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Implantable drug delivery systems: An overviews

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Abstract

Implant are sterile solid mass that contains medicine, prepared by different ways like extrusion, moulding or contraction. The conventional routes of medicine administration has limited control over medicine release and maintaining constant tube remedial medicine attention for longer ages of time. To avoid these problems associated with application of traditional lozenge forms, there was essential need for development of new lozenge forms which would discharge medicines at controlled rate for original exertion. This led to enhancement of Novel Drug Delivery Systems (NDDS) that offers optimisation of remedial parcels of medicines and makes them safer, productive and reliable over traditional ways of administration. Implantable medicine delivery system IDDS forms a part of new medicine delivery system. This route of administering specifics allows targeted distribution, position particularity, constant release rate, low quantum of medicine conditions, and minimisation of adverse goods with bettered efficacity. It provides possibility of administering medicines once daily to monthly which else preliminarily bear frequent diurnal dosing. Different implantable technologies are presently in use for numerous remedial operations similar as in dentistry, ophthalmology, contraception and oncology. Remedial medicine Delivery styles give veritably little, if any, control over the timing and pattern of medicine release drug attention immersion at the point of action. Undetermined drug attention in tube is a typical and egregious issue with the Traditional cure system. Therefore to overcome similar problems sweats have been made by experimenters and pharmaceutical scientists to the Betterment of the medicine delivery system and that lead to the development of the Novel Drug Delivery System (NDDS). NDDS is the Approach and technology to deliver the medicine in low attention and follow the zero- order release of the medicine in a controlled manner. Also, the NDDS's development results in the creation of an implantable medicine delivery system (IDDS). A system for implantable drug delivery is a new approach of drug delivery. In this fashion, the drug is delivered under controlled conditions to the precise position where the implant is placed. The expression, medication, evaluation criteria, and unborn aspects of the implantable medicine delivery system are the subjects of this study.

Keywords: Implantable drug delivery system; Implant; Target; Drug; Treatment

1. Introduction

Implantable drug delivery systems are placed under the skin and designed to release medicines into the bloodstream without the reprise insertion of needles. "A sterile medicine delivery device for subcutaneous implantation having the capability to deliver the medicines at a controlled rate over a prolonged period of time, comprising a rod shaped polymeric inner matrix with an elongated body and two ends". Oral route is the most accepted route for delivery of medicines, but it possesses disadvantages due to declination of the medicines by the acidic/alkaline conditions of stomach and intestine. The medicine is also subordinated to first pass metabolism. That lead to issues of compliance To overcome these faults of oral route. New medicine delivery systems have been developed With the arrival of IV administration, there sounded to have disadvantages of having high attention of medicine in tube that further may lead to toxin. The IV infusion was used to exclude the peak vale medicine situations. So, to ameliorate the condition new controlled delivery, implantable medicine delivery system (IDDS) was initiated by Lafarge in 1861, in bullet form for

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long term nonstop administration of crystalline hormone, but the release profile, couldn't be controlled, with duration of "ctio' and wasn't constant also danckwert et al in 1930, by introduced SR implantable delivery system to be administered by subcutaneous route.

Implantable medicine delivery systems are located beneath the skin. The case may have the feeling of small bump, present under the skin. This is intended to deliver the medicines in bloodstream, over a period of time, without insertion of multiple injections. This delivery system possesses number of advantages as mentioned below. Some medicine also get degraded in the acidic pH of the stomach some medicine irritate of the gastrointestinal tract and these medicine also show first order and the first pass metabolism of the medicine take place that lead to reduce medicine attention in the blood. Because the oral routes of medicine administration having disadvantage and difficulties also therefore to overcome this problem like several medicines can not be administered through the oral route of administration it may be due to the declination of the medicine either acidic or alkaline pH and may also degraded by the gastric juice or gastric enzyme. A wide range of experimental and exploration is going on across the world to pierce the stylish system of medicine delivery in mortal body. It's important that out the system of medicine delivery that has controlled and sustained release of the medicine tube and at the point of action target point.

Implantable device contain an active pharmaceutical agent in a rate controlled system and are available in variety of sizes and shapes, These device releases the medicine at the asked point and at a destined rate. Implantable bias are most suitable for habitual conditions where controlled delivery is needed for extended period of time. Implants can be either

Polymeric medicine implants: These biodegradable or non-degradable and differ in shapes similar as rod, cylinder, ring, film, etc. sizes and medicine release mechanisms.

Implantable mini-pumps: these function by bibulous or mechanical means.

An implant uses technical administration to supplicate the remedy. They're generally placed subcutaneously using a suitable injector or by gash, into the interstitial of the external face of the upper arm, the anterior area of the ham or the lower portion of the tummy. Implants may also be surgically fitted intraperitoneally or in the vitreous depression of the eye known as intravitreal implant. These are packaged collectively in sterile vials or antipode stripes.

2. Ideal properties of implantable drug delivery system

- Improve patient compliance by reducing the dosing frequency during the therapy.
- It should release the drug in a controlled manner and to maintain a drug level in the therapeutic range thus reducing side effects.
- It should allow easy termination of the therapy by a medical practitioner.
- It should be and safe and stable with good mechanical strength.
- It should be easily sterilize.
- It should be economical and easy to manufacture.
- It should not present any medical complication.
- It should be biocompatible.
- It should be chemically inert, non-carcinogenic and hypoallergenic in nature.
- The implant should be easily removable by medicinal personnel to discontinue treatment.

3. Advantages and disadvantages of implantable drug delivery system

3.1. Advantages

- Targeted drug Delivery can achieve by the implantable drug delivery system.
- Improved patient compliance.
- Reduced wastage of the drug.
- Improved efficiency.
- Minimum dose is required.
- Reduced side effects.
- Convenient therapy.
- Provide continuous sustained drug discharge over extended duration.
- Avoid the first pass metabolism.

- Improved bioavailability of drug.

3.2. Disadvantages

- Interactions between host and implant.
- Insertion of big size implants requires surgical
- Interventions which can be unpleasant.
- Treatment cannot be abruptly stopped.
- Possibility of inadequate release of drug.
- Predicted danger of device failure.
- Chances of adverse reactions due to the local high
- Concentration of drug at site of implantation.

3.3. Limitations

- Chances of toxicity.
- Painful.
- Dose tapering is not easy in case of need.
- Need for surgery to insert the device.
- Increased effectiveness and efficiency.

3.4. Benefits

- Convenience
- Improved drug delivery
- Compliance
- Potential for controlled release
- Flexibility

4. Approaches in implantable drug delivery systems

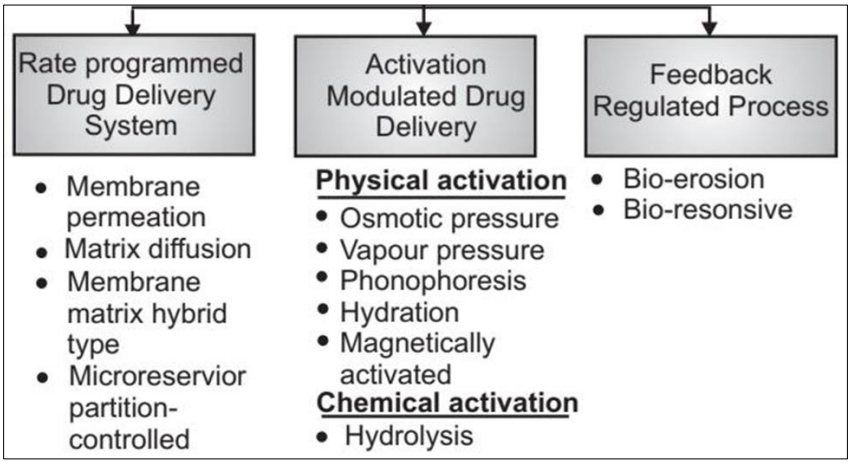

Figure 1 Approach in IDDS

4.1. Rate programmed drug delivery system

In such kind, the controlled or rate programmed devices, the release of substance from the system is designed with a certain rate period. This is fulfilled by optimizing the system design of the drug delivery system to control the molecular diffusion of drug molecules in and/or across the barrier medium within or surrounding the drug delivery system.

4.2. Activated modulated drug delivery system

In this, the release of drugs from the delivery system is controlled or activated by some physical, chemical, and biological processes or by any supplied external energy source. Drug release is controlled by the energy input or any applied process

4.3. Feedback regulated drug delivery system

Feedback-regulated drug delivery vehicles are capable of utilizing the physiological response as a signal to modulate drug release (i.e., activate, decreasing or terminate medicine discharge) from the carrier. This type of system regulates assure the better therapeutic potency to treat, mainly when the drug shows any serious or critical effect at a high amount.

4.3.1. Bio-erosion regulated

It consists of drug particles dispersed in a biodegradable matrix composed of poly (vinyl methyl ether) half-ester coated with a layer of immobilized urease. In a solution with neutral pH, the polymer erodes slowly. However in the presence of urea, the surface urease of the drug delivery system results in metabolism of urea to ammonia causing an increase in the pH activates which in turn activates the degradation of polymer matrix and accelerates the rate of drug release.

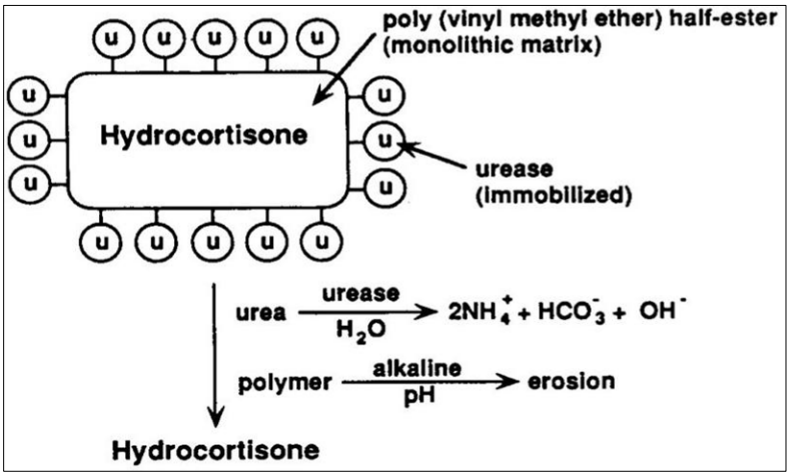

Figure 2 Bioerosion regulated

4.3.2. Bioresponsive Systems

It consists of the drug core enclosed by a bioresponsive polymeric membrane. The permeability of the polymer membrane to the drug molecule is governed by the concentration of a biochemical agent in the tissue where the device is implanted. A device using bioresponsive glucose-triggered insulin delivery system was eloped in which the reservoir comprising of insulin is enclosed in a hydrogel membrane developed containing NR, groups. In an alkaline solution, the NR, groups exist at neutral condition resulting in unswollen membrane which is impermeable to insulin. However as the glucose penetrates into the membrane, it is enzymatically oxidized by glucose oxidase entrapped in the membrane to form gluconic acid. This results in protonation of NR, groups to NR_2H and swelling of the hydrogel membrane making insulin easily permeable through it. The amount of insulin delivered is bioresponsive to the concentration of glucose penetrating into the device.

Example: glucose-triggered insulin delivery system

5. Mechanisms of drug discharge from implant device

There are primarily four ways of medication discharge through the implant devices polymer disintegration, optimized expansion, osmosis and simple diffusion. Implants acting by optimized expansion, water absorption in device controls drug discharge which is generally inadequate over normal dispersion and thus contributes to a steady proportion of release. The disintegration of expanded matrix allows diffusion of drug mainly and improving the disintegrating capacity of the matrix significantly enhances the efficiency of the implant. Osmosis mediated release and free diffusion techniques of drug release are appropriate for delivering drugs linearly where the quantity of liberated relies proportional to square root of discharge duration. Osmosis is simple passage of aqueous molecules from an area of low concentration to a greater concentration via a semipermeable membrane which creates a pressure gradient. Diffusion works by process in which solute moves voluntary in all areas to saturate chemical composition. The mobile substances are called diffusants and a membrane through which diffusants travels is known as diffusional barrier. The concentration gradient is the impulsion for the release of medicament from system. However the discharge profile of drugs depends upon contents of delivery system which in turn relies on factors like imbibition, osmotic pressure, and

passive diffusion, and molecules stability, diffusion coefficient in polymer, drug content, and disintegration rate of polymer in drugs content and disintegration rate of polymer in vivo.

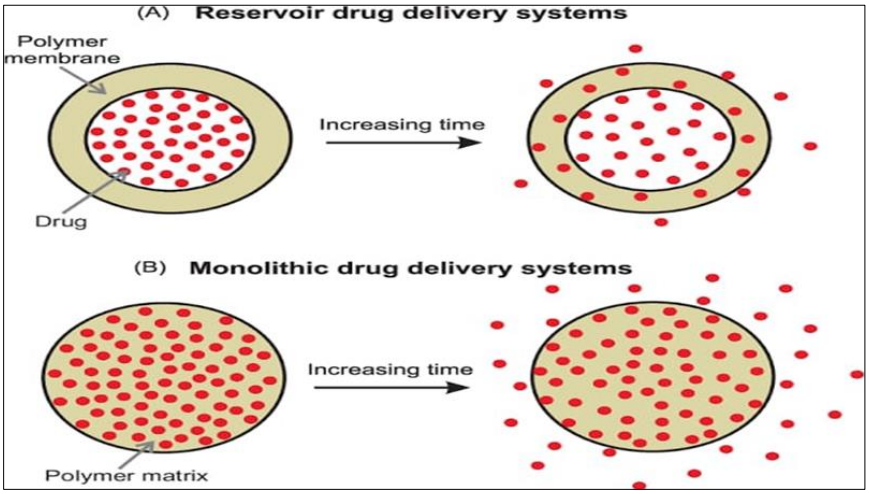

Figure 3 Drug discharge from implant device

6. Methods of preparation of implants

There are mainly three methods for the preparation of implants that are discussed below A number of factors need to be considered when choosing a manufacturing method for production of an implantable drug delivery devices including: cost, efficiency and differences in properties of the produced implants. Implants can be manufactured using a variety of techniques including compression, solvent casting, hot melt extrusion, injection moulding or more recently 3D printing. Thermoplastic polymers such as PLA or PLGA can produce implants using techniques such as: hot moulding, injection Moulding, compression or extrusion Implants prepared by different techniques are unlikely to form polymers with exactly the same microporous structure and will degrade at differentiates and, therefore, will have different in vitroandin vivo release profiles compared the process of hot moulding and compression as techniques to make intra-ocular implants, and found that, the manufacturing technique significantly influenced the polymer degradation and, therefore, drug release from the resulting implants with compressed implants showing an increased rate of drug release than their moulded counterpart.

6.1. Extrusion method

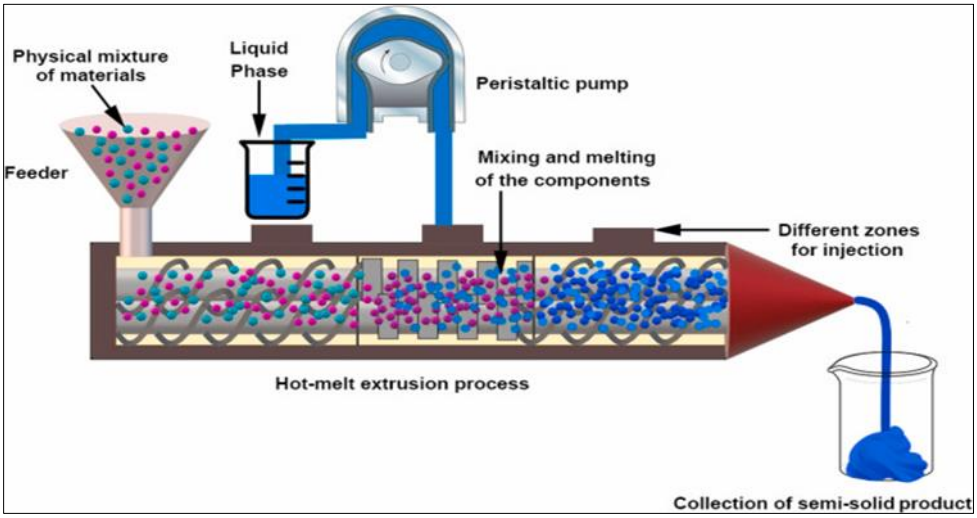

Figure 4 Hot melt extrusion

Firstly selected drug is dissolved in a suitable solvent system to produce a solution. After that polymer is added into the solution slowly and allowed to stand for 10-15 minutes for soaking purposes. The swollen material developed had been

blended uniformly till it forms a dough-like material. The dough was transferred into the extruder cylinder and had been extruded in the form of long rods by the help nozzle. Implants dried the whole night at room temperature, and then cut into the optimum size and dried at 40 °C.

6.2. Compression Method

The polymer and drug were dissolved to develop the solution. The produced solution was subjected to freeze-drying to produce a uniform cake. The cake was subjected to compression for the development of the implant. Implants have been developed by utilizing a Carver hydraulic press at a pressure of 1 metric ton, utilizing a stainless steel system developed for this objective, comprised of 1mm diameter cylindrical punches set.

6.3. Solvent Casting

In the solvent casting method, the polymer is first dissolved in a suitable solvent, then the resulting solution is cast into a mould and the solvent is removed by evaporation Implants produced by this method often result in films or laminar implants. A disadvantage of this method is the need for large amounts of organic solvent, which can have an effect on the stability of drugs and toxicity, and may give rise to environmental concerns.

6.4. Moulding Method

Solution of polymer and the drug was firstly prepared in a suitable solvent system and then subjected for the lyophilization and converted to a uniform cake after that before the prepared cake was molded into rods through a Teflon sheet heated on a hot plate at a temperature about 100-120 °C.

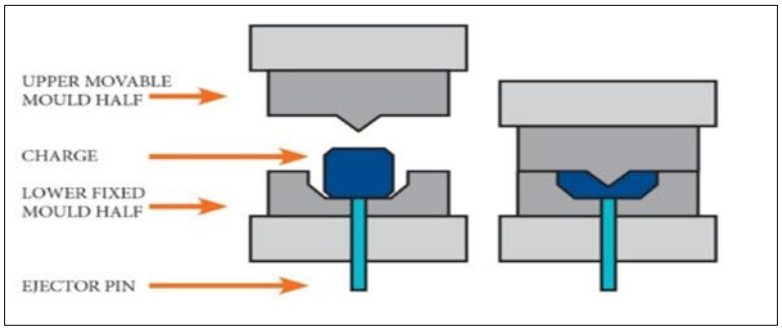

Figure 5 Moulding

6.5. 3D Printing

It is an inexpensive, consistent and versatile procedure and can be useful in future especially in quick manufacture of Standard units for investigatory purposes. However, it is not Used in mass production but its suitability progressed in 2015 When FDA approved one such material. This technique is mainly applied in creating prostheses and implants used in dentistry and orthopaedics.

7. Evaluation parameters of implantable drug delivery system

Various parameters are implemented in the evaluation of implants after manufacture by any appropriate method. These are as follows-

- **Shape and size:** The size of an implant is verified using Vernier Callipers under light.
- **Uniform Thickness:** The individual thickness of separate implants as well as the variations among them is determined by using Vernier Callipers. At least three specimens must be determined and average value is found out.
- **Uniform Weight:** The aim of this test is to calculate the uniform weight of each implant. The test is performed by random selection of twenty implants and weighing them separately. Mean weight is obtained. From the results, two implants must not weigh more than the mean weight and none of them must have two fold value of mean.
- **Swelling Index:** A specimen is placed in swelling solution of phosphate buffer pH 7 for an hour and the weight is estimated. The remaining solution is cautiously removed by gently cleaning with dry sheet. The magnitude of swelling for every unit at any instant is determined by given formula:

$$Swelling\ Index = W2 - W1\ /W1X\ 100$$

Where, W2 and W1 represent the specimen's mass at specified instant and in dried form correspondingly

- **In-vitro dissolution profile:** In-vitro dissolution profile of the implant is crucial in estimation of release and the stability of drug. Dissolution medium is taken in a container while optimal conditions and RPM are fixed. The implant is placed in the vessel and the paddle is rotated. The samples are taken out after specific time intervals. The samples are there after examined by UV visible spectrophotometry at a particular wavelength. The procedure is repeated for at least three observations and the average value is noted.
- **Stability testing:** This test is done to detect disparities in standard of drug accompanied by time and storage characteristics like temperature, moisture, light, shelf life, etc.
- **Interaction analysis between polymer and drug:** Implant containing drug is analysed using FTIR for finding suitability of drug with other formulation components and possibility of such interactions**.**

Table 1 ICH recommendations for stability tests

Condition	Observation	Environment	Term
Normal	Extended	298º K ± 2º K / 60% ± 5%Or 303º K ± 2º K / 65% ± 5%	1 Year
	Intermediate	303º K ± 2º K / 65% ± 5%	Six Months
	Quick	313º K ± 2º K / 75% ± 5%	Six Months
Storage In Freezer	Extended	279º K ± 5ºk	1 Year
Storage In Refrigerator	Intermediary	298º K ± 2ºk / 60% ± 5%	Six Months
	Extended	278º K ± 3ºk	1 Year

8. Application of implantable drug delivery system

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. The Gliadel wafer approved one of the first implantable brain cancer treatment to deliver chemotherapy directly to the tumors site. Another example the Zoladex biodegrable implantable rod delivering goserelin acetate for treating prostate cancer.
- **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. Ocusert, containing pilocarpine 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 pilocarpine 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.
- **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.
- **Immunization:** Polymeric implants are being investigated to achieve pulsatile or continuous administration of the antigen for prolonged period of time to obtain better immune response to antigens. Wise et al developed an implant composed of ethylene-vinyl acetate copolymer pellets to deliver bovine serum albumin. Results showed that the immune response achieved by the implant was comparable to that of two injections of bovine serum albumin in complete Freund's adjuvant (Freund's adjuvant is an o/w emulsion containing bacteria).
- **Dental application:** For numerous dental applications including local prolonged administration of fluoride antibacterial and antibiotics, polymeric implants have been evaluated. Stannous fluoride was integrated into

different dental cements for sustained release fluoride delivery. Another dispersed In the hydroxyethyl methacrylate and methyl methacrylate copolymer 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.

- **Narcotic antagonisms:** Long term narcotic antagonism is provided by implantable Device of naltrexone hydrochloride. It liberates its base from Hydrochloride or palmitic acid salt and is available in different Polymers and formulations.
- **Other uses:** Insulin preparations are widely administered via biofeedback operated implantable devices in which drug is released based On pharmacological requirements of body at a specifie Instance.

Table 2 Applications of implants in various conditions

Brand	Site of placement	Structure	Medication	Uses
Norplant® Jadelle®	Subcutaneously	Silicone	Levonorgestrel	Contraceptive
Implanon® Nexplanon®	Subcutaneously	PEVA	Etonogestrel	Contraceptive
Zoladex®	Subcutaneously	PLGA	Goserelin	Prostate adenocarcinoma
Med Launch	Subcutaneously	PLGA	Risperidone	Schizophrenia
Probuphine®	Subcutaneously	PEVA	Buprenorphine	myalgia
Oncogel®	Intratumorally	PLGA + PEG PLGA	Paclitaxel	Oesophageal carcinoma
Retisert®	Intraocular	GCC,PVA	Fluocinolone	Non-contagious uveitis
Vitrasert®	Intraocular	PVA,PLVA	Ganciclovir	MV retinitis in AIDS

9. Conclusion

The drug can be administered by different routes like oral drug delivery, transdermal, and implant etc. the maturity of drugs are responsible for all the drug delivery systems. An implantable drug delivery system is an effective and good drug delivery system and releases the medicine over a long period. Implantable drug delivery system is an innovative approach towards rate-controlled drug delivery at needed therapeutic Concentration. The Primary focus needed is enhancement of biodegradable and Biocompatible substances, reduction in immunogenicity and toxin of the polymer and its by-products during decomposition, discharge profile together with posterior development in the pre-existing device. In the future, these Systems can give excellent zero- order medicine release kinetics profile in vivo for longer duration of time which makes it Suitable for dragged use. These systems have the capability to reduce the need of frequent dosing, is overall cost effective, ameliorate the efficacity of medicines and increase patient Compliance which will ultimately be patient friendly.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have known conflict of interest to declare.

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