

Implantable Drug Delivery System: A Review

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Abstract: In the past, drugs were frequently administered orally, as liquids or in powder forms. To avoid problems incurred through the utilization of the oral route of drug administration, new dosage forms containing the drug(s) were introduced. As time progressed, there was a need for delivery systems that could maintain a steady release of drug to the specific site of action. Therefore, drug delivery systems were developed to optimize the therapeutic properties of drug products and render them more safe, effective, and reliable. Implantable drug delivery systems (IDDS) are an example of such systems available for therapeutic use. The study of currently available implantable drug delivery systems is the main focus of this review. The major advantages of these systems contain targeted local delivery of drugs at a constant rate, fewer drugs required to treat the disease state, minimization of probable side effects, and better efficacy of treatment. Due to the development of such sustained release formulations, it is now possible to administer unstable drugs once a week to once a year that in the past required frequent daily dosing. Preliminary studies using these systems have shown superior effectiveness over conventional methods of treatment. However, one limitation of these newly developed drug delivery systems is the fact that their cost-to-benefit ratio (cost/benefit) is too high which restricts their use over conventional dosage forms. Some of the most recently discovered implants are in the early developmental stages and more rigorous clinical testing is required prior to their use in standard practice.

Keywords: Implantable drug delivery, modulated drug delivery, implants, drug delivery systems, implantable pumps, recent technologies.

1. INTRODUCTION

Orally administered drug must be protected against denaturation in the gastrointestinal tract and should be capable of absorption across the wall of the stomach or the intestine. After absorption and upon reaching the portal circulation, it must be resistant to hepatic enzymes. The rate of drug absorption and elimination should ensure the blood levels within the therapeutic range. Moreover, the amount of intact drug that reaches the site of action should be sufficiently large to obtain desired therapeutic effect but

insufficient to cause untoward side effects. A controlled drug action may be achieved by either chemically modifying the drug moiety or by formulating it in a specific way to control its release. Oral controlled release dosage forms can provide efficacy for about 24 hours. The main drawback of oral dosage form is the long transit time of approximately 12 hours through the gastrointestinal tract (GIT). If drug cannot be administered orally, a parenteral route of delivery is an alternative. Many proteins/peptides and other drugs, which are susceptible to the adverse conditions of GIT, are

administered intravenously. Unfortunately, in intravenous drug administration, the duration of drug action is short for majority of therapeutically active agents and therefore frequent injections are required. The development of injectable controlled-release dosage forms is more likely to succeed commercially than alternative routes of delivery, assuming that these dosage forms provide the desired efficacy and safety. In case of topical drug administration, the percutaneous absorption of most drugs is limited due to physiological characteristics of the drugs and presence of highly impermeable stratum corneum. Implantable drug delivery devices are devoid of aforementioned limitations associated with oral, intravenous, topical drug administration vis-à-vis subcutaneously implantable drug delivery devices offer one unique advantage of a retrievable mechanism^[1].

For integration of various therapeutic agents with different physicochemical characteristics and for improved mechanism of drug release, number of additives is now used. Thus, more current implantables generally contain the therapeutic agent in a rate controlling systems. Implantables are available in various sizes and shapes. While oral delivery is considered the preferred method of administering many drugs, additional methods employing pulmonary, infusion, and implantable systems have been developed to overcome drug delivery constraints. For example, many macromolecules are either digested in the gastrointestinal tract or are not well absorbed into the bloodstream. Oral administration may also not be appropriate for drugs that require a rapid onset of action. Similarly, pulmonary systems such as inhalers require drugs to be absorbed into the bloodstream from the lungs. Drug delivery by injection has other disadvantages. Patients must choose between traveling to a treatment site and maintaining a home supply. Furthermore, the discomfort of frequent injections leads to poor patient compliance. Finally, a multiple, timed drug-injection regimen is complicated to administer and may require a clinician's help. Portable infusion systems allow unassisted intravenous administration; however, these systems can only administer drugs in liquid form and require both a transcutaneous catheter and an external pump.

Fully implantable drug delivery devices are desirable where alternate forms of delivery are not preferred or not possible. These devices allow drugs to be delivered at efficacious locations and rates without the issue of patient compliance. An advanced implantable system can be used to precisely control the rate of drug delivery. Some drugs are only therapeutic when administered in a pulsatile pattern, similar to the way they are produced in the body. Alternatively, some therapies require drugs to be released continuously to maintain a therapeutic level for an extended time.

Pulmonary, transdermal, intravenous or subcutaneous injection or infusion^[2], and implantable systems have been developed for situations where oral drug delivery is not optimal or feasible^[3]. Implantable drug delivery devices are particularly desirable where compliance with a prescribed drug regimen is critical. Such devices allow a drug to be delivered at a specific rate without regular physician or patient intervention. Currently available drug delivery implants can be divided into two main categories, based on whether they deliver drug in a passive or active manner. Polymer depots are the most common passive drug delivery systems. They are designed to maintain a constant diffusion rate of drug out of the polymer, or they degrade in the body at a particular rate, thereby releasing drug at that rate. Conventional programmable IDDDs use 25-50% of the implanted device volume for a battery that is intended to last the entire duration (5-10 years) of the implant. However, in typical IDDDs medication is typically refilled every 10 weeks by transdermal injection into a subcutaneous refill port (Figure 1.1)^[4].

This research is motivated by the consideration that the overall volume efficiency of an IDDD, which is critical to its placement and usability (particularly in paediatric cases), can be improved substantially if the conventional battery is replaced with a smaller battery that is recharged. It is preferable that the recharging occurs in the same session that the drug reservoir is refilled, although not necessarily at precisely the same time^[5]. While wireless power transfer is possible for very low-power applications^[6], DC recharge capability^[7] offers high current levels and may be more suitable for IDDDs (Figure 1.2).

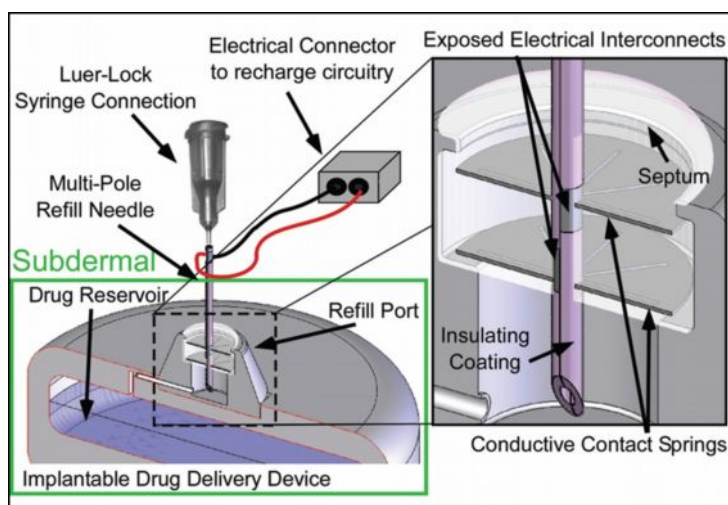


Figure 1.1: The system view: A two-pole needle is inserted into the refill port of a drug delivery device. Inset: A close view of the two needle halves making electrical contact with springs inside the septum.

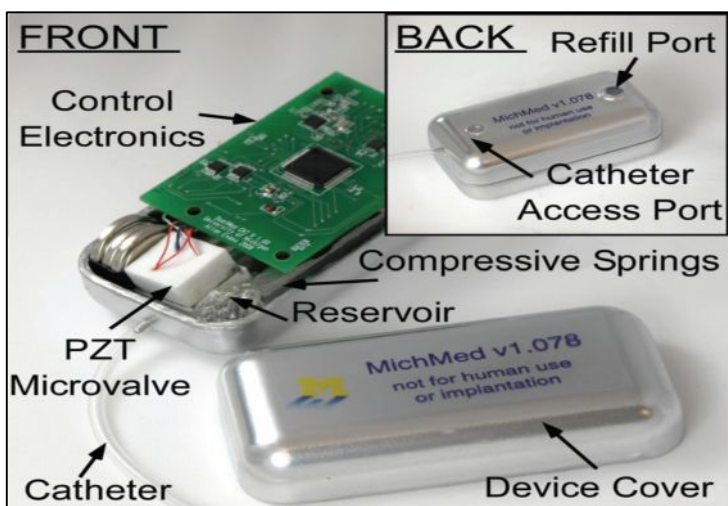


Figure 1.2: A photo of the front of an assembled microvalve-regulated drug delivery device with the back side refill port shown inset^[8].

Over the last two decades, the field of controlled drug delivery has been faced with two major challenges. One has been achieving sustained zero-order release of a drug substance over a prolonged period of time. This goal has been met by a wide range of techniques, including osmotically driven pumps^[9], matrices with controllable swelling^[10] diffusion^[11, 12] or erosion rates^[13], non-uniform drug loading profiles^[14-16], and multi-layered matrices^[17]. The second of these challenges is the controlled delivery of a therapeutic molecule or protein in a schematic of a pulsatile or staggered

fashion. Two different methodologies have been heavily investigated as possible solutions to these requirements. One is the fabrication of a delivery system that releases its payload at a predetermined time or in pulses of a predetermined sequence. The other is to develop a system that can respond to changes in the local environment. These systems have been shown to alter their rate of drug delivery in response to stimuli including the presence or absence of a specific molecule, magnetic fields, electric fields, ultrasound, light, temperature, and mechanical forces.

2. ADVANTAGES OF IMPLANTABLE DRUG DELIVERY SYSTEM

The advantages of implantation therapy include.

Convenience:

Effective concentration of drug in the blood can be maintained for longer period of time by techniques such as continuous intravenous infusion or repeated injections. On the other hand, under these treatments patients are regularly required to visit hospital throughout administration for uninterrupted medical monitoring. A short-acting medicine worsens the condition, as the quantity of injections or the infusion rate need to be increased to maintain a therapeutically effective level of the drug. On the other hand, implantation treatment permits patients to get medication outside the hospital setting with marginal medical observation. Implantation treatment is also characterized by a lower occurrence of infection associated problems in comparison to indwelling catheter-based infusion system.

Improved drug delivery:

The drug is distributed locally or in systemic circulation with least interference by metabolic or biological barriers. For example, the drug moiety bypassed the GIT and the liver. The by-passing effect is beneficial to drugs, which are either easily inactivated or absorbed poorly in the GIT and/or the liver before systemic distribution^[1].

Compliance:

By allowing a reduction, or complete elimination, of patient-involved dosing compliance is increased hugely. Patient can forget to take a medicine, but drug delivery from an implant is not dependent of patient input. Periodical refilling is involved in some implantables but despite this limitation the patient has less involvement in delivering the required medication.

Potential for controlled release:

Implants are available which deliver drugs by zero-order controlled release kinetics. The advantages of zero order controlled release are:

- (a) Peaks (toxicity) and troughs (ineffectiveness) of conventional therapy is avoided,
- (b) Dosing frequency is reduced,
- (c) Patient compliance is increased.

Potential for bio-responsive release:

Bio-responsive release from implantables is an area of on-going research.

Potential for intermittent release:

Intermittent release can be facilitated by externally programmable pumps. Intermittent release can facilitate drug release in response to such factors as:

- (a) Circadian rhythms,

- (b) Fluctuating metabolic requirements,
- (c) Pulsatile release of many peptides and proteins.

Flexibility:

In the choice of materials, methods of manufacture, degree of drug loading, drug release rate etc. considerable flexibility is possible. From a regulatory viewpoint, it is regarded as a new product and can lengthen the market protection of the drug for an additional 5 years (for a new drug entry) or 3 years (for existing drugs)^[18-21].

3. DISADVANTAGES OF IMPLANTABLE DRUG DELIVERY SYSTEM

The disadvantages of implantables include:

Invasive:

To initiate therapy either a minor or a major surgical procedure is required to initiate therapy. Appropriate surgical personnel is required for this, and may be time-consuming, traumatic. This causes some scar formation at the site of implantation and surgery-related complications in a very small number of patients. Uncomfortable feeling for the patient wearing the device.

Danger of device failure:

There is no associated danger with this treatment that the device may for some reason fail to work. This again requires surgical involvement to correct^[1].

Termination:

Osmotic pumps and non-biodegradable polymeric implants also are surgically recovered at the end of therapy. Although surgical recovery is not required in biodegradable polymeric implants. Its on-going biodegradation makes it difficult to end drug delivery, or to maintain the accurate dose at the end of its lifetime.

Limited to potent drugs:

In order to minimize patient's discomfort the size of an implant is usually kept small. Therefore most implants have a limited loading capacity so that frequently only somewhat potent medicines such as hormones may be appropriate for delivery by implantable devices.

Biocompatibility issues:

Concerns over body reactions to a foreign substance often increase the issues of biocompatibility and safety of an implant.

Possibility of adverse reactions:

A high concentration of the drug delivered by an implantable device at the implantation site may produce adverse reactions.

Commercial disadvantages:

An enormous amount of R&D investment, effort and time is required in the development of an IDDS. If a new material is proposed to formulate an implant its incompatibility and safety must be carefully evaluated to secure the approval of regulatory organisations. These issues can attribute to noteworthy delay in the progress, marketing and price of a new implant [18-21].

4. IMPLANTABLE DRUG DELIVERY DEVICES**4.1 Field of Controlled Drug Delivery**

Implantable controlled drug delivery methods are also useful to deliver medication to those parts of the body which are immunologically isolated and regular modes of drug delivery cannot reach them, for example, the cornea. The field of controlled drug delivery today employs mechanisms such as transdermal patches, polymer implants, bioadhesive systems, and microencapsulation [22-24].

4.1.1 Transdermal Patches

Transdermal patches generally have hollow microneedles made of a biocompatible polymer through which the drug is delivered below the skin. Transdermal patches have numerous advantages compared with other systems of drug delivery: the drugs are not degraded in the GIT, they are painless, and they deliver a constant dosage without the need for patient's compliance [25]. A renowned example for transdermal patches is the nicotine patch.

4.1.2 Polymer Implants

Polymer implants are biodegradable polymers loaded with the drug molecules. The polymer degrades when it comes in interaction with body fluids and in the process releases drug molecules. The rate of degradation of the polymer, and hence the drug release, can be optimized by modifying the properties of the polymers. The polymer material which are most widely used for these applications include, but are not restricted to, Polyglycolic acid (PGA), Polylactic acid (PLA), Polyurethane and the combinations of these in different proportions.

4.1.3 Bioadhesives

Bioadhesives are substances which form bonds with biological surfaces. The most common substances which are used in this case are polymer hydrogels. The principle of operation is similar to polymer implants in this that they too are loaded with drugs and release drugs at a specific rate when in

contact with body fluids. Hydrogels are water-swollen polymer networks. The polymer chains may be held together by either physical forces or covalent cross-links. By design of the hydrogel constituents, they can be made responsive to their chemical or physical environment. At a temperature of 35-40 °C it collapses into a denser, more compact structure due to a switch in the balance of solution and hydrophobic forces as the temperature is raised [26].

4.1.4 Microencapsulation

Microencapsulation refers to the method of covering the drug molecule with a material which will prolong the time before the drug is resorbed, so that it will remain in the viable state and will be released when it reaches the intended destination. There are a variety of ways in which microencapsulation is done. Some of them are use of polymer microspheres, liposomes, nanoparticles etc. [25]. The above devices are 'passive devices' and deliver the drug gradually in very small amounts with precision. But they are not capable of delivering the drug in a non-linear fashion or 'on demand'. They cannot be programmed to deliver drug when required and stop when not required [22, 23].

4.1.5 Some Important Passive Devices

There are some drug delivery devices which deserve a special mention.

4.1.5.1 Microchip Drug Reservoirs

These devices came out of the lab of Dr. Robert Langer lab at MIT. It is one of the very first truly MicroElectro Mechanical Systems (MEMS) based drug delivery systems (**Figure 4.1**). The design incorporates multiple sealed compartments, which are opened on demand to deliver dose of a drug [24]. Fabrication of these microchips began by depositing, 0.12 μm of low stress, silicon nitride on both sides of prime grade (100) silicon wafers using a vertical tube reactor. The silicon nitride layer on one side of the wafer was patterned by photolithography and electron cyclotron resonance (ECR) enhanced reactive ion etching (RIE) to give a square device (17mm x 3mm x 17 mm) containing 34,480 square reservoirs. The silicon nitride served as an etch mask for potassium hydroxide solution at 85.8°C, which anisotropically etched square pyramidal reservoirs (**Figure 4.1 b**) into the silicon along the (111) crystal planes until the silicon nitride on the opposite side of the wafer was reached.

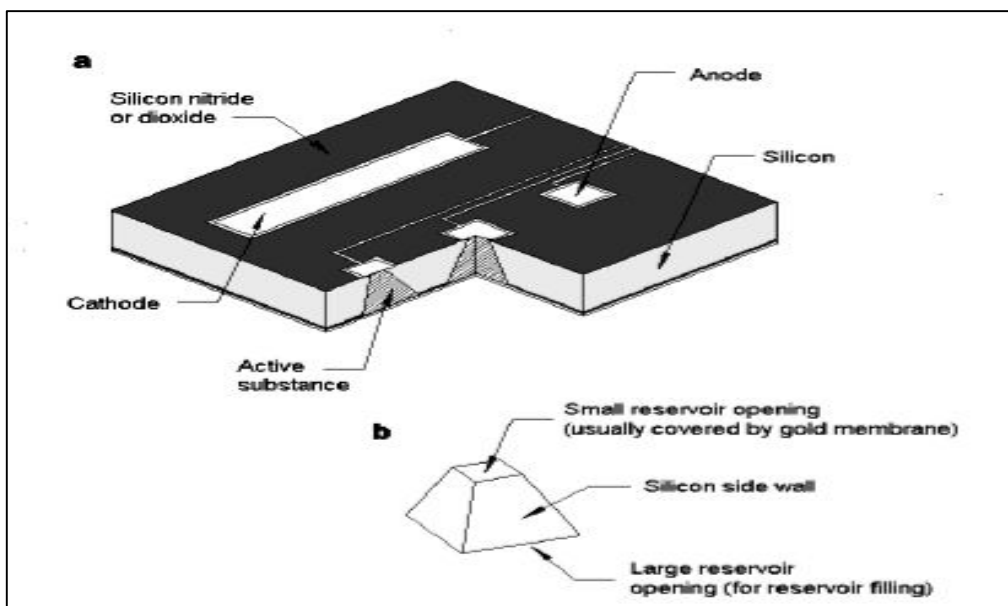


Figure 4.1. Microchip drug reservoir.

4.1.5.2 Immuno-isolating Capsules

These devices are not drug delivery systems in the conventional sense. They deliver insulin in the body but rather than store it in the device they contain pancreatic islet cells which make insulin and deliver through the nanoporous membrane of the device. Microfabrication techniques have been applied to create a biocapsule for effective immunoisolation of transplanted islet cells for the treatment of diabetes^[27]. The fabrication of nanochannels in the membrane structure consists of two steps. First, surface micromachining nanochannels in a thin film on the top of a silicon wafer. Second, releasing the membrane by etching away the bulk of the silicon wafer underneath the membrane. These nanopore membranes are designed to allow the permeability of glucose, insulin, and other metabolically active products, while at the same time, preventing the passage of cytotoxic cells, macrophages, and complement. The membranes are bonded to a capsule that houses the pancreatic islet cells. Because the difference in the size of insulin, which must be able to pass freely through the pores and the size of the IgG immunoglobins, which must be excluded, is only matter of a few nanometers, the highly uniform pore distribution provided by micromachine membranes is essential for effective immunoisolation and therapeutic effect.

4.1.5.3 Diffusion Chambers

A diffusion chamber from Debiotech Inc. They hold a cargo of drugs and are sealed with a semi-permeable membrane. These are used for delivering fairly large amount of drugs and in some cases more than one drug. The membrane surface area is large compared to the reservoir resulting in the increased delivery rates. These reservoirs are generally not used for long term delivery^[28].

4.1.5.4 Diffusion Controlled Implanted Tubes^[29-32]

These use a narrow aperture to provide a slow delivery rate of drugs. They are used for long-term release of highly potent drugs, with the release times in the order of years. A good example is the five-year-duration birth control implants based on elastomeric tubes^[33]. A similar example is that of the DurosTM osmotic pump from ALZA Corporation. This non-biodegradable, osmotically driven system^[2] is intended to enable delivery of small drugs, peptides, proteins, DNA and other bioactive macromolecules for systemic or tissue-specific therapy. The DUROS[®] implant is a miniature cylinder made from a titanium alloy, which protects and stabilizes the drug inside, using ALZA's proprietary formulation technology. Water enters into one end of the cylinder through a semi-permeable membrane; the drug is delivered from a port at the other end of the cylinder at a controlled rate suitable to the specific therapeutic agent. The delivery can be over a period of 12 months.

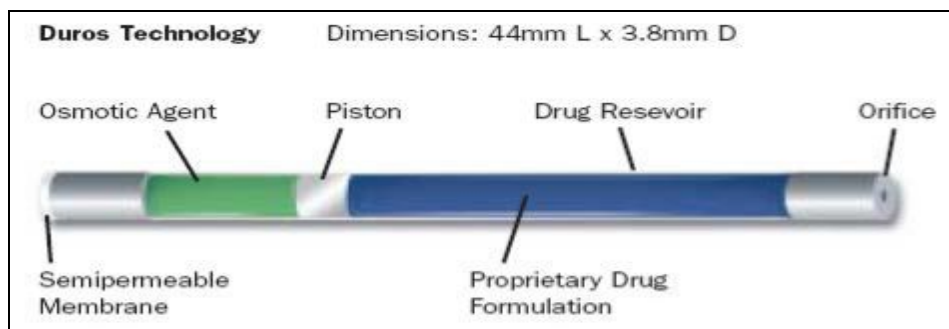


Figure 4.2Duros osmotic pump (Alza -Mountain View, CA, USA).

4.2 Implantable Pump Systems

The primary characteristic that distinguishes a pump from other controlled-release systems is that the primary driving force for delivery by a pump is not the concentration difference of the drug between the concentration and surrounding tissue, but rather, a pressure difference. This pressure difference can be generated by pressurizing a drug reservoir, by osmotic action, or by direct mechanical actuation. The first such device to see extensive clinical use was reported in the early 1970s. The development and commercialization of the unit was a joint effort between industry and academia, in this case the University of Minnesota and the Infusaid Company. It used a bellows-type pump activated by partially liquefied Freon. The Freon was reliquified with each transcutaneous refill of the implantable device, and the administration of the drug was constant. There were no electronics or batteries in the device. But the later devices by the same company and Medtronic came with significant advancements. These more sophisticated units include a refillable reservoir, a mechanical pumping/valving mechanism, advanced electronics that control the drug administration and which can be programmed telemetrically from outside the body, and a primary lithium battery^[34]. The ideal drug delivery system should have certain characteristics. It must deliver a drug within a range of prescribed rates for extended periods of time (usually the range of drug delivery rates is in tens of $\mu\text{l}/\text{min}$). It should include features such as reliability, chemical, physical and biological stability, and be compatible with drugs. The pump must be non-inflammatory, nonantigenic, noncarcinogenic, nonthrombogenic, and have overdose protection. The pump must be convenient to use by both the patient and the health professional, have long reservoir and battery life, easy programmability, and be implantable under local anaesthesia. There must also be a simple means to monitor the status and performance of the pump, and both the interior and exterior of the pump must be sterilizable^[25]. The pump must maintain accuracy and

precision of delivery over a period of 2 to 5 years to justify the surgery associated with implantation of the pump. The presence of a finite reservoir life, a finite battery life, patient-to-patient variability in drug demands or long-term changes in an individual patient's drug demand require that the implantable device be convenient to use.

Examples of important devices currently in use are as follows:

4.2.1 Medtronic Synchronized

The most widely used implantable drug delivery system is the Minimed Medtronic Insulin delivery pump. As the name suggests it is used as artificial pancreas for patients with Diabetes Mellitus. The Minimed pump (which is the maker of the pump later acquired by Medtronic) has a peristaltic minipump^[2] which delivers $0.50\mu\text{l}$ per stroke. Depending upon a patient's insulin requirements, the implantable insulin pump reservoir is refilled with fresh insulin every two to three months. A needle is inserted through the skin into the pump fill port. To assure refill safety, the negative pressure in the pump will automatically draw the special U-400 insulin from the syringe into the reservoir only after the needle has been securely connected inside the fill port^[35]. The body of the implantable pump is made of titanium which is the preferred choice for biocompatibility considerations. The battery used is carbon monofluoride which lasts for 6 to 7 years at the least. It can be programmed with an external communicator. The pump is 8.1 cm. in diameter and 2.0 cm thick. The safety features include negative pressure reservoir with passive filling, pump system error shut down, unique code sequencing to synchronize pump and PPC (Personal Pocket Communicator).

4.2.2 Debiotech

The MIP implantable pump will perhaps be the first MEMS based implantable pump to enter the market. It is proposed that it is going to be the heart of a high performance programmable implantable drug delivery system.



Figure 4.3 MIP implantable MEMS pump (Debiotech-Lausanne, Switzerland).

The MIP is a piezo-actuated silicon micropump. The working principle is a volumetric pump with out-of-plane pumping membrane, which compresses a chamber in a reciprocating movement and which is associated to a pair of check valves in order to direct the liquid flow. The chip is a stack of four layers bonded together: two (purple) silicon plates with micromachined pump structures and two (dark blue) glass pieces with through-holes. Added to the stack is a piezoelectric ceramic disc (green), responsible for the actuation and two titanium fluid connectors (grey), hermetically joined to the chip^[18].

5. THE IDDS SYSTEM

5.1 Conceptual Design

The IDDS system proposed in this thesis has the following components:

- a) Micropump
- b) Reservoir
- c) Power Module
- d) Control Circuitry and RF Telemetry

5.2 Components of IDDS

5.2.1 Micropump

The micropump is an on-demand active device that can be electrically controlled to deliver specific volumes of therapeutic agents. The micropump provides the driving mechanism to deliver the drug from the reservoir to the catheter. The requirements for drug delivery include small size and high reliability. The IDDS should be capable of delivering drugs against a back pressure of blood in the range of 8mmHg to 12mmHg in the veins or greater than 120mmHg in the arteries. The IDDS uses an ‘in-plane’ silicon pump^[36] fabricated from silicon-

on-insulator (SOI) wafer by deep reactive ion etching (DRIE) process

5.2.2 Reservoir

The reservoir plays an important role in determining the size of the implantable device. Our reservoir is similar in design to the vascular access ports. These ports have been demonstrated to have good bio-stability and bio-compatibility^[34]. The reservoir should have smooth contours, hold at least 5 ml of the drug and be easily accessible for refilling. A subcutaneous position for the port-like reservoir was chosen for the IDDS. The size of the reservoir can be varied based on need at the same time retaining the size of the pump. For reasons of biocompatibility, titanium or silicone reservoir will be used. It must be noted that there is no set dosage for continuous infusion for chemotherapy. The dosage, infusion rate and drug combination can vary depending on the treatment requirements. The port is connected to the implantable unit via a catheter.

5.2.3 Power Management

Without taking into account the power required by the RF unit, the estimated power consumption for the target 10 μ l/min delivery rate is in the range of 100-500 mW. This figure is estimated based on the power consumption of the micropump necessary to generate required diaphragm displacements. As a result, commercially available miniature lithium-ion batteries^[28, 35] would discharge in less than 48 hours continuous operation. Therefore, a power management system employing recharging of the power source is necessary in the IDDS. One possibility is recharging from outside of the body using through-skin electrical interconnects. A much better alternative would be wireless power transmission using RF coils^[2, 36, 37].

5.2.4 Control and Telemetry Circuitry

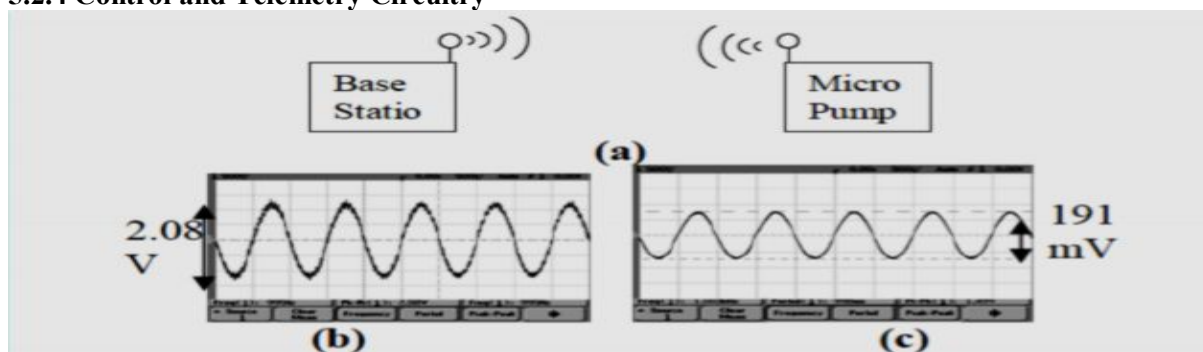


Figure 5.1 (a) Telemetry set up (b) transmitted and (c) received signal

In figure 5.1 the telemetry test setup is placed 5m apart. The transmitted signal is a 1.2 mVp-p amplified by a factor of 2000 and received signal is 191 mV. The modulated signal is a 1 KHz sine wave with a 433 MHz carrier^[38]. The telemetry module consists of a transmitter unit and a receiver unit. Our goal is to integrate the telemetry and microfluidic devices to deliver a completely implantable drug delivery mechanism, including power management, size considerations and control circuit integration.

6. THERAPEUTIC APPLICATIONS OF IDDS

Ocular disease

Numerous different implantable systems have been estimated to deliver sustained ocular delivery. These

comprise membrane-controlled devices, implantable infusion systems and implantable silicone devices. Ocular insert (ocuser) having pilocarpine base and alginic acid in a drug reservoir surrounded by a release-rate controlling ethylene-vinyl acetate membrane is an example of the membrane-controlled system^[39-41]. The ocuser system offers an initial rupture followed by a near zero order transport of pilocarpine^[42] at 20 or 40 µg/h for a span of seven days. The device is well tolerated in adults, with suitable control of intraocular pressure and minimal side effects^[43-46]. However it looks to be poorly tolerated in the geriatric patients where most of the therapeutic requirement exists. Implantables evaluated for ocular cancer management include silicone rubber balloon having an antineoplastic agent.

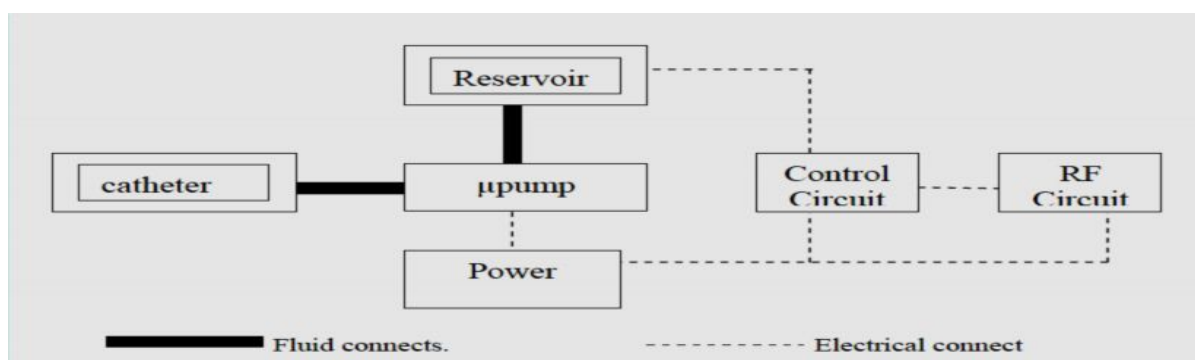


Figure 5.2 Block diagram.

Block Diagram (Figure 5.2) shows the relationship between the different components of the IDDS.

Contraception

Norplant a sub-dermal implant for long-lasting transport of the contraceptive agent levonorgestrel recently been approved for marketing by the FDA. The device consists of six silicone membrane capsules each having about 36 mg of levonorgestrel. The capsules are placed sub-dermally on the inside of the upper arm or the forearm in a fan-shaped pattern through a trocar from a single trocar entry point. Clinically, Norplant users have a net pregnancy rate of below 1.5 in 100 women at 4 years. At the end of 4 years 42 % of the women continued with the technique representing acceptability comparable with other techniques. Other polymer-based systems under study for contraception contain vaginal rings usually composed of silicon rubber used for 3 to 76 months often with a removal period of one week monthly to allow for menstruation; the progestasert an ethylenevinyl acetate copolymer intrauterine drug-releasing device which persists for one year and suspensions of injectable microspheres or rods composed of biodegradable polymers^[41].

Dental application

For numerous dental applications including local prolonged administration of fluoride antibacterial and antibiotics, polymeric implants have been evaluated. Stannous fluoride was integrated into different dental cements for sustained release fluoride delivery. Another dispersed in the hydroxyethyl methacrylate and methyl methacrylate copolymer hydrogel coated with an outer layer of the same copolymers in different ratio so as to be rate limiting in drug release. The device, about 8 mm long and having 42 mg of fluoride in the core was attached to the buccal surface of the maxillary first molar and designed to release 0.5 mg/day of fluoride for 30 days^[47-49].

Immunization

Polymeric implants are being evaluated for better immune response to antigens. The concept here is to offer pulsatile or continuous administration of the antigen over a prolonged period of time. Wise et al. evaluated immunization efficiency of ethylene-vinyl acetate copolymer pellets having bovine serum albumin as model antigen. The immune response was comparable to that achieved by two injections of bovine serum albumin in complete Freund's adjuvant (Freund's adjuvant is an o/w emulsion containing bacteria).

Cancer

Silicone rod implants analogous to those used for delivery of levonorgestrel have been evaluated for delivery of ethinylestradiol or testosterone propionate

in persons with prostate cancer. Lupron depot produced by Takeda chemical industries is an implantation system providing one month depot release of leuprolide acetate, a synthetic analogue of the gonadotropin-releasing hormone (GhRH). The implant containing biodegradable microspheres made from polylactic – glycolic copolymer at 1:1 compositions having 10% leuprolide acetate for the management of prostate cancer. Zoladex produced by ICI Pharma provides one month depot release of goserelin acetate from a biodegradable implantable rod for the management of prostate cancer.

Narcotic antagonists

Naltrexone has been comprehensively evaluated in implant from long term delivery of narcotic antagonists. Naltrexone freebases its hydrochloride or the pamoate acid salt has been formulated in a various polymers and dosage forms for prolonged narcotic antagonist activity.

Other applications

Various insulin delivery systems have been formulated and evaluated for a biofeedback approach and have been described before. These are biofeedback controlled system, where the drug release rate is reliant on the body's requirement for the drug at a specified time. From a therapeutic perspective these systems may come closest to reproducing the release from a gland for example the pancreas. Various mechanisms have been employed to attain self-regulated delivery^[2, 41].

The above mentioned applications are few examples of therapeutic applications of implantable drug delivery system.

7. FUTURE PROSPECTS

At present much research is being conducted in the region of implantable drug delivery systems. Despite this fact, much work is still required in the regions of biodegradable and biocompatible substances, the kinetics of drug release, and more improvement of present systems before many of these preparations can be used. In the future, scientists remain expectant that many of these systems can be prepared with best zero-order release kinetics profiles, *in vivo*, over long times, allowing for prolonged use in constantly sick patients. New medicines are continuously being prepared. Several of these medications are developed from proteins and peptides which are very unstable when taken through oral route. By using new types of prolonged-release drug delivery systems, delivering such drugs at constant rates will be possible over a prolonged period of time and will exclude the necessity for multiple dosing. It is expected that in the

upcoming years, improvement of new implantable systems will help cost reduction of drug treatment, increase the effectiveness of drugs, and enhance patient compliance^[50-52].

8. CONCLUSION

Recently Implantable drug delivery is one of the technology sectors that often overlooked in the development of new drug delivery by the formulation, research and development in many pharmaceuticals. Implanted drug delivery technologies have ability to reduce the frequency of patient driven dosing and to deliver the compound in targeted manner. Many product utilizing implant delivery technologies are being utilized for many therapeutics applications such as, dental, ophthalmic, oncological disease. As with any implanted material, issues of biocompatibility need to be investigated, such as the formation of a fibrous capsule around the implant and, in the case of erosion-based devices, the possible toxicity or immunogenicity of the by-products of polymer degradation. Additionally, convenient methods of triggering drug delivery from the externally controlled delivery systems need to be developed in order for

them to be of practical use. These issues, coupled with the potential therapeutic benefits of pulsatile dosing regimens, should ensure that the current high level of interest in this area will extend well into the future and result in significant advances in the field of controlled drug delivery. A large number of companies are involved in the development of new drug delivery systems, which is evident by an increased number of products in the market and the number of patents granted in the recent past. Tomorrow's drugs definitely will be more challenging in terms of the development of delivery systems, and pharmaceutical scientists will have to be ready for a difficult task ahead.

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