**Title:** IMPLANTABLE THERAPEUTIC SUBSTANCE DELIVERY DEVICE

**Abstract:** An implantable therapeutic substance delivery pump is typically implanted into a patient at a location appropriate for the therapy that interferes as little as practicable with patient activity such as subcutaneous in the lower abdomen. The invention refers to an implantable therapeutic substance delivery device (1) comprising a therapeutic substance reservoir (3), and a pump (4) configured to pump a therapeutic substance from the reservoir to an outlet (22). The pump has a power rotor (41) and two parallel idler rotors (42) adjacent to the power rotor. The idler rotors have screw threads which intermesh with a screw thread (43) in the power rotor wherein the idler rotors and power rotor are encased in an enclosure (51) dimensioned to allow axial rotation of the rotors.
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Implantable therapeutic substance delivery device

FIELD OF THE INVENTION

This disclosure relates to an implantable therapeutic substance delivery device comprising a therapeutic substance reservoir, and a pump configured to pump a therapeutic substance from the reservoir to an outlet. The device can be implanted in a patient for controlled delivery of the therapeutic substance.

BACKGROUND OF THE INVENTION

An implantable therapeutic substance delivery pump is typically implanted by a clinician into a patient at a location appropriate for the therapy that interferes as little as practicable with patient activity such as subcutaneous in the lower abdomen. The device can be implanted to infuse the therapeutic fluid or other therapeutic substance at a programmed infusion rate and predetermined location to treat the medical condition. Such devices allow reliable and accurate delivery of the therapeutic substance preventing patient complications caused by inadequate or unintended therapeutic substance delivery.

The optimum concentration of the therapeutic substance can vary greatly from patient to patient as well as during the course of the treatment. Therefore, an ideal delivery system should be able to control the concentration of the therapeutic substance at the optimum therapeutic level during the course of the treatment. This can be done by constant infusion or by pulsatile time-varying infusion.

The major advantages of implantable therapeutic substance delivery devices include both targeted and local delivery of therapeutic substances at a constant rate, less therapeutic substance required to treat the disease state, minimization of possible side effects, and enhanced efficacy of treatment. Also, these delivery devices are capable of protecting therapeutic substances which are unstable in vivo and which would normally require frequent dosing.

Implantable delivery devices are particularly desirable where compliance with a prescribed drug regimen is critical. Such devices allow a therapeutic substance to be delivered at a specific rate without regular physician or patient intervention. Implantable therapeutic substance delivery devices can be used to treat conditions such as pain, spasticity,
cancer, and a wide variety of other medical conditions. The therapeutic substance can for example be a medicine, a mixture of medicines or co-reactive components of a medicine, a placebo, a non-medicinal substance, dietary supplements, contrast agents, nutrients, probiotics, gases, fluids, liquids, radiological agents, imaging or medical markers, etc. The therapeutic substance can be administrated as a liquid, but also as nano-particles or encapsulated in nano-spheres or micro-spheres which can be suspended in liquid carrier, such as an oil.

Implantable therapeutic substance delivery devices are typically provided with a pump to transport the therapeutic substance from a reservoir to an outlet of the device. An example of an implantable therapeutic substance pump is disclosed in WO 02/083208.

Therapeutic substance delivery devices are typically used for accurate delivery of small doses. For this reason, possible leakage via the pumping mechanism can have undesirable effects on the dosing.

The object of the present invention is to provide a reliable implantable therapeutic substance delivery device with a pump with reduces risk of leakage of therapeutic substance.

SUMMARY OF THE INVENTION

The object of the invention is achieved with an implantable therapeutic substance delivery device comprising a therapeutic substance reservoir, and a pump configured to pump a therapeutic substance from the reservoir to an outlet, the pump comprising a power rotor and at least two parallel idler rotors adjacent to the power rotor, the idler rotors having screw threads intermeshing with a screw thread on the power rotor wherein the idler rotors and power rotor are encased in an enclosure dimensioned to allow axial rotation of the rotors.

Accurately machined precisely intermeshing threads of the rotors enfold the liquid being pumped and act as seals in relation to each other and to the pump body or sleeve in which they rotate. The power rotor and idler rotors turn inside of the enclosure which can be machined to close tolerances. Flow through a screw pump is in the axial direction of the power rotor. The inlet hydraulic fluid or the therapeutic substance that surrounds the rotors is trapped as the rotors rotate. This fluid or substance is pushed uniformly with the rotation of the rotors along the axis and is forced out the other end. The fluid or substance delivered by screw pumps does not rotate, but moves linearly. The power rotor does not drive the idlers but the forces, which forces are of a hydraulic nature if a fluid is used, act on screw flanks
and turn the idlers without torque, thus reducing the friction. No gears are required to transmit power between the rotors. As radial forces on the idlers are taken up by the surrounding cylindrical surfaces, no other bearings are required. Axial forces on the screw threads, caused by the pressure differential between inlet and outlet are balanced hydraulically within the pump. In this pump configuration pressure is reduced, the power rotor is centralized and radial loads are absorbed. As a result, very accurately dosing of the therapeutic substance is made possible with effectively reduced risk of leakage.

Although the system can use three or even more idler rotors, the use of two idler rotors will generally be sufficient.

The implantable device will typically have a housing encasing the pump and the reservoir. The housing will have an outlet for delivery of the therapeutic substance.

The therapeutic substance reservoir can for example be a balloon of a flexible material, such as a rubber or a rubber-like plastic. Such a balloon reservoir can provide pump-inlet-pressure preventing back-stream leakage if the reservoir pressure is set to exceed the external pressure.

The therapeutic substance can be led outside the reservoir by the pump via a dedicated channel connecting the pump outlet to the outlet of the reservoir. The channel can for example be made of an elastic material, such as a rubber, in order to absorb the initial pressure created by the pump.

A catheter can be used to create a pathway for the therapeutic substance to flow from the pump to the delivery site. Optionally, two or more catheters can be used to allow site specific and independent delivery of the therapeutic substance to be administered to different body sites.

To further enhance controllability of the therapeutic substance outflow, a capillary flow restrictor can be placed directly at the end of the therapeutic substance channel or at the end of the catheter, if so desired.

Optionally, the delivery device is provided with a refill port or septum. This way it can be replenished with the therapeutic substance, so the period the pump can be implanted may not be limited by therapeutic substance capacity.

The therapeutic substance delivery device according to the present invention can comprise a motor to drive the pump. The motor can for example be a stepper motor, particularly if pulsatile delivery is required. The power rotor may also be driven by another actuator mechanism, e.g. by back pressure, a piezo-based actuator, osmotic pressure, an electro-magnetical actuator, etc.
A power source can be used to provide power to the pump and optionally other components of the implantable device. The power source can for instance be a battery. An exemplary battery is a thin film lithium battery (e.g., available from Frontedge Technologies TM, located in Baldwin Park, California, US), having a small footprint and a suitable shelf life (e.g., 1% discharge/year). The battery may further be selected from other known batteries, such as photo lithium, silver oxide, lithium coin cells, zinc air cells, alkaline, etc... Alternatively or additionally the device may use passive power. It is contemplated that the power source includes a device configured for scavenging power from another device, which may employ electrostatic, micro fuel cells, micro-heat, temperature gradient, etc.

The delivery device can comprise electronic circuitry to control the pump. Optionally, the electronic circuitry is capable of receiving and transmitting data, which include device identification number, sensor(s) data, remaining drug quantity, remaining battery power, time and date of last refill. The electronic circuitry can be programmed prior to implantation or after implantation, e.g. via a wireless link. The circuitry can be programmed to work in several modes, such as single shot delivery, continuous flow delivery, complex profiled delivery, sensor triggered delivery, or combinations thereof.

The implantable therapeutic substance delivery device may be remotely controllable. The implantable therapeutic substance delivery device may be used in situations where ultra low medicine dosing is appropriate.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be elucidated with reference to the figures wherein:

Figure 1 shows in longitudinal cross section a therapeutic substance delivery device according to the present invention;

Figure 2 in detail the rotors of the pump of the device of Figure 1;

Figure 3 in cross section the rotors of the device of Figure 1;

Figure 4 in detail the power rotor of the pump in Figure 1.

DETAILED DESCRIPTION OF THE EMBODIMENTS

Figure 1 shows an implantable therapeutic substance delivery device 1 comprising a housing 2 encasing a therapeutic substance reservoir 3 of a rubber material, a pump 4 disposed within the therapeutic substance reservoir 3, a pump support 5, a motor 6, a power source 7, electronic circuitry 8, and a sensor 9.
The housing 2 is a cylindrical body with bulging end walls 21 and an outlet 22. The housing is made of a bio-compatible material. Near the bulging end walls 21, the housing 2 is provided with a number of stitches ears 23. These ears 23 have the function to fixate the device in the tissue of a patient by means of stitches (not shown). The device needs proper positioning to administer the drugs at the exact predetermined location. The stitches ears 23 enable this proper positioning. The housing 2 is further provided with a therapeutic substance refill septum 24 to provide access to the therapeutic substance reservoir 3, and a degas septum 25, to provide access to the space around the therapeutic substance reservoir 3 within the housing 2. Antenna rings 26 are embedded in the housing wall to receive remote control signals. Part of the housing wall is formed by a semi-permeable venting membrane 27.

Therapeutic substance delivery reduces the pressure in the rubber balloon reservoir 3, resulting in reduced volume of the rubber balloon 3. This creates an underpressure in the space surrounding the therapeutic substance reservoir balloon 3. Due to the underpressure, ambient gas is sucked into the interior of the housing 2 via the semi-permeable venting membrane 27. The therapeutic substance reservoir 3 can be refilled via septum 26. During refill, gas can escape via degas septum 25.

The rubber therapeutic substance reservoir 3 has a refill opening 31 leak tight connected to the refill septum 24, an outlet opening 32 in line with the outlet opening 22 of the housing 2, and a pump opening 33, where the pump support 5 enters the interior of the reservoir 3. The balloon reservoir 3 is attached to the pump support 5 along the edge of pump opening 33 in a leak tight manner. A therapeutic substance delivery channel 34 leads from the pump 4 via outlet opening 32 of the therapeutic substance reservoir 3 to the outlet opening 22 of the housing 2. The edge of outlet opening 32 of therapeutic substance reservoir 3 and the edge of the outlet opening 22 in housing 2 are attached to the wall of therapeutic substance channel 34 in a leak tight manner. Outside the housing 2, the therapeutic substance channel 34 is operatively connected to a catheter 35 to lead the delivered therapeutic substance to the patients’ tissue to be treated. The free end 36 of the catheter 35 narrows to form a capillary flow restrictor.

The pump 4 is a three screw pump, shown in more detail in Figure 2. The pump 4 comprises a power rotor 41 and two parallel idler rotors 42 at opposite sides of the power rotor 41. The power rotor 41 and the idler rotors 42 are provided with precisely intermeshing screw threads 43, 44. As shown in Figure 3, the idler rotors 42 and power rotor 41 are encased in an enclosure 51 dimensioned to allow axial rotation of the rotors 41, 42. As
shown in Figure 1, the enclosure 51 has an inlet 52 at one end of the rotors and an outlet 53 at their other end, which other end is connected to therapeutic substance channel 34.

As can be seen in Figure 1, the pump 4 is held in place by pump support 5. This support 5 comprises a radial disc 73 dividing the interior of the housing 2 into two sections: a first section 54 containing the balloon reservoir 3 and a second section 55 containing the stepper motor 6, the power source 7, the electronic control circuitry 8 and sensor 9. Radial disc 73 and enclosure 51 form integral parts of the pump support 5 made of one single piece.

Motor 6 is a stepper motor. A shaft 61 passes the support 5 via a central opening to engage the power rotor of pump 4.

The power source 7 is a battery, which provides power to the pump 4, control circuitry 8 and sensor 9. The battery can be a thin film lithium battery photo lithium, silver oxide, lithium coin cells, zinc air cells, alkaline, or any other suitable type of battery.

The delivery device 1 comprises electronic control circuitry 8 located within the housing 2 to control the pump. The electronic control circuitry 8 is capable of receiving and transmitting data via antenna rings 26. The electronic control circuitry 8 can be programmed prior to implantation or after implantation, e.g. via a wireless link.

Sensor 9 serves to detect biological parameters, such as temperature, pressure, or the presence of certain biochemical substances. The readings can be sent to the outside via antenna rings 26 or used for activating the stepper motor 6 and pump 4 via the electronic control circuitry 8.

Possible leakage levels of the disclosed embodiment can be estimated as follows. The volume (Ditum), pushed forward by the pump after one turn of the power rotor, can be calculated using:

\[
D_{\text{turn}} = \frac{\pi}{4} \left[ (d_{PR}^o)^2 - (d_{PR}^i)^2 \right] \frac{\sin \theta}{\sin \psi} \text{ m}^3
\]

Wherein \( \theta \) is the helix angle, \( \rho \) is the power rotor pitch [mm], \( l_h \) is the length of a tooth of the power rotor [mm], \( d_{PR}^o \) is the power rotor outer diameter [mm], \( d_{PR}^i \) is the power rotor inner diameter [mm], as also shown in Figures 3 and 4.

For typical parameters values: \( d_{PR}^o = 3 \text{ mm} \), \( d_{PR}^i = 2.4 \text{ mm} \), \( p = 1.6 \text{ mm} \), \( l_h = 0.6 \text{ mm} \) and \( \theta \approx 20^\circ \) one can calculate the volume pushed in one turn of the power rotor:
In the case a step-motor, which requires 20 steps to complete a turn, is used the amount that can be pushed forward in one step is 375 nL.

If the pressure difference between the balloon therapeutic substance reservoir and the outlet is about 40 kPa and the gap \((d_G = d_{PR}^C - d_{PR}^O = d_{IR}^C - d_{IR}^O)\) between a rotor and the surrounding it channel is about 5 \(\mu m\) the leakage \(\Phi_L, [rr^2s^{-1}]\) through the pump is estimated using the formula (derived from Hagen-Poiseuille for an annular slit):

\[
\Phi_L = \frac{AP\pi(d_{PR}^C - d_{PR}^O)^4}{128\eta/\ell_h} \quad \frac{2AP\pi(d_{IR}^C - d_{IR}^O)^4}{128\eta/\ell_h} = \frac{3\pi AP(dJ)}{128\eta/\ell_h}
\]

Wherein:

- \(AP\) is the pressure difference between the pressure at the reservoir and pressure at the outlet of the catheter (e.g. blood or tissue pressure) [Pa];
- \(\eta\) is the liquid viscosity [Pa.s].

The leakage can now be calculated using typical system parameters values:

\(l_a = 0.6 \text{ mm}, \quad d_G = 0.005 \text{ mm}, \quad \eta = 1 \text{ Pa.s}, \quad AP = 1 \text{ Pa and } n = 4\)

\[
\Phi_L = \frac{3 \times 3.14 \times 40 \times 10^{-3} \times 0.005^4}{128 \times 1 \times 4 \times 0.6} \approx 8 \times 10^{-7} \text{ mm}^3 \text{s}^{-1} = 0.8 \text{ mL} \text{s}^{-1}
\]

The obtained shows that the leakage through the pumping mechanism is extremely low.

Furthermore, the drug may be suspended in oil with higher viscosity. This will further reduce the leakage. Such oils are known e.g. in the field of dermatology and are called "fat oils". They may comprise forms of glycerin, combined with one or more organic fatty acids. These oils may also comprise lipids (natural, occurring in skin), vitamins and colorants. Oils are characterized in that they are liquid at room temperature. Examples of vegetable and animal oils are soybean oil, fish oil, mineral oil, coconut oil, palm kernel oil.
Furthermore, the drug may be encapsulated in a carrier shell (e.g. degradable micro-spheres). If the diameter of these spheres is higher than the distance between the rotors and the rotors and the walls (tolerances) (e.g. > 5 µm) there will be virtual no leakage.

The leakage can be further reduced, e.g., by wholly or partially coating the contact faces of the idlers and/or the power stator with hydrophobic material, such as a non-stick coating, e.g. based on fluoropolymers and/or polysilanes.

While the invention has been illustrated and described in detail in the drawings and foregoing description, such illustration and description are to be considered illustrative or exemplary and not restrictive; the invention is not limited to the disclosed embodiments.

Other variations to the disclosed embodiments can be understood and effected by those skilled in the art in practicing the claimed invention, from a study of the drawings, the disclosure, and the appended claims. Therapeutic substance delivery device may be used in a configuration wherein the medicine is in a liquid form, encapsulated in carrier shells (e.g. in the form of micro-spheres) or suspended in oil.

Devices, elements and components, known per se, have not been described in detail, as the skilled person is familiar with the matter. In the claims, the word "comprising" does not exclude other elements or steps, and the indefinite article "a" or "an" does not exclude a plurality. A single mechanism or other unit may fulfill the functions of several items recited in the claims. 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. Any reference signs in the claims should not be construed as limiting the scope.
CLAIMS:

1. An implantable therapeutic substance delivery device (1) comprising a therapeutic substance reservoir (3), and a pump (4) configured to pump a therapeutic substance from the reservoir (3) to an outlet (22), the pump (4) comprising a power rotor (41) and at least two parallel idler rotors (42) adjacent to the power rotor (41), the idler rotors (42) having screw threads (43) intermeshing a screw thread in the power rotor wherein the idler rotors and power rotor are encased in an enclosure (51) dimensioned to allow axial rotation of the rotors (41, 42).

2. Therapeutic substance delivery device according to claim 1 wherein the therapeutic substance reservoir (3) is an expandable balloon of a flexible material encased in a housing (2) comprising a semi-permeable section (27) and a degas septum (25).

3. Therapeutic substance delivery device according to claim 2 wherein the pump (4) is disposed in the reservoir (3).

4. Therapeutic substance delivery device according to claim 3 wherein the power rotor (41) is driven by a stepper motor (6) located outside the therapeutic substance reservoir (3).

5. Therapeutic substance delivery device according to claim 1 having a sensor (9) for medicine dose monitoring and control.

6. Therapeutic substance delivery device according to claim 5 wherein the sensor (9) is an optical, electrical, mechanical or chemical sensor.

7. Therapeutic substance delivery device according to claim 1 wherein the outlet of the delivery device (22) is connected to a catheter (35).
8. Therapeutic substance delivery device according to claim 7 wherein the end of the catheter (35) is a capillary flow restrictor (36).
A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M5/142 F16H39/34

According to International Patent Classification (IPC) as to both national classification and IPC

B. RELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61M F16H

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

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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Date of mailing of the international search report 06/04/2009

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