A Review on Implantable and Insertable Drug Delivery Systems

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ABSTRACT

Implantable drug delivery system is an umbrella term comprising several technologies including polymeric controlled release system, matrix and erodible and rupturable membrane, pumps acting on various stimuli, micro electro mechanical and nano electro mechanical systems and drug releasing inserts. In recent decades, we have witnessed a paradigm shift from traditional drug delivery due to underlying limitations of conventional dosage forms like lower bioavailability, instability due to intra enterocyte and hepatic first pass metabolism, toxicity due to elevated blood levels and poor tissue distribution owning to low half-life of the molecules. With aid of implantable drug delivery a site specific and controlled release of molecule may be anticipated in addition to better patient compliance and fewer untoward events like drug resistance. The release kinetics and pharmacokinetic tissue distribution depend on the property of drug molecule, type of delivery system and chemical nature of the polymer containing the drug. In addition to that various pump systems acting on broadly principles of mechanical activation, electrostatic activation, piezoelectric conductivity, thermopneumatically controlled, electro-osmotic and electrochemical mechanisms have shown their proficiency in biomedical field. Also, there are some atypical insertable forms of drug delivery systems providing local tissue distribution of drug in a controlled manner. Although a lot of progress in this research has been initiated and applications of implantable drug delivery are continuously increasing there is still a need to incorporate various categories of these delivery systems in practical drug delivery that will substantiate research and development in the future

Keywords: Implants, inserts, implantable pump, non-biodegradable and biodegradable polymers

INTRODUCTION

Conventional drug delivery systems comprising of intermittent intravenous and popular oral-drug administration, are not exception of having potential disadvantages including high plasma concentrations of drugs that may lead to toxicity or to sub-therapeutic blood levels and drug resistance in long term administration due to host cell as well as target cell adaptation instances. Controlled release kinetics achieved its momentum in therapeutic field for having potential advantages like maintenance of drug concentration in plasma for a longer time interval that minimized the frequency of dosing as well as optimization of the drug efficacy over side effects. With the advancement in pharmaceutical field therapy has changed its path and sustained and controlled release devices are devoid of time-programmed administration within the living system that require synchronization and balance with the time as well as hormonal levels, multi-nutritional and hydration balance and personalized physical activities [1].

Implantable drug delivery system is gaining its focus in recent drug delivery trends having time-specific and site-specific delivery which opens the path for personalized and individualized medicine. Extensive study in proteomics and transcriptomics in the biomolecular research and biotechnological approaches emerged some drug molecules those are not suitable candidates for conventional drug delivery system owning to static biological barriers like blood brain barrier, hepatic first pass metabolism and efflux pumps as well as dynamic physiological conditions like body temperature, blood pressure, metabolism, respiration and enzymatic reactions [2,3]. In the late 1930s research began by Danckwerts *et al.*[4], on sustained release implantable drug delivery systems administered by

subcutaneous route. This discovery sparked an interest in the area of implants leading to further studies and the demand for implantable systems that increased 14% per year, through 1998, to $5.9 billion annually. In case of development of an implantable drug delivery device in the field of pharmaceutical product development, several approaches have been proposed till date. Extensive studies have been carried out in systems acting either to deliver drug by electrically or mechanically driven pump or stimuli and use of erodible and biocompatible polymer matrix and involvement of the fabrication technologies like micro-electro fabrication and nano electro fabrication and mechanically driven approaches. In choosing a medication in relation to implantable drug delivery system consideration of pharmacokinetics, effect-duration, efficacy, adverse effects and beneficial outcomes are required. This review on implantable drug delivery system gives a comprehensive emphasis on mechanism of several approaches as well as disease targets, revisits the existing technologies in hand and also introduces theoretical approaches to emerging discipline such as target based molecule and electromechanical fabrication technologies [2,3,4].

TARGETS AND DISEASES WITH ESTABLISHED IMPLANTABLE DRUG DELIVERY APPLICATIONS

Ocular Disease

Improvement of ocular contact time, enhancement of corneal permeability and enhancement of site specificity are major focuses while optimization of ocular drug delivery systems are performed [5]. Sub-conjunctival implantation at the site of a filtering surgery in the anterior segment of the eye for the prevention of glaucoma filtering surgery failure and intra-corneal implants for the delivery of anti-angiogenic and or anti-inflammatory agents are two of the major approaches in ocular drug delivery. Polymers (Table 1)and copolymers of PLA (Poly lactic acid) and PLGA (poly lactic-co-glycolic acid) are synthesized by condensation reaction at high temperature and release from these polymers usually follows a three phase's pattern: initial drug-burst, diffusive phase and a final drug burst.

Table 1. List of various polymers used in implantable drug delivery system

Polymer	Application examples	Type	Ref
Poly(dimethyl siloxane)	Rate controlling membrane for catheter, adhesives, tissue grafting, backing membrane and stents	Non-biodegradable	[28,31]
Poly (methyl methacrylate)	Tissue and bone osseograft, intraocular inserts	Non-biodegradable	[32]
Poly (ethylene)	Orthopaedic parts	Non-biodegradable	[28,33]
Poly(ethylene co vinyl)	Drug delivery rate controlling membrane	Non-biodegradable	[31,33]
Poly (ethylene terephthalate)	Vascular graft, tissue graft and orthopaedic stents	Non-biodegradable	[33]
Poly (lactide)	Microparticles, polymeric beads associated with pulsed delivery	Biodegradable	[35,36]
Poly (anhydride)	Matrix in monolithic devices	Biodegradable	[35]

Lacriserts, introduced by Merck, Sharp, Dohme in 1981 is a sterile rod shaped device made of hydroxypropyl cellulose without any preservative. It weighs 5 mg and measures 12.7 mm in diameter with a length of 3.5 mm, inserted into the inferior fornix where it imbibes water from the conjunctiva and cornea, forms a hydrophilic film which stabilizes the tear film and hydrates and lubricates the cornea. SODI; Soluble Ocular Drug Insert made from acrylamide, N-vinylpyrrolidone and ethylacrylate is inserted into the inferior fornix where it imbibes water from the conjunctiva and cornea, forms a hydrophilic film which stabilizes the tear film and hydrates and lubricates the cornea. Among several technologies available within the non-biodegradable type of ophthalmic inserts,

Ocusert developed by Alza corporation consisting of two outer layer of ethylene vinyl acetate enclosing the inner core of pilocarpine gelled with alginate releases pilocarpine at constant rate of 20 to 40 µg/hr around the clock for 7 days. Therapeutic pre-soaked hydrophilic contact soft lenses are often used to aid corneal wound healing in patients with infection, characterised by marked thinning of the cornea. It has been seen that most of the drug contact lenses is released within 30 minutes [5,6].

Sensory Neural Hearing Loss

It is a degenerative process of sensory cells associated to the aging and genetic disorders to environmental exposure to loud sound and toxic followed by secondary degeneration of auditory neurons. Presence of blood-labyrinth drug barrier acts as 'tight junctions' between adjacent cells in the inner ear and organs protecting delicate sensory structure within from foreign particles preventing direct delivery of the fluids of the inner ear [7]. An implantable drug delivery apparatus for delivering drug into cochlea of human ear over a period of time includes a drug supply reservoir to supply drugs into delivery channel and an acurator for delivering drugs into determined location. Drugs perfused into the perilymph compartment of scala tympanii have ready access to hair cells of synaptic regions of hair cells and synaptic regions of the hair cells [7].

Contraception

An advancement in the field of contraceptive drug delivery have been achieved by the aid of sub-dermal implantable drug delivery devices placed under the skin of upper arm as an effective mean of contraception and intra-uterine implantable devices releasing hormones as a mean of site-specific delivery. Nexplanon® and implanon® made and marketed by Merck and Co. consists of a thin, flexible, made of ethylene vinyl acetate copolymer single rod shaped implant containing progestin etonorgestrel as an effective mean of reversible and long acting contraception [8]. Statistical review shows the systems are now used by 11 million women around the world and approved for use in over 60 countries as of 2003. Norplant® approved by United States Food and Drug Administration in 1990 was developed by Sheldon J. Segal and H. B. Croxatto at the population council [8]. It consists of a set of six small sillicone capsules having dimensions of 2.4 mm X 34 mm each filled with 36 mg of levonorgestrel for sub-dermal application. A similar approach was developed under the brand name of Jadelle® except consisting of two small silicon rods having dimensions of 2.5 mm X 43 mm each containing 75 mg of levonorgestrel in polymer matrix [9].

Dental Applications

Periodontal disease known as periodontitis is an inflammatory response due to the overgrowth of anaerobes, spirochaetes and micro-aerophilic organism in the sub-gingival plaque and is demonstrated to be the most common cause of tooth loss and soft tissue damage. The periodontal pocket allows easy placement of a delivery device owning to have an average depth of 6-8 mm that conforms to maximize the targeted and site-specific delivery, minimizing systemic side effects [8].

Brain and Intra-Thecal Delivery

Systemic administration of drugs in the treatment of ischemic, metabolic, congenital and degenerative disorders of central and peripheral nervous systems cannot surpass limitations like systemic adverse drug reaction and decreased concentration of drug at the target site, peripheral metabolism of centrally administered drugs, inadequate blood-brain barrier penetration, erratic drug absorption, serum protein binding and poor patient compliance [10]. Bradbury *et. al.* have successfully demonstrated the infusion of dopamine in the central area of left and right amygdala for 9 days using Alzet osmotic pump. A large amount of neuroleptics can be used to treat or manipulate neurological disorders including L-dopa

and carbidopa encapsulated in a polymer in Parkinson's disease, polymer containing choline, acetylcholine or cholinergic agonists in Alzheimer's disease, excitatory amino acid neurotransmitter such as MK801 in Huntington's disease and gangliosides in trauma such as spinal cord injury by enhancing the rate of regeneration of neurons to bring about an extensive degree of behavioural recovery [11]. Siegel *et. al.* have developed a surgically implanted haloperidol containing lactide-co-glycolide, a biodegradable polymer and fabricated with haloperidol by solvent casting and compression moulding [10,11].

VARIOUS STIMULI AND MECHANISMS OF DRUG RELEASE OF IMPLANTABLE DRUG DELIVERY

Systems Based on Diffusion

Rate limiting factors of drug release are diffusion of drug through the polymer, nature and chemistry of biodegradable and surface of non-biodegradable polymers used to prepare dosage forms, for example, polymethylsiloxane, dissolution of drug, and usage of biodegradable polymers, for example, polylactic acid and polyglycolic acid [13].

Polymer Membrane Permeation

Here the formulation is totally or partially encapsulated by spray coating, injection moulding or micro-encapsulation within a drug reservoir and the drug release surface is covered by a rate limiting polymeric membrane having a specific permeability for the drug.

Matrix Diffusion

Chappa *et. al.* have demonstrated a combination of degradable and non-degradable matrices, where an active agent is delivered from a non-degradable polymer network which is interspersed into the degradable polymer [13]. Figure 1 gives the representative idea of such kind of delivery system.

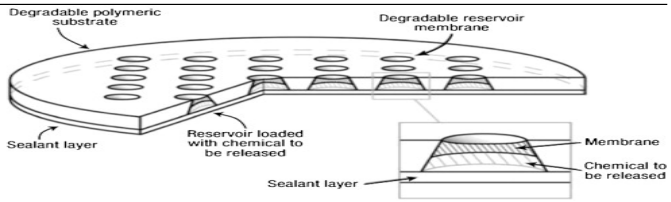

Figure 1. Passive, matrix controlled drug delivery system including bioerodible PLGA implant (Reproduced with permission from figure 1 in [12])

Micro-Reservoir Partition

Micro dispersion technique is utilised for preparation of drug reservoir and it is fabricated by aqueous suspension of drug using a high energy technique into a biocompatible polymer such as silicone elastomer to form a homogeneous dispersion of many discrete, unreachable microscopic drug reservoir and the device can be further coated with polymer to modify the mechanism of rate release [14].

SYSTEMS BASED ON ACTIVATION PROCESS

Activation by Osmotic Pressure

In this type drug reservoir can be either a solid or a suspension is contained in a semi-permeable chamber. The release is activated through a specially formed orifice and rate is modulated by controlling the osmotic gradient. The Alzet® osmotic pump demonstrated in Figure 2 works on the mentioned mechanism.

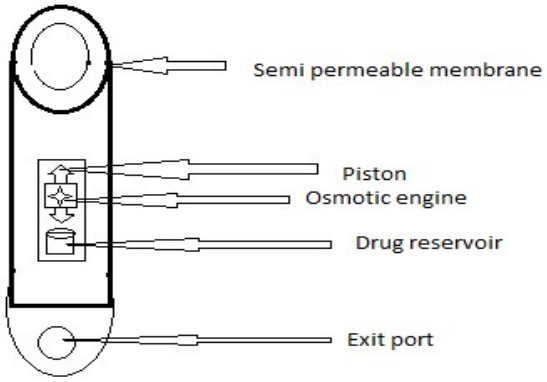

Figure 2. Alzet osmotic pump

After implantation, water from the surrounding tissue fluids is imbibed through the semi permeable membrane at a controlled rate that dissolves the osmogen creating an osmotic pressure differential across the membrane expanding the osmotic sleeve. Since the outer shell is rigid, it squeezes the inner flexible drug reservoir and drug solution containing ionized drugs macromolecules, steroids, and peptides like insulin can be delivered by such a device is expelled in a constant volume per unit time fashion and continues until the reservoir is completely collapsed [16]. Duros^{TM} osmotic pump from ALZA Corporation shown in Figure 3 is non-biodegradable, osmotically driven system is intended to enable delivery of small drugs, peptides, proteins, nucleic acids and other bioactive macromolecules for systemic or tissue-specific therapy [17].

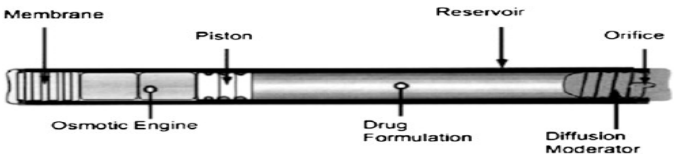

Figure 3. Diagram of DUROS® osmotic pump (Reproduced with permission from [17])

Activation by Vapour Pressure

An infusate chamber acts as the drug reservoir of solution formulation and a pumping system physically separated from the vapour pressure chamber containing vaporizable fluids such as fluorocarbon that vaporizes at body temperature creating a vapour pressure that pushes below to move upward and forces the drug to get delivered. Vapour pressure powered pumps Infusaid^{TM} acts in this mechanism that is at a given temperature, a liquid in equilibrium with its vapour phase exerts a constant pressure that is independent of enclosing volume and the volatile liquid vaporizes at the body temperature and creates a vapour pressure that compresses the bellows and expels the infusate through a series of flow regulators at a constant rate successfully delivering insulin and morphine in terminally ill cancer patients.

Activation By Chemical Processes

Based on the type of polymer used, the mode of biodegradation mechanism may be suggested. It can follow hydrolysis, ionization, hydration, oxidation, protonation of anionic polymer and decarboxylation to rupture and release the drug. Hydrolysis may be observed in several bio erodible polymers like Co (lactic-glycolic), poly-(orthoester), poly-(anhydride) [18].

Activation By Electrical Energy

Various battery powered system have been demonstrated to follow a controlled release of drugs like insulin and other hormonal supplements are proficient over conventional dosage forms that often result peaks in blood glucose level and metabolic disorders upon long term usage. Here electricity is the source of energy to activate the process [19].

Activation By Ultrasound

Ultrasound often provides the cavitation in the form of energy that serves dual roles in both activating the system in a pulsed fashion and enhancement of absorption through physical and biological barriers. Various systems have been shown to follow the procedure of enhancement by this system [8,14].

Activation By Magnetic Field

In this kind of delivery, small magnetic beads are uniformly distributed in the polymers. Depending on the intensity and duration of applied magnetic energy, the systems have shown to follow a modulated and controlled release pattern. A oscillatory field is applied through which modulation of release is achieved [14].

Systems Based on Electro Chemical and Electro-Mechanical Process

The systems are typically designed to work on the property of electrolysis and often considered desirable over MEMS based systems owning to

limited power requirement, lower heat energy loss, easier fabrication and reversibility. Figure 4 provides an overview of the system.

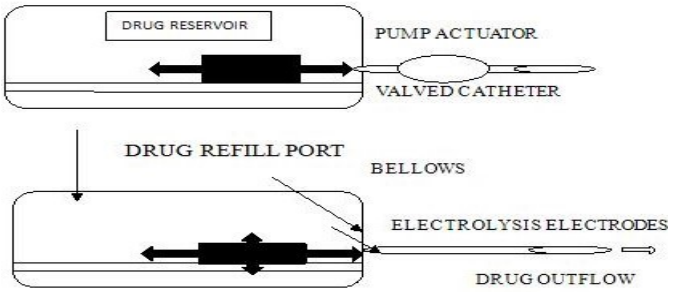

Figure 4. Activation of carrier by electrolysis

Other systems based on micro electro mechanical system and nano electro mechanical system based on different actuation scheme are mostly electrostatic, piezoelectric, thermopneumatic, shape memory alloy, bimetallic, electromagnetic and phase change. They deal with microfabrication and microfluidics concerned with development of miniature devices that can sense, pump, mix and monitor small volumes of fluids. Figure 5 shows an integrated drug delivery system [19].

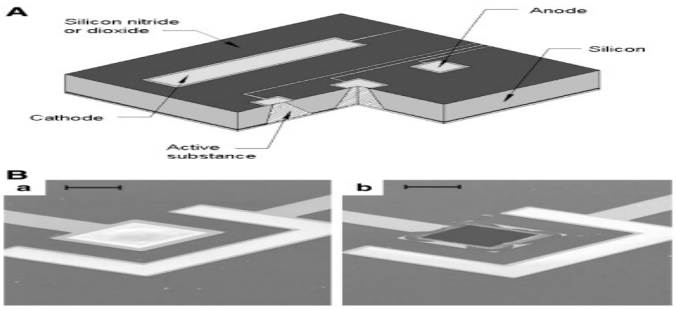

Figure 5. An electrochemically actuated drug delivery implant a) cross sectional view showing reservoirs, b) reservoir caps of microchips (a) before and (b) after actuation (Reproduced with permission from [14]

VARIOUS APPROACHES OF IMPLANTABLE DRUG DELIVERY SYSTEMS

Several literatures have described the utilities and approaches of implantable drug delivery systems till date with their applications in different areas. The available systems are broadly classified into two major categories namely non-degradable and degradable systems [20]. A brief review of various inserts has been available in the Table 2. Various polymeric stents comprising of both degradable and non degradable polymers approved by regulatory authority is given in Table 3..

Non-Biodegradable Systems

Various non-biodegradable systems including the matrix type, membrane enclosed systems, and permeation controlled systems that are commercially available are composed of various polymers namely silicones, acrylates and copolymers, poly urethane, vinyl ethyl copolymers and ethyl vinyl acetate and copolymers.

Table 2. List of various insertable drug deliveries with summary of their applications

Inserts	Description	Application
Non erodible ocular insert	PVA (Polyvinyl alcohol) EVA (ethylene vinyl acetate) and silicon are permeable to certain lipophilic substances but impermeable to hydrophilic drugs.	Ocusert containing inner core of pilocarpine gelled with alginate [4,5].
Erodible ocular inserts	Polymers and copolymers of PLA (Poly lactic acid) and PLGA (poly lactic-co-glycolic acid).	Lacriserts, The SODI(soluble ocular drug insert), Minidisc [5]
T shaped contraceptive vaginal ring	They are inserted in the body of uterus consist a rate controlling cylindrical PEVA reservoir containing the hormone. In the other case a system comprising a T shaped polyethylene frame surrounded by silicon membrane for continuous copper release.	Progestasert, Mirena, Nuva Ring [37]
Inorganic osseograft	Composed of fragmented pieces from various parts of body that are used to form cancellous bone autografts and they are biocompatible since formed from periosteum, endosteum from host cells	Tissue and bone autografts [38]
Aluminium phosphorus oxide ceramics	Extended delivery of analgesics, proteins and steroids are achieved by compressing calcined materials followed by high temperature treatment for extended period of time	ALCAP [34]

Slow diffusion from the saturated layer of polymeric matrix provides to be a mode of sustained release depending on the erosion rate while the thickness of the polymeric layer provides

to control the diffusion of drug in reservoir type systems [21]. The major limitation of such kind of delivery is that surgical removal upon completion of delivery may be anticipated and in some cases dose dumping may create a major concern limiting its potential. Septopal®, another non-biodegradable type of delivery composed of poly metyl methacrylate has shown proficiency in delivery of antibitics like kanamycin, tobramycin and ceftriaxone to reduce systemic toxicities.

Table 3. List of several polymer based drug eluting stents approved by FDA

Company	Trade Name	Drug	Polymer
Abbott Vascular	Xience V	Everolimus	PVDF-HEP with PBMA primer
Boston Scientific	Taxus	Paclitaxel	SIS
Biotronik GmbH	Dreams	Paclitaxel	PLA-microdots in albuminal side
Bioabsorbable Therapeutics	Ideal	Sirolimus Salicylate	Adipic acid
Johnson and Johnson/ Cordis	Cypher	Sirolimus	PEVA blend with PBMA topcoat and Parylene C primer
Medtronic	Endeavor	Zotarolimus	PC

The use of polymethyl siloxane in the delivery of tobramycin also reports achievement of controlled release [8, 21]. The revolutionary approach in terms of reduction in restenosis causing 60-75% of blockage in artery by releasing drug in a controlled fashion from the eluting stent has shown to be promising [22]. Vitrasert® implant composed of compressed drug tablet, overcoated with polyvinyl alcohol and poly ethyl vinyl acetate to combat CMV releases galacyclovir when implanted intravitreally [5, 22].

Biodegradable Systems

To overcome the major limitations of the non-biodegradable systems, like minor surgical treatment and local tissue damage, biodegradable systems are the choice in terms of regulatory concern, patient compliance and time controlled release and minimally invasive. On the contrary, the limiting concerns of such systems include complete study of polymer properties, mechanism of release as well as degradation and lack of cost-efficacy with more complexicity. Most of the cases, aliphatic polyesters based upon poly-lactide-co-glyclide, poly- orthoesters, phosphoesters and poly anhydrides are demonstrated. Various depot injections consisting of fully absorbable material properties have been demonstrated in various studies. In addition to delivery of a wide range of drugs in various sites, it also has shown proficiency in treatment of cancer and pain by fully absorbable drug eluting stents and partially erodible systems. In case of cancer treatment, Giadel® wafer approved by FDA in 1996 comprised of dime-sized biodegradable poly-anhydride disks, 1.45 cm in diameter and 1 cm thick have shown proficiency in delivery of carmustine after successful removal of glioma [24]. Zoladex® manufactured by AstraZeneca indicated for palliative treatment of advanced breast and ovarian carcinoma is comprised of gosorelin acetate as a synthetic peptide analogue of luteinizing hormone in a matrix of poly lactic co glycolic acid and drug is released by a combination of diffusion controlled and erosion triggered mechanism and when injected with a 14G needle [25]. Drug eluting bio-absorbable vascular scaffold is designed to perform anti platelet activity potentially decreasing its need in future like Absorb™ developed by Abbott Vascular, undergoing randomized clinical trials in United States since January, 2013 [26].

Implantable Pump Systems

Implantable pump systems are superior to various available conventional routes of drug delivery in terms of operational handling, automation of control, programming in a fabricated pathway. Broadly they are classified with respect to mechanism of drug release in osmotic pumps,

infusion pumps and mechanically activated pumps towards the drug delivery [27].

Implantable Insert Systems

In addition to the polymeric drug delivery various implantable and insertable systems are there composed of rupturable and non rupturable coatings. Additionally for periodontal diseases, bone resorption mechanisms and other rate controlling systems are composed of such kind of delivery. It has been established that various ocular inserts have shown their promising results in terms of drug release in situ. Site specific delivery of drugs in female reproductive tract has been required for contraception as well as treatment for disorders and diseases. T shaped copper releasing stents and vaginal rings are common approaches cited and discussed in this aspect [28,29]. A brief review of various inserts has been available in the Table 2. Various polymeric stents comprising of both degradable and non degradable polymers approved by regulatory authority is given in Table 3. Scanning Electron Microscopy (SEM) photomicrographs of the ceramic implants and drug eluting stents are demonstrated in Figure 6.

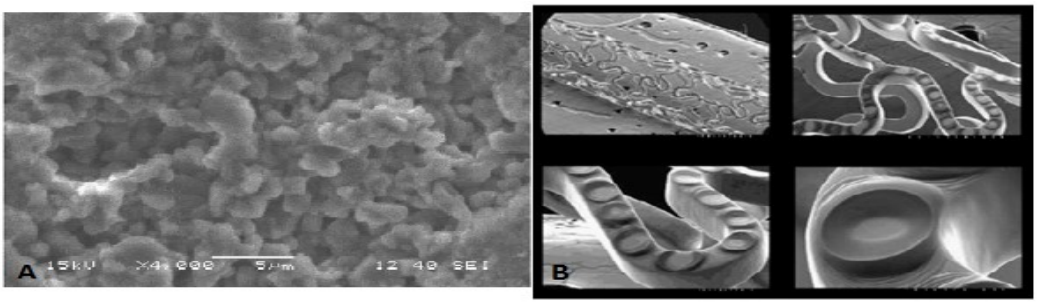

Figure 6. SEM cross sectional image of A. Aluminium phosphate implant and B. JACTAX™ stents with microdots (Reproduced with permission from Fig 6. in [18]

CONCLUSION AND FUTURE SCOPE OF IMPLANTABLE DRUG DELIVERY SYSTEM

Despite of enormous and extensive researches are currently undergoing in this field, there are several scopes in future research in this respect. Polymer sciences, fabrication technologies, release controlling parameters are also associated with such kind of delivery. In addition to the regulatory requirements and concerns, high expense of the treatment, complexity of the network and lack of awareness among the patients in this regard may be causes of less popularity among physicians as well as the patient. In future specifically modulated treatment such as gene therapy, personalized medicines may be coupled with the microchip control of the drug delivery and ascertain better patient compliance [39, 40].

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