(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 November 2015 (26.11.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/177788 A1

(51) International Patent Classification:
A61M 15/08 (2006.01)

(21) International Application Number:
PCT/IL2015/050527

(22) International Filing Date:
18 May 2015 (18.05.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/996,922 19 May 2014 (19.05.2014) US

(71) Applicant: **INHALETECH LLC** [US/US]; 1499 W. River Road, Minneapolis, MN 55411 (US).

(72) Inventor; and
(71) Applicant *(for GT only)*: **HADASH, Joseph** [IL/IL]; 26 Hagolan Street, 7313300 Lapid (IL).

(72) Inventor: **HADASH, Yair**; 26 Hagolan Street, 7313300 Lapid (IL).

(74) Agents: **GUTTMAN, Thomas** et al.; Luzzatto & Luzzatto, P.O. Box 5352, 8415202 Beer Sheva (IL).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

[Continued on next page]

(54) **Title**: DEVICE AND METHOD FOR ADMINISTERING MEDICAMENTS TO THE BRAIN

(57) **Abstract**: The present invention provides a system for administering a therapeutic substance to a brain, for example a brain of a person afflicted by a neurodegenerative disorder. The system may include communicating with the person and locating it via a smartphone, characterizing the level of its alertness or cognitive abilities, and initiating the substance release via a vocal signal. The system enables to bypass the blood brain barrier while also reducing undesired systemic concentration peaks of the substance.

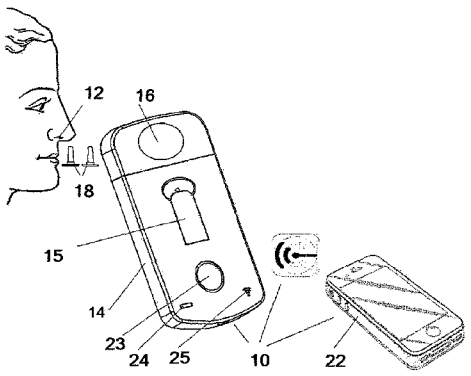

Fig. 1

WO 2015/177788 A1

Published:

— *with international search report (Art. 21(3))*

DEVICE AND METHOD FOR ADMINISTERING MEDICAMENTS TO THE BRAIN

Field of the Invention

The present invention relates to a device and a method for delivering substances to the brain, while bypassing the blood brain barrier and reducing undesired systemic concentration peaks of the substances.

Background of the Invention

Most drugs do not enter the brain through the blood stream due to the neuro-protective mechanism known as the blood brain barrier [The Merck Manual of Diagnosis and Therapy, 1999, 17th Ed., page 2562]. It has been shown that drugs administered as nose drops can enter the brain directly without entering the blood stream; however, none of the considered drug-targeting strategies for bypassing the blood brain barrier (BBB) have been proved sufficiently effective, and the dangerous side effects due to systemic overdose have been difficult to control [for example see Miyake M.M. and Bleier B.S.: Am. J. Rhinol. Allergy, 2015, 29(2), 124-7]. The direct path from the nasal cavity to the brain along the olfactory nerves was considered, for example, for intranasal delivery of insulin for the patients suffering from Alzheimer's disease, as intranasal insulin was shown to improve memory, attention, and functional status in patients in the early stages of Alzheimer's disease and those with mild cognitive impairment; however, any systemic insulin increase can have sever effects and must be, therefore, strictly prevented [Hanson L.R. and Frey W.H.: BMC Neurosci. 2008, 9(Suppl 3): S5]. A need is felt for drug delivery systems for administering medicaments to the brain without dangerous changes of the systemic drug levels. Particularly, a need is felt for drug delivery systems for patients suffering from disorders associated with the central nervous system (CNS), wherein the disorders limit the capabilities of the patients to fully cooperate during the process of

administering the drugs. Only in the U.S. there are more than five million people suffering from the Alzheimer's disease. It is therefore an object of the invention to provide a system for delivering medicaments to the brain of a human subject that suffers from a CNS disorder.

It is another object of the invention to provide a drug delivery system for administering a medicament to a subject while bypassing the BBB.

It is a further object of the invention to provide a device and a method for administering a medicament to a subject, while precluding dangerous systemic concentrations of said medicament.

It is a still further object of the invention to provide a device and a method for delivering a substance to the brain of a subject while precluding undesired increases of the substance concentrations in the blood or plasma of said subject.

It is also an object of the invention to provide a device and a method for administering a medicament to a subject suffering from a condition selected from neurologic disorders and psychiatric disorders, while precluding systemic overdose of said medicament.

It is still another object of the invention to provide a device and a method for administering a medicament to a subject with lowered level of alertness or reduced cognitive abilities.

It is further an object of the invention to provide a drug delivery system for administering a medicament to a subject comprising processing parameters associated with the level of alertness or the cognitive abilities of said subject.

Other objects and advantages of present invention will appear as description proceeds.

Summary of the Invention

This invention provides a device for delivering a dose of a substance to the brain of a subject while bypassing the blood brain barrier, comprising i) a canister for holding a liquid comprising said substance; ii) a voice sensor configured to generate an electrical signal within a portion of the device in response to a vocal signal; iii) a processor configured to receive said electrical signal as a command for either starting a motor or blocking the motor; iv) a valve associated with said motor and configured to release a part of said dose into nasal cavities of said subject when the motor is started, wherein the substance is pumped from said canister in the form of solution or suspension and released into said cavities in the form of aerosol; v) an integrator for registering the total quantity of the released substance; wherein said substance passes through said nasal cavities via ethmoid bone to the brain of the subject, and wherein said dose is divided into a plurality of said predetermined parts to reduce the peak tissue concentrations and/or peak systemic concentrations of said substance. In some embodiments of the invention, said integrator may be incorporated within said processor. Said vocal signal may be a speech of said subject or of attending personnel. Said vocal signal may be a certain word or a certain word sequence. In one embodiment, said vocal signal is a speech of said subject who starts the motor and initiates the release of a part of said dose to its nostrils when such release is required. In another embodiment, said vocal signal is a speech of said personnel who either starts the motor when the release of the medicament is required or blocks the motor when the release of the medicament is not required or is undesired. In a preferred embodiment of the invention, provided is a device for delivering a daily dose of a medicament to the brain of a subject while bypassing the blood brain barrier, comprising i) a canister for holding a solution or suspension of said medicament; ii) a voice

sensor configured to generate an electrical signal within a portion of the device in response to speech of the subject; iii) a processor configured to receive said electrical signal as a command for starting a motor; iv) a valve associated with said motor and configured to release a part of said dose in the form of medicament aerosol into nasal cavities of said subject when the motor is started; v) an integrator for registering the total quantity of the released medicament; wherein said medicament passes through said nasal cavities via ethmoid bone to the brain of the subject, and wherein said daily dose is divided into a plurality of said predetermined parts to reduce the peak tissue concentrations and/or peak systemic concentrations of said medicament. The device according to the invention preferably comprises a loudspeaker enabling the subject to hear attending personnel or family members who may affect the subject or give vocal commands. The processor in one embodiment of the device according to the invention further records the speech of said subject when said subject responds to questions aimed at characterizing the level of alertness or cognitive abilities of the subject. Said processor may further provide cognitive parameters corresponding to the reactions of said subject to the questions. In a preferred embodiment of the invention, the size of the dose or of it's a part thereof in said device is affected by the cognitive parameters provided by said processor. Said sensor in the device of the invention may comprise a smartphone, or may be associated with a smartphone, which connects the subject with attending personnel or family members. Said smartphone preferably comprises GPS and enables to locate the subject.

The substance delivered by the device of the invention is preferably a medicament for treating or preventing a condition selected from neurologic or psychiatric disorders. Examples of the neurologic disorders are pain, headache, dementia, seizure disorders, and others, including migraine, Alzheimer's diseases, Parkinson diseases, epilepsy, and others. Examples of the psychiatric disorders include anxiety disorders, mood disorders,

schizophrenia, drug dependence, and others. The device according to the invention for delivering a dose of the medicament for treating or preventing said condition to the brain of the subject while bypassing the blood brain barrier usually comprises i) a canister for holding a of solution or suspension of said medicament; ii) a voice sensor configured to generate an electrical signal within a portion of the device in response to speech of the subject; iii) a processor configured to receive said electrical signal as a command for starting a motor; iv) a valve associated with said motor and configured to release a part of said dose in the form of aerosol into nasal cavities of said subject when the motor is started; and v) an integrator for registering the total quantity of the released medicament; wherein said speech results in moving the soft palate of the subject and in naturally separating the nasal cavities from the airways and limits the quantity of the medicament which enters to the blood system. In a preferred embodiment of the invention, the device delivers a substance which is a medicament for treating a neurodegenerative disorder. In one preferred embodiment, said substance is insulin and said neurodegenerative disorder is Alzheimer's disease.

The invention is directed to a method for delivering a dose of a substance to the brain of a subject while bypassing the blood brain barrier, comprising i) generating an electrical signal in response to a vocal signal by a voice sensor; processing said electrical signal by a processor; ii) activating by said processor a motor associated with a valve configured to release a part of said dose of said substance into nasal cavities of said subject when the motor is started; iii) releasing said part of the dose in the form of aerosol, wherein said substance is pumped from a canister where it is in the form of solution or suspension; and iv) registering the total quantity of the substance released during certain period; wherein said substance passes through said nasal cavities via ethmoid bone to the brain of the subject, and wherein said dose is divided into a plurality of said predetermined parts to reduce the peak tissue concentrations and/or peak systemic concentrations of said substance. Said

vocal signal is preferably a speech of said subject or of attending personnel. The method of the invention preferably further comprises recording the speech of said subject when responding to questions aimed at characterizing the level of alertness or cognitive abilities of the subject. In a preferred embodiment, the method of the invention comprises a step of characterizing the level of alertness or cognitive abilities of the subject. The method preferably comprises providing cognitive parameters of said subject. In a preferred embodiment, the sensor in the method of the invention comprises a smartphone which connects the subject with attending personnel or family members. The method preferably comprises locating the subject by a GPS associated with the smartphone. Said substance in the method of the invention is preferably a medicament for treating or preventing a condition selected from neurologic or psychiatric disorders. In a preferred embodiment of the method according to the invention, said speech results in moving the soft palate of the subject, thereby naturally separating the nasal cavities from the airways and limiting the quantity of the medicament which enters to the blood system of the subject. Said substance is preferably a medicament for treating Alzheimer's disease, such as insulin.

The invention provides a system for delivering a dose of a substance to the brain of a subject while bypassing the blood brain barrier, comprising i) a canister for holding a liquid comprising said substance; ii) a voice sensor configured to generate an electrical signal within a portion of the device in response to a vocal signal; iii) a processor configured to receive said electrical signal as a command for either starting a motor or blocking the motor; iv) a valve associated with said motor and configured to release a part of said dose into nasal cavities of said subject when the motor is started, wherein the substance is pumped from said canister in the form of solution or suspension and released into said cavities in the form of aerosol; and v) an integrator for registering the total quantity of the released substance; wherein said substance passes through said nasal cavities via ethmoid bone to the brain of

the subject, and wherein said dose is divided into a plurality of said predetermined parts to reduce the peak tissue concentrations and/or peak systemic concentrations of said substance. The system preferably comprises also a loudspeaker enabling the subject to hear attending personnel or family members who may affect the subject or give vocal commands. In a preferred embodiment, the system of the invention further comprises a smartphone which connects the subject with attending personnel or family members. The system preferably further comprises GPS for locating said subject. In a preferred embodiment, the system delivers a medicament for treating or preventing a condition selected from neurologic or psychiatric disorders.

Brief Description of the Drawings

The above and other characteristics and advantages of the invention will be more readily apparent through the following examples, and with reference to the appended drawings, wherein:

Fig. 1. is a conceptual drawing illustrating a system according to one embodiment of the invention that includes an intranasal medication delivery device (IMDD) and a computing device in relation to a user;

Fig. 2. is a conceptual drawing illustrating a device according to Fig. 1 with a back side maintenance door;

Fig. 3. is a conceptual drawing illustrating an IMDD according to one embodiment of the invention;

Fig. 4. is another conceptual drawing illustrating an example IMDD according to one embodiment of the invention;

Fig. 5. is a still another conceptual drawing illustrating an example IMDD according to one embodiment of the invention;

Fig. 6. to Fig. 8 are a flow of computing device screens representing an example of a process for delivering sub-doses (pulses) of medication according to one embodiment of the invention, comprising IMDD detecting speech via a voice sensor (microphone);

Fig. 9 to Fig. 11 are conceptual drawings illustrating an example valve

within a metered dose compartment of an IMDD according to one embodiment of the invention; closing of the valve of the device, followed by opening and closing again, are visualized in the drawings;

Fig. 12 is a scheme illustrating an existing manufactured aerosol spray device (MDI-actuated with flow sensor), and Precision Olfactory Delivery (POD) device or Nasal Metered Dose Inhaler (MDI) - to be incorporated into a device (add on) in one embodiment of the invention; and

Fig. 13 is a conceptual drawing illustrating a system including the motor, BT+processor+sensor, and battery, according to one embodiment of the invention, including the commercial aerosol device as shown in Fig. 12 and a computing device in relation to a user.

Detailed Description of the Invention

A drug delivery system has now been provided which enables to deliver a substance to the brain of a subject while keeping a relatively low systemic concentration of said substance. The invention relates to medical devices and, more particularly, to the delivery of intranasal content by medical devices. The invention also relates to a drug delivery system comprising collecting clinical and/or cognitive data of the user. Since drugs administered as nose aerosols can advantageously enter the brain directly without entering the blood stream, via olfactory nerves passing from the nasal cavity to the brain via ethmoid bone, potentially new solutions to the old problem of bypassing the BBB appear; however, there are factors which limit the simple utilization of this phenomenon, including escape of the delivered medicament to other body parts, resulting in an undesired systemic concentration of the medicament. For example, it is known that it is difficult to treat patients with insulin without causing side effects. The present invention addresses this problem by efficient dosing the aerosolized drug to the patient suffering from Alzheimer's diseases in certain time intervals, in accordance with the instant state of the patient, characterized, in one embodiment, also by means

of the cognitive parameters collected in the system. The system of the invention may comprise and employ cognitive tests. In a system according to the invention, the drugs are delivered from the container to the nose and to the brain while using nose aerosols or nasal sprays. In a preferred embodiment of the invention, the nasal delivery system comprises atomized pump. In one preferred embodiment, the system of the invention delivers intranasal insulin to the brain without causing the unwanted side effects in sub-doses determined by the system in accordance with parameters comprising the instant state of the patient, the mental state of the patient, the level of alertness of the patient, the instant cognitive abilities of the patient, and the total daily predetermined dose. The system according to the invention may be employed for administering medicaments to patients suffering from other CNS conditions, including neurodegenerative disorders, via nasal drug delivery systems without losses of the dosage into other parts of the body, such as to the respiratory tract including lungs; for example, the system of the invention may be employed for delivering growth factors or nerve growth factors to the brain afflicted with Parkinson's disease.

Generally, the invention relates to techniques and systems for controlling the release of a substance into a patient nostrils. For example, an intranasal medication dosing device (IMDD) may be configured to trigger the release of at least a portion of a dose of medication in response to words spoken by a patient. The IMDD may include a vocal sensor (microphone) that generates a signal; the signal may comprise an air flow through a processor element caused by a speaking action of the patient. In response to a command based on the signal indicative the speech, the IMDD may control a motor pushing a canister effecting the valve to open and release at least a portion of a dose of medication stored in the canister coupled to the PMDD. In some examples, the IMDD may include processors and/or modules to generate the command such that the IMDD is configured to operate individually. In other examples, a computing device (e.g., a mobile computing device such as a smartphone,

tablet computer, notebook computer, or portable medical device) may generate the command for controlling the electrical motors to push the canister and let the valve to release the medication. The smartphone also enables a constant communication line between the patient and the nursing personnel, wherein the line may be always opened and used by either of them. The communication can be initiated by simply pushing a button or by emitting/generating a voice signal. The IMDD may transmit the signal indicative of the patient speech to the computing device, the computing device may generate the command for controlling the pushing motor and the valve, and the computing device may subsequently transmit the command to the IMDD for controlling the delivery of the medication from a canister coupled to the IMDD. By offloading at least some of the processing functions to the computing device, the IMDD may benefit from additional functionality of the computing device and be manufactured at a reduced cost. In other example, the accumulation of Mini-mental state exam (MMSE)/ Mini-cog exam answers/results, or accumulating of clinical data can be analyzed and transferred to central data collecting system. Questionnaires for assessing the state of mind, or degree of dementia, and diaries including quantities/times, as well as detailed programs for drug delivery may be advantageously employed. In one example, the invention provides a method that includes generating a signal indicative of speech within a processor device, receiving, by a processor, a command based on the signal and associated with a motor pushing the canister valve configured to at least partially control release of a medication via the attached nostrils of the device (or nostril tips or nostril insertions), and controlling, by the processor and based on the received command, the motor pushing and releasing the canister valve to release at least a portion of a dose of the medication into the attached nostrils. In another example, the disclosure describes a intranasal medication dosing device including a valve configured to at least partially control release of medication, a vocal sensor configured to generate a signal indicative of speech within a processor, and the processor configured to

receive a command based on the signal and associated with the valve and control, based on the received command, the valve to release at least a portion of a dose of the medication into the attached nostrils. In another example, the disclosure describes a system including a housing configured to accept a medication canister containing a medication, a dispensing portion coupled to the housing, a valve configured to at least partially control release of medication from the medication canister, a inhaling sensor configured to generate a signal indicative of inhaled air flow within respiratory system, and a processor configured to receive a command based on the signal and associated with the valve, and control, based on the received command, the valve to release at least a portion of a dose of the medication into the nostrils within the dispensing device. In another example, the disclosure describes a computer-readable storage medium comprising instructions that, when executed by one or more processors of a computing device, cause the one or more processors to receive data indicative of inhaling air flow within the user respiratory system, responsive to receiving the data, generate, based on the received data, a command associated with a valve configured to at least partially control release of a medication via the intranasal medication dosing device, and wherein the command indicates one of an open configuration or a closed configuration of the valve, and transmit the command to a communication unit associated with the intranasal medication dosing device. Examples of several aspects of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages will be apparent from the description and drawings, and from the claims.

This invention provides various techniques and systems for controlling the release of a substance into nostrils of the patient, particularly a patient suffering from a neurological or psychiatric diseases, for example a neurodegenerative diseases. Typically, patients requiring nasal medications to treat various disorders and conditions may rely upon nasal delivery

devices to obtain the prescribed medication. In one embodiment, the patient attempts to coordinate an inhaled breath with manual handling of a medication container or nasal device. The invention particularly aims at delivering substance in response to detecting a vocal signal, such as speech. For example, a patient may use an IMDD to receive substance directed to the olfactory mucosa.

Some embodiments of the invention are schematically related to in the attached drawings. Fig. 1 is a conceptual drawing illustrating an example system 10 that includes intranasal medication delivery device (IMDD) 14 and computing device 22 in relation to user 12. IMDD 14 may include a nozzle tips 18 and housing 16, and a handle for manual operation 15, and a switch for manual/electrical operation 23, and an indicator for power 24, and an indicator for communication 25, Nozzle tips 18 may be removably attached to housing 16, permanently coupled to housing 16, or formed with housing 16. Fig. 2 is a conceptual drawing illustrating an example of the back side of the intranasal medication delivery device (IMDD) 14 that includes a sliding panel 19. Fig. 3 the housing may be configured to accept canister 20 wherein the canister includes metered dose valve 31 a orifice 32 and nozzle tip 18 in the end, on the anther end it is the electro mechanical motor 35 connected to the canister, and a communication and control circuit 36. Fig. 4 is the housing which may be configured to accept canister 20 wherein the canister includes metered dose valve 31 a orifice 32 and nozzle tip 18 in the end, on the anther end it is the electro mechanical motor 35 connected to the canister, and a communication and control circuit 36, and power supply reservoir 37 and a power charger 38. Fig. 5 is the drawing illustrating the housing 16 that may be configured to accept canister 20, wherein canister 20 includes a medication to be dispensed via IMDD 14. Canister 20 may be replaceable or exchangeable such that IMDD 14 can accept a variety of different canisters containing any number of different medications. Fig. 6 to Fig. 8 show a flow of computing device screens representing the example of

process for delivering sub-doses (pulses) of medication from a IMDD based on detected speech within the voice sensor (microphone). Fig. 9 is a conceptual drawing illustrating an example valve within a metered dose compartment of the IMDD, in steady state position when the dose of the content 100 is liquid and sealed in the canister when the releasing tunnel 111 not connected to the content 100, keeping the releasing pipe 101 empty. Fig. 10 is a conceptual drawing illustrating an example valve within a metered dose compartment of the IMDD, when the canister is pushed down, in opening position when the dose of the liquid content 100 is released via the releasing tunnel 111 that connected to the content 100, keeping the releasing pipe 101 full of the released content 100. Fig. 11 is a conceptual drawing illustrating an example when valve within a metered dose compartment of the IMDD is in close position, the canister is pulled up, and when the remaining of the dose of the liquid content 100 is sealed again, releasing tunnel 111 is disconnected from the content 100, keeping the releasing pipe 101 empty again.

In a method of the invention, a drug is transferred nearly directly to the brain, so that smaller doses can be used, minimizing potential systemic toxicity and precluding undesired great gradients of the therapeutic substance inside the body.

Because of the known limitation, the olfactory pathway as a conduit for transmission of drugs to the CNS have not been fully utilized so far. The invention provides in one embodiment a new means for handling one of the most painful medical problems of the Western world, Alzhemer's diseases which afflicts nearly everybody at certain age, usually appearing at the age of around 60 and, in an extrapolation, afflicting nearly everybody around the age of 120, practically appearing in more than 10% of people 65 and older in the U.S. The system of the invention may be employed for delivering medicaments in additional conditions afflicting the CNS, including

dementias, depression, schizophrenia, headaches such as migraine or cluster headache, and other conditions which may be treated or prevented by a nasal spray.

While the invention has been described using some specific examples, many modifications and variations are possible. It is therefore understood that the invention is not intended to be limited in any way, other than by the scope of the appended claims.

CLAIMS

1. A device for delivering a dose of a substance to the brain of a subject while bypassing the blood brain barrier, comprising
   i) a canister for holding a liquid comprising said substance;
   ii) a voice sensor configured to generate an electrical signal within a portion of the device in response to a vocal signal;
   iii) a processor configured to receive said electrical signal as a command for either starting a motor or blocking the motor;
   iv) a valve associated with said motor and configured to release a part of said dose into nasal cavities of said subject when the motor is started, wherein the substance is pumped from said canister in the form of solution or suspension and released into said cavities in the form of aerosol; and
   v) an integrator for registering the total quantity of the released substance;
   wherein said substance passes through said nasal cavities via ethmoid bone to the brain of the subject, and wherein said dose is divided into a plurality of said predetermined parts to reduce the peak systemic concentration of said substance.

2. The device of claim 1, wherein said vocal signal is a speech of said subject or of attending personnel.

3. The device of claim 1, wherein said vocal signal is a certain word or a certain word sequence.

4. The device of claim 2 or 3, wherein said vocal signal is a speech of said subject who starts the motor and initiates the release of a part of said dose to its nostrils when such release is required.

5. The device of claim 2 or 3, wherein said vocal signal is a speech of said personnel who either starts the motor when the release of the medicament is required or blocks the motor when the release of the medicament is not required.

6. A device according to claim 1, for delivering a daily dose of a medicament to the brain of a subject while bypassing the blood brain barrier, comprising

i) a canister for holding a solution or suspension of said medicament;

ii) a voice sensor configured to generate an electrical signal within a portion of the device in response to speech of the subject;

iii) a processor configured to receive said electrical signal as a command for starting a motor;

iv) a valve associated with said motor and configured to release a part of said dose in the form of medicament aerosol into nasal cavities of said subject when the motor is started; and

v) an integrator for registering the total quantity of the released medicament;

wherein said medicament passes through said nasal cavities via ethmoid bone to the brain of the subject, and wherein said daily dose is divided into a plurality of said predetermined parts to reduce the peak systemic concentration of said medicament.

7. The device of claim 1, further comprising a loudspeaker enabling the subject to hear attending personnel or family members who may affect the subject or give vocal commands.

8. The device of claim 1, wherein said processor further records the speech of said subject who responds to questions aimed at characterizing the level of alertness or cognitive abilities of the subject.

9. The device of claim 8, wherein said processor provides cognitive parameters corresponding to the reactions of said subject.

10. The device of any one of claims 1 to 9, wherein the size of said dose or its parts are affected by the cognitive parameters provided by said processor.

11. The device according to claim 1, wherein said sensor comprises a smartphone which connects the subject with attending personnel or family members.

12. The device of claim 11, wherein said smartphone comprises GPS and enables to locate the subject.

13. The device of claim 1, wherein said substance is a medicament for treating or preventing a condition selected from neurologic or psychiatric disorders.

14. A device according to claim 13, for delivering a dose of the medicament for treating or preventing said condition to the brain of the subject while bypassing the blood brain barrier, comprising
    i) a canister for holding a of solution or suspension of said medicament;
    ii) a voice sensor configured to generate an electrical signal within a portion of the device in response to speech of the subject;
    iii) a processor configured to receive said electrical signal as a command for starting a motor;
    iv) a valve associated with said motor and configured to release a part of said dose in the form of aerosol into nasal cavities of said subject when the motor is started;

v) an integrator for registering the total quantity of the released medicament;

wherein said speech moves the soft palate of the subject and naturally separates the nasal cavities from the airways and limits the quantity of the medicament which enters to the blood system.

15. The device of claim 14, wherein said substance is a medicament for treating a neurodegenerative disorder.

16. The device of claim 15, wherein said substance is insulin and said neurodegenerative disorder is Alzheimer's disease.

17. A method for delivering a dose of a substance to the brain of a subject while bypassing the blood brain barrier, comprising

i) generating by a voice sensor an electrical signal in response to a vocal signal;

ii) processing said electrical signal by a processor;

iii) activating by said processor a motor associated with a valve configured to release a part of said dose of said substance into nasal cavities of said subject when the motor is started;

iv) releasing said part of the dose in the form of aerosol, wherein said substance is pumped from a canister where it is in the form of solution or suspension; and

v) registering the total quantity of the substance released during certain period;

wherein said substance passes through said nasal cavities via ethmoid bone to the brain of the subject, and wherein said dose is divided into a plurality of said predetermined parts to reduce the peak systemic concentration of said substance.

18. The method of claim 17, wherein said vocal signal is a speech of said subject or of attending personnel.

19. The method of claim 17, further comprising recording the speech of said subject when responding to questions aimed at characterizing the level of alertness or cognitive abilities of the subject.

20. The method of claim 17, further comprising characterizing the level of alertness or cognitive abilities of the subject.

21. The method of claim 17, further comprising providing cognitive parameters of said subject.

22. The method of claim 17, wherein said sensor comprises a smartphone which connects the subject with attending personnel or family members.

23. The method of claim 17, further comprising locating the subject by a GPS associated with the smartphone.

24. The method of claim 17, wherein said substance is a medicament for treating or preventing a condition selected from neurologic or psychiatric disorders.

25. The method of claim 17, wherein said speech moves the soft palate of the subject, thereby naturally separating the nasal cavities from the airways and limits the quantity of the medicament which enters to the blood system of the subject.

26. The method of claim 24, wherein said condition is Alzheimer's disease and said substance is insulin.

27. A system for delivering a dose of a substance to the brain of a subject while bypassing the blood brain barrier, comprising
    i) a canister for holding a liquid comprising said substance;
    ii) a voice sensor configured to generate an electrical signal in response to a vocal signal;
    iii) a processor configured to receive said electrical signal as a command for either starting a motor or blocking the motor;
    iv) a valve associated with said motor and configured to release a part of said dose into nasal cavities of said subject when the motor is started, wherein the substance is pumped from said canister in the form of solution or suspension and released into said cavities in the form of aerosol; and
    v) an integrator for registering the total quantity of the released substance;
    wherein said substance passes through said nasal cavities via ethmoid bone to the brain of the subject, and wherein said dose is divided into a plurality of said predetermined parts to reduce the peak systemic concentration of said substance.

28. The system of claim 27, further comprising a loudspeaker enabling the subject to hear attending personnel or family members who may affect the subject or give vocal commands.

29. The system of claim 27, further comprising a smartphone which connects the subject with attending personnel or family members.

30. The system of claim 27, further comprising GPS for locating the subject.

31. The system of claim 27, wherein said substance is a medicament for treating or preventing a condition selected from neurologic or psychiatric disorders.

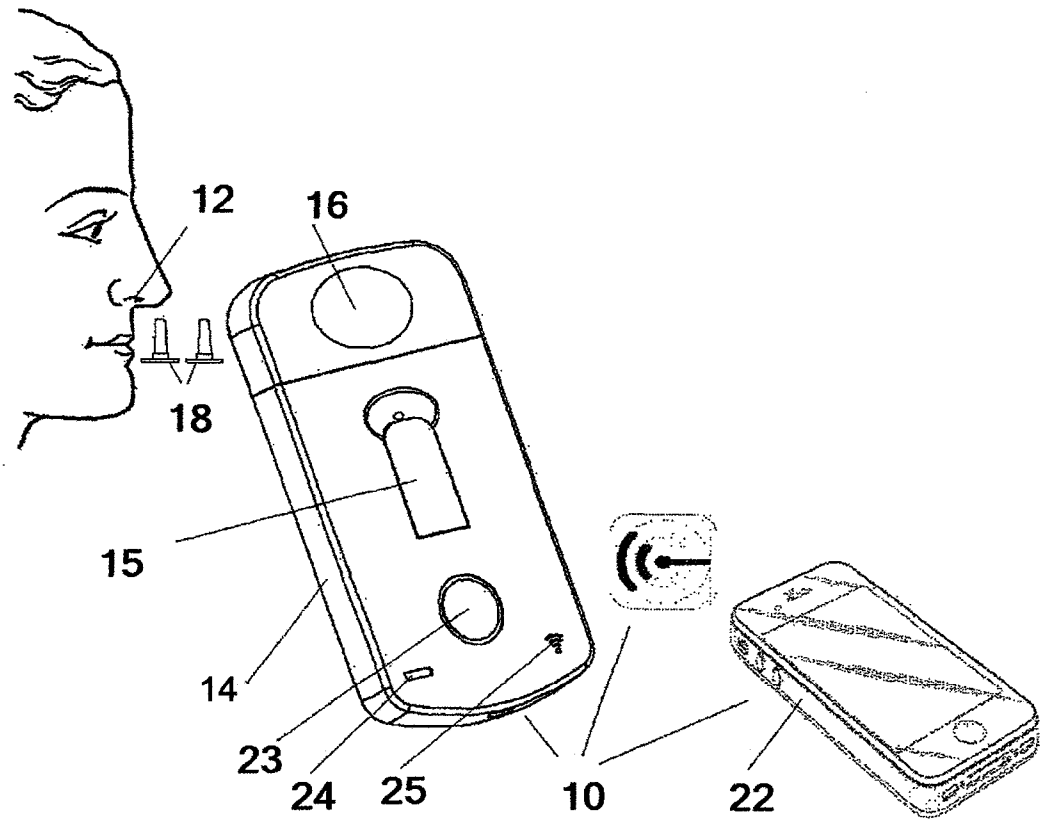

Fig. 1

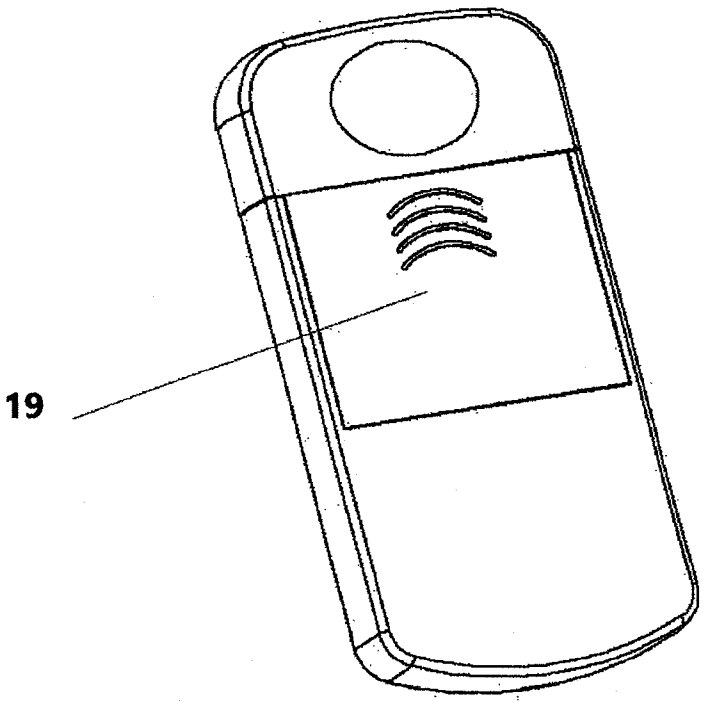

Fig. 2

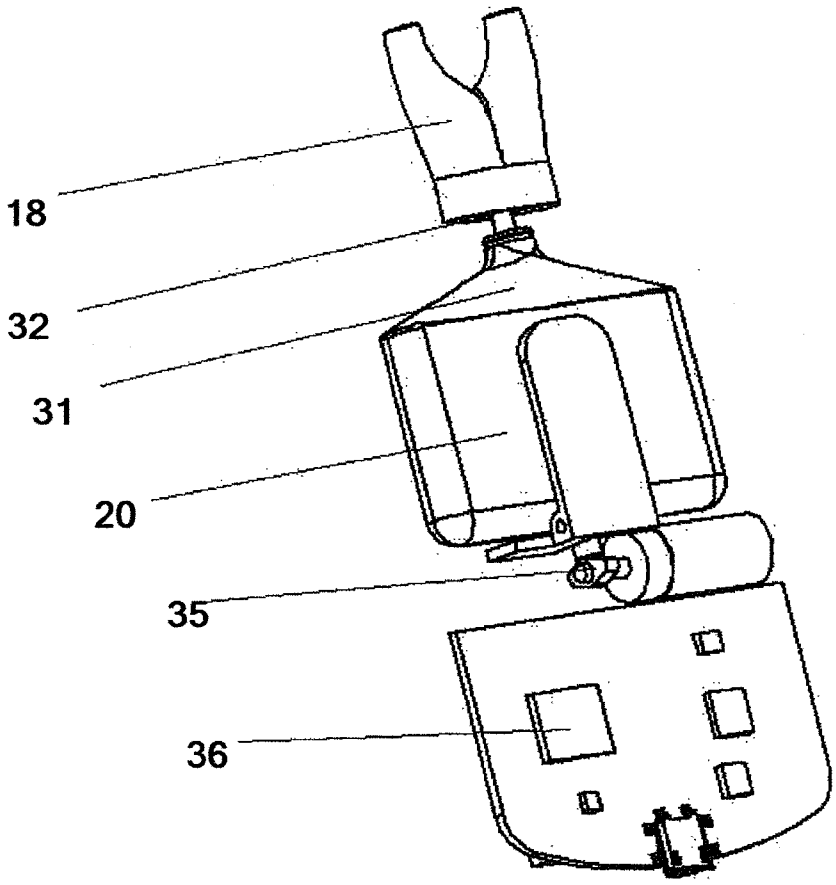

Fig. 3

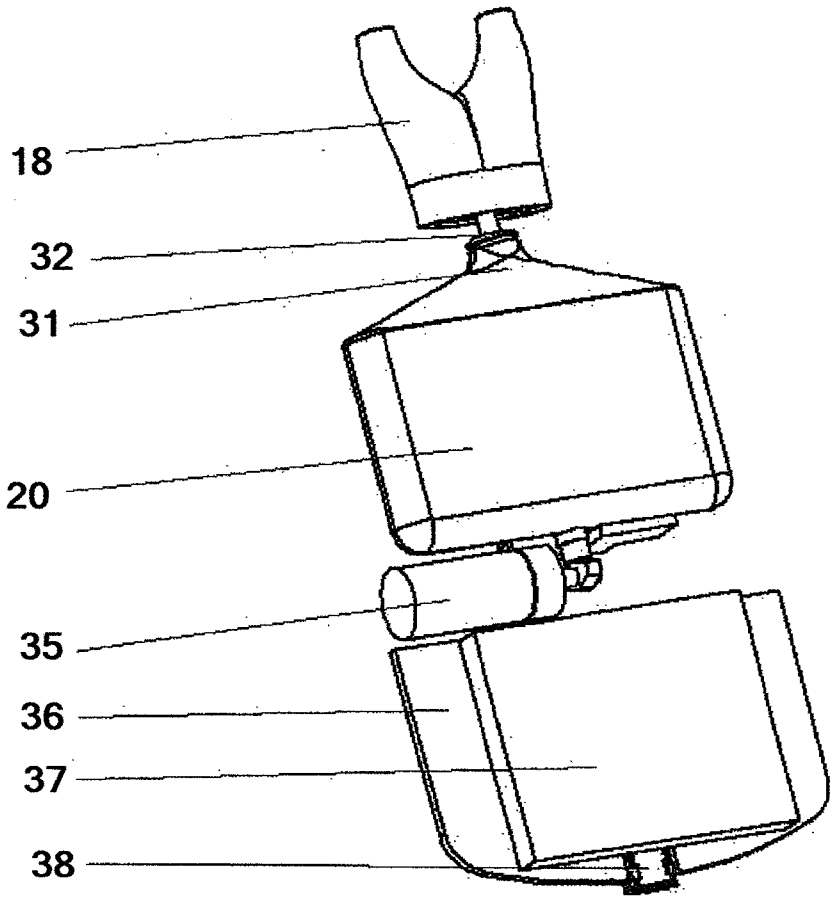

Fig. 4

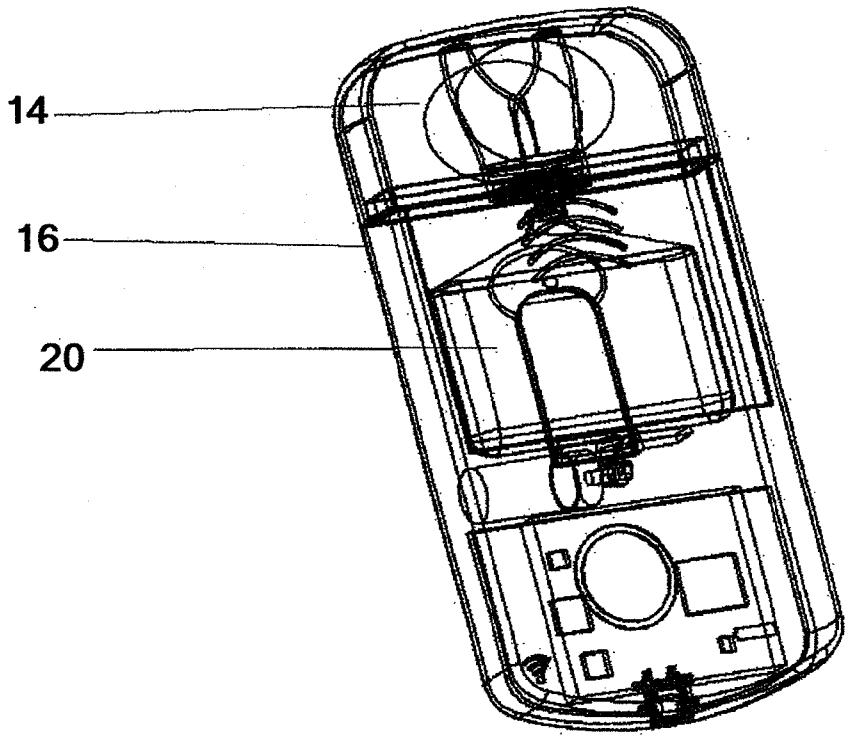

Fig. 5

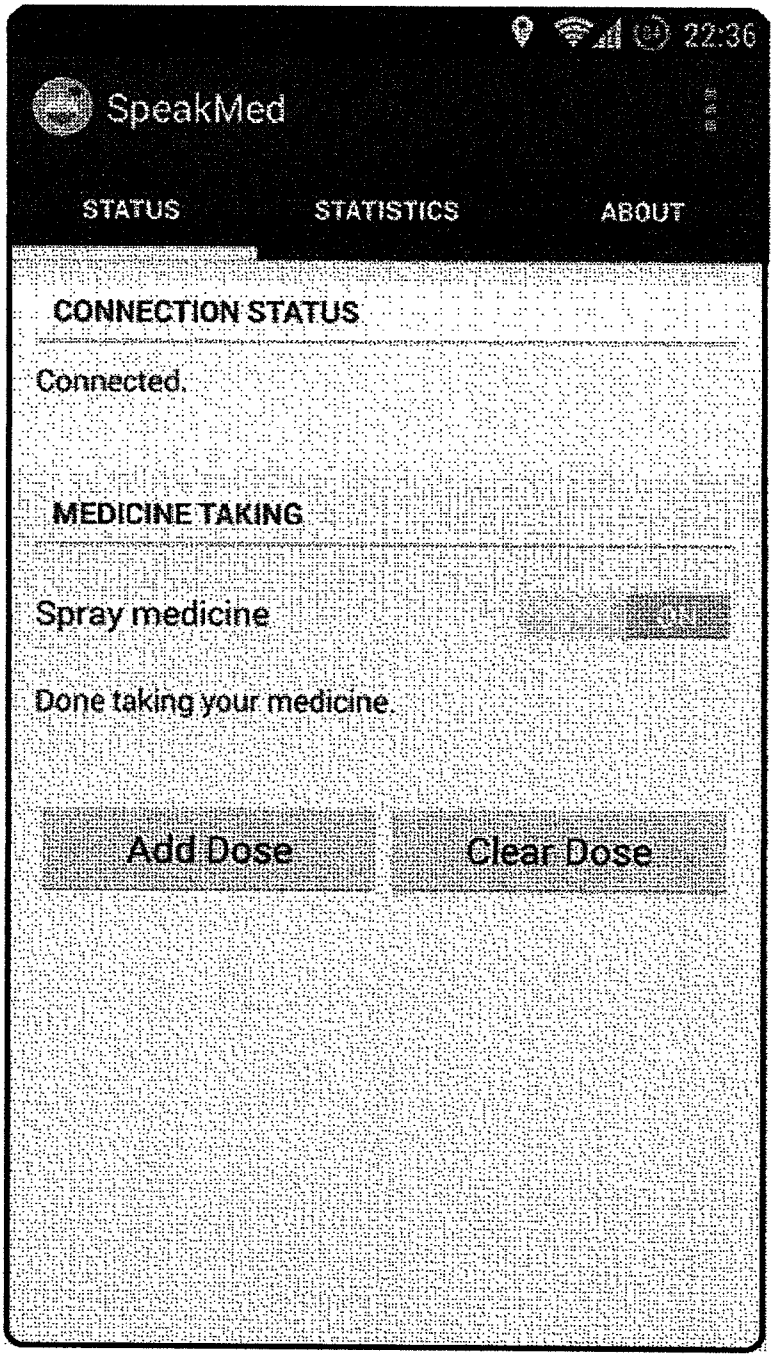
22:36
SpeakMed
STATUS
STATISTICS
ABOUT
CONNECTION STATUS
Connected.
MEDICINE TAKING
Spray medicine
Done taking your medicine.
Add Dose
Clear Dose

Fig. 6

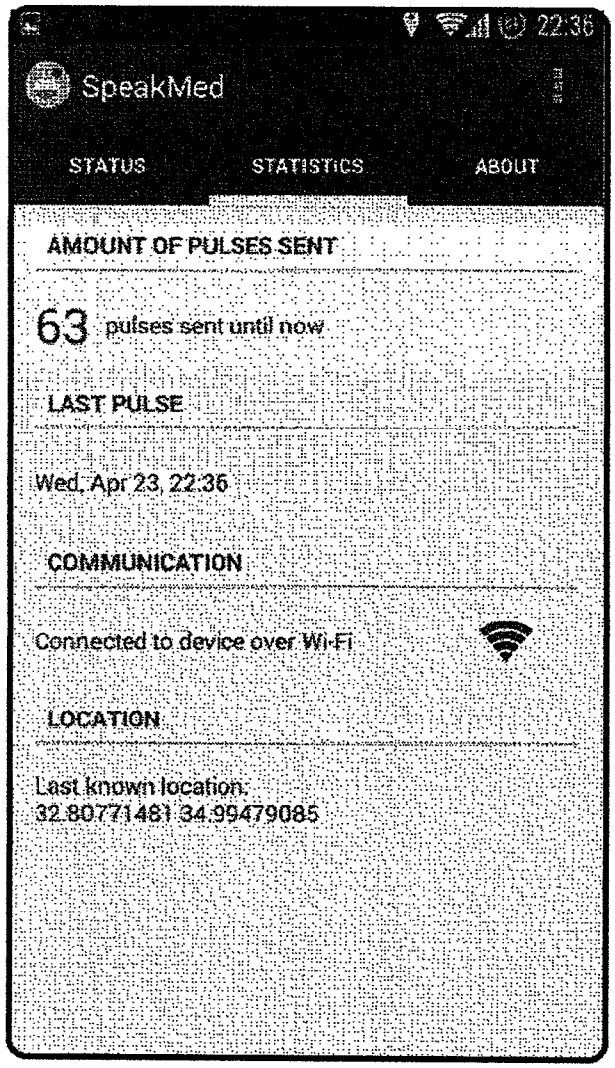
22:36
SpeakMed
STATUS
STATISTICS
ABOUT
AMOUNT OF PULSES SENT
63 pulses sent until now
LAST PULSE
Wed, Apr 23, 22:36
COMMUNICATION
Connected to device over Wi-Fi
LOCATION
Last known location:
32.80771481 34.99479085

Fig. 7

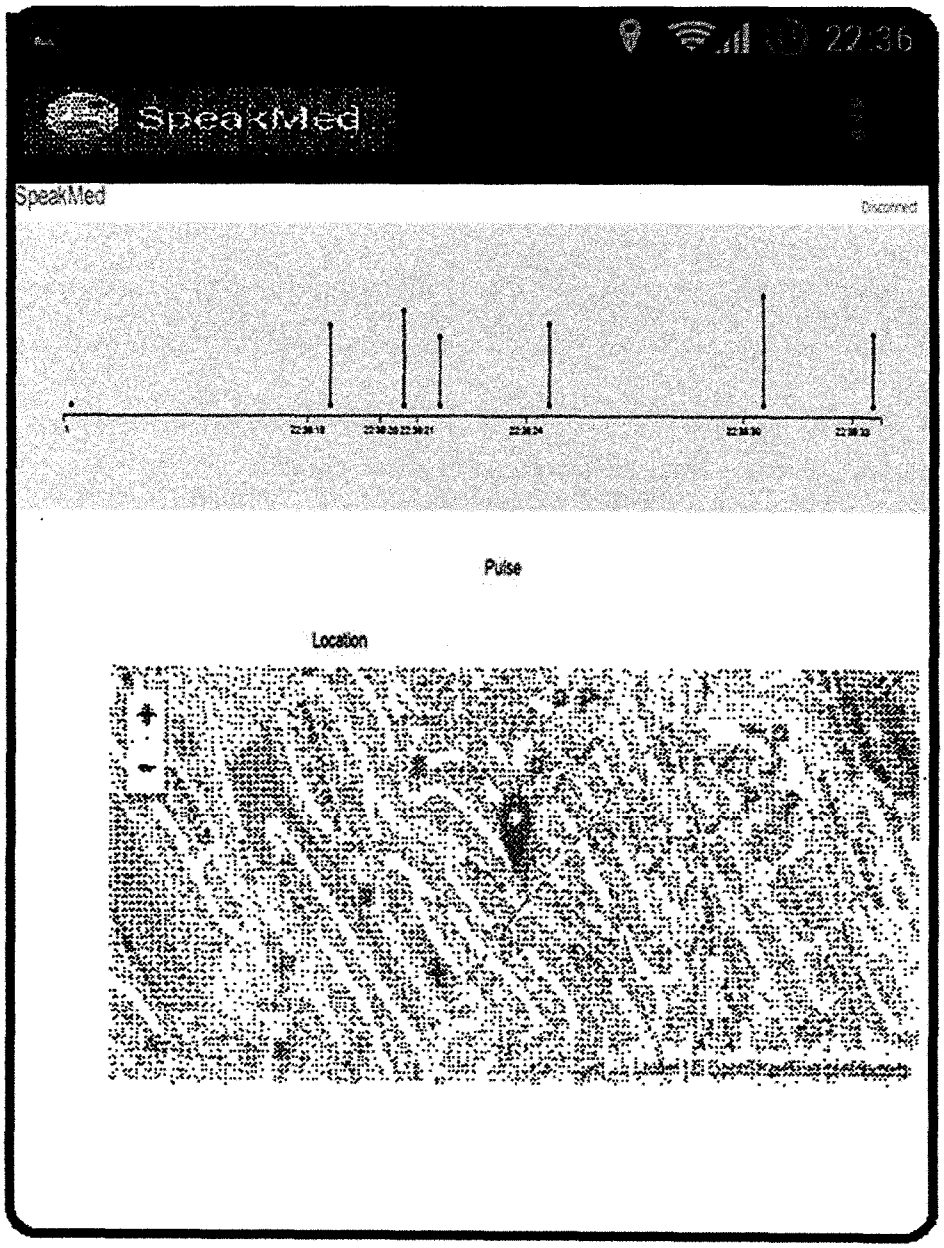

Fig. 8

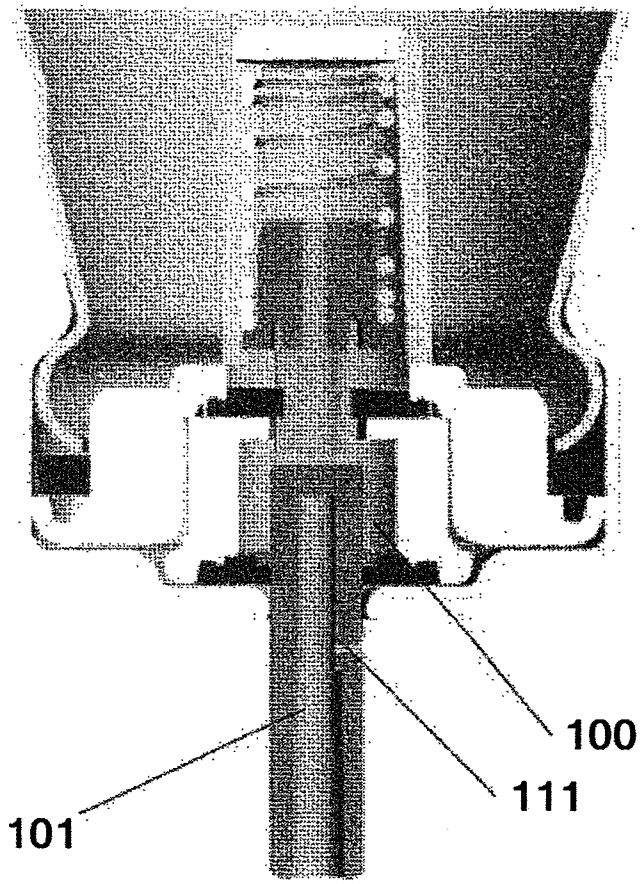

Fig. 9

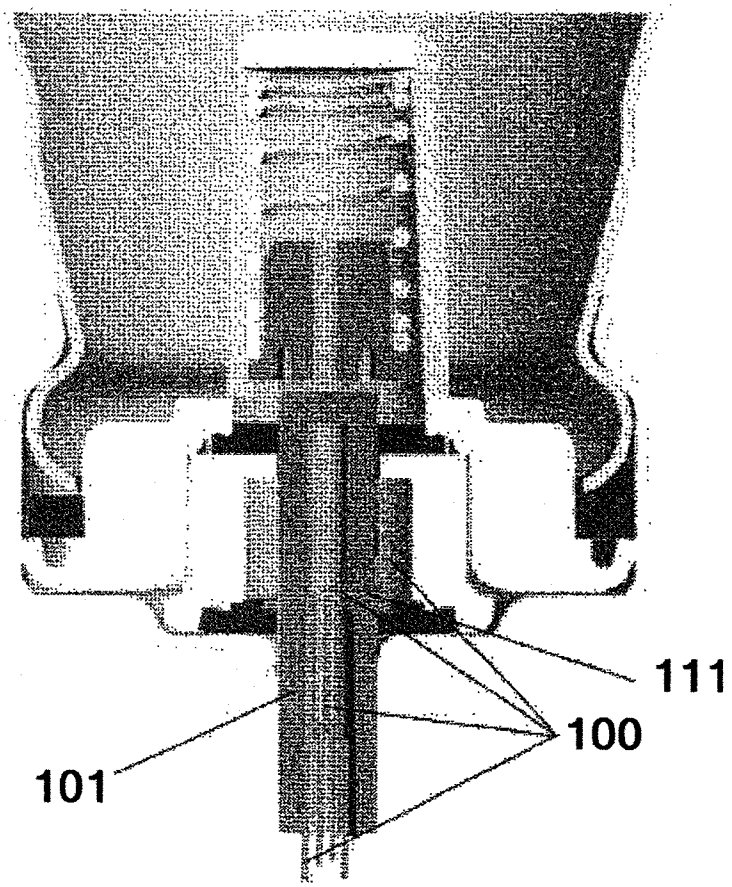

Fig. 10

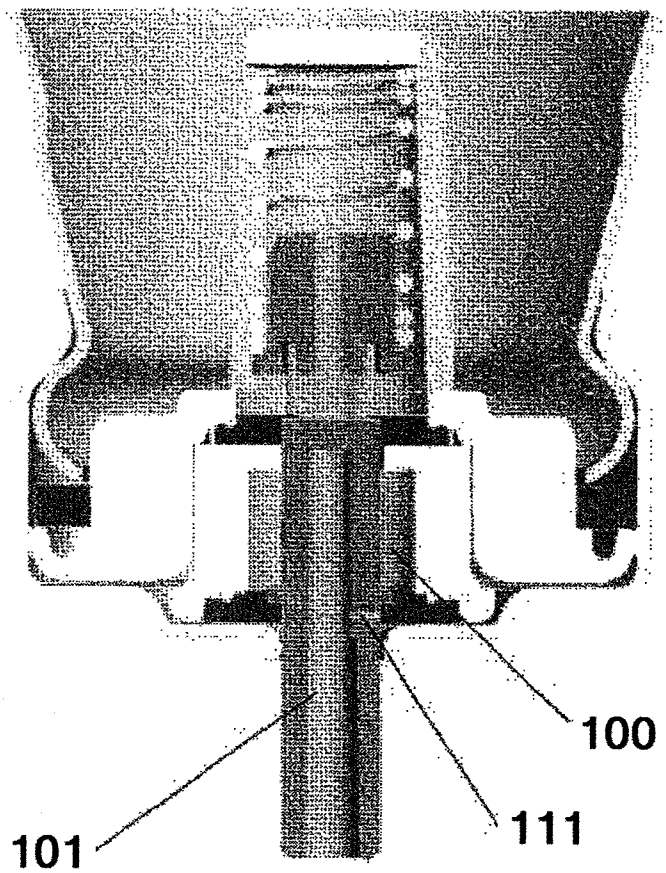

Fig. 11

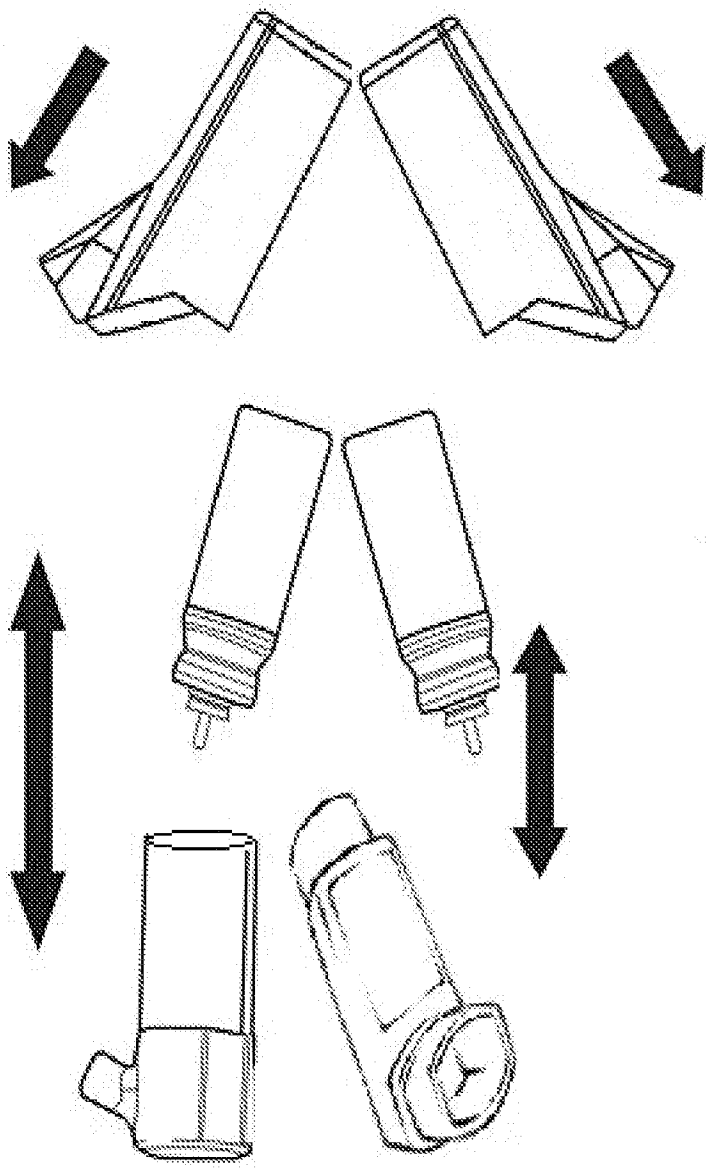

Fig. 12

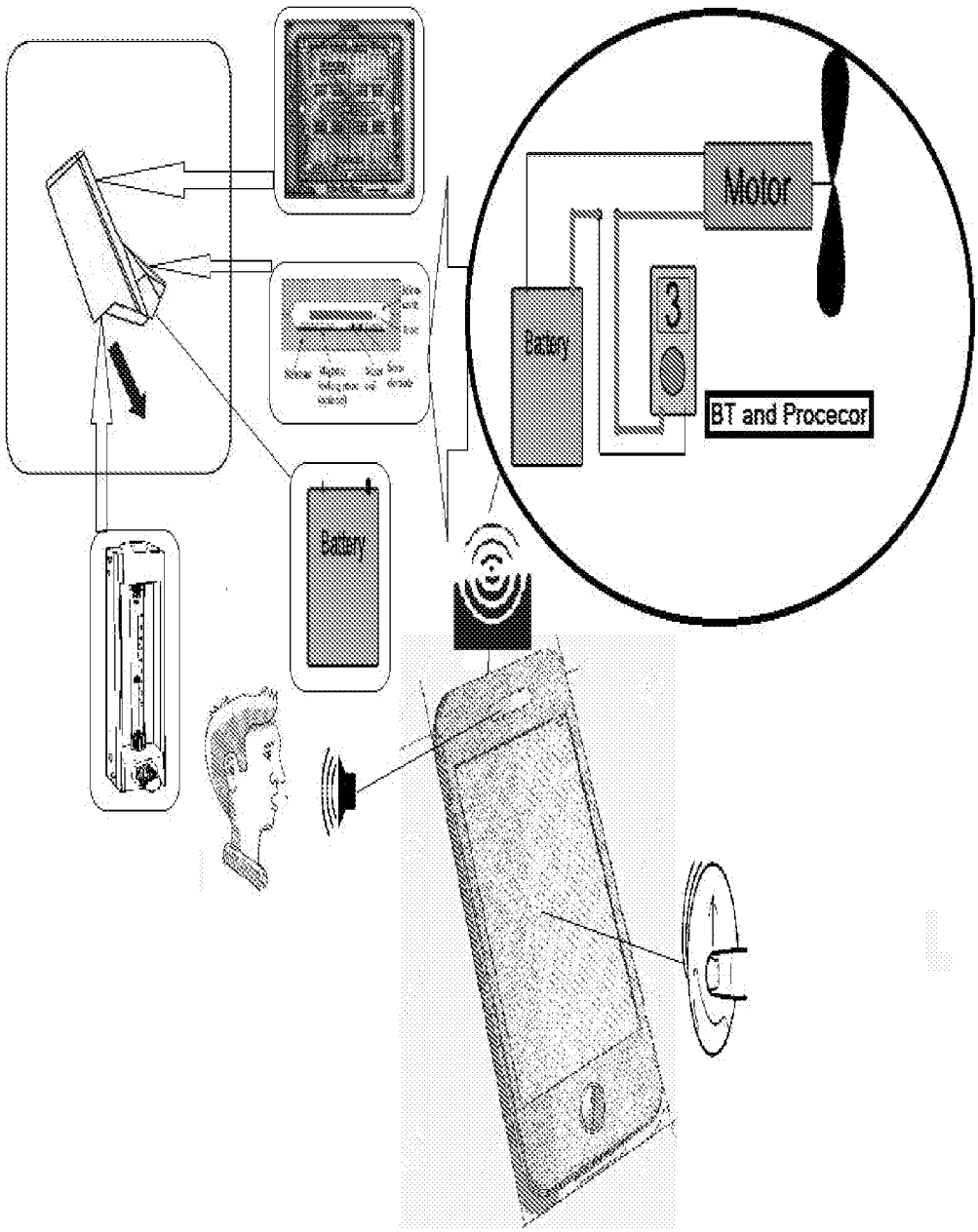

Fig. 13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2015/050527

A. CLASSIFICATION OF SUBJECT MATTER
IPC (2015.01) A61M 15/08

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 (2015.01) A61M

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Databases consulted: THOMSON INNOVATION, FamPat database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/0231667 A1 (HORTON ET AL.) 25 Nov 2004 (2004/11/25) paragraphs [0001], [0002], [0005]-[0010]; [0017]-[0020], [0070], [0084]-[0090], [0199]-[0202]; figures 1-5	1-5,7-13,15-31
A	WO 2013/128447 A1 (SIPNOSE LTD.) 06 Sep 2013 (2013/09/06) the whole document (particularly, page 71, lines 17-23; page 81, lines 9-16, 28-30; figure 2)	1-5,7-13,15-31
A	US 2006/0130832 A1 (SCHECHTER ET AL.) 22 Jun 2006 (2006/06/22) the whole document	1-5,7-13,15-31

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

☒ See patent family annex.

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

Date of the actual completion of the international search	Date of mailing of the international search report
30 Aug 2015	30 Aug 2015

Name and mailing address of the ISA:	Authorized officer
Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Facsimile No. 972-2-5651616	SEGAL Liviu Telephone No. 972-2-5651782

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2015/050527

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 6,14
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
See extra sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet):

* Claims Nos.: 6,14
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claim 6, which refers to claim 1 as dependent claim, restating features which are undistinguishable from the features which have been already defined in claim 1. Due to said restatement, its appear that an unjustified redundancy is involved with claim 6, in a manner which renders uncertainty regarding the structural features which are additional claimed by this claim, and further regarding the scope of protection sought, contrary to Article 6 PCT. The same objection applies to claim 14.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2015/050527

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
US 2004/0231667 A1	25 Nov 2004	US 2004231667 A1	25 Nov 2004
		AT 331549 T	15 Jul 2006
		AU 2002328277 A1	23 Dec 2002
		AU 2002345757 A1	23 Dec 2002
		DE 60212837 D1	10 Aug 2006
		DE 60212837 T2	21 Jun 2007
		EP 1395319 A2	10 Mar 2004
		EP 1395320 A2	10 Mar 2004
		EP 1395320 B1	28 Jun 2006
		GB 0114175 D0	01 Aug 2001
		GB 0114176 D0	01 Aug 2001
		GB 0123941 D0	28 Nov 2001
		JP 2004528150 A	16 Sep 2004
		JP 2004528151 A	16 Sep 2004
		US 2005022806 A1	03 Feb 2005
		WO 02100468 A2	19 Dec 2002
		WO 02100468 A3	01 May 2003
		WO 02100469 A2	19 Dec 2002
		WO 02100469 A3	01 May 2003
WO 2013/128447 A1	06 Sep 2013	WO 2013128447 A1	06 Sep 2013
US 2006/0130832 A1	22 Jun 2006	US 2006130832 A1	22 Jun 2006
		US 7832394 B2	16 Nov 2010
		US 2006131350 A1	22 Jun 2006
		US 8091545 B2	10 Jan 2012
		WO 2006069343 A2	29 Jun 2006
		WO 2006069343 A3	19 Apr 2007