can be seen in Fig. 15 the device comprises the nose piece 504 (to be place within the nasal cavity of the patient), the mouth piece 502 (to be place within the mouth of the patient, a container 503 for accommodating the medicament 506 to be delivered to the nasal cavity of the patient. The actuation mechanism (for activating the device and delivering medicament to the patient's nasal) comprises a first unidirectional valve 507, a membrane 508, an intermediate compartment 511 (for accommodating a uni-dose amount of medicament to be delivered to the patient's nasal), at least one spring 509 and a second valve means 510.

Prior to the actuation of device 500, the unidirectional valve 507 enable to filling of intermediate compartment 511 with the uni-dose amount of medicament 506 (as will be described hereinafter, this is enabled due to the fact that after said medicament is released to the nasal, vacuum is created

in said intermediate compartment **511**, which 'draw' said medicament **506** through unidirectional valve **507**).

Fig. **16a** illustrated the device **500** while being place in the nose and mouth of the patient. Fig. **16b** illustrates the activation of the device **500**, namely, the sucking of air through mouth piece **502**.

Reference is now being made to Figs. **17-19b**, illustrating the actuation mechanism. Once the patient intake air (through mouthpiece **502**) membrane **508** is drawn downwardly (in the direction of container **503**. Membrane **508** is in communication with said spring **509**; such that, when membrane **508** is drawn downwardly, said spring **509** is loaded and compressed.

Said spring **509** is in physical communication with valve means **510** such that, when spring **509** is loaded and compressed (as a result of the downwards movement of the membrane **508**) valve means **510** are opened and the medicament **506** are released to the patient's nasal.

It should be pointed out that valve means **510** additionally comprising sealing means **512** adapted to seal the passage of medicament form the intermediate compartment **511** to the nasal without the actuation of the patient (i.e., air suction).

Once the medicament is released to the nasal cavity, vacuum is created in the intermediate compartment **511**, which eventually enables the withdrawal of another uni-dose amount of medicament **506** from the container **503** through unidirectional valve **507**.

Reference is now made to Figs. **18a-18b** and **19a-19b** which provide a closer view of the actuation step of device **500**. Figs. **18a-18b** illustrates the device **500** prior to the actuation step and Figs. **19a-19b** illustrates the device **500** post the actuation.

As mentioned above, prior to the actuation, intermediate compartment **511** is filled with a uni-dose amount of medicament. In this stage, the valve means **510** is closed and sealing means **512** seals said intermediate compartment **511** from releasing medicament to the patient.

Figs. **19a-19b** illustrates the device **500** post actuation. As mentioned above, once the patient intake air, membrane **508** is actuated and withdrawn downwardly such that spring **509** is loaded and compressed. Once spring **509** is compressed, valve **510** is opened and the medicament is released from the intermediate compartment **511** to the nasal cavity.

Reference is now made to Figs. **20-26d** which illustrates a second embodiment **600** of the above mentioned concept.

According to this embodiment, a further step of 'charging' or 'loading' the inhaling-actuating device **600** with the uni-dose amount of medicament **506**.

Reference is now made to Fig. **20** which illustrates the main components of inhaling-actuating device **600**, which comprises a mouthpiece **502**, a nosepiece **504**, a unidirectional valve **507**, a container **503** for accommodating the medicament **506** and a loading mechanism **513**.

Reference is now made to Fig. **21** and Figs. **22a-22c** which provides a closer view of the loading mechanism **513**. As can be seen in Figs. **22a-22b** the loading mechanism **513** comprises a rotating knob **514**, a first actuator **515** and a second actuator **516**, complementary to said first actuator.

When the user wishes to load the device **600**, he rotates knob **514** (see Fig. **21**). Said rotating knob comprises a spiral elevating means **518** in communication with said first actuator **515**. Rotation of the rotating knob **514** rotates the spiral elevating means **518** which eventually elevates the first actuator **515** and pushes the same into the complementary second actuator **516**.

The first actuator **515** is characterized by at least two wings **515a** and **515b**, each of which comprises a protrusion (i.e., a bulge) **515c-515d**, respectfully.

Said complementary second actuator **516** comprises two grooves **516a** and **516b** adapted to accommodate said bulge **515c** and **515d**.

Said complementary second actuator **516** is further coupled to a third complementary actuator **517**. Said third complementary actuator **517** comprises, like actuator **515**, at least two wings **517a** and **517b**, each of which comprises a protrusion (i.e., a bulge) **517c** and **517d** (**517d** is not shown), respectfully.

Once said rotating knob **514** is rotated and the first actuator is elevated into the complementary second actuator **516** and into the third complementary actuator **517**; bulges **515c** and **515d** are being positioned inside said grooves **516a - 516b** of the second actuator **516**. Said bulges **515c** and **515d** are being held in place by the bulges **517c** and **517d** of the third complementary actuator **517** (see Figs. **22a-22b**).

Such movement of said actuator creates vacuum inside the intermediate compartment **511**, and thus, the device **600** is loaded with the dose to be delivered to the patient (see Fig. **22c**).

Reference is now made to Figs. **23-25** which illustrates the activation of device **600** (namely, the air intake by the user, as seen in Fig. **25**). When the user intake air, the medicament **506** is released to

the user and membrane **508** is elevated upwardly. Said membrane is coupled to said third complementary actuator **517**.

Once said membrane **508** is elevated said third complementary actuator **517** is elevated as well. Said elevation pushes said wings **517a** and **517b** inwardly so as to release said wings **515a** and **516b** of actuator **515**. And thus, to return actuator **515** to its initial position (the pre-loading position).

Reference is now made to Figs. **26a-26d** closely illustrating the discharge of the actuator **515** to its initial position. Fig. **26a** illustrates the actuator **515** (namely the bulge **515d**) coupled the third complementary actuator **517** (namely to bulge **517d**). Once the membrane **508** is elevated (the user intake air) the third complementary actuator **517** is elevated, thus freeing said bulge **515d** of actuator **515** from bulge **517d** of the third complementary actuator **517** (see Fig. **26b-26d**).

As mentioned above, the main difference between the first embodiment (device **500** illustrated in Figs. **12-19**) and the second embodiment (device **600** illustrated in Fig. **20-26d**) is the fact that the device of the first embodiment is reloaded automatically (i.e., once the medicament is released from the intermediate compartment **511**, vacuum is created in the same and another dose of medicament is withdrawn to said intermediate compartment **511**) and in the second embodiment, the loading is manual (i.e., the patient is required to actively load the device **500**).

It should be made clear that simultaneously, with the movement of **517** and the return of **515** to its initial position, medicament **506** is released to the patient.

Reference is now made to Fig. **26e** which illustrates the same. Once, the membrane **508** is activated, valve **510** is opened and the medicament **506** is released to the nasal cavity.

Reference is now made to Figs. **27-28** illustrating another embodiment of the present invention, in which both the above mentioned mechanisms are actuated not by in taking (inhaling) air by the user. According to Figs. **27-28**, the medicament dispensing is actuated by the pressing (i.e., application of force) on a spring-like surface **520** which is in mechanical communication with membrane **508** and actuates the same.

Such a feature is highly important since, unlike the previous mechanisms (based on the intake of air by the patient, i.e., a subjective feature), this mechanism is based on a press of a button (an objective feature). For example, a relatively ill and weak patient may not have enough strength to inhale the required amount of air so as to activate the mechanism or to intake the required amount of the uni-dose medicament. Such a mechanism eliminates such a problem.

Reference is now made to Figs. 29-38 illustrating a third mechanism based on the intake of air.

According to the third embodiment the inhaling-actuating device 700 comprises a mouthpiece 502, a nosepiece 504 and an actuator 531 rotated around a hinge 530 (see Fig. 29).

Fig. 30 illustrates a cross sectional view of the same. In the Fig. it can be seen that the hinge 530, around which said actuator 531 is rotated, is mechanically coupled to a spring 532 by means of a connector 533. Said spring 532 is maintained retracted (i.e., loaded) by means of a casing 534 (as will be disclosed hereinafter). Said inhaling-actuating device 700 further comprises a container for containing a medicament 506 (not shown).

Reference is now made to Figs. 31-35, illustrating the actuation of device 700.

Fig. 31 illustrates device 700 prior to the actuation. Fig. 32 illustrates the first step of the actuation in which actuator 531 is rotated around hinge 530. said rotation engage spring 532 and loads the same (i.e., compress the same). A second spring 535, encased within a casing 536 is linearly moved along a path which is substantially perpendicular to the main longitudinal axis of spring 532 and casing 534.

Case 534 of spring 532 is characterized by at least one groove 537 into which at least a portion of casing 536 of spring 535 is inserted so as to maintain spring 532 loaded.

As mentioned, said movement of said spring 535 and casing 536 engages with the casing 534 of spring 532 (namely inserted into groove 537) so as to spring 532 loaded (compressed).

Figs. 33-34 illustrate the next step, in which medicament 506 is loaded into device 700.

Fig. 35 illustrates the final step in which the device 700 is actuated.

As described above, the activation is initiated by the intake of air by the user. Once the user inhale (see arrows 538) a membrane 508 (which is mechanically coupled to spring 535) is withdrawn away from spring 532. said movement of said membrane withdraw also said spring 535 and casing 536 (from groove 537 of spring 532).

Said withdraw unload spring 532 and the same is retracted to the initial position. Said retraction is characterized by a piston-like movement. I.e., when spring 532 is retracted, the same applies compression forces on container 503 so as to be 'pushed' out. Such pushing extracts said medicament 506 and the same is delivered to the nasal cavity of the patient (see arrow 540).

Reference is now made to Figs. **36-37** which better illustrates the loading stage of the medicament **506** into device **700**. Such loading is enabled due to the fact that the top part **550** of device **700** is reversibly coupled to the same.

When spring **502** is loaded (i.e., casing **536** is at least partially within groove **537** of casing **534**), the top part **550** of device **700** is de-coupled from device **700** and medicament **506** can be inserted into the same. Fig. **37** illustrates a closer view of the medicament loading.

Reference is now made to Figs. **38a-38b** illustrating the top part **550** prior to and post loading. As seen in Fig. **38a** container **503** (containing the medicament **506**) is inserted into the complementary top part (sized and shape so as to accommodate the same) **550**. Fig. **38b** illustrates the top part **550** containing said container **503** containing said medicament **506**.

Reference is now made to Figs. **39-41**, illustrating a fourth embodiment of the inhaling-actuating device **800**. According to this embodiment, the device **800** comprises a container **503** containing a medicament **506** to be delivered to the nasal cavity, a unidirectional valve **560**, an intermediate container **511**, a second unidirectional valve **561** and a membrane **508**.

Prior to the actuation of the device **800** the intermediate container **511** is filled with a uni-dose amount of medicament **506** (this is enabled due to the fact that once the medicament is release to the nasal cavity, vacuum is generated within the intermediate container **511**; thus, medicament is withdrawn into the same through unidirectional valve **561**).

Once the patient intake air (see Fig. **40**), device **800** is actuated. Reference is now made to Fig. **40** illustrating the actuation mechanism.

Once the user inhale air (see arrows **562**), membrane **508** is elevated. Membrane **508** is mechanically coupled to said valve **560**, such that when said membrane **508** is elevated, valve **560** is elevated as well.

The elevation of valve **560** is characterized by a piston-like movement. I.e., when valve **560** is elevated, the same applies pressure on valve **561**, such that the medicament **506**, contained within intermediate container **511** is now released from the same into the nasal cavity (see arrows **564**).

It should be pointed out that it is within the core concept of the present invention in which the nosepiece **504** can be designed and configured to be shaped for the one or two nostrils.

In the foregoing description, embodiments of the invention, including preferred embodiments, have been presented for the purpose of illustration and description. They are not intended to be exhaustive or to limit the invention to the precise form disclosed. Obvious modifications or variations are possible in light of the above teachings. The embodiments were chosen and described to provide the best illustration of the principals of the invention and its practical application, and to enable one of ordinary skill in the art to utilize the invention in various embodiments and with various modifications as are suited to the particular use contemplated. All such modifications and variations are within the scope of the invention as determined by the appended claims when interpreted in accordance with the breadth they are fairly, legally, and equitably entitled.

CLAIMS

1. A drinking-actuated device adapted for delivering a substance to a nasal cavity of a subject, said device comprising:
 - a. a container for containing said substance;
 - b. a nosepiece extending from said device for placement in proximity to a nose of said subject, said nosepiece being in fluid communication with said container;
 - c. a valve mechanically connectable to said container, characterized by at least two configurations: (i) an ACTIVE CONFIGURATION in which said valve enables delivery of predetermined amount of said substance from said container to said nasal cavity via said nosepiece; and, (ii) an INACTIVE CONFIGURATION;
 - d. a mouthpiece extending from said device for placement in a mouth of said subject; and,
 - e. a trigger mechanism adapted to reconfigure said valve from said ACTIVE CONFIGURATION to said INACTIVE CONFIGURATION, and vice versa;

wherein said mouthpiece is fluidly connectable by means of a tubule to a fluid reservoir containing a fluid, said fluid reservoir is adapted to supply said fluid to said mouth of said subject via said mouthpiece;

further wherein said trigger mechanism is adapted to reconfigure said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION for a predetermined period of time in response to a pressure gradient generated by suction applied by said subject to said tubule for drinking said fluid through said tubule.

2. The drinking-actuated device according to claim 1, wherein said trigger mechanism is adapted to reconfigure said valve from said ACTIVE CONFIGURATION to said INACTIVE CONFIGURATION when said pressure gradient is absent.
3. The drinking-actuated device according to claim 1, wherein said trigger mechanism comprises a controlling member adapted to move reciprocally in responsive to said pressure gradient; said controlling member is characterized by having at least two configurations: (i) an CLOSED CONFIGURATION in which said fluid is not provided to said subject via said tubule and said valve is in said INACTIVE CONFIGURATION; and, (ii) an OPENED CONFIGURATION in which said subject drinks said fluid through said tubule and said valve is in said ACTIVE CONFIGURATION.

4. The drinking-actuated device according to claim 3, wherein in said CLOSED CONFIGURATION, said controlling member is adapted to block the passage of said fluid from said fluid reservoir to said mouthpiece.
5. The drinking-actuated device according to claim 3, wherein said trigger mechanism further comprises flexible membrane, said flexible membrane is adapted to reconfigure its shape in response to said pressure gradient caused by said suction applied by said subject to said tubule, such that said controlling member is reconfigured from said CLOSED CONFIGURATION to said OPENED CONFIGURATION, and vice versa.
6. The drinking-actuated device according to claim 5, wherein said controlling member is characterized by at least three portions: a first end positioned at least partially within said tubule; a middle portion mechanically connected with said membrane; and, a second end in communication with said valve.
7. The drinking-actuated device according to claim 6, wherein said first end of said controlling member is substantially perpendicular to said tubule and substantially vertically movable within said tubule.
8. The drinking-actuated device according to claim 6, wherein in the reconfiguration of said controlling member from said CLOSED CONFIGURATION to said OPENED CONFIGURATION, said first end is adapted to move within and with respect to said tubule.
9. The drinking-actuated device according to claim 5, wherein said controlling member comprises a first aperture fluidly communicating said membrane and said mouthpiece, said first aperture is adapted to transfer said pressure gradient from said tubule to said membrane, so as to reconfigure said membrane such that said controlling member is reconfigured from said CLOSED CONFIGURATION to said OPENED CONFIGURATION.
10. The drinking-actuated device according to claim 5, wherein said controlling member comprises a second aperture adapted to facilitate passage of said fluid through said controlling member when said controlling member is in said OPENED CONFIGURATION, said passage of said fluid within said second aperture is adapted to preserve said controlling member in said OPENED CONFIGURATION while said fluid passes through said controlling member.
11. The drinking-actuated device according to claim 1, wherein said valve is reconfigurable from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION when said pressure gradient is above a predetermined threshold.

12. The drinking-actuated device according to claim 1, wherein said valve comprises a spring which is at least partially tensed in said INACTIVE CONFIGURATION, and at least partially released in said ACTIVE CONFIGURATION.
13. The drinking-actuated device according to claim 1, wherein said valve comprises a spring which is at least partially released in said INACTIVE CONFIGURATION, and at least partially tensed in said ACTIVE CONFIGURATION.
14. The drinking-actuated device according to claim 1, wherein said drinking of said fluid by said subject is adapted to cause the soft palate of said subject to be closed, so that the nasal passageways of the nose of said subject is substantially isolated from the remainder of the pulmonary system.
15. The drinking-actuated device according to claim 1, wherein said tubule is at least partially a straw.
16. The drinking-actuated device according to claim 1, further comprising a piston adapted to compress said substance within said container.
17. The drinking-actuated device according to claim 16, wherein said valve is adapted to move said piston towards said substance when said valve is configured to said ACTIVE CONFIGURATION.
18. The drinking-actuated device according to claim 1, wherein the operation of said trigger mechanism is synchronized with said drinking of said fluid by said subject.
19. The drinking-actuated device according to claim 1, wherein said trigger mechanism comprises a pulsation mechanism adapted to reconfigure said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION and vice versa in sequence of pulses, each of which is characterized by a predetermined length of pulse, said valve adapted to a release said predetermined amount of said substance according to said sequence of pulses.
20. The drinking-actuated device according to claim 19, wherein in each said pulse at least two doses of said predetermined amount of said substance are released.
21. The drinking-actuated device according to claim 1, wherein said nosepiece is in fluid communication with said valve by means of a spray nozzle.
22. The drinking-actuated device according to claim 1, wherein said spray nozzle is characterized by a diameter which influences on said predetermined period of time.
23. The drinking-actuated device according to claim 1, wherein said container is a syringe.

24. The drinking-actuated device according to claim 1, further comprising a cap adapted to cover at least a portion of the components of said device for sterilization purposes.
25. The drinking-actuated device according to claim 24, wherein said cap comprises an opening.
26. The drinking-actuated device according to claim 1, wherein said container adapted to be connected to an external container, said external container adapted to fill said container with said substance.
27. The drinking-actuated device according to claim 26, wherein said external container adapted to fill said container with a predetermined dose of said substance.
28. The drinking-actuated device according to claim 1, further comprising indicating means adapted to indicate the amount of said substance within said container.
29. The drinking-actuated device according to claim 28, wherein said indicating means is a transparent window located on a side of said container.
30. The drinking-actuated device according to claim 1, wherein said fluid is selected from a group consisting of: water, a juice, a fluid medication, a cold fluid, a warm fluid, or any combination thereof.
31. The drinking-actuated device according to claim 1, wherein said substance is a drug selected from a group consisting of: Anti-Angiogenesis agents, Antisense, anti-ulcer, butorphanol, Calcitonin and analogs, COX-II inhibitors, desmopressin and analogs, dihydroergotamine, Dopamine agonists and antagonists, Enkephalins and other opioid peptides, Growth hormone and analogs, growth hormone releasing hormone, Growth hormone antagonists, IgE suppressors, Insulin, insulinotropin and analogs, Ketamine, Kytril, Leutenizing hormone releasing hormone and analogs, lidocaine, metoclopramide, Midazolam, Narcotic analgesics, neuraminidase inhibitors, nicotine, Non-steroid anti-inflammatory agents, Oligosaccharides, ondansetron, Parathyroid hormone and analogs, Parathyroid hormone antagonists, Prostaglandin antagonists, Prostaglandins, Recombinant soluble receptors, scopolamine, Serotonin agonists and antagonists, Sildenafil, Terbutaline, vasopressin, or any combination thereof.
32. The drinking-actuated device according to claim 1, wherein the substance is a vaccine with or without carriers and/or adjuvant selected from the group consisting of: Prophylactics and therapeutic antigens, subunit protein, peptide and polysaccharide, polysaccharide conjugates, toxoids, genetic based vaccines, live attenuated, reassortant, inactivated, whole cells, viral and bacterial vectors for the treatment of arthritis, *Lactobacillus species: Lactobacillus acetotolerans, Lactobacillus acidifarinae, Lactobacillus acidipiscis, Lactobacillus*

acidophilus (Doderlein bacillus), *Lactobacillus agilis*, *Lactobacillus algidus*, *Lactobacillus alimentarius*, *Lactobacillus amylolyticus*, *Lactobacillus amylophilus*, *Lactobacillus amylotrophicus*, *Lactobacillus amylovorus*, *Lactobacillus animalis*, *Lactobacillus antri*, *Lactobacillus apodemi*, *Lactobacillus aviarius*, *Lactobacillus bif fermentans*, *Lactobacillus brevis*, *Lactobacillus buchneri*, *Lactobacillus camelliae*, *Lactobacillus casei*, *Lactobacillus catenaformis*, *Lactobacillus ceti*, *Lactobacillus coleohominis*, *Lactobacillus collinoides*, *Lactobacillus composti*, *Lactobacillus concavus*, *Lactobacillus coryniformis*, *Lactobacillus crispatus*, *Lactobacillus crustorum*, *Lactobacillus curvatus*, *Lactobacillus delbrueckii*, *Lactobacillus delbrueckii* subsp. *Bulgaricus*, *Lactobacillus delbrueckii* subsp. *Lactis*, *Lactobacillus diolivorans*, *Lactobacillus equi*, *Lactobacillus equigenerosi*, *Lactobacillus farraginis*, *Lactobacillus farciminis*, *Lactobacillus fermentum*, *Lactobacillus fornicalis*, *Lactobacillus fructivorans*, *Lactobacillus frumenti*, *Lactobacillus fuchuensis*, *Lactobacillus gallinarum*, *Lactobacillus gasseri*, *Lactobacillus gastricus*, *Lactobacillus ghanensis*, *Lactobacillus graminis*, *Lactobacillus hammesii*, *Lactobacillus hamsteri*, *Lactobacillus harbinensis*, *Lactobacillus hayakitensis*, *Lactobacillus helveticus*, *Lactobacillus hilgardii*, *Lactobacillus homohiochii*, *Lactobacillus iners*, *Lactobacillus ingluviei*, *Lactobacillus intestinalis*, *Lactobacillus jensenii*, *Lactobacillus johnsonii*, *Lactobacillus kalixensis*, *Lactobacillus kefiranofaciens*, *Lactobacillus kefiri*, *Lactobacillus kimchii*, *Lactobacillus kitasatonis*, *Lactobacillus kunkeei*, *Lactobacillus leichmannii*, *Lactobacillus lindneri*, *Lactobacillus malefermentans*, *Lactobacillus mali*, *Lactobacillus manihotivorans*, *Lactobacillus mindensis*, *Lactobacillus mucosae*, *Lactobacillus murinus*, *Lactobacillus nagelii*, *Lactobacillus namurensis*, *Lactobacillus nantensis*, *Lactobacillus oligofermentans*, *Lactobacillus oris*, *Lactobacillus panis*, *Lactobacillus pantheris*, *Lactobacillus parabrevis*, *Lactobacillus parabuchneri*, *Lactobacillus paracollinoides*, *Lactobacillus parafarraginis*, *Lactobacillus parakefiri*, *Lactobacillus paralimentarius*, *Lactobacillus paraplantarum*, *Lactobacillus pentosus*, *Lactobacillus perolens*, *Lactobacillus plantarum*, *Lactobacillus pontis*, *Lactobacillus psittaci*, *Lactobacillus rennini*, *Lactobacillus reuteri*, *Lactobacillus rhamnosus*, *Lactobacillus rimae*, *Lactobacillus rogosae*, *Lactobacillus rossiae*, *Lactobacillus ruminis*, *Lactobacillus saerimneri*, *Lactobacillus sakei*, *Lactobacillus salivarius*, *Lactobacillus sanfranciscensis*, *Lactobacillus satsumensis*, *Lactobacillus secaliphilus*, *Lactobacillus sharpeae*, *Lactobacillus siliginis*, *Lactobacillus spicheri*, *Lactobacillus suebicus*, *Lactobacillus thailandensis*, *Lactobacillus ultunensis*, *Lactobacillus vaccinofermentans*, *Lactobacillus vaginalis*, *Lactobacillus versmoldensis*, *Lactobacillus vini*, *Lactobacillus vitulinus*, *Lactobacillus zaeae*, *Lactobacillus zymae*, Probiotics selected from a group consisting of Lactic acid bacteria (LAB) and bifidobacteria, or any combination thereof; said

substance is used for the treatment of at least one selected from a group consisting of cholera, moraxella catarrhali, cocaine addiction, HIB, meningococcus, measles, mumps, rubella, varicella, yellow fever, Respiratory syncytial virus, pneumococcus, streptococcus, typhoid, influenza, hepatitis, including hepatitis A, B, C and F, polio, HIV, parainfluenza, rotavirus, CMV, chlamydia, non-typeable haemophilus, moraxella catarrhalis, human papilloma virus, tuberculosis including BCG, gonorrhoea, asthma, atherosclerosis, malaria, otitis media, E-coli, Alzheimers, H. Pylori, salmonella, diabetes, cancer and herpes simplex, Staphylococcus aureus, Streptococcus, or any combination thereof.

33. The drinking-actuated device according to claim 1, wherein said substance is used for the treatment of at least one selected from a group consisting of cholera, moraxella catarrhali, cocaine addiction, HIB, meningococcus, measles, mumps, rubella, varicella, yellow fever, Respiratory syncytial virus, pneumococcus, streptococcus, typhoid, influenza, hepatitis, including hepatitis A, B, C and F, polio, HIV, parainfluenza, rotavirus, CMV, chlamydia, non-typeable haemophilus, moraxella catarrhalis, human papilloma virus, tuberculosis including BCG, gonorrhoea, asthma, atherosclerosis, malaria, otitis media, E-coli, Alzheimers, H. Pylori, salmonella, diabetes, cancer and herpes simplex, Staphylococcus aureus, Streptococcus, CNS disorder, brain disorders such as: brain cancer, acute brain injury, spinal cord injury, Alzheimer disease, Neurogenesis, Parkinson's disease, depression, Epilepsy, schizophrenia by the delivery of substances such as: Neurotrophins, BDNF, GDNF, anti EGF receptor AB, Enzymes as Lysosomal enzyme, Neuregulin or any combination thereof.
34. The drinking-actuated device according to claim 1, wherein said substance is a therapeutic substance selected from a group consisting of: Agents for the common cold, Anti-addiction, anti-infectives, analgesics, anesthetics, anorexics, antiarthritics, anti-allergy agents, antiasthmatic agents, anticonvulsants, anti-depressants, antidiabetic agents, anti-depressants, anti-diuretics, anti-emetics, antihistamines, anti-inflammatory agents, antimigraine preparations, antimoion sickness preparations, antinauseants, antineoplastics, anti-obesity, antiosteoporeteic, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, anticholinergics, benzodiazepine antagonists, bone stimulating agents, central nervous system stimulants, hormones, hypnotics, immunosuppressives, prostaglandins, proteins, peptides, polypeptides and other macromolecules, psychostimulants, rhinitis treatment, sedatives, sexual hypofunction, tranquilizers and vitamins including B12, probiotics, natural oils, natural ingredients, peptide or protein therapeutic agent such as cytokines, hormones, clotting factors, vaccines, monoclonal antibody or any combination thereof.

35. The drinking-actuated device according to claim 1, wherein said substance may be delivered to said nasal cavity in a form selected from the group consisting of: a powder, a granule, a cachet, a capsule, a tablet, a paste, a cream, a gel, an ointment, a salve, a foam, a paste, a lotion, a cream, an oil suspension, a spray, a suspension, a solution, an emulsion, a patch, a stick, a spray, preferably a nasal spray, or a buccal spray, a mouth wash, an aerosol, in a venture effect, a drink, and a solution.
36. The drinking-actuated device according to claim 1, wherein said substance is selected from a group consisting of natural oils; Mint oils, Peppermint oil, Spearmint oil, Menthol, Olive oil, Eucalyptus oil, Amino acids, fatty acids and any combination thereof.
37. A method for delivering a substance to a nasal cavity of a subject, said method comprising steps of:
 - a. providing a drinking-actuated device adapted for delivering a substance to a nasal cavity of a subject, said device comprising: (i) a container for containing said substance; (ii) a nosepiece extending from said device for placement in proximity to a nose of said subject, said nosepiece being in fluid communication with said container; (iii) a valve mechanically connectable to said container, characterized by at least two configurations: (i) an ACTIVE CONFIGURATION in which said valve causes a delivery of predetermined amount of said substance from said container to said nasal cavity via said nosepiece; and, (ii) an INACTIVE CONFIGURATION in which said substance is not delivered to the nose of said subject; (iv) a mouthpiece extending from said device for placement in a mouth of said subject; and, a trigger mechanism adapted to reconfigure said valve from said ACTIVE CONFIGURATION to said INACTIVE CONFIGURATION, and vice versa; (v) wherein said mouthpiece is fluidly connectable by means of a tubule to a fluid reservoir containing a fluid, said fluid reservoir is adapted to supply said fluid to said mouth of said subject via said mouthpiece;
 - b. placing said nosepiece in or around the nose of said subject;
 - c. fluidly connecting said tubule to a fluid reservoir;
 - d. placing said mouthpiece in the mouth of said subject;
 - e. drinking said fluid through said mouthpiece, thereby reconfiguring said valve via said trigger mechanism from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION for a predetermined period of time in response to a pressure

gradient generated by suction applied to said tubule while said subject drinks said fluid through said tubule;

- f. releasing a predetermined amount of said substance from said container to said nosepiece;
38. The method for delivering a substance to a nasal cavity of a subject according to claim 37, further comprising step of reconfiguring said valve via said trigger mechanism from said ACTIVE CONFIGURATION to said INACTIVE CONFIGURATION when said pressure gradient is absent.
39. The method for delivering a substance to a nasal cavity of a subject according to claim 37, additionally comprising step of providing said trigger mechanism with a controlling member adapted to move reciprocally within said tubule and said valve in responsive to said pressure gradient; said controlling member is characterized by having at least two configurations: (i) an CLOSED CONFIGURATION in which said fluid is not provided to said subject via said tubule and said valve is in said INACTIVE CONFIGURATION; and, (ii) an OPENED CONFIGURATION in which said subject drinks said fluid through said tubule and said valve is in said ACTIVE CONFIGURATION.
40. The method for delivering a substance to a nasal cavity of a subject according to claim 37, wherein in said CLOSED CONFIGURATION, said controlling member is adapted to block the passage of said fluid from said fluid reservoir to said mouthpiece.
41. The method for delivering a substance to a nasal cavity of a subject according to claim 37, further comprising steps of: providing said trigger mechanism with a flexible membrane; reconfiguring the shape of said flexible membrane in response to said pressure gradient; and, thereby reconfiguring said controlling member is from said CLOSED CONFIGURATION to said OPENED CONFIGURATION, and vice versa.
42. The method for delivering a substance to a nasal cavity of a subject according to claim 41, wherein said controlling member is characterized by at least three portions: a first end positioned at least partially within said tubule; a middle portion mechanically connected with said membrane; and, a second end in communication with said valve.
43. The method for delivering a substance to a nasal cavity of a subject according to claim 41, further comprising steps of providing said controlling member with a first aperture fluidly communicating between said membrane and said mouthpiece, transferring said pressure gradient from said tubule to said cavity via said first aperture, thereby reconfiguring said

controlling member from said OPENED CONFIGURATION to said CLOSED CONFIGURATION.

44. The method for delivering a substance to a nasal cavity of a subject according to claim 41, further comprising steps of providing said said controlling member with a second aperture adapted to facilitate passage of said fluid through said controlling member when said controlling member is in said OPENED CONFIGURATION, said passage of said fluid within said second aperture is adapted to preserve said controlling member in said OPENED CONFIGURATION while said fluid passes through said controlling member.
45. The method for delivering a substance to a nasal cavity of a subject according to claim 37, further comprising step of reconfiguring said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION when said pressure gradient is above a predetermined threshold.
46. The method for delivering a substance to a nasal cavity of a subject according to claim 37, further comprising step of providing said valve with a spring which is at least partially tensed in said INACTIVE CONFIGURATION, and at least partially released in said ACTIVE CONFIGURATION.
47. The method for delivering a substance to a nasal cavity of a subject according to claim 37, further comprising step of providing said valve with a spring which is at least partially released in said INACTIVE CONFIGURATION, and at least partially tensed in said ACTIVE CONFIGURATION.
48. The method for delivering a substance to a nasal cavity of a subject according to claim 37, further comprising step of closing the soft palate of said subject as a result of said step (f) of drinking said fluid, and thereby substantially isolating the nasal passageways of the nose of said subject from the pulmonary system.
49. The method for delivering a substance to a nasal cavity of a subject according to claim 37, wherein said tubule is at least partially a straw.
50. The method for delivering a substance to a nasal cavity of a subject according to claim 37, further comprising step of compressing said substance within said container via a piston.
51. The method for delivering a substance to a nasal cavity of a subject according to claim 50, further comprising step of moving said piston towards said substance via said valve when said valve is configured to said ACTIVE CONFIGURATION.

52. The method for delivering a substance to a nasal cavity of a subject according to claim 37, further comprising step of synchronizing the operation of said trigger mechanism with said drinking of said fluid by said subject.
53. The method for delivering a substance to a nasal cavity of a subject according to claim 37 further comprising step of providing said trigger mechanism with a pulsation mechanism adapted to reconfigure said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION and vice versa in sequence of pulses, each of which is characterized by a predetermined length of pulse, said valve adapted to release said predetermined amount of said substance according to said sequence of pulses.
54. The method for delivering a substance to a nasal cavity of a subject according to claim 53, further comprising step of releasing in each said pulse at least two doses of said predetermined amount of said substance.
55. The method for delivering a substance to a nasal cavity of a subject according to claim 37, wherein said nosepiece is in fluid communication with said valve by means of a spray nozzle.
56. The method for delivering a substance to a nasal cavity of a subject according to claim 37, wherein said spray nozzle is characterized by a diameter which influences on said predetermined period of time.
57. The method for delivering a substance to a nasal cavity of a subject according to claim 37, wherein said container is a syringe.
58. The method for delivering a substance to a nasal cavity of a subject according to claim 37, further comprising step of providing said device with a cap adapted to cover at least a portion of the components of said device for sterilization purposes.
59. The method for delivering a substance to a nasal cavity of a subject according to claim 58, wherein said cap comprises an opening.
60. The method for delivering a substance to a nasal cavity of a subject according to claim 37, wherein said container adapted to be connected to an external container, said external container adapted to fill said container with said substance.
61. The method for delivering a substance to a nasal cavity of a subject according to claim 60, further comprising step of filling said container by said external container with a predetermined dose of said substance.

62. The method for delivering a substance to a nasal cavity of a subject according to claim 37, further comprising step of providing said container with indicating means adapted to indicate the amount of said substance within said container.
63. The method for delivering a substance to a nasal cavity of a subject according to claim 62, wherein said indicating means is a transparent window located on a side of said container.
64. The method for delivering a substance to a nasal cavity of a subject according to claim 37, further comprising step of selecting said fluid from a group consisting of: a water, a juice, a fluid medication, a cold fluid, a warm fluid, or any combination thereof.
65. The method for delivering a substance to a nasal cavity of a subject according to claim 37, wherein said substance is a drug selected from a group consisting of: Anti-Angiogenesis agents, Antisense, anti-ulcer, butorphanol, Calcitonin and analogs, COX-II inhibitors, desmopressin and analogs, dihydroergotamine, Dopamine agonists and antagonists, Enkephalins and other opioid peptides, Growth hormone and analogs, growth hormone releasing hormone, Growth hormone antagonists, IgE suppressors, Insulin, insulinotropin and analogs, Ketamine, Kytril, Leutenizing hormone releasing hormone and analogs, lidocaine, metoclopramide, Midazolam, Narcotic analgesics, neuraminidase inhibitors, nicotine, Non-steroid anti-inflammatory agents, Oligosaccharides, ondansetron, Parathyroid hormone and analogs, Parathyroid hormone antagonists, Prostaglandin antagonists, Prostaglandins, Recombinant soluble receptors, scopolamine, Serotonin agonists and antagonists, Sildenafil, Terbutaline, vasopressin, or any combination thereof.
66. The method for delivering a substance to a nasal cavity of a subject according to claim 37, additionally comprising step of selecting said substance from a vaccine with or without carriers and/or adjuvant selected from the group consisting of: Prophylactics and therapeutic antigens, subunit protein, peptide and polysaccharide, polysaccharide conjugates, toxoids, genetic based vaccines, live attenuated, reassortant, inactivated, whole cells, viral and bacterial vectors for the treatment of arthritis, *Lactobacillus species*: *Lactobacillus acetotolerans*, *Lactobacillus acidifarinae*, *Lactobacillus acidipiscis*, *Lactobacillus acidophilus* (*Doderlein bacillus*), *Lactobacillus agilis*, *Lactobacillus algidus*, *Lactobacillus alimentarius*, *Lactobacillus amylolyticus*, *Lactobacillus amylophilus*, *Lactobacillus amylotrophicus*, *Lactobacillus amylovorus*, *Lactobacillus animalis*, *Lactobacillus antri*, *Lactobacillus apodemi*, *Lactobacillus aviarius*, *Lactobacillus bifermentans*, *Lactobacillus brevis*, *Lactobacillus buchneri*, *Lactobacillus camelliae*, *Lactobacillus casei*, *Lactobacillus catenaformis*, *Lactobacillus ceti*, *Lactobacillus coleohominis*, *Lactobacillus collinoides*, *Lactobacillus composti*, *Lactobacillus concavus*, *Lactobacillus coryniformis*, *Lactobacillus*

crispatus, *Lactobacillus crustorum*, *Lactobacillus curvatus*, *Lactobacillus delbrueckii*, *Lactobacillus delbrueckii subsp. Bulgaricus*, *Lactobacillus delbrueckii subsp. Lactis*, *Lactobacillus diolivorans*, *Lactobacillus equi*, *Lactobacillus equigenerei*, *Lactobacillus farraginis*, *Lactobacillus farciminis*, *Lactobacillus fermentum*, *Lactobacillus fornicalis*, *Lactobacillus fructivorans*, *Lactobacillus frumenti*, *Lactobacillus fuchuensis*, *Lactobacillus gallinarum*, *Lactobacillus gasseri*, *Lactobacillus gastricus*, *Lactobacillus ghanensis*, *Lactobacillus graminis*, *Lactobacillus hammesii*, *Lactobacillus hamsteri*, *Lactobacillus harbinensis*, *Lactobacillus hayakitensis*, *Lactobacillus helveticus*, *Lactobacillus hilgardii*, *Lactobacillus homohiochii*, *Lactobacillus iners*, *Lactobacillus ingluviei*, *Lactobacillus intestinalis*, *Lactobacillus jensenii*, *Lactobacillus johnsonii*, *Lactobacillus kalixensis*, *Lactobacillus kefiranoferiens*, *Lactobacillus kefir*, *Lactobacillus kimchii*, *Lactobacillus kitasatonis*, *Lactobacillus kunkeei*, *Lactobacillus leichmannii*, *Lactobacillus lindneri*, *Lactobacillus malefermentans*, *Lactobacillus mali*, *Lactobacillus manihotivorans*, *Lactobacillus mindensis*, *Lactobacillus mucosae*, *Lactobacillus murinus*, *Lactobacillus nagelii*, *Lactobacillus namurensis*, *Lactobacillus nantensis*, *Lactobacillus oligofermentans*, *Lactobacillus oris*, *Lactobacillus panis*, *Lactobacillus pantheris*, *Lactobacillus parabrevis*, *Lactobacillus parabuchneri*, *Lactobacillus paracollinoides*, *Lactobacillus parafarraginis*, *Lactobacillus parakefiri*, *Lactobacillus paralimentarius*, *Lactobacillus paraplantarum*, *Lactobacillus pentosus*, *Lactobacillus perolens*, *Lactobacillus plantarum*, *Lactobacillus pontis*, *Lactobacillus psittaci*, *Lactobacillus rennini*, *Lactobacillus reuteri*, *Lactobacillus rhamnosus*, *Lactobacillus rimae*, *Lactobacillus rogosae*, *Lactobacillus rossiae*, *Lactobacillus ruminis*, *Lactobacillus saerimneri*, *Lactobacillus sakei*, *Lactobacillus salivarius*, *Lactobacillus sanfranciscensis*, *Lactobacillus satsumensis*, *Lactobacillus secaliphilus*, *Lactobacillus sharpeae*, *Lactobacillus siliginis*, *Lactobacillus spicheri*, *Lactobacillus suebicus*, *Lactobacillus thailandensis*, *Lactobacillus ultunensis*, *Lactobacillus vaccinoferens*, *Lactobacillus vaginalis*, *Lactobacillus versmoldensis*, *Lactobacillus vini*, *Lactobacillus vitulinus*, *Lactobacillus zaeae*, *Lactobacillus zymae*, Probiotics selected from a group consisting of Lactic acid bacteria (LAB) and bifidobacteria, or any combination thereof; said substance is used for the treatment of at least one selected from a group consisting of cholera, moraxella catarrhali, cocaine addiction, HIB, meningococcus, measles, mumps, rubella, varicella, yellow fever, Respiratory syncytial virus, pneumococcus, streptococcus, typhoid, influenza, hepatitis, including hepatitis A, B, C and F, polio, HIV, parainfluenza, rotavirus, CMV, chlamydia, non-typeable haemophilus, moraxella catarrhalis, human papilloma virus, tuberculosis including BCG, gonorrhoea, asthma, atherosclerosis, malaria, otitis media, E-

- coli, Alzheimers, H. Pylori, salmonella, diabetes, cancer and herpes simplex, , Staphylococcus aureus, Streptococcus, or any combination thereof.
67. The method for delivering a substance to a nasal cavity of a subject according to claim 37, wherein said substance is used for the treatment of at least one selected from a group consisting of cholera, moraxella catarrhali, cocaine addiction, HIB, meningococcus, measles, mumps, rubella, varicella, yellow fever, Respiratory syncytial virus, pneumococcus, streptococcus, typhoid, influenza, hepatitis, including hepatitis A, B, C and F, polio, HIV, parainfluenza, rotavirus, CMV, chlamydia, non-typeable haemophilus, moraxella catarrhalis, human papilloma virus, tuberculosis including BCG, gonorrhoea, asthma, atherosclerosis, malaria, otitis media, E-coli, Alzheimers, H. Pylori, salmonella, diabetes, cancer and herpes simplex, Staphylococcus aureus, Streptococcus, CNS disorder, brain disorders such as: brain cancer, acute brain injury, spinal cord injury, Alzheimer disease, Neurogenesis, Parkinson's disease, depression, Epilepsy, schizophrenia by the delivery of substances such as: Neurotrophins, BDNF, GDNF, anti EGF receptor AB, Enzymes as Lysosomal enzyme, Neuregulin or any combination thereof.
68. The method for delivering a substance to a nasal cavity of a subject according to claim 37, wherein said substance is a therapeutic substance selected from a group consisting of: Agents for the common cold, Anti-addiction, anti-infectives, analgesics, anesthetics, anorexics, antiarthritics, anti-allergy agents, antiasthmatic agents, anticonvulsants, anti-depressants, antidiabetic agents, anti-depressants, anti-diuretics, anti-emetics, antihistamines, anti-inflammatory agents, antimigraine preparations, antion motion sickness preparations, antinauseants, antineoplastics, anti-obesity, antiosteoporotic, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, anticholinergics, benzodiazepine antagonists, bone stimulating agents, central nervous system stimulants, hormones, hypnotics, immunosuppressives, prostaglandins, proteins, peptides, polypeptides and other macromolecules, psychostimulants, rhinitis treatment, sedatives, sexual hypofunction, tranquilizers and vitamins including B12, probiotics, natural oils, natural ingredients, peptide or protein therapeutic agent such as cytokines, hormones, clotting factors, vaccines, monoclonal antibody or any combination thereof.
69. The method for delivering a substance to a nasal cavity of a subject according to claim 37, wherein said substance may be delivered to said nasal cavity in a form selected from the group consisting of: a powder, a granule, a cachet, a capsule, a tablet, a paste, a cream, a gel, an ointment, a salve, a foam, a paste, a lotion, a cream, an oil suspension, a spray, a

suspension, a solution, an emulsion, a patch, a stick, a spray, preferably a nasal spray, or a buccal spray, a mouth wash, an aerosol, in a venture effect, a drink, and a solution.

70. The method for delivering a substance to a nasal cavity of a subject according to claim 37, additionally comprising step of selecting said substance from a group consisting of natural oils; Mint oils, Peppermint oil, Spearmint oil, Menthol, Olive oil, Eucalyptus oil, Amino acids, fatty acids and any combination thereof.
71. An air-intake actuated device adapted for delivering a substance to a nasal cavity of a subject, said device comprising:
- a. a container for containing said substance;
 - b. a nosepiece extending from said device for placement in proximity to a nose of said subject, said nosepiece being in fluid communication with said container;
 - c. a valve mechanically connectable to said container, characterized by at least two configurations: (i) an ACTIVE CONFIGURATION in which said valve enables delivery of predetermined amount of said substance from said container to said nasal cavity via said nosepiece; and, (ii) an INACTIVE CONFIGURATION, in which said valve prevents delivery of said predetermined amount of said substance from said container to said nasal cavity;
 - d. a mouthpiece extending from said device for placement in a mouth of said subject; and,
 - e. a trigger mechanism adapted to reconfigure said valve from said ACTIVE CONFIGURATION to said INACTIVE CONFIGURATION, and vice versa;

wherein said trigger mechanism is activated by means of said subject intaking air through said mouthpiece;

further wherein said trigger mechanism is adapted to reconfigure said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION for a predetermined period of time in response to said subject intake of air.

72. The air-intake actuated device according to claim 71, wherein said trigger mechanism is adapted to reconfigure said valve from said ACTIVE CONFIGURATION to said INACTIVE CONFIGURATION when said subject ceases said intake.
73. The air-intake actuated device according to claim 71, wherein said trigger mechanism comprises a flexible membrane; said membrane is in mechanical communication with said

- valve; such that when said subject intake air, said membrane is relocated from its initial position and said valve is opened.
74. The air-intake actuated device according to claim 71, additionally comprising an intermediate compartment adapted to be filled with predetermined amount of said substance; such that said delivery of said substance to said subject is from said intermediate compartment.
 75. The air-intake actuated according to claim 71, wherein the operation of said trigger mechanism is synchronized with said intake of air by said subject.
 76. The air-intake actuated according to claim 71, wherein said trigger mechanism comprises a pulsation mechanism adapted to reconfigure said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION and vice versa in sequence of pulses, each of which is characterized by a predetermined length of pulse, said valve adapted to release said predetermined amount of said substance according to said sequence of pulses.
 77. The air-intake actuated according to claim 76, wherein in each said pulse at least two doses of said predetermined amount of said substance are released.
 78. The air-intake actuated according to claim 71, wherein said nosepiece is in fluid communication with said valve by means of a spray nozzle.
 79. The air-intake actuated according to claim 71, wherein said spray nozzle is characterized by a diameter which influences on said predetermined period of time.
 80. The air-intake actuated according to claim 71, further comprising a cap adapted to cover at least a portion of the components of said device for sterilization purposes.
 81. The air-intake actuated according to claim 80, wherein said cap comprises an opening.
 82. The air-intake actuated according to claim 71, wherein said container adapted to be connected to an external container, said external container adapted to fill said container with said substance.
 83. The air-intake actuated according to claim 82, wherein said external container adapted to fill said container with a predetermined dose of said substance.
 84. The air-intake actuated according to claim 71, further comprising indicating means adapted to indicate the amount of said substance within said container.
 85. The air-intake actuated according to claim 84, wherein said indicating means is a transparent window located on a side of said container.

86. The air-intake actuated according to claim 71, wherein said substance is a drug selected from a group consisting of: Anti-Angiogenesis agents, Antisense, anti-ulcer, butorphanol, Calcitonin and analogs, COX-II inhibitors, desmopressin and analogs, dihydroergotamine, Dopamine agonists and antagonists, Enkephalins and other opioid peptides, Growth hormone and analogs, growth hormone releasing hormone, Growth hormone antagonists, IgE suppressors, Insulin, insulinotropin and analogs, Ketamine, Kytril, Leutenizing hormone releasing hormone and analogs, lidocaine, metoclopramide, Midazolam, Narcotic analgesics, neuraminidase inhibitors, nicotine, Non-steroid anti-inflammatory agents, Oligosaccharides, ondansetron, Parathyroid hormone and analogs, Parathyroid hormone antagonists, Prostaglandin antagonists, Prostaglandins, Recombinant soluble receptors, scopolamine, Serotonin agonists and antagonists, Sildenafil, Terbutaline, vasopressin, or any combination thereof.
87. The air-intake actuated according to claim 71, wherein said substance is a vaccine with or without carriers and/or adjuvant selected from the group consisting of: Prophylactics and therapeutic antigens, subunit protein, peptide and polysaccharide, polysaccharide conjugates, toxoids, genetic based vaccines, live attenuated, reassortant, inactivated, whole cells, viral and bacterial vectors for the treatment of arthritis, *Lactobacillus species*: *Lactobacillus acetotolerans*, *Lactobacillus acidifarinae*, *Lactobacillus acidipiscis*, *Lactobacillus acidophilus* (*Doderlein bacillus*), *Lactobacillus agilis*, *Lactobacillus algidus*, *Lactobacillus alimentarius*, *Lactobacillus amylolyticus*, *Lactobacillus amylophilus*, *Lactobacillus amylotrophicus*, *Lactobacillus amylovorus*, *Lactobacillus animalis*, *Lactobacillus antri*, *Lactobacillus apodemi*, *Lactobacillus aviarius*, *Lactobacillus bifermentans*, *Lactobacillus brevis*, *Lactobacillus buchneri*, *Lactobacillus camelliae*, *Lactobacillus casei*, *Lactobacillus cateniformis*, *Lactobacillus ceti*, *Lactobacillus coleohominis*, *Lactobacillus collinoides*, *Lactobacillus composti*, *Lactobacillus concavus*, *Lactobacillus coryniformis*, *Lactobacillus crispatus*, *Lactobacillus crustorum*, *Lactobacillus curvatus*, *Lactobacillus delbrueckii*, *Lactobacillus delbrueckii subsp. Bulgaricus*, *Lactobacillus delbrueckii subsp. Lactis*, *Lactobacillus diolivorans*, *Lactobacillus equi*, *Lactobacillus equigenerosi*, *Lactobacillus farraginis*, *Lactobacillus farciminis*, *Lactobacillus fermentum*, *Lactobacillus fornicalis*, *Lactobacillus fructivorans*, *Lactobacillus frumenti*, *Lactobacillus fuchuensis*, *Lactobacillus gallinarum*, *Lactobacillus gasseri*, *Lactobacillus gastricus*, *Lactobacillus ghanensis*, *Lactobacillus graminis*, *Lactobacillus hammesii*, *Lactobacillus hamsteri*, *Lactobacillus harbinensis*, *Lactobacillus hayakitensis*, *Lactobacillus helveticus*, *Lactobacillus hilgardii*, *Lactobacillus homohiochii*, *Lactobacillus iners*, *Lactobacillus ingluviei*, *Lactobacillus intestinalis*, *Lactobacillus jensenii*, *Lactobacillus johnsonii*, *Lactobacillus kalixensis*,

Lactobacillus kefiranofaciens, *Lactobacillus kefiri*, *Lactobacillus kimchii*, *Lactobacillus kitasatonis*, *Lactobacillus kunkeei*, *Lactobacillus leichmannii*, *Lactobacillus lindneri*, *Lactobacillus malefermentans*, *Lactobacillus mali*, *Lactobacillus manihotivorans*, *Lactobacillus mindensis*, *Lactobacillus mucosae*, *Lactobacillus murinus*, *Lactobacillus nagelii*, *Lactobacillus namurensis*, *Lactobacillus nantensis*, *Lactobacillus oligofermentans*, *Lactobacillus oris*, *Lactobacillus panis*, *Lactobacillus pantheris*, *Lactobacillus parabrevis*, *Lactobacillus parabuchneri*, *Lactobacillus paracollinoides*, *Lactobacillus parafarraginis*, *Lactobacillus parakefiri*, *Lactobacillus paralimentarius*, *Lactobacillus paraplantarum*, *Lactobacillus pentosus*, *Lactobacillus perolens*, *Lactobacillus plantarum*, *Lactobacillus pontis*, *Lactobacillus psittaci*, *Lactobacillus rennini*, *Lactobacillus reuteri*, *Lactobacillus rhamnosus*, *Lactobacillus rimae*, *Lactobacillus rogosae*, *Lactobacillus rossiae*, *Lactobacillus ruminis*, *Lactobacillus saerimneri*, *Lactobacillus sakei*, *Lactobacillus salivarius*, *Lactobacillus sanfranciscensis*, *Lactobacillus satsumensis*, *Lactobacillus secaliphilus*, *Lactobacillus sharpeae*, *Lactobacillus siliginis*, *Lactobacillus spicheri*, *Lactobacillus suebicus*, *Lactobacillus thailandensis*, *Lactobacillus ultunensis*, *Lactobacillus vaccinostercus*, *Lactobacillus vaginalis*, *Lactobacillus versmoldensis*, *Lactobacillus vini*, *Lactobacillus vitulinus*, *Lactobacillus zaeae*, *Lactobacillus zymae*, Probiotics selected from a group consisting of Lactic acid bacteria (LAB) and bifidobacteria, or any combination thereof; said substance is used for the treatment of at least one selected from a group consisting of cholera, moraxella catarrhali, cocaine addiction, HIB, meningococcus, measles, mumps, rubella, varicella, yellow fever, Respiratory syncytial virus, pneumococcus, streptococcus, typhoid, influenza, hepatitis, including hepatitis A, B, C and F, polio, HIV, parainfluenza, rotavirus, CMV, chlamydia, non-typeable haemophilus, moraxella catarrhalis, human papilloma virus, tuberculosis including BCG, gonorrhoea, asthma, atherosclerosis, malaria, otitis media, E-coli, Alzheimers, H. Pylori, salmonella, diabetes, cancer and herpes simplex, Staphylococcus aureus, Streptococcus, or any combination thereof.

88. The air-intake actuated according to claim 71, wherein said substance is used for the treatment of at least one selected from a group consisting of cholera, moraxella catarrhali, cocaine addiction, HIB, meningococcus, measles, mumps, rubella, varicella, yellow fever, Respiratory syncytial virus, pneumococcus, streptococcus, typhoid, influenza, hepatitis, including hepatitis A, B, C and F, polio, HIV, parainfluenza, rotavirus, CMV, chlamydia, non-typeable haemophilus, moraxella catarrhalis, human papilloma virus, tuberculosis including BCG, gonorrhoea, asthma, atherosclerosis, malaria, otitis media, E-coli, Alzheimers, H. Pylori, salmonella, diabetes, cancer and herpes simplex, Staphylococcus aureus, Streptococcus, CNS disorder, brain disorders such as: brain cancer, acute brain injury,

spinal cord injury, Alzheimer disease, Neurogenesis, Parkinson's disease, depression, Epilepsy, schizophrenia by the delivery of substances such as: Neurotrophins, BDNF, GDNF, anti EGF receptor AB, Enzymes as Lysosomal enzyme, Neuregulin or any combination thereof.

89. The air-intake actuated according to claim 71, wherein said substance is a therapeutic substance selected from a group consisting of: agents for the common cold, Anti-addiction, anti-infectives, analgesics, anesthetics, anorexics, antiarthritics, anti-allergy agents, antiasthmatic agents, anticonvulsants, anti-depressants, antidiabetic agents, anti-depressants, anti-diuretics, anti-emetics, antihistamines, anti-inflammatory agents, antimigraine preparations, antmotion sickness preparations, antinauseants, antineoplastics, anti-obesity, antiosteoporeteic, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, anticholinergics, benzodiazepine antagonists, bone stimulating agents, central nervous system stimulants, hormones, hypnotics, immunosuppressives, prostaglandins, proteins, peptides, polypeptides and other macromolecules, psychostimulants, rhinitis treatment, sedatives, sexual hypofunction, tranquilizers and vitamins including B12, probiotics, natural oils, natural ingredients, a peptide or protein therapeutic agent such as cytokines, hormones, clotting factors, vaccines, monoclonal antibody or any combination thereof.
90. The air-intake actuated according to claim 71, wherein said substance may be delivered to said nasal cavity in a form selected from the group consisting of: a powder, a granule, a cachet, a capsule, a tablet, a paste, a cream, a gel, an ointment, a salve, a foam, a paste, a lotion, a cream, an oil suspension, a spray, a suspension, a solution, an emulsion, a patch, a stick, a spray, preferably a nasal spray, or a buccal spray, a mouth wash, an aerosol, in a venture effect, a drink, and a solution.
91. The air-intake actuated according to claim 71, wherein said substance is selected from a group consisting of natural oils; Mint oils, Peppermint oil, Spearmint oil, Menthol, Olive oil, Eucalyptus oil, Amino acids, fatty acids and any combination thereof.
92. A method for delivering a substance to a nasal cavity of a subject, said method comprising steps of:
 - a. providing an air-intake actuated device adapted for delivering a substance to a nasal cavity of a subject, said device comprising: (i) a container for containing said substance; (ii) a nosepiece extending from said device for placement in proximity to a nose of said subject, said nosepiece being in fluid communication with said container; (iii) a valve mechanically connectable to said container, characterized by at least two configurations: (i) an ACTIVE CONFIGURATION in which said valve

enables delivery of predetermined amount of said substance from said container to said nasal cavity via said nosepiece; and, (ii) an INACTIVE CONFIGURATION, in which said valve prevents delivery of said predetermined amount of said substance from said container to said nasal cavity; (iv) a mouthpiece extending from said device for placement in a mouth of said subject; and, a (v) trigger mechanism adapted to reconfigure said valve from said ACTIVE CONFIGURATION to said INACTIVE CONFIGURATION, and vice versa; wherein said trigger mechanism is activated by means of said subject intaking air through said mouthpiece; further wherein said trigger mechanism is adapted to reconfigure said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION for a predetermined period of time in response to said subject intake of air;

- b. placing said nosepiece in or around the nose of said subject;
 - c. placing said mouthpiece in the mouth of said subject;
 - d. inhaling air; thereby reconfiguring said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION for a predetermined period of time in response;
 - e. releasing a predetermined amount of said substance from said container to said nosepiece;
93. The method for delivering a substance to a nasal cavity of a subject according to claim 92, further comprising step of reconfiguring said valve via said trigger mechanism from said ACTIVE CONFIGURATION to said INACTIVE CONFIGURATION when said subject ceases said intake.
94. The method for delivering a substance to a nasal cavity of a subject according to claim 92, additionally comprising step of providing said trigger mechanism with a flexible membrane; said membrane is in mechanical communication with said valve; such that when said subject intake air, said membrane is relocated from its initial position and said valve is opened.
95. The method for delivering a substance to a nasal cavity of a subject according to claim 92, additionally comprising step of providing said device with an intermediate compartment adapted to be filled with predetermined amount of said substance; such that said delivery of said substance to said subject is from said intermediate compartment.

96. The method for delivering a substance to a nasal cavity of a subject according to claim 92, further comprising step of synchronizing the operation of said trigger mechanism with said drinking of said fluid by said subject.
97. The method for delivering a substance to a nasal cavity of a subject according to claim 92, further comprising step of providing said trigger mechanism with a pulsation mechanism adapted to reconfigure said valve from said INACTIVE CONFIGURATION to said ACTIVE CONFIGURATION and vice versa in sequence of pulses, each of which is characterized by a predetermined length of pulse, said valve adapted to release said predetermined amount of said substance according to said sequence of pulses.
98. The method for delivering a substance to a nasal cavity of a subject according to claim 97, further comprising step of releasing in each said pulse at least two doses of said predetermined amount of said substance.
99. The method for delivering a substance to a nasal cavity of a subject according to claim 92, wherein said nosepiece is in fluid communication with said valve by means of a spray nozzle.
100. The method for delivering a substance to a nasal cavity of a subject according to claim 92, wherein said spray nozzle is characterized by a diameter which influences on said predetermined period of time.
101. The method for delivering a substance to a nasal cavity of a subject according to claim 92, further comprising step of providing said device with a cap adapted to cover at least a portion of the components of said device for sterilization purposes.
102. The method for delivering a substance to a nasal cavity of a subject according to claim 101, wherein said cap comprises an opening.
103. The method for delivering a substance to a nasal cavity of a subject according to claim 92, wherein said container adapted to be connected to an external container, said external container adapted to fill said container with said substance.
104. The method for delivering a substance to a nasal cavity of a subject according to claim 103, further comprising step of filling said container by said external container with a predetermined dose of said substance.
105. The method for delivering a substance to a nasal cavity of a subject according to claim 92, further comprising step of providing said container with indicating means adapted to indicate the amount of said substance within said container.

106. The method for delivering a substance to a nasal cavity of a subject according to claim 105, wherein said indicating means is a transparent window located on a side of said container.
107. The method for delivering a substance to a nasal cavity of a subject according to claim 92, wherein said substance is a drug selected from a group consisting of: Anti-Angiogenesis agents, Antisense, anti-ulcer, butorphanol, Calcitonin and analogs, COX-II inhibitors, desmopressin and analogs, dihydroergotamine, Dopamine agonists and antagonists, Enkephalins and other opioid peptides, Growth hormone and analogs, growth hormone releasing hormone, Growth hormone antagonists, IgE suppressors, Insulin, insulinotropin and analogs, Ketamine, Kytril, Leutenizing hormone releasing hormone and analogs, lidocaine, metoclopramide, Midazolam, Narcotic analgesics, neuraminidase inhibitors, nicotine, Non-steroid anti-inflammatory agents, Oligosaccharides, ondansetron, Parathyroid hormone and analogs, Parathyroid hormone antagonists, Prostaglandin antagonists, Prostaglandins, Recombinant soluble receptors, scopolamine, Serotonin agonists and antagonists, Sildenafil, Terbutaline, vasopressin, or any combination thereof.
108. The method for delivering a substance to a nasal cavity of a subject according to claim 92, additionally comprising step of selecting said substance from a vaccine with or without carriers and/or adjuvant selected from the group consisting of: Prophylactics and therapeutic antigens, subunit protein, peptide and polysaccharide, polysaccharide conjugates, toxoids, genetic based vaccines, live attenuated, reassortant, inactivated, whole cells, viral and bacterial vectors for the treatment of arthritis, *Lactobacillus species*: *Lactobacillus acetotolerans*, *Lactobacillus acidifarinae*, *Lactobacillus acidipiscis*, *Lactobacillus acidophilus* (*Doderlein bacillus*), *Lactobacillus agilis*, *Lactobacillus algidus*, *Lactobacillus alimentarius*, *Lactobacillus amylolyticus*, *Lactobacillus amylophilus*, *Lactobacillus amylotrophicus*, *Lactobacillus amylovorus*, *Lactobacillus animalis*, *Lactobacillus antri*, *Lactobacillus apodemi*, *Lactobacillus aviarius*, *Lactobacillus bifermentans*, *Lactobacillus brevis*, *Lactobacillus buchneri*, *Lactobacillus camelliae*, *Lactobacillus casei*, *Lactobacillus cateniformis*, *Lactobacillus ceti*, *Lactobacillus coleohominis*, *Lactobacillus collinoides*, *Lactobacillus composti*, *Lactobacillus concavus*, *Lactobacillus coryniformis*, *Lactobacillus crispatus*, *Lactobacillus crustorum*, *Lactobacillus curvatus*, *Lactobacillus delbrueckii*, *Lactobacillus delbrueckii subsp. Bulgaricus*, *Lactobacillus delbrueckii subsp. Lactis*, *Lactobacillus diolivorans*, *Lactobacillus equi*, *Lactobacillus equigenerosi*, *Lactobacillus farraginis*, *Lactobacillus farciminis*, *Lactobacillus fermentum*, *Lactobacillus fornicalis*, *Lactobacillus fructivorans*, *Lactobacillus frumenti*, *Lactobacillus fuchuensis*, *Lactobacillus gallinarum*, *Lactobacillus gasseri*, *Lactobacillus gastricus*, *Lactobacillus ghanensis*,

Lactobacillus graminis, *Lactobacillus hammesii*, *Lactobacillus hamsteri*, *Lactobacillus harbinensis*, *Lactobacillus hayakitensis*, *Lactobacillus helveticus*, *Lactobacillus hilgardii*, *Lactobacillus homohiochii*, *Lactobacillus iners*, *Lactobacillus ingluviei*, *Lactobacillus intestinalis*, *Lactobacillus jensenii*, *Lactobacillus johnsonii*, *Lactobacillus kalixensis*, *Lactobacillus kefiranofaciens*, *Lactobacillus kefiri*, *Lactobacillus kimchii*, *Lactobacillus kitasatonis*, *Lactobacillus kunkeei*, *Lactobacillus leichmannii*, *Lactobacillus lindneri*, *Lactobacillus malefermentans*, *Lactobacillus mali*, *Lactobacillus manihotivorans*, *Lactobacillus mindensis*, *Lactobacillus mucosae*, *Lactobacillus murinus*, *Lactobacillus nagelii*, *Lactobacillus namurensis*, *Lactobacillus nantensis*, *Lactobacillus oligofermentans*, *Lactobacillus oris*, *Lactobacillus panis*, *Lactobacillus pantheris*, *Lactobacillus parabrevis*, *Lactobacillus parabuchneri*, *Lactobacillus paracollinoides*, *Lactobacillus parafarraginis*, *Lactobacillus parakefiri*, *Lactobacillus paralimentarius*, *Lactobacillus paraplantarum*, *Lactobacillus pentosus*, *Lactobacillus perolens*, *Lactobacillus plantarum*, *Lactobacillus pontis*, *Lactobacillus psittaci*, *Lactobacillus rennini*, *Lactobacillus reuteri*, *Lactobacillus rhamnosus*, *Lactobacillus rimae*, *Lactobacillus rogosae*, *Lactobacillus rossiae*, *Lactobacillus ruminis*, *Lactobacillus saerimneri*, *Lactobacillus sakei*, *Lactobacillus salivarius*, *Lactobacillus sanfranciscensis*, *Lactobacillus satsumensis*, *Lactobacillus secaliphilus*, *Lactobacillus sharpeae*, *Lactobacillus siliginis*, *Lactobacillus spicheri*, *Lactobacillus suebicus*, *Lactobacillus thailandensis*, *Lactobacillus ultunensis*, *Lactobacillus vaccinostrercus*, *Lactobacillus vaginalis*, *Lactobacillus versmoldensis*, *Lactobacillus vini*, *Lactobacillus vitulinus*, *Lactobacillus zeae*, *Lactobacillus zymae*, Probiotics selected from a group consisting of Lactic acid bacteria (LAB) and bifidobacteria, or any combination thereof; said substance is used for the treatment of at least one selected from a group consisting of cholera, moraxella catarrhali, cocaine addiction, HIB, meningococcus, measles, mumps, rubella, varicella, yellow fever, Respiratory syncytial virus, pneumococcus, streptococcus, typhoid, influenza, hepatitis, including hepatitis A, B, C and F, polio, HIV, parainfluenza, rotavirus, CMV, chlamydia, non-typeable haemophilus, moraxella catarrhalis, human papilloma virus, tuberculosis including BCG, gonorrhoea, asthma, atherosclerosis, malaria, otitis media, E. coli, Alzheimers, H. Pylori, salmonella, diabetes, cancer and herpes simplex, , Staphylococcus aureus, Streptococcus, or any combination thereof.

109. The method for delivering a substance to a nasal cavity of a subject according to claim 92, wherein said substance is used for the treatment of at least one selected from a group consisting of cholera, moraxella catarrhali, cocaine addiction, HIB, meningococcus, measles, mumps, rubella, varicella, yellow fever, Respiratory syncytial virus, pneumococcus, streptococcus, typhoid, influenza, hepatitis, including hepatitis A, B, C and F, polio, HIV,

parainfluenza, rotavirus, CMV, chlamydia, non-typeable haemophilus, moraxella catarrhalis, human papilloma virus, tuberculosis including BCG, gonorrhoea, asthma, atherosclerosis, malaria, otitis media, E-coli, Alzheimers, H. Pylori, salmonella, diabetes, cancer and herpes simplex, Staphylococcus aureus, Streptococcus, CNS disorder, brain disorders such as: brain cancer, acute brain injury, spinal cord injury, Alzheimer disease, Neurogenesis, Parkinson's disease, depression, Epilepsy, schizophrenia by the delivery of substances such as: Neurotrophins, BDNF, GDNF, anti EGF receptor AB, Enzymes as Lysosomal enzyme, Neuregulin or any combination thereof.

110. The method for delivering a substance to a nasal cavity of a subject according to claim 92, wherein said substance is a therapeutic substance selected from a group consisting of: Agents for the common cold, Anti-addiction, anti-infectives, analgesics, anesthetics, anorexics, antiarthritics, anti-allergy agents, antiasthmatic agents, anticonvulsants, anti-depressants, antidiabetic agents, anti-depressants, anti-diuretics, anti-emetics, antihistamines, anti-inflammatory agents, antimigraine preparations, antinausea preparations, antineoplastic agents, anti-obesity, antiosteoporosis, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, anticholinergics, benzodiazepine antagonists, bone stimulating agents, central nervous system stimulants, hormones, hypnotics, immunosuppressives, prostaglandins, proteins, peptides, polypeptides and other macromolecules, psychostimulants, rhinitis treatment, sedatives, sexual hypofunction, tranquilizers and vitamins including B12, probiotics, natural oils, natural ingredients, peptide or protein therapeutic agent such as cytokines, hormones, clotting factors, vaccines, monoclonal antibody or any combination thereof.
111. The method for delivering a substance to a nasal cavity of a subject according to claim 92, wherein said substance is delivered to said nasal cavity in a form selected from the group consisting of: a powder, a granule, a cachet, a capsule, a tablet, a paste, a cream, a gel, an ointment, a salve, a foam, a paste, a lotion, a cream, an oil suspension, a spray, a suspension, a solution, an emulsion, a patch, a stick, a spray, preferably a nasal spray, or a buccal spray, a mouth wash, an aerosol, in a ventouse effect, a drink, and a solution.
112. The method for delivering a substance to a nasal cavity of a subject according to claim 92, additionally comprising step of selecting said substance from a group consisting of natural oils; Mint oils, Peppermint oil, Spearmint oil, Menthol, Olive oil, Eucalyptus oil, Amino acids, fatty acids and any combination thereof.

1/22

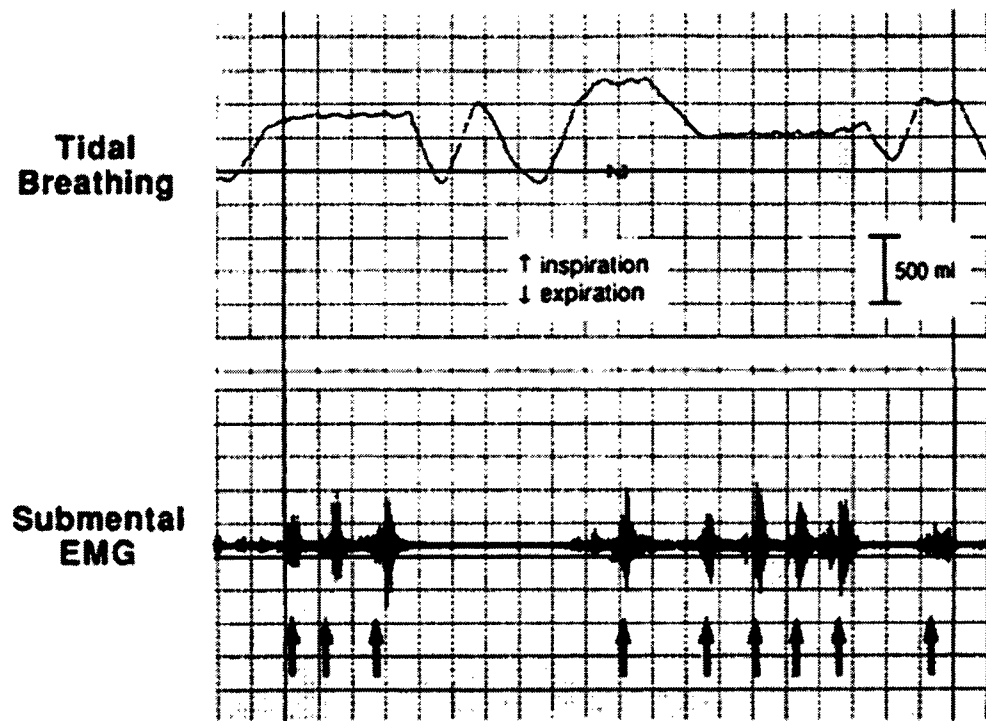
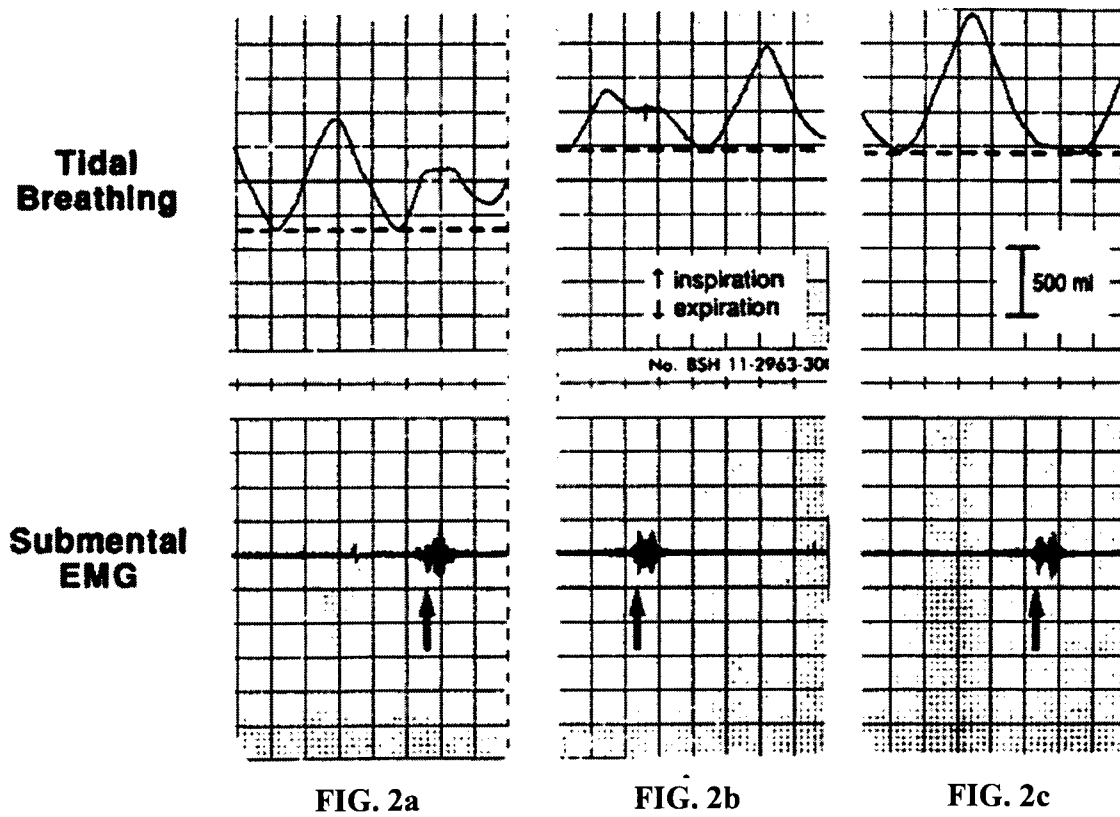


Fig. 1



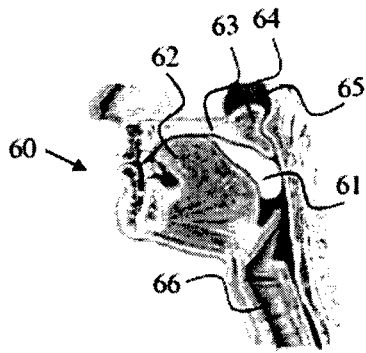


FIG. 3a

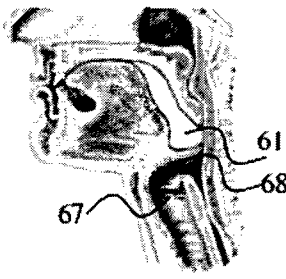


FIG. 3b

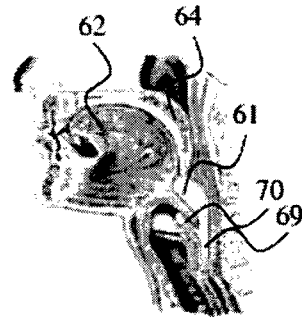


FIG. 3c

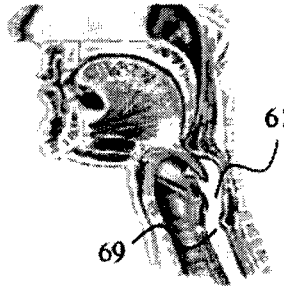


FIG. 3d

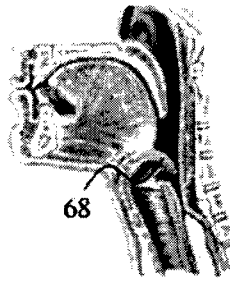


FIG. 3e



FIG. 3f

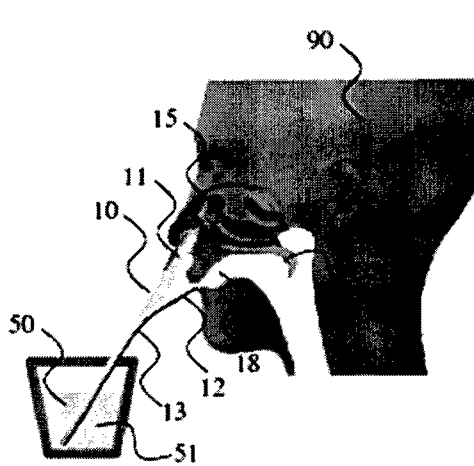


FIG. 4a

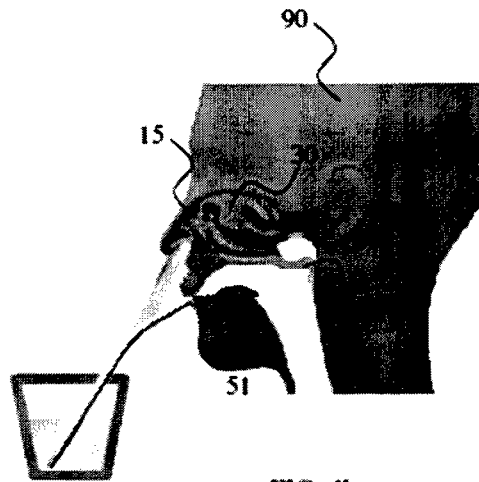


FIG. 4b

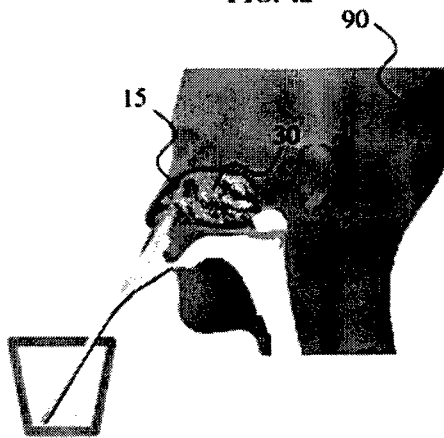


FIG. 4c

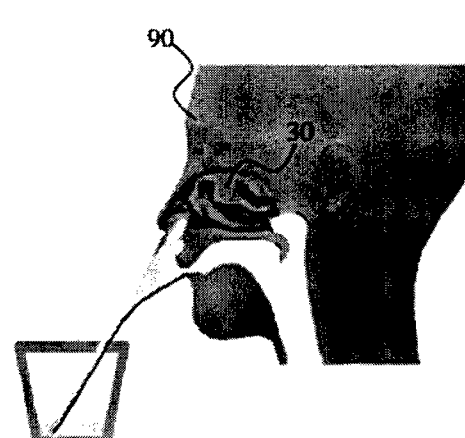


FIG. 4d

3/22

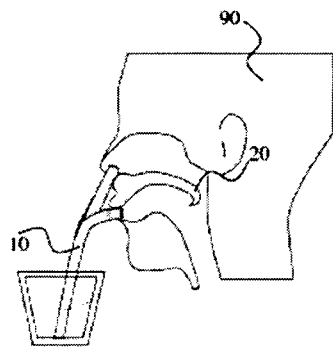


FIG. 4c

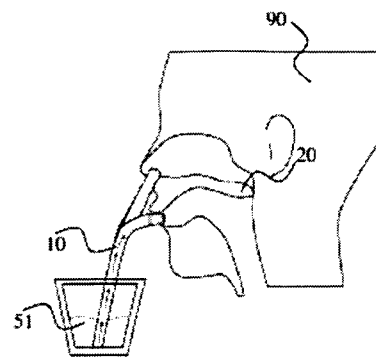


FIG. 4f

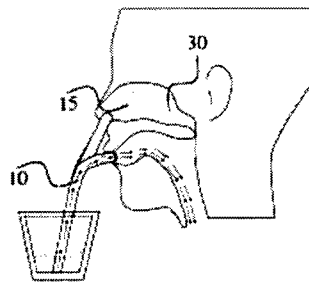


FIG. 4g

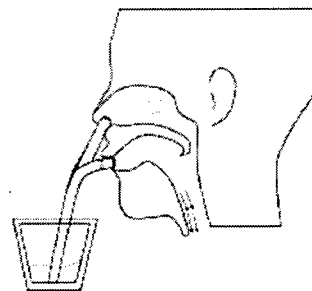


FIG. 4h

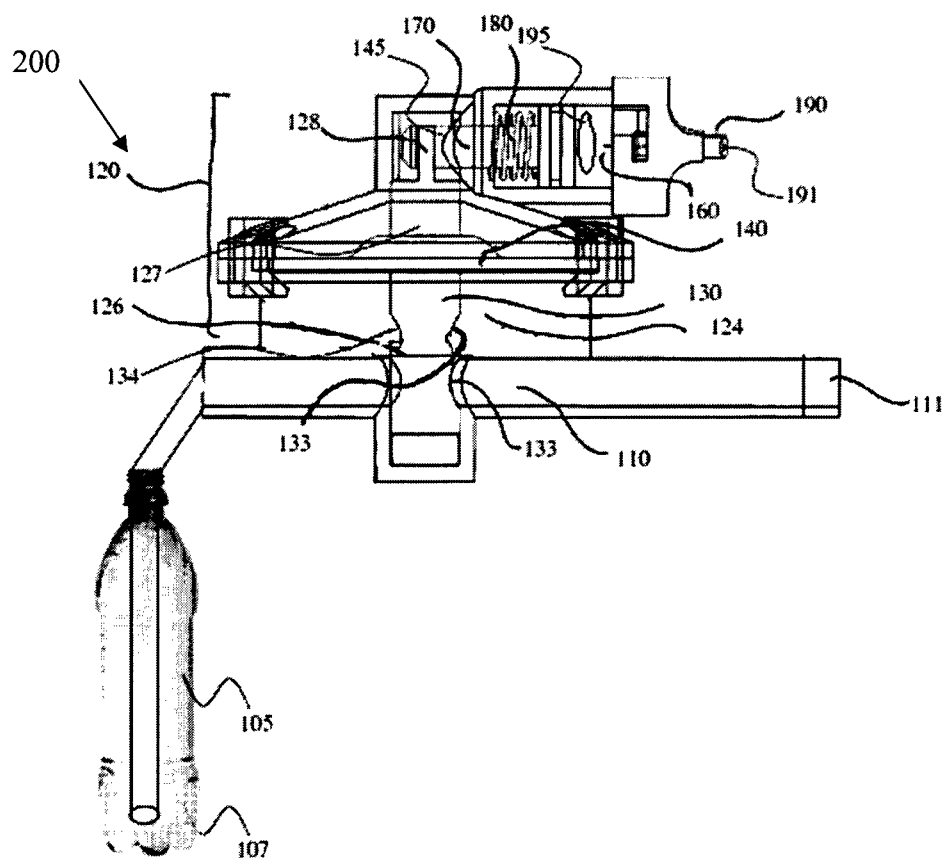


Fig. 5

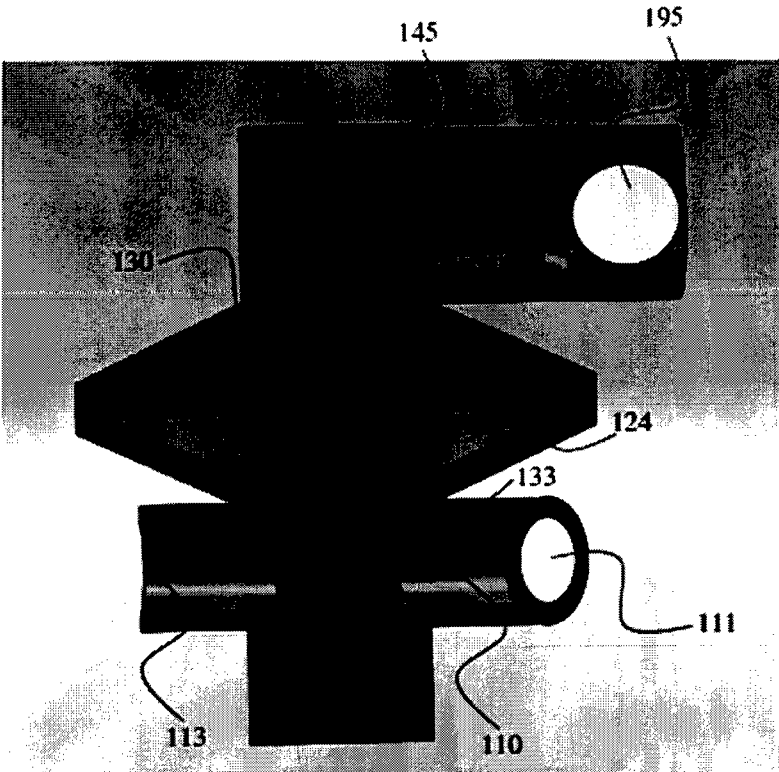


Fig. 6

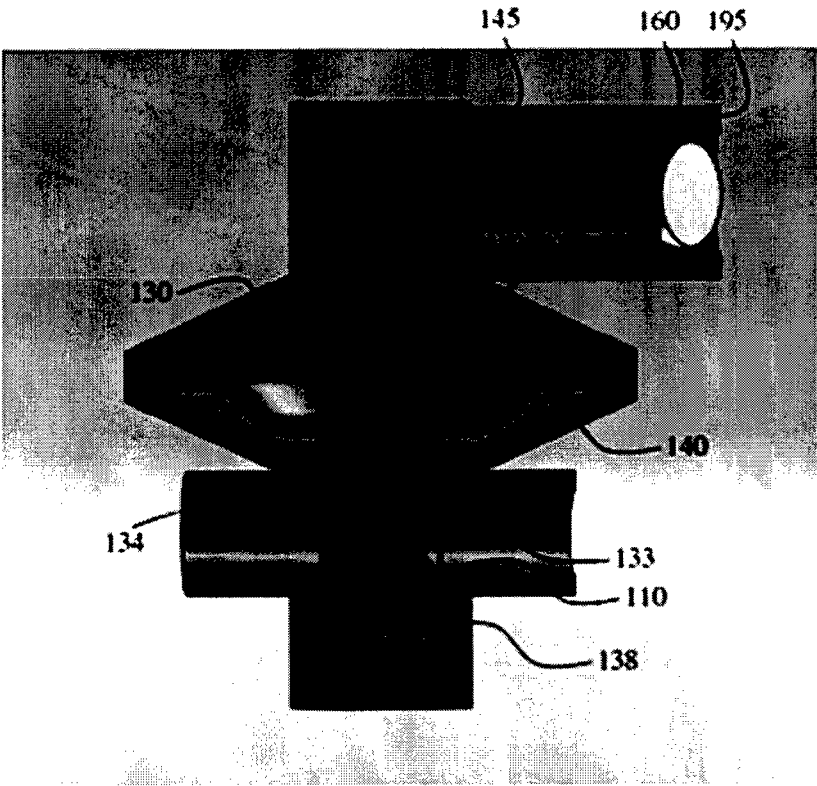


Fig. 7



Fig. 8

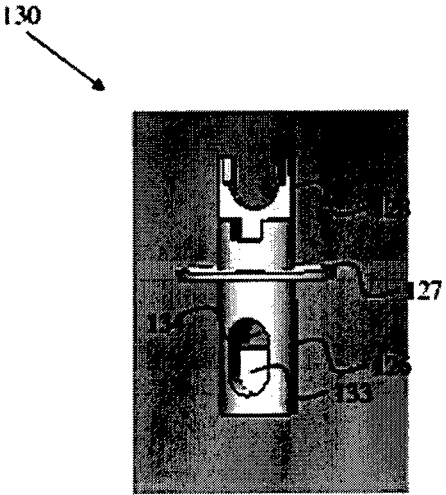


Fig. 9

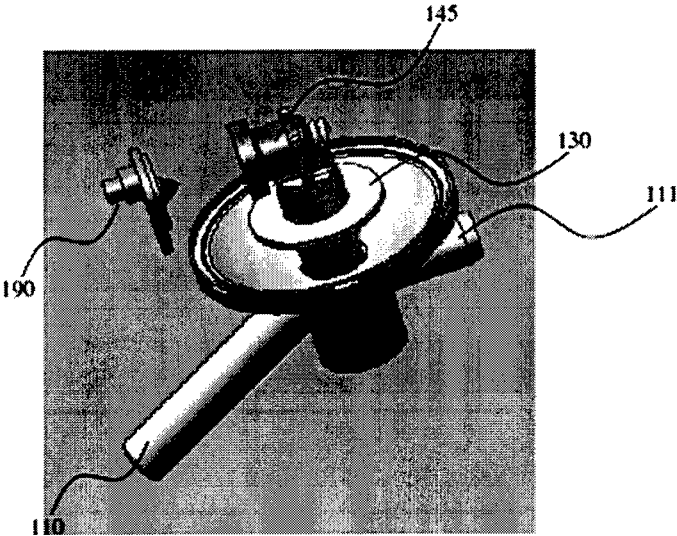


Fig. 10

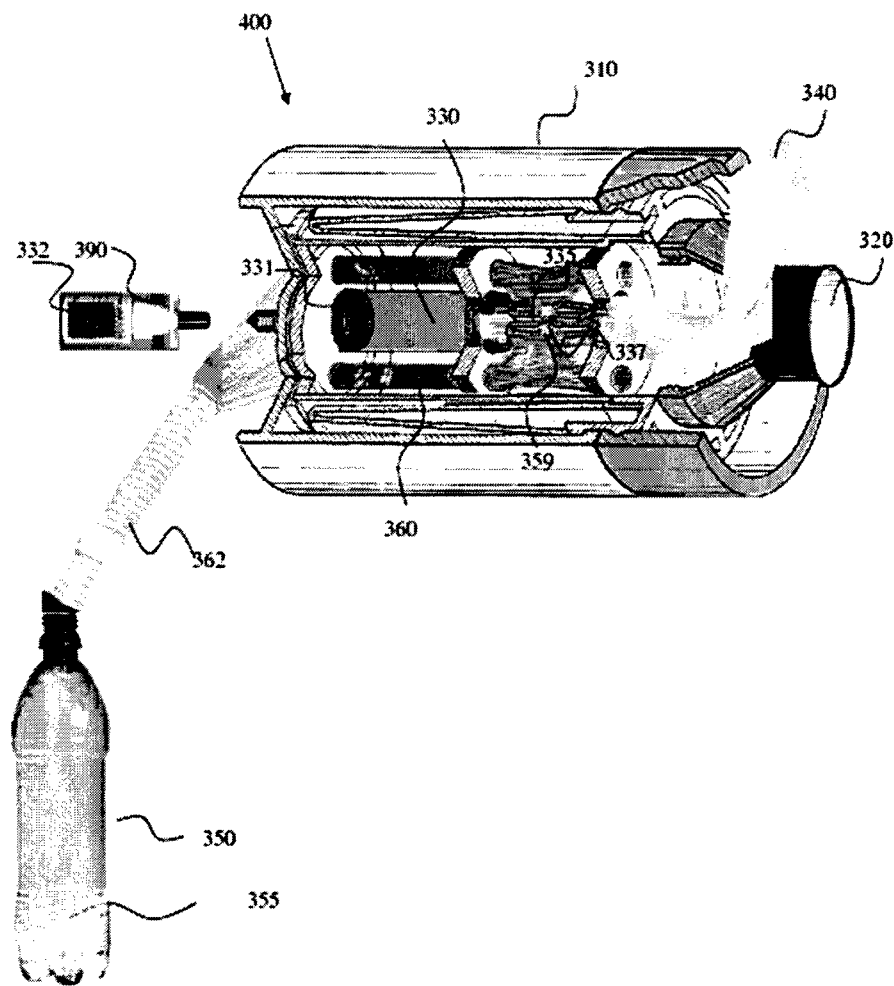


Fig. 11

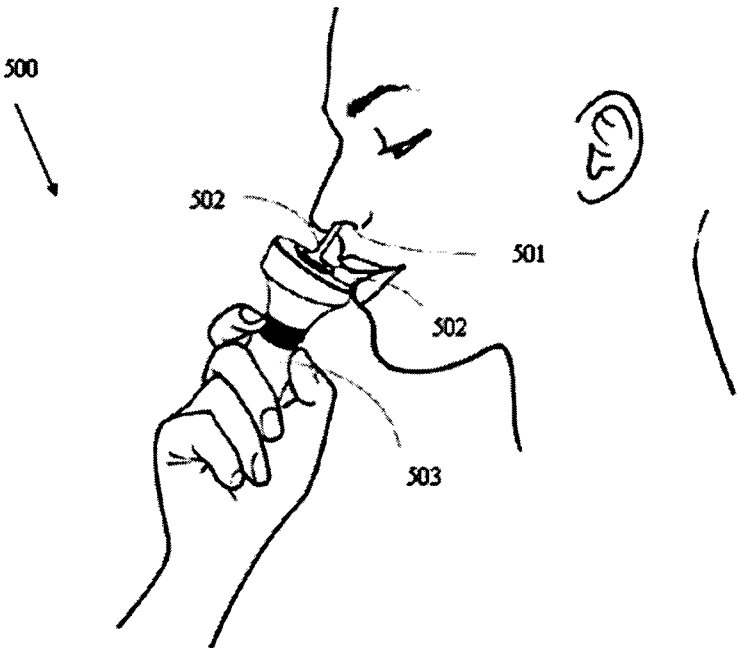


Fig. 12

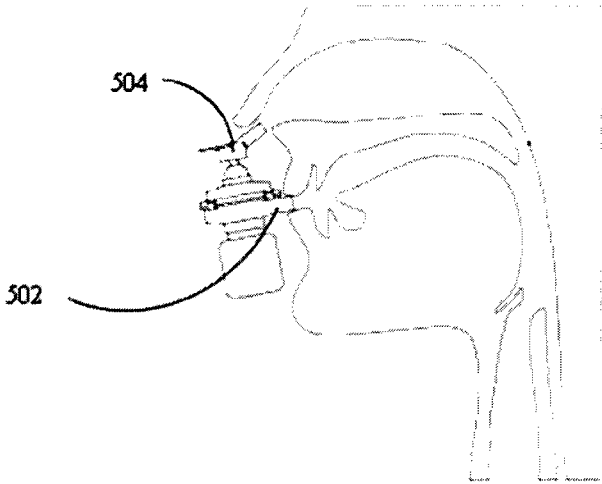


Fig. 13

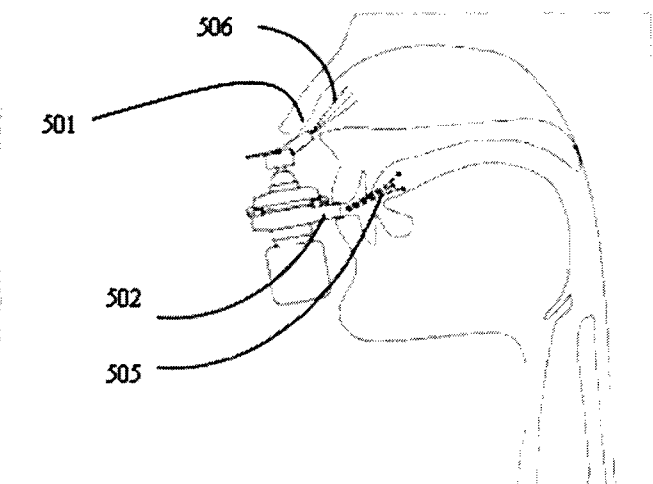


Fig. 14

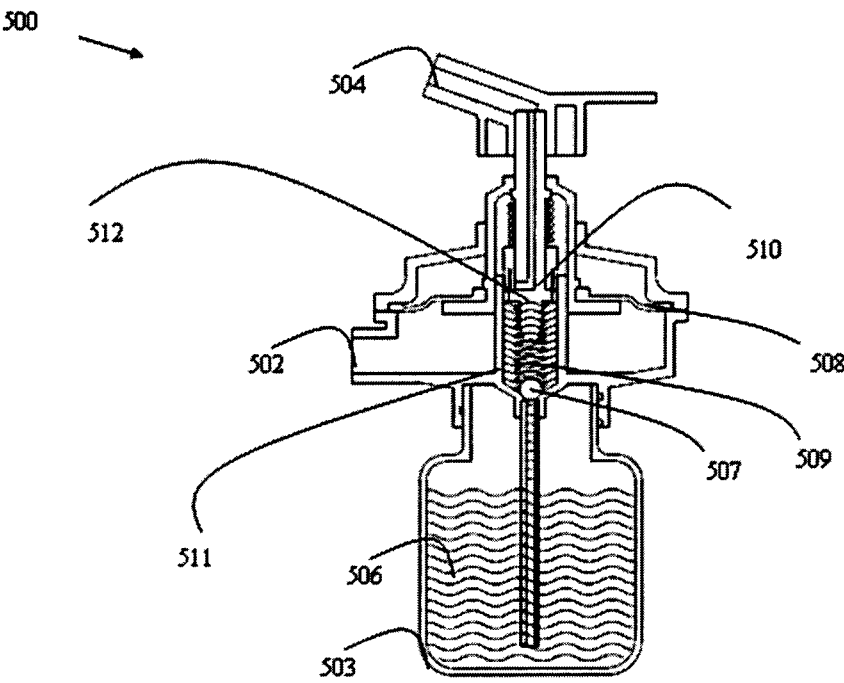
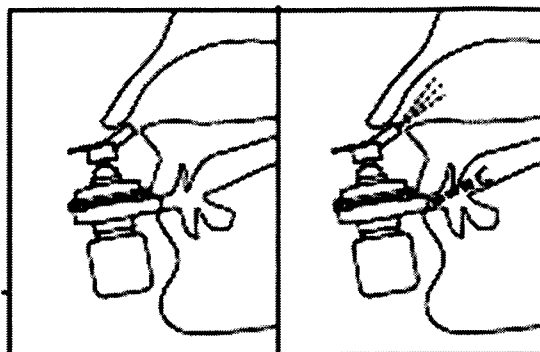
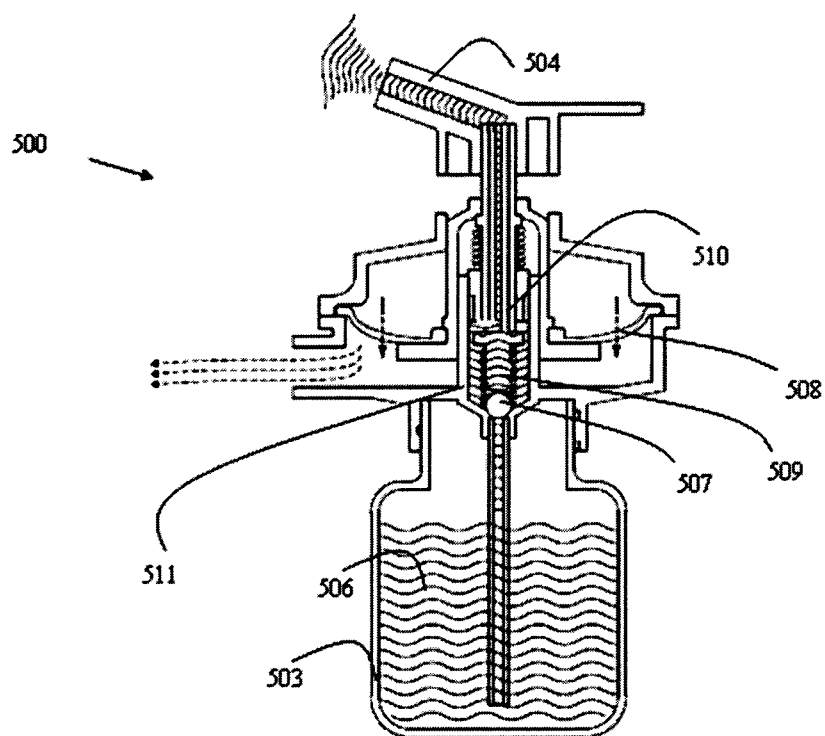


Fig. 15

8/22

**Fig. 16a** **Fig. 16b****Fig. 17**

9/22

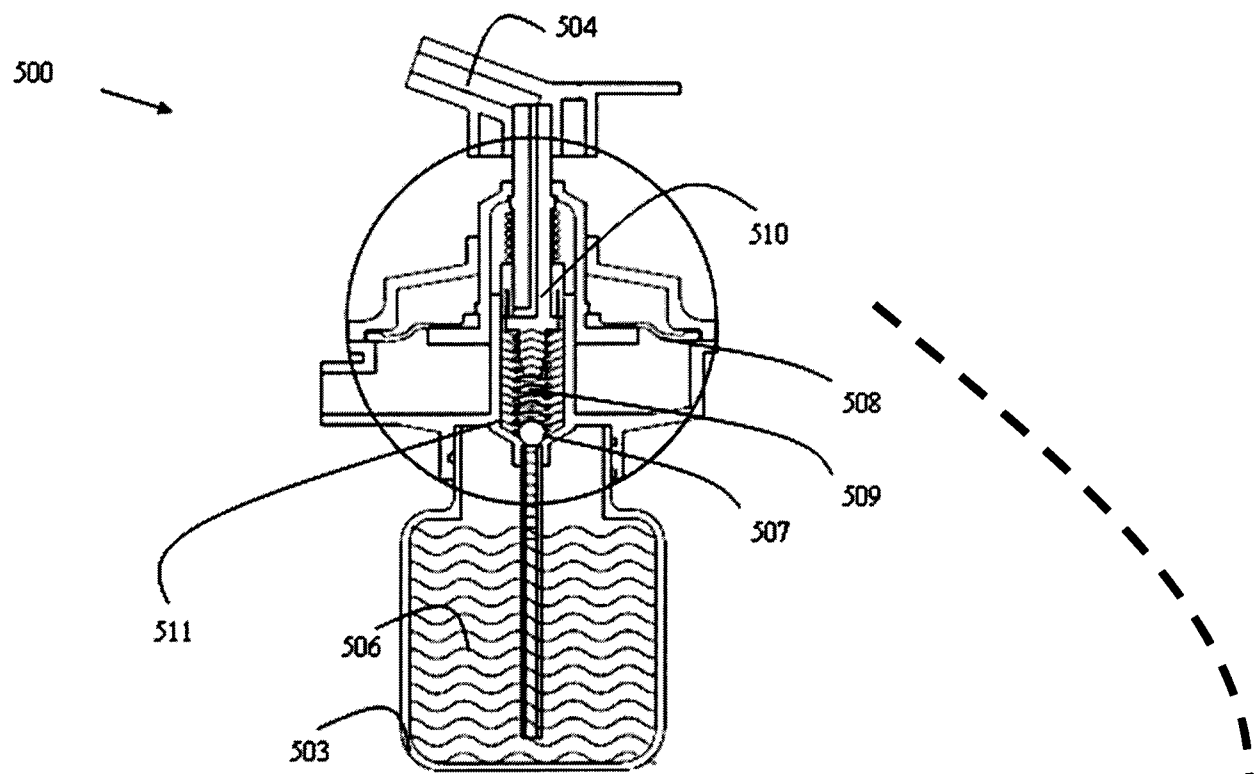


Fig. 18a

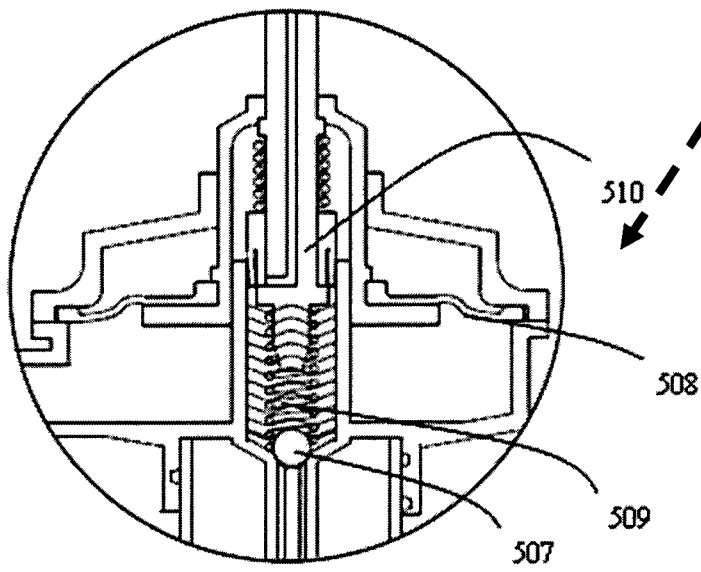
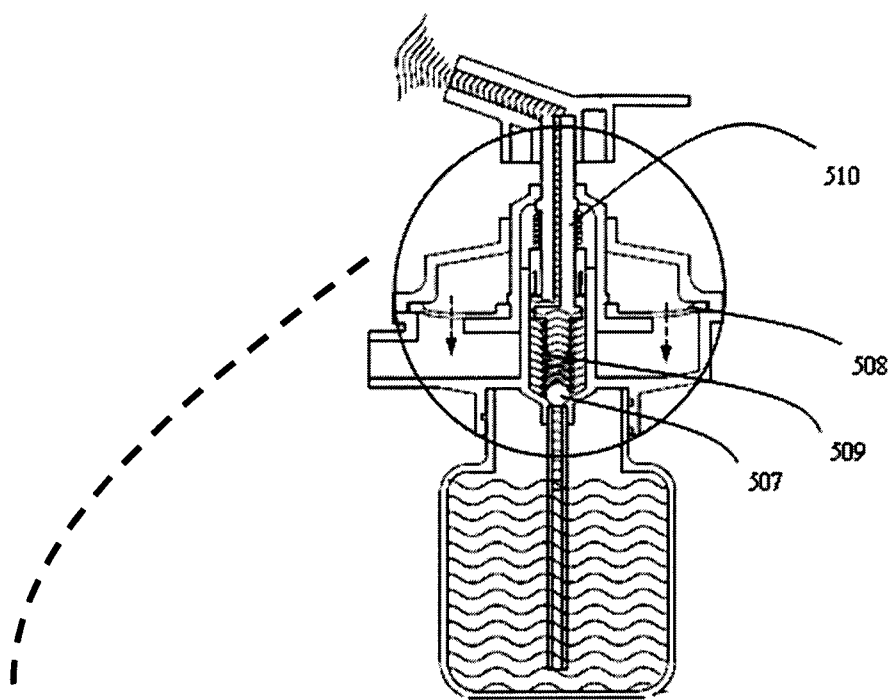
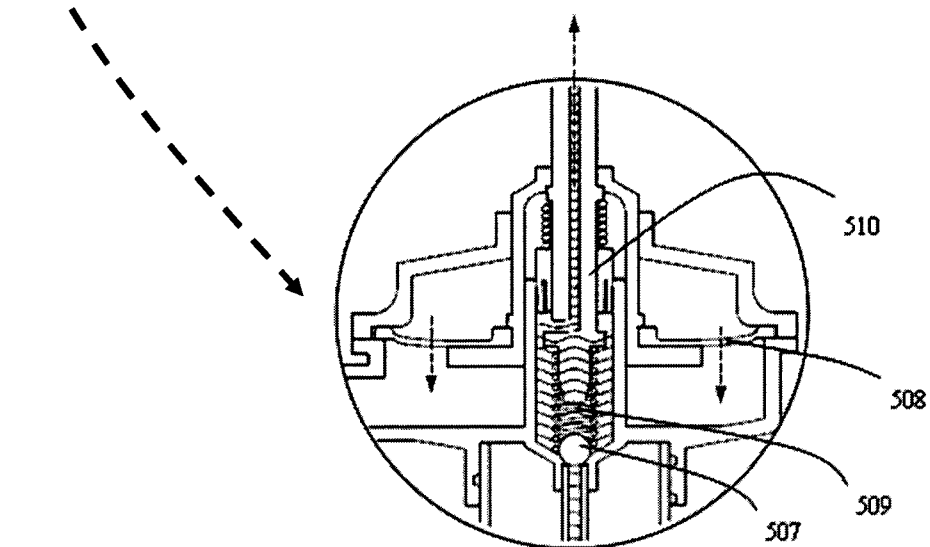
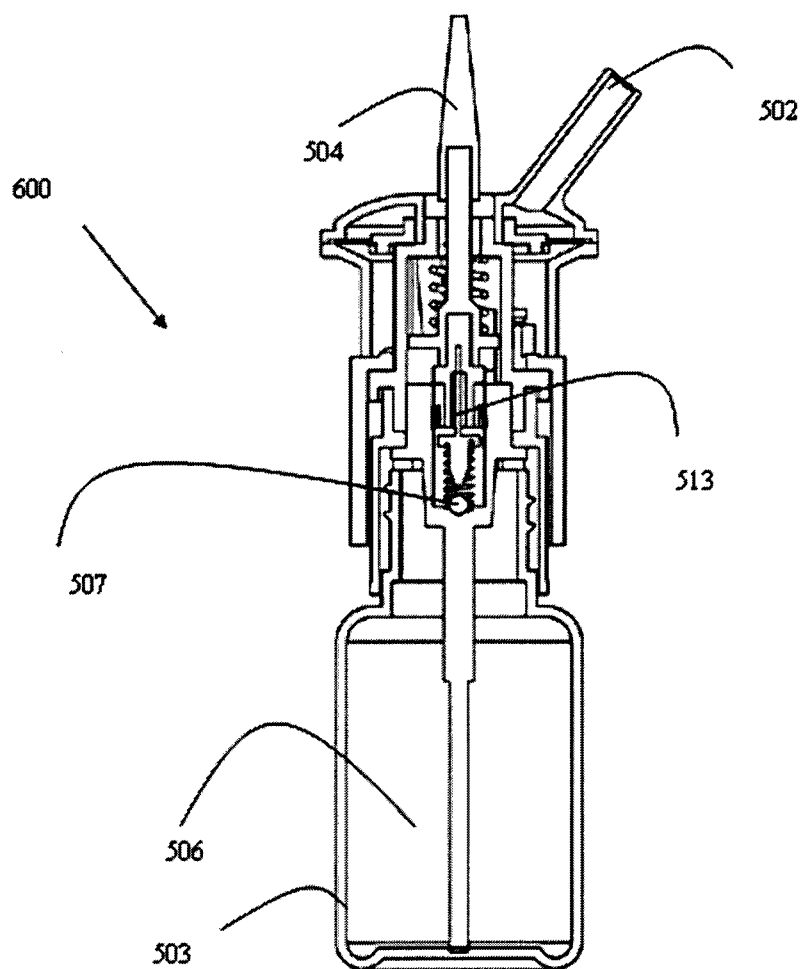
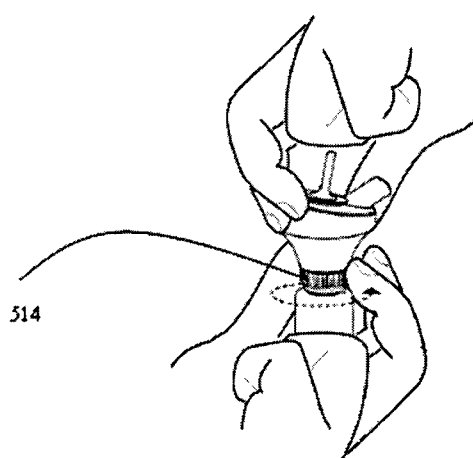


Fig. 18b

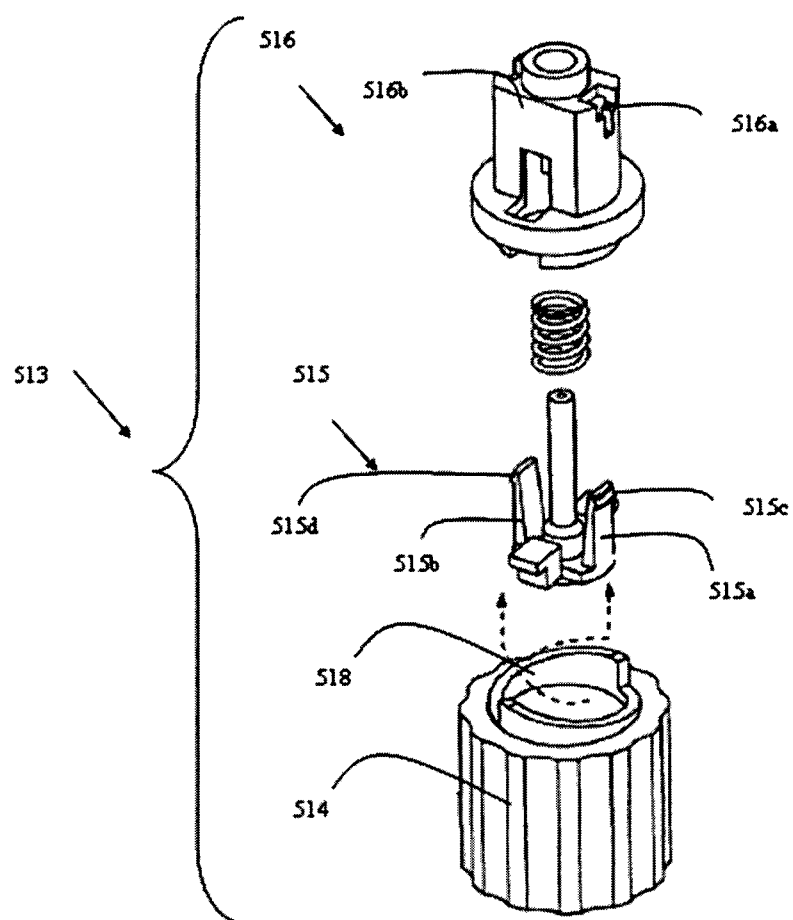
10/22

**Fig. 19a****Fig. 19b**

11/22

**Fig. 20****Fig. 21**

12/22

**Fig. 22a**

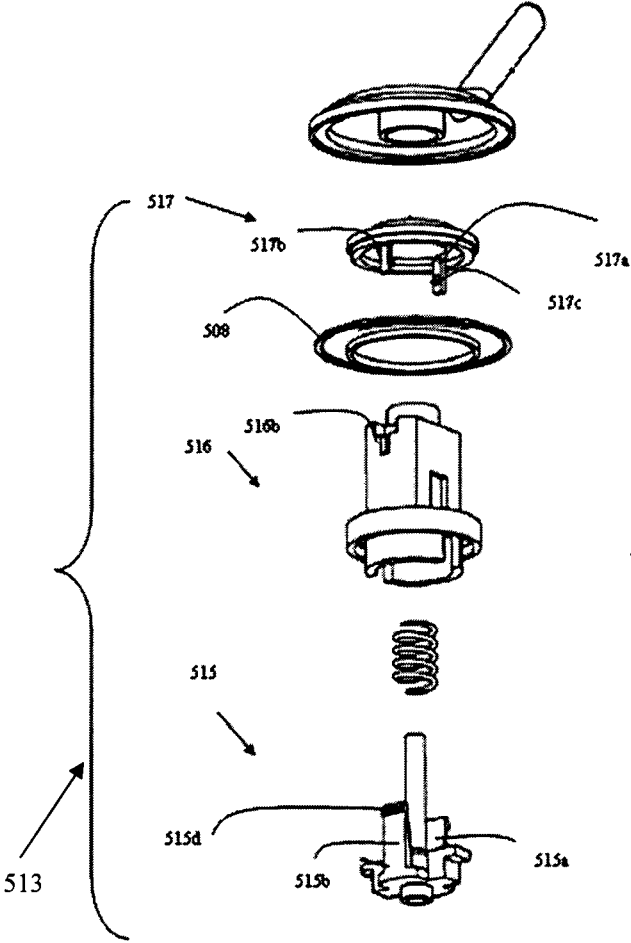


Fig. 22b

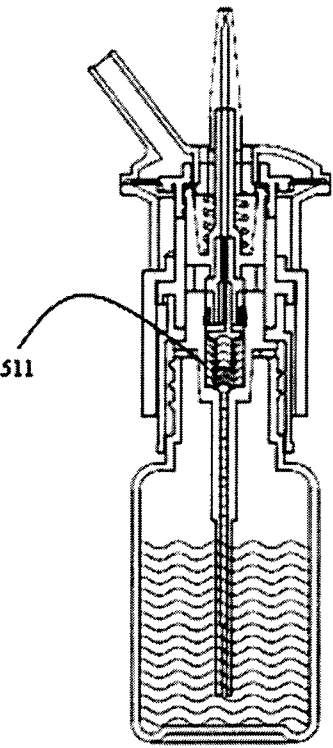
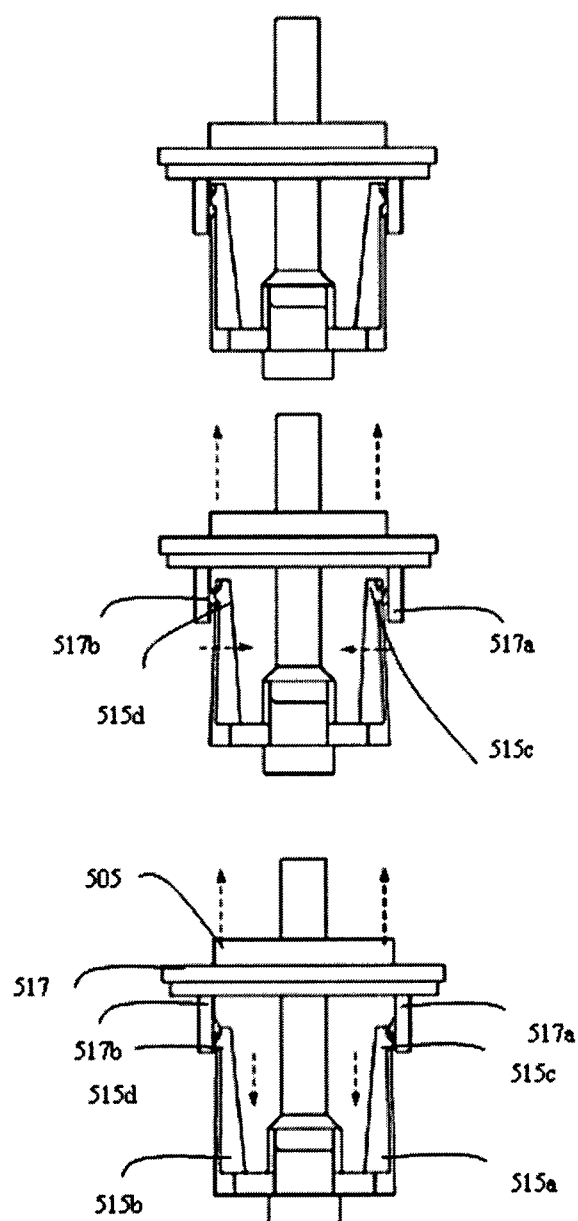


Fig. 22c

14/22

**Fig. 23**

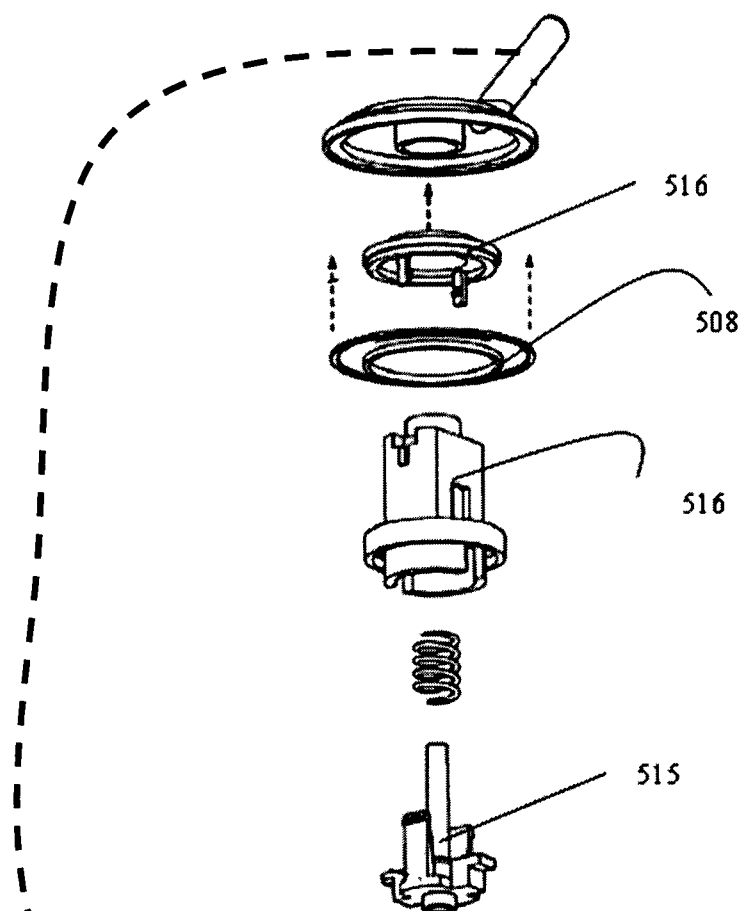


Fig. 24

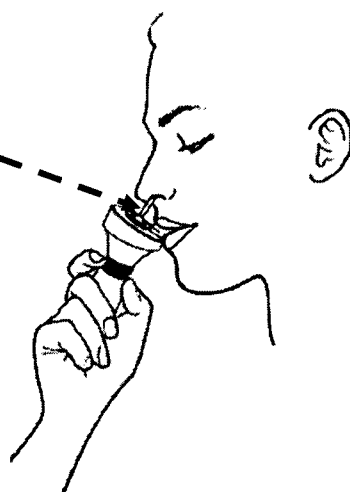
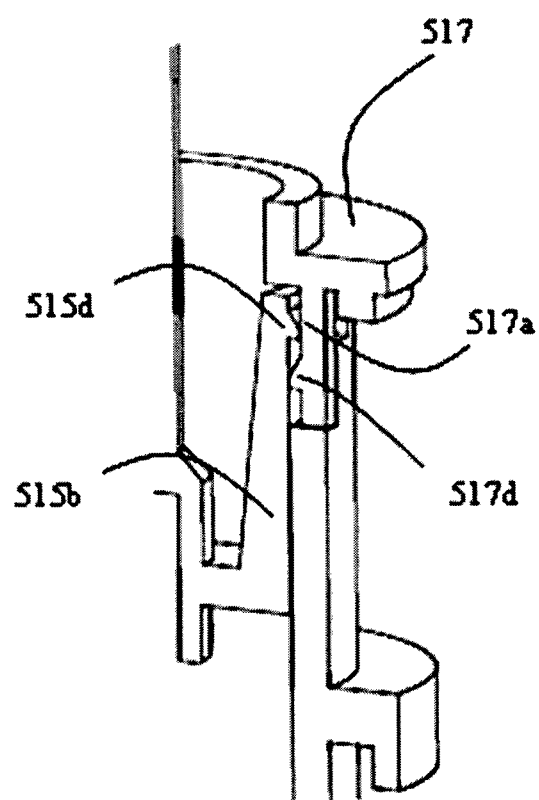
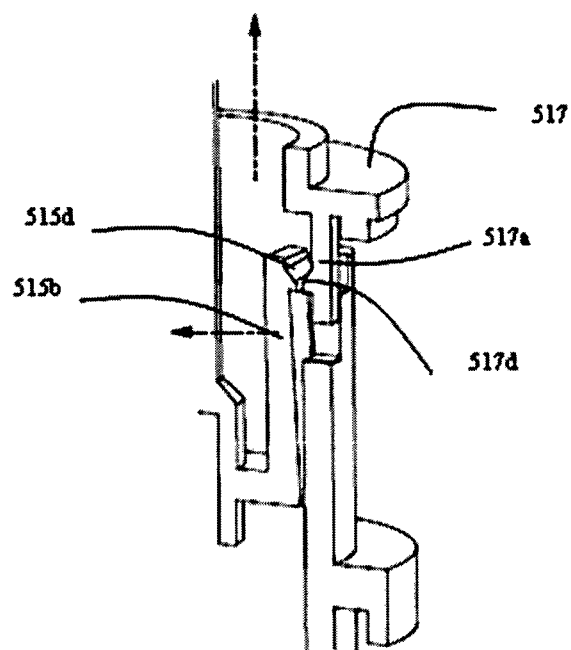


Fig. 25

16/22

**Fig. 26a****Fig. 26b**

17/22

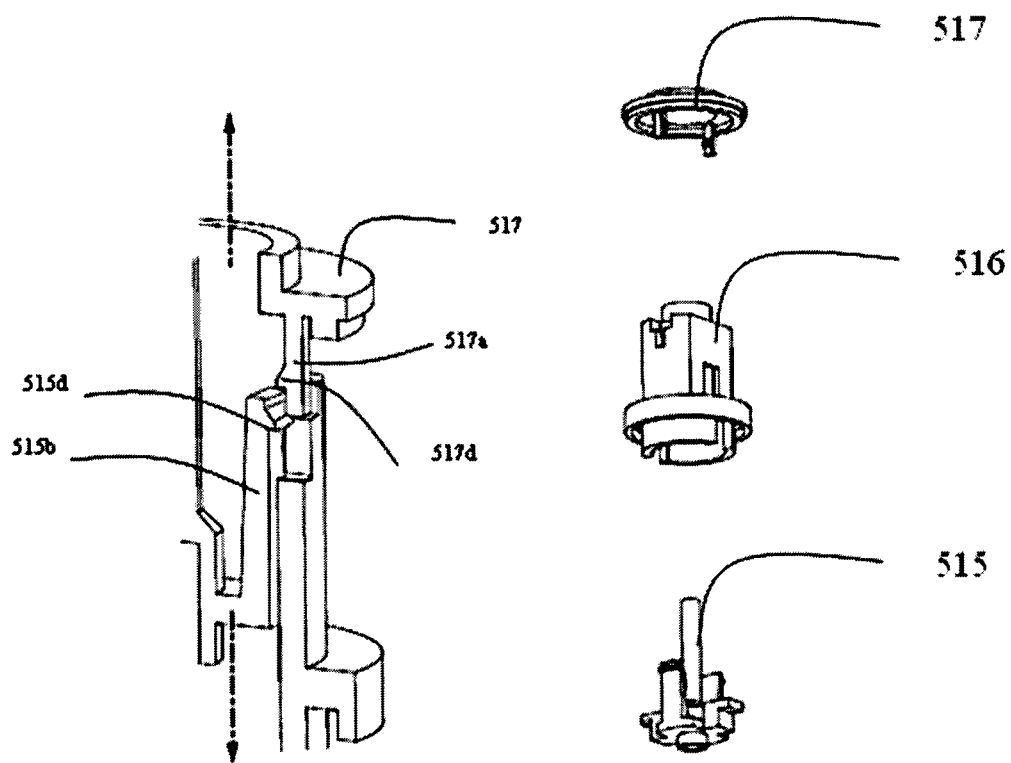


Fig. 26c

Fig. 26d

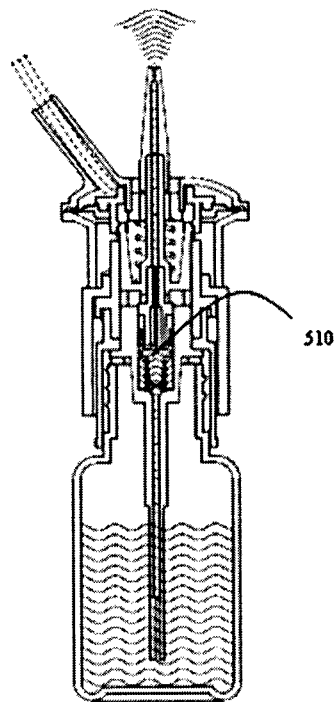
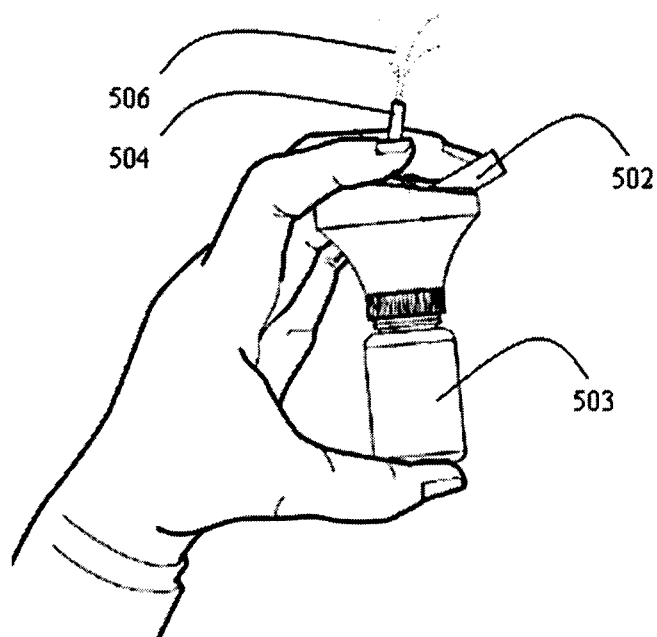
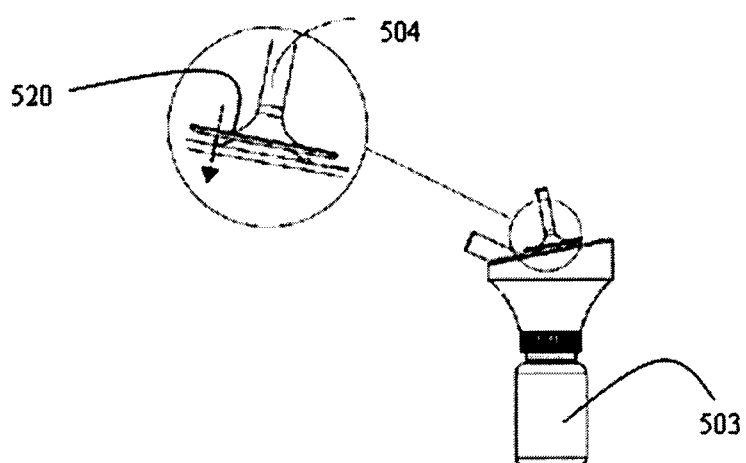


Fig. 26e

18/22

**Fig. 27****Fig. 28**

19/22

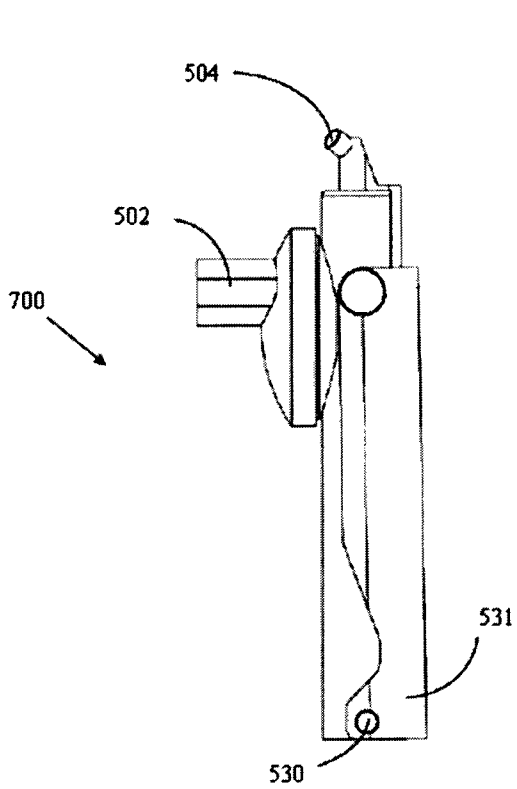


Fig. 29

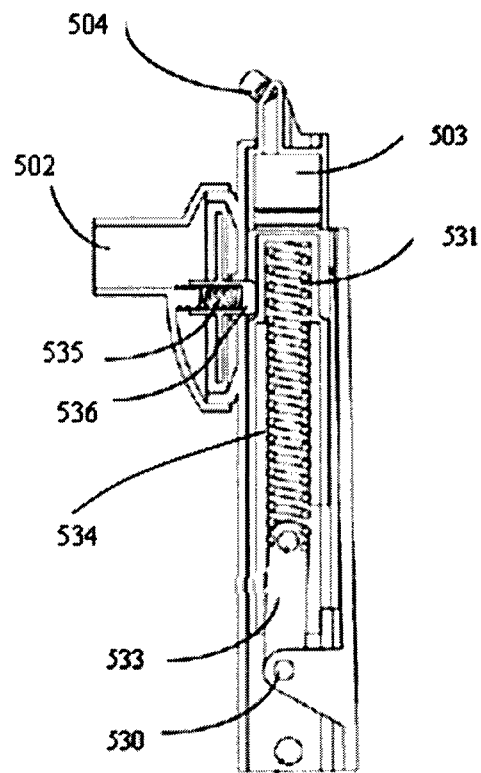


Fig. 30

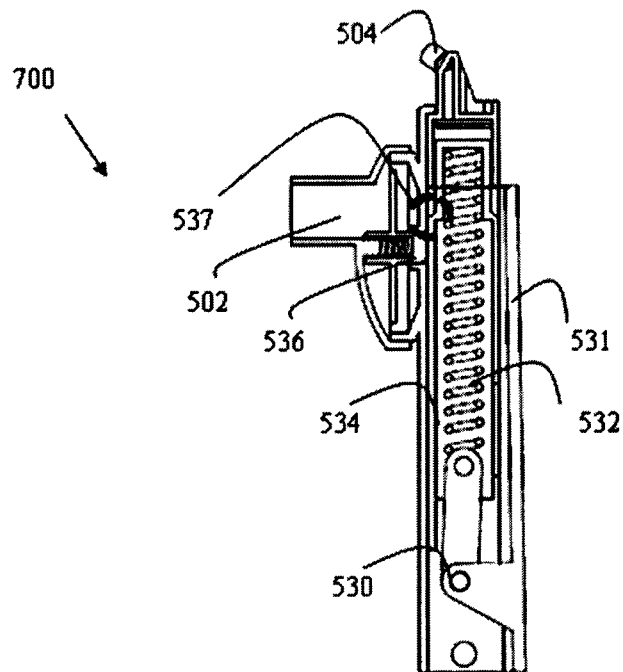


Fig. 31

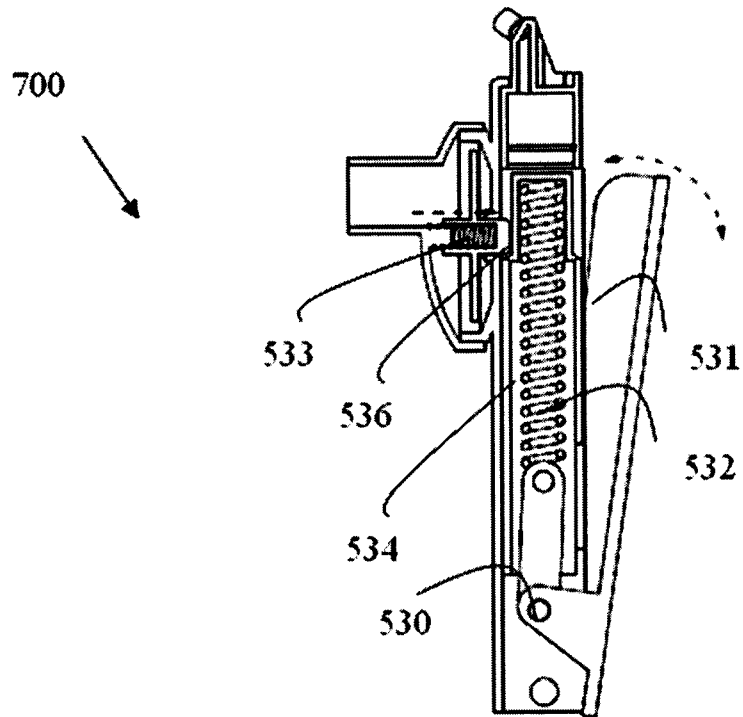


Fig. 32

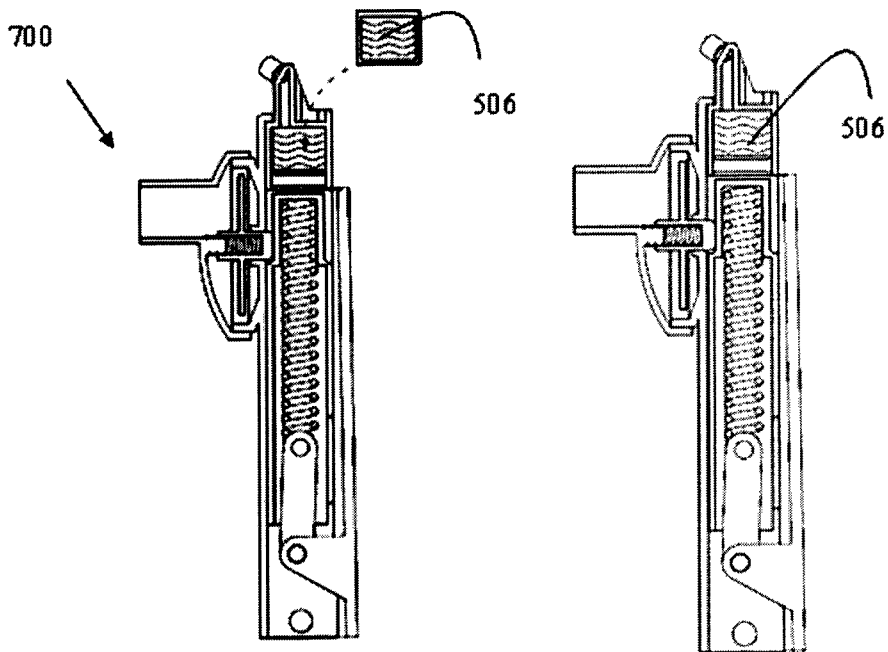


Fig. 33

Fig. 34

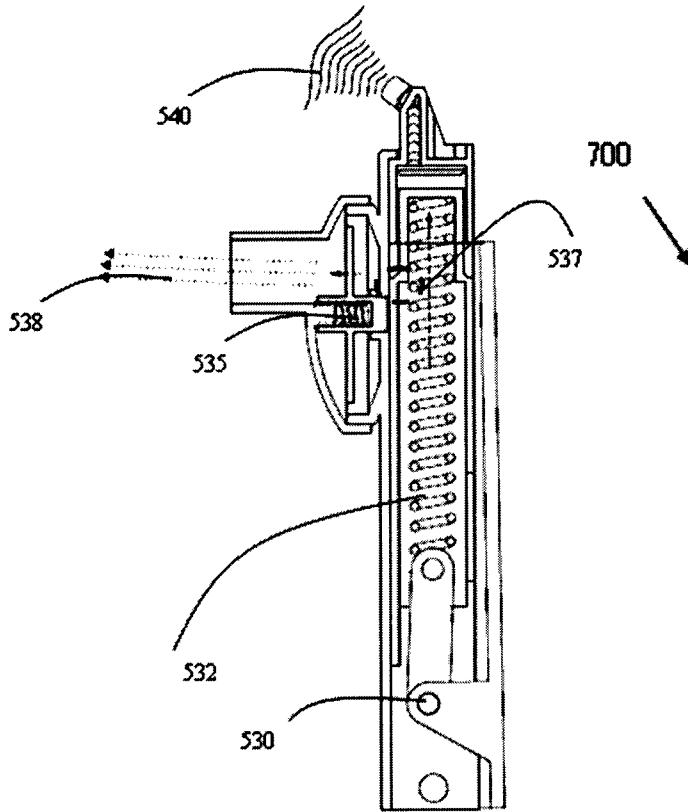


Fig. 35

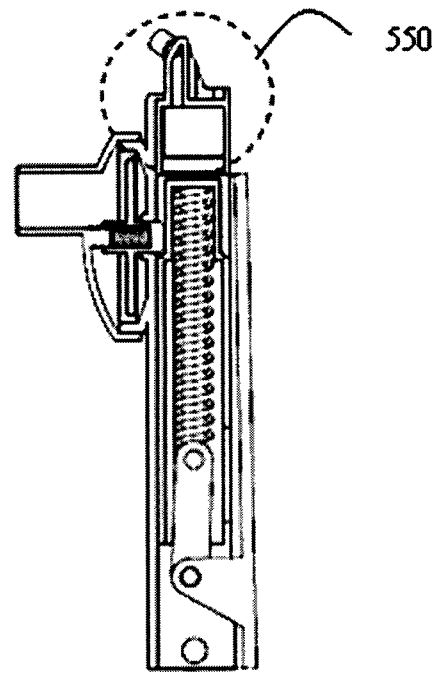


Fig. 36

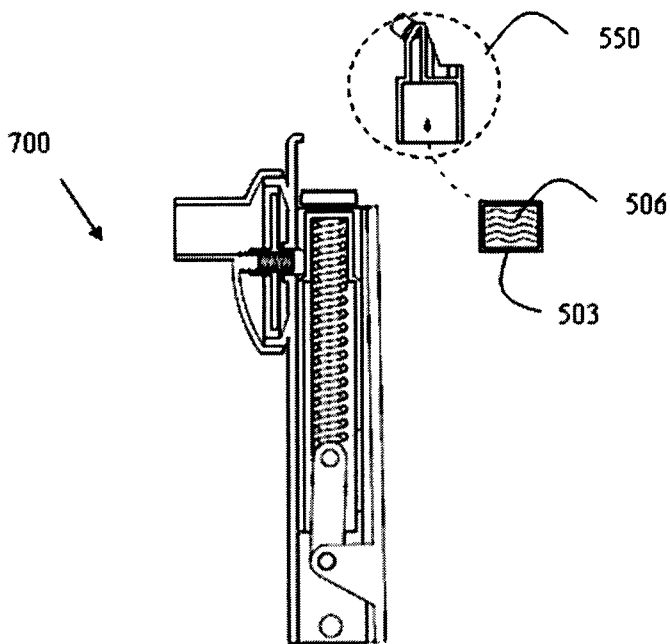


Fig. 37

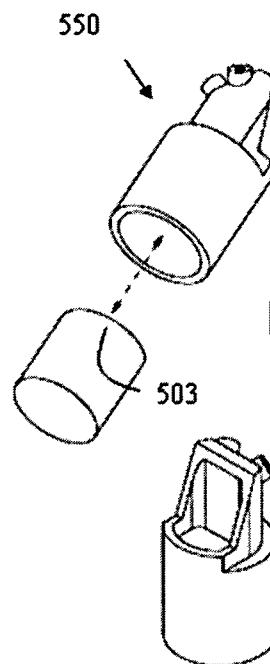


Fig. 38a

Fig. 38b

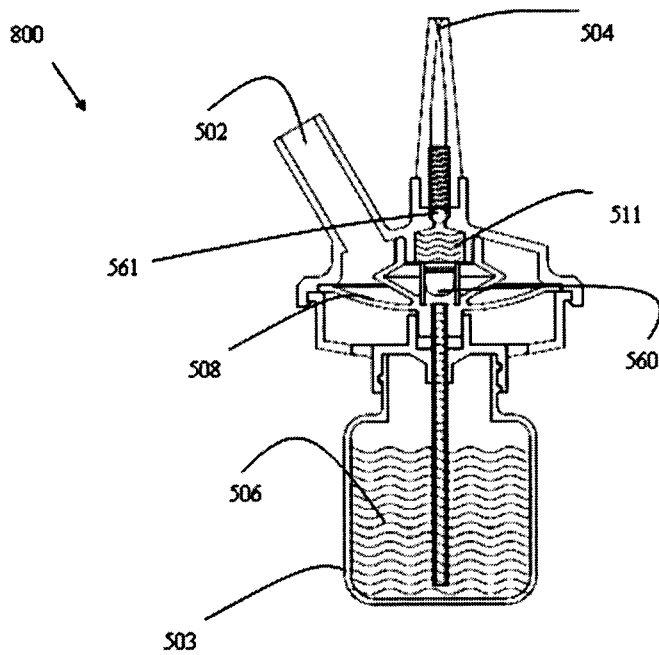


Fig. 39

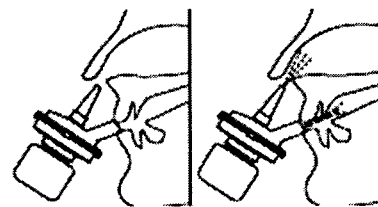


Fig. 40

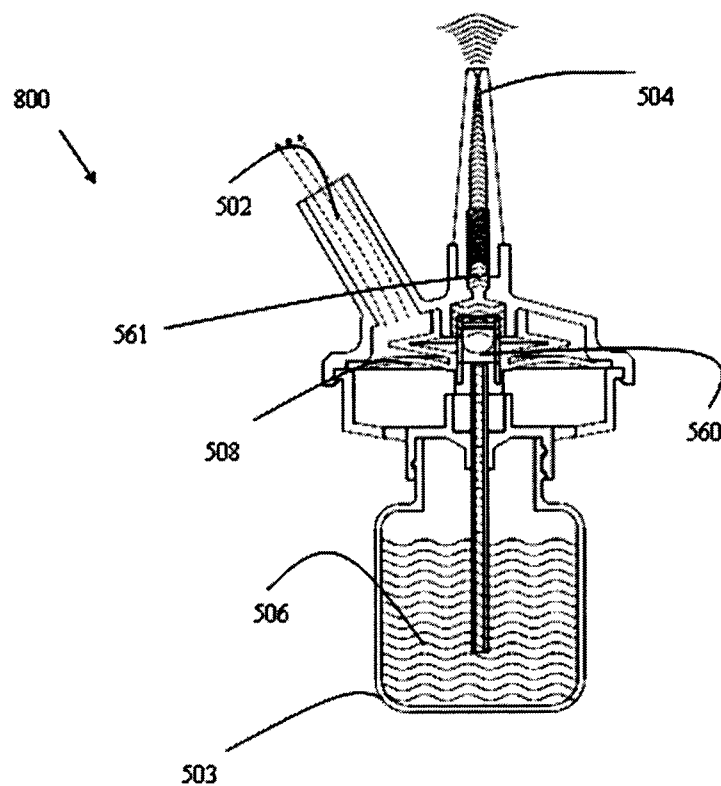


Fig. 41

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL 11/00702

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61M 15/02 (2011.01)

USPC - 128/203.18

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)

IPC: A61M 15/02 (2011.01)

USPC: 128/203.18

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

IPC: A61M 11/00, 11/02, 15/00, 15/02, 16/00 (2011.01)

USPC: 128/200.14, 200.21, 200.23, 200.24, 203.12, 203.18, 203.22, 203.29; 215/387, 388; 220/703, 705, 707; 604/94.01

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

PubWest (PGPB,USPT,EPAB,JPAB), Google (Patents, Scholar); Keywords: drink\$4, swallow\$4, palate, nose, nasal\$4, spray\$4, deliver\$4, djupe\$land, imbib\$4, suck\$4, drink, beverage, liquid, water, juice, puls\$4, pulsat\$4, dose, dosage, cartridge, container, capsule, refill\$4, recharg\$6, valve, station, apparatus, device, agent, pharmaceutical, medicine,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/0125371 A1 (Djupe\$land et al.) 07 June 2007 (07.06.2007) para [0001], [0149], [0227], [0228], [0231], [0236]; Fig. 14, 15, 31-33	1-112
Y	US 6,050,444 A (Sugg) 18 April 2000 (18.04.2000) col 2, ln 23-45; col 5, ln 25-48; Fig. 1, 2, 5-7	1-70, 96
Y	US 6,543,445 B1 (Hopper) 08 April 2003 (08.04.2003) col 7, ln 5-18; col 7, ln 40-50; Fig. 1	14, 48
Y	US 2004/0112378 A1 (Djupe\$land) 17 June 2004 (17.06.2004) para [0166], [0167], [0183]-[0186]; Fig. 9A-9D	16, 17, 21, 22, 50, 51, 55, 56, 78, 79, 99, 100
Y	US 2005/0121023 A1 (Braithwaite) 09 June 2005 (09.06.2005) para [0059], [0069], [0094], [0098], [0104]	19, 20, 53, 54, 71-112
Y	US 2007/0158352 A1 (Cheng) 12 July 2007 (12.07.2007) para [0024], [0031]; Fig. 1, 4	24, 25, 28, 29, 58, 59, 62, 63, 80, 81, 84, 85, 101, 102, 105, 106
Y	US 2005/0268909 A1 (Bonney et al.) 08 December 2005 (08.12.2005) para [0072]	26, 27, 60, 61, 82, 83, 103, 104
Y	US 2009/0205658 A1 (Tanaka et al.) 20 August 2009 (20.08.2009) para [0112]	32, 33, 66, 67, 87, 88, 108, 109
Y	US 2006/0110471 A1 (Nichols) 25 May 2006 (25.05.2006) para [0013]	36, 70, 91, 112

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

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