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Review Article

Implantable Drug Delivery System: An Innovative Approach

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Abstract

The conventional routes of drug administration has limited control over drug release and maintaining constant plasma therapeutic drug concentrations for longer periods of time. To avoid these problems associated with utilization of traditional dosage forms, there was essential need for development of new dosage forms which would discharge drugs at controlled rate for local activity. This led to improvement of Novel Drug Delivery Systems (NDDS) that offers optimisation of therapeutic properties of drugs and makes them safer, productive and dependable over traditional ways of administration. Implantable drug delivery system (IDDS) forms a part of novel drug delivery system. This route of administering medications allows targeted distribution, location specificity, constant release rate, low amount of drug requirements, and minimisation of adverse effects with improved efficacy. It provides possibility of administering drugs once weekly to yearly which otherwise previously require frequent daily dosing. Different implantable technologies are currently in use for many therapeutic applications such as in dentistry, ophthalmology, contraception and oncology. However, the expensiveness of this newly improved drug delivery system is quite high which hinders its large scale use. Moreover, the recently developed devices require further enhancement and hence thorough scientific trials are needed before wide implementation in populations.

Keywords: Implantable drug delivery, implants, drug delivery system, implantable pump, modulated drug delivery, novel drug delivery system

INTRODUCTION

Despite of progression and innovations in novel administration of drugs, regulation of constant uniform plasma therapeutic index of drugs is still a big concern. The potential harm of using periodic oral or IV drug administration comprises of elevated concentration of medication (peaks) which contribute to adverse effects or inadequate concentration of medication (troughs) which can lead to failure of therapy. The old way to overcome the issue of the variable concentrations of medication includes constant intravenous infusion rate dependent on medication pharmacokinetic profile. In order to minimise these unwanted outcomes, there is a need of modern approach in achieving optimised rate of drug discharge.[1]

Implantable drug delivery systems have potential superiority in regional administration with better pharmacologic outcomes at minimum doses. Due to which, they lower possible toxicities thereby improving likelihood for medication adherence. This kind of administration enables convenient delivering of medications that are ordinarily incompatible to be taken by oral way, escapes presystemic elimination as well as enzymatic destruction in abdomen, thus, remarkably enhancing bioavailability.[2]

Implantable devices have ability to minimise the need of frequent drug intake as well as authorize medication needs with approachable way. At present, these devices are commonly employed in many therapeutic areas such as contraception, chemotherapy, dentistry etc. The expanding production and market availableness of implants are evident of immense growth in this sector (figure 1).[3]

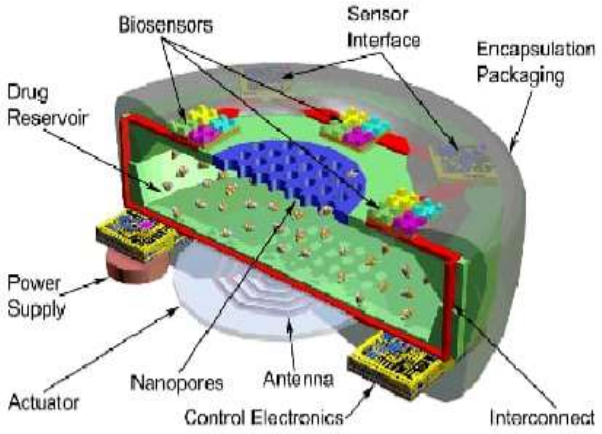


Figure 1: Illustration of an implantable drug device[44]

Implantables are commonly selected for their property of extended use with constant release of medicament which will eventually promote the patient compliance.[4]

IDEAL REQUIREMENTS

The ideal requirements of an implantable device are-

- Exhibit zero order or modulated drug release kinetics for constant delivery rate to minimise adverse effects.
- The dosing frequency shall be minimised for enhancing patient adherence and must fully discharge the medication during duration of therapy.
- Safe, stable and effective with good mechanical strength.

- Comfortable to extract by medical practitioner to suspend treatment in case of need.
- Easily sterilizable.
- Free from any complicated process of insertion and hence adaptable.
- No possible serious complications.
- Relatively inexpensive.
- Non-toxic and non-carcinogenic.[5]

ADVANTAGES

- Targeted action.
- Helpful in delivery of drugs exhibiting short *in vivo* half-lives.
- 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.

BENEFITS

- Convenience
- Improved drug delivery
- Compliance
- Potential for controlled release
- Flexibility.[6]

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.

LIMITATIONS

- Chances of toxicity.
- Painful.
- Dose tapering is not easy in case of need.
- Need for surgery to insert the device.[7]

CLASSIFICATION OF IMPLANTABLE POLYMERIC DRUG DELIVERY DEVICE SYSTEMS

Polymers are the key elements in implantable systems as they provide extended and optimised drug release. They act as rate-limiting membrane in implant system and the choice of which must be done in keeping view of host biocompatibility and ease of sterilization.[8]

The polymers in implants are mainly categorised into two major groups -

1. Passive polymeric implants:

They are simple, singular and uniform devices, mainly contains simple drug loaded in biocompatible matrix. They do not have any mobile part or technique and depend on passive diffusion for release of drug load. Passive devices can be subcategorised as non-biodegradable and biodegradable.[9]

A. Non-Biodegradable polymeric implant systems-

The most common commercial forms are matrix-controlled or polymeric system and membrane enclosed reservoir. Polymers like polyurethanes, polyacrylates, silicones or heteropolymers like polyethylene vinyl acetate (PEVA) are widely used. In the matrix-controlled organisation, a medicament is uniformly distributed across the base. Gradual dispersion of embedded medicament gives sustained release from delivery system. The dynamics of expulsion and release rate of medicament is inconstant and relies on amount of substance in the base. A reservoir type system contains compact drug protected by non-biodegradable porous layer whose diameter as well as penetrability qualities influence release kinetics.[10, 11]

These devices are durable during their lifespan but need to be replaced after the drug load is exhausted to avoid any negative impacts like infection, tissue harm and cosmetic imperfections. These types of systems are widely utilized in contraception. Norplant is one of the earliest, widely developed reservoir implant.[12]

B. Biodegradable polymeric implant systems-

These systems offer advantages over non bio-degradable ones and hence are more popular. Polymeric substances such as polycaprolactone (PCL), polylactic acid (PLA), or polylactic-co-glycolic acid (PLGA) are typically used for formulation. The most desirable property is that it uses inert polymers that split into small pieces and further absorption and elimination takes place inside body thus do not require any incision to extract out the device thereby improving patient acceptance and compliance. But these systems require the degeneration of base of polymer for release of medicament which is dependent on various factors like any change in body pH or temperature and therefore extremely variable in individuals. (Table 1) [13, 14]

Their formulation is furthermore intricate than that of non-biodegradable ones. Numerous factors are taken in view for their formulation. Disintegration profile of polymeric base inside the body should be stable for keeping continuous drug discharge. To obtain more uniform and constant drug release, a flattened slab-like design without edge erosion offers zero-order profile is preferred.[15]

Two types of bio-degradable devices are present. They are reservoir system and monolithic types (figure 2). Reservoir system is similar in construction and mechanism of drug release as described in non-biodegradable systems. However, these bio disintegrated systems contain outer membranous layer of polymer which disintegrates at moderate pace than that of dispersion across membrane. As a result, membrane stays unaffected releasing behind the medicament entirely. This intact membrane gets deteriorated inside the body which is finally excreted out. The other kind is monolithic where medicament is disseminated in a polymeric substance and shows gradual erosion with a steady release inside the body.[16]

Table 1: Examples of biodegradable polymers

Class	Examples
Polypeptides	Soy protein, Zein, Silk
Polysaccharides	Cellulose, Starch, Xanthan
Polyesters	Polylactic acid, Polyvinyloxyalkonates
Lipids	Surfactants, Waxes
Polyphenols	Lignin, Tannin
Speciality polymers	Natural rubber, Nylon (from castor oil), Shellac

2. Active or dynamic polymeric implants:

This kind of Implantables use definite propulsion in regulating discharge of medicine across the aid. Thus it offer advanced standard in drug discharging. They use some sorts of energy dependent methods for positive impulse to regulate discharge. The power origin can range different from osmotic pressure gradient to electromechanical forces.[17]

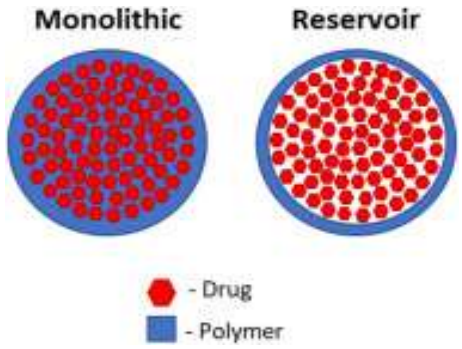


Figure 2: Types of dynamic or active implantables [45]

IMPLANT PUMPS

Various drugs need exterior source to control amount and expulsion which is not achieved by biodegradable or non-biodegradable systems except in magnetically modulated devices. The presence of sophisticated microsystems have made easy in designing pumps as little adequate that it can be implanted hypodermally to deliver drugs.

Pumps discharge medications via pressure difference which is obtained by pressing the reserve either osmotically or mechanically resulting in flow of drug at optimised way. The pumps should possess desirable properties like non-inflammatory, non-thrombogenic, nonantigenic, noncarcinogenic, convenience, long reserve and battery life, easily organisable, and can be inserted using local anaesthesia. It should also be simple to check the condition and working of the system. Hence, pump systems deliver drugs with ideal precision.[18, 19]

Presently five groups of implant pumps are present. These pumps are infusion, osmotic, peristaltic, positive displacement and modulated discharge microsystems.

Types of implant pumps:

Infusion pumps

Infusion pumps distribute the stored medicament inside the body with the help of a fluorinated hydrocarbon as energy source. They were earlier used in delivering insulin to diabetic people who need more than one dose in a day. This results in plasma peaks and troughs of insulin which may lead to diabetes induced complications.

The pump contains disc-like container constructed by lightweight bio composite titanium that comprises of foldaway that divides the container interiorly in two isolated compartments. The former compartment comprises of the energy source while the latter stores insulin. A gas forces the stored drug to expel via sift and course controller which gives optimised drug delivery at a mentioned temperature. It does not require external source of energy to drive the pump. A load of stored dose is released across a silicone rubber membrane that itself seals then moved across a Teflon layer when pump stock is refilled. The device is recharged by the force of the delivery drive that pressurises the device. Apart from application in insulin delivery, it is found useful in field of anticoagulation and chemotherapy (figure 3A).[20, 21]

Osmotic pumps

Osmotic pumps are extensively prevalent of all implant types. These devices involve medication confined in a selectively permeable membrane that permits an inward movement of aqueous fluids in the device by simple osmosis. The built hydrostatic pressure forces invariable expulsion of medication through an orifice in membrane of system and whose swiftness in discharge can be altered by modifying the structure of semi-permeable membrane. However, the pace of discharge remains persistent or zero order till stored load is been exhausted (figure 3B).[22, 23]

Peristaltic pumps

Peristaltic pumps work by external source of power mainly by batteries and consist of cylindrically rotating apparatus. An exterior source modulates the flow of drug from it. This class of pumps are made of a rubber membrane of silicone and their duration of use is dependent on the battery as energy source used. These systems are quite expensive to be used in standard practice in market.[24]

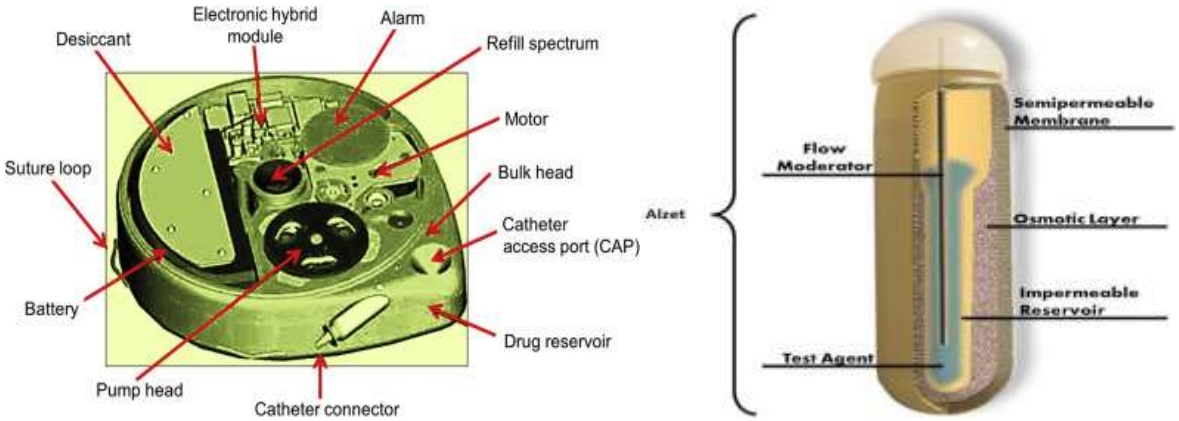


Figure 3: (A) An overview of infusion pump [46] (B) Schematic representation of Alzet osmotic pump [47]

MECHANISM OF DRUG DISCHARGE FROM IMPLANT DEVICES

There are primarily four ways of medication discharge through the implant devices – polymer disintegration, optimised expansion, osmosis and simple diffusion. Implants acting by optimised 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 drug relies proportionally 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 vivo* (figure 4).[25-27]

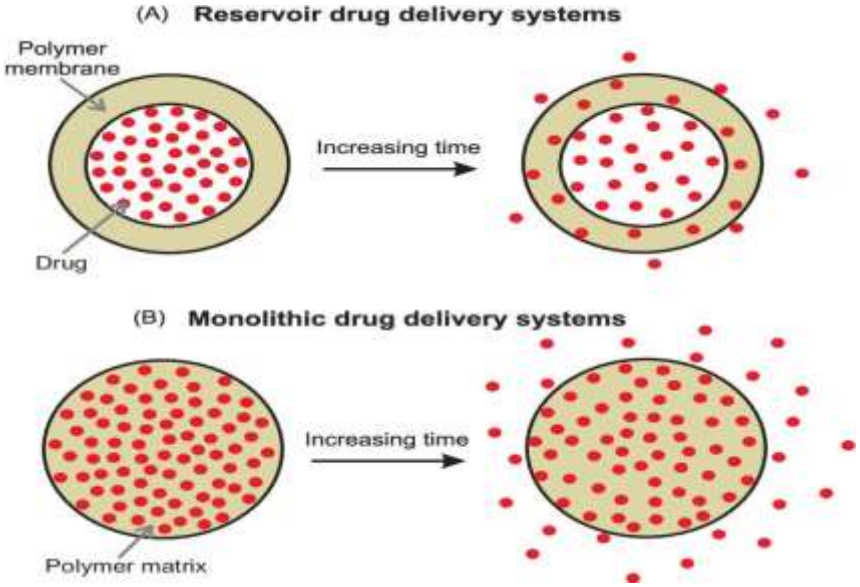


Figure 4: Demonstration of drug release from polymer matrices [48, 49]

METHODS OF IMPLANT MANUFACTURE

The important methods of preparation of implants are described below:

1. Hot melt extrusion:

The drug is made to dissolve in an appropriate solvent to make a solution mixture. Then polymer is slowly incorporated and allowed to soak for 15-20 minutes. The swollen product is mixed thoroughly till it forms like dough and moved into ejection cylinder and elongated rod-like structure is obtained with use of showerhead. The product is made to dry overnight at ambient temperature and trimmed into required dimensions. Finally, it is dehydrated at 41 *c to obtain finished product. Extrusion can be carried out simultaneously which allows efficient output (figure 5A). Polymeric substances are required to be thermoplastic like poly amide aliphatic polyesters like PLA, PGA, and PLGA. It requires nonsolvents. However, this may result in degeneration of heat sensitive medications. Zoladex® and Implanon® like devices are produced by this technique.[28, 29]

2. Compaction:

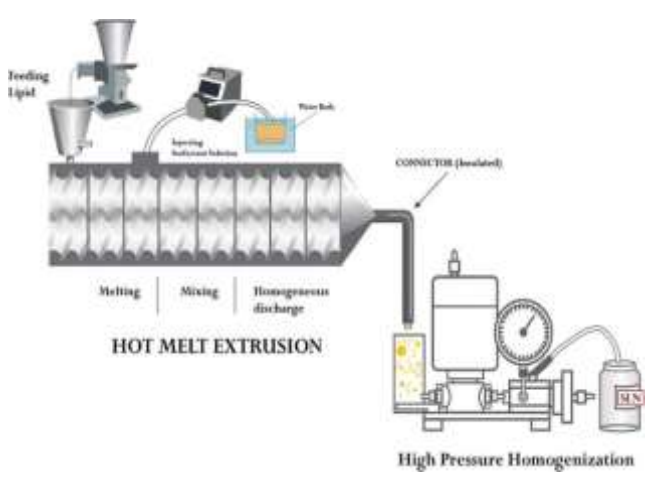
The drug with polymer are diffused to make a suspension and subjected to lyophilisation to produce a cake. It is further exposed to compaction to derive an implant by Carver hydraulic machine with a force of a metric ton. It offers advantage of no usage of heating and solvents thus ideally compatible for designing implants that embody thermo labile matter notably proteinaceous content. These implantables show a quick release profile which necessitates optimisation by layering them. Additionally, implants produced have asymmetrical appearance having numerous cavities that can further contribute in unsteady discharge. [30, 31]

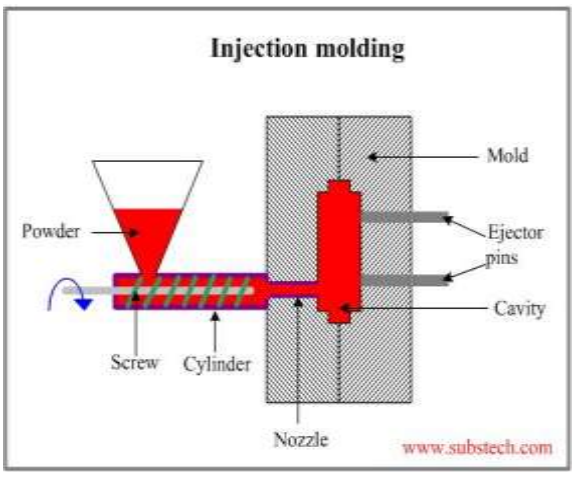
3. Moulding:

The polymeric material is subjected to heating then incorporated in form of a mould followed by solidification. A decrease occurs in relative molecular mass of the polymers due to high heat applied. Molecular mass as well as dispersability may be lowered using different ways and is furthermore amplified by this method. Due to which, these types of implantables disintegrated earlier as compared to factory-made mistreatment injections moulding (figure 5B).[32]

4. 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.[33]





A B

Figure 5: Methods of manufacture of implants- (A) Hot melt extrusion method [50] (B) moulding method [51]

EVALUATION PARAMETERS OF IMPLANTS

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

A. Shape and size: The size of an implant is verified using Vernier Callipers under light.

B. 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.[34, 35]

C. 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 twofold value of mean.[36]

D. 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. [37] The magnitude of swelling for every unit at any instant is determined by given formula:

$$Swelling\ Index = \frac{W2-W1}{W1} \text{ X } 100$$

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

E. *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 thereafter examined by UV visible spectrophotometry at a particular wavelength. The procedure is repeated for at least three observations and the average value is noted.[38]

F. 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. (Table 2).

Table 2: 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
	Intermediary	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

G. 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 [39]

THERAPEUTIC APPLICATIONS OF IDDS

1. Contraception:

Implants are widely used in contraceptive purposes. Norplant is a type of implant placed sub-dermally intended for sustained discharge of levonorgestrel (used in contraception). It comprises of 6 silicon membrane units, every one having 36 microgram of drug. The capsule release 70 mcg daily in initial three months and further reduction in release to 30 mcg daily for around 800 days and offer constant release rate for five years. Another example includes Progestasert which is an intrauterine implant made of ethylene vinyl acetate

copolymer. This device is used for 3-6 months and can be removed for a week in a month at time of menstrual period.[40]

2. Ocular use:

Membrane controlled devices, silicone devices, infusion devices and different implantable devices are popularly used to deliver drugs for prolonged ocular use. Ocusert is a classic example of membrane controlled device containing a pilocarpin with alginate inside medication reserve enclosed with ethylene vinyl acetate membrane. This device provides outburst of drug initially then follows zero order release profile of drug at 20-40 milligrams hourly for weekly period. It extends good management of intraocular pressure (IOP) with insignificant adverse outcomes and is well accepted in adults whereas poorly tolerated in elderly people.[41]

3. Cancer:

Silicone rod implants are useful in administration of ethinylestradiol and testosterone propionic acid in treatment of prostate adenocarcinoma. Lupron depot offers release of leuprolide acetate for a month, which is structurally similar to gonadotropin-releasing hormone (GnRH). Zoladex depot unleashes goserelin acetate from a biodegradable rod for one month and is used to treat prostate adenocarcinoma.[42]

4. Narcotic antagonism:

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.

5. 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 specified instance (Table 3).[43]

Table 3: Applications of implants in various conditions

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

PEVA- Polyethylene vinyl acetate, PLGA- Polylactic coglycolic acid, PVA- Polyvinyl alcohol , MCC-Microcrystalline cellulose CMV- Cytomegalovirus, AIDS- Acquired immunodeficiency syndrome.

CONCLUSION

Implantable drug delivery system is an innovative approach towards rate controlled drug delivery at required therapeutic concentrations. This approach has other distinct superiority over the traditional administration ways. This is a developing area with much advancements and research going on. The primary focus required is improvement of biodegradable and biocompatible substances, reduction in immunogenicity and toxicity of the polymer and its by-products during disintegration, discharge profile together with subsequent development in the pre-existing devices. In the future, these systems can provide excellent zero-order drug release kinetic profile *in vivo* for longer duration of time which makes it suitable for prolonged use. These systems have the capability to reduce the need of frequent dosing, is overall cost-effective, improve the efficacy of drugs and increase patient compliance which will eventually be patient friendly. Since many newer drugs are continuously developing from proteinaceous substances that are unsuitable to be administered orally, the use of these novel devices will prove to be a remarkable approach in capturing the drawbacks associated with previous drug delivery systems.

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