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A Study on Implantable Micropump Systems for Drug Delivery

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Abstract

Systemic drug delivery is the most prevalent form of the drug administration; but it is not possible to extend this approach of drug delivery to the all of diseases. In the traditional approaches of drug delivery, the drug spreads through whole of the body and this could cause severe side effects in the healthy parts. In addition, in some parts of our body like the eye, ear and brain, there are biological barriers against drug penetration which made the drug delivery to these organs as a challenging work. Micropumps are one of the MEMS devices with great capabilities in controlled drug administration. Despite commercial kinds of micropumps in insulin therapy, they have not widely used for the other treatments. Our study showed that there are some important ongoing investigations in order to use the micropumps in the new treatment methods of some incurred diseases.

Keywords: drug delivery, micropump, metronomic chemotherapy, ocular disease, cochlear disease, insulin therapy

Introduction

The aim of different drug delivery methods is to release a specific dosage of a drug by a certain rate and during an adequate period of time, in the targeted tissue.

The variations of the drug concentration at the targeted tissue could be depicted in the concentration-time profiles.

As demonstrated in Fig.1, the drug concentration should remain in the therapeutic window, between the lower functional threshold and the upper cytotoxic limit [1]. These two limiting levels could be altered for different drugs and patients.

In fact, this is the role of drug delivery approaches to exactly transfer the drug to the target point, and keep it at the predefined influential conditions [1].

But what are the difficulties in front of the drug delivery systems to achieve this important task?

In spite of advances in medical and pharmaceutical sciences, the modern drugs are being more and more potent and the side effects of these new drugs are also being more hazardous.

As a general categorization, the drugs may take effect on the diseased organ in a systemic way or be administered directly to the tissue which is affected by the disease [2].

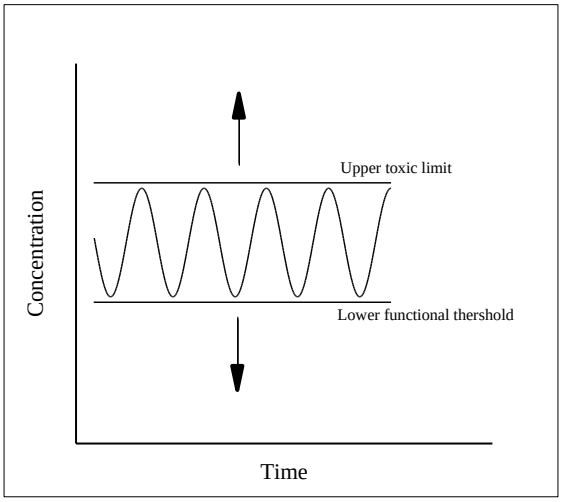

Fig. 1 Therapeutic window is used to show the desired concentration of drug during the affecting time at the targeted tissue. The window could be shifted up and down or goes narrower or wider for different patients or drugs.

The main disadvantage of most prevalent systemic routes like oral and intravenous injection, is the wide spread of the drugs all around the body. This widespread manner could cause the drug, not be able to reach the desired concentration at the targeted tissue [3,4] and

therefore the overdose of the drug would be necessary to take effect and after it, the extensive side effects on the other parts of the body would be unavoidable [4]. These side effects could be very serious in treatment of both acute and chronic diseases.

The release and degradation rates are also two other important parameters affecting on the treatment performance [1]; for example, in the insulin therapy for the type I diabetic patients, the rate of insulin perfusion should be close to the rate of insulin discharged by the pancreatic cells [5,6].

Although attending to the release and degradation rates could lead to the desired drug stability, it is not always practical to reach it by the traditional forms of drug delivery.

Concentration fluctuation is one of the weakness points of traditional delivery approaches. As an example, regarding to the fast degradation rate of "Basic Fibroblast Growth Factors", control of the dose and rate of delivery of bFGFs plays a determinant role in the stimulation of the mesenchymal cells to regenerate a lost tissue [7].

The barriers against the penetration of the drugs are the other difficulty in the traditional forms of drug delivery [2]. Some important organs, such as the posterior intraocular space [8], intracochlear segments [9] and central nervous system [10] are inaccessible parts to the systemic drug delivery approaches.

In order to overcome the mentioned problems which are associated with the traditional drug delivery methods, several investigations have been performed to discover newer drug delivery devices, able to access to the hidden segments of the body and maintain the drug at the desired therapeutic window.

Utilizing the implantable drug delivery devices is widely being investigated and examined. Bioadhesives, polymer implants, transdermal patches, microencapsulation, microchip drug reservoirs, immuno-isolating capsules, diffusion chambers etc. are examples of the sustained released implantable devices which have been commercialized.

Despite better achievements in employing these new devices, in some cases more modern apparatuses were necessary to release the drug in a controlled profile [7]. Micropumps appear to be good candidates in response to the controlled release demand.

Micropumps

Micropumps are one of the main components of the microfluidic devices with a wide variety of biomedical applications. Their capability in accurately pushing the microfluids through the microchannels has made them act as the heart of such different diagnostic and drug delivery microdevices. They might be coupled with microfilters, micromixers, microdispensers, microneedles etc. in different microdevices [11].

Implantable pumping systems are such controllable devices capable of pumping drugs with certain flow rates in a specific programmed regimen. The micropump, as the heart of such a system impulses the drug from the reservoir to the target place with high performance, reliability and accuracy.

As schematically shown in Fig. 2, a typical implantable pumping system is consisted of the drug reservoir, micropump, valves, microsensors, michrochannels, catheter and the related control circuits [12].

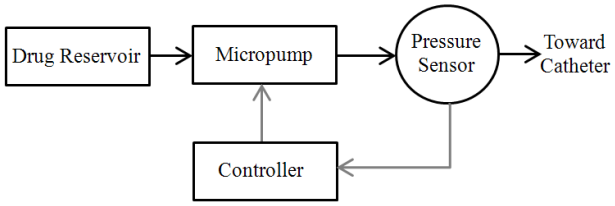

Fig. 2 Schematic view of a typical drug delivery pumping system. Black arrows are microchannels and the gray ones are the signals

Generally, micropumps could be divided into two major groups: "Mechanical" and "non-Mechanical". The mechanical ones include moving parts and moving or fixed check valves. These mechanical micropumps usually use actuation sources like Piezoelectric, Electromagnetic, Pneumatic, Electrostatic, Shape Memory Alloys, Thermo-pneumatic, Bimetallic actuators etc. [11, 13].

The non-mechanical ones convert non-mechanical energy into kinetic energy and some of its examples are Electro-hydrodynamic, Electro-wetting, Ultrasonic Flow Generation, Marangoni pumps, Buoyancy-Driven micropumps etc. [11, 13].

There are some review papers [12, 13] and books [11] describing the mechanism of action of micropumps with different actuation sources, but the focus of this paper is on the application of micropumps in drug delivery. In the following sections, four challenging cases in drug delivery, including metronomic chemotherapy, intraocular and intracochlear drug delivery and insulin therapy have been discussed and reviewed. In all of these cases, the micropump comes into use when the traditional approaches fail to be useful.

Metronomic drug delivery

Metronomic chemotherapy is a relatively newborn concept in the treatment of the cancerous patients. According to the extensive researches in metronomic therapies, in this method, long period administration of low doses of the certain cytotoxic agents could make effect on the tumor's endothelium and causes the tumor's angiogenesis to be inhabited. Besides, decreasing the severe side effects of the conventional chemotherapy is the other advantage of this method [14, 15].

Due to the need for accurate control of the drug dosing, utilizing the micropump in metronomic chemotherapy could be so useful. Therefore Professor Woias's research team at the Institute of Microsystems Engineering in Freiburg aimed to define an

interdisciplinary project on the design and fabrication of an active micropump, capable for metronomic therapy [16].

They put the base of their metronomic pumping system on a novel two stage pressure-independent micropump, which was designed before by the same group [17]. Also due to the well controllability and low response time of piezoelectric actuators, these actuators were good choices to be used as the actuation source of their micropump [17].

The stability of the driven flow is critical point in the success of metronomic approach and the micropump should meet it precisely; but the blood and tissue pressure fluctuations are the disturbing factors that prevent the stability of flow rate in the common micropumps [17].

As illustrated in Fig. 3(a), usually in the conventional forms of piezoelectric micropumps, there is a middle membrane which is activated by a piezoelectric actuator to go up and down. These pumps have suction and compression phases and the flow comes to and goes out of the chamber through the passive valves. But as it is shown in Fig. 3(b), in the novel two stage micropumps, the passive valves have been replaced by two back to back active valves. This system has two separate piezo-actuators and works during a three phase regimen. Three phases of re-fill, transfer and delivery are demonstrated in Fig. 4. At the refill phase, the pressure of chamber equals to the inlet pressure, at the transfer phase, it is equal to the outlet pressure and at the third phase, it is equal to the cut-off pressure. The cut-off pressure is dependent on actuation voltage and membrane compliance. Considering that only 0.8% of the membrane would be exposed to the outlet pressure and the rest is under cut-off pressure, it could be concluded that the cut-off pressure is almost backpressure independent [16].

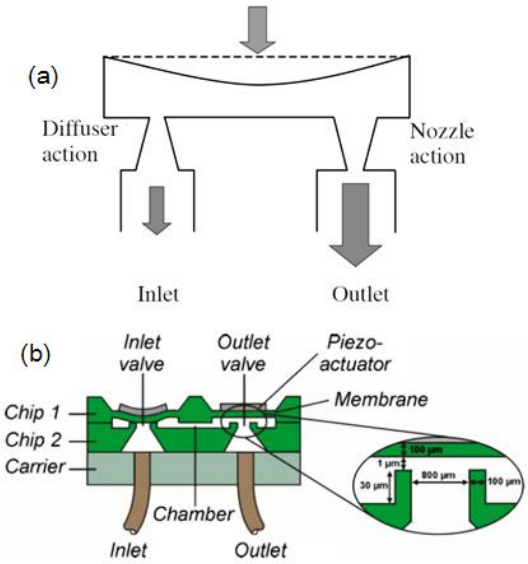

Fig. 3 (a) The conventional form of piezoelectric micropumps with a membrane and two passive valves (b) The novel design of backpressure-independent micropump [17]

To ensure the flow stability, a pressure sensor was also placed at the pump's downstream. This sensor was continuously monitoring the flow pressure and alarming by occurrence of any occlusion in the flow. The signals of the pressure sensor were being sent to an 8-bit controller to adjust the frequency of the actuation voltage which was applied to the valves [17].

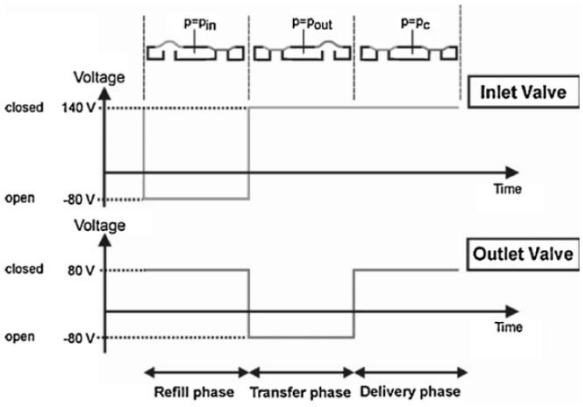

Fig. 4 Three phases of action of the pump and the chamber's pressure during every phase [17]

After the first experiment, the group executed some modifications on the actuation sequences of the valves and their chamber design [18]. New actuation sequence made it more efficacious in pushing the fluids in the forward direction and also capable of pumping even gaseous fluids [18].

The modifications in the chamber shape also increased the compression ratio of the pump and reduced its dead volume which helped it to achieve a better performance [18].

The fully autonomous self-priming micropump was able to supply a precise flow rate of between $0.1\mu l/min$ and $50\mu l/min$ in a patient specific release profile and ensured up to a backpressure of $30kPa$. The size of the prototype was measured as $45\times30\times25\ mm^3$ and the resolution of the pump was adjustable between $10nl$ and $200nl$ [18].

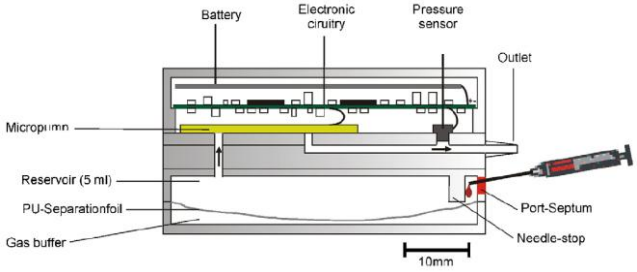

Fig. 5. Schematic view of the whole of pumping system [17]

In order to examine the suitability of this device in the metronomic chemotherapy, it was tested in the rats with prostate carcinoma. During this animal test, doxorubicin, a cancer drug was being transferred to the rat's body by

metronomic doses, see Fig. 6. The metastasis of rat's prostate carcinoma is similar to the humans' prostate [19].

The test results showed the applicability of the use of the active micropumps in the metronomic treatment of the prostate carcinoma in the rats [19].

Fig. 6 The pumping system were connected to the rat through a backpack [17]

Intraocular drug delivery

In the previous section, the application of the micropumps in metronomic chemotherapy was discussed. As it was mentioned, in the metronomic drug delivery, the stability of the outlet flow was the key feature of the active backpressure-independent micropump. Intraocular drug delivery is another field of application of micropumps which has been surveyed in this paper. But what is the reason of the micropump's utilization in drug delivery to the intraocular space?

Intraocular drug delivery is one of the most challenging portions of the ocular diseases treatment [8]. Although the traditional forms of the drug delivery, including oral medication, eye drops and direct injection into the intraocular space are being applied in these treatments, the need to the newer approaches seems to be undeniable [20].

In treatment of the diseases related to the anterior segments of the eye (cornea, conjunctiva, sclera and anterior uvea), eye drops are mostly being used. The investigations show that due to the fast drainage from the eye's surface, at the best conditions, the bioavailability of drug could reach to less than 5%. The corneal and conjunctiva barriers are the obstacles against the penetration of the drugs to the anterior segments of the eye [20, 21].

The access of the drug to the posterior segments of eye (retina, vitreous, choroid) is much more challenging. The topical ocular medications are not applicable in these parts and only systemic approaches or direct injections are the possible ways of traditional drug delivery to these tissues [21, 22].

Low drug absorption in the eye is the greatest problem associated with the systemic delivery approaches. Therefore, drug overdosing would be unavoidable in order to take appropriate effect on the targeted tissue [21].

The other approach, intraocular injection is also an invasive method and may cause even endophthalmits and thus, it is not an ideal scheme especially for chronic treatments [21].

Today, many of the ocular posterior diseases, such as retinitis pigmentosa, age related macular degeneration, diabetic retinopathy and glaucoma are remained incurable with the traditional forms of drug delivery [20, 21].

On the other hand, eye's sensitivity and delicacy makes the implication of implantable devices so difficult. Despite these difficulties, Lo and his colleagues at the University of Southern California designed and fabricated the first manual micropump, able to transfer the drug to the anterior and posterior parts of the eye [23]. As it is shown in Fig. 7, The tiny flexible micropump was able to be settled on the eye curvature, under the conjunctiva (a thin layer of tissue covering the sclera) and sutured to the sclera (white portion of the eye) [23].

The main parts of this micropump were consisted of a refillable reservoir, transscleral cannula for drug delivery and a check valve to prevent the backflow of the fluid from eye to the micropump because of the backpressure push [23].

By attention to the extraordinary limitations on the eye's surface, the group decided to use a manual actuator on this preliminary pump to simplify the structure and also prevent the need to the massy supplements like controller, batteries etc. [23].

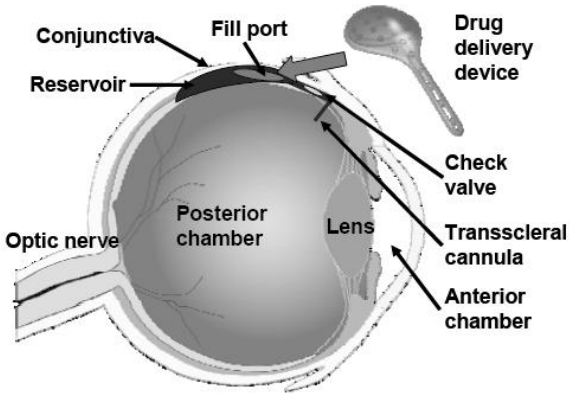

Fig. 7 The manual micropump is implanted subconjunctivally and the cannula tube is entered the anterior segment of eye sphere [23]

The reservoir was fabricated by the PDMS which has the "self-sealing" ability. The tests were shown that till the first 12 punctuations by a 30 gauge non-coring needle, the maximum internal pressure in the PDMS reservoir was decreased a little by each punctuation, but after the 12^{th} punctuation, no significant change were observable in the maximum pressure [24].

Finally, surgical implantation was done on a enucleated porcine eye. The reservoir was attached to the eye's surface by the suture tabs and a small tube was entered through a tiny incision at the limbus to the anterior segment of the eye [23].

The results of the test showed that some geometrical corrections should be considered on the pump's shape to improve its surgical handling [23].

After the first experiment, the same group in a combination with another group from California Institute of Technology started a new project to develop the manual intraocular micropump. In the latter project, the electrolysis actuator was selected as the actuation source of the system. The main causes for this selection were its low energy consumption, simple structure and its large displacement [24].

This drug delivery system was consisted of a refillable and resealable PDMS reservoir, transscleral cannula and the micropump system [24].

The transsceleral cannula was made of Parylene which is a strong, biocompatible and flexible material. As illustrated in Fig. 8, this cannula could be inserted through a tiny incision at the wall to the anterior or posterior intraocular spaces [24].

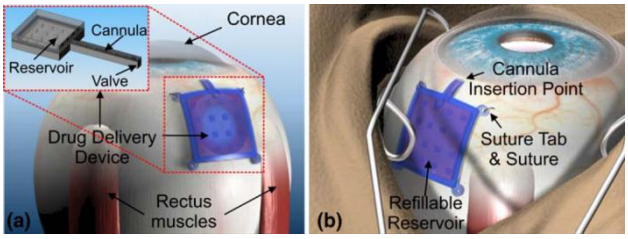

Fig. 8 (a) The electrolysis micropump should be settled between the Rectus muscles (b) The device is again implanted under the conjunctiva layer and the cannula is inserted through a tiny incision at the limbus [24]

Finally, the pumping system was undergone to the bench-top and surgical testing [24].

By adjusting the current, both continuous and bolus flow regimes were tested at the normal and pathologic backpressures. The flow rates were measured in $PL/\min$ to $\mu L/\min$ which is an appropriate flow rate for intraocular drug delivery. Also the preliminary ex-vivo test was performed on an enucleated procine eye and showed its feasibility in drug delivery to the intraocular segments [24].

The examinations done on the system, showed some of its failure points. The important failures should be dissolved to make it ready for chronic in-vivo experiments. One of these challenges was the oxidization of the drug, in vicinity of the electrolysis reaction [25].

The wires being used in the power supplement and relatively large power consumption were two other challenges in front of the pumping system to get ready for chronic in-vivo experiments [25].

Li et al. from University of Southern California made the following correctional activities to dissolve the declared problems [25]:

- Separating the drug reservoir and the electrolysis chamber
- Using a Paryline bellows membrane between the drug and electrolysis chamber to prevent unwanted pH changes and drug degradation
- Optimization of the shape of the electrodes to decrease the energy consumption
- Eliminating the wires and using from a wireless power source

Although more investigations is necessary for this device to be prescribed in the treatment of ocular chronic diseases, by applying these correctional decisions (Fig. 9), they could reach the performance of the system from a little less than 50%, to almost 80%. Also, by decreasing the energy consumption and making it wireless, the system was practically made ready for the in-vivo animal examinations [25].

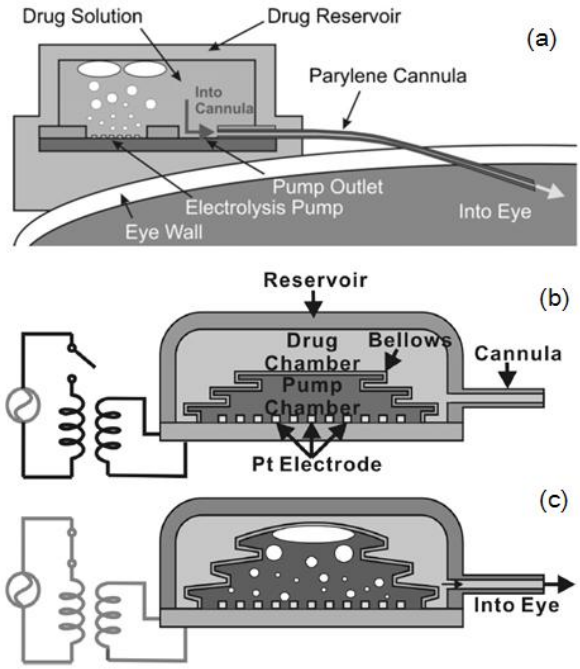

Fig. 9 (a) The preliminary electrolysis pump for ocular drug delivery. The electrolysis was done in the drug's chamber [20] (b) Drug chamber is separated by the Paryline bellows [25] (c) Gas formation caused drug to be pushed toward the eye [25]

Intracochlear Drug Delivery

Undoubtedly, hearing loss is one of the most prevalent kinds of human disorders. There are 250 million people all over the world suffering the symptoms of hearing loss [26]; according to the NIDCD (National Institute of Deafness and Other Communication Disorders) report, almost 2-3 children out of every one thousand births in the United States are born deaf or hard-of-hearing [27].

Sensorineural hearing loss is a kind of the auditory disorders which in the most prevalent form, the hair cells' damage is the main cause of it. The hair cells are sound receptors of the auditory system located in the cochlear of the inner ear. Exposure to severe noises, toxic chemicals,

genetical factors and aging, are known to be some of the reasons of hair cell dysfunction [28, 29].

Todays, thanks to the new molecular insights into the degenerative process of cochlear and auditory nerves, new pharmacies are being proposed to take effect on the remodeling of the damaged or dead hair cells [28].

But the great challenge in these therapies is how to deliver these pharmacies to the intracochlear space.

Due to the existence of blood-Labyrinth barriers, the systemic accessibility to the intracochlear space is severely restricted like the intraocular ones. The blood-Labyrinth barriers limit the concentration and the size of the agent's molecules to enter the inner ear through the blood circulation [28].

Such a great challenge in the drug delivery to the cochlear, gathered a multidisciplinary research group at Charles Stak Draper Laboratory, in Cambridge, Mass., and at Massachusetts Eye and Ear Infirmary (MEEI) to focus on the new approaches to gain the access to the cochlear space [28].

The research group utilized a reciprocating solenoid micropump with a stroke volume of $0.5\mu l$ at pressures up to $100MPa$ manufactured by Wilson Greatbatch in an implantable pumping system to push the drug to the targeted tissue. The pumping system was designed to be located out of the body, between the ear and temporal bone and near the cochlea [28].

A hole was drilled into the cochlear bone to make the catheter able be inserted into the scala tympani one of the perilymph-filled cavities in the cochlear of the human ear [28].

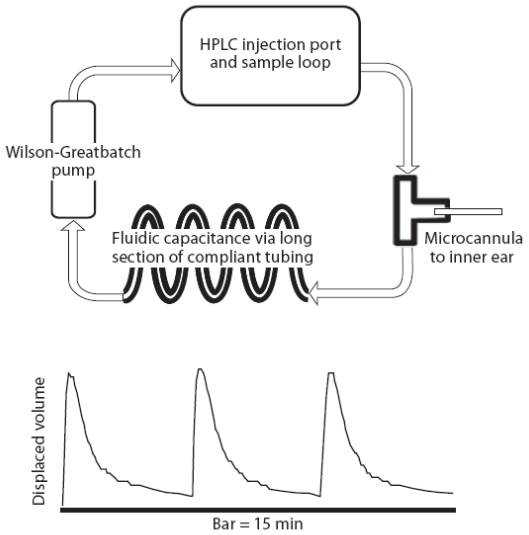

Fig. 10 Scematic view of the first reciprocating infusion system in intracochlear drug delivery [30]

Perilymph is an extracellular fluid located within the cochlea; by pushing the drug into the scala tympani cavity, the drug would be mixed with the perilymph liquid and would be able to take effect on the hair cells [28].

Although the mixture of the perilymph and drugs could effect on the stimulation of the dead hair cells to regrow, some important considerations should be regarded in using this method [28]

The total volume of perilymph liquid in the human's cochlea is about $160\mu l$; therefore the drug concentration should be precisely adjusted to maintain at the therapeutic window. The more important subject is that a little deviation from the dose limit may cause the pressure of mixture to be increased in a harmful way [28].

The cochlea structure and its neurons are very sensitive to the external force and pressure; according to the experiments on the guinea pig inner ear, addition of more than $5\mu l$ fluid to the intracochlear space, leads to a rise in threshold to the acoustic stimulation [28].

In order to dissolve this problem in drug delivery to cochlea, they used a reciprocating perfusion system to push the drug to the cochlea in the push phase and then withdraw it in the pull phase. The former phase was prolonging a few seconds and the latter was prolonging a few minutes. By this method, they were able to send the drug to the cochlea with a zero net flow and in a more controlled manner to prevent the hair cells to be damaged. As illustrated in Fig. 10, they were used long compliant tubing in the return line to the micropump to cause the pull phase to be performed slowly. By passing the lag time, the pump was being stimulated again by $15V$ pulses at selectable frequencies of $0.1\,\text{to}\,10Hz$ [28].

The number of the pulses in each cycle was depending on the necessitated drug dosage and the pumping was continued to achieve the desired dose on the target tissue [28].

In-vivo tests of the pumping system were done on the guinea pig's ear to check its applicability in cochlea drug delivery without damaging it. They filled the reservoir by a drug with temporarily dampening effect on hearing and then inserted the catheter to the different locations in the cochlear tube. Biologically, the entrance of the cochlear tube is responsible for the high frequencies and by going deeper inside the tube, higher frequencies would be sensed [28].

The experiment results showed that the pigs temporarily lost their hearing senses of the frequencies that their locations in the cochlea were affected by the catheter [28].

After the first experiment, the research team designed and fabricated the second generation of the reciprocating system. As shown in Fig. 11(a), in the new system, the long compliant tubes were replaced by a membrane-based tunable microfluidic capacitor to reduce the size of the system [30].

The third generation design came closely after the second, had a simpler design and structure. As illustrated in Fig. 11(b), in the third design, control of the withdrawal or infusion of the drug were performed by a

piston actuator. In the push phase, the piston was applying a great force downward to the membrane to infuse the drug to the intracochlear space in a few seconds. In the second phase, it was releasing its force gradually and causing the withdrawal of the drug to the pump. This design was much more controllable than the two previous generations.

The animal tests showed the ability of the reciprocating infusion system in exact delivery of the agents to the intracochlear space without any damage to the cochlea structure and its nervous cells [30].

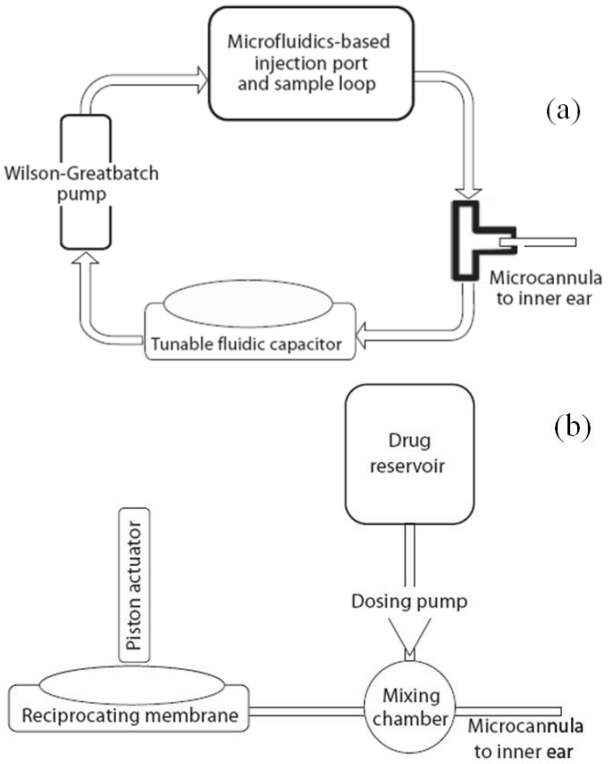

Fig. 11(a) Second generation of the reciprocating infusion system. The long compliant tubes are replaced by the tunable fluidic capacitor (b) Third generation of the reciprocating system. The third generation had so better controllability [30]

Insulin pumps

Insulin pumps are widely being used in the diabetic patients all around the world. In fact, insulin pumps are the first commercialized kinds of micropumps, which have been entered to the market since three decades ago [31].

In a normal human, the glucose concentration is between $60\,\text{to}\,120 mg/dl$; if the glucose concentration goes higher than this range, the person is called a diabetic patient. Insulin is the hormone responsible for the balancing the glucose level in our bodies [32].

Basically, diabetes has two major types I and II. During the former which more occurs in the young people, the insulin production is halted in an abnormal way and thus, the insulin injection is necessary to survive [33].

The latter type is more prevalent at the ages more than 35. Low insulin production and resistance against the insulin, could be the reasons of type II diabetes [33].

Although strict diet regimens and exercises should be applied by the diabetic patients, the insulin injection is also necessary, especially for the type I patients [34].

At the early years of micropump adventure, these devices were only proposed as a treatment for type I diabetic patients, but nowadays, they are also being proposed for many of the type II diabetic patients [35].

Multiple daily injections (MDI) was the traditional form of insulin therapy which is already being used in the developing countries. During MDI, depending on the glucose level, the patient has to inject insulin several times a day [35]. But the invasive approach, its harmfulness, low capability in mimicking the pancreatic insulin discharge profile etc. caused the researchers to develop the insulin micropumps to deliver the insulin in a predefined pattern [36].

Typically, the insulin pumps have two continuous basal and bolus meal profiles of injection [37].

Almost half of the dose is being transferred continuously to the subcutaneous tissue over the whole day and the next half is injected before the meals in 3 or 5 onsets [37].

Today, there are several insulin pump producers all around the world; Accu-Chek, Animas, Debiotech, Deltec, Insulet, Medtronic and Sooil USA are some of the most these companies. During the recent years, after the development of the formal types of insulin pumping systems, now the most investigations in this branch is attended in the integration of the pumping systems with the glucose sensing chips [32, 38, 39]. The “closed loop” insulin pumps would be able to have a real-time monitoring of the glucose level and adjust the insulin pumping rate depending on it. This feature could be a very good option, especially for the patients with a serious syndrome. In the serious patients, six to seven measurements a day or even continuous monitoring is suggested. To our knowledge, one type of these closed loop pumping systems has come to the market by Medtronic Diabetes.

Other Applications

Although we could not find many publications, there are several evidences on the extensive investigations in utilization of the micropumps in the treatment of some other diseases like Osteoporosis, Infertility, Parkinson, Alzheimer, Multiple Sclerosis etc.

Also the authors of this paper have an ongoing investigational project on the application of micropumps in drug delivery to the temporomandibular joint (TMJ).

Conclusions

By attention to the progresses in medical and pharmaceutical sciences, newer drug delivery devices are necessary to use. Micropumps are accurate controlled

release devices which potentially have many applications in the drug delivery. Localizing the drug delivery, reducing the dose of potent drugs, increasing and stabilizing the drug concentration at the targeted tissue, reducing side effects, accessing behind the barriers, releasing in the patient's appropriate profile etc. are some of the advantages of micropumps.

In addition to the preliminary specifications like safety and accuracy, every micropump should meet some extraordinary qualifications, depending on its exact mission. For example, in the intraocular drug delivery, the micropumps must be miniaturized in order to be implanted on the eye surface. In the intracochlear drug administration, the pressure increase in the cochlea must be guaranteed to prevent the hair cells to be damaged. In metronomic chemotherapy, the stability of the flow is very important and finally in insulin therapy, the insulin infusion should mimic the pancreatic discharge profile.

By attention to the advances in microfluidics, microfabrication and extended researches which are being done in the utilization of micropumps in drug delivery; it seems that the micropumps will widely come into the market for treatment of some incurred diseases by the next years.

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