Implantable Drug Delivery Systems - Design Process

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The market of programmable implantable pumps has bound to a monopolistic situation, inducing high device costs, thus making them inaccessible to most patients. Micro-mechanical and medical innovations allow improved performances by reducing the dimensions. This affects the consumption and weight, and, by reducing the number of parts, the cost is also affected. This paper presents the procedure followed to design an innovative implantable drug delivery system. This drug delivery system consists of a low flow pump which shall be implanted in the human body to relieve pain. In comparison to classical known solutions, this pump presents many advantages of high interest in both medical and mechanical terms. The first section of the article describes the specifications which would characterize a perfect delivery system from every points of view. This concerns shape, medication, flow, autonomy, biocompatibility, security and sterilization ability. Afterwards, an overview of existing systems is proposed in a decisional tree. Positive displacement motorized pumps are classified into three main groups: the continuous movement group, the fractioned translation group and the alternative movement group. These systems are described and the different problems which are specific to these mechanisms are presented. Since none of them fully satisfy the specifications, an innovation is justified.. The decisional tree is therefore extended by adding new principles: fractioned refilling and fractioned injection within the fractioned translation movement group, spider guiding system within the alternative translation movement group, rotational bearing guided device and notch hinge guided device in the alternative rotation movement group.

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1. Introduction

The explosion of new technologies, and particularly recent innovations in micro-mechanical and medical areas, opens new ways and offers new advisability of treating patient disease. Nevertheless, recent surveys made in collaboration with medical scientists have clearly shown a lack of medical implantable pumping devices. The analysis displayed in this paper introduces a recent specification sheet drawn up owing to the collaboration of medical scientists. State of the art analysis of the different existing devices points out the existing gap between available solutions and patient needs. Having been developed in the aim of satisfying these needs, innovative designs are hereby presented and classified in the existing device decisional tree. Detailed advantages of the various systems are described in this paper.

2. Specification sheet

Collaboration between medical practitioners and engineers has allowed the authors to precisely point out the optimal way to satisfy patient requirements regarding implantable drug delivery devices. Table 1 presents a typical specification sheet which could be inferred from this analysis.

Table 1 Specification sheet (adapted from Alcimed)

Shape, dimensions, weight	Medication flow	Autonomy	Implantation and compatibility	Security
No sharp edges	Reference[2]: 0.3ml/h – 7.5 ml/day	Refilling[2] delay : 3 days to 3 month (depending on applications)	Working temperature: 35-42°C	Negative pressure reservoir
e.g. flat ellipsoid	Minimum[2] : 0.1ml/day	Battery life time : more than 3 years	Pump housing materials[3]: classVI (>29 days)	Active pump
Maximum dimensions: 40mm*25mm *15mm	Injection unit[2] : 0.2 μl		Inner parts of the pump[3] : medication compatibility	No leak at rest
Weight : less than 150g			Complete sterilization ability	

A streamlined, flat, small shape, flat ellipsoid for example, and light weight, induce minimal constraints and bring maximal comfort to the patient. Flexible medication delivery allowing flow rates of about 0.3 ml per hour and an injection unit of roughly 0.2 μl, covers patient needs and medical practitioner's requirements. A delay of three days to three months between two refilling actions allows enough mobility for the patient, whereas 3 years' timespan must be regarded as being the minimum battery life. Biomaterials admitting sterilization, satisfying EU-10993 class VI standard and compatible with medication are selected. Body temperature (between 37°C and 42°C) does not raise any problems. A negative pressure reservoir and appropriate non-return valves insure the security of the device, especially if a peculiar layout completely avoids any leak at rest.

3. State of the art

3.1 Introduction

Known implantable pumping systems always consist of a medication storage device, a pumping system and a perfusion system. The paper presented here, focuses on the pumping systems only, leaving other systems for later analysis. Pumping systems can be separated into hydraulic, guiding and actuating sub-systems as shown in Fig. 1. Hydraulic itself can be split into a mechanical principle, a distribution system (valve) and a sealing system.

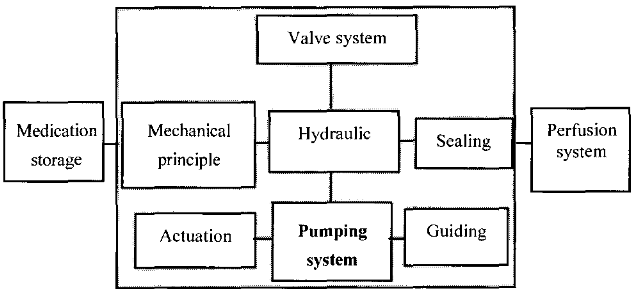

Fig. 1 Implantable drug delivery sub-system

3.2 Classification chart

A classification chart which summarizes existing implantable drug delivery systems is presented in Fig. 2. Because of lethal risks, simple accumulators (under pressure systems) are ruled out with regard to actually motorized pumps. Non-volumetric devices are equally excluded because no metering of drug dispensed volume is provided. Finally, positive displacement devices are separated into a continuous motion group and an alternative motion group.

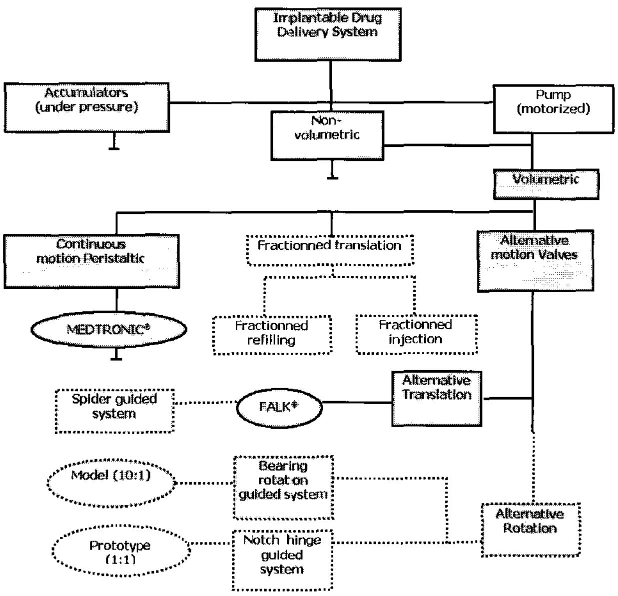

Fig. 2 State of the art of pumping devices

3.3 The Peristaltic Principle

The Peristaltic Principle is represented by the Medtronic's Synchromed pump which is the only programmable pump on the market. In such a pump, rollers revolving motion (Fig. 3) induced by a rotary actuator crushes a tube containing the medication agent; this tube is connected to the negative pressure tank and the rollers motion promotes medication flow from the tank to the perfusion system.

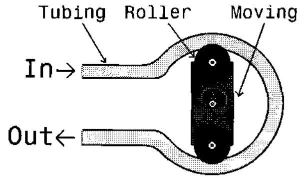

Fig. 3 Peristaltic Pump Principle stem

The main advantages of this peristaltic principle lie in an absence of valves, an absence of any potential leakage problems from the tank to the perfusion system. On the other hand, problems result from the energy consumption peak required each time a roller begins squeezing the tube after a revolution. This considerably reduces the battery life. Moreover, the high number of components needed due to the high reduction ratio between the high speed electric motor and the rollers pair, involves tremendous manufacturing and assembly problems.

A Design For Manufacturing and Assembly study (DFMA study) [1] has been made. This study consists in following some criteria to ensure efficiency of the design via adaptation assembly ratings and the determination of components leading to the worst assembly time. According to the DFA method, a design efficiency of 7 % ensues and a theoretically total assembly time of 1160 seconds is required. The worst assembly times concerns the screws (20.60 sec., 18 sec. and 12 sec), the crowns (13.60 sec.), the washers (13 sec.), the tubing (11.75 sec.), the tubing protection (11.50 sec.) and the shafts (11.30 sec.).

The peristaltic pump gearing system strongly increases the number of parts and involves very small parts and costly assembly operations. This system presents not less than 12 screws, 18 rings, 8 ruby sockets, several pins promoting high assembly time and thus high subassembly times. With regard to the functionality of the product, only twenty parts could be involved [1] (an electromagnet, a rotor, a stator, a ring, a main frame, an upper and a lower bearing, eight ruby parts, four gears, a bridge, a tubing, a moving part frame and two bearings) leading to a more efficient assembly process. This number of parts could not be more reduced without a change in the technical solution.

3.4 The Alternative Translation Motion Group

The Alternative Translation Motion Group is well represented by the US 4,568,250 and the US 6,193,497 Falk patent. The simplest principle to inject a small amount of liquid, namely the "syringe principle" has to be improved to avoid contamination risks arising owing to the piston movement in an open chamber as shown in Fig. 4.

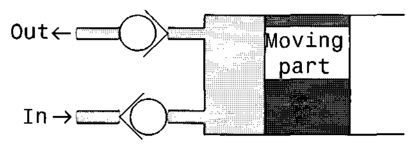

Fig. 4 Syringe Principle

The twin chamber concept introduced by Falk and presented in Fig. 5 allows avoiding such contamination problems and offers many other advantages.

The simultaneous suction and delivery phases occur when the actuator causes the displacement of the moving part toward the right. The admission valve 1 then opens and the transfer valve 2 then closes The admission chamber volume increases and the backflow chamber volume decreases. This causes a fluid flow through the inlet tubing and the exit tubing.

The transfer phase occurs when the actuator is released and a return spring causes the movement of the mobile part toward the left. The admission valve 1 is then closed and the transfer valve 2 opened;

the admission chamber volume is decreasing and the backflow chamber volume increasing: fluid flow occurs through the transfer channel.

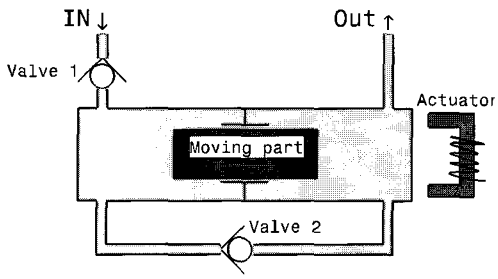

Fig. 5 Alternative Translation Movement (Falk)

Main Falk's pump advantages are the absence of contamination risks from the outside and the hermetically sealed pumping system, since the electromagnet acts on the piston through the container wall. On the other hand, problems result from friction between the moving part and the housing which can induce fluid contamination by particle release and wear, decreasing the device autonomy; unavoidable and variable leakage between the moving part and the housing impairs metering precision, the presence of valves decreases security and the high parts count increases the total cost of the system.

4. Innovative designs

Innovative design phases have been undertaken with the aim of decreasing the presented gap. As the work proceeded, values and limits of various concepts were grasped through analysis, simulations or tests, which allowed further progress.

Successive suggested innovations are described here below: the Fractioned Refilling or Injection Pump, the Spider Guided System, the Rotation Guided Bearing System, the Vane System and finally the Notch Hinge Guided System.

4.1 The Fractioned Refilling or Injection Pump

4.1.1 Introduction

Traditional actuators are often inoperative at small dimensions and are advantageously replaced by new kinds of actuators. Piezoelectric actuators and shape memory alloys (SMA) are widely described in,[12] a work describing the conception and realization of a micro-grasping tool (Fig. 6).

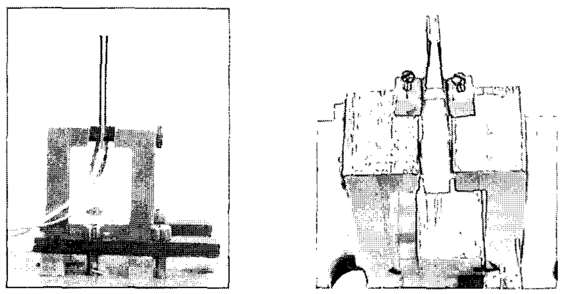

Fig. 6 Piezoelectric and SMA grasping tool

The inverse piezoelectric effect is based on the deformation of a polarized crystal when submitted to an electrical field. The deformation is longitudinal, transverse or flexinal, depending on the polarization direction, the field direction and the elaboration of the crystal. SMA consists in a crystal exhibiting two different crystal states: martensitic and austenitic. These two states are dissociated regarding the transformation phase temperature in such a way that a deformed crystal in its martensitic phase recovers its initial shape when heated above the transformation phase temperature. The two aforementioned actuators can be compared regarding the following criteria:

- the linearity of displacement versus supply signal,
- the presence of hysteresis,
- the amplitude of the displacements
- the response time
- the efficiency.

The study performed in [12] confirmed the linearity of the examined piezoelectric (PZT -66% PbO, 21% ZnO2, 11% TiO2- from the Philips Company) actuator with a light hysteresis. The studied SMA (NiTi flexinol 100 from the Mondo-Tronics Company) exhibited non linear behavior with a strong hysteresis. Piezoelectric actuators are on the other hand interesting regarding their high level of accuracy and their high strength but have a poor displacement magnitude (0.1%-0.2% of the total length). The SMA are interesting regarding the high level of deformation when heated (3%-5% of the total length). The piezoelectric micro-grasping tool had a 12 times shorter response (Fig. 7) time than the SMA micro-grasping tool response time

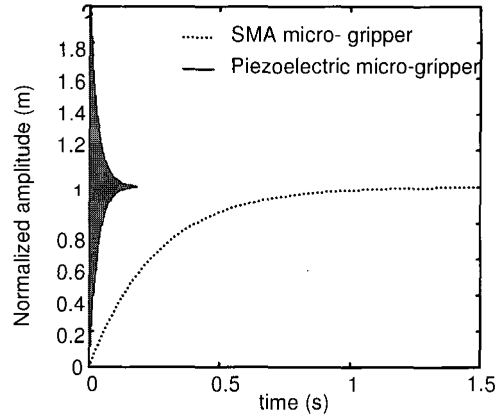

Fig. 7 Piezoelectric vs. SMA response time

The piezoelectric actuator was thus, based on these criteria, taken as a first choice for the design of an implantable device keeping in mind that the displacement amplitude problem can be solved using piezoelectric stacks and that the efficiency is better than the SMA efficiency.

4.1.2 Design process

The challenge consists in finding a medium to obtain a continuous medication flow whereas piezoelectric actuators often entail jerky movements. The design process followed here is based on an analogy approach (widely described in[7]). In order to simplify the design process description, work was initially conducted without any medication fluid. The focus was subsequently put on the mechanical aspects taking, as objective, to draw benefit from some well known discrete systems, rendering them continuous by the analogy principle. Once this is done, additional elements necessary to the fluid flow may be added in a second step.

4.1.3 The mechanical analogy principle

The Ratchet Principle (Fig. 8) is a discrete system which consists in a moving part (sprocket wheel) and a locking part (the ratchet itself), the latter being spring loaded and oscillating around a fixed axis.

This system allows one to obtain a continuous motion in one direction only (counterclockwise in Fig. 8) and is locked in the other direction (clockwise in Fig. 8). This locking is obtained thanks to the location of the spring loaded locking part into one of the cavities of the wheel. This is the so called 'free wheel' which was one of the main improvements in bicycle design. Another application of such a system is for example on pulleys used on sailboats to allow to reduce the effort of a sailor pulling on a rope.

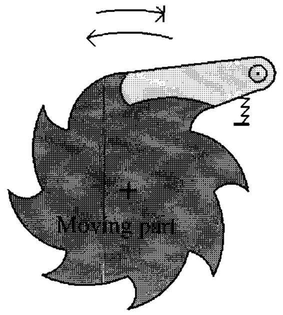

Fig. 8 The Ratchet Principle

One can derive from the ratchet principle a linear system by locating the teeth along a straight line. Two ratchet systems used as indicated in Fig. 9 lead to a Jacking System: one ratchet supports the load while other reaches the following cog to move one extra step.

The drawback of these systems is the discrete number of stop positions due to the discrete number of teeth of the wheel and the noise which occurs when the locking part falls into place.

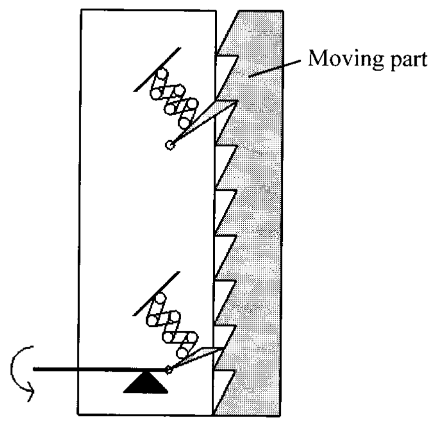

Fig. 9 The Jack Principle

Using the analogy principle from a discrete motion to a continuous motion, the ratchet principle can be improved by using a moving part and a fixed part receiving spring loaded locking balls or rollers arranged as in Fig. 10. This is called the Plain Free Wheel Principle.

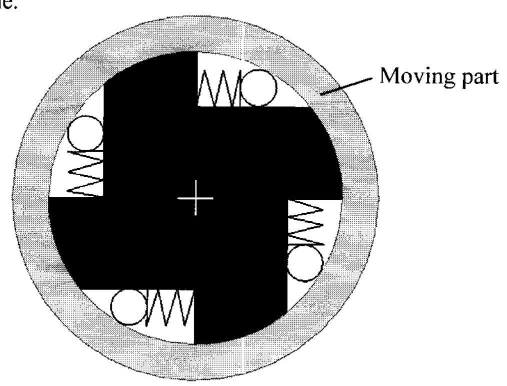

Fig. 10 The Plain Free Wheel Principle

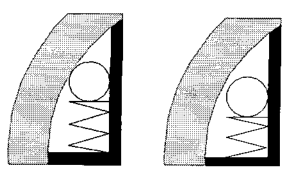

Fig. 11 Locked and unlocked locking balls

This system allows one to obtain a continuous motion in one direction (counterclockwise in the Fig. 10) and is locked in the other direction (clockwise in the Fig. 10). In this case, free rotation is allowed when the locking elements are loaded (when the wheel turns in the counterclockwise direction) (spring compressed) and locked when the wheel turns in the clockwise direction (spring relaxed). Locking is due to friction and cam jamming effect. The weak mass renders the inertia tiny and thus the locking phase instantaneous. This principle has been used for a long time in the rear axle of bicycles because noise suppression is important and because such axles can be used for braking action. It has also been used for the winches on racing sailboats to avoid the noise which could reveal sail adjustments to the opponents. It has been proved in,[8] that taking as hypothesis that the action of the non return spring and that the weight of the locking ball can be neglected, the non sliding condition is given by

$$f > \sqrt{\frac{R - 2r - a}{R + a}} \qquad (1)$$

where:

f = rubbing coefficient
R = internal radius of the moving part
r = radius of the locking ball
a = distance given in Fig.12

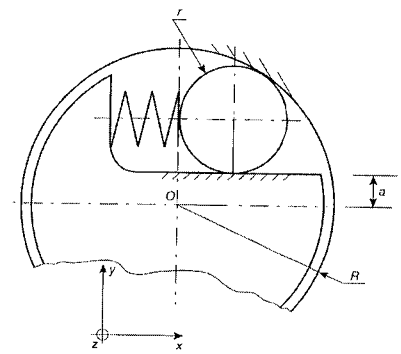

Fig.12 The working condition of the free wheel

In a similar way as the plain free wheel system is a continuous motion adaptation of the ratchet principle, a linear system can be derived from the jack principle by locating the locking elements along a straight line.

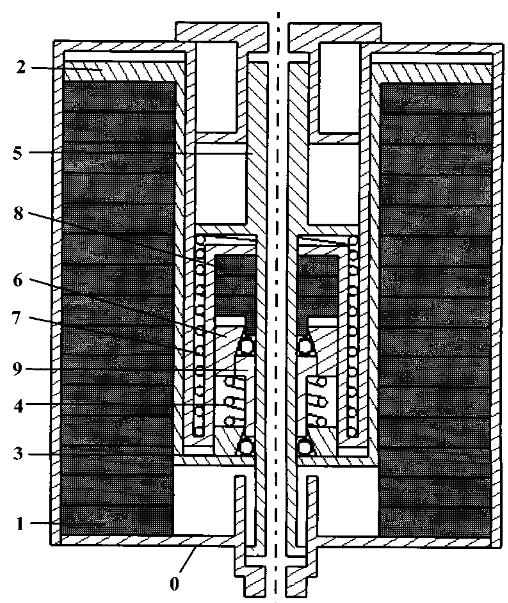

Fig. 13 The Fractioned System Principle

The Fractioned System obtained, shown in Fig. 13, comprises two piezoelectric actuators (the main and the unlocking one). The device also comprises a stirrup part shaped transmission member, two locking cones, two springs and one single moving hollow part The main frame has been separated into three parts regarding the assembly process. The Fig. 13 shows the mechanical principle of the system in an intermediate working position of the moving part without any representation of the valves and the fluid.

The Fig. 14 shows the detail of the locking cone in its intermediate position. The valves and the fluid will be added in the representation of the fractioned refilling principle (Fig. 15) and in the representation of the fractioned injection principle (Fig. 16) respectively shown in their extreme working position of the moving part.

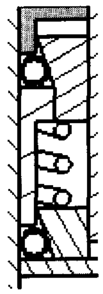

Fig. 14 Detail of the locking cones

The first phase occurs when actuator I (1) causes the upward displacement of the stirrup (2). The balls of locking cone I (3) then become free and return spring I (4) is compressed while the moving part (5) remains at the same place. The balls of locking cone II (6) are locked in such a way that the moving part cannot go upward. Then return spring I causes the motion of the moving part downward as soon as the actuator I is released since the balls of locking cone I are locked (moving part can go downward). The motion of actuator I thus allows to obtain step by step downward motion of the moving part while return spring II (7) becomes progressively compressed.

The second phase occurs when actuator II (8) liberates the balls of locking cone II and the balls of locking cone I thanks to the downward motion of the intermediate part (9) (N.B. locking cone II represented here as a separate part to explain the working principle of the system is a fixed part bound to the frame 0). Since moving part is free, return spring II causes a quick continuous upward motion of the mobile part.

The advantages of this system lie in obtaining of continuous motion in one direction and locking in 'any' chosen position and absence of noise.

4.1.4 Adaptation of the fractioned principle to a pump

This principle can advantageously be adapted by adding some new elements necessary to the fluid flow. A Fractioned Refilling Principle can be reached by adding two valves, one in the moving part and the other in the frame, as indicated in Fig. 15. The fluid is also added in this figure and the darkness of the represented fluid is proportional to the reached pressure. The working principle remains the same as previously explained. Positioning the valves as shown on Fig. 15 allows to obtain a step by step refilling phase linked to the action of actuator I since a downward motion of the moving part means transfer valve II opened and delivery valve I closed. On the other hand, a quick delivery phase is obtained by the action of actuator II since delivery valve II is closed and transfer valve I open. This system is particularly suitable in applications for which a high pressure is required in the catheter when the medication dose is released and for which the refilling time is not critical.

The shift of transfer valve I and delivery valve II invert the fluid flow from the upper part of the system to its lower part and allow to obtain a Fractioned Injection Principle shown on Fig. 16. The displacement of the balls of locking cone I by actuator I promotes the delivery phase step by step. The release of return spring II causes the refilling process in one step in quite a similar way as in the former system notwithstanding the inversion of filling and delivery.

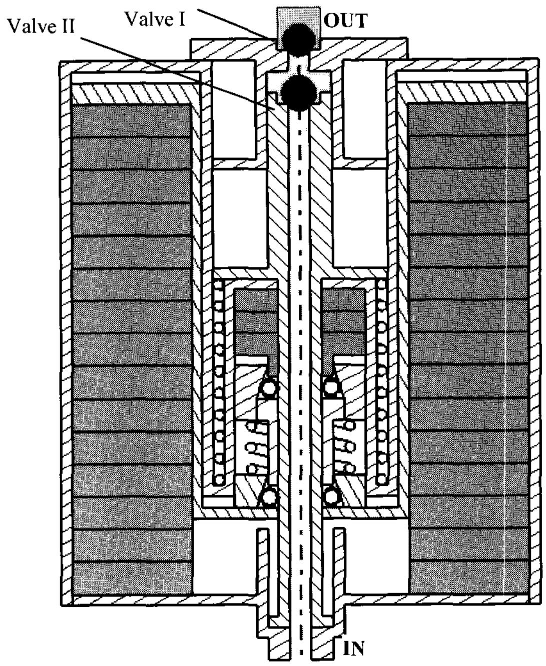

Fig. 15 The Fractioned Refilling Principle

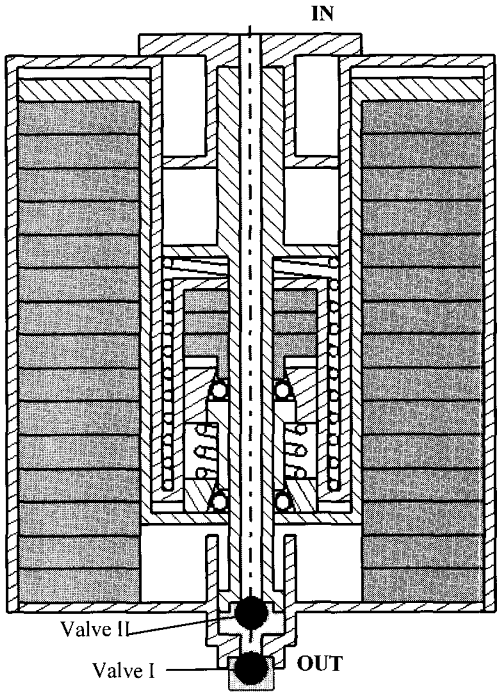

Fig. 16 The Fractioned Injection Principle

5. Falk principle improvement

Successive suggested innovations based on the Falk principle are proposed here below.

5.1 The Spider Guided system

The Spider Guided System shown in Fig. 17, takes advantage from Falk's principle but is on the way of canceling its major drawbacks.

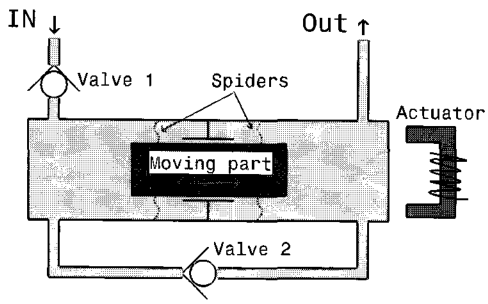

Fig. 17 The Spider guiding system

The suction and delivery phase, as well as the transfer phase, are similar to these met in Falk's pump. Spider guiding systems avoids friction between the moving piston and its housing, removes contamination problems by particle release and specially wear, thus improving the metering precision. Moreover, spider guiding system could to advantage use the spiders themselves as one way valves. On the other hand, though better controlled, leakage remains, and the spider stiffness increases the energy consumption and decreases the device autonomy; parts count is still high and spiders manufacture, manipulation and assembly aren't easy owing to their small dimensions.

5.2 The Bearing Rotation Guided System

The Bearing Rotation Guided System, schematically displayed in Fig. 18 is a rotational motion adaptation of the Falk's system, thought to improve the moving part guiding quality.

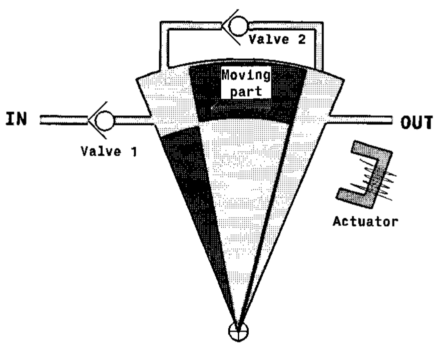

Fig. 18 The Bearing Rotation Guided System

Rotational motion of the moving part again induces suction/delivery phase and transfer phase, similar to these of Falk and Spider Guided System pumps.

5.3 The Vane System

The Vane System, schematically described in the first part of Fig. 19, though quite similar to the previous one, offers some improvements.

The contamination from the outside remains avoided, the medication fluid still insures the lubrication, the manipulation and the assembly of very small parts like spiders disappears, the parts count is reduced, and the absence of spider deformation forces reduces the power consumption and thus increases the autonomy. However, leakage problems between moving part and housing still remain; moreover, bearing precision and dimensions lead to new difficulties. Effective pumping steps, correct valve work and some interesting phenomenon have been observed on a 10:1-scale Plexiglas mock-up, which can be seen in the second part of Fig. 19.

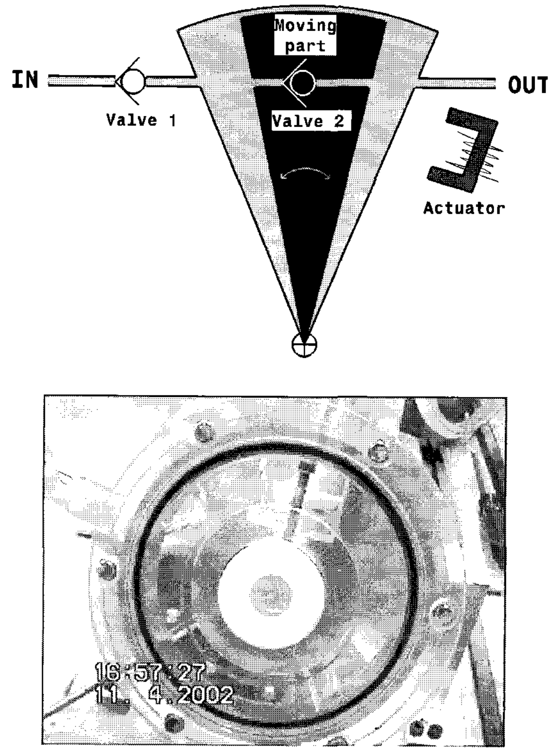

Fig. 19 The Spider Guiding System

5.4 The Notch Hinge Guided System

The Notch Hinge Guided System (first part of Fig. 20) cancels bearings problems.

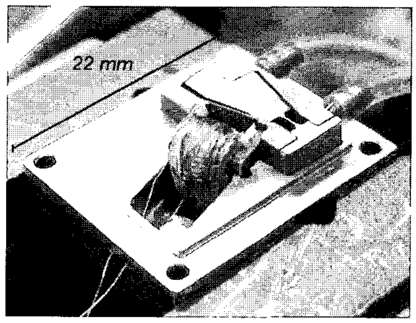

Fig. 20 The Notch Hinge Guided System

The flexible guiding system is allowed for small angular displacements, location accuracy is now easily achieved, lubrication problem totally disappears and a still more reduced number of parts leads to a highly compact, secure and cheap system. Pumping steps, valves work and a number of interesting way of working features have been analyzed on a 1:1-scale titanium prototype which has been built and can be seen on the photograph of the right part of Fig. 11. Parts machining, handling and assembly become quite easy. Unfortunately, leakage problems however still remain, making flow metering still inaccurate. According to the DFA analysis, a design efficiency 1of 17 % ensues and a theoretically total assembly time of 157 seconds is required. The worst assembly time concerns the ruby balls (19.50 sec.), the valve seats (16.30 sec.) and the connectors (10.45 sec). A practical assembly time obtained by laboratory tests is 174 sec. The notch hinge pump, designed according to the functionality of the product, allows us to obtain a direct motion of the magnetic notch hinge without any reducing gear, thus limiting the number of parts. It could be possible to reach a total of seven parts by directly manufacturing the two connectors into the housing and replacing the valve seats and the ruby balls by thin strip valves. This would however increase the global cost of the device since connectors and valves are standard or semi-standard parts, the manufacture of a complicated part is expensive and the handling and insertion of complex parts might involve assembly times problems.

5.5 Conclusions

A comparison of the different systems is given in Table 2.

Table 2 Comparison of all systems

	Synchromed Peristaltic Pump (Medtronic)	Falk's pump	Spider Guided System	Rotation Guided Systems	Notch Hinge
No contamination	++	-	+	-	0
No leakage problems	++	-	-	--	--
No guiding problems	0	0	+	0	+
Security	++	0	0	+	+
Flow metering accuracy	+	0	0	--	-
No lubrication need	+	++	++	+	++
Reduced parts count	--	0	-	0	++
Autonomy	--	-	--	0	-
Cost	--	0	-	-	+
Total	2	-1	-1	-4	3

One can state that:

- The Peristaltic Principle, used by the only programmable implantable pump now on the market doesn't satisfy medical practitioner's needs;
- Improvements brought by US 4,568,250 and US 6,193,477 Falk patents could allow new designs and reduce the gap between peristaltic pump and these needs;
- The Fractioned Refilling System offers an absence of guiding problems, a good flow metering accuracy and an absence of lubrication need but could be improved regarding the contamination problems, the leakage problems, the number of parts involved and the autonomy.
- The Spider Guided System avoids friction between piston and bore but is hindered by spiders stiffness;
- The Bearings Rotation Guided System avoids energy consumption due to spiders stiffness and drastically reduces the number of parts;
- The Notch Hinge Guided System avoids bearings problems, increases positioning accuracy and offers a highly compact pumping device.

NB: The criteria involved could be bound to a weight regarding the importance of the criteria.

6. Conclusions

The proposed fractioned refilling and injection drug delivery system has been designed based on an analogy approach which draws benefits from well known discrete systems, making them continuous. This approach allows the use of truly suitable (regarding the dimensions involved) piezoelectric actuators to obtain a continuous medication flow, whereas piezoelectric actuators often entail jerky movements. The advantages of this system lie in obtaining continuous motion in one direction and locking in 'any' chosen position, as well as absence of noise. The fractioned refilling system is particularly suitable for applications in which a high pressure is required in the catheter when the medication dose is released and for which the refilling time is not critical. The fractioned injection system is suitable for applications for which the injection time is not critical. We can assent that the combination of the two systems could become very suitable for typical illnesses which require a basal and a bolus rate: the fractioned refilling system allows to reach the basal rate while the fractioned injection system allow to reach the bolus rate. Based on the comparison criteria involved in [2] and [3], the fractioned system principle takes a relative good position: absence of guiding problems, good flow metering accuracy and absence of lubrication need. However, some improvements could be brought regarding the contamination and leakage problems, the number of parts involved and the system autonomy. Based on the Falk principle, other systems have been developed in the aim to improve these problems. A step by step procedure leads to the Notch Hinge principle which seems to present promising characteristics. A 1:1 scale titanium prototype has been built and tested but leakage problems remains a problem which disturb the tests and doesn't allow to collect precisely data regarding flow metering accuracy and repeatability.

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