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IMPLANTABLE CONTROLLED RELEASE DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT.

Origins of rate controlled implantable drug delivery dates back to 1964 when silicone implants were used to prolong a drug effect. Despite much activity in the years since 1964, the progress to a safe, effective and acceptable implant system(s) has been slow. The critical factors in implant research which need to be addressed include: erodibility, reproducibility, lack of irritation and carcinogenicity, lack of dose dumping, duration and pulses. While it is possible to surgically implant and remove drug-containing devices or polymeric matrices, the requirement for such intervention could have a significant negative impact on the acceptability of a product candidate. In recent years, two implant systems have been approved for human use; (a) a silicone-based device (Norplant®), and (b) a system based on lactide/glycolide copolymers to release a luteinizing hormone - releasing hormone (LHRH) agonist for treatment of male reproductive tract tumours. This approach to drug

delivery is very appealing for a number of classes of drugs, particularly those that cannot be given via the oral route, and drug candidates whose therapeutic index is relatively large. This article reviews the background to implantable drug delivery systems, the rationale behind using implantable drug delivery systems, the types of systems being currently researched, and the various methods available for their evaluation.

INTRODUCTION.

Technological innovations in pharmaceutical drug delivery systems in the last decade and in the future have and promise to radically change the field of pharmacotherapy. Many experts predict that by the year 2 000 drugs will be more specific in pharmacodynamic action, more site selective, more closely resemble natural products such as peptides and proteins, and will be given less often and in lower quantities[1]. Increasing the site selectivity of a drug basically involves preventing the drug molecules from coming across the many biological barriers that a drug molecule has to escape before coming into the vicinity of the active receptor site. Some of these barriers include binding to plasma proteins, transport across the GIT membrane, removal via the lymphatic system, first pass hepatic effects, and transport across the blood brain barrier, to mention a few. All of these biological barriers prevent a vast number of molecules (sometimes up to 100%) from actually reaching their targeted site of action. One way to bypass many of the biological barriers and to overcome incomplete transport to the desired site of action, and/or sufficiently sustained action after reaching the target tissue as well as to lower the side-effects on the healthy tissue is to physically deliver the drug to its

specific site of action. This is traditionally done by means of designing drug delivery systems that are administered as close as possible to their target site of action, e.g. suppositories, eye drops, creams, inhalation aerosols, injections, and such. Drug administration with these delivery systems often leads to fluctuations in blood levels of drug, side effects and noncompliance. It is well established that dosage form design can modify drug action. A new, more far reaching and positive expression of this principle is taking shape as dosage form design advances to control the rate of drug release from its delivery system and this may contribute to the therapeutic value of a drug.

One means of administering drugs that are, (1) more site selective, (2) given less often, and (3) require smaller dosages, is through implantable controlled release drug delivery systems (ICRDDS). The precedent for implantable drug delivery systems to provide long-term continuous therapy dates back to the last century and the development of subcutaneously implantable drug pellets. The simplest implantable devices in current usage are administered subcutaneously and depend solely upon extremely slow dissolution of heavily compressed drug (e.g. oestradiol implants) to provide a very extended period of drug release.

ICRDDSs can offer the following advantages:

(1) Improved control of drug levels at the specific site of action. This is due to the elimination of "peaks and troughs" resulting from periodic dosing and uneven dosing intervals. A well designed ICRDDS releases drug at constant rate over long periods of time. This then leads to fewer side effects from too

high or too low a dose. In addition, less total drug is required to elicit the same therapeutic effect.

(2) Drugs are delivered as near as possible to their target sites of action and undesirable effects on other sites in the body are minimised.

(3) Some protection of drugs that are rapidly metabolised or have short ***in vivo*** half lives is afforded by ICRDDSs.

(4) For drugs that cannot be administered by other routes and where compliance is likely to be a major problem.

(5) In cases of extreme allergies or side effects to drugs already administered, immediate removal of implants is possible in contrast to injectable drug delivery systems and in many cases less uncomfortable and traumatic as compared to "stomach pumps" (if a stomach pump is indeed possible) with oral drug delivery systems.

(6) If the only therapeutically active form of a drug can be administered via the I.V. route , e.g. insulin, an ICRDDS may be more suitable and less painful to patients over a long period of time.

However, there are a few disadvantages of ICRDDS, and these must be weighed against the advantages of developing an ICRDDS. Disadvantages of ICRDDSs may include:

(1) Toxicity or lack of biocompatibility of the materials used for the implant.

(2) Harmful byproducts from ICRDDSs may form, specifically for biodegradable forms.

(3) Most ICRDDSs require minor surgery to implant and to remove from the administered site if it is not a biodegradable system.

(4) Pain and discomfort may be caused by the presence of the implant.

(5) ICRDDSs can be more expensive than non ICRDDSs due to the cost of the polymer, pump, or manufacturing procedure.

(6) Leaks and variable, imprecise drug release may occur in ICRDDSs.

It could be argued, however, that if an ICRDDS is properly formulated, has undergone extensive clinical trials, and is manufactured under strict quality control procedures (as all pharmaceuticals are and should be), then toxicity, lack of biocompatibility, and the occurrence of leaks and uncontrolled release of ICRDDSs, should not occur and therefore, not be considered as inherent disadvantages.

The major issue is: can we make implants sufficiently reliable in the biological milieu to deliver potent drugs at a well defined rate and with a duration of release which will permit a frequency of administration acceptable to the patient? Despite the difficulties inherent in the development of safe, effective and manufacturable implant systems, the evidence from two products suggests that this goal can

be achieved. The potential usefulness of such devices in human and animal health care is enormous and is well worth pursuing. As with all drug delivery areas, success will only be achieved by use of appropriate multidisciplinary teams dedicated to the research programme and to persevering with efforts to overcome the difficulties.

HISTORICAL BACKGROUND.

According to Blackshear[2], the scientific concept of implantable drug delivery systems originated with R. Deansby and A.S. Parkes, who in about 1937 presented at the Royal Society of Medicine in London a paper describing the effects of various hormone preparations on the growth of livestock. They apparently implanted compressed pure crystalline oestrone pellets under the skin of brown leghorn capons. They then assessed the effect of the oestrone by shaving areas of the chicken's breast and observed the appearance of new feathers as they appeared. One subcutaneous oestrone pellet caused female feathers to grow on the male birds for as long as three months.

A year later in 1938, P.M.F. Bishop of Guy's Hospital in London used implantable compressed oestrogen pellets subcutaneously to treat young woman suffering from premature menopause. Their results indicated that some degree of oestrogen replacement continued for as long as five weeks after implantation as assessed by an average decrease of 50% in the number of hot flushes experienced per day.

This technique of implanting solid compressed pellets of pure drug quickly spread to other drug

compounds, specifically the steroid hormones. These single compressed pellets are the simplest form of implantable drug delivery systems. They are produced on single punch tabletting presses under special aseptic conditions. The die cavity is filled by hand, since the drug compounds do not readily flow and lubricant and other additives are precluded. The pellets are usually compressed as cylinders with flat faces (usually 2 - 3mm in diameter and approximately 2mm in thickness). They are also usually supplied in individual sterile containers and normally find greater use in veterinary than human medicine[3]. The implant pellets release their contents into the subcutaneous tissue mainly via a process of slow erosion and diffusion. The rate of release depends primarily on the surface area of the implant, its particle size and the solubility of the drug in the body fluids.

Sixteen years later, J. Folkman and D.M. Long[4] investigated the use of silicone rubber as a carrier for prolonged drug therapy. Silicone rubber capsules were prepared and implanted in the cardiac muscle of dogs. Although crude, these capsules did provide controlled release for many classes of drugs and the silicone rubber elicited very little inflammatory response.

Since these early days, great progress has been made in the development of ICRDDSs. The latest ICRDDSs are bioerodible, can release macromolecular and micromolecular drugs of almost any conceivable class at a controlled rate of release from a few hours up to 100 days. Release at almost perfect zero-order rates, can be exogenously controlled to produce impulse doses, directly into the blood stream via small mechanical ICRDDSs, and do not rely on biological environmental factors such as

pH and temperature that can produce patient to patient variation in release characteristics.[5]

TECHNIQUES OF IMPLANTING.

ICRDDSs are implanted in vivo by means of various techniques, depending on whether they are in the form of microspherical beads, pellets or capsules, or miniaturized mechanical devices. Microspherical beads in the particle size range of 600 microns are normally suspended in an inert liquid vehicle and injected via 16 gauge or larger needles at a subcutaneous site nearest to the target site. The advantage of microspheres is that in most cases a local anaesthetic is not required and the implantation procedure is rather simple. Pellet or capsular forms of ICRDDSs are placed subcutaneously by means of a small incision in the skin. Before implantation, the skin nearest the intended target site of the implant, is covered with an iodine or other suitable antiseptic solution, and the area anaesthetized using a local anaesthetic. A transverse operational incision normally not longer than 1,5cm long is then made. The pellet or capsule is placed under the skin and moved away from the incision. The incision is then stitched and covered with an iodine or other suitable collodion.

Mechanical or pump type ICRDDSs can either be implanted under local or general anaesthetic depending on their size. In general they are not normally larger than 5cm in diameter and can be implanted under local anaesthetic. In some cases, however, the devices have to be connected via a catheter into an artery or vein, and therefore, it is best to implant them under general anaesthetic[2].

TYPES OF ICRDDSs.

There are two major classes of ICRDDSs. The first major class consists of polymeric ICRDDSs which utilise different types of polymers and polymer membranes to control the release of drugs to biological systems. The second major class consists of mechanical pump-type ICRDDSs which utilise an infusion pump-type action to control the release of drug.

POLYMERIC ICRDDSs

Many different types of polymeric systems are available for controlling the release of drugs in various types of drug delivery systems. Langer[5], in an excellent review article on polymeric delivery systems for controlled drug release, characterises polymeric drug delivery systems according to their mechanisms of controlled release as follows:

DIFFUSION CONTROLLED SYSTEMS

RESERVOIR SYSTEMS - in which a core of drug is surrounded by a polymer membrane which controls the rate of release of the drug to the biological environment[6,7]. The important feature of these systems is that diffusion through the polymer membrane is the rate limiting step[8,9]. Figure 1, graphically describes such a system. Potential disadvantages of reservoir systems are that they are not biodegradable and if the polymer membrane should rupture, it could be potentially dangerous depending on the type of drug being used.

To overcome the problem of nonbiodegradability of reservoir type systems, Eeninck et al[10] have formulated

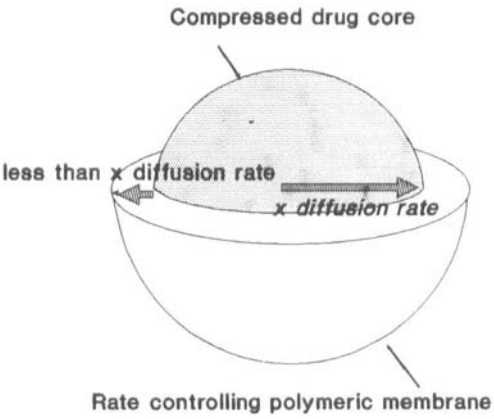

FIGURE 1.
Schematic diagram of a reservoir polymeric drug delivery system.

biodegradable hollow polymer fibres (approximately 700 - 800 microns outside diameter and 445 - 600 microns internal diameter) to control the release of hormones. Refer to figure 2 below for a schematic diagram of a biodegradable polymer fibre system. Like other reservoir systems, the rate of release is controlled by diffusion through the polymer membrane, but once most of the active drug is released, the polymer then biodegrades and therefore, there is no need to remove the polymer afterwards. Another advantage of such a system, is that the small drug loaded polymer fibres can be applied subdermally with a simple injection device and are still large enough to be removed via minor surgery when neccessary. The most important parameter of such hollow fibres, is that the polymer should only biodegrade after the active drug has been released or at least biodegrade at such a slow rate as to remain intact during most of the drug delivery.

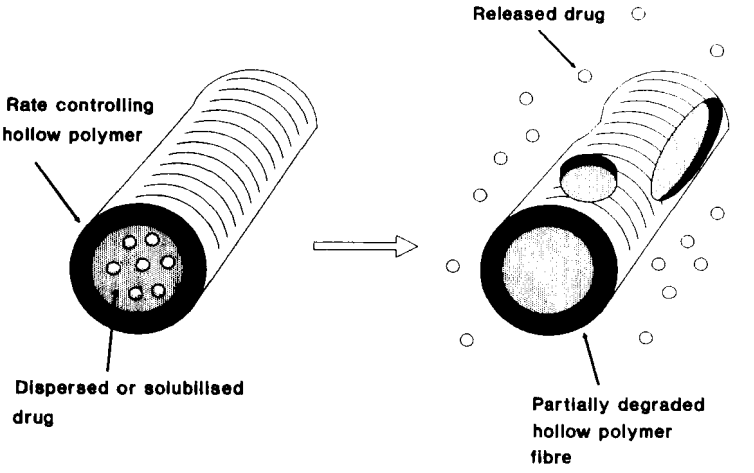

FIGURE 2.

Schematic diagram of a reservoir hollow biodegradable polymeric fibre drug delivery system.

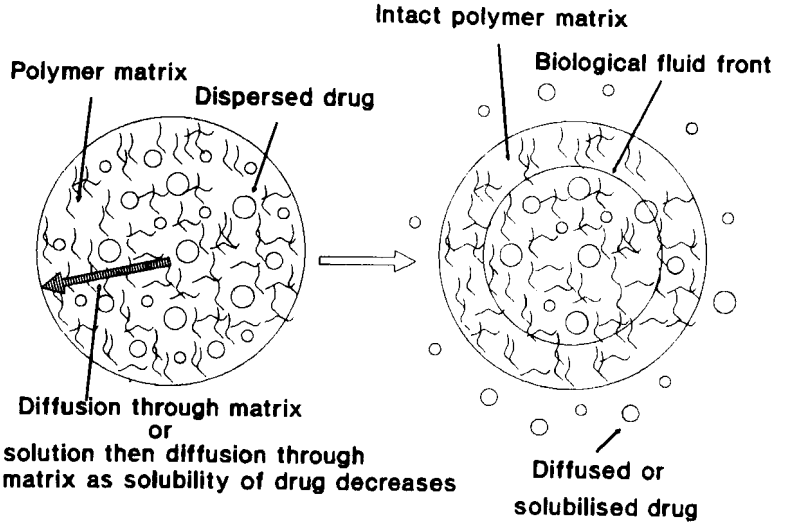

FIGURE 3.

Schematic diagram of a matrix polymeric drug delivery system.

MATRIX SYSTEMS - in which the active drug is uniformly distributed throughout a solid nonbioerodible polymer. Again, as in reservoir systems, drug diffusion through the polymer matrix is the rate limiting step (see figure 3). As the active drug becomes less soluble in the polymer matrix, the drug is released via a solution-diffusion mechanism. If the active drug is insoluble in the polymer it can also be released via a leaching through intergranular openings in the matrix[11].

The major disadvantage of matrix type systems, is their nonbiodegradable nature and that as time passes, the diffusion path (the tortuosity of the capillary system) increases as the drug is extracted leading to the square root kinetics described by Higuchi[12]. Hsieh, Rhine and Langer[13], have demonstrated that an inwardly releasing hemisphere shape (refer to figure 4 below) more closely approximates zero order release kinetics in order to overcome the contineous declining rate associated with square root kinetics.

The theory behind the inwardly releasing hemisphere is that as the drug diffusion path increases, so does the area of release with greater amount of drug available to go into solution. Therefore, as the rate of release decreases due to the increased diffusion path, the rate of drug dissolution and diffusion is increased due to the increase in surface area exposed to penetrating biological fluids which compensates for the increased diffusion path.

CHEMICALLY CONTROLLED SYSTEMS

BIOERODIBLE SYSTEMS - in which drug is dispersed in a polymer which is slowly biologically eroded at a

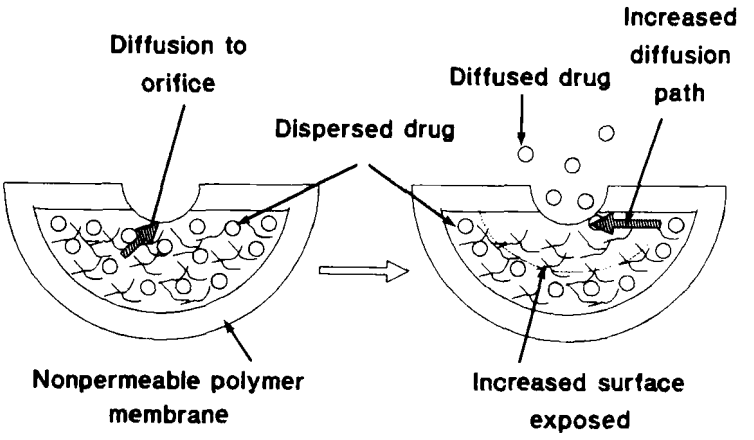

FIGURE 4.

Schematic diagram of an inwardly releasing hemisphere polymeric drug delivery system.

controlled rate. Like matrix systems, the drug is evenly dispersed throughout the polymer and is manufactured in essentially the same manner. However, unlike matrix systems, which depend on solution-diffusion type mechanisms for controlled release, bioerodible systems release according to the rate of polymer bioerosion. It should be noted however, that in practice some diffusion of the drug from the polymer matrix does occur. The major advantage of bioerodible systems is that the bioerodible polymer is eventually absorbed by the body. This then alleviates the need for surgical removal resulting in a more positive attitude of patients towards therapy.

One of the major drawbacks of bioerodible systems (specifically those shaped as rods, spheres or cylinders) is that as the implant is eroded, the surface area of the implant decreases. Figure 5 below schematically represents this type of situation.

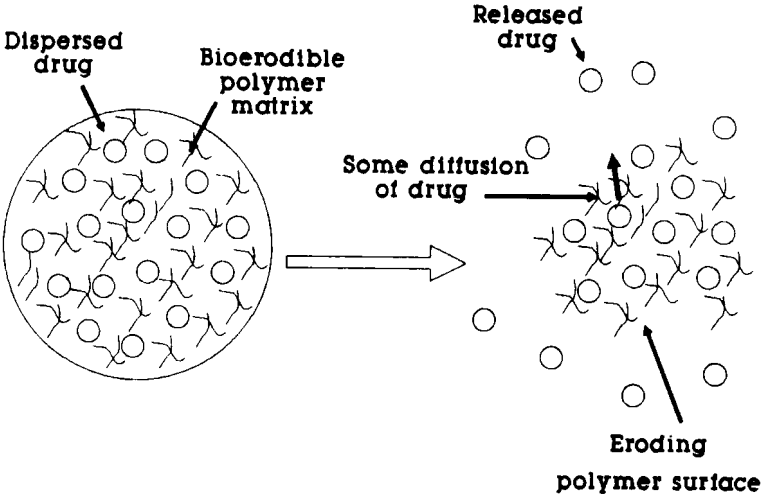

FIGURE 5.
Schematic diagram of a bioerodible polymeric drug delivery system.

Therefore, in order to attain a more uniform and constant release it would be necessary to utilize a geometry that did not change its surface area as a function of time. A flattened slab shape that has no edge erosion is probably the closest type of shape that approximates zero order release.

Bioerodible polymers release active drugs at a controlled rate via three major mechanisms[14]:

(1) Water soluble polymers insolubilised by degradable cross-links (refer to figure 6 below), e.g. polyorthoesters.

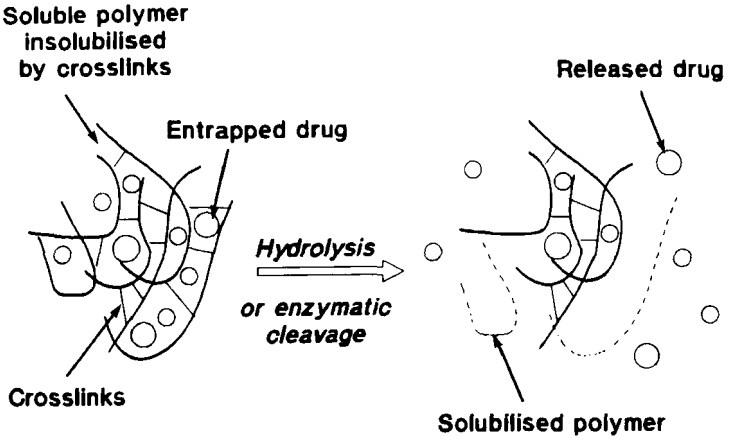

FIGURE 6.

Schematic diagram of a bioerodible polymeric matrix insolubilised by degradable polymer crosslinks.

(2) Water insoluble polymers solubilised by hydrolysis, ionization, or protonation of pendant side groups (refer to figure 7 below), e.g. N,N - diethylaminoacetate.

(3) Water insoluble polymers solubilised by backbone-chain cleavage to small water soluble molecules (refer to figure 8 below), e.g. polylactic acids.

In most cases, the mechanism of bioerosion is a combination of all three mechanisms. However, besides surface bioerosion, many polymers are susceptible to bulk bioerosion and diffusion of drug to some extent (those that erode due to backbone-chain cleavage).

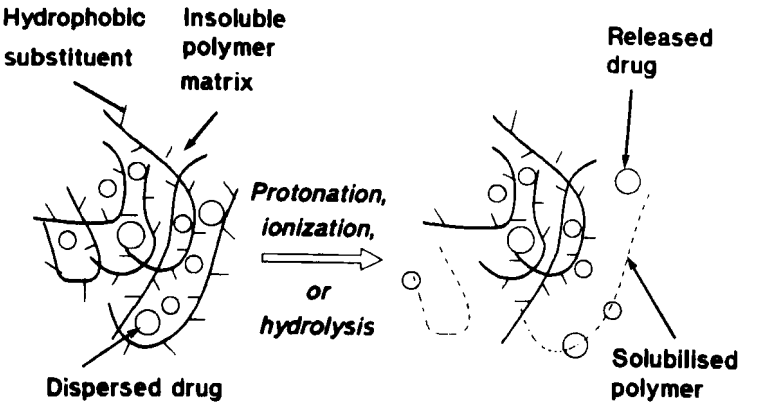

FIGURE 7.

Schematic diagram of a bioerodible polymeric matrix solubilised by protonation, ionization or hydrolysis.

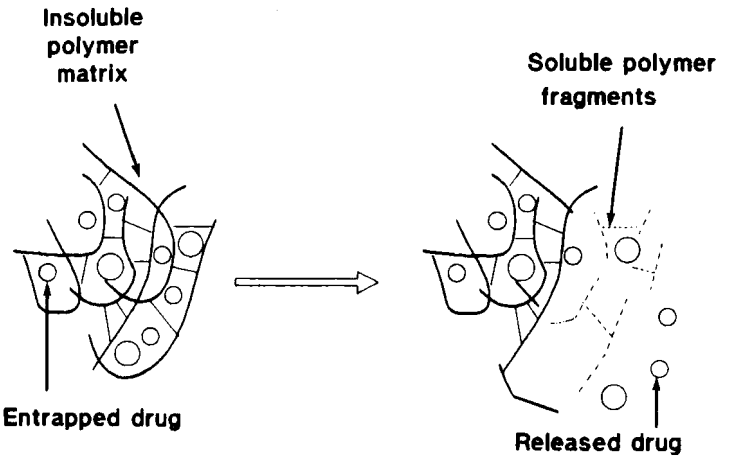

FIGURE 8.

Schematic diagram of a bioerodible polymeric matrix solubilised by backbone cleavage.

SWELLING CONTROL SYSTEMS

In these systems the drug is dissolved or dispersed within a polymer matrix and is not able to diffuse through that matrix. Environmental biological fluid is then imbibed into the matrix at a controlled rate, causing it to swell and release the drug entrapped in that part of the polymer[15]. Thus, the release rate is determined by the rate of diffusion of biological fluid into the polymer (refer to figure 9 below).

MAGNETICALLY CONTROLLED SYSTEMS

In this system, drug and small magnetic beads are uniformly dispersed within a polymer. Upon exposure to aqueous medium, drug is released in a fashion typical of diffusion controlled matrix systems. However, upon exposure to an oscillating external magnetic field, drug is released at a much higher rate. This is probably due

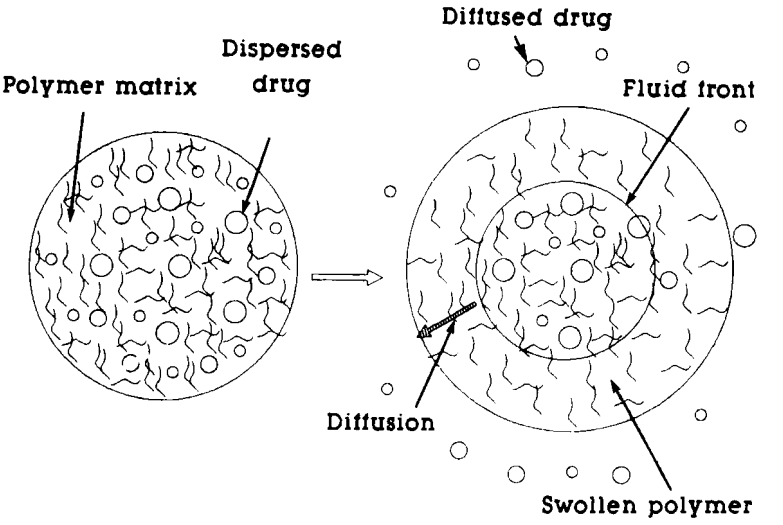

FIGURE 9.

Schematic diagram of a swelling controlled polymeric drug delivery system.

to the compression of the polymer due to the movement of the dispersed magnets[16] (refer to figure 10 below).

CLINICAL APPLICATIONS OF POLYMERIC ICRDDSs

Polymeric ICRDDSs have been used in a wide range of clinical applications utilising many different types of release mechanisms.

As previously mentioned, the use of polymers to deliver contraceptive steroids has been one of the first and widest applications of polymeric ICRDDSs. Implants being investigated for contraception range from non-biodegradable silicone rubber implants to bioerodible copolymer implants that have the ability to release

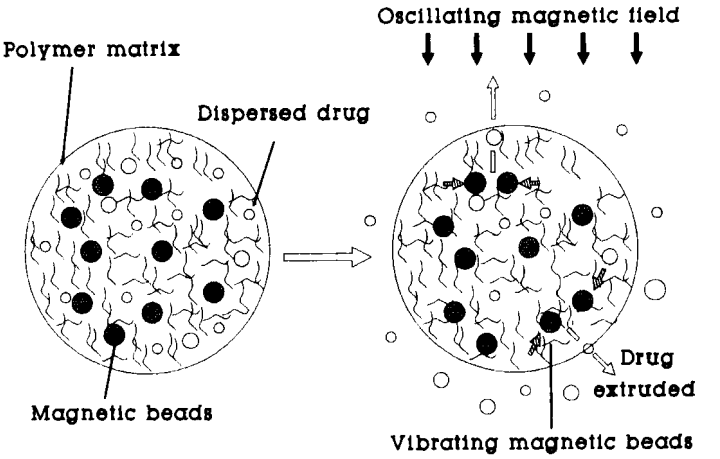

FIGURE 10.

Schematic diagram of a magnetically controlled polymeric drug delivery system.

constant levels of hormones over long periods of time[17-26].

In order to meet the need for a long acting narcotic antagonist formulation with forced patient compliance, many different narcotic antagonist implantable systems have been investigated. Clinical investigations range from long acting naltrexone zinc tannate complexes through to the coupling of naltrexone to biodegradable poly(α- amino acids)[27-37].

Polymeric ICRDDSs have also been used to treat certain forms of cancer with reasonable success. Non-bioerodible silicone pellets of testosterone have been used to treat patients with prostate cancer[38]. Bioerodible poly (l[+]-lactic acid) polymers of cyclophosphamide, doxorubicin, and cis-dichloro diammine platinum have also been evaluated as long acting anticancer systems[39-40].

A major development has been seen with the introduction of a biodegradable gaserelin implant (Zoldax®; ICI) for treatment of hormone-responsive prostate cancer. Zoladex is a biodegradable matrix system; drug is intimately mixed with a lactide-glycolide copolymer and release occurs by diffusion through aqueous pores produced as the drug-polymer matrix degrades. The depot is injected subcutaneously into the anterior abdominal wall, and since the implant is biodegradable, there is no need to remove the device. Occasional local reactions such as slight bruising have been reported at the injection site. The implant is readily administered without the need for anaesthetic, but a spray preparation such as ethyl chloride may be used if the patient is concerned.

Other clinical applications in which ICRDDSs have been reasonably successful include, antimalarial systems[41-43], anticoagulation systems[44], immunization systems[45], diabetic systems[46-47], antiinflammatory systems[48], and antibiotic systems[49-50].

MECHANICAL ICRDDSs

The second major type of ICRDDS are the mechanical ICRDDSs which release drug via mechanical pump type mechanisms. As the technology of miniaturization and biocompatibility develops further, it is expected that many more different types of mechanical ICRDDSs will become clinically available and will be even more sophisticated than they are at the present time. Some of the various types of mechanical ICRDDSs that have been clinically investigated are discussed below.

INFUSION PUMPS

One of the first completely implantable mechanical controlled release drug delivery systems to be developed and that is commercially available, is the Infusaid (Infusaid Corp., Sharon MA) infusion pump. The pump consists of a disc shaped canister of light weight biocompatible titanium which contains a collapsible welded bellows. The bellows separates the canister interior into two chambers, one of which contains a vapour-liquid mixture of a fluorocarbon propellant, the other contains the drug infusate. At body temperature, the vapour pressure exerted by the propellant gas forces fluid from the drug infusate chamber through a filter and a flow regulator, and provides a constant rate of drug infusate ejection at a given temperature. Even though the fluid flow is consistent for a given pump at a constant

temperature and viscosity, the drug delivery rate can be modified by altering the concentration of the active drug in the infusate. A self sealing septum in the pump which is punctured by means of a percutaneous injection is available for refilling, and the pressure exerted by a syringe condenses the driving propellant, thus concurrently rejuvenating the propellant gas power source and refilling the infusate chamber.

In more advanced designs[49], the valve is accommodated in a small module attached to the side of a pump together with an infusion regulator to compensate for the effects of changes in ambient pressure and temperature. In these later designs a subsidiary injection port and companion check valve to provide direct access to the feed canula has also been included. A pressure transducer and associated transmitter can also be included to make pressure data available for flowrate and reservoir volume level determinations. Infusion pumps of this type have been used successfully in animal and human studies for a wide variety of conditions over the past 20 years[50-51].

PERISTALTIC PUMPS

Peristaltic pumps are mainly rotary solenoid-driven type pumps[52-54]. Laser-welded titanium chambers are used to receive the pump, electronics, and battery. It is essential that the chambers are coated with silicone polymers for reinforced biocompatibility. Deflated silicone rubber pouches of approximately 0,5mm thick walls able to withstand more than 60psi are used as the drug reservoirs. The pouches are percutaneously refilled through a silicone rubber septum in the drug reservoir. Silicone rubber tubing is also used to connect the pump to the drug reservoir. Stainless steel helix reinforced

silicone rubber tubing is used as a catheter which contains a low pressure valve at the end to prevent backflow of biological fluids. An electronic external remote control is then used to control the pump rate and hence the flow rate and dose of the drug.

OSMOTIC PUMPS

Several dosage forms have been developed that use an osmotic pressure differential to drive the release of drug from a reservoir at a controlled rate[55-56]. In this type of device, the drug reservoir is in a semipermeable housing (mostly a cellulose ester membrane). The housing is normally filled with NaCl or any other suitable osmotic agent. The semipermeable membrane allows the passage of water but not of drug. Aqueous biological fluid that penetrates the housing builds up enough osmotic pressure within it to drive the drug out through a small orifice which can control the release rate according to its diameter. The drug is normally housed in a flexible impermeable membrane which collapses in accordance with the increase of hydrostatic pressure. Refer to figure 11 below.

POSITIVE DISPLACEMENT PUMPS

The vast majority of positive displacement pumps utilise piezoelectric disc benders[57]. Delicate discs of flexible piezoelectric material are bonded to brass and then glued to flexible tubing, thereby forming a bellows type structure. Upon application of a voltage, the piezoelectric discs bend to form spherical surfaces. When this bellows type structure is connected via a three-way solenoid driven valve to a drug reservoir, and a voltage

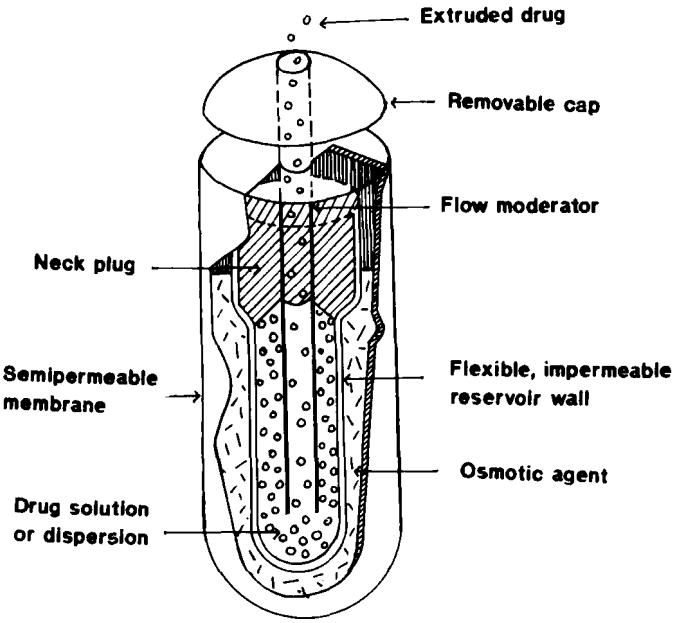

FIGURE 11.

Schematic diagram of an Alzet® mini-osmotic pump (shown in partial section).

is applied, the valve can be opened or closed in sequence with the flexing inwards or outwards of the disc bender bellows. Flexing outwards causes suction of a drug solution while voltage of an opposite polarity causes inward flexing and forces drug out through a delivery catheter. Control of the voltage pulse chain results in control of the delivery rate. Other types of positive displacement pumps are driven by a solenoid-type diaphragm. When a solenoid is activated a diaphragm driven by the solenoid pressurizes a drug chamber to open an outlet valve to a delivery catheter. An inlet valve prevents back-flow into the reservoir.

CONTROLLED RELEASE MICROPUMPS

Controlled release micropumps utilise diffusion across a rate controlling membrane to appropriate basal delivery, while a rapidly oscillating piston acting on a compressible disc of foam increases the delivery. Without an external power source, the concentration difference between the drug reservoir and the delivery site is sufficient to cause diffusion of the drug to the delivery site; this is basal delivery. Increased delivery is achieved without valves by repeated compression of the foam disc by a coated mild steel piston. The driving piston is located within a solenoid and compression of the foam disc results when a current is applied to the solenoid coil.

CLINICAL APPLICATIONS OF MECHANICAL ICRDDSs

As of yet, not many mechanical ICRDDSs are being extensively used in commercial practice. This is probably due to the fact that many of them are still undergoing clinical evaluation and constant technological modifications. There are however, a number of clinical situations being investigated for which implantable pumps are and can be extremely useful. The most useful and promising application of implantable pumps is in the treatment of insulin-dependant diabetes. The applicability of implantable pumps in the treatment of insulin-dependant diabetes is due to the fact that the more sophisticated pumps (specifically those with external control) can almost recreate an 'artificial endocrine pancreas' which can deliver insulin as it is needed in direct relationship to elevations in blood glucose levels[58-63].

Mechanical ICRDDSs have also been quite extensively investigated for use in chemotherapy. They are able to deliver constant levels of chemotherapeutic agents to specific target organs and to some extent to localised tumors[51,64-68]. Thromboembolic disease that is refractory to treatment with oral anticoagulants or antiplatelet agents has been successfully treated using implantable pumps with very few complications[50,69]. The long-term intravenous infusion of various antiarrythmic drugs using a totally implanted drug.delivery system has also been investigated and has come up with good preclinical results[70].

BIOCOMPATIBILITY OF IMPLANTS

Many different types of materials have been used for implantable drug delivery systems, ranging from bioerodible collagen through to nonbiodegradable titanium metal. It is important that all materials used for implants being physically and chemically stable, but vitally important that the materials are biocompatible. Desirable criteria for implantable drug delivery biomaterials include:

(1) The biomaterial must be inherently chemically inert in that it does not cause any biological effect or interact with other adjuvants in the formulation.

(2) The biomaterial must not be physically or chemically (for mechanical ICRDDSs) modified by local tissues.

(3) It must not cause any inflammatory or foreign body reaction in the body.

(4) The biomaterial must not be carcinogenic. This criteria also includes the breakdown products from bioerodible polymers.

(5) The biomaterial should not cause any allergic or hypersensitivity reactions.

(6) It should be mechanically stable at the implant site in that it does not loose shape over long periods of time. For bioerodible polymers, they should degrade in a controlled fashion in that they decrease proportionally in size.

(7) The biomaterial must be capable of being manufactured in different shapes and consistencies.

(8) It must be sterilizable without affecting any chemical, physical or mechanical properties.

(9) The biomaterial must have the ability to be easily removed after its therapeutic duration or for repairs for nonbioerodible materials.

(10) Must be compatible with a wide range of drugs.

(11) Should be mechanically sound over as long a period as is possible, especially for implantable pump delivery systems.

(12) Does not cause any thrombogenicity.

The development and search for new biomaterials is a long and complex process, of which the test for biocompatibility forms a major aspect. Therefore, reliable methods must be devised to predict in an

accurate fashion the final biocompatibility of candidate biomaterials and should be tested in the early stages of development. Time and money can then be spent only on those biomaterials that show biocompatibility in the early stages of development.

An implanted biomaterial in contact with tissue can induce many responses due to its physical properties, and these responses are evident from the epithelial encapsulation, a thickening of the connective tissue fibrous capsule, and the presence of giant cells. Likewise, chemical reaction between the biomaterial and tissue can inhibit epithelial growth, induce connective tissue inflammation and epithelial hypertrophy, vascoulization of tissue, and a related build-up of acellular fluids. Additional responses not attributable to the implant biomaterial itself can arise from the presence of ingredients used in its manufacture, e.g. polymerization additives during polymer production. Such antigenic substances could cause infection that is characterised by the invasion of epithelium by leucocytes, the inhibition of epithelial growth, and the presence of extensive inflammatory tissue.

Some of the many tests that have been used to evaluate the biocompatibility of biomaterials for implants are discussed below.

BLOOD COMPATIBILITY TESTING

One of the most popular methods used to test blood compatibility of biomaterials is the kinetic clotting test. In the kinetic clotting test, venous blood from a dog enters a specifically designed chamber, that contains the test biomaterial, through a short segment of silicone

rubber tubing[71]. The quantity of blood clot and the amount of free haemoglobin are measured spectrophotometrically at 254nm at periodic intervals. While this test is useful, it only measures the end product (the blood clot) and not the factors determining blood compatibility. Therefore, there is no guarantee that the biomaterial is fully blood compatible if there is no clot formation. There could also be problems with the venous blood coming into contact with the silicone tubing before the test biomaterial. Silicone in itself, could also activate coagulation factors.

A second test that could be used to evaluate the blood compatibility of biomaterials is the **ex vivo** measurement of the amount of thrombus and the estimation of its platelet and fibrin content by radiotracer techniques[72-73]. Carotid arterial blood to the jugular vein of a dog is connected **ex vivo** to two test chambers containing stainless steel shafts (one coated with test biomaterial and the other as a control). The connection shunt is a 20cm long silicone rubber tube. Again, as with the kinetic clotting test, the silicone rubber shunt could create interpretation problems on the suitability of the biomaterial. Also the centrifugal force of the rotating stainless steel shafts and the difficulty of coating the shaft with test biomaterial causes test and result interpretation problems.

Other tests that have been useful to evaluate the blood compatibility of biomaterials include;

(1) critical surface tension tests[74-75],

(2) haemolysis and shear stress tests[76], and

(3) caval ring implant tests[77].

TISSUE COMPATIBILITY AND BIODEGRADATION TESTING

Whether the aim is to develop a biostable (mechanical implants) or biodegradable (polymer implants) drug delivery system, it is important that the degree of biodegradation is accurately evaluated. The degree of tissue toxicity of the implant and the resulting degradation products also need to be assessed, preferably prior to implantation into patients. An **in vitro** test that is quick to perform and that provides a considerable amount of useful biocompatibility information, is the chick embryo organ culture test[78]. Using sterile technique, the organs of 8 - 14 day old Leghorn chick embryos are removed immediately following decapitation of the embryos. The organs are then removed, cleaned, and cut into 0,5cm X 0,5cm fragments. The fragments are rinsed in basic salt, placed in roller tubes with Trowell TS medium, supplemented with 10% chick serum, 5% chick embryo extract, 125 units per millilitre of penicillin/streptomycin mixture, and 2 mM of L-glutamine. The radiolabelled biomaterials in powder form, if possible, are added to the cultures and incubated in a CO_2 incubator at 37°C and rotated at a rate of 1 r.p.m. for varying periods of time. Percentage degradation of the biomaterial is tested by means of centrifuging the biomaterial and then filtering through Whatman no.1 filter paper. The radioactivity in the filtrate is measured and then compared to the original amount in the biomaterial. Biocompatibility of the biomaterials can also be studied using histological and electron microscopic evaluation. In this way nuclear changes, chromatin patterns, cytoplasmic vascuolization, epithelial encapsulation, and the presence of acellular fluids can be checked.

Gourlay **et al**[79] developed an effective **in vivo** technique for the screening of biomaterials for biocompatibility. The test is based on grading acute and subacute tissue reactions at one week and four weeks, respectively, following implantation into rats. The method seems to be reproducible over a wide range of polymers tested. The six tissue response indicators used to evaluate the biocompatibility of the biomaterials were:

(1) Degree of muscle cell damage.

(2)Total thickness of reaction.

(3) Overall cell density.

(4) Number of polymorphonuclear leucocytes and erythrocytes.

(5) Number of eosinophils, lymphocytes, and foreign-body giant cells.

(6) Number of fibrocytes and mononuclear phagocytes.

Langer **et al**[80] have used the rabbit cornea as an effective implant site to evaluate the biocompatibility of polymeric drug delivery systems. They maintain that the **in vivo** cornea as an implant site has several advantages as compared to other organs. The advantages include its clarity, avascularity, sensitivity, and convenient access to view many tissue reactions. The test is particularly suitable for accessing the inflammatory response of biomaterials.

Probably one of the most useful protocols for assessing the biocompatibility of biomaterials has been

suggested by Gilchrist and Courtney[81]. The protocol is based on biological tests directly on materials as well as on extracts of the materials. Each test is scored arithmetically, based on a measured response. Accordingly, a cumulative toxicity index can be calculated from which a grading of materials can be produced. The screening tests for acute toxicity include:

(1) Tissue culture of biomaterial and extracts, including cell growth inhibition.

(2) Induction of haemolysis and erythrocyte osmotic fragility.

(3) Systemic toxicity and **in vitro** mutagenicity.

(4) Isolated heart test.

(5) Subacute and chronic intramuscular implantation.

One of the major advantages of the above protocol, is that it has the support of the United States Food and Drug Administration.

Although the biocompatibility tests mentioned above can be extremely useful, no one individual test is conclusive proof of biocompatibility. One should use a combination of as many tests as is economically viable. Even then, the tests are not conclusive, especially when it comes to long term bioerodible systems that could form toxic products or adverse reactions after long periods of time. The tests are useful however, in screening the suitability of various potential biomaterials during the preliminary stages of research. Ultimately, many long term human clinical trials are required to conclusively determine the biocompatibility of candidate biomaterials.

CONCLUSION

Even though implantable drug delivery systems were first investigated in the last century, commercially they are still in their infancy. Very few products are commercially available for clinical use. There has however, been a renewed interest in ICRDDSs in the past 15 years, and it is expected that many more ICRDDSs will be commercially available before the turn of the century. It is also envisaged that ICRDDSs will be used for many more different types of treatments and diseases, specifically in the antibiotic market.

One of the most pressing problems that the medical profession still faces today, is the problem of patient compliance. In the past, patients and physicians have not (and are not really expected to) fully comprehended the importance of constant therapeutic drug blood levels in effective drug therapy. Many effective drug therapies have failed, not due to the nature of drug formulation, but due to incorrect dosing intervals and their subsequent effect on therapeutic blood levels. ICRDDSs can be used as an effective means of solving this patient compliance problem in some conditions. Also, drugs in the past that have normally been considered toxic due to the variability of their blood levels over the period of treatment, could be held within safe limits and therapeutic blood levels by means of reformulating them into ICRDDSs.

Despite the fact that research work has reached a significant level, additional work needs to be performed on ICRDDSs. As far as can be ascertained, bioerodible implants that release drugs **in vivo** at ideal zero-order or even pseudo steady state rates over a long period of

time have not been developed. Furthermore, if more ICRDDSs are to become commercially available, many additional biomaterials that are fully biocompatible must be developed and adapted into effective drug delivery systems. More effective biocompatibility tests of shorter duration and wider application need to be developed. Conclusively, cost effective drug delivery systems with ease of manufacturing is essential before additional ICRDDSs can become commercially attainable. Yamakawa **et al**[82] have recently reported the formulation of a simple double-layered insulin implant that is easy to manufacture in a reproducible manner. The formulation consisted of a double-layered implant which incorporated a low molecular weight (less than 10 000) poly(lactic acid) polymer matrix containing insulin and a poly(lactic acid) layer which was coated partially on one of the surfaces of the insulin:polymer matrix. The doubled-layered implants were compared with single-layered matrix implants from the standpoint of the **in-vitro** dissolution test and the **in-vivo** performance. **In-vitro** release rates were controlled by changing the amount of poly(DL-lactic acid) used in the polymer layer. In an **in-vivo** test using diabetic animals, the double-layered implants provided a sustained release of insulin for 19 days, as judged by the changes in blood glucose levels and serum insulin levels after the subcutaneous implantation.

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