Review Article

Implantable Drug Delivery Systems: An Overview

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ABSTRACT

Controlled drug through diffusion and activation-based drug delivery devices have become commercially feasible due to converging technologies and regulatory accommodation. Combination products constructed using implantable technology offer revolutionary opportunities to address unmet medical needs related to dosing. These products have the potential to completely control drug release, meeting requirements for on-demand pulsatile or adjustable continuous administration for extended periods. Implantable technologies, materials science, data management, and biological science have significantly developed in recent years, providing a multidisciplinary foundation for developing integrated therapeutic systems. If small-scale biosensor and drug reservoir units are combined and implanted, a wireless integrated system can regulate drug release, receive sensor feedback, and transmit updates. The tools such as microfabrication technology, information science, and systems biology are being combined to design increasingly sophisticated drug delivery systems that promise to significantly improve medical care.

Introduction

With the advancement in development and technology, number of new-drug therapies have been invented, but maintaining steady therapeutic drug concentration levels, *in vivo*, has been a major problem. When using intermittent IV or oral-drug administration, the potential disadvantages of such drug therapies include: high plasma concentrations of drugs that may lead to toxicity or low drug levels that cause to sub-therapeutic blood levels, and, potentially, cause drug resistance in some instances. In the past, the only way to eliminate the peak and trough plasma levels of drug therapy was by continuously IV infusing a patient at a constant rate based on the pharmacokinetics of the drug. In order to alleviate this problem, a new system for obtaining controlled drug delivery was essential. Research began, in the late-1930s by Danckwerts *et al*., on sustained release implantable drug delivery systems administered by subcutaneous route.[1] This discovery sparked an interest in the area of implants leading to further studies and the demand for implantable systems will increase 14% per year, through 1998, to $5.9 billion annually.

The implantable therapeutic systems are mainly approached for

- long term,
- continuous drug administration, and
- controlled release.

Ideal requirements of implantable drug delivery systems.

- Environmentally stable.
- Biocompatible.
- Sterile.
- Biostable.
- Improve patient compliance by reducing the frequency of drug administration over the entire period of treatment.
- Release the drug in a rate-controlled manner that leads to enhanced effectiveness and reduction in side effects.
- Readily retrievable by medical personnel to terminate medication.
- Easy to manufacture and relatively inexpensive.

Advantages of the implantable drug-delivery system.

- Improved efficiency.
- Very effective.
- Small dose is sufficient to elicit the action. For example, progesterone 2–8 mg
- Reduced side effects.
- On-spot delivery.
- Convenient therapy.
- Provide linear delivery for long periods of time, from a few weeks to many months.
- Plasma drug levels are continuously maintained in a therapeutically desirable range,

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- Harmful side effects from systemic administration can be reduced or eliminated by local administration from a controlled release system.
- Drug administration may be improved and facilitated in underprivileged areas where good medical supervision is not available.
- Administration of drugs having short *in vivo* half-lives may be greatly facilitated.
- Continuous small amounts of drug may be less painful than several large doses.
- Patient compliance may be improved.
- This method is relatively less expensive and less wasteful of the drug.

Limitations of the implantable drug delivery system.

- Possible toxicity.
- Need for microsurgery to implant the system.
- Possible pain.
- Difficulty in shutting off release if necessary.

Drug release depends upon

- diffusion of drug through the polymer,
- nonbiodegradable polymers used to prepare dosage forms, for example, polymethylsiloxane,
- dissolution of drug, and
- usage of biodegradable polymers, for example, polylactic acid and polyglycolic acid.

Mechanism of implantable drug delivery systems.

Most implanted drug delivery systems are based on three basic delivery mechanisms.

- Swelling control.
- Osmotic pumping.
- Diffusion.

In solvent-activated systems a swelling or osmotic mechanism is involved.[2] Applications have been made in the areas of dentistry, immunization, anticoagulation, cancer, narcotic antagonists, and insulin delivery.[3] Nowadays, number of drugs have been used for the implantable drug delivery systems as shown in Table 1.

Non-degradable and biodegradable implant systems

Non-degradable systems

There are several types of nondegradable implantable drug delivery systems available on the marketplace today, but the nondegradable matrix system and reservoir systems are the two most common forms [Figure 1].

In the polymeric matrix system, the drug is dispersed homogeneously, inside the matrix material. Slow diffusion of the drug through the polymeric matrix material provides sustained release of the drug from the delivery system.

Table 1: Drugs used for the implantable drug delivery systems

Name of Drugs	Purpose
Progestin + estradiol,megestrol,norgestrel	Contraception
Ibuprofen,naproxen,phenylbutazone	Polyarthritis
Cyclophosphamide,merchloroethamide	Cancer
Deoxycortisone	Antihypertensive studies
Morphine	Narcotic addiction studies
Pilocarpine	Glaucoma

The reservoir-type system, on the other hand, consists of a compact drug core surrounded by a permeable nondegradable membrane whose thickness and permeability properties can control the diffusion of the drug into the body.[4] The release kinetics of drug from this system suggest that if the concentration of the drug within the reservoir is in constant equilibrium with the inner surface of the enclosed membrane, the driving force for diffusional release of the agent is constant and zero-order release kinetics of the drug from the delivery system is obtained.[5] This type of system, however, has several disadvantages. The outer membrane of most of these systems is nondegradable. Therefore, after drug has been released, minor surgery is necessary for the removal of the delivery system from the body. There is also a possibility that membrane rupture will potentially lead to "drug dumping" during therapy. Depending on the type of drug involved in the reservoir, "drug dumping" may result in untoward toxic side effects from drug plasma concentrations that exceed maximum safety levels. The possibility of "drug dumping" has made the reservoir system a less popular method of drug delivery.

In the past, nondegradable systems have also been studied for use in the administration of anticancer drugs such as doxorubicin. Microcapsules containing a nondegradable exterior and compressed doxorubicin reservoir interior have been studied. This type of administration was compared to biodegradable polymer matrices containing doxorubicin. In such experiments, the biodegradable polymers did not cause any toxic reactions within the body and were preferred over the nonbiodegradable polymers that remained in the body after the drug was released.[6]

Matrix systems are also commonly used as nondegradable implants. These systems consist of uniformly distributed drug throughout a solid nonbiodegradible polymer.[7] Like the reservoir systems, matrix systems rely on the diffusion of drug particles through the nondegradable fibrous network of the polymer to obtain sustained release of the drug. However, the kinetic release of drug from these formulations is not constant and depends upon the volume fraction of the agent in the matrix. The greater the concentration of the dissolved agent within the matrix, the greater the release from the system.[8]

Another type of nondegradable system is the magnetically controlled release system. In this type of formulation, small magnetic beads are uniformly dispersed within a polymer [Figure 2]. When the unit is exposed to a biological system, normal diffusion of the drug due to a concentration gradient is seen. However, upon exposure

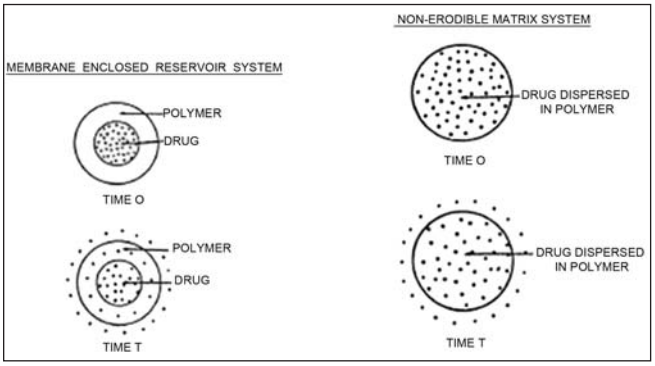

Figure 1: Cross-sectional view of idealized nonerodible reservoir and matrix systems, showing diffusion of the drug across the polymer

to an external oscillating magnetic field, larger quantities of drug can be released quickly.[1] The major advantage of this type of drug delivery system is the possibility of manipulating the release kinetics of the drug by using external magnetic stimuli.[8]

Biodegradable systems

Biodegradable systems have gained much popularity over nondegradable delivery systems.[9,10] The major advantages of biodegradable systems include the fact that the inert polymers, used for the fabrication of the delivery system, are eventually absorbed or excreted by the body. This alleviates the need for surgical removal of the implant after the conclusion of therapy thereby increasing patient acceptance and compliance.[11]

However, developing biodegradable systems is a more complicated task than formulating nondegradable systems. When fabricating new biodegradable systems, many variables must be taken into consideration. For instance, the degradation kinetics of the polymer, *in vivo*, must remain at a constant rate to maintain sustained release of the drug. Many factors can affect the rate of degradation of the polymer in the body. Alterations in body pH or temperature can cause a transient increase or decrease in the degradation rate of the system. The surface area of the delivery system also plays an important role in its degradation.[12] As the system is eroded, the surface area of the implantable system decreases. Thus, the change in shape of the drug delivery system that will occur, *in vivo*, should be taken into account during the formulation design. In order to attain a more uniform and constant release, it is necessary to use geometrical shapes whose surface area does not change as a function of time during erosion.[13] A flattened slab-type shape that has no edge erosion is the shape that approximates most closely a zero-order release kinetic profile.[14] Some manufactures have also designed systems that contain a bioerodable inert core coated with the active drug matrix to alleviate the change in surface area problem encountered during erosion. Another problem that occurs with bioerodable systems is the slow diffusion of the drug from the polymer matrix.[8] Diffusion of the drug usually occurs at a slower rate than the bioerosion of the system and is dependent upon the chemical nature of the polymeric substance utilized in the formulation of the drug delivery system. This becomes a major challenge to overcome when developing bioerodable systems whose use is intended for extended release applications or in situations in which the drug has a narrow therapeutic index.[15]

Two different types of biodegradable delivery systems are currently available. The first type, a reservoir system, is similar in structure to the nondegradable reservoir type described earlier. The mechanism of drug release from both systems is quite similar.[16] However, these bioerodible systems, in contrast, contain an exterior polymeric membrane that degrades at a slower rate than the expected rate of drug diffusion through the membrane. Therefore, the membrane remains intact while the drug is released completely. Eventually, the exterior polymeric membrane is degraded, *in vivo*, and, ultimately, eliminated. The second type of bioerodible system consists of drug dispersed in a polymer, monolithic type, which is slowly eroded, *in vivo*, by biological processes at a controlled rate.[1] The most popular biodegradable polymers currently being investigated include polyglycolic acid, polylactic acid, polyglycolic-lactic acid, polyaspartic acid, and polycaprolactone.[4] The use of ethyl vinyl acetate copolymer matrices for the delivery of macromolecular drugs such as insulin has also been studied extensively.[17,18] A new form of lactic acid/lysine copolymer, chemically attached to a biologically active peptide, is being developed and tested which could function as a matrix for the mammalian cells.[19] This new copolymer effectively promotes cell adhesion to an otherwise nonadherent surface, and this system will, hopefully, play a major role in the development of implantable polymers in the future.[20]

Implantable pump systems

Many different drugs require external control of delivery rate and volume. Such control cannot be obtained when using biodegradable or nondegradable delivery systems with the exception of the magnetic-type delivery systems. Pump systems have been used to provide the control needed in these situations. Recently, due to the availability of advanced microtechnology, it has been possible to create pump systems small enough to implant, subcutaneously, for drug delivery.[21] This allows the patient to maintain the control of drug release without the need for an external pump system. In recent advances, insulin implantable pump systems have been invented and used for the control of type-1 diabetes as shown in Figure 3.

Pump systems differ from other implantable systems due to their mechanism of drug delivery. Pump systems release drugs through

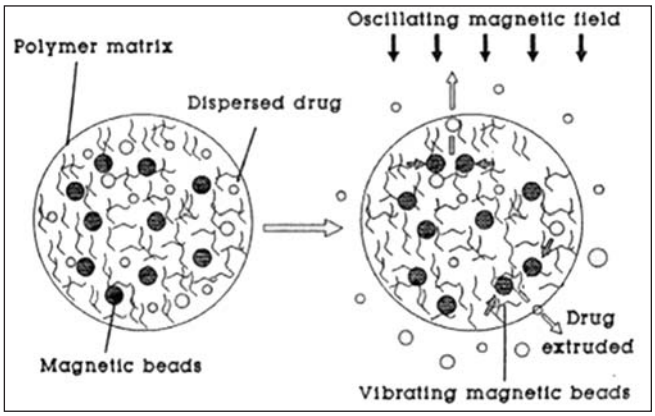

Figure 2: Schematic of a magnetically controlled polymeric drug delivery system illustrating increased drug release from the system after exposure to an oscillating magnetic field

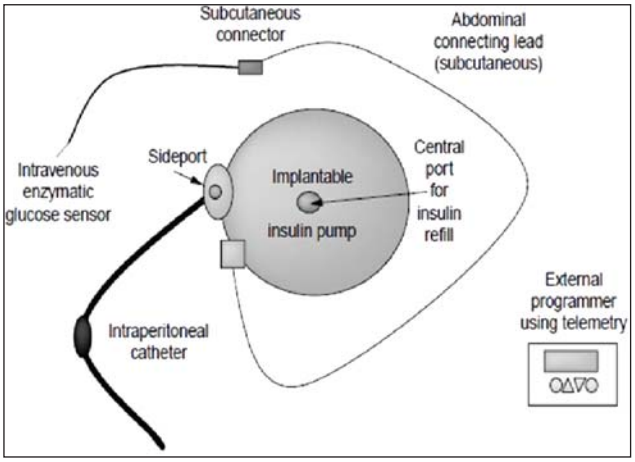

Figure 3: Schematic of an insulin implantable pump

a pressure difference generated gradient that results in the bulk flow of a drug at controllable rates.[22] To date, five different types of implantable pump systems have been tested including infusion pumps, peristaltic pumps, osmotic pumps, positive displacement pumps, and controlled release micropumps.

Infusion pumps

Infusion pumps are implantable mechanical systems that utilize a fluorocarbon propellant to administer the drug, *in vivo*. Such pumps were initially developed for the administration of insulin to diabetic patients. Infusaid (Infusaid Corp. Sharon, MA, USA) was one of the first commercially available pumps for this use. Normally, insulin-dependent diabetics require injections once or twice daily. This type of dosing results in abnormal peaks and valleys in blood glucose levels. It is believed that such poor control of blood glucose levels may lead to diabetic complication such as heart and kidney disease.[12] It is felt that continuous insulin infusion using such pumps may help eliminate these risk factors in the diabetic population. The pump consists of a disc-shaped canister made of light-weight biocompatible titanium which contains a collapsible welded bellow.[23] The bellow separates the canister interior into two separate chambers. The first chamber contains the fluorocarbon propellant and the second contains the insulin formulation[8] [Figure 4].

The gas pushes the drug through a filter and a flow regulator that provides a constant rate of drug administration at a given temperature. The delivery rate is adjusted by changing the drug concentration in the pump reservoir.[24] The advantage of this system involves the fact that no external energy source is needed to drive the pump action. When the pump reservoir is refilled, an injection of drug through a membrane consisting of a self-sealing silicone rubber and Teflon septum is administered. The force of the injection recompresses the fluorocarbon propellant thereby recharging the system. In addition to insulin therapy, the use of this pump system in the delivery of anticoagulant and chemotherapeutic agents has also been investigated.[25]

Peristaltic pumps

Peristaltic pumps consist of rotary solenoid-driven systems that run via an external power source which is usually a battery.[1] Peristaltic systems, like the infusion pump systems, are filled through a silicone rubber septum and can be used for several years depending on the life span of the battery-powered system [Figure 5]. The advantage of this type of system is that the rate of drug administration can be controlled by an external remote control system. These systems, however, have proven to be very costly, and, thus, have not been seen in standard practice to date.

Osmotic pumps

Osmotic pumps have proven to be the most popular type of implantable drug delivery systems. The osmotic pump, also known as Oros or the gastrointestinal therapeutic system, was first described by Theeuwes and Yum, and released for use by Alza Corporation.[26,27] This pump consists of a drug reservoir surrounded by a semipermeable membrane. The surrounding membrane allows a steady influx of water and biological fluid into the reservoir through the process of osmosis. The hydrostatic pressure built from this influx causes a steady release of the drug from an opening in the membrane called the *drug portal*. The rate of drug release is constant or zero-order until the drug within the reservoir is completely depleted. Changing the rate of drug administration of these systems can only occur by changing the structure of the semipermeable membrane that requires removal of the system.[28]

Osmotic pump systems containing hydromorphone have been subcutaneously implanted for the use of pain management. Results have shown that Alzet's osmotic pumps release 262 mg/h of hydromorphone to produce stable plasma concentrations of approximately 30–40 mg/mL over a 2-week period. This type of delivery system is advantageous over other systems since the "initial burst effect," seen in other forms of degradable or nondegradable matrix systems, does not occur.[29] The prolonged release of drug at a constant rate has been shown to be effective in the treatment and management of chronic pain. Therefore, such systems may be used more extensively in the future.

Positive displacement pumps

Positive displacement pumps have been developed to provide continual insulin delivery in diabetic patients. Most of these systems utilize piezoelectric disk benders affixed to flexible tubing. Such pumps are made by first exposing the disks to certain voltages so that they form spherical surfaces.[30,31] The bellow-type system is then connected to a drug reservoir via a three-way solenoid driven

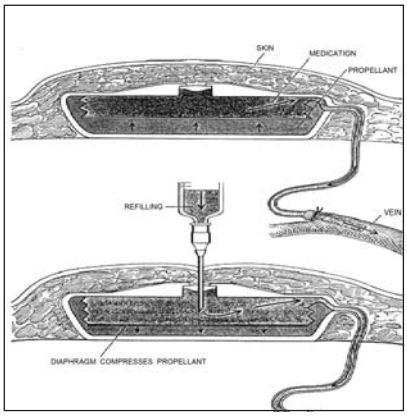

Figure 4: An implantable propellant driven pump system during operation (top) and during refilling (bottom)

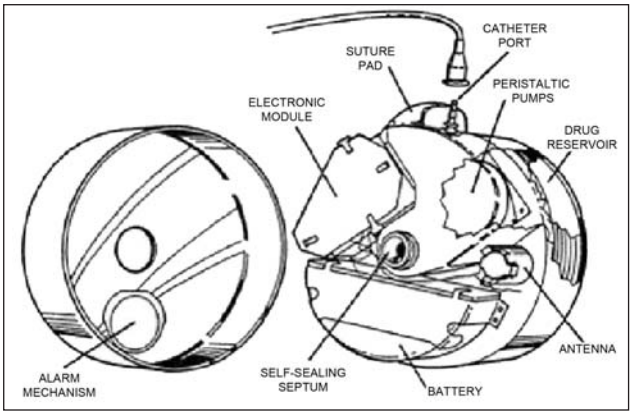

Figure 5: Cross-sectional view of an implantable peristaltic pump showing all important components

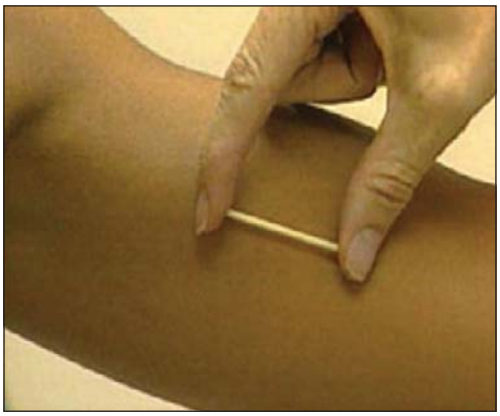

Figure 6: Schematic of an implantable rod

valve. When exposed to electrical pulses, the valves in the pump open or close depending on the direction of the pulse. This action causes the release of drug in a controlled manner based on the rate of the electrical pulse. Other types of positive displacement pumps using similar designs are currently being developed for the delivery of insulin.[4]

Implantable rods

Implantable rods are prepared with the help of different type of biodegradable and nonbiodegradable polymers. Figure 6 shows the implantable rod release the drug in a controlled manner.[16]

Conclusion

A research work and novel technique is currently being conducted in the area of implantable drug delivery systems. However, much work is still needed in the areas of biodegradable and biocompatable materials, the kinetics of drug release, and further development of current systems before many of these formulations can be used. In the future, researchers remain hopeful that many of these systems can be developed with ideal zero-order release kinetics profiles, *in vivo*, over long periods of time, allowing for extended use in chronically ill patients.

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