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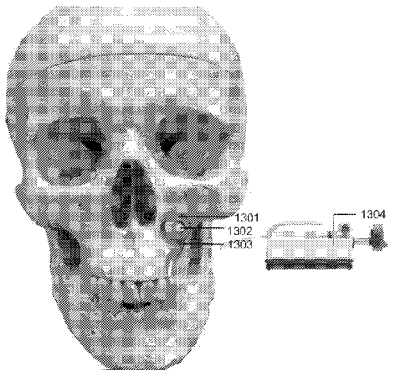


Fig-13 B

(57) Abstract: The present invention provides devices and methods for controlled and continuous delivery of drugs into the brain by bypassing the blood brain barrier, without the need for any surgical manipulation of the brain. The respiratory mucosa in the maxillary sinus or in the nasal region is surgically accessed from the oral or maxillofacial region through a window made on the bone overlying the mucosa. The device is used to deliver drugs in a continuous and controlled manner either beneath or above the respiratory mucosa depending on the clinical requirements, drug formulation and the volume of drug used. The drug distributes into the brain from the delivery site by bypassing the blood brain barrier without causing any significant increase of the drug in the peripheral circulation. The device can be used for continuous and controlled drug delivery into the brain by bypassing the blood brain barrier for a number of medical conditions.

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PATENT CO-OPERATION TREATY UTILITY PATENT APPLICATION

INTERNATIONAL PHASE

DRUG DELIVERY SYSTEM AND METHOD FOR CONTROLLED AND CONTINUOUS DELIVERY OF DRUGS INTO THE BRAIN BY BYPASSING THE BLOOD BRAIN BARRIER.

CROSS-REFERENCE TO RELATED APPLICATIONS:

[0001]This application claims priority from **the United States Non-Provisional Utility Patent Application No: 15177347 filed in United States on June 9, 2016, the Indian Complete Patent Application No: 201641014398 filed in India on April 26, 2016 and the Indian Complete Patent Application No: 3904/CHE/2015 filed in India on July 30, 2015**.

[0002] Application No: 3904/CHE/2015 filed in India on July 30, 2015 is a patent of addition to the Indian Complete Patent Application No: 1430/CHE/2014 filed in India on March 19, 2014. The mentioned applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION:

[0003]The present invention relates to devices, systems and methods for controlled and continuous delivery of drugs into the brain by bypassing the blood brain barrier, without the need for any surgical manipulation of the brain. The drug is delivered using an implantable device either beneath or above the respiratory mucosa, by surgically creating a window on the bone overlying the respiratory mucosa and accessing the connective tissue side of the respiratory mucosal lining from the oral or maxillofacial region. The locally delivered drug may be transported through the neural, vascular or lymphatic routes or a combination of these routes and delivered into the brain

by bypassing the blood brain barrier in human or animal patients. Accordingly the present invention relates to the fields of drug delivery and medicine especially Oral and Maxillofacial Surgery, Neuroanatomy and Neurology.

BACKGROUND OF THE INVENTION:

[0004]The present invention relates to implantable devices, systems and methods for controlled and continuous delivery of drugs into the brain by bypassing the blood brain barrier, without the need for any surgical manipulation of the brain

[0005]The brain has good blood supply. As the brain is a highly sensitive organ, the cells lining the blood vessels in the brain are tightly arranged without any spaces between them to form a natural barrier called as the blood brain barrier. This blood brain barrier prevents entry of any foreign substance into the brain and thereby protects the brain. At the same time, it also prevents drugs present in the circulating blood from entering into the brain. Hence it is not practically possible to treat many medical conditions of the brain, even though the cause of the disease and the drug required for the treatment are known, because of the simple reason that the drug cannot enter the brain.

[0006] In the recent years, more information about the central nervous system and blood brain barrier have been unraveled using advanced molecular and imaging techniques. This has led to identification of newer therapeutic targets for drugs at the molecular level. New drugs have also been developed which can act on these molecular targets. Though in vitro studies and pre-clinical studies are positive for these drugs, they show high failure rate when administered in humans. This is mainly because the drugs are not able to enter the brain in the required therapeutic concentration to produce the pharmacologic effects. In fact, 98% of small drugs and almost 100% of large drugs

are not able to cross the barrier. Hence there is a need for an effective drug delivery route which can deliver the drug into the brain at the right concentration in a continuous but controlled manner.

[0007]The methods available today for delivering drugs directly into the brain are mostly invasive. The methods include placement of micro-catheters or implants into the brain or use of various techniques to open the blood brain barrier. These techniques however make the brain also prone to infection as the brain gets exposed to the external environment. Advancement in the field of proteomics and genomics has led to discovery of therapeutic targets at the level of molecules or genes in the brain, leading to development of newer drugs. But these drugs also get destroyed when given orally. Hence alternative routes for drug delivery are the need of the hour.

[0008]Recent studies have shown that the nasal route can be used as a non-invasive route to deliver the drugs directly to the brain. But this route has limitations because controlled and continuous delivery of drugs at predetermined rates has not yet been achieved. The drugs also have to withstand mucociliary clearance, local enzymatic degradation and cross the epithelial layer before they reach the underlying connective tissue for further absorption. Hence only a smaller quantity of the total drug that is delivered, is finally absorbed. Drugs modified for endogenous transport mediated delivery across the blood brain barrier, using the naturally occurring molecular transport mechanisms at the endothelial cell have been developed for a few medical conditions. Yet the concentration of the drug delivered across the blood brain barrier using this technique is not predictable. Protein mediated drug delivery and viral mediated gene therapy may also induce immune mediated complications. Systemic routes like intra venous or intra-arterial need high concentration of the drug. Moreover intra-arterial route results in severe complications. Therefore an effective alternative route which can deliver drugs into the brain in a controlled and continuous

manner, for a long period of time, without any complications or discomfort to the patient holds immense potential.

[0009] Trigeminal nerve supplies the nasal respiratory mucosa and the maxillary sinuses and relays at the nuclei in the brainstem. Cerebrospinal fluid has also been found to drain through nasal lymphatics. The nasal lymphatic channels are free of valves and can hence be used for drug delivery. Blood vessels in the nasal and maxillary sinus region may also transfer the drugs to the brain. The veins from the maxillary sinus and the nasal region drain into the pterygoid venous plexus which is further connected to the cavernous sinus. Therefore the drugs delivered locally in these regions can drain reach the pterygoid venous plexus and be further transferred into the cavernous sinus. The drugs can then enter the cerebral circulation at higher concentration without causing systemic toxicity either through the counter current mechanism at the cavernous sinus or through the perivascular pathways. Hence the drug delivered locally beneath the respiratory mucosa, may be transported from the nasal and maxillary sinus region through the neural, lymphatic and the vascular routes into the brain by bypassing the blood brain barrier.

[0010]The air circulation in the maxillary sinus is unique. The maxillary sinus fills with air during expiration and is emptied of air during inspiration. Hence a drug delivered into the maxillary sinus by perforating the sinus lining mucosa from the connective tissue side can be easily inhaled when the air inside the maxillary sinus is emptied during inspiration. The drug can further come in contact with the nasal respiratory and olfactory mucosa for absorption. Also the mucus on the maxillary sinus lining mucosa is moved towards the ostium opening and into the middle meatus of nose because of the muco-ciliary action. Hence the drug delivered on the maxillary sinus lining mucosa can also be transported by the muco-ciliary action through the ostial opening into the middle meatus and onto the nasal respiratory mucosa. Because of the increased retention time of

the drug on the mucosal surface, higher quantity of the drug can be inhaled and be deposited on the nasal respiratory and olfactory mucosa for further absorption into the underlying connective tissue.

[0011] Goblet cells in the maxillary sinus lining mucosa secrete mucus. Drugs can be engineered for uptake from the connective tissue into the goblet cells, for further secretion along with mucus by the goblet cells. This can result in mucus loaded with high concentration of drug molecule for inhalation. The inhaled drug can be deposited on the nasal respiratory mucosa and olfactory mucosa for further absorption.

[0012]It therefore would be desirable to deliver drugs into the brain using a device without any need for surgical manipulation of the brain. It would further be desirable to provide a device which can be surgically implanted with its delivery tip located beneath or above the respiratory mucosa, by surgically creating a window on the bone overlying the respiratory mucosa and accessing the connective tissue side of the respiratory mucosal lining from the oral or maxillofacial region. It would also be desirable to deliver the drug in a controlled and continuous manner by connecting the device to an external drug infusion pump. The drug from the respiratory mucosa can be transported through the neural, vascular, lymphatic, inhalation or a combination of all these routes and delivered into the brain by bypassing the blood brain barrier and without causing any systemic toxicity.

SUMMARY OF THE INVENTION

[0013]One aspect of the present invention provides a drug delivery system for delivering drugs into the brain, by bypassing the blood brain barrier. The drug delivery system comprises an implantable hollow device made of titanium or any other biocompatible material, intended for

placement into the bone overlying the respiratory mucosa of the maxillary sinus and the nasal cavity and a drug delivery assembly made of a biocompatible material intended for transferring therapeutic agents from an external drug reservoir into the central lumen of the implantable hollow device. An external drug infusion pump is used for providing continuous and controlled drug delivery of therapeutic agents from the external drug reservoir into the central lumen of the implantable hollow device.

[0014]Another aspect of the invention provides a method of drug delivery into the brain by bypassing the blood brain barrier. The device is used to deposit the drug beneath the respiratory mucosa, by surgically creating a bone window on the overlying bone and accessing the connective tissue side of the respiratory mucosal lining from the oral or maxillofacial region. The drug delivered locally beneath the respiratory mucosa, may be transported from the nasal and maxillary sinus region through the neural, lymphatic and the vascular routes into the brain by bypassing the blood brain barrier.

[0015] An alternative method of drug delivery into the brain by bypassing the blood brain barrier is provided wherein the tip of the drug delivery device is placed into the maxillary sinus and above the level of the epithelial lining of the respiratory mucosa, by surgically creating a bone window on the overlying bone and perforating the overlying respiratory mucosa from the connective tissue side. The mucosa is perforated by removing the circumscribed bone with the trephine drill along with the underlying respiratory mucosa attached to the bone. The drug delivered into the maxillary sinus can be easily inhaled during inspiration and can be deposited at the nasal respiratory and olfactory mucosa for further absorption. The drug can also be transported through the ostial opening into the middle meatus and onto the nasal respiratory mucosa by muco-ciliary action. This results in increased retention time of the drug on the mucosal surface and so higher quantity of the

drug can be absorbed into the connective tissue vasculature at the respiratory mucosa and the olfactory mucosa.

[0016]Another aspect of the invention provides drug molecules that are engineered for uptake into the goblet cells of the maxillary sinus lining epithelium, from the underlying connective tissue for further secretion by the goblet cells along with mucus. This can result in mucus loaded with high concentration of drug molecule for inhalation, which can be deposited on the nasal respiratory mucosa and the olfactory mucosa for further absorption.

[0017]Another aspect of the invention provides drug molecules that are engineered for affinity to specific sites of the brain. This provides the required concentration of the drug in the targeted anatomical site in the brain.

[0018]The present invention is illustrated by the accompanying drawings of various embodiments and the detailed description given below. The drawings are not to scale. The detailed description and drawings merely depict exemplary embodiments of the present invention, for explanation and understanding and therefore should not be taken to limit the scope of the invention to the specific embodiments. Accordingly the scope of the invention is to be defined solely by the appended claims and equivalents thereof. It will be appreciated that the components of the present invention illustrated in the drawings could be arranged, sized and designed in a number of different configurations.

[0019] Implantable devices and methods for controlled and continuous drug delivery into the brain by bypassing the blood brain barrier for a number of medical conditions including Parkinson's, Alzheimer, Pain Management, Epilepsy and Drug Addiction are provided.

BRIEF DESCRIPTION OF THE DRAWINGS:

[0020] Fig.1 shows the isometric side view, longitudinal sectional view and three dimensional view of the single unit device.

[0021] Fig.2 shows the isometric side view, longitudinal sectional view and three dimensional view of a multi-unit device comprising an implant with a central tubular inlet with external threads, a drug delivery assembly and a retention cap

[0022] Fig.3 shows the isometric side view, longitudinal sectional view and three dimensional view of a multiunit device comprising an implant with a completely open apex and smooth and rounded walls.

[0023] Fig.4 shows the isometric side view and three dimensional view of a multiunit device comprising an implant with a central tubular inlet with internal threads at the cervical third and a drug delivery assembly with external threads at its cervical part.

[0024] Fig.5 shows the placement and removal tools for use with the device.

[0025] Fig.6 shows the device in the form of a dental implant with an internal spline in the internal wall of body of the implant.

[0026] Fig.7 shows an abutment in the form of a drug delivery system comprising a miniaturized internal drug infusion pump and drug reservoir intended for use with the device in the form of a dental implant.

[0027] Fig.8 shows the surgical placement of the device in the form of a dental implant in the maxillary alveolar ridge, along with the placement and removal tools.

[0028] Fig.9 shows a mini plate with a central reservoir dial comprising a porous base and with internal threads which is closed with a cap with external threads.

[0029] Fig.10 shows a mini plate with a reservoir dial comprising an angulated upper body for ease of access.

[0030] Fig 11 shows the implant with the porous apical tip located beneath the respiratory mucosa.

[0031] Fig 12 shows the implant with the porous apical tip located above the level of the respiratory mucosa.

[0032] Fig 13 shows the implant placed on the anterior wall of the maxillary sinus with the drug delivery tubing extending into the buccal sulcus. The drug delivery tubing is connected to an external drug infusion pump for continuous and controlled drug delivery.

[0033] Fig 14 shows a root canal treated tooth whose apex is in contact with the respiratory mucosa intended for use as a natural drug delivery device.

[0034] Fig 15 shows the brain values of dopamine in a rabbit obtained using High performance Liquid Chromatography, after in vivo drug delivery of dopamine from beneath the respiratory mucosa.

[0035] Fig 16 shows the blood values of dopamine in a rabbit obtained using High performance Liquid Chromatography, after in vivo drug delivery of dopamine from beneath the respiratory mucosa.

[0036] Fig 17 shows the brain values of lignocaine in a rabbit obtained using High performance Liquid Chromatography, after in vivo drug delivery of lignocaine into the maxillary sinus and on

the epithelial surface of maxillary sinus mucosa by perforating the lining mucosa from the connective tissue side.

[0037] Fig 18 The blood values of lignocaine in a rabbit obtained using High performance Liquid Chromatography, after in vivo drug delivery of lignocaine into the maxillary sinus and on the epithelial surface of maxillary sinus mucosa by perforating the lining mucosa from the connective tissue side.

DETAILED DESCRIPTION OF THE INVENTION

[0038]The following detailed description of exemplary embodiments of the invention makes reference to the accompanying drawings which form a part hereof. The exemplary embodiments of the invention and the method to practice the invention are hereby illustrated in the accompanying drawings. Though the exemplary embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, it should be appreciated that various changes of the invention may be made without departing from the spirit and scope of the present invention. Accordingly the scope of the invention is to be defined solely by the appended claims and equivalents thereof.

[0039]It must be appreciated that, in the specification and in the appended claims, the singular forms “a,” “an” and “the” refer to plural forms unless the context clearly dictates otherwise. Therefore reference to “the surgical placement” refers to one or more steps and “a therapeutic agent” refers to one or more therapeutic agents.

DEFINITIONS

[0040]In describing and claiming the invention, the following terminology will be used to denote the definitions set forth below

[0041]As used herein, "coronal end," "top end" and "upper end" may be used interchangeably to refer to the end of the device that is present above the level of the ring and remains above the bone when implanted into the surgical site.

[0042]As used herein "coronal part," "top part" and "upper part" may be used interchangeably to refer to the part of the device that projects above the level of the ring and remains above the bone when implanted into the surgical site.

[0043]As used herein, "apical end," "bottom end" and "lower end" may be used interchangeably to refer to the end of the device that is present below the level of the ring and remains below the bone, in contact with the respiratory mucosa when implanted into the surgical site.

[0044]As used herein "caudal part" "bottom part" and "lower part" may be used interchangeably to refer to the part of the device that projects below the level of the ring and remains within the bone when implanted into the surgical site

[0045]As used herein "proximal part," and "mesial part" may be used interchangeably to refer to the part which is nearest to the point of reference or the part that is closest to the median plane of the device.

[0046]As used herein "distal part" refers to the part which is away from the point of reference or the part that is farther away from the median plane of the device.

[0047]As used herein "cervical third" refers to the upper third part of the lower part of the body of the device that extends from below the level of the ring, or to the upper third part of the body of the device in the form of a dental implant, wherein the body is divided horizontally by imaginary lines into three equal parts

[0048]As used herein "middle third" refers to the middle third part of the lower part of the body of the device that extends from below the level of the ring, or to the middle third part of the body of the device in the form of a dental implant, wherein the body is divided horizontally by imaginary lines into three equal parts

[0049]As used herein "apical third" refers to the lower third part of the lower part of the body of the device that extends from below the level of the ring, or to the lower third part of the body of the device in the form of a dental implant, wherein the body is divided horizontally by imaginary lines into three equal parts.

[0050]As used herein, "superior surface" may be used to refer to the upper surface of a flat or similar shaped embodiment.

[0051]As used herein, "inferior surface" may be used to refer to the lower surface of a flat or similar shaped embodiment.

[0052]As used herein, "inlet," "outlet" and "tubular opening" may be used interchangeably to refer to the part of the device that is tubular in shape and is located on the upper part of the device, to which a drug delivery tubing can be attached for drug delivery into the device.

[0053]As used herein, "central lumen," and "central vent" may be used interchangeably to refer to the central hollow space within the body of the device, which further opens to the outside through the inlet on the coronal end and through multiple holes at the apical end.

[0054]As used herein, "apical wall" may be used to refer to the wall comprising the rounded apical end and part of the apical third of the lower part of the device.

[0055]As used herein, "slot" and "cleft" may be used interchangeably to refer to a vertical opening in the upper end of the inlet intended for placement of the drug delivery tubing.

[0056]As used herein, "drug delivery assembly" refers to a hollow tubing comprising a vertical part intended for placement into the device and a lateral tube extending from the side of the vertical part, wherein the mesial end of the tube is intended for placement into the slot of an inlet present on the device.

[0057]As used herein, "intra implant part" refers to the vertical part of the drug delivery assembly intended for placement into the device.

[0058]As used herein, "external drug delivery tubing" or "external tubing" may be used interchangeably to refer to the lateral tube extending from the side of the vertical part intended for placement in the slot of an inlet.

[0059]As used herein, "tubing," and "drug delivery tubing" may be used interchangeably to refer to the tube attached to the inlet of the device.

[0060]As used herein, "intra oral part" refers to the part projecting into or the part facing the oral cavity.

[0061]As used herein, "intra bony part" refers to the part within the bone or below the level of the bone.

[0062]As used herein "intra-pulpal part" refers to the part that is within the pulp cavity of the tooth.

[0063]As used herein, "osseointegration" refers to the process of bone formation around the implant and on the surface of the implant facing the bone.

[0064]As used herein, "abutment," refers to the removable part that can be placed into the device which is in the form of a dental implant. It may be in the form of a drug delivery assembly or a drug reservoir with an in-built drug infusion pump.

[0065]As used herein "external involute spline" refers to an involute spline whose tip surface is located on the external surface of the body of the embodiment.

[0066]As used herein "internal involute spline" refers to an involute spline whose tip surface is located on the internal surface of the body of the embodiment.

[0067]As used herein, "claw," refers to the curved part of the tool that is used for holding a retention cap by its margin.

[0068]As used herein, "shaft," refers to the narrow and straight part of the instrument, present between the head and the handle.

[0069]As used herein, "reservoir," and "drug reservoir" may be used interchangeably to refer to a body comprising a cavity intended to hold a therapeutic agent. The therapeutic agent may be in a form in which it can be easily transferred from the reservoir into the device in a controlled and continuous manner. As used herein, "external drug reservoir," refers to a reservoir which is present

outside the patient. It is connected to the device in the patient by a tubing whenever drug delivery is required.

[0070]As used herein, "internal drug reservoir," refers to a reservoir which is present within the implant. It may be in the form of a cavity within the abutment.

[0071]As used herein, "infusion pump," and "drug infusion pump" may be used interchangeably to refer to the device that can move the therapeutic agent from the reservoir to the inside of the device in a controlled and continuous manner.

[0072]As used herein, "therapeutic agent," and "drug" may be used interchangeably to refer to an agent or substance that can produce a pharmacologic effect in a human or animal patient when administered into the patient or that is useful as a diagnostic agent when administered in a patient.

[0073]The surgical steps claimed in the methods, can be executed by changing the order of steps or by avoiding some steps depending on the clinical requirements and are not limited to the order presented in the claims unless otherwise stated. Accordingly the scope of the invention should be determined by the appended claims and their legal equivalents, rather than by the descriptions and examples given herein.

DRUG DELIVERY DEVICE:

[0074]In the preferred embodiment, the single unit implantable device has a hollow cylindrical or tapered body which is closed at both the ends. The body comprises a lower part and an upper part, with a barrier ring located on the outer surface of the body between the two parts. The outer surface of the lower part of the implant body that is located below the circular ring comprises threads from the cervical third to the middle third. The apical part is smooth and has a plurality of holes through

the apical wall. The holes may be macro-holes, micro-holes, nano-holes or a combination. A central lumen is present within the body. The central lumen extends from the upper part of the body to the lower part of the body and is defined by the surrounding internal wall of the implant. The central lumen further opens to the external surface at the coronal part through an inlet and at the apical end through a plurality of holes at the apical wall of the implant body. This porous apical end is placed in close proximity to the respiratory mucosa. The coronal end of the implant has an external hex for holding and placement of the implant. A drug delivery inlet is present below the level of the external hex on the side of the upper part of the body of the implant for the attachment of a drug delivery tubing. The inlet may be in the form of an opening with or without internal threads or in the form of a tubular projection. The tubular inlet may have a smooth external surface or have external or internal threads. The tubular inlet may be perpendicular to the external surface of the body of the implant or angulated towards the coronal end. The inlet opens into the central lumen present within the body of the device, wherein the central lumen further opens to the exterior through the plurality of holes at the apical end. A drug delivery tubing is attached to the inlet and the free end of the drug delivery tubing is connected to an external drug reservoir attached to a drug infusion pump for controlled drug delivery whenever required. A circular ring is present below the inlet which prevents the accidental inward displacement of the implant into the maxillary sinus or into the nasal cavity. The implant is made of titanium or any other biocompatible material. The tubing is also made of a resilient and biocompatible material that allows good soft tissue adaptation. The device is manufactured in varying diameters and lengths to suit the different clinical requirements.

[0075]The device delivers one or more drugs in a controlled and continuous manner, locally at the surgical site in the respiratory mucosal region which can then be transported by neural, vascular,

lymphatic or inhalation routes or by a combination of these routes into the brain by bypassing the blood brain barrier.

[0076]Exemplary, non-limiting embodiments of the brain drug delivery device are illustrated in Fig 1-18. These figures illustrate variations of the drug delivery device and the methods for use.

[0077]The preferred embodiment is illustrated in Figure**1. Referring to FIG. 1 Fig: A** refers to the isometric side view of the single unit device. **101** refers to the smooth apical end with a plurality of holes through the apical wall of the body of the implant intended for placement either beneath or above the respiratory mucosa .**102** refers to the threads on the outer surface of the implant located at the cervical third and middle third of the lower part of the implant body.**103** refers to the barrier ring intended for preventing the unintentional inward displacement of the implant into the maxillary sinus or the nasal cavity.**104** refers to the inlet intended for connection to the drug delivery tubing.**105** refers to the drug delivery tubing. The end one of the tubing is either friction fit or threaded onto or into the inlet. The end two of the tubing is free and has a nozzle at the free end .**106** refers to the nozzle at the free end of the drug delivery tubing which may be placed in the buccal sulcus overlying the mucosa, in the buccal gingival sulcus or in the palatal gingival sulcus. The nozzle at the free end of the tubing can be closed with a temporary cap. **107** refers to the external hex on the head part of the implant which is intended to fit into a placement tool and thereby assist in holding and placement of the implant into the surgical site. **Fig: B** refers to the longitudinal sectional view of the implant. **101** refers to the smooth and rounded apical end of the implant with a plurality of holes. **102** refers to the threads on the outer surface of lower part of the implant.**103** refers to the barrier ring.**104** refers to the inlet to which the drug delivery tubing is connected. **107** refers to the external hex. **108** refers to the central lumen. **109** refers to the external threads on the inlet. **Fig: C** refers to the 3D rendered view of **Fig: A**.

[0078]An alternative embodiment is illustrated in **Fig. 2.** The alternative embodiment is a multiunit device comprising an inlet located centrally at the coronal end of the implant body. The inlet further comprises external threads at its cervical third and a vertical slot extending from its tip to its middle third. The drug delivery assembly comprises an intra implant part and an external drug delivery tubing. The intra implant part is tapering in shape and comprises a central lumen within the body and a plurality of holes through the wall at the apical end. The drug delivery tubing is tubular in shape comprising a central lumen and is attached to the side of the intra-implant part. The central lumen of the intra implant part and the drug delivery tubing are continuous with each other. When the intra-implant part is pushed into central lumen within the implant, the proximal end of the drug delivery tubing is also slid across the vertical slot on the side of the inlet. A cap is threaded onto the external threads on the inlet. The cap covers the slot and extends till the surface of the tubing. The cap retains the intra-implant part within the implant. An external hex is present below the inlet that helps in holding and placing the implant. A circular ring is present below the external hex which prevents the accidental inward displacement of the implant into the maxillary sinus or into the nasal cavity. **Referring to FIG. 2, Fig: A** refers to an isometric side view of a multi-unit drug delivery device. **201** refers to the smooth apical end with a plurality of holes through the apical wall of the body of the implant intended for placement either beneath or above the respiratory mucosa .**202** refers to the threads on the outer surface of the implant located at the cervical third and middle third of the lower part of the implant body. **203**. Refers to the barrier ring. **204**. Refers to the external hex. **205** Refers to the outer threads on the tubular inlet.**206** Refers to the intra implant part of the drug delivery assembly. **207** Refers to the external tubing of the drug delivery assembly.**208** Refers to the nozzle at the free end of the drug delivery tubing **209**. Refers to the cap with internal threads that can be threaded onto the drug delivery inlet. It retains

the intra implant part within the implant. **210** refers to the plurality of holes at the apex of the intra implant part of the drug delivery assembly. **Fig: B** is a longitudinal sectional view of the lower part of the implant body and the components comprised within. **201**. Refers to the porous apical end. **202.** Refers to the external threads **203**. Refers to the barrier ring. **204**. Refers to the external hex. **206.** Refers to the intra implant part of the drug delivery assembly with a central lumen and porous tip. **207.** Refers to the external tubing of the drug delivery assembly. **208.** Refers to the nozzle at the free end of the drug delivery tubing. **209.** Refers to the cap with internal threads that is threaded onto the drug delivery inlet. It retains the intra implant part within the implant.**210.** Refers to the porous apical end of the intra implant part of the drug delivery assembly within the implant. **Fig: C** is a 3D rendered view of Fig A. **Fig: D** is a 3D rendered view of Fig B.

[0079]Another preferred embodiment is illustrated in **Fig: 3**.The alternative embodiment is a multiunit implant assembly comprising a completely open apex with beveled and outwardly flaring internal walls and smooth and rounded margins and an inlet located centrally at the coronal end of the implant body. The inlet further comprises external threads at its cervical third and a vertical slot extending from its tip to its middle third. The drug delivery assembly comprises an intra implant part and an external drug delivery tubing. The intra implant part is tapering in shape and comprises a central lumen within the body and a plurality of holes through the wall at the apical end. The drug delivery tubing is tubular in shape comprising a central lumen and is attached to the side of the intra-implant part. The central lumen of the intra implant part and the drug delivery tubing are continuous with each other. When the intra-implant part is pushed into central lumen within the implant, the proximal end of the drug delivery tubing is also slid across the vertical slot on the side of the inlet. The tip of the intra-implant part is positioned at the apical opening of the central lumen which is located below the level of the outer rounded apical margins. A cap is

threaded onto the external threads on the inlet. The cap covers the slot and extends till the surface of the tubing. The cap retains the intra-implant part within the implant. An external hex is present below the inlet that helps in holding and placing the implant. A circular ring is present below the external hex which prevents the accidental inward displacement of the implant into the maxillary sinus or into the nasal cavity. **Referring to Fig.3, Fig: A** refers to an isometric side view of a multi-unit implant with a completely open apex .**301**. Refers to the completely open apex with smooth and rounded margins. **302.** Refers to the external threads **303**. Refers to the barrier ring. **304**. Refers to the external hex. **305** Refers to the outer threads on the tubular inlet.**306** Refers to the intra implant part of the drug delivery assembly. **307** Refers to the external tubing of the drug delivery assembly. **308** Refers to the nozzle at the free tip of the drug delivery tubing. **309**. Refers to the cap with internal threads that can be threaded onto the drug delivery inlet. It retains the drug delivery assembly within the implant. **310.** Refers to the plurality of holes at the apex of the intra implant part of the drug delivery assembly. **Fig: B** is a longitudinal sectional view of the lower part of the implant body and the components comprised within. **301**. Refers to the completely open apex with smooth and rounded margins. **302.** Refers to the external threads **303**. Refers to the barrier ring. **304**. Refers to the external hex. **306.** Refers to the intra implant part of the drug delivery assembly with a central lumen and porous tip which is placed short of the apical margin. **307.** Refers to the external tubing of the drug delivery assembly. **308.** Refers to the nozzle at the free end of the drug delivery tubing. **309.** Refers to the cap with internal threads that is threaded onto the drug delivery inlet. It retains the intra implant part within the implant.**310.** Refers to the porous apical end of the intra implant part of the drug delivery assembly within the implant. **Fig: C** is a 3D rendered view of Fig A. **Fig: D** is a 3D rendered view of Fig B.

[0080]An alternative embodiment is illustrated in **Fig.4.** The alternative embodiment comprises a multi-unit implantable device with a body in the form of a hollow cylindrical tube with the upper end open and the apical end closed. The apical end is rounded with a plurality of holes through the apical wall and the upper end comprises a drug delivery inlet with internal threads. The external surface of the upper part of the body further comprises an external hex below the drug delivery inlet and a barrier ring below the external hex. A central lumen is present within the body comprising tapering walls defined by the internal wall of the body of the device. The central lumen communicates with the exterior through an inlet at the upper end and the plurality of holes in the wall at the apical end. Threads are present on the external surface of the lower part of the body at the cervical third, below the level of the ring. An inlet is located at the upper end of the device, comprising internal threads at its cervical third. An external hex is located below the inlet at the upper part of the device. A circular ring is located below the level of the tubular inlet and comprises a convex and smooth upper surface and a flat and smooth undersurface facing the bone. The drug delivery assembly comprises a tapered intra-implant part with external threads at its upper part and an external drug delivery tubing attached to the upper end of the intra-implant part. The intra-implant part is threaded into the inlet wherein the external walls of the intra implant part fit tightly to the internal walls of the implant except at the apical third. A space is present at the apical third between the internal wall of the implant and the external wall of the intra-implant part, wherein the drug is initially delivered. The drug further moves out through the holes at the apical end of the implant. **Referring to Fig.4, Fig: A** refers to an isometric side view of a multi-unit implant with the tubular central outlet with internal threads at the top or coronal aspect.**401**. Refers to the porous apical end. **402.** Refers to the external threads **403**. Refers to the barrier ring. **404**. Refers to the external hex. **405** Refers to the tubular outlet with internal threads.**406** Refers to the intra

implant part of the drug delivery assembly. **407** Refers to the external tubing of the drug delivery assembly. **408** Refers to the nozzle at the free tip of the drug delivery tubing.**409** refers to the external hex on the upper end of the intra implant part **410**. Refers to the porous apical end of the intra implant part of the drug delivery assembly within the implant. **411**. Refers to the external threads on the intra-implant part of the drug delivery assembly. The intra-implant part is threaded into the inlet. **Fig: B** is a 3D rendered view of Fig A.

[0081]The drug delivery device is held and placed in the surgical site using specialized instruments because of the limited anatomical space available for use and the need for sterilized instruments. The instruments may be hand held or rotary. The instruments may be in the form of ratchets or spanners of varying sizes and length. The instruments basically consist of a head and a handle. The head adapts to the external hex present on the implant or on the retention cap. The head may be of varying diameters. The handle may be of varying lengths and angulations. The handle may be hand held and used or may be attached to a low speed rotary handpiece. The preferred embodiments are illustrated in Figure 5. **Referring to FIG. 5, 5X** refers to the external hex on the implant **Fig: A** Refers to the spanner for placement and removal. **501.** Refers to the head which adapts to the external hex on the implant. **502.** Refers to the handle. **Fig: B** Refers to an angulated spanner. **503.** Refers to the head which adapts to the external hex on the implant. **504.** Refers to the angulated handle. **Fig: C** refers to the hand held ratchet. **505.** Refers to the head which adapts to the external hex on the implant. **506.** Refers to the handle. **Fig: D** refers to an angulated hand held ratchet. **507.** Refers to the head which adapts to the external hex on the implant.**508.** Refers to the angulated handle. **Fig: E** refers to a hand held rotating placement and removal tool. **509.** Refers to the head which adapts to the external hex on the implant **510.** Refers to the rotating finger rest. **Fig: F** refers

to a rotary placement and removal tool. **511.** Refers to the head which adapts to the external hex on the implant. **512.** Refers to the shank that can fit into the rotary instrument.

[0082]Another preferred embodiment is illustrated in **Fig. 6.** In this embodiment, the device is in the form of a hollow dental implant made of titanium alloy or any other biocompatible material with external threads. The implant has micro holes at the apical part of the implant body. The holes connect the central lumen defined by the internal surface of the implant with the nasal respiratory mucosa or the maxillary sinus lining mucosa. The implant has an internal involute spline within the implant body. The implant has internal threads at the cervical end. The disposable abutment made of a bio-compatible material has a body comprising an intra-oral part and an intra-implant part with a barrier ring on the external surface between the two parts. The external surface of the intra-implant part of the abutment has an external involute spline and a micro-porous apical end. The abutment further comprises a central lumen that communicates to the exterior through a drug delivery tubing at the coronal end of the intraoral part of the abutment. The external involute spline of the abutment fits into internal involute spline of the dental implant. The plurality of holes at the apical tip of the abutment is in alignment and in line with the plurality of holes at the apex of the implant. A cervical ring comprising an external hex with a central hole at the upper part outer and external threads at the lower part is slid from the top of the abutment and threaded into the inner threads at the cervical part of the implant. The inner aspect of the cervical ring adapts closely and tightly to the outer surface of the abutment to form a tight junction without any micro-leakage. The drug is delivered into the central lumen through the drug delivery tubing extending from the coronal end of the intraoral part of the abutment. In an alternative embodiment, the cervical ring is of variable heights depending on the soft tissue requirements and is well adapted to the wall of the abutment on tightening. **Fig: A** refers to the isometric side view of the dental implant **601** refers

to the apical pores in the implant.**602** refers to the external threads on the implant.**603** refers to the smooth cervical end.**604** refers to the apical holes of the abutment.**605** refers to the external involute spline on the abutment .**606** refers to the barrier ring .**607** refers to the intra-oral part of the abutment.**608** refers to the external threads on the cervical ring.**609** refers to the cervical ring.**610** refers to the external hex on the cervical ring. **611** refers to the drug delivery tubing. **612** refers to the nozzle at the distal free end of the tubing. **Fig: B** refers to the 3 D rendered view of Fig A. **Fig: C** refers to the isometric side view of the dental implant and the placement tool.**601** refers to the apical holes in the implant.**602** refers to the external threads on the implant.**603** refers to the smooth cervical end.**613** refers to the external involute spline on the placement tool .**614** refers to the barrier ring on the placement tool .**615** refers to the shank of the placement tool.**616** refers to the external hex on the hand held placement tool. **Fig: D** refers to the 3 D rendered view of Fig C. **613** refers to the external involute spline on the placement tool .**614** refers to the barrier ring on the placement tool .**615** refers to the shank of the placement tool.**616** refers to the external hex on the hand held placement tool. **617** refers to the internal cervical threads within the implant. **618** refers to the internal spline within the implant. **619** refers to the central lumen within the implant.

[0083]The alternative embodiments of the abutment, intended for use with the device in the form of a dental implant is illustrated in **Fig 7**. Referring to **Fig: 7, Fig A** is a 3D rendered view of the abutment. **701** refers to the inlet on the coronal tip of the abutment intended for attaching a drug delivery tubing. **702** refers to the intra-oral part of the abutment. **703** refers to the barrier ring.**704** refers to the external involute spline. **705** refers to the apical holes. **Fig B** is the longitudinal section of Fig A**. 706** refers to the central lumen within the body of the implant. In an alternative embodiment, specially designed abutments in the form of drug reservoirs comprising in-built,

miniature, osmotically or electronically controlled infusion pumps are used for drug delivery with the device. **Fig C** refers to the abutment comprising a drug reservoir in the lower part, an osmotic compartment holding the osmotic agent in the middle part and a semipermeable membrane separating the middle part from the upper part. The upper part has a space to hold an injected osmotic solvent. When the solvent is injected into the upper part, the solvent moves across the semipermeable membrane into the osmotic compartment and causes it to expand, thereby pushing the drug out from the reservoir at a predetermined rate through the apical holes.**701** refers to the inlet on the coronal tip of the abutment intended for delivering the osmotic solvent. **702** refers to the intra-oral part of the abutment that holds the osmotic solvent. **703** refers to the barrier ring. **705** refers to the apical holes. **707** refers to the semipermeable membrane separating the middle part and the upper part of the abutment.**708** refers to the osmotic compartment.**709** refers to the drug reservoir. **Fig D** refers to the abutment comprising a drug reservoir in the lower part and an electronic drug infusion pump in the upper part. **702** refers to the intra-oral part of the abutment that holds the electronic drug infusion pump. **703** refers to the barrier ring. **705** refers to the apical holes. **709** refers to the drug reservoir. **710** refers to the electronic drug infusion pump In an alternative embodiment, the abutment may be used as a drug reservoir for continuous drug delivery, by modifying the size of the plurality of holes at the apical part of the abutment into holes that equal the size of the drug molecule. This results in delivery of the drug molecules at a pre-determined rate. **Fig E** refers to the abutment used as an internal drug reservoir. **702** refers to the intra-oral part of the abutment. **703** refers to the barrier ring. **705** refers to the apical holes. **709** refers to the drug reservoir compartment extending from the lower to upper part of the abutment. In an alternative embodiment, the intra oral part of the abutment may be angulated above the level

of the cervical ring. In another alternative embodiment, the inlet on the abutment may be in the form of an opening with internal threads and located on the side of the intra-oral part.

[0084]In the case of preparing the surgical site on the maxillary alveolar process, an osteotomy dental drill of appropriate length and diameter is used. The osteotomy is stopped short by 1mm of the maxillary sinus lining mucosa or the nasal respiratory mucosa. The apical 1mm of bone is gently broken with a bone compression tool or with an elevator by gentle tapping. Care is taken not to tear the respiratory mucosa in the nasal or the maxillary sinus region. Placement of the device in the form of a dental implant into the alveolar bone using the required instruments is illustrated in **FIG. 8. 801**. Refers to the ratchet for holding the bone compression tool. **802** refers to the bone compression tool being used for enlarging the soft osteotomy site and for breaking the apical wall to access the respiratory mucosa.**803** refers to the osteotomy site in the maxillary region underlying the respiratory mucosa.**804** refers the porous apical end of the implant. **805** refers to the body of the implant being placed into the osteotomy site. **806** refers to the placement tool used for placing the implant into the osteotomy. **807** refers to the ratchet for holding the placement tool. **808** shows the abutment placed into the implant. **809** shows the cervical retention cap comprising a central hole being placed across the intra oral part of the abutment. The cap further comprises a plurality of holes at the periphery on the superior surface of the upper part. **810** refers to the projections at the tip of the placement tool intended for placement into the holes on the superior surface of the upper part of the ring. **811** refers to the body of the placement tool.**812** refers to the rotating end intended for finger rest on the placement tool. **813** refers to the claw of the removal tool.**814** refers to the handle of the removal tool. **815** Refers to the vertically moveable shank of the device.**816** refers to the rotating end intended for finger rest on the removal tool. **817** refers to

the inlet in the upper end of the abutment. **818** refers to the maxillary sinus or the nasal cavity comprising respiratory lining mucosa.

[0085]Another preferred embodiment is illustrated in **Fig. 9.** In the preferred embodiment, an implantable single unit drug delivery device is provided that comprises a mini plate with a central drug reservoir dial wherein the reservoir has a porous base with parallel walls, external or internal threads at the top part of the dial wall and a cap with internal or external threads made of a resilient, biocompatible material that self-seals whenever penetrated by a needle are used for drug delivery. The porous base of the drug reservoir dial comprises macro holes, micro holes or nano holes and is intended for placement beneath or above the respiratory mucosa. The drug is delivered into the drug reservoir dial using a needle that may be connected to a syringe or an external drug infusion pump. The needle penetrates the cap and deposits the drug into the drug reservoir dial. Alternatively a reservoir containing a drug with a rate limiting membrane at the base can also be placed into the dial. The drug reaches the respiratory mucosa through the holes in the drug reservoir dial base. The mini plate is secured to the bone by screws. **Referring to FIG: 9, Fig** A shows the top view of a mini plate with a central micro-porous or nanoporous drug reservoir dial and straight limbs. **901** refers to the straight limb with screw holes. **902** refers to the central drug reservoir dial with internal or external threads. A cap is threaded onto the threads **903** refers to the micro-porous or nanoporous base of the drug reservoir dial. The drug is deposited into the dial. **Fig B** shows a top view of the mini plate with a central micro-porous or nanoporous drug reservoir dial and a left L shaped limb. **901** refers to the straight limb with screw holes. **902** refers to the central drug reservoir dial with internal or external threads. A cap is threaded onto the threads **903** refers to the micro-porous or nanoporous base of the drug reservoir dial. The drug is deposited into the dial. **904** refers to the left L shaped limb with screw holes. **Fig C** shows the top view of a mini plate

with a central micro-porous or nanoporous drug reservoir dial and a right L shaped limb. **901** refers to the straight limb with screw holes. **902** refers to the central drug reservoir dial with internal or external threads. A cap is threaded onto the threads **903** refers to the micro-porous or nanoporous base of the drug reservoir dial. The drug is deposited into the dial. **904** refers to the right L shaped limb with screw holes. **Fig D** shows the cap made of a resilient, biocompatible material that self-seals whenever penetrated by a needle. **905** refers to the holes used for holding the cap while threading it onto the reservoir dial. **906** refers to the self-sealing part of the cap into which needles can be inserted. **907** refers to the threads on the cap. The threads can be external or internal.

[0086]An alternative embodiment comprises a mini plate with a central reservoir dial wherein the reservoir has a porous base with angulated walls and a cap made of a resilient, biocompatible material that self-seals whenever penetrated by a needle. The upper end of the cap has an external hex and the lower part of the cap has internal or external threads. The angulation helps in ease of placing the needle tip into the reservoir for drug delivery from the oral cavity, when the mini plate is located on concave surfaces like the anterior wall of the maxillary sinus. The alternative embodiment is herein illustrated in Figure10. **Referring to FIG: 10, Fig** A shows the side view of a mini plate with a central drug reservoir dial, comprising a hollow body with an upper angulated part and a lower straight part, a straight limb and an L shaped limb between the two parts of the dial. **1001** refers to the straight limb with screw holes. **1002** refers to the central drug reservoir dial with angulated walls comprising internal or external threads at the upper part. **1003** refers to the cap that is threaded onto the threads **1004** refers to the straight part of the reservoir dial comprising a micro-porous or nanoporous base intended for placement below the respiratory mucosa. **1006** refers to the retention screw **.Fig B** shows the top view of a mini plate with a central drug reservoir dial, comprising a hollow body with an upper angulated part and a lower straight part with straight

limbs between the two parts of the dial. **1001** refers to the straight limb with screw holes. **1002** refers to the central drug reservoir dial with angulated walls comprising internal or external threads at the upper part. **1003** refers to the cap that is threaded onto the threads. **1006** refers to the retention screw. **Fig C and D** show the top view of a mini plate with a central angulated drug reservoir dial comprising a straight limb and an L shaped limb. **1001** refers to the straight limb with screw holes. **1002** refers to the central drug reservoir dial with angulated walls comprising internal or external threads at the upper part. **1003** refers to the cap that is threaded onto the threads **1005** refers to the L shaped limb. It may point to the right or to the left. **1006** refers to the retention screw.

II. METHOD FOR DRUG DELIVERY:

A. SURGICAL PREPARATION OF THE IMPLANTATION SITE

[0087]A full thickness buccal or palatal mucosal flap is elevated. A bone window is marked on the bone overlying the respiratory mucosa using a bone trephine drill of appropriate length and diameter. The bone window can be surgically prepared at a number of anatomical sites which also include the hard palate forming the floor of the maxillary sinus or the nasal cavity, anterior wall of the maxillary sinus or the zygomatic process of the maxilla. The bone window can be gently pried out with the rotating trephine drill without damaging the underlying respiratory mucosa. Alternatively the circumscribed bone can be removed gently without damaging the underlying mucosa using a piezo instrument. The respiratory mucosa is gently released and elevated from the surrounding bone margins without tearing the respiratory mucosa by using a soft tissue elevator of appropriate diameter.

[0088]In the case of preparing the surgical site on the maxillary alveolar process, an osteotomy dental drill of appropriate length and diameter is used. The osteotomy is stopped short by 1mm of

the maxillary sinus lining mucosa or the nasal respiratory mucosa. The apical 1mm of bone is gently broken with a bone compression tool or with an elevator by gentle tapping. Care is taken not to tear the respiratory mucosa in the nasal or the maxillary sinus region.

SURGICAL PLACEMENT OF THE IMPLANT

[0089]A ratchet or implant placement tool which fits into the external hex on the implant is used to hold and place the implant. The implant of the correct diameter and length is gently threaded into the prepared osteotomy site using a hand held ratchet or a rotary placement tool. Alternatively the implant can be gently press fit into the osteotomy hole. The barrier ring prevents the accidental displacement of the implant into the maxillary sinus or the nasal cavity. The respiratory lining mucosa is further elevated by the smooth apical end of the implant. The porous apical part of the hollow implant is thus in contact with the connective tissue base of the respiratory lining mucosa. The drug delivery assembly or the delivery tubing is attached to the implant at the drug delivery inlet. The elevated soft tissue flap is placed back in position and the entire assembly is allowed to heal. The outer end of the drug delivery tubing can be placed in the buccal sulcus overlying the oral mucosa, in the buccal gingival sulcus or in the palatal gingival sulcus. The nozzle at the free end of the tubing can be closed with a temporary cap. Whenever needed, the tubing can be attached to an external drug infusion pump for controlled drug delivery.

B. LOCATION OF THE APICAL POROUS TIP OF THE DEVICE WITH RESPECT TO THE RESPIRATORY MUCOSA

[0090]1. The porous apical tip of the implant may be surgically placed beneath the intact respiratory mucosa at a number of anatomical sites which also include the maxillary sinus, hard palate forming the floor of the nasal cavity or maxillary sinus, the zygomatic process of the maxilla

or the nasopalatine foramen. The drug can be delivered beneath the intact respiratory mucosa which is the connective tissue side of the respiratory mucosa in a continuous and controlled manner through the plurality of holes through the apical wall of the hollow implant, by connecting the drug delivery tubing of the implant to an external drug reservoir attached to a drug infusion pump. The drug distributes into the brain by bypassing the blood brain barrier from the delivery site without increasing the concentration of the drug in the peripheral circulation. The drug delivery route into the brain may either be through the neural, lymphatic or the vascular route or a combination of all the routes. This is useful for drugs which need to be given in precise concentrations and in low volumes. Drugs can thus be delivered into the brain by bypassing the blood brain barrier.

[0091]Referring to **FIG. 11**: Fig: A refers to the isometric view of the maxillofacial implantable drug delivery device placed beneath the nasal respiratory mucosa or the maxillary sinus lining mucosa.**1101** refers to the respiratory mucosal lining. **1102** refers to the smooth porous apical end of the implant. **1103** refers to the drug delivered under the respiratory mucosa. **1104** refers to the surrounding alveolar bone.**1105** refers to the overlying oral mucosa.**1106** refers to the threads on the outer surface of the implant.**1107** refers to the barrier ring.**1108** refers to the drug delivery tubing .**1109** refers to the nozzle at the free tip of the drug delivery tubing.**1110** refers to the external hex. **Fig B** is a 3D rendered view of Fig A.

[0092]2. The porous apical tip of the implant may be also placed into the maxillary sinus and above the level of respiratory mucosa by perforating the respiratory mucosa from underneath or the connective tissue side. The drug can be delivered from an external drug reservoir into the maxillary sinus and onto the epithelial surface of the mucosal lining, in a continuous and controlled manner through the plurality of holes at the apical wall of the implant by using an external drug infusion pump. The drug can then be easily inhaled during inspiration since the air in the normal maxillary

sinus empties during routine inspiration and fills with air during expiration. The inhaled drug can be further deposited on the nasal respiratory and olfactory mucosa for absorption. Moreover because of the muco-ciliary action, the drug can also be transported from the maxillary sinus onto the nasal respiratory mucosa through the ostial opening at the middle meatus. This drug can be further be inhaled to reach the olfactory mucosa also. Because of the extra time taken for muco ciliary clearance from the maxillary sinus to the nasal respiratory mucosa, the retention time of the drug on the mucosal surface is increased, resulting in absorption of higher quantity of the drug. This route is useful for drug formulations that are inhalable and can be given in larger volumes.

[0093]Referring to **Fig 12**: Fig: A refers to the isometric view of the maxillofacial implantable drug delivery device placed into the maxillary sinus with the tip above the level of the lining respiratory mucosa.**1201** refers to the respiratory mucosal lining. **1202** refers to the smooth microporous apical end of the implant. **1203** refers to the drug delivered above the respiratory mucosa.**1204** refers to the surrounding alveolar bone.**1205** refers to the overlying oral mucosa. **1206** refers to the threads on the outer surface of the implant.**1207** refers to the barrier ring.**1208** refers to the drug delivery tubing .**1209** refers to the nozzle at the free tip of the drug delivery tubing.**1210** refers to the external hex. **Fig B** is a 3D rendered view of Fig A.

D. CONTROLLED AND CONTINUOUS DRUG DELIVERY.

[0094]The nozzle at the free end of the drug delivery tubing which is located over the oral mucosa in the buccal sulcus, at the buccal gingival sulcus or the palatal gingival sulcus is connected to an external reservoir attached to a drug infusion pump. The external electronically controlled infusion pump provides a continuous and controlled rate of delivery of drugs at the range of milliliters, microliters or nanoliters into the implant. This is essential to provide drug delivery without traumatizing the respiratory mucosa, to prevent backflow of drug from the device due to high rate

of drug inflow and to prevent leakage or overflow of the drug across the mucosal delivery site due to high rate and large volume of drug delivery at the implant-mucosal interface. The preferred method is illustrated in **Fig: 13**. **Fig A** shows the device placed at the anterior wall of the maxillary sinus. **1301** refers to the barrier ring. **1302** refers to the external hex. **1303** refers to the drug delivery tubing. **Fig B** shows the device connected to an external drug reservoir attached to a drug infusion pump. **1304** refers to the external drug infusion pump comprising a drug reservoir that is attached to the free end of the drug delivery tubing of the device.

[0095]Alternatively, as in **Fig: 7**: **C and D,** an abutment comprising an internal drug reservoir at the intra-implant part which is controlled by a miniature drug infusion pump located in the intra-oral part, can be used with the device in the form of a dental implant for controlled and continuous drug delivery. This system can be used when the device is intended for placement into the alveolar ridge, small quantity of drug has to be delivered over a period of time, and access is available to change the abutment after the drug is delivered. Alternatively **as in Fig :7: E**, the abutment may be used as a drug reservoir for continuous drug delivery, by modifying the plurality of holes at the apical part of the abutment into holes that equal the size of the drug molecule. This results in delivery of the drug molecules at a pre-determined rate.

OPTIONAL PROCEDURES FOR DIFFERENT CLINICAL SITUATIONS

[0096]In case of emergency, the drug can be directly delivered beneath the respiratory mucosa on the connective tissue side using the drug delivery assembly which is connected to an external drug reservoir attached to a drug infusion pump.

[0097]A biocompatible cement can be applied to the undersurface of the barrier ring of the implant to fix the barrier ring to the underlying bone. This retains the implant in position and prevents movement during immediate drug delivery.

[0098]The barrier ring of the implant may also be provided with screw holes at the periphery or with retentive limbs containing screw holes. Mini screws can be placed in the holes if additional retention is required.

[0099]In another form of the embodiment as illustrated in **Fig: 14**, a root canal treated tooth whose apex is in contact with the respiratory mucosa is used as a natural drug delivery device. After biomechanical preparation of the pulp cavity of the tooth till the apex, the coronal part of the tooth is prepared for the crown. An additional vertical slot is prepared on the tooth extending from the occlusal surface to the middle part of buccal or palatal wall. A crown is made using a biocompatible material. A cylindrical tube open at both the ends is included as a part in the crown at the middle third of the palatal or buccal wall, further wherein the intra oral end of the tube that opens into the oral cavity at the buccal or palatal side has internal threads and the intra pulpal end of the tube that opens into the pulp chamber is smooth with a straight or an apically curved end. The part of the crown with the cylindrical tube is slid into the vertical slot in the crown of the tooth during the cementation of the crown. A drug delivery tubing is threaded into the open end of the inlet tube on the buccal or palatal side for drug delivery. The opening is closed with a disposable cap when not in use. **Fig: 14** shows an upper molar with its root tips in close proximity to the overlying maxillary sinus lining mucosa. **1401** refers to the maxillary sinus lining.**1402** refers to the opening at the root apex.**1403** refers to the enlarged and debrided pulp canal.**1404** refers to the alveolar bone.**1405** refers to the gingiva. **1406** refers to the pulp chamber. **1407** refers to the vertical slot on the buccal

wall.**1408** refers to the tooth prepared for receiving the prosthetic crown.**1409** refers to the drug delivery inlet on the prosthetic crown. **1410** refers to the prosthetic crown.

[0100]In cases where the device in the form of a dental implant which is placed into the alveolar ridge, a dental crown with a buccal or palatal inlet is used with an abutment that also has a corresponding inlet opening on the side of the intra-oral part. Drug is delivered into the implant through the inlet in the abutment which in turn is accessed through the inlet in the buccal or palatal wall of the crown. The inlet opening in the crown is closed with a screw when not used for drug delivery.

[0101]In cases where mini plates with drug reservoir dials are used, a full thickness mucosal flap is elevated. Appropriate diameter of bone is removed with a bur or a piezo instrument, without damaging the overlying respiratory epithelium. The dial is placed into the osteotomy with its porous base in close proximity to the respiratory mucosa. The mini plate is fixed to the bone by mini screws .The top of the dial is closed with a threaded cap which is biocompatible and self-seals when penetrated by a needle. The flap is replaced over the reservoir and allowed to heal. Drug can be injected into the reservoir dial space using a needle from the overlying anaesthetized mucosa whenever needed.

E. APPLICATIONS OF THE DELIVERY DEVICE

[0102]The brain drug delivery implant can be used for a single dose of drug delivery and then removed or can be retained at the anatomical site for a longer period of time if multiple doses of the drug is required. A single drug or a combination of drugs can be delivered. Stem cells and small interference RNAs can also be delivered into the brain using this device and the methods.

[0103]Hence this this device and the methods can be used to deliver the drugs into the brain bypassing the blood brain barrier in patients with Alzheimer, Parkinson, Drug addiction, Cancer, White matter disease, Pain management, Brain infections, Psychiatric conditions and a myriad of other relevant medical conditions.

[0104]The brain drug delivery device and the methods of drug delivery thereof will be further understood by reference to the following non-limiting examples.

Example1

CONTROLLED AND CONTINUOUS DELIVERY OF DRUGS BENEATH THE RESPIRATORY MUCOSA

[0105]The device was surgically placed in a rabbit in the maxillary sinus region by removing the bone overlying the respiratory mucosa. The tip of the device was placed beneath the maxillary sinus lining mucosa in close proximity to the connective tissue side of the mucosa. Dopamine was infused in a controlled and continuous manner under the maxillary sinus mucosa of the rabbit for twenty minutes at the rate of 1 milliliter per hour by using an external drug infusion pump connected to the implanted device. Whole body perfusion was done using a peristaltic pump with warm physiological saline for 20 minutes at a controlled rate. The perfused brain was then resected at the end one hour from the start of the procedure. Brain samples from different parts of the brain was analyzed using High Performance Liquid Chromatography. There was an increased concentration of dopamine in all parts of the brain except diencephalon when compared with the normal. Thus the drug had bypassed the blood brain barrier. **Fig: 15** refers to the comparative brain values of dopamine using High Performance Liquid Chromatography, between the control and the rabbit in which dopamine was delivered in vivo in a continuous and controlled manner under the

maxillary sinus mucosa using the drug delivery system. During the procedure, a blood sample was collected before drug delivery. Three blood samples were then collected at intervals of 10, 20 and 30 minutes respectively following start of drug delivery. The samples were analyzed using High Performance Liquid Chromatography. The blood values dipped during drug delivery at the 10 and 20 minute interval. The drug delivery was stopped at the twentieth minute. Subsequently the blood value peaked again at the 30 minute interval. **Fig: 16** refers to blood values of dopamine in the rabbit after in vivo delivery of dopamine under the maxillary sinus mucosa using the device. This shows that dopamine delivered using the device had reached the brain by bypassing the blood brain barrier and may have effected a low dopamine peripheral response by a feedback mechanism in the brain during drug delivery. The peripheral value would have increased after the central negative feedback control had ceased once the drug delivery was stopped. Moreover there was no increase of the drug in peripheral circulation during drug delivery.

Example2

CONTROLLED AND CONTINUOUS DELIVERY OF DRUGS ABOVE THE RESPIRATORY MUCOSA

[0106]The device was placed into the maxillary sinus of a rabbit by perforating the maxillary sinus mucosa from the connective tissue side and placing the implant tip into the sinus cavity and above the epithelial layer. Lignocaine was infused in a controlled and continuous manner for twenty minutes at the rate of 1.5 milliliter per hour by using an external drug infusion pump connected to the implanted device. Whole body perfusion was done using a peristaltic pump with warm physiological saline for 20 minutes at a controlled rate. The perfused brain was then resected at the end one hour from the start of the procedure. Brain samples from different parts of the brain

was analyzed using High Performance Liquid Chromatography. There was an increased concentration of Lignocaine in some parts of the brain as shown in the **Fig: 17**. Thus the drug had bypassed the blood brain barrier. But the tissue distribution was lesser and the tissue concentration was less when compared to a similar volume of the drug delivered beneath the respiratory mucosa. During the procedure, a blood sample was collected before drug delivery. Three blood samples was then collected at intervals of 10, 20 and 30 minutes respectively following start of drug delivery. The samples were analyzed using High Performance Liquid Chromatography. There was no drug in the peripheral circulation. **Fig: 18** refers to the blood values of Lignocaine in the rabbit after the in vivo delivery of Lignocaine into the maxillary sinus cavity and onto the epithelial surface of the maxillary sinus mucosa using the device

[0107]The above mentioned methods and device are only illustrative of the principle of the present invention. Modifications and variations of the methods and devices including but not limited to, variations in size, materials, shape, assembly, function, use and mode of operation will be obvious to those of ordinary skill in the art from the foregoing detailed description. Such modifications and variations made without departing from the spirit and scope of the invention set forth herein are intended to come within the scope of the appended claims.

We claim

1. A drug delivery system for delivering drugs into the brain, by bypassing the blood brain barrier comprising

an implantable hollow device made of titanium or any other biocompatible material, intended for placement into the bone overlying the respiratory mucosa of the maxillary sinus and the nasal cavity.

a drug delivery assembly made of a biocompatible material intended for transferring therapeutic agents from an external drug reservoir into the central lumen of the hollow implantable device.

a drug infusion pump intended for providing continuous and controlled drug delivery from an external drug reservoir into the central lumen of the implantable hollow device

a therapeutic agent intended for delivery into the brain

an instrument kit for placing and removing the implantable device and the accompanying components.

2. The device of claim 1, wherein the device comprises

a body in the form of a hollow cylindrical tube with both the ends closed, wherein the apical end is rounded with a plurality of holes through the apical wall and the upper end comprises an external hex, the external surface of the upper part of the body further comprising a drug delivery inlet on one side below the external hex and a barrier ring below the drug delivery inlet.

a central lumen comprising parallel walls, defined by the internal wall of the body of the device, wherein the central lumen extends from the upper part of the body to the lower part of the body and further communicates with the exterior through an inlet at the upper part and through a plurality of holes that are sized to deliver drugs at the required rate through the apical wall.

threads on the external surface of the lower part of the device, wherein the threads are present at the cervical third and the middle third of the part of the body below the level of the ring.

an external hex at the top end of the device intended for holding and placement of the implant.

a tubular inlet comprising external threads, located below the level of the external hex and at the side of the upper part of the device, wherein the inlet is intended for the attachment of a drug delivery tubing.

a circular ring located below the level of the tubular inlet, comprising a convex and smooth upper surface and a flat and smooth undersurface facing the bone, wherein the ring is intended to prevent the accidental inward displacement of the implant into the maxillary sinus or the nasal cavity.

a drug delivery tubing wherein the mesial end with internal threads is intended for connection to the inlet on the implant and the distal end with a nozzle is intended for connection to an external drug reservoir, wherein the drug reservoir is further connected to a drug infusion pump.

3. The device of claim 2, wherein the device comprises

a body in the form of a hollow, tapered tube with both the ends closed, wherein the apical end is rounded with a plurality of holes through the apical wall and the upper end comprises an external hex, the external surface of the upper part of the body further comprising a drug delivery inlet on one side below the external hex and a barrier ring below the drug delivery inlet.

a central lumen comprising tapering walls, defined by the internal wall of the body of the device, wherein the central lumen extends from the upper part of the body to the lower part of the body and further communicates with the exterior through an inlet at the upper part and through a plurality of holes that are sized to deliver drugs at the required rate through the apical wall.

threads on the external surface of the lower part of the device, wherein the threads are present at the cervical third of the part of the body below the level of the ring.

an external hex at the top end of the device intended for holding and placement of the implant.

a tubular inlet comprising a smooth external surface and internal threads, located below the level of the external hex and at the side of the upper part of the device, wherein the inlet may be angulated at varying degrees to the external surface of the upper part of the body of the device and is intended for the attachment of a drug delivery tubing.

a circular ring with flat superior and inferior surfaces comprising a plurality of holes through the ring near its peripheral margin, into which mini screws may be threaded into for providing additional retention, wherein the ring is located below the level of the tubular

inlet and is intended for preventing the accidental inward displacement of the implant into the maxillary sinus or the nasal cavity.

a drug delivery tubing wherein the smooth mesial end is intended for connection to the inlet on the implant and the distal end with a nozzle is intended for connection to an external drug reservoir, wherein the drug reservoir is further connected to a drug infusion pump.

4. The device of claim 2, wherein the drug delivery inlet on the side of the implant comprises an opening with internal threads.

5. The drug delivery assembly in claim 1, wherein the drug delivery assembly comprises

an intra-implant part with a tapering body comprising a central lumen with tapering walls defined by the internal wall of the body, wherein the central lumen further opens to the exterior through a the plurality of holes that are sized to deliver drugs at the required rate through the apical wall, wherein the intra-implant part is intended for placement into the central lumen of the implant body.

an outer tubular part extending from the side of the intra implant part, comprising a central lumen with parallel walls defined by the internal wall of the external tubing, the central lumen of the external tubing being further continuous with the central lumen of the intra implant part, wherein the mesial part of the external tubing extending from the side of the intra implant part is intended for placement into the vertical slot of the drug delivery inlet on the implant.

a nozzle at the distal, free end of the external tubing placed above the level of the oral mucosa, intended for connection to an external drug reservoir and for ease of clinical access.

a disposable, temporary cap for closing the nozzle when not in use.

6. The device as claimed in claim 1wherein the device is in the form of a multiunit implant comprising

a body in the form of a hollow cylindrical tube with the upper end open and the apical end closed, wherein the apical end is rounded with a plurality of holes through the apical wall and the upper end comprises a drug delivery inlet, the external surface of the upper part of the body further comprising an external hex below the drug delivery inlet and a barrier ring below the external hex.

a central lumen comprising tapering walls, defined by the internal wall of the body of the device, wherein the central lumen communicates with the exterior through an inlet at the upper end and through a plurality of holes that are sized to deliver drugs at the required rate through the apical wall.

threads on the external surface of the lower part of the device, wherein the threads are present at the cervical third of the part of the body below the level of the ring.

an inlet located at the upper end of the device, comprising external threads at the cervical third and a vertical slot extending on one side of the body of the inlet from the tip to the middle third, wherein the inlet is intended for the placement of a drug delivery assembly into the central lumen of the implant.

an external hex located below the inlet at the upper part of the device, intended for holding and placement of the implant.

a circular ring located below the level of the tubular inlet, comprising a convex and smooth upper surface and a flat and smooth undersurface facing the bone, wherein the ring is

intended to prevent the accidental inward displacement of the implant into the maxillary sinus or the nasal cavity.

a drug delivery assembly, wherein the mesial part of the external tubing extending from the side of the intra-implant part is slid into the vertical slot of the inlet on the implant, when the tapered intra-implant part is placed into the central lumen of the implant body, further wherein the distal free end of the external tubing is intended for connection to an external drug reservoir attached to a drug infusion pump.

a cap comprising an external hex at its upper part and internal threads at its lower part wherein the cap is intended for closing the open inlet of the implant and to retain the drug delivery assembly within the implant.

7. The device as claimed in claim 1wherein the device is in the form of a multiunit implant comprising

a body in the form of a hollow cylindrical tube open at both the ends, wherein the open apical end comprises beveled and outwardly flaring internal walls with smooth and rounded margins and the open upper end comprises a drug delivery inlet, the external surface of the upper part of the body further comprising an external hex below the drug delivery inlet and a barrier ring below the external hex.

a central lumen comprising tapering walls defined by the internal wall of the body of the device and limited apically at the point where the internal wall flares outwards, wherein the central lumen is located below the level of the apical margin of the implant and communicates with the exterior through the open apex.

threads on the external surface of the lower part of the device, wherein the threads are present at the cervical third of the part of the body below the level of the ring.

an inlet located at the upper end of the device, comprising external threads at the cervical third and a vertical slot extending on one side of the body of the inlet from the tip to the middle third, wherein the inlet is intended for the placement of a drug delivery assembly into the central lumen of the implant.

an external hex located below the inlet at the upper part of the device, intended for holding and placement of the implant.

a circular ring located below the level of the tubular inlet, comprising a convex and smooth upper surface and a flat and smooth undersurface facing the bone, wherein the ring is intended to prevent the accidental inward displacement of the implant into the maxillary sinus or the nasal cavity.

a drug delivery assembly, wherein the mesial part of the external tubing extending from the side of the intra-implant part is slid into the vertical slot of the inlet on the implant, when the tapered intra-implant part is placed into the central lumen of the implant body, wherein the location of the tip of the intra-implant part is further defined by the apical limit of the central lumen and is therefore located below the apical margin of the implant, further wherein the distal free end of the external tubing is intended for connection to an external drug reservoir attached to a drug infusion pump.

a cap comprising an external hex at its upper part and internal threads at its lower part wherein the cap is intended for closing the open inlet of the implant and to retain the drug delivery assembly within the implant.

8. The device as claimed in claim 1wherein the device is in the form of a multiunit implant comprising

a body in the form of a hollow cylindrical tube with the upper end open and the apical end closed, wherein the apical end is rounded with a plurality of holes through the apical wall and the upper end comprises a drug delivery inlet with internal threads, the external surface of the upper part of the body further comprising an external hex below the drug delivery inlet and a barrier ring below the external hex.

a central lumen comprising tapering walls defined by the internal wall of the body of the device, wherein the central lumen communicates with the exterior through an inlet at the upper end and through a plurality of holes that are sized to deliver drugs at the required rate through the apical wall.

threads on the external surface of the lower part of the device, wherein the threads are present at the cervical third of the part of the body below the level of the ring.

an inlet located at the upper end of the device, comprising internal threads at the cervical third, wherein the inlet is intended for the placement of a drug delivery assembly into the central lumen of the implant.

an external hex located below the inlet at the upper part of the device, intended for holding and placement of the implant.

a circular ring located below the level of the tubular inlet, comprising a convex and smooth upper surface and a flat and smooth undersurface facing the bone, wherein the ring is intended to prevent the accidental inward displacement of the implant into the maxillary sinus or the nasal cavity.

a drug delivery assembly comprising a tapered intra-implant part with a central lumen that opens to the exterior through the plurality of holes that are sized to deliver drugs at the required rate through the apical wall, the intra implant part further comprising an external drug delivery tubing attached to its upper end and external threads at its upper part, wherein the intra-implant part comprising external threads is threaded into that part of the inlet of the implant that comprises internal threads, thereby adapting the external wall of the intra-implant part tightly to the internal walls of the implant except at the apical part, wherein a space exists at the apical part defined by outer wall of the apical part of the intra-implant part and the internal wall of the apical part of the implant, into which the drug is initially delivered for further transfer to the exterior through the plurality of holes through the apical wall of the implant, further wherein the distal end of the external tubing is intended for connection to an external drug reservoir attached to a drug infusion pump.

9. The device as claimed in claim 1wherein the device is in the form of a dental implant comprising

a body in the form of a hollow cylindrical tube with an open upper end and a closed lower end, wherein the apical end is rounded with a plurality of holes through the apical wall and the upper end is open and comprises internal threads at the cervical third, the body further comprising threads on the external surface of the body at the cervical third and middle third.

a central lumen within the body of the device defined by the surrounding internal wall which communicates to the exterior through a plurality of holes that are sized to deliver drugs at the required rate through the apical wall.

an internal involute spline on the internal wall intended for assisting in holding and placement of the implant.

an abutment with a hollow body comprising a smooth intra-oral part, an intra implant part with an external involute spline and a barrier ring on the external surface of the body between the intra-oral part and the intra implant, the body further comprising a central lumen which extends from the intra oral part to the intra implant part of the body and is defined by the internal wall of the body of the abutment, further wherein the central lumen communicates to the exterior through the drug delivery tubing at the coronal end and a plurality of holes that are sized to deliver drugs at the required rate through the apical wall.
a cap comprising an external hex with a central hole at its upper part and external threads at its lower part, intended for placement into the open end of the implant comprising internal threads, wherein the cap retains the abutment within the implant.

10. The device as claimed in claim 1wherein the device is in the form of a mini plate with a central reservoir dial comprising,

a hollow cylindrical reservoir dial with a closed lower end comprising a plurality of holes that are sized to deliver drugs at the required rate through the apical wall, forming the base and an open upper end comprising threads located internally at the cervical third, with limbs extending on the sides of the dial from the middle part, further wherein the upper part of the body of the reservoir dial, above the level of the limbs is perpendicular to the base.
a cap made of a resilient, biocompatible material that self-seals whenever penetrated by a needle, comprising a single row of a plurality of holes that are spaced uniformly in a circular arrangement along the outer margin of the superior surface of the upper part and are intended for assisting in holding and placement, and a lower part with threads located externally intended for placement into the open part of the reservoir dial.

limbs extending from the reservoir dial wherein the limbs may be straight or L shaped comprising screw holes intended for placement of screws for retention.

11. The device as claimed in claim 10 wherein the device is in the form of a mini plate with a central reservoir dial comprising,

a hollow cylindrical reservoir dial with a closed lower end comprising a plurality of holes that are sized to deliver drugs at the required rate through the apical wall, forming the base and an open upper end comprising threads located externally at the cervical third, with limbs extending on the sides of the dial from the middle part, further wherein the upper part of the body of the reservoir dial, above the level of the limbs is angulated with respect to its base.

a cap made of a resilient, biocompatible material that self-seals whenever penetrated by a needle, comprising an upper part with a central external hex intended for assisting in holding and placement, and a lower part with threads located internally intended for placement onto the open part of the reservoir dial.

limbs extending from the reservoir dial wherein the limbs may be straight or L shaped comprising screw holes intended for placement of screws for retention.

12. A method for delivering drugs under the respiratory mucosa using the drug delivery system, for use in delivering a drug into the brain by bypassing the blood brain barrier, without causing any increase of the drug in the peripheral circulation, comprising the following steps

elevating a full thickness mucoperiosteal flap over the bone overlying the respiratory mucosa in the maxillary sinus or nasal cavity region, preferably from the buccal mucosal or the palatal mucosal region.

using a bone trephine drill of appropriate diameter and length to circumscribe a bone window.

using the slowly rotating trephine drill to pry away the overlying bone without tearing the underlying respiratory mucosa or using a piezo-instrument to remove the circumscribed bone without tearing the underlying respiratory mucosa.

releasing and elevating the intact respiratory mucosal lining from the bony margins and from the surrounding walls using a soft tissue elevator of appropriate size and shape.

placing the drug delivery device of required diameter and length into the surgical site using the placement instruments, wherein the apical end of the implant comprising a plurality of holes is placed beneath and in contact with connective tissue side of the respiratory mucosa.

connecting the mesial end of the drug delivery tubing to the inlet on the implant and placing the distal free end of the tubing with the nozzle at a level overlying the oral mucosa in the buccal sulcus, at the buccal gingival sulcus or the palatal gingival sulcus.

repositioning of the surgical flap and placement of sutures.

allowing the surgical site to heal and the implanted device to osseointegrate adequately.

after adequate healing, whenever drug delivery to the brain is required, the disposable cap of the nozzle at the free end of the tubing is removed and the nozzle is connected to an external drug reservoir attached to an infusion pump.

a drug that can be given in small quantities without causing any systemic or local complications is delivered in a continuous and controlled manner using the external drug

infusion pump at a rate that does not cause backflow of the drug at the implanted site or cause leakage and overflow across the overlying mucosal lining.

13. The method in claim 12, wherein drug is delivered into the brain by bypassing the blood brain barrier without causing any increase in the peripheral circulation through the following routes wherein

the drug that is absorbed in the connective tissue of the overlying respiratory mucosa , may be transferred through the neural route, vascular route ,by the counter-current mechanism at the cavernous sinus or by the lymphatic route ,into the brain by bypassing the blood brain barrier.

the drug that is absorbed in the connective tissue of the overlying respiratory mucosa, may also be engineered for uptake into the goblet cell, for further secretion along with mucus by the goblet cell in the maxillary sinus lining epithelium if the clinical situation demands more retention time on the respiratory mucosal epithelial surface, wherein the drug may be further transported by mucociliary action over a larger area of respiratory mucosa for further absorption in the maxillary sinus and nasal cavity.

14. The method in claim 12, wherein the device is placed into the maxillary sinus with its apical tip above the level of the respiratory lining mucosa for use in delivering a drug into the brain by bypassing the blood brain barrier, without causing any increase of the drug in the peripheral circulation, comprising the following steps

elevating a full thickness mucoperiosteal flap over the bone overlying the respiratory mucosa in the maxillary sinus or nasal cavity region, preferably from the buccal mucosal or the palatal mucosal region.

using a bone trephine drill of appropriate diameter and length to circumscribe a bone window.

removing the circumscribed bone with the trephine drill along with the underlying respiratory mucosa attached to the bone.

placing the implant of required diameter and length into the surgical site using the placement instruments, wherein the apical end of the implant comprising a plurality of holes is placed into the maxillary sinus and is located above the level of the epithelial layer of the respiratory lining mucosa.

connecting the mesial end of the drug delivery tubing to the implant and placing the distal free of the tubing with the nozzle at a level overlying the oral mucosa in the buccal sulcus, at the buccal gingival sulcus or the palatal gingival sulcus.

repositioning of the surgical flap and placement of sutures.

allowing the surgical site to heal and the implanted device to osseointegrate adequately.

after adequate healing, whenever drug delivery to the brain is required, the disposable cap of the nozzle at the free end of the tubing is removed and the nozzle is connected to an external drug reservoir attached to a drug infusion pump.

a drug that is in the form of an inhalable formulation or that can be given in larger volumes without systemic or local complications is delivered in a continuous and controlled manner using the external drug infusion pump at a rate that does not cause backflow of the drug at the implanted site or cause leakage and overflow across the overlying mucosal lining.

15. The method in claim 14, wherein drug is delivered into the brain by bypassing the blood brain barrier without causing any increase in the peripheral circulation through the following routes wherein

as the normal maxillary sinus is emptied of air during the inspiratory phase of the respiratory cycle, the drug which is locally delivered into the maxillary sinus is inhaled from the maxillary sinus during normal inspiration to reach the nasal respiratory mucosa and the olfactory mucosa, from where the drug is further absorbed into the connective tissue for delivery into the brain through the neural, vascular or lymphatic route by bypassing the blood brain barrier.

as the normal maxillary sinus lining epithelial cells move the mucus through the ostium into the middle meatus and onto the nasal respiratory mucosa, the drug which is locally delivered into the maxillary sinus is moved across the epithelial surface of the respiratory lining mucosa through the ostium into the middle meatus and onto the nasal respiratory mucosa resulting in increased retention time on the respiratory mucosal surface leading to absorption of increased quantity of the drug into the underlying connective tissue and further delivery into the brain through the neural, vascular or lymphatic route by bypassing the blood brain barrier .

16. The drug infusion pump in claim 1, wherein the unit comprises

an external drug reservoir holding the therapeutic agent intended for delivery into the brain

an electronically controlled external drug infusion pump capable of delivering drugs from the reservoir at a desired rate in a controlled and continuous manner, intended to deliver

the therapeutic agent without causing either backflow of drug at the surgical site wherein the device is implanted or leakage and overflow of the drug across the overlying mucosa.

17. The drug infusion pump in claim 1, wherein an abutment intended for placement into a drug delivery device in the form of a dental implant is used for providing controlled and continuous drug delivery at predetermined rates and comprises of any one of the following embodiments

A hollow abutment comprising a drug reservoir located within the central lumen at the lower part of the body and an electronically or osmotically driven drug infusion pump located within the central lumen at the upper part of the body, intended for delivering the drug in a continuous and controlled manner from the drug reservoir to the exterior, through a plurality of holes that are sized to deliver drugs at the required rate through the apical wall.

A hollow abutment intended for use as a drug reservoir comprising a central lumen extending from the upper part of the body to its lower part defined by the internal wall of the body of the abutment, the lower part of the body further comprising a plurality of holes that are sized to deliver drugs in a continuous manner at the required rate through the apical wall.

A hollow abutment with a central lumen that opens to the exterior, at the upper end through an inlet comprising internal threads and at the apical end through a plurality of holes that are sized to deliver drugs at the required rate through the apical wall ,wherein the inlet at the upper end is intended for connecting a drug delivery tubing that is further connected to an external reservoir attached to an external drug infusion pump , and the lower part is intended for placement into the hollow drug delivery device in the form of a dental implant

comprising a plurality of holes that are sized to deliver drugs at the required rate through the apical wall and also correspond to the position of holes in the apical wall of the abutment.

18. The therapeutic agent in claim 1, wherein the drug comprises drug molecules that may

be sized to aid drug delivery into the brain.

have affinity to specific receptors in the brain wherein the drug localizes at targeted sites.

19. The instrument kit in claim 1, wherein the kit comprises

a hand held ratchet comprising a head intended for adaption to the external hex on the implant and a handle which may be either straight or angulated.

a motor driven hex driver comprising a head intended for adaption to the external hex on the implant and a straight shank ,wherein the free end of the shank is intended for placement into a rotary handpiece.

a spanner comprising a head intended for adaption to the external hex on the implant and a handle which may be either straight or angulated.

a driver comprising a plurality of projections at the free margins, wherein the projections are intended for placement into the holes of the retention cap.

a cap remover comprising a pair of claws with handles intended for holding the margins of the retention cap, a vertically moveable shank and a rotating finger rest on the top end of the shank .

20. A method of drug delivery, wherein a natural tooth with its root tip in contact with the respiratory mucosa is used for delivering drugs into the brain by comprising the following steps.

Performing an access cavity at the crown part of the tooth

Extirpating the pulp and performing biomechanical preparation of the tooth and enlarging the pulp canals to appropriate size till the apex.

Preparing a vertical slot of the appropriate dimensions on the buccal or palatal wall of the crown of the tooth.

Making an impression of the tooth.

Designing a crown with an inlet on the buccal or palatal wall, wherein the inlet comprises a cylindrical tube open at both the ends, the inlet comprising internal threads at the intraoral end and a smooth intra pulpal end which may be either straight or curved apically.

Placing and positioning the crown on the tooth with the cylindrical inlet placed into the vertical slot present on the tooth, wherein the lower margin of the inlet is located at the base of the vertical slot on the buccal or palatal wall so that the pulp cavity can be accessed from the outside through the inlet.

Closing the inlet with a disposable screw when not in use.

Using a drug delivery tubing, to connect the inlet in the crown to an external drug reservoir attached to a drug infusion pump, for controlled and continuous drug delivery into the pulp cavity of the tooth, whereby the drug is further transferred to the connective tissue side of the overlying respiratory mucosa through the apical foramina.

AMENDED CLAIMS
received by the International Bureau on 05 December 2016 (05.12.2016)

1. A drug delivery system for delivering drugs into the brain, by bypassing the blood brain barrier comprising :

an implantable hollow device made of titanium or any other biocompatible material comprising a coronal part and an apical part, the said apical part comprising a closed apical end and a plurality of holes through the apical wall (101; 201; 401; 1102; 1202), wherein an inlet at the coronal part (104; 205; 405) opens into a central lumen defined by the internal wall of the body of the device (108; 206), the said central lumen further opens to the exterior through the said plurality of holes at the apical part (101; 201; 401; 1102; 1202), further wherein when the device is implanted into the bone overlying the connective tissue of the respiratory mucosa of the maxillary sinus and the nasal cavity, the apical part of the device comprising the plurality of holes is in contact (1102) with the connective tissue of the respiratory mucosa or is adjacent (1202) to the respiratory mucosa ;

a drug delivery assembly made of a biocompatible material comprising an intra-implant part (206; 306; 406; 605) and an external tubular part (207; 307; 407; 611), wherein the intra-implant part is placed into the central lumen of the said device through the inlet and retained with a cap (209; 309; 409; 609); further wherein the distal end of the external tubular part is connected to a drug infusion pump to transfer therapeutic agents from an external drug reservoir into the central lumen of the said device;

a drug infusion pump (1304) comprising a pump and an external drug reservoir, wherein the external drug reservoir is connected to the distal end of the said drug delivery assembly, to provide continuous and controlled drug delivery to the respiratory mucosa through the plurality of holes at the apical part of the said device.

a therapeutic agent (1103;1203) to be delivered into the brain from the connective tissue of the respiratory mucosa; and

an instrument kit (501;503;505;507;509;511;801;806;807;812;814) to place and remove the said device and the accompanying components.

2. The device of claim 1, wherein the device comprises

a body in the form of a hollow cylindrical tube(102;1106;1206) with both the ends closed, wherein the apical end is rounded with a plurality of holes(101;1102;1202) through the apical wall and the upper end comprises an external hex(107;5X;1110;1210;1302), the external surface of the upper part of the body further comprising a drug delivery inlet (104) on one side below the external hex and a barrier ring(103;1107;1207;1301) below the drug delivery inlet.

a central lumen comprising parallel walls (108), defined by the internal wall of the body of the device, wherein the central lumen extends from the upper part of the body to the lower part of the body and further communicates with the exterior through an inlet (104) at the upper part and through a plurality of holes (101; 1102; 1202) that are sized to deliver drugs at the required rate through the apical wall.

threads (102; 1106; 1206) on the external surface of the lower part of the device, wherein the threads are present at the cervical third and the middle third of the part of the body below the level of the ring.

an external hex(107;1110;1210;1302;5X) at the top end of the device for holding and placement of the implant.

a tubular inlet (104)comprising external threads(109), located below the level of the external hex and at the side of the upper part of the device, wherein the inlet is for the attachment of a drug delivery tubing(105;1108;1208;1303).

a circular ring(103;1107;1207;1302) located below the level of the tubular inlet, comprising a convex and smooth upper surface and a flat and smooth undersurface facing the bone, wherein the ring prevents the accidental inward displacement of the implant into the maxillary sinus or the nasal cavity.

a drug delivery tubing (105;1108;1208;1303) wherein the mesial end with internal threads is connected to the inlet (104) on the implant and the distal end with a nozzle (106;1109;1209) is connected to an external drug reservoir, wherein the drug reservoir is further connected to a drug infusion pump.

3. The device of claim 2, wherein the device comprises

a body in the form of a hollow, tapered tube (102) with both the ends closed, wherein the apical end is rounded with a plurality of holes (101) through the apical wall and the upper end comprises an external hex (107), the external surface of the upper part of the body further comprising a drug delivery inlet (104) on one side below the external hex and a barrier ring (103) below the drug delivery inlet.

a central lumen comprising tapering walls (108), defined by the internal wall of the body of the device, wherein the central lumen extends from the upper part of the body to the lower part of the body and further communicates with the exterior through an inlet (104) at the upper part and through a plurality of holes (101) that are sized to deliver drugs at the required rate through the apical wall.

threads (102)on the external surface of the lower part of the device, wherein the threads are present at the cervical third of the part of the body below the level of the ring.

an external hex (107)at the top end of the device for holding and placement of the implant.

a tubular inlet (104) comprising a smooth external surface and internal surface, located below the level of the external hex and at the side of the upper part of the device,

wherein the inlet may be angulated at varying degrees to the external surface of the upper part of the body of the device and is for the attachment of a drug delivery tubing (105).

a circular ring (103) with flat superior and inferior surfaces comprising a plurality of holes through the ring near its peripheral margin, into which mini screws may be threaded into for providing additional retention, wherein the ring is located below the level of the tubular inlet and prevents the accidental inward displacement of the implant into the maxillary sinus or the nasal cavity.

a drug delivery tubing (105;1108;1208;1303)wherein the smooth mesial end is connected to the inlet on the implant and the distal end with a nozzle is connected to an external drug reservoir, wherein the drug reservoir is further connected to a drug infusion pump.

4. The device of claim 2, wherein the drug delivery inlet (104) on the side of the implant comprises an opening with internal threads.

5. The drug delivery assembly in claim 1, wherein the drug delivery assembly comprises

an intra-implant part (206) with a tapering body comprising a central lumen with tapering walls defined by the internal wall of the body, wherein the central lumen further opens to the exterior through a plurality of holes that are sized to deliver drugs at the required rate through the apical wall (210), wherein the intra-implant part is placed into the central lumen of the implant body (202).

an outer tubular part (207) extending from the side of the intra implant part (206), comprising a central lumen with parallel walls defined by the internal wall of the external tubing (207), the central lumen of the external tubing (207) being further continuous with the central lumen of the intra implant part (206), wherein the mesial

part of the external tubing extending from the side of the intra implant part is placed into the vertical slot of the drug delivery inlet (205) on the implant.

a nozzle (208) at the distal, free end of the external tubing placed above the level of the oral mucosa, for connection to an external drug reservoir and for ease of clinical access.

a disposable, temporary cap for closing the nozzle (208) when not in use.

6. The device as claimed in claim 1wherein the device is in the form of a multiunit implant comprising

a body in the form of a hollow cylindrical tube (202) with the upper end open (205) and the apical end closed (201), wherein the apical end is rounded with a plurality of holes (201) through the apical wall and the upper end comprises a drug delivery inlet (205), the external surface of the upper part of the body further comprising an external hex (204) below the drug delivery inlet and a barrier ring (203) below the external hex.

a central lumen (206) comprising tapering walls, defined by the internal wall of the body of the device, wherein the central lumen communicates with the exterior through an inlet (205) at the upper end and through a plurality of holes (201) that are sized to deliver drugs at the required rate through the apical wall.

threads on the external surface (202) of the lower part of the device, wherein the threads are present at the cervical third of the part of the body below the level of the ring.

an inlet (205) located at the upper end of the device, comprising external threads at the cervical third and a vertical slot extending on one side of the body of the inlet from the tip to the middle third, wherein the inlet is for the placement of a drug delivery assembly (206) into the central lumen of the implant.

an external hex (204) located below the inlet at the upper part of the device, for holding and placement of the implant.

a circular ring (203) located below the level of the tubular inlet, comprising a convex and smooth upper surface and a flat and smooth undersurface facing the bone, wherein the ring prevents the accidental inward displacement of the implant into the maxillary sinus or the nasal cavity.

a drug delivery assembly (206), wherein the mesial part of the external tubing (207) extending from the side of the intra-implant part is slid into the vertical slot of the inlet (205) on the implant, when the tapered intra-implant part (206) is placed into the central lumen of the implant body, further wherein the distal free end (208) of the external tubing is for connection to an external drug reservoir attached to a drug infusion pump.

a cap (209) comprising an external hex at its upper part and internal threads at its lower part wherein the cap is for closing the open inlet of the implant and to retain the drug delivery assembly within the implant.

7. The device as claimed in claim 1wherein the device is in the form of a multiunit implant comprising

a body in the form of a hollow cylindrical tube open at both the ends (302), wherein the open apical end (301) comprises beveled and outwardly flaring internal walls with smooth and rounded margins and the open upper end comprises a drug delivery inlet (305), the external surface of the upper part of the body further comprising an external hex (304) below the drug delivery inlet and a barrier ring (303) below the external hex.

a central lumen (306) comprising tapering walls defined by the internal wall of the body of the device and limited apically at the point where the internal wall flares outwards, wherein the central lumen is located below the level of the apical margin (301) of the implant and communicates with the exterior through the open apex.

threads (302) on the external surface of the lower part of the device, wherein the threads are present at the cervical third of the part of the body below the level of the ring.

an inlet (305) located at the upper end of the device, comprising external threads at the cervical third and a vertical slot extending on one side of the body of the inlet from the tip to the middle third, wherein the inlet is for the placement of a drug delivery assembly into the central lumen of the implant.

an external hex (304) located below the inlet at the upper part of the device, for holding and placement of the implant.

a circular ring(303) located below the level of the tubular inlet, comprising a convex and smooth upper surface and a flat and smooth undersurface facing the bone, wherein the ring prevents the accidental inward displacement of the implant into the maxillary sinus or the nasal cavity.

a drug delivery assembly (306), wherein the mesial part of the external tubing (307) extending from the side of the intra-implant part is slid into the vertical slot of the inlet on the implant, when the tapered intra-implant part (310) is placed into the central lumen of the implant body, wherein the location of the tip of the intra-implant part is further defined by the apical limit of the central lumen and is therefore located below the apical margin of the implant (301), further wherein the distal free end (308) of the external tubing is for connection to an external drug reservoir attached to a drug infusion pump.

a cap (309) comprising an external hex at its upper part and internal threads at its lower part wherein the cap is for closing the open inlet of the implant and to retain the drug delivery assembly within the implant.

8. The device as claimed in claim 1wherein the device is in the form of a multiunit implant comprising

a body in the form of a hollow cylindrical tube (402) with the upper end open (405) and the apical end closed, wherein the apical end is rounded with a plurality of holes through

the apical wall (401) and the upper end comprises a drug delivery inlet (405) with internal threads, the external surface of the upper part of the body further comprising an external hex (404) below the drug delivery inlet and a barrier ring (403) below the external hex.

a central lumen comprising tapering walls defined by the internal wall of the body of the device, wherein the central lumen communicates with the exterior through an inlet at the upper end (405) and through a plurality of holes that are sized to deliver drugs at the required rate through the apical wall (401).

threads (402) on the external surface of the lower part of the device, wherein the threads are present at the cervical third of the part of the body below the level of the ring.

an inlet (405) located at the upper end of the device, comprising internal threads at the cervical third, wherein the inlet is for the placement of a drug delivery assembly into the central lumen of the implant.

an external hex (404) located below the inlet at the upper part of the device, for holding and placement of the implant.

a circular ring (403) located below the level of the tubular inlet, comprising a convex and smooth upper surface and a flat and smooth undersurface facing the bone, wherein the ring prevents the accidental inward displacement of the implant into the maxillary sinus or the nasal cavity.

a drug delivery assembly comprising a tapered intra-implant part (406) with a central lumen that opens to the exterior through the plurality of holes that are sized to deliver drugs at the required rate through the apical wall(410), the intra implant part further comprising an external drug delivery tubing (407) attached to its upper end and external threads (411) at its upper part, wherein the intra-implant part comprising external threads is threaded into that part of the inlet of the implant that comprises internal

threads, thereby adapting the external wall of the intra-implant part tightly to the internal walls of the implant except at the apical part, wherein a space exists at the apical part defined by outer wall of the apical part of the intra-implant part and the internal wall of the apical part of the implant, into which the drug is initially delivered for further transfer to the exterior through the plurality of holes (401) through the apical wall of the implant, further wherein the distal end of the external tubing (408) is for connection to an external drug reservoir attached to a drug infusion pump.

9. The device as claimed in claim 1wherein the device is in the form of a dental implant comprising

a body in the form of a hollow cylindrical tube (602) with an open upper end (603) and a closed lower end (601), wherein the apical end is rounded with a plurality of holes through the apical wall (601) and the upper end (603) is open and comprises internal threads at the cervical third (617), the body further comprising threads (602) on the external surface of the body at the cervical third and middle third.

a central lumen (619) within the body of the device defined by the surrounding internal wall which communicates to the exterior through a plurality of holes that are sized to deliver drugs at the required rate through the apical wall (601).

an internal involute spline (618) on the internal wall for assisting in holding and placement of the implant.

an abutment (605) with a hollow body comprising a smooth intra-oral part (607), an intra implant part with an external involute spline (605) and a barrier ring (606) on the external surface of the body between the intra-oral part and the intra implant, the body further comprising a central lumen which extends from the intra oral part to the intra implant part of the body and is defined by the internal wall of the body of the abutment, further wherein the central lumen communicates to the exterior through the drug

delivery tubing (611) at the coronal end and a plurality of holes that are sized to deliver drugs at the required rate through the apical wall (601).

a cap (609) comprising an external hex (610) with a central hole at its upper part and external threads (608) at its lower part, for placement into the open end of the implant comprising internal threads (617), wherein the cap retains the abutment within the implant.

10. The device as claimed in claim 1wherein the device is in the form of a mini plate with a central reservoir dial comprising,

a hollow cylindrical reservoir dial (902) with a closed lower end comprising a plurality of holes that are sized to deliver drugs at the required rate through the apical wall, forming the base (903) and an open upper end comprising threads located internally at the cervical third, with limbs (901) extending on the sides of the dial from the middle part, further wherein the upper part of the body of the reservoir dial, above the level of the limbs is perpendicular to the base.

a cap (906) made of a resilient, biocompatible material that self-seals whenever penetrated by a needle, comprising a single row of a plurality of holes (905) that are spaced uniformly in a circular arrangement adjacent to the outer margin of the superior surface of the upper part and for assisting in holding and placement, and a lower part with threads (907) located externally for placement into the open part of the reservoir dial (902) with internal threads.

limbs extending from the reservoir dial wherein the limbs may be straight (901) or L shaped (904) comprising screw holes for placement of screws for retention.

11. The device as claimed in claim 10 wherein the device is in the form of a mini plate with a central reservoir dial comprising,

a hollow cylindrical reservoir dial (1002) with a closed lower end (1004) comprising a plurality of holes that are sized to deliver drugs at the required rate through the apical wall, forming the base and an open upper end comprising threads located externally at the cervical third, with limbs (1001) extending on the sides of the dial from the middle part, further wherein the upper part of the body of the reservoir dial, above the level of the limbs is angulated (1002) with respect to its base.

a cap (1003) made of a resilient, biocompatible material that self-seals whenever penetrated by a needle, comprising an upper part with an external hex for assisting in holding and placement, and a lower part with threads located internally for placement onto the open part of the reservoir dial with external threads.

limbs extending from the reservoir dial wherein the limbs may be straight (1001) or L shaped (1005) comprising screw holes for placement of screws for retention.

12. A method for delivering drugs under the respiratory mucosa (1101) using the drug delivery system, for use in delivering a drug into the brain by bypassing the blood brain barrier, without causing any increase of the drug in the peripheral circulation, comprising the following steps

elevating a full thickness mucoperiosteal flap over the bone overlying the respiratory mucosa in the maxillary sinus or nasal cavity region, preferably from the buccal mucosal or the palatal mucosal region.

using a bone trephine drill of appropriate diameter and length to circumscribe a bone window.

using the slowly rotating trephine drill to pry away the overlying bone without tearing the underlying respiratory mucosa or using a piezo-instrument to remove the circumscribed bone without tearing the underlying respiratory mucosa.

releasing and elevating the intact respiratory mucosal lining from the bony margins and from the surrounding walls using a soft tissue elevator of appropriate size and shape.

placing the drug delivery device (1106) of required diameter and length into the surgical site (502;504;506;508;510;512) using the placement instruments, wherein the apical end of the implant comprising a plurality of holes (1102) is placed beneath and in contact with connective tissue side of the respiratory mucosa (1101).

connecting the mesial end of the drug delivery tubing (1108) to the inlet on the implant and placing the distal free end of the tubing with the nozzle (1109) at a level overlying the oral mucosa in the buccal sulcus, at the buccal gingival sulcus or the palatal gingival sulcus.

repositioning of the surgical flap and placement of sutures.

allowing the surgical site to heal and the implanted device to osseointegrate adequately.

after adequate healing, whenever drug delivery to the brain is required, the disposable cap of the nozzle (1109) at the free end of the tubing is removed and the nozzle (1109) is connected to an external drug reservoir attached to an infusion pump (1304).

a drug that can be given in small quantities without causing any systemic or local complications is delivered in a continuous and controlled manner using the external drug infusion pump at a rate that does not cause backflow of the drug at the implanted site or cause leakage and overflow across the overlying mucosal lining.

13. The method in claim 12, wherein drug is delivered into the brain by bypassing the blood brain barrier without causing any increase in the peripheral circulation through the following routes wherein

the drug that is absorbed in the connective tissue of the overlying respiratory mucosa , may be transferred through the neural route, vascular route ,by the counter-current mechanism at the cavernous sinus or by the lymphatic route ,into the brain by bypassing the blood brain barrier.

the drug that is absorbed in the connective tissue of the overlying respiratory mucosa, may also be engineered for uptake into the goblet cell, for further secretion along with mucus by the goblet cell in the maxillary sinus lining epithelium if the clinical situation demands more retention time on the respiratory mucosal epithelial surface, wherein the drug may be further transported by mucociliary action over a larger area of respiratory mucosa for further absorption in the maxillary sinus and nasal cavity.

14. The method in claim 12, wherein the device is placed into the maxillary sinus with its apical tip (1202) above the level of the respiratory lining mucosa (1201) for use in delivering a drug into the brain by bypassing the blood brain barrier, without causing any increase of the drug in the peripheral circulation, comprising the following steps

elevating a full thickness mucoperiosteal flap over the bone overlying the respiratory mucosa in the maxillary sinus or nasal cavity region, preferably from the buccal mucosal or the palatal mucosal region.

using a bone trephine drill of appropriate diameter and length to circumscribe a bone window.

removing the circumscribed bone with the trephine drill along with the underlying respiratory mucosa attached to the bone.

placing the implant (1206) of required diameter and length into the surgical site using the placement instruments(502,504,506,508,510,512), wherein the apical end of the

implant comprising a plurality of holes is placed into the maxillary sinus and is located above the level of the epithelial layer of the respiratory lining mucosa.

connecting the mesial end of the drug delivery tubing(1208) to the implant and placing the distal free of the tubing with the nozzle(1209) at a level overlying the oral mucosa in the buccal sulcus, at the buccal gingival sulcus or the palatal gingival sulcus.

repositioning of the surgical flap and placement of sutures.

allowing the surgical site to heal and the implanted device to osseointegrate adequately.

after adequate healing, whenever drug delivery to the brain is required, the disposable cap of the nozzle (1209) at the free end of the tubing is removed and the nozzle (1209) is connected to an external drug reservoir attached to a drug infusion pump (1304).

a drug that is in the form of an inhalable formulation or that can be given in larger volumes without systemic or local complications is delivered in a continuous and controlled manner using the external drug infusion pump at a rate that does not cause backflow of the drug at the implanted site or cause leakage and overflow across the overlying mucosal lining.

15. The method in claim 14, wherein drug is delivered into the brain by bypassing the blood brain barrier without causing any increase in the peripheral circulation through the following routes wherein

as the normal maxillary sinus is emptied of air during the inspiratory phase of the respiratory cycle, the drug which is locally delivered into the maxillary sinus is inhaled from the maxillary sinus during normal inspiration to reach the nasal respiratory mucosa and the olfactory mucosa, from where the drug is further absorbed into the

connective tissue for delivery into the brain through the neural, vascular or lymphatic route by bypassing the blood brain barrier.

as the normal maxillary sinus lining epithelial cells move the mucus through the ostium into the middle meatus and onto the nasal respiratory mucosa, the drug which is locally delivered into the maxillary sinus is moved across the epithelial surface of the respiratory lining mucosa through the ostium into the middle meatus and onto the nasal respiratory mucosa resulting in increased retention time on the respiratory mucosal surface leading to absorption of increased quantity of the drug into the underlying connective tissue and further delivery into the brain through the neural, vascular or lymphatic route by bypassing the blood brain barrier .

16. The drug infusion pump in claim 1, wherein the unit comprises

an external drug reservoir holding the therapeutic agent for delivery into the brain

an electronically controlled external drug infusion pump capable of delivering drugs from the reservoir at a desired rate in a controlled and continuous manner, wherein the said pump delivers the therapeutic agent without causing either backflow of drug at the surgical site where the device is implanted, or leakage and overflow of the drug across the overlying mucosa.

17. The drug infusion pump in claim 1, wherein an abutment placed into a drug delivery device in the form of a dental implant provides controlled and continuous drug delivery at predetermined rates and comprises of any of the following embodiments

A hollow abutment comprising a drug reservoir (709) located within the central lumen at the lower part of the body and an electronically (710) or osmotically (707) driven drug infusion pump located within the central lumen at the upper part (702) of the body,

for delivering the drug in a continuous and controlled manner from the drug reservoir to the exterior, through a plurality of holes (705) that are sized to deliver drugs at the required rate through the apical wall.

A hollow abutment as a drug reservoir (709) comprising a central lumen extending from the upper part (702) of the body to its lower part defined by the internal wall of the body of the abutment, the lower part of the body further comprising a plurality of holes (705) that are sized to deliver drugs in a continuous manner at the required rate through the apical wall.

A hollow abutment with a central lumen that opens to the exterior, at the upper end through an inlet (701) comprising internal threads and at the apical end through a plurality of holes (705) that are sized to deliver drugs at the required rate through the apical wall ,wherein the inlet at the upper end is connected to a drug delivery tubing that is further connected to an external reservoir attached to an external drug infusion pump , and the lower part is placed into the hollow drug delivery device in the form of a dental implant (619) comprising a plurality of holes (601) that are sized to deliver drugs at the required rate through the apical wall and also correspond to the position of holes (705) in the apical wall of the abutment.

18. The therapeutic agent in claim 1, wherein the drug comprises drug molecules that may

be sized to aid drug delivery into the brain.

have affinity to specific receptors in the brain wherein the drug localizes at targeted sites.

19. The instrument kit in claim 1, wherein the kit comprises

a hand held ratchet comprising a head (505;507) for holding the external hex (5X) on the implant and a handle which may be either straight (506) or angulated (508).

a motor driven hex driver comprising a head (511) for holding the external hex (5X) on the implant and a straight shank (512) ,wherein the free end of the shank is connected to a rotary handpiece.

a hand driven hex driver comprising a head (509) for holding the external hex (5X) on the implant and a rotating finger rest (510) at the free end of the shank.

a spanner comprising a head (501;503) for holding the external hex (5X) on the implant and a handle which may be either straight (502) or angulated (504).

a driver (811) comprising a plurality of projections (810) at the free margins, wherein the projections are for placement into the holes of the retention cap(809).

a cap remover(815) comprising a pair of claws(813) with handles(814) for holding the margins of the retention cap(809), a vertically moveable shank(815) and a rotating finger rest(816) on the top end of the shank .

20. A method of drug delivery, wherein a natural tooth (1408) with its root tip (1402) in contact with the respiratory mucosa (1401) is used for delivering drugs into the brain by comprising the following steps.

Preparing an access cavity at the crown part of the tooth

Extirpating the pulp and performing biomechanical preparation of the tooth and enlarging the pulp canals (1403) to appropriate size till the apex (1402).

Crown preparation with a vertical slot (1407) of the appropriate dimensions on the buccal or palatal wall of the crown of the tooth.

Making an impression of the tooth.

Making a crown (1410) with an inlet (1409) on the buccal or palatal wall, wherein the inlet comprises a cylindrical tube open at both the ends, the inlet comprising internal threads at the intraoral end and a smooth intra pulpal end which may be either straight or curved apically.

Placing and positioning the crown on the tooth, wherein when the part of the crown comprising the cylindrical inlet (1409) is placed into the vertical slot (1407) present on the tooth, the lower margin of the inlet is located at the base of the vertical slot on the buccal or palatal wall, such that the pulp cavity (1406) can be accessed from the outside through the inlet (1409).

Closing the inlet with a disposable screw when not in use.

Using a drug delivery tubing, to connect the inlet in the crown to an external drug reservoir attached to a drug infusion pump, for controlled and continuous drug delivery into the pulp cavity (1406) of the tooth, whereby the drug is further transferred to the connective tissue side of the overlying respiratory mucosa (1401) through the apical foramina (1402).

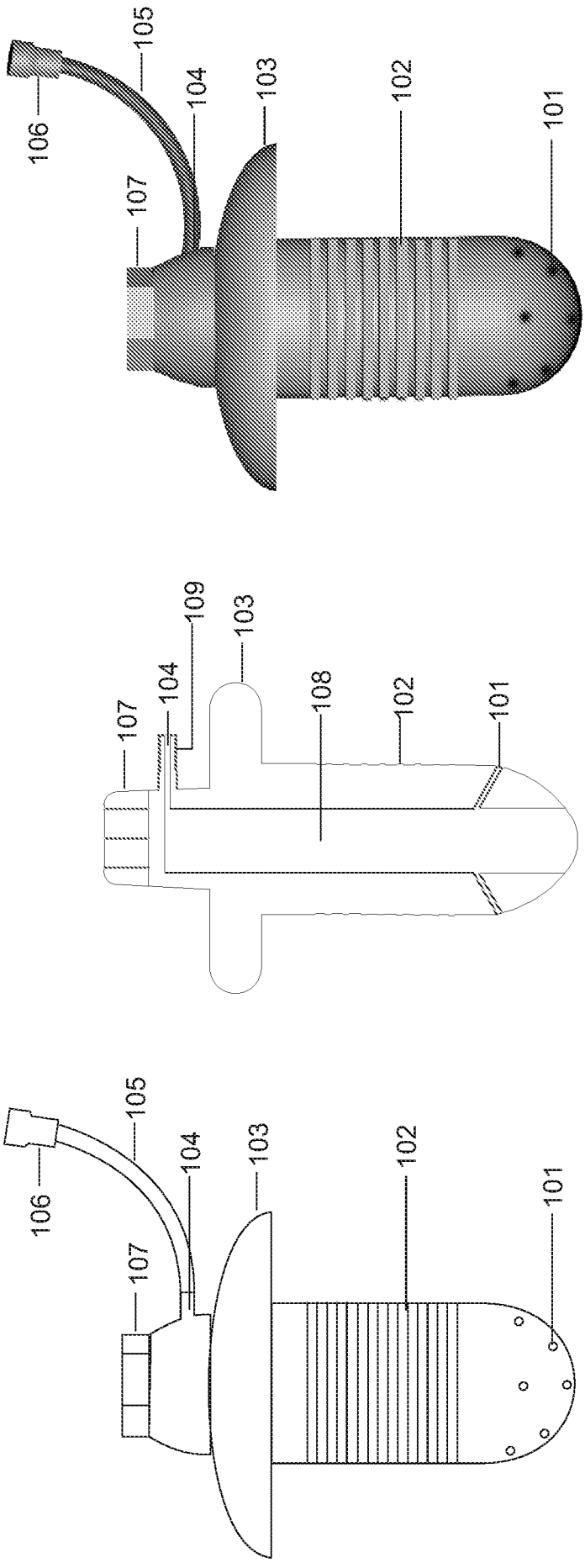


Fig-1

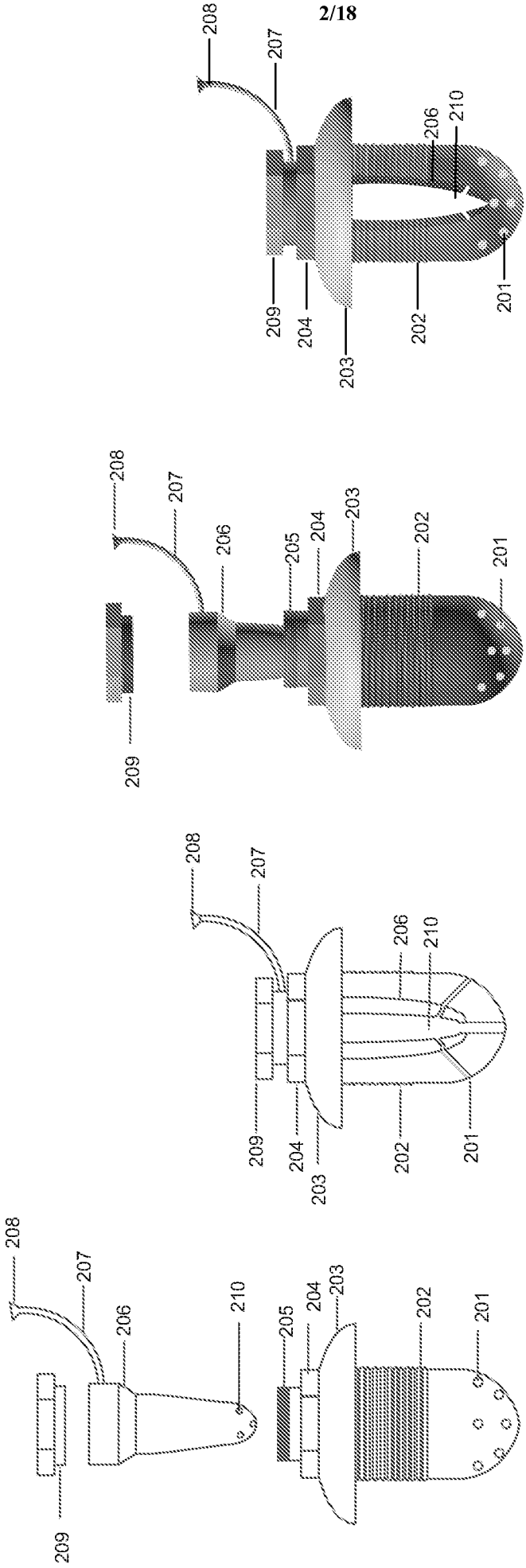

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Fig-2

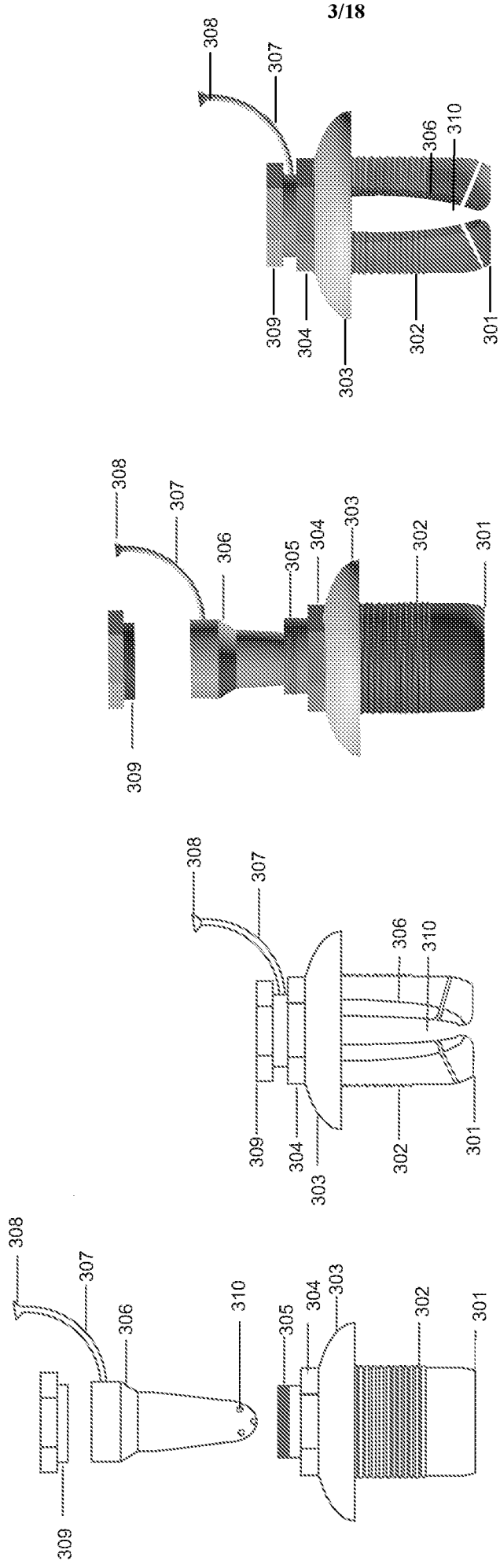


Fig-3

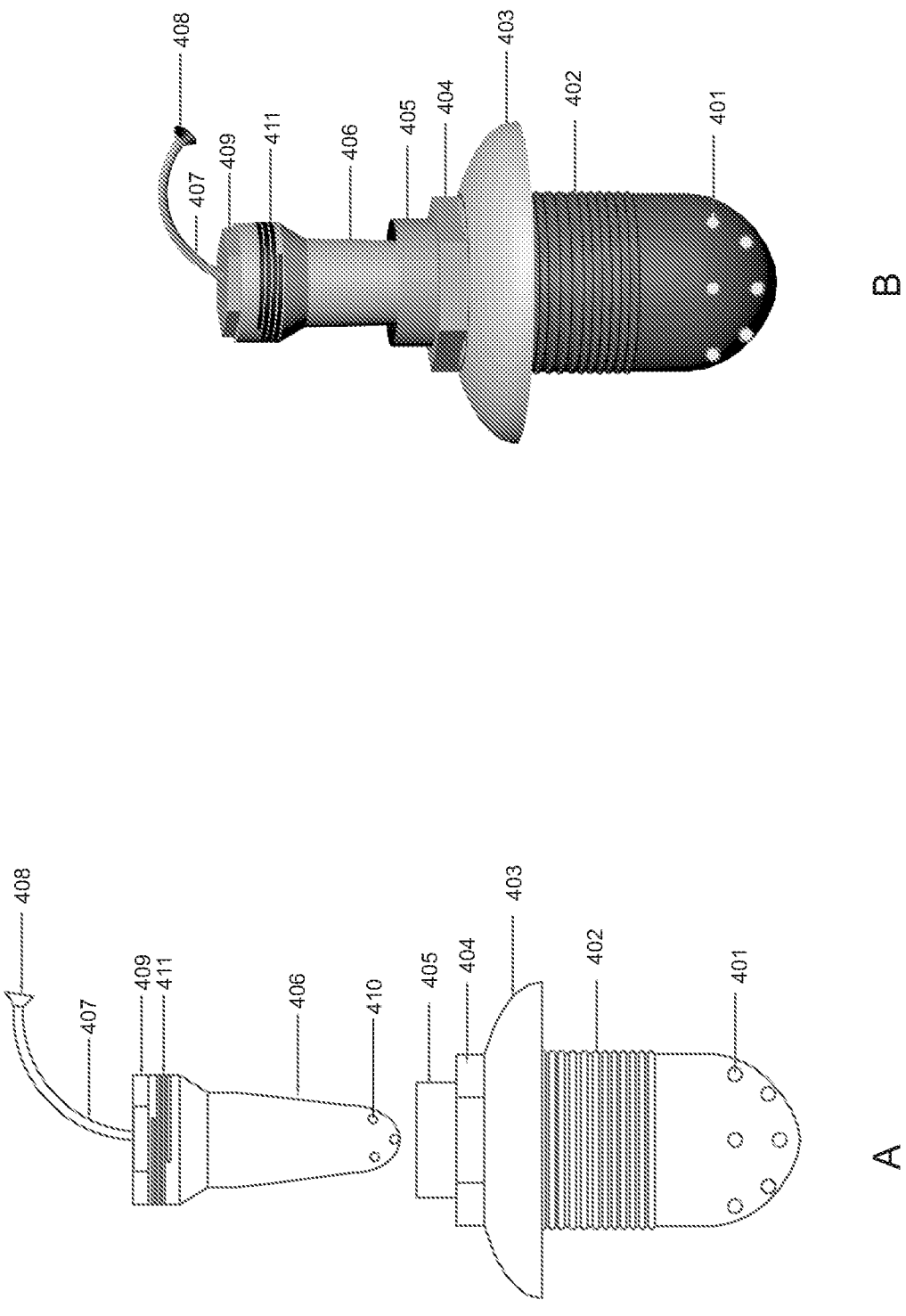

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Fig-4

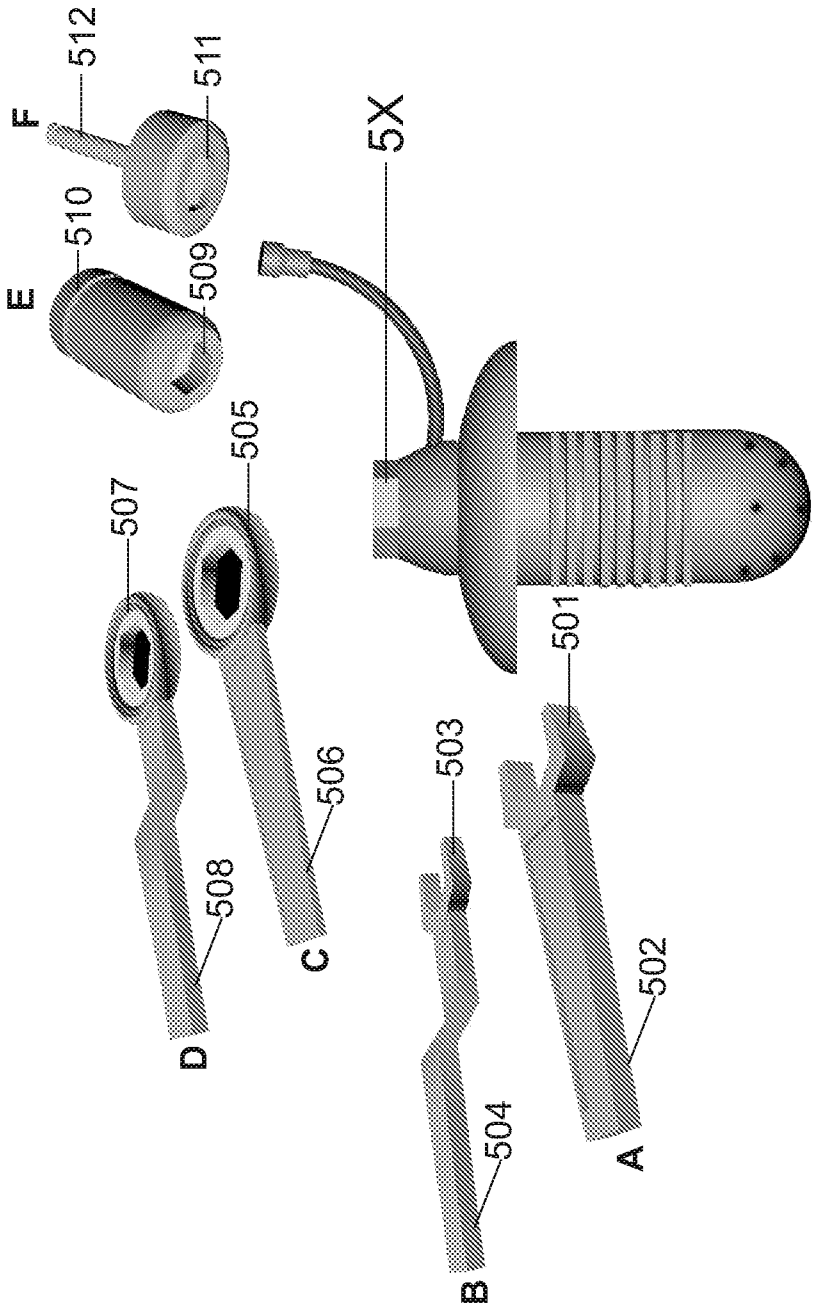


Fig-5

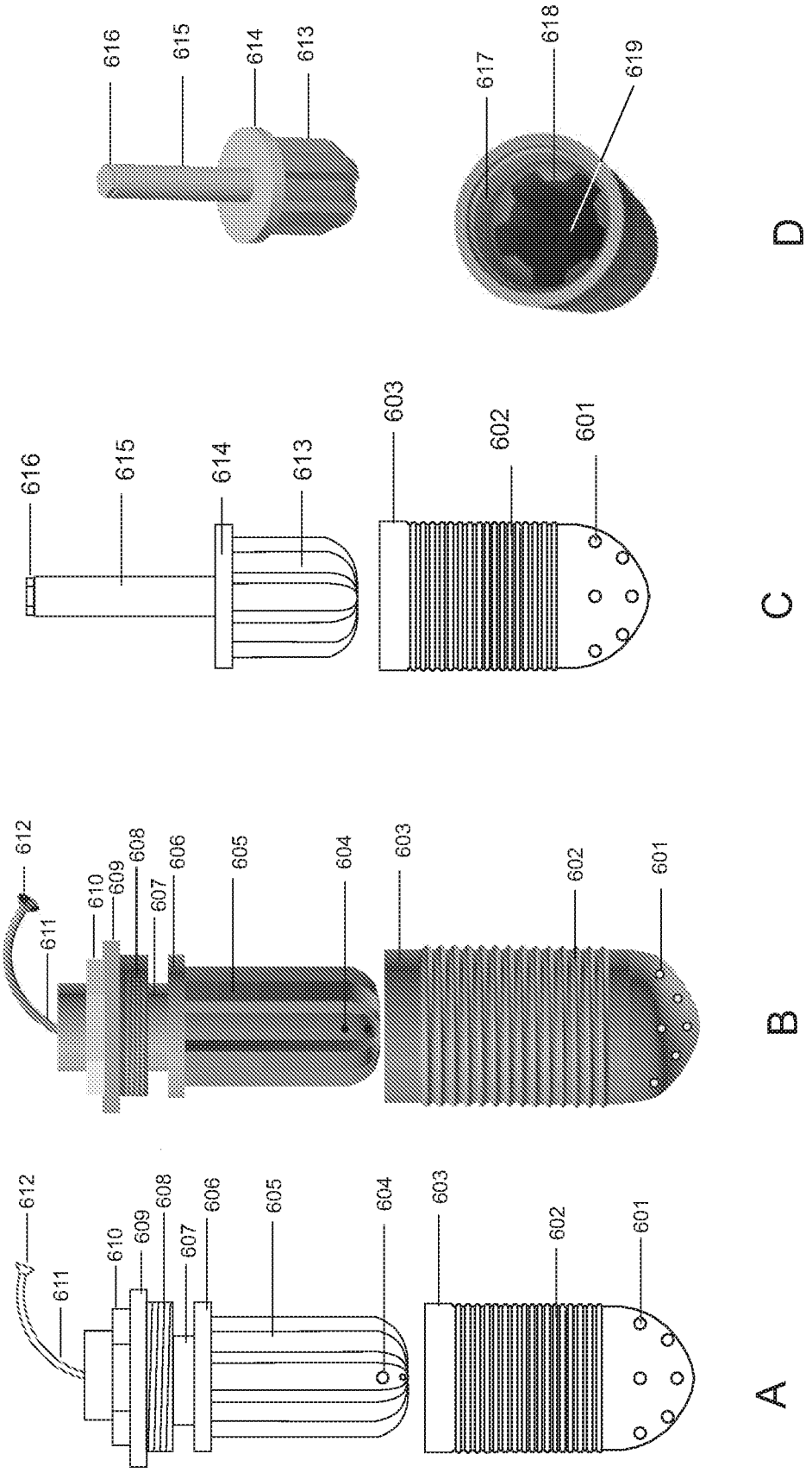

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Fig-6

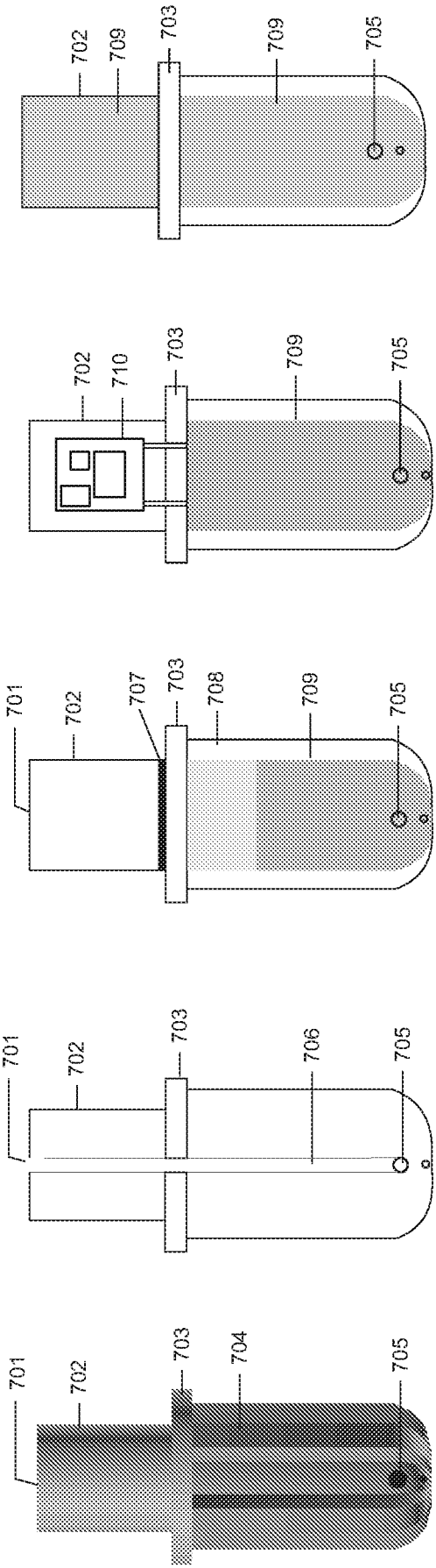

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Fig-7

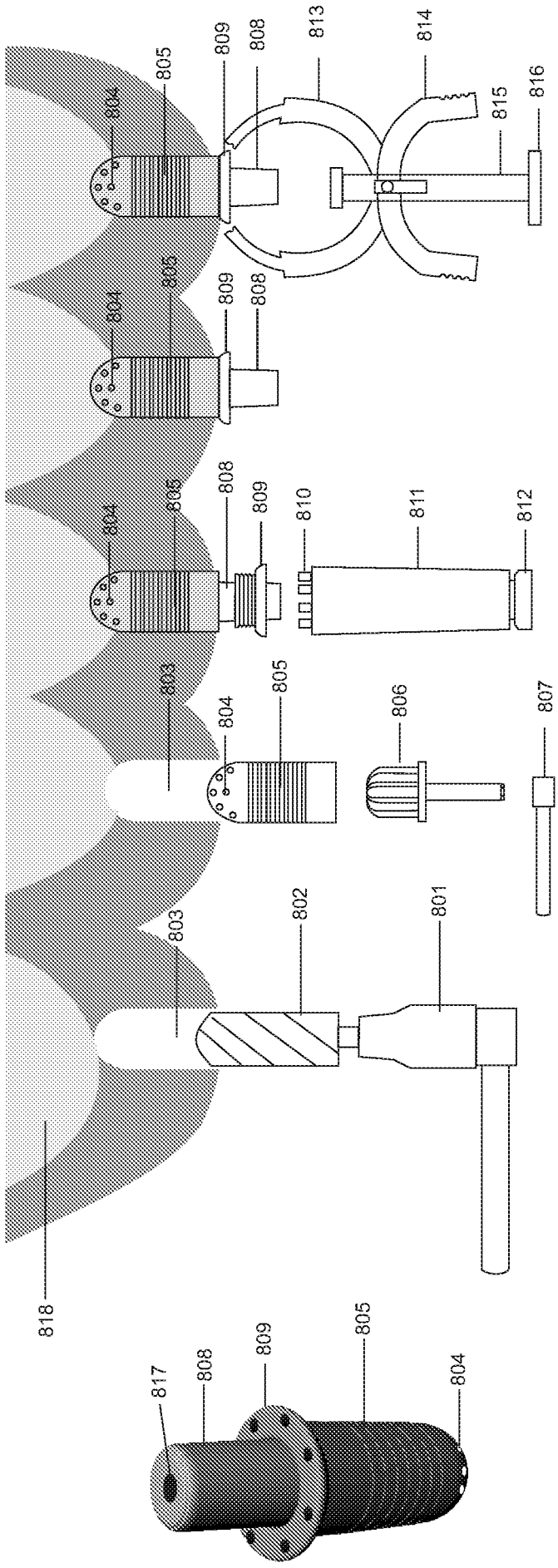

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Fig-8

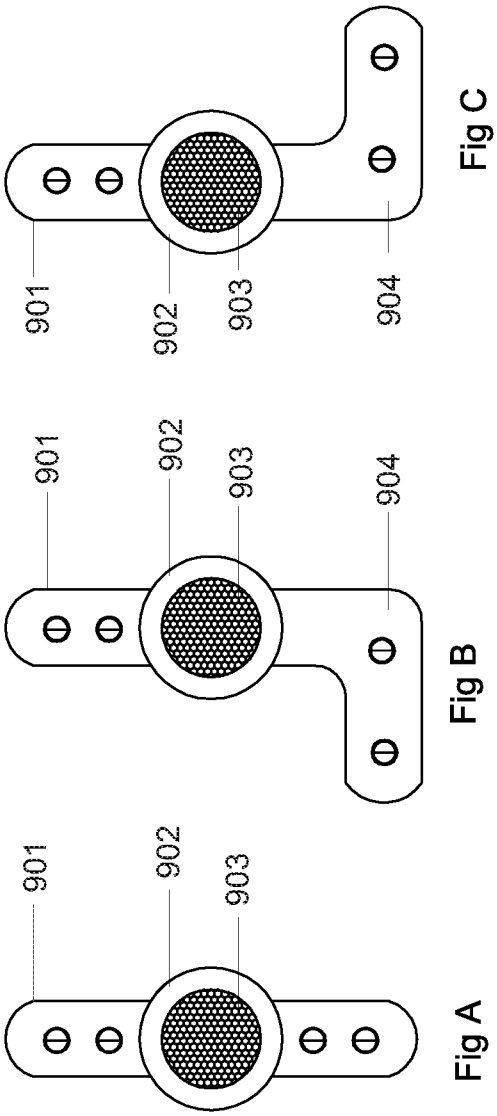
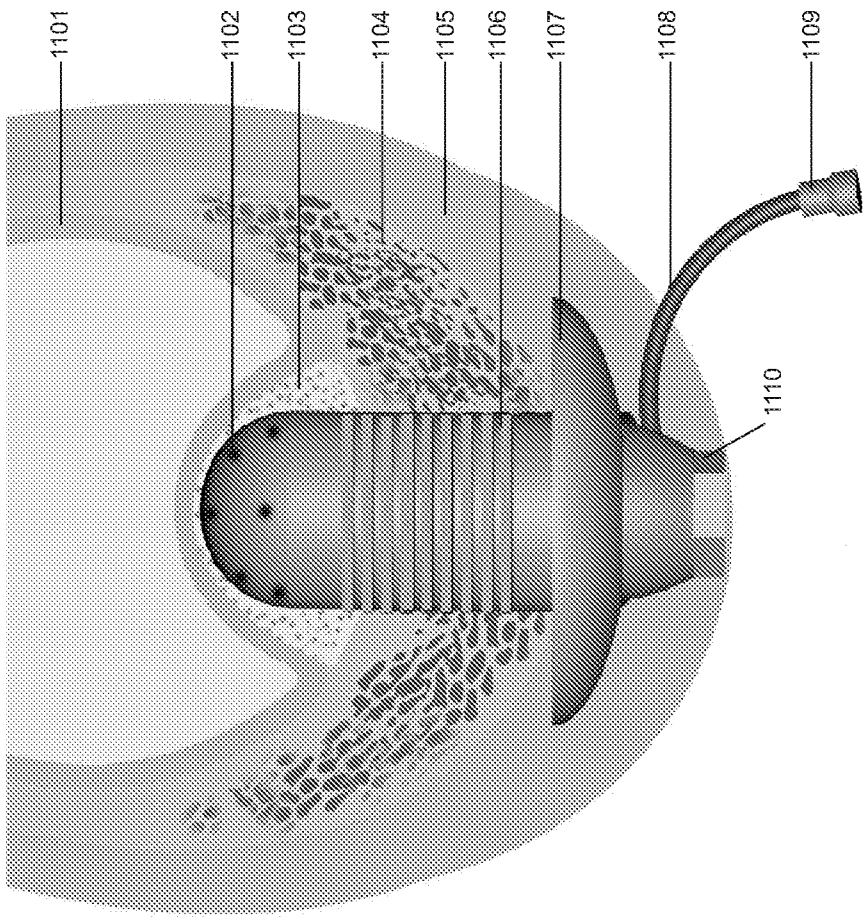

901
902
903
904
Fig C
901
902
903
904
Fig B
901
902
903
Fig A
905
907
906
Fig D

Fig-9


1101
1102
1103
1104
1105
1106
1107
1108
1109
1110
B

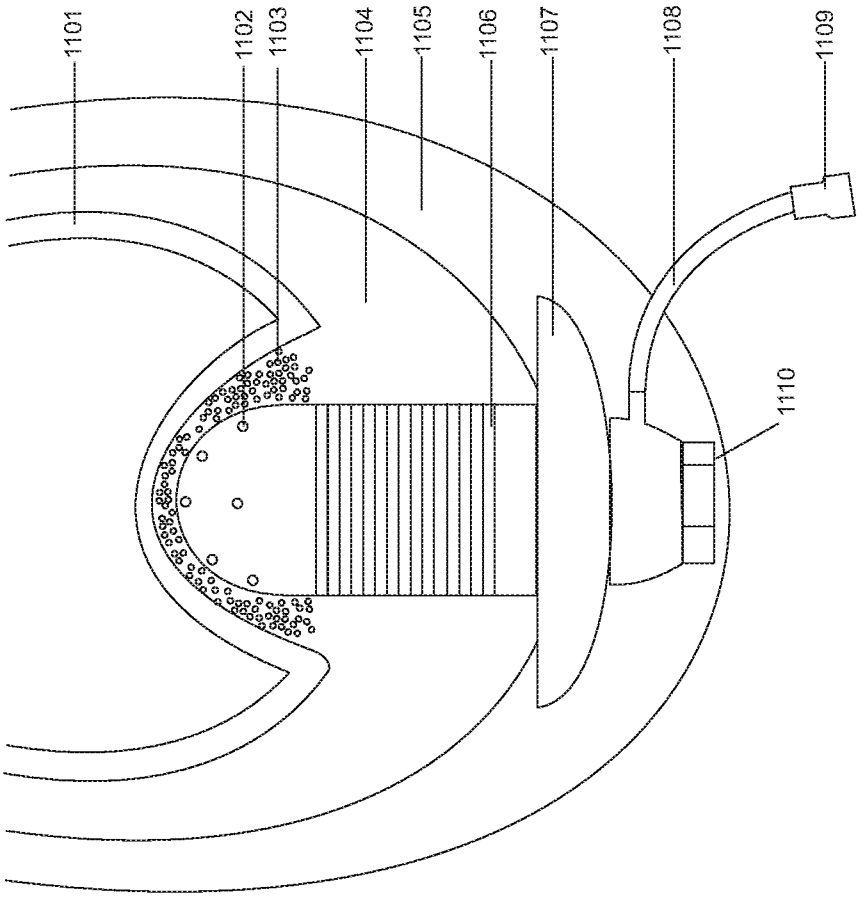

1101
1102
1103
1104
1105
1106
1107
1108
1109
1110
A

Fig-11

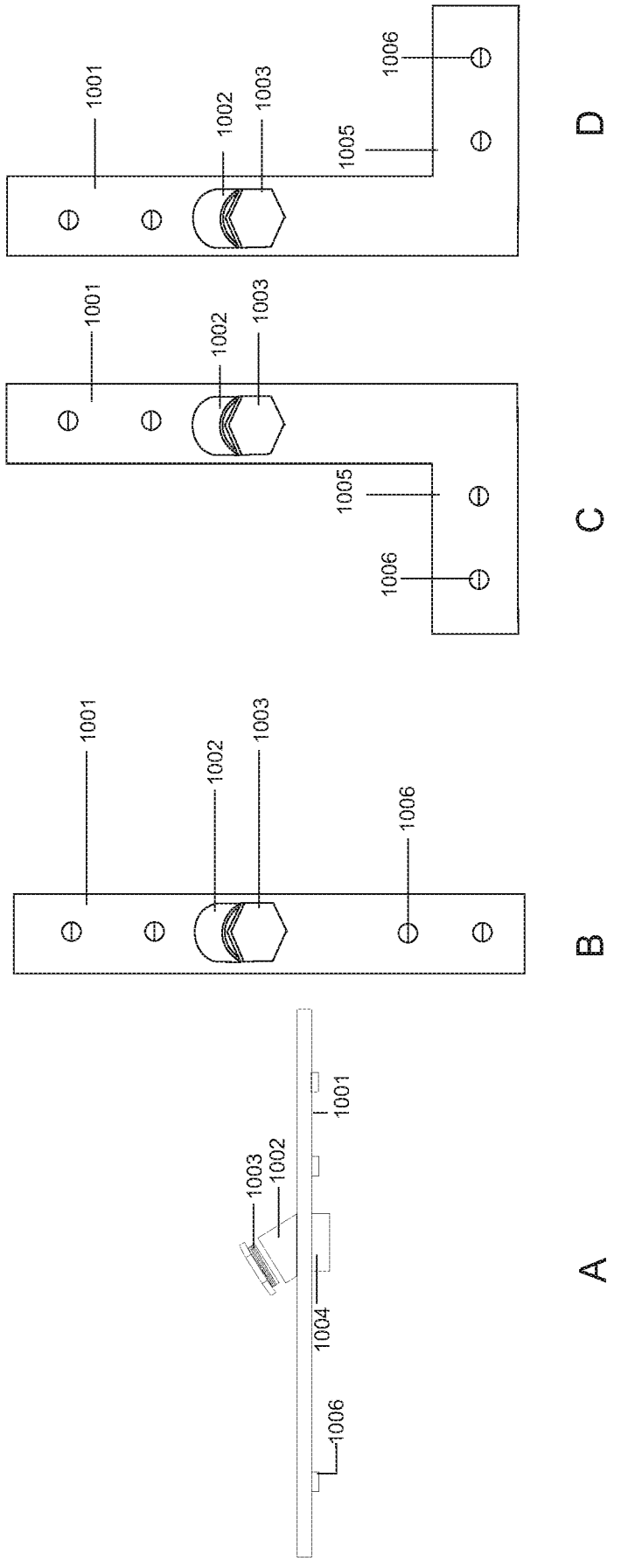
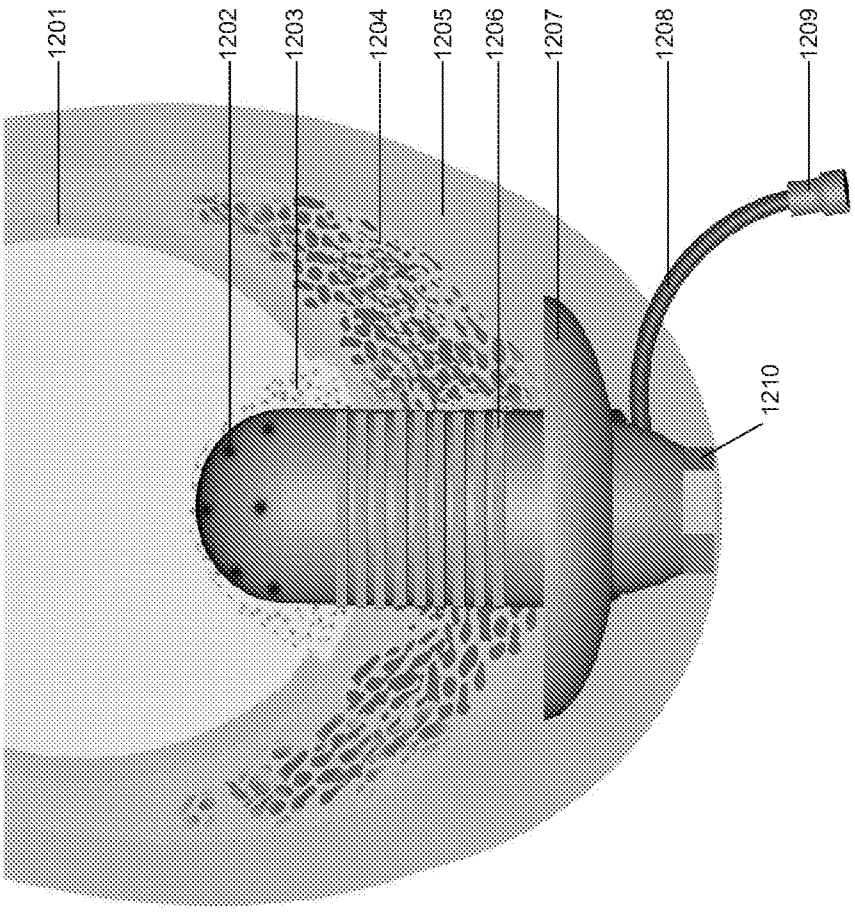


Fig-10


1201
1202
1203
1204
1205
1206
1207
1208
1209
1210
B

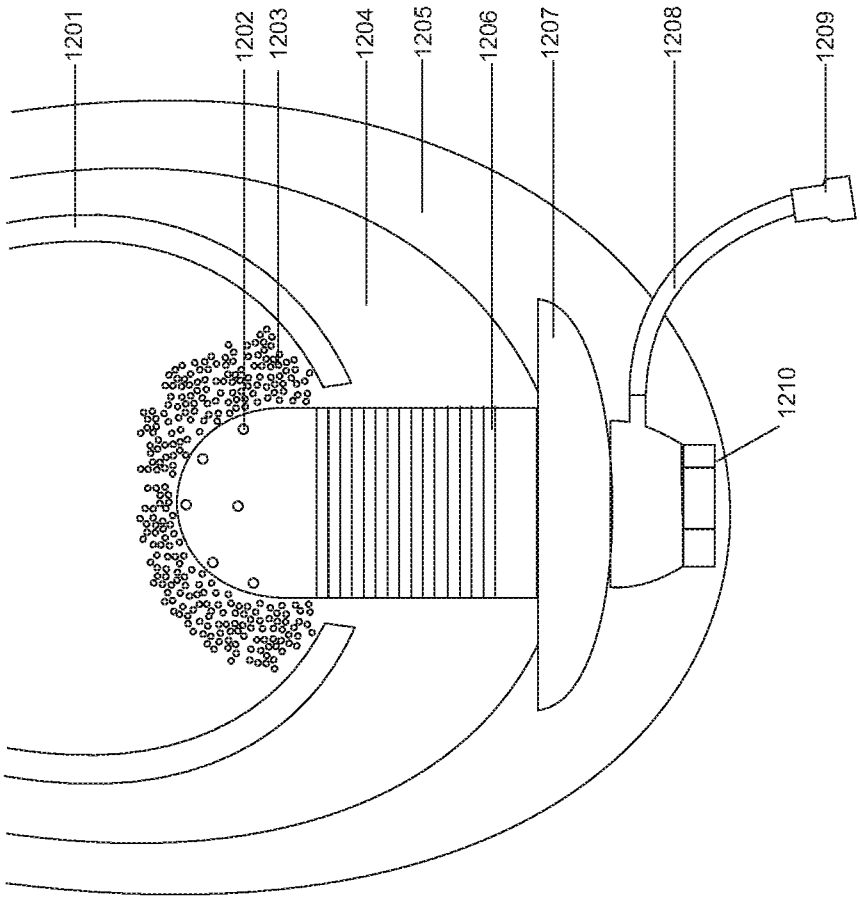

1201
1202
1203
1204
1205
1206
1207
1208
1209
1210
A

Fig-12

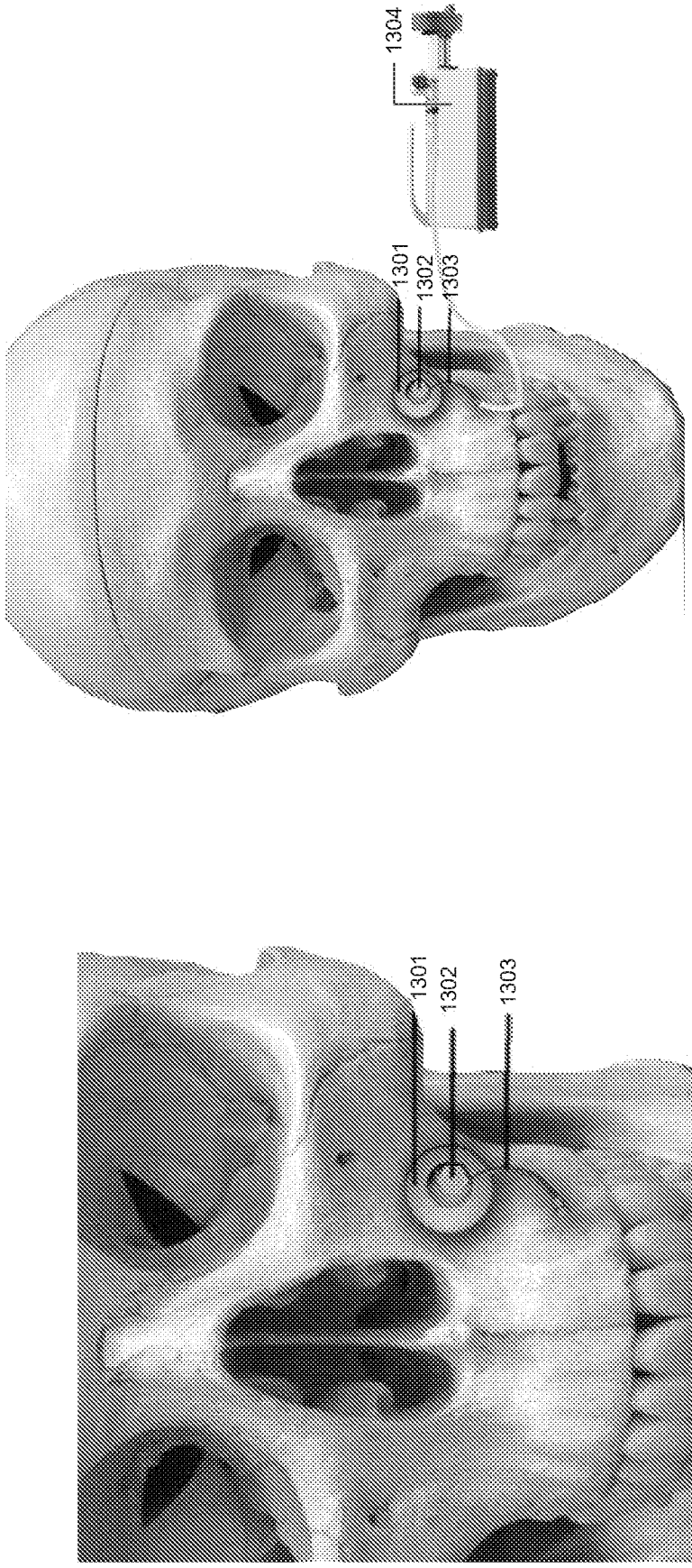


Fig-13

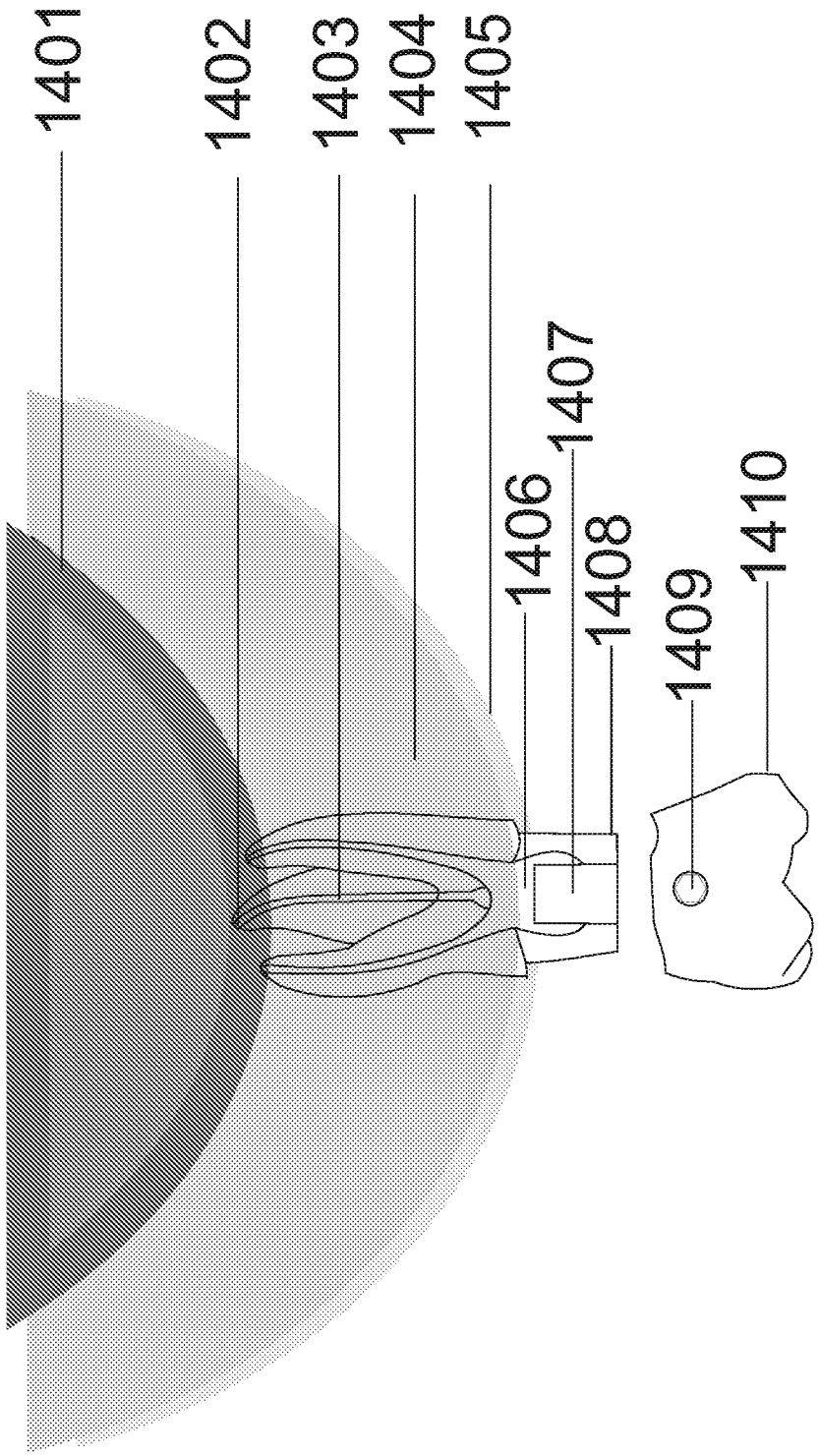
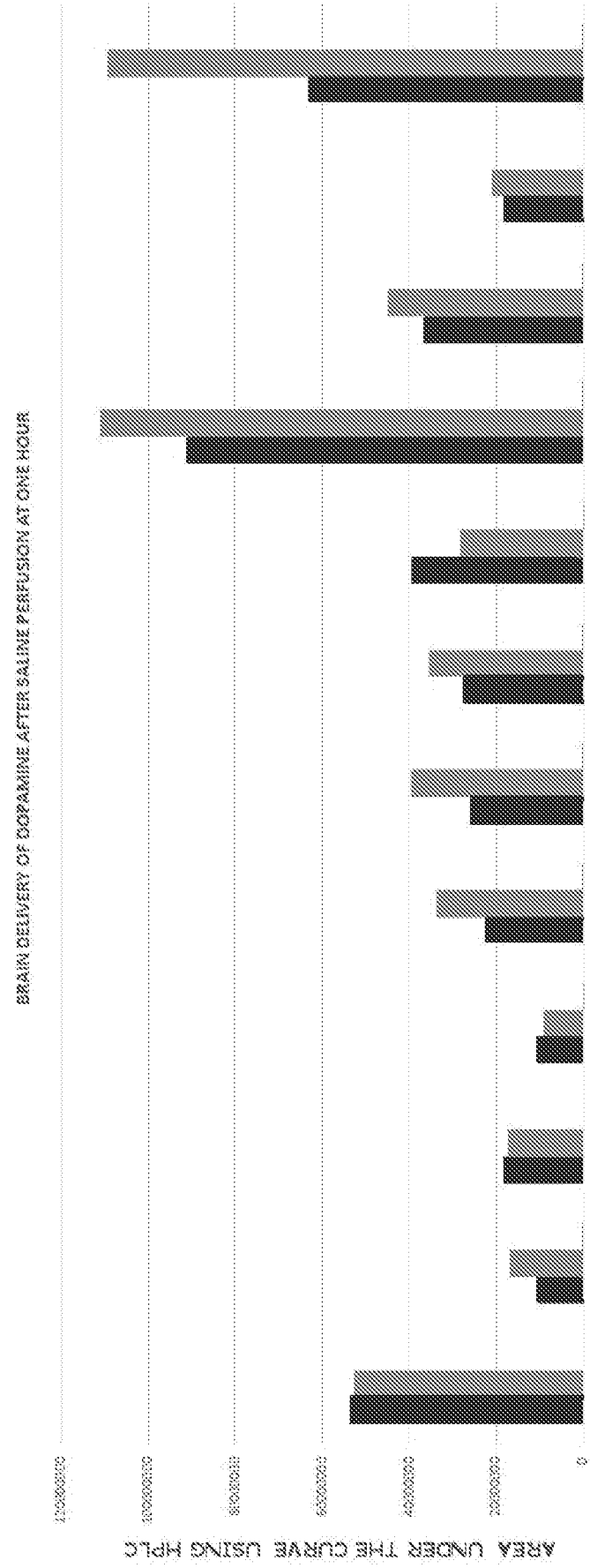


Fig-14



	RESPIRATORY MAXILLARY SINUS MUCOSA	DURAMATER	OLFACTORY BULB AND TRACT	OPTIC NERVE	MEDULLA	PONS	MIDBRAIN	DIENCEPHALON	CEREBELLUM	HIPPOCAMPUS	CAUDATE	CORTEX
CONTROL	53844985	18757660	18446854	10845966	22635982	25986648	27721985	39281085	91325366	36732120	19461746	63267408
DOPAMINE	52523741	16948943	17217527	9138081	33614474	39489739	35331685	28374856	111195472	45089441	11801268	109229058
PERCENTAGE INCREASE OF AREA UNDER CURVE	-2.454	57.5	-6.1238	-15.746	48.5	51.89	27	-27.76	21.75	22.75	14.328	72.637

Fig-15

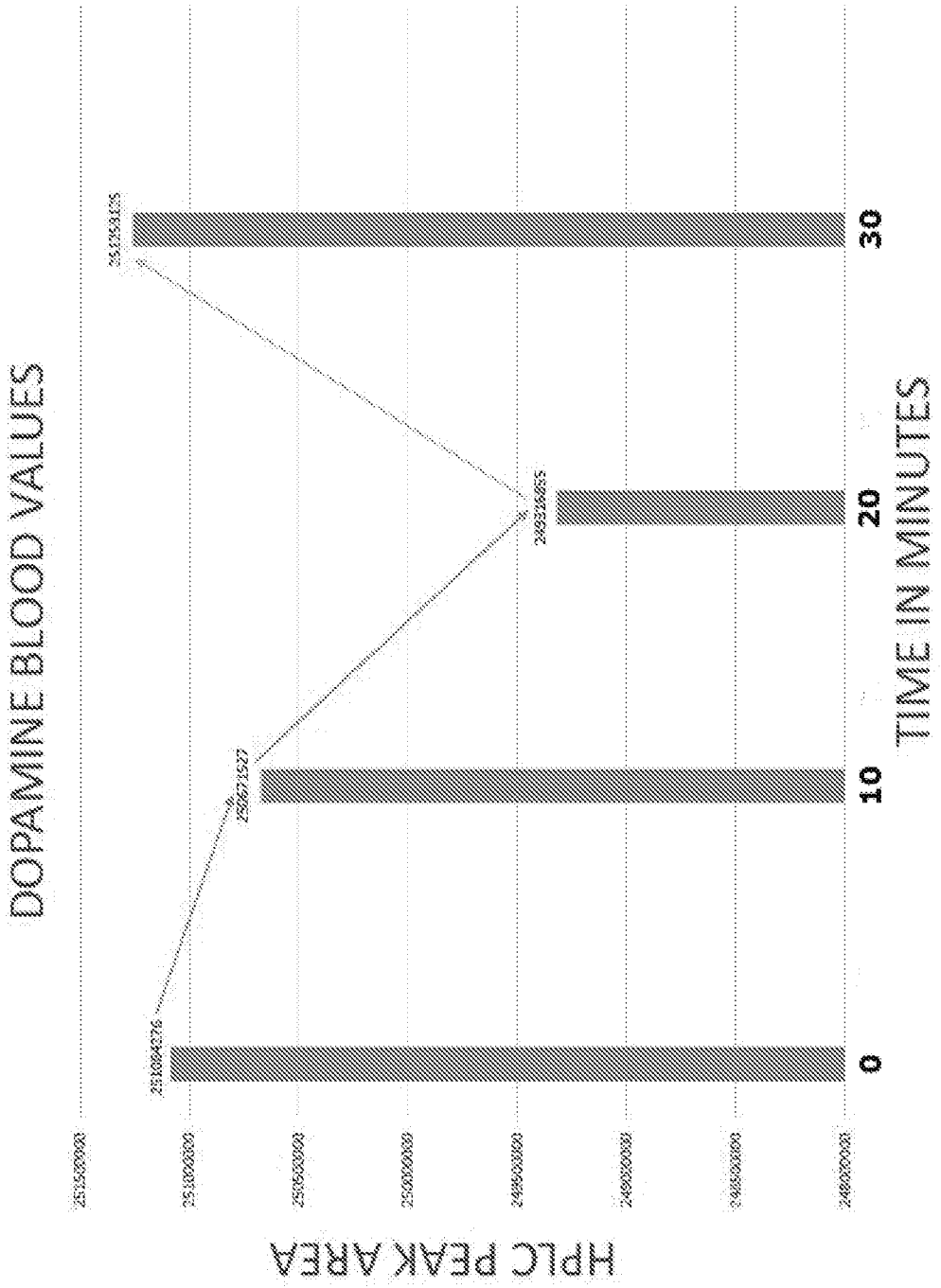

DOPAMINE BLOOD VALUES
HPLC PEAK AREA
TIME IN MINUTES
0
10
20
30
251564276
250671527
249336685
251353135

Fig-16

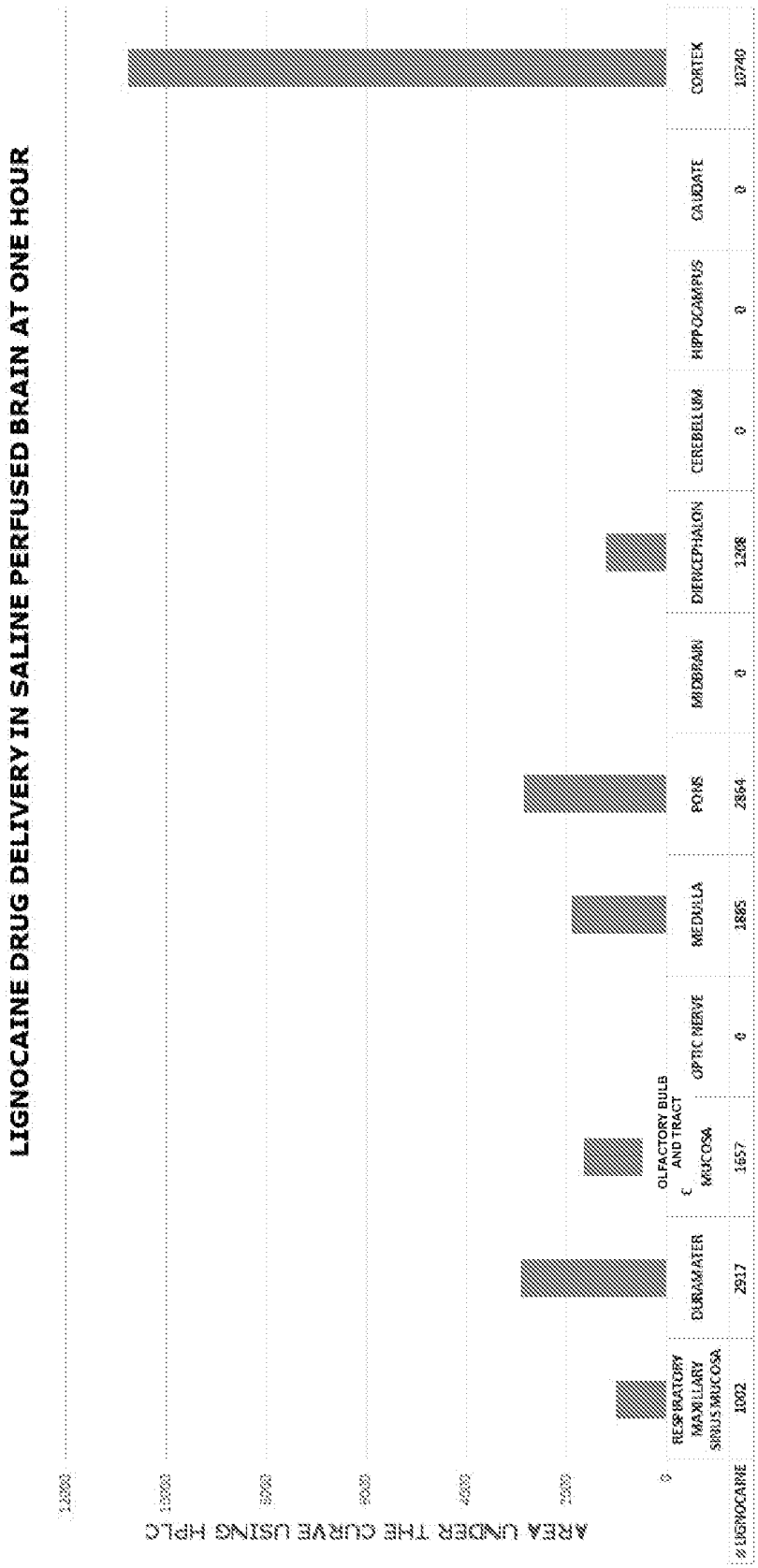

LIGNOCAINE DRUG DELIVERY IN SALINE PERFUSED BRAIN AT ONE HOUR
AREA UNDER THE CURVE USING HPLC
TISSUE CONCENTRATION USING HPLC ANALYSIS
% LIGNOCAINE
RESPIRATORY MAXILLARY SINUS MUCOSA
DURA MATER
OLFACTORY BULB AND TRACT
OPTIC NERVE
MEDULLA
PONS
MIDBRAIN
DIENCEPHALON
CEREBELLUM
HIPPOCAMPUS
CAUDATE
CORTEX
% LIGNOCAINE 1302 2917 1657 0 1885 2864 0 1208 0 0 0 18749

Fig-17

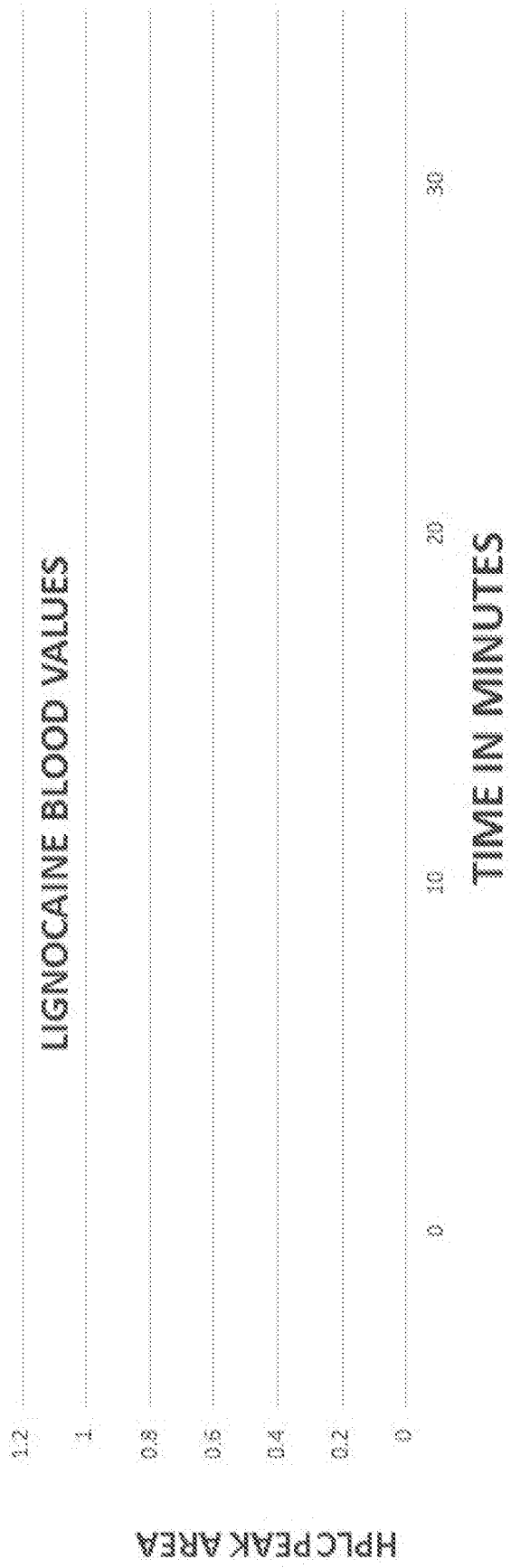

LIGNOCAINE BLOOD VALUES
HPLC PEAK AREA
1.2
1
0.8
0.6
0.4
0.2
0
0
10
20
30
TIME IN MINUTES

Fig-18

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/053899

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M5/142
ADD.

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)
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)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/098768 A1 (RENISHAW IRELAND LTD [IE]; FIELDER PAUL DAVID [GB]; JOHNSON DAVID EWEN) 18 August 2011 (2011-08-18) figures 1, 2 the whole document	1-11, 16-19
X	WO 00/33814 A2 (CHIRON CORP [US]) 15 June 2000 (2000-06-15) abstract the whole document	1-11, 16-19
X	US 2002/183683 A1 (LERNER EDUARD N [NL]) 5 December 2002 (2002-12-05) abstract the whole document	1-11, 16-19
X	US 2007/255237 A1 (LOBL THOMAS J [US] ET AL) 1 November 2007 (2007-11-01) the whole document	1-11, 16-19

☐ 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
22 September 2016	05/10/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schindler-Bauer, P

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/053899

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. [X] Claims Nos.: 12-15, 20
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

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

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

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

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

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

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

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

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

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 12-15, 20

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy This search Authority is not required to search an international application relating to methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic method. Independent claim 12 and the depending claims 13-15 and 20relate to a method for delivering drugs into the brain via the respiratory mucosa, and do therefore fall under the exclusion as set out in Rule 39.1(iv) PCT.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2016/053899

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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