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Drug mixing device and drug delivery device

FIELD OF THE INVENTION

This invention relates to a drug mixing device for hydrating a solid drug, the mixing device comprising a drug compartment for comprising the solid drug, means for providing water to the electrode for hydrating the solid drug and electronics for controlling the providing of the water to the solid drug.

This invention further relates to a drug delivery device comprising such a drug mixing device.

BACKGROUND OF THE INVENTION

Implantable Drug Delivery (IDD) is a growing area of interest as there are many benefits compared to for example oral delivery of an active substance to a patient. These benefits include a better control of the therapeutic window, local administration (higher dosing, fewer side-effects) and, very important, improved patient comfort.

There are a number of methods published for IDD, ranging from (polymeric) depots releasing the active substance (drug) to implantable mini-pumps. By combining pump technology with electronics, sensors and/or telemetry units, a very well controlled administration of an active substance can be achieved. In most configurations the active substance is present in liquid form (often as a solution) and the actuator transports fluid. However as for many active substances the potency decreases in time, e.g. due to hydrolysis, (auto)polymerization, end-group modification and aggregation. In addition more and more peptide based drugs are used. These molecules can only be stored for longer periods of time in hydrated state at typically -80°C or lower or in lyophilized state under ambient conditions. Often stabilizers (such as mannitol) and buffers (such as HEPES-hemisodium) are added to stabilize these molecules. Another important issue is that several drugs only slowly dissolve in a water environment. For these kind of active substances direct release would result in slowly dissolving solid drug particles due to which bioavailability and drug absorption rates will become unpredictable. Thus, there is a need for pumps in which drugs can be stored in dry (solid) form in which drug is dissolved prior to release.

An implantable drug delivery device which stores drugs in solid form is described in US patent 6,458,118. US 6,458,118 describes an implantable drug delivery device comprising drugs contained within capsules. Using capsules enables storing the drugs in solid form. The device further comprises a reservoir with a carrier fluid that will dissolve the drug when freed from the capsule, a drug releaser for freeing the microencapsulated drug from the capsule and an electromechanical pump to convey the dissolved drug to a catheter, through which the drug is delivered to a target site within a patient. The solid drug is hydrated before delivery to the patient.

This device has several disadvantages. First, when the drug is released from the capsule, capsule material is left behind. As it is not desirable to release the capsule material in the patient's body, a reservoir is needed for collecting it. As a result, the device may become too large, or the amount of drugs that can be stored in it may become too small. Furthermore, storing the carrier fluid also requires a lot of space, thereby further increasing the size of the device.

OBJECT OF THE INVENTION

It is an object of the invention to provide a drug mixing device for hydrating a solid drug, which drug mixing device has a large drug storing capacity relative to its dimensions.

SUMMARY OF THE INVENTION

According to a first aspect of the invention, this object is achieved by providing a drug mixing device for hydrating a solid drug, the drug mixing device comprising a drug compartment for comprising the solid drug and oxygen, a fuel compartment for comprising a hydrogen rich fluid, a proton exchange membrane being situated in between the drug compartment and the fuel compartment, an anode electrode in the fuel compartment, a cathode electrode in the drug compartment, and an electronic circuit for coupling the anode electrode to the cathode electrode, such that water is produced at the cathode electrode for hydrating the solid drug.

In fact, this arrangement functions as a fuel cell. At the anode, the fuel undergoes an oxidation process and thereby protons (H^+) and electrons (e^-) are released. The proton exchange membrane (PEM) is a membrane that is designed such negatively charged substances, such as electrons, cannot pass the membrane while positively charged particles, such as protons, pass the membrane. Diffusion causes the released protons to pass the PEM

into the drug compartment. The released electrons are picked up by the anode and flow through the electronic circuit to the cathode. At the cathode in the drug compartment, the available oxygen picks up the protons and the electrons to form water molecules (H_2O). The water produced in this way will dissolve the solid drug which is also contained in the drug compartment.

While water is produced in the drug compartment, an electrical current is generated and flows through the electric circuit. This current may be stored in a rechargeable battery and or used for further operational units of the mixing device (e.g. telemetry unit, internal or external sensors) or for power consuming elements used for delivery of the hydrated drug to the patient.

In a preferred embodiment the device comprises multiple drug compartments, each drug compartment comprising a cathode electrode, solid drug and oxygen, the electronic circuit being arranged for selectively producing water at the cathode electrode in at least one of the drug compartments. Each drug compartment may provide a separate drug dosage at a different moment in time. This enables controlling the amounts and time schedule of the delivery of a drug to a patient's body. One fuel compartment with one anode may be coupled to all individual cathodes via a controller which controls when an electrical current may flow through a particular cathode. Alternatively, a separate fuel compartment is provided for each drug compartment.

The drug and/or fuel compartments may have a changeable volume in order to compensate for pressure changes that arise because of the chemical processes occurring during operation of the mixing device. Gas produced at the anode may be utilized for compressing the drug compartment and to initiate drug delivery from the drug compartment to the patient.

These and other aspects of the invention are apparent from and will be elucidated with reference to the embodiments described hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings:

Figure 1 schematically shows a drug mixing device according to the invention, Figure 2 schematically shows a drug delivery device according to the invention,

Figure 3 schematically shows part of another drug delivery device according to the invention,

Figure 4 shows a cross section of a drug delivery device with multiple drug compartments,

Figure 5 shows another cross section of the drug delivery device of figure 4 and

Figure 6 shows a cross section of a tubular drug delivery device with multiple compartments.

DETAILED DESCRIPTION OF THE INVENTION

Figure 1 schematically shows a drug mixing device 10 according to the invention. The mixing device comprises a fuel compartment 11 with an anode 15. The fuel compartment 11 comprises a hydrogen rich fuel, such as methanol (CH_3OH), gaseous or liquid hydrogen (H_2) or borohydrate (BH^-). When methanol is used as the fuel, the fuel compartment should also comprise some water (H_2O) to enable oxidation of the methanol. A borohydrate solution should further comprise hydroxide-ions (OH^-) to enable the oxidation.

A person skilled in the art of fuel cells will know many more suitable fluids for use in the fuel compartment 11. Exemplary oxidation reactions occurring in the fuel compartment are:

for methanol as fuel: $2 \text{CH}_3\text{OH} + 2 \text{H}_2\text{O} \rightarrow 2 \text{CO}_2 + 12 \text{H}^+ + 12 \text{e}^-$, or

for hydrogen as fuel: $2 \text{H}_2 \rightarrow 4 \text{H}^+ + 4 \text{e}^-$.

A drug compartment 12 comprises the drug in solid form. The drug may, e.g., be (lyophilized) synthetic or natural drugs or peptides, known for its limited shelf life while hydrated. The drug is located in an oxygen (O_2) rich environment. In case the drug is prone to oxidative degeneration the drug particles may have to be coated with a water soluble, oxygen impermeable coating. The fuel compartment 11 and the drug compartment 12 are separated by a proton exchange membrane (PEM) 13. The PEM 13 is designed to conduct protons (H^+) while being impermeable to other particles or molecules, such as electrons (e^-), oxygen, hydrogen or water. PEMs can be made from either pure polymer membranes or from composite membranes where other materials are embedded in a polymer matrix. One of the most common and commercially available PEM materials is Nafion. The PEM enables protons, produced by oxidation of the fuel in the fuel compartment 11 to diffuse into the drug compartment 12. The electrons that are produced at the anode 15 in the fuel compartment 11 flow through the electronic circuit 17 to the cathode 14 in the drug compartment 12. Cathode 14 is preferably positioned in close proximity to membrane 13 such that the available oxygen, protons and electrons in the drug compartment 12 combine to form water molecules which are used for hydrating the solid drug. A person skilled in the art can come up with

several electrode configurations, such as porous electrodes in proximity to the membrane or printed electrodes on the surface of the membrane. The water is produced according to, e.g., the following reactions:

for methanol as fuel: $3 \text{O}_2 + 12 \text{H}^+ + 12 \text{e}^- \rightarrow 6 \text{H}_2\text{O}$, or

5 for hydrogen as fuel: $\text{O}_2 + 4 \text{H}^+ + 4 \text{e}^- \rightarrow 2 \text{H}_2\text{O}$.

The exemplary overall reactions in the mixing device 10 according to the invention are thus:

for methanol as fuel: $2 \text{CH}_3\text{OH} + 3 \text{O}_2 \rightarrow 2 \text{CO}_2 + 4 \text{H}_2\text{O}$, or

for hydrogen as fuel: $2 \text{H}_2 + \text{O}_2 \rightarrow 2 \text{H}_2\text{O}$.

10 Preferably, the electronic circuit 17 is programmable, such that the mixing may occur according to a programmed time schedule. If the mixing device 10 is part of an implantable drug delivery device, the schedule may be stored in the electronic circuit 17 before implantation. Alternatively, the electronic circuit 17 may be programmed after implementation via a wireless communication unit 19. The communication unit 19 may also
15 be used for reporting operational information of the mixing device 19 to a user. The electric power needed for operation of the electronic circuit 17 and the communication unit 19 may at least partially be obtained from the chemical reactions occurring at the anode 15 and cathode 14. The electrical current flowing through the electronic circuit 17 may be used to charge a capacitor or rechargeable battery 18 in order to store the electrical power for later use.

20 Additional oxygen may be provided to the drug compartment by a (pressurized) oxygen reservoir 101. Oxygen may also be produced inside the mixing device via a chemical reaction. For example, the combination of a so-called 'active oxygen source' (such as sodium perborate, sodium percarbonate, sodium perphosphate, sodium persulphate or urea peroxide) in combination with an activator (such as Tetraacetylenediamine) will
25 release oxygen. Contrary to oxygen producing canisters, these compounds decompose at a significant slower rate and in a closed system (tank or pump system discussed in example 1), after reaching a certain pressure a balanced system will be formed. This means that once oxygen is used by the fuel cell new oxygen will be produced. One component of special interest is CaO_2 . A person skilled in the art can come up with several alternative oxygen
30 producing compounds.

If the active ingredient remains stable while in contact with the oxygen source, it also could be mixed. Then the fuel cell will start by using oxygen from air or oxygen present in the compartment and once water is released the oxygen source will produce oxygen needed for the remaining part of the dissolving process.

Figure 2 schematically shows a drug delivery device 20 according to the invention. This drug delivery device 20 has many features in common with the drug mixing device 10 of figure 1 and mixes the drug with water in the same way as described above. The drug compartment 12 further comprises a semi permeable membrane 21 for separating the drug compartment 12 from the external environment of the drug delivery device 20. The drug can leave the drug delivery device 20 through the membrane 21, but only when it is dissolved in water. The membrane 21 also avoids water or other substances from the external environment to enter the drug compartment 12. The release of the drug may occur based on diffusion only, but in order to increase and provide control over the release rate, electrophoresis or electro-diffusion may be used. The rechargeable battery 18 or another electrical power source may be discharged over the cathode electrode 14 and an external electrode 22. This will cause an electric field at the position of the membrane 21. This electric field will increase the diffusion rate of hydrated drug molecules through the membrane 21. By controlling the voltages at the electrodes 14, 22, the electrical field strength is controlled. By controlling the electric field strength, the diffusion rate of the hydrated drug into the environment can be controlled.

Figure 3 schematically shows part of another drug delivery device according to the invention. In this embodiment, the drug is comprised in a gas tight bag 33 filled with the solid drug and oxygen. The oxygen may be provided in the form of pressurized oxygen or air. The gas tight bag 33 is enclosed in a larger compartment 31, which is preferably also filled with some pressurized gas. The cathode (not shown) is situated in the gas tight bag 33. Water produced at the cathode dissolves the solid drug. While oxygen inside the gas tight bag 33 is used for producing water, the pressure inside the gas tight bag 33 decreases. The volume of the gas tight bag 33 will decrease for compensating the pressure difference between the inside and the outside of the gas tight bag 33.

A flow restrictor 32 is provided for controlling the flow of dissolved drug to the environment. The flow restrictor 32 may, e.g., be pressure based and/or electronically switched. Increasing the pressure on the gas tight bag 33 may increase the flow of dissolved drug through the flow restrictor. The pressure on the gas tight bag 33 may be increased by providing a gas flow into the larger compartment 31, e.g., by directing the carbon dioxide (CO₂) produced at the anode to the larger compartment. Alternatively, a reservoir filled with pressurized gas may be provided for compensating pressure fluctuations and/or squeezing the gas tight bag 33. As a further alternative, gas may be produced by the mixing device, using electrolysis.

In an alternative embodiment (not shown) of a drug mixing device according to the invention, the drug compartment and the fuel compartment may be separated by a movable wall. While, e.g. carbon dioxide is produced in the fuel compartment and oxygen is consumed in the drug compartment, the wall will move from the fuel compartment to the drug compartment and the pressure on both sides will remain in balance. Additional gas pressure may be applied for delivering the dissolved drug to the environment via a pressure based flow restrictor.

Figure 4 shows a cross section of a drug delivery device 40 with multiple drug compartments 12. Each compartment comprises drugs, oxygen and a cathode. Different drug compartments 12 may comprise different types and/or different amounts of drugs. The electronic circuit selectively initiates production of water at one or more of the cathodes in order to dissolve the drug in the respective drug compartment 12.

Figure 5 shows another cross section of the drug delivery device 40 of figure 4. Although the device 40 comprises multiple drug compartments 12, only one fuel compartment 11 with one anode is provided. Alternatively, a group of drug compartments 12 or even a single drug compartment 12 may be coupled to a separate fuel compartment with a respective anode. Separate fuel compartments may comprise different types of fuel.

The device 40 shown in figure 4 and 5 comprises four electrodes with different functions. The anode 51 is situated at the fuel compartment 11 side of the PEM 13. The cathode 52 is situated at the drug compartment side of the PEM 13. Preferably, each drug compartment has a separate cathode 52 for enabling mixing in individual drug compartments 12. A rechargeable battery is charged via the anode 51 and the cathode 52. By measuring a conductance between the cathode electrode 52 and an electrode 53 at the outer membrane 21 of the drug compartment, the concentration of the hydrated drug may be monitored. The delivery of the drug to the environment may start after the conductance reaches a predetermined value. Diffusion of the hydrated drug from through the outer membrane 21 to the external environment may be enhanced by discharging the rechargeable battery via two electrodes 53, 54 situated at each side of the outer membrane 21.

Figure 6 shows a cross section of a tubular drug delivery device 60 with multiple drug compartments 12. In principle, this embodiment works in a way similar to the embodiment of figures 4 and 5. A tubular central fuel compartment 11 with an anode is surrounded by multiple drug compartments 12. Each drug compartment 12 comprises a cathode and is separated from the central fuel compartment 11 by a PEM 13.

It should be noted that the above-mentioned embodiments illustrate rather than limit the invention, and that those skilled in the art will be able to design many alternative embodiments without departing from the scope of the appended claims. In the claims, any reference signs placed between parentheses shall not be construed as limiting the claim. Use
5 of the verb "comprise" and its conjugations does not exclude the presence of elements or steps other than those stated in a claim. The article "a" or "an" preceding an element does not exclude the presence of a plurality of such elements. The invention may be implemented by means of hardware comprising several distinct elements, and by means of a suitably programmed computer. In the device claim enumerating several means, several of these
10 means may be embodied by one and the same item of hardware. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage.

CLAIMS:

1. A drug mixing device (10, 20, 40, 60) for hydrating a solid drug, the drug mixing device (10, 20, 40, 60) comprising:
 - a drug compartment (12) for comprising the solid drug and oxygen,
 - a fuel compartment (11) for comprising a hydrogen rich fluid,
 - 5 - a proton exchange membrane (13) being situated in between the drug compartment (12) and the fuel compartment (11),
 - an anode electrode (15, 51) in the fuel compartment (11),
 - a cathode electrode (14, 52) in the drug compartment (12), and
 - an electronic circuit (17) for coupling the anode electrode (15, 51) to the
 - 10 cathode electrode (14, 52), such that water is produced at the cathode electrode (14, 52) for hydrating the solid drug.
2. A drug mixing device (10, 20, 40, 60) as claimed in claim 1, wherein the electronic circuit (17) comprises a capacitor or rechargeable battery (18), the electronic
- 15 circuit (17) being arranged for charging the capacitor or rechargeable battery (18) using an electrical current flowing from the cathode electrode (14, 52) to the anode electrode (15, 51).
3. A drug mixing device (40, 60) as claimed in claim 1, wherein the drug compartment (12) further comprises two electrodes (52, 53) for measuring a conductance
- 20 inside the drug compartment (12).
4. A drug mixing device (40, 60) as claimed in claim 3, wherein one of the two electrodes (52, 53) for measuring a conductance is the cathode electrode (52).
- 25 5. A drug mixing device (40, 60) as claimed in claim 1, the device (40, 60) comprising multiple drug compartments (12) for comprising the solid drug and oxygen, each drug compartment (12) comprising a cathode electrode (52), the electronic circuit (17) being arranged for selectively producing water at the cathode electrode (52) in at least one of the drug compartments (12).

6. A drug mixing device (10, 20, 40, 60) as claimed in claim 1, further comprising an oxygen reservoir (101) for providing oxygen to the drug compartment (12).

5 7. A drug mixing device (10, 20, 40, 60) as claimed in claim 1, wherein a volume of the drug compartment (33) is changeable.

8. A drug mixing device (10, 20, 40, 60) as claimed in claim 7, further comprising means for applying gas produced at the anode electrode (15, 51) for generating a
10 pressure for changing the volume of the drug compartment (33).

9. A drug mixing device (10, 20, 40, 60) as claimed in claim 7 or 8, wherein the drug compartment (33) is a flexible gas tight bag.

15 10. A drug mixing device (10, 20, 40, 60) as claimed in claim 8, wherein also a volume of the fuel compartment (11) is changeable.

11. A drug delivery device (20, 40, 60) for delivering a hydrated drug to a delivery site in a human or animal, the drug delivery device (20, 40, 60) comprising a drug mixing
20 device as claimed in one of the preceding claims, wherein the drug compartment (12) comprises delivery means (21, 32) for delivering the hydrated drug.

12. A drug delivery device (20, 40, 60) as claimed in claim 11, wherein the drug delivery means is a semi permeable membrane (21), separating the drug compartment (12)
25 from the delivery site, the semi permeable membrane (21) being impermeable for molecules coming from the delivery site and being permeable for the hydrated drug coming from the drug compartment (12).

13. A drug delivery device (20, 40, 60) as claimed in claim 12, wherein the
30 electronic circuit (17) is arranged for applying an electric field over the semi permeable membrane (21) for enhancing the delivery of the hydrated drug to the delivery site.

1/3

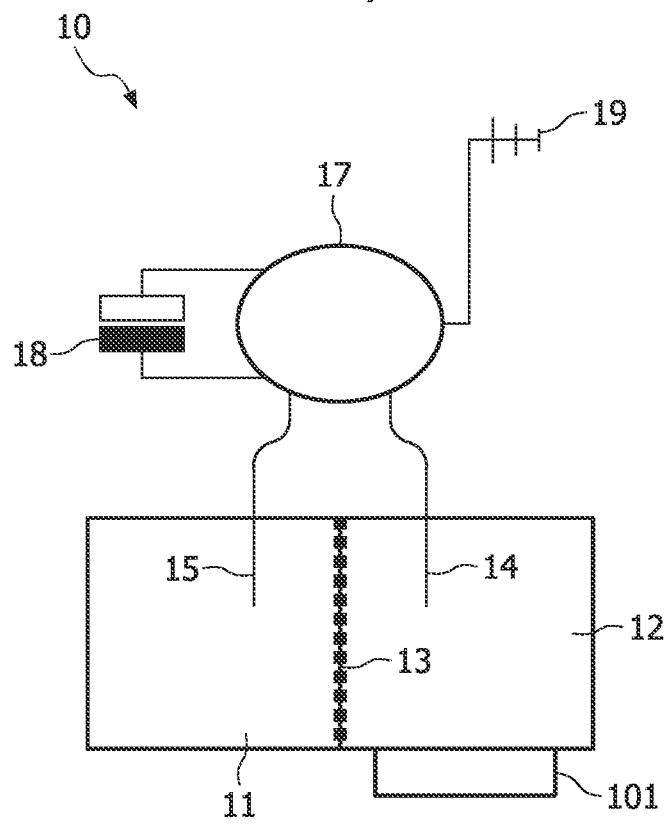


FIG. 1

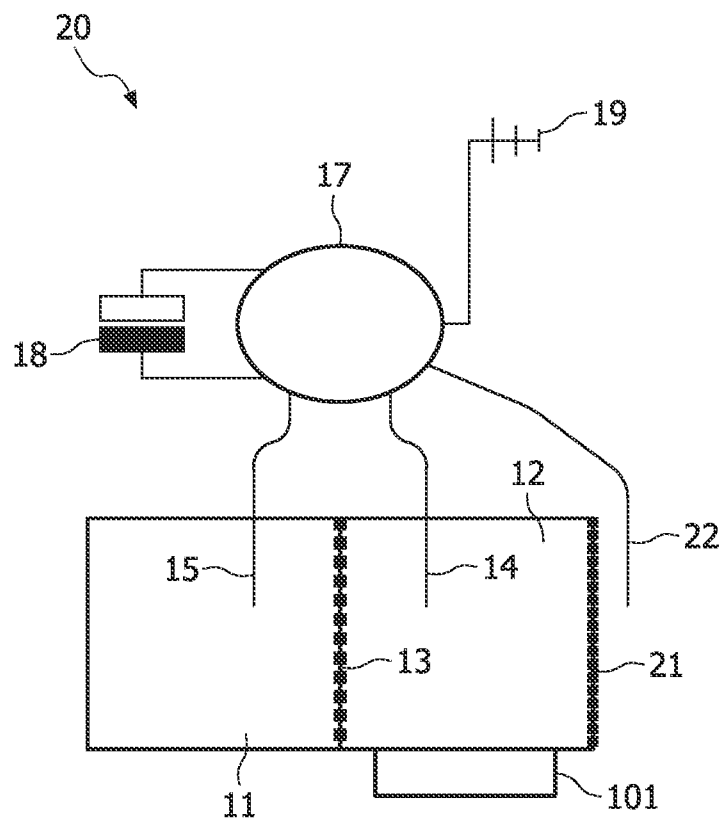


FIG. 2

2/3

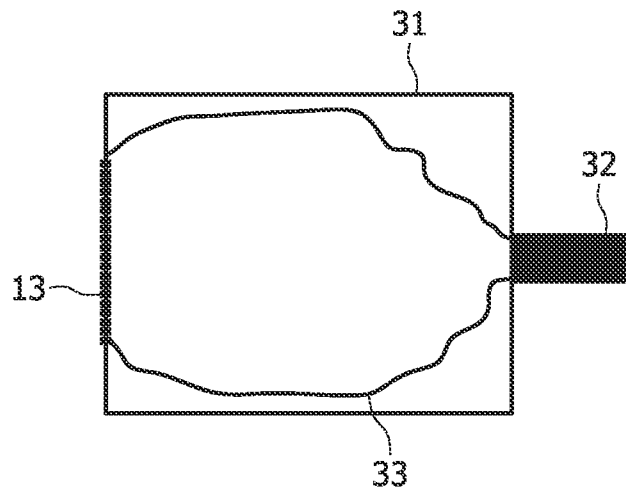


FIG. 3

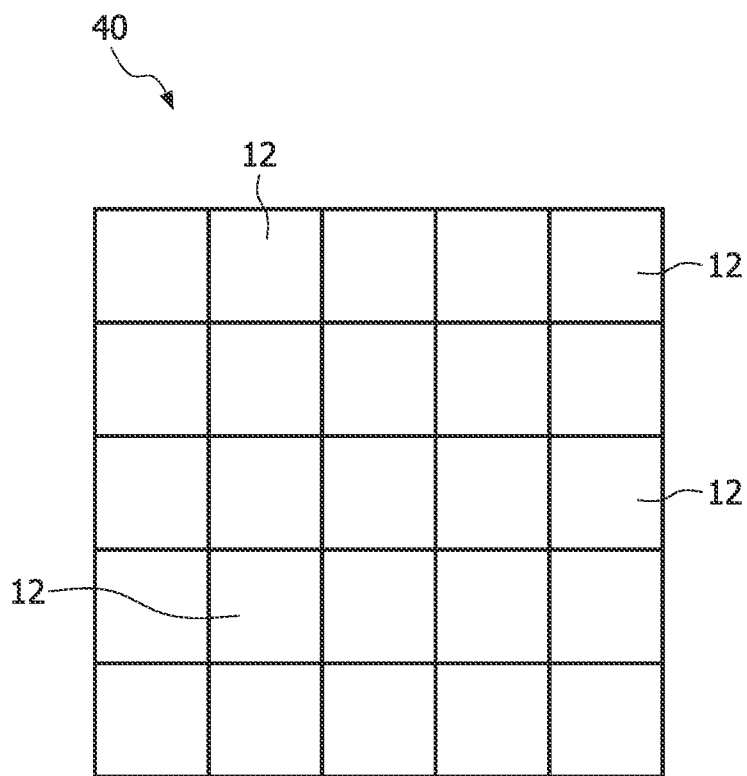


FIG. 4

3/3

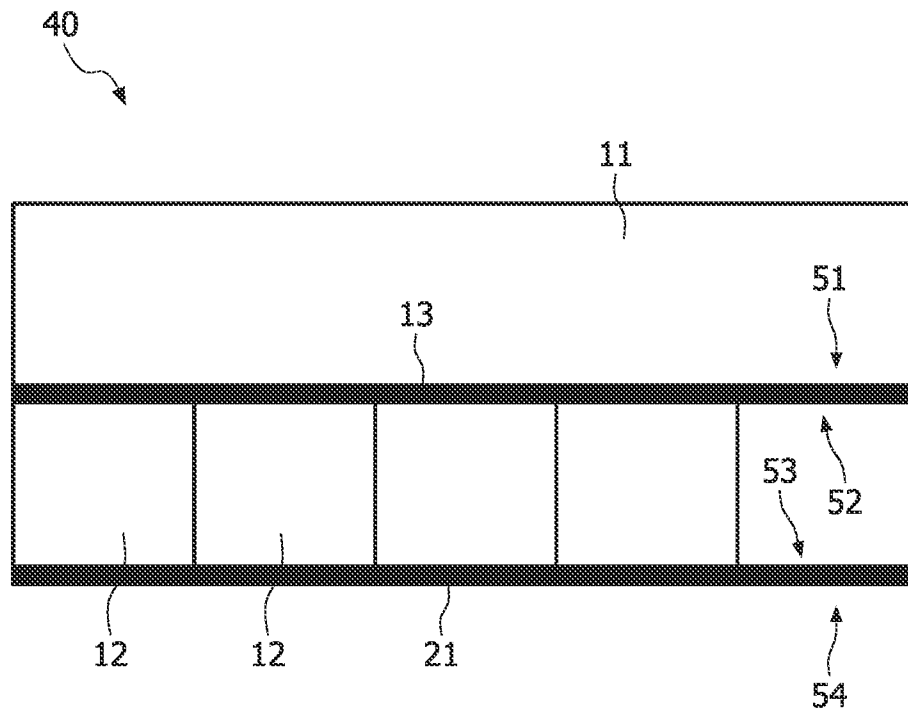


FIG. 5

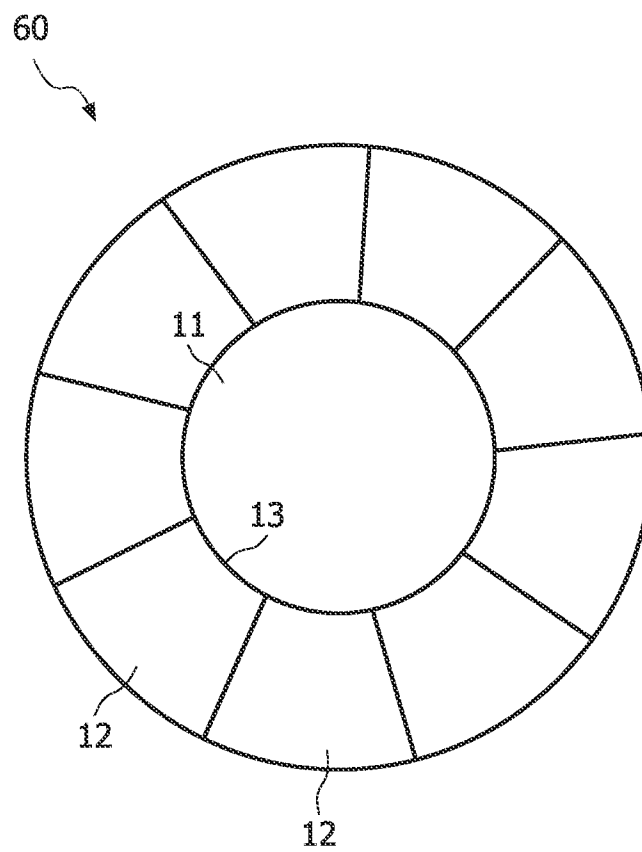


FIG. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/053728

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61M5/142 A61M5/14 H01M8/00

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 H01M

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 practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 217 894 A (FRANETZKI MANFRED [DE]) 19 August 1980 (1980-08-19) the whole document	1-13
A	US 2006/116641 A1 (GORDON JOHN H [US] ET AL) 1 June 2006 (2006-06-01) the whole document	1-13
A	US 2004/241528 A1 (CHIAO MU [US] ET AL) 2 December 2004 (2004-12-02) the whole document	1-13

☐ 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 document but published on or after the international filing date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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