INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Review Article

IMPLANTABLE DRUG DELIVERY SYSTEMS: AN UPDATED REVIEW

Vaibhav Rajesh Bharad*, Aijaz A. Sheikh, R.H.Kale, K.R.Biyani

PRMSS Anuradha College of pharmacy Chikhli, Dist-Buldhna (MS) India

ABSTRACT

It's a real need to develop drug delivery system that could maintain a specific site of action. Therefore, drug delivery system were developed to optimize the therapeutic properties of drug products and render then more safe effective and reliable as compared to many other drug delivery systems Implantable pumps and implants for variable rate delivery are at crude stage of development. Implantable devices allow the site specific drug administration where the drug is needed most for example implants include in the treatment of brain tumors or prostate cancer Implantable devices allow for sustained release by the therapeutic agent. The major advantages of this system contain targeted local delivery of drug at constant rate, lesser amount of drug is required to treat the disease condition minimization of probable side effect and better efficacy treatment due to development of implantable drug delivery devices it's possible to administer unstable drugs once a week to once a year that in the past required to take at frequent daily dosing.

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

INTRODUCTION

New method in the domain of drug delivery are taking place at much faster pace in contract with last two decades the experts predicts that in the upcoming years the drugs will be more specific in their pharmacodynamic action and more site selectivity of drug basically involves preventing the drug molecules from the coming across the many biological barrier that drugs molecule has to face before reaching to the active receptor site some of the barrier include binding to the plasma proteins, transports across GIT membrane removal via lymphatic system first pass hepatic effects and transports across the blood brain barrier. All of these biological barriers prevent the large amounts of drug molecules (sometimes 100%) from reaching to their targets site of action to overcome various biological barriers the implantable drug delivery devices should be preferred to be used [1]. Implantable drug delivery device are free from such limitations associated with oral intravenous.

Topical drug administration subcutaneous implantable drug delivery devices offer one unique advantage of redeemable mechanisms therefore the implants are the advanced drug delivery system that are inserted completely under the skin through minor surgical incision or injected through a large bore needle the System delivery drugs and fluids into the blood stream without repeated insertion of needle. Implantable drug delivery system has the potential to reduce the frequency of patient driven dosing and also to deliver the therapeutic command in a targeted manner presently this system is being utilized for many therapeutic application such as contraception treatments of cancer dental disease etc. also Large number of companies are involved in the development of this system which is evident by increased number of implant available in the market [2].

ADVANTAGES OF IMPLANTABLE DRUG DELIVERY SYSTEM

Implantable drug delivery system has the following advantages

Convenience: Effective concentration of the drug in the blood can be maintained for longer period of time by techniques such as continuous intravenous infusions or repeated injections on the other hand under this treatment patients are regularly required to visit hospital throughout administration for uninterrupted medical monitoring. A short acting medicine worsens the condition, as the quantity of injections or the infusion rate need to be increased to maintain a therapeutically effective level of drug. On the other hand, implantation treatment permits patients to get medication outside the hospital setting with marginal medical observation. Implantation

treatment is also characterized by lower occurrence of infection associated problems in comparison to indwelling catheter based infusion system.

Improved Drug Delivery: The drug gets distributed locally or in systemic circulation by bypassing or minimal interfering with metabolic or biological barriers. This is beneficial for those drugs which are absorbed in gastrointestinal tract and in liver before systemic distribution.

Compliance: Patient compliance may be highly improved because of the reduction or complete elimination of patient involved dosing. Although, certain implants require periodic refilling, but unlike other routes of drug administration, the patient has very less involvement in delivering the medication.

Potential for Controlled Release: Implants offer zero order controlled release kinetics that,

(a) Helps to avoid peaks (toxicity) and troughs (infectiveness) of conventional therapy is avoided.

(b) Helps to reduce dosing frequency.

(c) Helps to increase patient compliance.

Potential for Intermittent Release: Extremely programmable pumps enable intermittent release of drug in response to factors like,

(a) Cardiac rhythm.

(b) Metabolic needs.

(c) Pulsatile release of many peptides and proteins

Flexibility: Various types of flexibilities, like materials, methods of manufactures, degree of drug loading, drug release rate, etc. are available in implants. They permit controlled delivery of hydrophilic as well as lipophilic drugs.

ADVANTAGES OF IMPLANTABLE DRUG DELIVERY SYSTEM

Implantable drug delivery system has following disadvantages

Invasive: To implant the certain cases a major surgery is required which results in the formation of scar at the site of implantation and also causes an uncomfortable feeling. Also well trained personnel is required for implanting the device.

Termination: Non-biodegradable polymeric implants need to be surgically removed from the body at the end of the treatment.

Danger of Device Failure: If the device fails to operate during the treatment due to any reason, the device should be surgically removed from the patient body.

Limited to Potent Drugs: In order to minimize patients discomfort the size of implant is usually kept small. Therefore most implants have limited loading capacity and only suitable for potent medicament.

Possibility of Drug Reactions: Dose dumping occurs at the site of implant leading to severe adverse reactions [3-6].

CLASSIFICATION OF IMPLANTABLE DRUG DELIVERY SYSTEMS

Classification of implantable drug delivery system includes;

Non degradable implantable drug delivery system: Membrane enclosed reservoirs and matrix controlled systems are by far the most common, several other variants of Non degradable implants are commercially available. The matrix materials used in all these systems are typically polymers, with a documented history of both preclinical and clinical evaluation. Commonly used polymers include elastomers such as silicones and urethanes, acrylates and their copolymers, and copolymers vinylidenefluoride and polyethylene vinyl acetate (PAVA) [7-10] within the polymeric matrices forming most passive monolithic implants, the drug is typically dispersed homogeneously throughout the matrix material [11]. Alternatively, reservoir type systems are characterized by a compact drug core, surrounded by a permeable Non degradable membrane, the permeability and thickness of which controls the diffusion of the drug into the body [12]. One of the earliest, widely developed, Non degradable reservoir implants is Norplant. This implantable drug delivery system was developed and trademarked by the population council in 1980, introduced worldwide in 1983. As stated earlier, it was approved by the US FDA in December 1990, following which marketing in the United States was initiated in February 1991 [13] This contraceptive system consist of six thin, flexible silicone capsules, each loaded with 36 mg of the hormone levonorgestrel. When implants subcutaneous, typically on the inside (Figure 1).

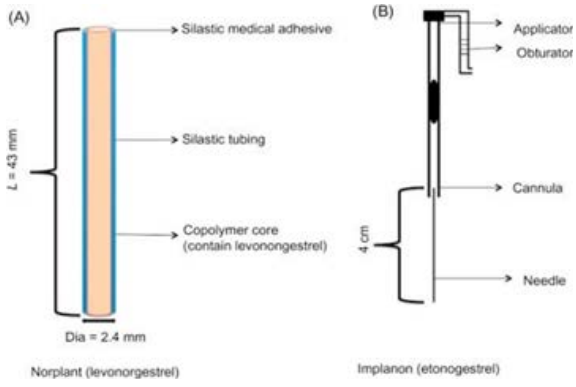

Figure 1: Non biodegradable implants (A) Norplant and (B) Implanon

Upper arm of female users [14], it is capable of offering contraceptive protection for up to 5 years. Its effectiveness and popularity may be gauged by the fact of its approval in 60 countries. While Norplant

ceased to be marketed in the United States in 2002, it is still available in other countries and has been successfully used by over 60 million women [15].

Another FDA-approved implantable drug delivery system contraceptive implants United States in 2006 [16]. It is a single-rod implant (length 4 cm, width 2 mm) and consists of PAVA core (reservoir) that encapsulates 68 mg of etonogestrel and releases drug over 3 years. The rate of drug release is controlled by a PEVA membrane covering the rod [17,18]. Protection from pregnancy can be extended beyond the initial 3 years upon removal and immediate replacement with fresh implant. Designed for easier subcutaneous insertion and removal than Norplant, Implanon has found just great acceptance by patients and providers alike [19].

Mechanism of Drug Release from Nondegradable Polymeric Matrices: Reservoir systems have the advantage of maintaining a relatively constant release rate, independent of the concentration gradient. This is likely to be mediated by thickness and permeability of the rate controlling polymeric membrane, and zero- order release kinetics may potentially be achieved. This is because, unlike direct diffusion, the driving force for release of the agent across the membrane is constant; assuming that concentration of drug within the reservoir constantly equilibrates with the inner surface of enclosed membrane [20]. In contrasts, drug release for matrix-type devices is more likely to be driven by the concentration gradient, and is mediated by diffusion lengths and the degree of swelling. In general, nonerodible, diffusion-controlled drug delivery systems work best for drugs with molecular weight of 1000 Dalton or less [21] (Figure 2).

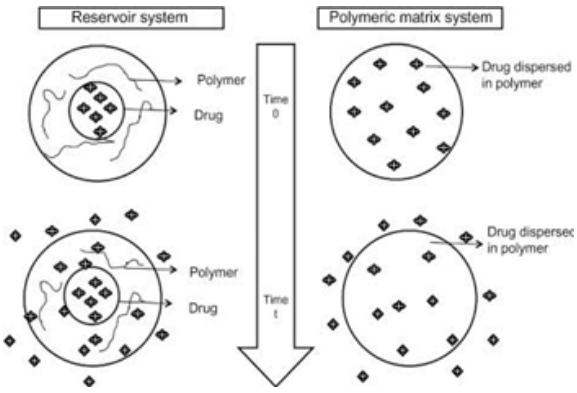

Figure 2: Cross sectional view of idealized reservoir system and matrix system, showing diffusion of drug across the polymer.

Biodegradable Implants: Biodegradable delivery systems are more popular than the non-degradable systems. The major advantages of biodegradable systems are that inert polymers are used for fabricating the delivery system, and these polymers ultimately get absorbed or excreted by the body. This eradicates the need for surgical removal of the implant after the end of treatment, and thus patient acceptance and compliance are enhanced [22,23].

Development of biodegradable system is more complicated than formulating non-degradable systems. Many variables should be considered during the fabrication of new biodegradable systems. Degradation kinetics of the polymer (in vivo) should remain constant to maintain sustain drug release. The degradation rate of polymer in the body is also by many factors. Any change in body pH or temperature can also transiently increase or decrease the degradation rate of the system. The surface area of the system also plays an important role in its degradation. Surface area of implantable system decreases its erosion. Thus, the change of shape of drug delivery system should be considered during the formulation design. A more uniform and constant release can be attained by using geometrical shapes whose surface area does not change with time when the system get eroded. A flattened slab- type shape with no edge erosion gives a zero order release kinetic profile [24,25]

Some manufactures have designed systems consisting of a bioerodible inert core coat with the active drug matrix to minimize the problem of change in surface area that occur during system erosion. Another problem of bioerodible systems is that drug diffusion form the polymeric occur at the rate slower than that of the bioerosion of the system. Diffusion of the drug depends on the chemical nature of the polymeric substance used in the formulation of drug delivery system. This problem should be overcome during the development of bioerodible systems as they are indented to be used for extended release of drug or when the drug has narrow therapeutic index [26].

At present, there are two different types of biodegradable delivery systems. The first type is reservoir system, which is similar to non-degradable reservoir system in structure and also drug release mechanism. These bioerodible systems consist of an exterior polymeric membrane that degrades at slower rate than the expected rate of drug diffusion through the membrane. Therefore, the membrane remains intact and the drug completely released. In the end, the exterior polymeric membrane degrades (in vivo) and gets excreted. The second type of bioerodible system is monolithic type, in which the drug dispersed in a polymer, gets slowly eroded (in vivo) by biological processes at a controlled rate. The most popular biodegradable polymers under investigation are polyglycolic acid, polyactic acid, polyaspartic acid and polycaprolactone. Ethyl vinyl acetate copolymer matrices for delivery of macromolecular drugs (such

as insulin) have also been studied [27].

IMPLANTABLE DRUG DELIVERY DEVICES

Field of Controlled Drug Delivery

Transdermal Patches: Transdermal patches generally have hollow micro needles made of a biocompatible polymer through which the drug is delivered below the skin. Transdermal patches have numerous advantages compared with other systems of drug delivery. The drugs are degraded in the GIT, they are pain less, and they deliver constant dosage without the need for patient's compliance [28].

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

Bioadhesives: Bioadhesives are substances which form bonds with biological surfaces. The most common substances which are used in this case are polymer hydro gels. The principal of action is similar to polymer implants in this they too are loaded with drugs and release drugs at a specific rate when in contact with body fluids. Hydro gels are water swollen polymers networks. The polymer chains may be healed together by either physical forces or covalent cross links. By design of hydro gel constituents, they can be made responsive to their chemical or physical environment. At temperature of 35-40 OC it collapses to denser, more compact structure due to a switch in the balance of solution and hydrophobic forces as the temperature is raised [29].

Microencapsulation: Microencapsulation refers to the method of covering the drug molecule with material which will prolong time before the drug absorbed, so that it will remain in the viable state and will be released when it reaches intended destination. There are variety of ways in which microencapsulation is done. Some of them are use of polymer microspheres, liposomes, and nanoparticles etc [30] the above devices are passive devices and deliver the drug in very small amounts with precision. But they are not capable of delivering the drug in nonlinear fashion or on demand. They cannot be programmed to deliver the drug when required and stop when not required.

Some Important Passive Devices

Diffusion Chamber: A diffusion chamber form Debiotech Inc. they hold a cargo of drugs and are sealed with semi permeable membrane. These used to delivering fairly large amount of drugs and in some cases more than one drug. The membrane surface area is large compared to the reservoir resulting in an increased delivery rates. These reservoirs are generally not used for long term delivery [31] (Figure 3).

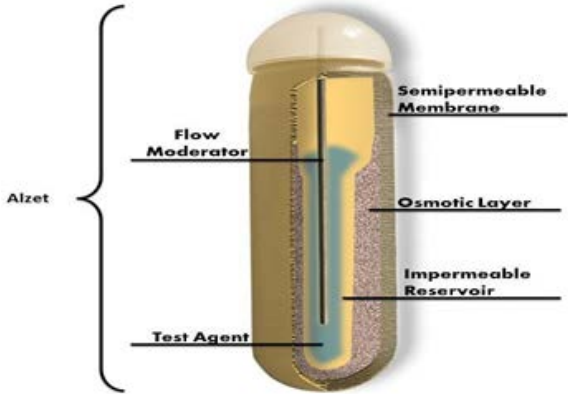

Figure 3: Schematic of an Alzet mini-osmotic pump (shown in partial section)

Implantable Pump Systems: External control of dosing is a requirement for many drugs, a feature that difficult to obtain when using biodegradable or non-degradable delivery systems. Pump system have been used to provide the higher precision and remote control needed in these situations. Additionally, they offer a number of advantages, such as evasion of the GI tract, avoidance of repeated injections, and improved release rate (faster than diffusion limited systems). With advance in microelectronics since the 1970s, remote control over delivery rate or integration of implantable sensors to create feedback-controlled drug delivery is now feasible. Implantable pumps primarily utilize osmosis, propellant- driven fluids, or electromechanically drives to generate pressure gradients and enable controlled drug release as described below [32].

Osmotic Pumps: Several dosages forms have been developed that use an osmotic pressure differential to drive the release of drug form a reservoir at a controlled rate [33] In this type of device, the drug reservoir is in semi- permeable 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 with can control the release rate according to its diameter. The drug is normally housed in flexible impermeable membrane which collapses in

accordance with the increase of hydrostatic pressure [34,35].

Therapeutic Application of Implantable Drug Delivery System

Cancer: The implantable drug delivery system has great potential to deliver have great potential to deliver chemotherapeutic drugs safely and effectively the affected side without causing any side effect. Brain, prostate and bladder cancer are few examples for which the implants are available in market [36,37] The Gliadel wafer approved one of the first implantable brain cancer treatment to deliver chemotherapy directly to the tumor site. Another example the zoladex biodegrable implantable rod delivering goserelin acetate for treating prostate cancer [38].

Ocular Therapy: Different implantable systems, including membrane controlled devices implantable silicone devices and implantable infusion systems have been investigated to provide prolong ocular drug delivery [39,40]. Ocusert, containing pilocarpin base and alginic acid in a drug reservoir surrounded by a release rate controlling ethylene-vinyl acetate membrane, is an example of membrane controlled system. This system provides an initial burst followed by a zero-order delivery of pilocarpin at 20-40 micro grams per hours for a week. Ocusert is well-tolerated in adults, and gives a satisfactory control of intraocular pressure with negligible side effects; but, it is poorly tolerated in geriatric where most of the therapeutic need exists [41].

Contraception: FDA has recently approved marketing of Norplant, a sub-dermal implant for long term delivery of levonorgestrel (contraceptive agent). This device consist of six silicon membrane capsules, each containing 36mg of levonorgestrel, which are placed sub-dermally on the inside of upper arm or forearm in fan shape pattern through a trocar form a single trocar entry point. Cumulatively these capsules deliver 70 micro grams per day (in vivo) for the first 100 days with a steady decrease to 30 micro grams per day at about 800 days, this delivery rate continuous for five years. Other polymer-based system being studied for contraception include vaginal ring of silicon rubber, which is used for 3-6 months with a removal period of one week monthly during menstruation; progestasert, an intrauterine drug release device of ethylene vinyl acetate copolymer, which least for a year and suspension of injectable microspheres or rods of biodegradable polymers [42].

Dental application: For numerous dental applications including local prolonged administration of fluoride antibacterial and antibiotics, polymeric implants have been evaluated. Stannous fluoride was integrated into different dental cements for sustained release fluoride delivery. Another dispersed in the hydroxyethal methacrylate and methyl methacrylate copolymer hydro gel coated with an outer layer of the same copolymer in different ratio so as to be rate limiting in drug release. The device, about 8 mm long and having 42 mg of fluoride in the core was attached to the buccal surface of the maxillary first molar and designed to release 0.5 mg/day of fluoride for 30 days [43-45].

FUTURE PROSPECTS

At present much research is being conducted in the region of implantable drug delivery systems. Despite this fact, much work is still required in the regions of biodegradable and biocompatible substance the kinetics of drug release, and more improvement of the present systems before many of these preparations can be used. In the feature, scientists remain expectant that many of the these systems can be prepared with best zero-order release kinetics profiles in vivo, over long times, allowing for prolonged use in constantly being prepared. Several of these medicines are continuously are developed from proteins and peptides which are very unstable when taken through oral route. By using new types of prolonged –release drug delivery systems, delivering such drug at constant rates will be possible over a prolonged period of time and will exclude the necessity for multiple dosing. It is expected that in the upcoming years, improvement of new implantable systems will help cost reduction of the drug treatment, increase the effectiveness of drugs, and enhance patient compliance [46,47].

CONCLUSION

Development of new drug candidates is expensive and time consuming. Improving the safety- efficacy ratio of “old “drugs has been attempted, using different methods such as individualizing drug therapy, dose titration, and therapeutic drug monitoring. Delivering drug at controlled rate, slow delivery, targeted delivery are other very attractive methods and have also been pursued vigorously.

IDDSs have seen reasonable clinical and commercial success as a mode of enhanced drug therapy. However, optimization of performance characteristics, including long-term biocompatibility and drug release kinetics is critical. Furthermore, clinical validation of current systems under development is essential for regulatory approval and their commercial success. However, as reviewed here, numerous commercial systems are able to attain nearly ideal zero-order release kinetics profiles in vivo, over extended time periods. IDDSs therefore present a viable, cost-effective and clinically acceptable alternative route of sustained drug delivery for chronically ill patients.

REFERENCES

1. W.A Check. New drugs and drug-delivery systems in the year 2000. AM J Hosp Pharm 1984; 41:1536-47.
2. Chien Yie W. Novel drug delivery systems. Marcel Dekker Inc 1982; 1:1-816.
3. Abhinandan AA, Vikas RA, Pallavi SJ and Rajshekhar MC. Formulation and Evaluation of Novel Biodegradable Sustain Released Matrix Implant of Gentamicin Sulphate. Res J Pharm Biol Chem Sci 2018; 9:451-463.
4. Chien Yie W. Novel drug delivery systems, Marcel Dekker Inc 1992.
5. Seaton's MF and Salminen L. Ocular Inserts for topical Delivery. Adv Drug del Rev 1995; 16:95-106.
6. Rhar RK and Vyas SP. Targeted and controlled drug delivery novel Carrier Systems. CBS Publisher and distributions 2002.
7. Maartje JLC, Mintsje DB, vanderhulst RR and Jan Willem CT. Two Hundreds case of ASIA syndrome following silicone implants: a Comparative study of 30 years and a review of current literature. Immunol Res 2016; 65:120-128.
8. De Witt D, Finley M, Lawin LDD, Finley MM and Laurie R. A blends comprising ethylene-vinyl acetate copolymer and poly (alkyl (meth) acrylates or poly (aromatic (meth) acry lates): Implantable medical device; permit stents releasing the bioactive agent over Time in vivo; provide clear coats, durability, biocompatibility, and release Kinetics: drug delivery device. US Patent Application 2005.
9. Nunes-Pereira J, Ribeiro S, Ribeiro C, Gombak CJ, Gama FM and et al. Poly (vinylidene fluoride) and copolymers as Porous membranes for tissue engineering applications. Polym Testing 2015; 44,234-241.
10. Shastri VP. Non degradable biocompatible polymers in medicine: past, present and future. Curr Pharm Biotechnol 2003; 4:331-337.
11. Martinez-Rus F, Ferreiroa A, Bartolome JF and Pradies G. Fracture resistance of crowns cemented on titanium and zirconia implant Abutments: a comparison of monolithic versus manually veneered all- Ceramic systems. Int J Oral Maxillofacial Implants 2012; 27:1448-1455.
12. Spice handler J. Demographic and Programmatic Consequences of Contraceptive Innovations. Springer 1989.
13. Rademacher KH, Vahdat HL, Dorflinger L, Owen DH and Steiner MJ. Global introduction of a low-cost contraceptive implant. Critical Issues in Reproductive Health. Springer 2014; 285-306.
14. Glasier A. Implantable contraceptives for women: effectiveness, discontinuation rates, returns of fertility, and outcome of pregnancies. Contraception 2002; 65:29-37.
15. Johansson ED. The return of the pharmaceutical industry to the Market of contraception. Steroids 2000; 65:709-711.
16. Bennink HJ. The pharmacokinetics and pharmacodynamic of Implanon, a single-rod etonogestrel contraceptive implant. Eur J Contracept Reprod Health Care 2000; 5:12-20.
17. Zheng SR, Zheng HM, Qian SZ, Sang GW and Kaper RF. A Randomized multicenter study comparing the efficacy and bleeding pattern of a single-rod (Implanon®) and a six-capsule (Norplant®) hormonal Contraceptive implant. Contraception 1999; 60:1-8.
18. Mascarenhas L, van Beek A, Bennink HC and Newton J. Twenty-Four month comparison of apolipoproteins A-1, A-II, and B in contraceptive Implant users (Norplant® and Implanon®) in Birmingham, United Kingdom. Contraception 1998; 58:215-219.
19. Fu Y and Kao WJ. Drug release kinetics and transport mechanisms of nonde- gradable and degradable polymeric delivery systems. Expert Opin Drug Deliv 2010; 7:429-444.
20. Siepmann J and Siepmann F. Modeling of diffusion controlled drug. Deliv J Control Rel 2012; 161:351-362.
21. Claes L and Ignatius A. Development of new, biodegradable Implants. Chirurq 2002; 73:990-996.
22. Tian H, Tang Z, Zhuang X, Chen X and Jing X. Biodegradable Synthetic polymers: preparation, fictionalization and biomedical Application. Prog Polym Sci 2012; 37:237-280.
23. Lance KD, Good SD, Mendes TS, Ishikiriyama M, Chew P and et al. In vitro and In vivo sustained zero-order delivery of rapamycin (sirolimus) from a biodegradable intraocular device sustained Zero-order delivery of rapamycin. Invest Ophthalmol Visual Sci 2015; 56:7331-7337.
24. Wu DQ and Chu CC. Biodegradable hydrophobic Hydrophilic hybrid hydro- gels: swelling behavior and controlled Drug release. J Biomater Sci Polym Ed 2008; 19:411-429.
25. Jiang T, Petersen RR, Call G, Ofek G, GAO J and et al. Development of chondroitin sulfate encapsulated PLGA microsphere Delivery systems with

control- label multiple burst releases for treating Osteoarthritis. J Biomed Mater Res B Appl Biomater 2011; 97:355-363.

26. Rahimi M, Mobedi H and Behnamghader A. In situ-forming PLGA Implants loaded with leuprolide acetate/β-cyclodextrin complexes: Mathematical modeling and degradation. J Microencapsul 2016; 33:355-364.
27. Ranade VV. Hollinger Mannifred a Drug Delivery system Boca Raston, fla. CRC press 1996.
28. Mathiowitz E and chickering DM. Bioadhesives drug Delivery system fundamental novel approaches and development. Marcel Dekker 1999.
29. Allababidi S and shah JC. Efficacy and Pharmacokinetics of site–specific Cefazolin delivery using Biodegradable implants in the prevention of post-operative wound infection. Pharm Res 1998; 325-333.
30. Banker Rw. In control release of biologically active agent. John Wiley and sons 1987.
31. Brissova M, Lacik I, Power AC, Anilkumar AV and Wang T. Control and Measurement of permeability for Design of microcapsule cell delivery system. J Biomed Mater Res 1998; 39:61-70.
32. Theeuwes F and Yum SI. Principles of the design and operation of generic osmotic pumps for the delivery of semisolid or liquid drug formulations. Ann Biomed Eng 1976; 4:343-53.
33. Gong W, Liu Y, Mei DY, Yang M and Mei XG. Preparation, release and Pharmacokinetics of resperidone elementary osmatic pump system. Drug Dev Ind Pharm 2015; 41:464-469.
34. Pan H, Jing H, Yang X, Pan W and Chen T. Synchronized and Controlled Release of metformin hydrochloride/gilpizipde form elementary Osmotic Delivery. Drug Dev Ind Pharm 2016; 43:1-35.
35. Barros AA, Browne S, Oliveira C, Lima E, Healy KE and et al. Drug- eluting biodegradable uretheral stent: New approach for Urothelial tumors of upper urinary tract cancer. Int J pharm 2016; 513:227-237.
36. Exner AA and Saidal GM. Drug- eluting polymer implants in cancer Therapy. Expert opin Drug Deliv 2008; 5:775-788.
37. Goldspiel BR and Koler DR. Goserelin acetate implant: a depot Luteinizing hormone- releasing hormone analog for advanced prostate cancer. Annual pharmacotherapy 1991; 25:769-804.
38. Barar J, Aghanejad A, Fathi M and Omidi Y. Advanced drug delivery and targeting technologies for the ocular diseases. Bioimpacts 2016; 6:49-67.
39. Yasukawa T, Ogura Y, Kimura H, Sakurai E and Tabata, Y. Drug Delivery form ocular implants. Expert Opin Drug Deliv 2006; 3:261-273.
40. Karthikeyan D, Bhowmick M, Pandey VP, Nanhakumar J, Sengottuvelu S and et al. The concept of ocular insert as drug Delivery systems: an overview. Asian J Pharm 2014; 192-200.
41. Jain NK. Advanced in controlled and novel Drug Delivery. CBS Publication and Distributors 2005; 219-223.
42. Koka S. The implant- mucosal interface and its role in the long term Success of end osseous oral implants: A review of the literature. Int J prosthodontics 1998; 2:421-432.
43. Sennerby L and roos J. Surgical determinants Of Clinical success of Osseo integrated oral implants: A Review of the literate. Int J prosthodontics; 1998; 2:408-410.
44. Rahman A, Konstantina D, Samuel Z, Rashid S , Solakoglu O and et al. Immediate placement and immediate proviousionalization of ITI Implants in Maxillary Non–restorable single teeth. A prelim rep 2004; 13:66-71.
45. Gupta PK, Hung CT and perrier DG. Quantition of the release of Doxorubicin from Colloidal Dosage forms using Dynamic Dialysis. J Pharm Sci 1987; 76:141-145.
46. Robinson DH and Sanpath S. Release Kintics of Tobramycin Sulphate from Polymethyl–metha–acrylates Implants. Drug Dev Ind Phram 1989; 15:2339-2357.
47. Vyas SP and Khar RK. Controlled Drug Delivery Concepts and Advances. Vallabh Prakashan 2008; 473-474.