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Implantable Drug Delivery Systems

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Abstract

Traditional drug delivery methods provide very little, if any, control over the timing and pattern of drug release Medication concentration absorption at the point of action. Undefined medication concentration in plasma is a typical and obvious issue with the traditional dose method. Thus to overcome such problems efforts have been made by researchers and pharmaceutical scientists to the betterment of the drug delivery system and that lead to the development of the Novel Drug Delivery System (NDDS). NDDS is the approach and technology to deliver the drug in low concentration and follow the zero-order release of the drug in a controlled manner. Additionally, the NDDS's development results in the creation of an implantable drug delivery system (IDDS). a system for implantable medication delivery is a new approach of medicine delivery In this technique, the medicine is delivered under controlled conditions to the precise location where the implant is placed. The formulation, preparation, evaluation criteria, and future aspects of the implantable drug delivery system are the subjects of this study.

Keywords: Implantable drug delivery systems, foreign body reactions, implantable polymeric systems ,implantable drug delivery device.

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1. Introduction

History

The concept of implantable drug delivery systems (IDDSs) in modern medicine may be traced to Deansby and Parkes who, in 1938, subcutaneously (SC) implanted compressed pellet of crystalline estrone to study their effect up on castrated male chickens. Folkman and Long pioneered implantable formulations, with drug release rates controlled by a polymeric membrane. (1), in the 1960s (Kumar et al, 2018). They investigated the use of silicone rubber (Silastic) for long-term drug delivery at a systemic level. In the year 1861, Lafarge introduced the concept of implantable system for sustained release drug administration. In the very beginning it was first introduced to produce the solid implants containing steroid hormones implantable system for long term delivery. (2)

Implantable drug delivery systems

Under the skin,implantable drug delivery systems are positioned to release medications into the bloodstream without the need for additional needle insertions. A sterile medication delivery system for a subcutaneous implantation that includes a rod-shaped inner matrix with an elongated body and two ends is capable delivering the medications over time at a predetermined rate. (3)Typically, implantation is carried out via surgical techniques, needles, or special implantation devices in subcutaneous or intramuscular tissue. Due to their high fat content, which promotes sluggish drug absorption, limited innervation, good hemoperfusion, and low innervation , subcutaneous. tissue or intramuscular tissue are the perfect sites for the implantation of drug-depot devices. (4)

Many medication classes are very interested in IDDSs, especially those that cannot be administered orally, have unpredictable gastrointestinal absorption, or benefit from site-specific dosage. Steroids, chemotherapy, antibiotics, and analgesics are a fewexamples.as well as birth control methods, as well as biologics like heparin or insulin. In order to improve patient compliance by reducing the frequency of drug administration throughout the course of treatment, rate-controlled drug release, environmental stability, biocompatibility, ease of sterilisation, ease of manufacture &relatively low cost, mechanical strength, and lack of surgical procedure are all requirements for implantable drug delivery.

The primary purposes of Implantable therapeutic devices are long-term, continuous medication administration, and regulated release. (5)

Figure1. Implantable drug delivery system

Ideal requirements of implantable drug delivery systems (6)

- Environmentally stable.
- Biocompatible.
- Sterile.
- Biostable.
- Improve patient compliance by reducing the frequency of drug administration over the entire period of treatment.
- Release the drug in a rate-controlled manner that leads to enhanced effectiveness and reduction in side effects.
- Readily retrievable by medical personnel to terminate medication.
- Easy to manufacture and relatively inexpensive.

Benefits of an implantable drug delivery system

- Increased effectiveness and efficiency.
- A small amount is enough to cause the desired effect.
- For instance, 2-8 mg of progesterone
- Lessened negative effects.
- Delivery right away.
- Practical therapy.
- Offer linear delivery over a protracted period of time,
- ranging from a few weeks to many months.
- Continuous maintenance of therapeutically acceptable
- medication levels in plasma
- Local administration via a controlled release method can
- lessen or eliminate harmful side effectxcessively and is relatively less expensive.

Limitations of the implanted medication delivery device

- Potential toxicology.
- The system must be implanted via microsurgery.
- It might hurt.
- Difficulty in if necessary turning off releases from systemic administration.
- Drug administration could be streamlined and Enhanced in underdeveloped areas without access to Quality medical supervision.
- Drug administration with brief in vivo half-lives may be made much easier.
- Constantly taking little doses of the medicine might be lessPainful than taking multiple high doses at once.
- The level of patient compliance might rise.

Disadvantages

- **Invasive:** The patient must undergo either a major or a minor surgical procedure in order to insert the implants.
- **Termination:** Non-biodegradable polymeric implants may be removed from the body after the conclusion of treatment via a surgical procedure.
- **Risk of device malfunction**: If the device doesn't function well during therapy for some reason, surgical steps should be done to remove it from the patient's body.
- **Only use potent pharmaceuticals**: Because the device is very small to lessen the discomfort of the patient, it is only possible to use very little amounts of potent drugs in this system.

Foreign body reaction

According to the FDA's definition of implants, IDDS is presumed to have ongoing interaction with the bodily fluids and surrounding tissues. All implantable materials and devices must satisfy the biocompatibility requirements, in accordance with the most recent safety regulations, in order to be given consideration for clinical approval . A foreign body reaction (FBR) is the local immune response that develops as a result of the interactions between the implant and the surrounding tissues. (7) FBR is a general protective mechanism that creates a fibrotic capsule to isolate the unidentified poorly biodegradable material from the surrounding tissues and the body as a whole. A chronic inflammatory process known as the FBR is brought on by the

implantation of artificial items like IDDSs.It has three main stages : acute inflamation,proliferative phase ,and fibrotic encapsulation of the implant.

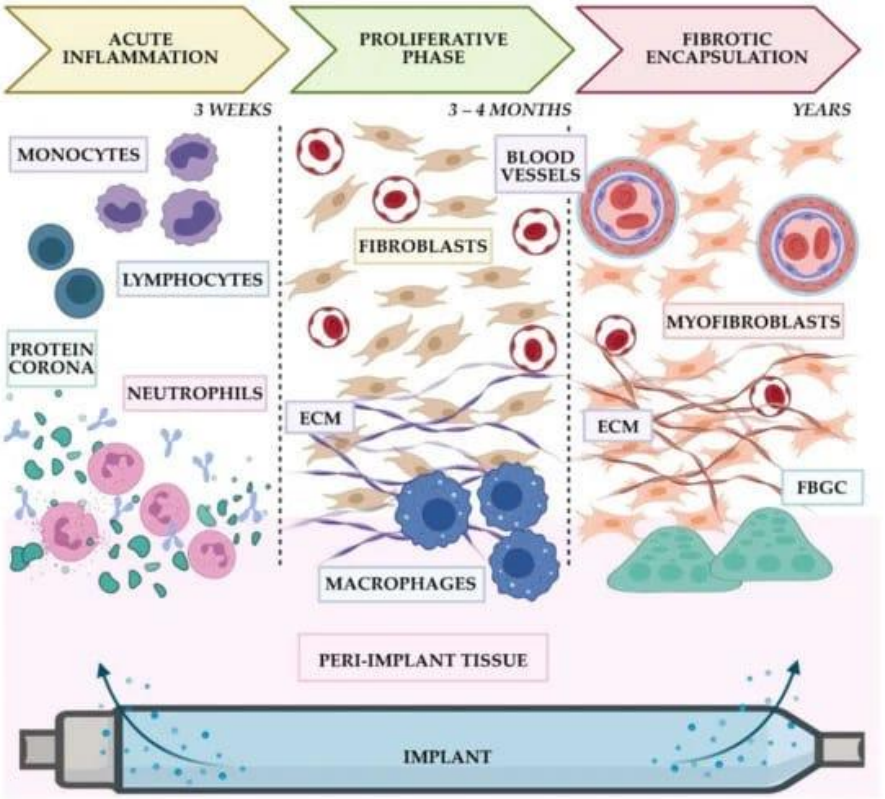


Figure 2. Schematic representation of the stages of foreign body reaction (FBR) to an IDDS

Implantable medication delivery systems' mechanisms

Three main delivery methods form the basis of the majority of implanted medication delivery systems.

• Controlling swelling
• The osmotic pump.
• Dispersion

A swelling or osmotic mechanism is engaged in systems that are activated by solvents. Applications for dentistry, vaccination, anticoagulation, cancer, narcotic antagonists, and insulin delivery have been made. Numerous medications are being employed in implanted drug delivery devices. (8)

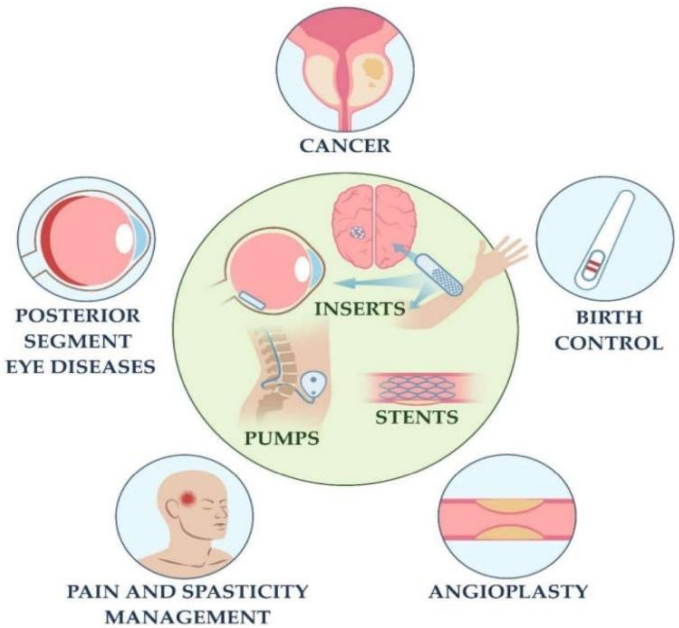


Figure 3. The main classes of commercially available IDDS and the areas of their application

A swelling or osmotic mechanism is engaged in systems that are activated by solvents.

Applications

- Dentistry,
- Vaccination,
- Anticoagulation,
- Cancer,
- Narcotic antagonists, and

- Insulin delivery have been made

Numerous medications are being employed in implanted drug delivery devices.

2. Implantable polymeric system classification

Passive implant: Passive implants typically consist of simple drugs and seem to be fairly straightforward, homogeneous, and singular implants.Packing in a substance or composite that is biocompatible. They do not involve implants some mechanical parts, by description, & rely on a passive, diffusion-mediated process to attenuate the release of drugs. The medication selection, its dosage, total device structure, polymer matrix & surface properties make treatment kinetic studies somewhat tunable. (9)

Non-Biodegradable Polymeric Implantable Systems : Non-biodegradable devices are frequently made using polymers like silicones, polyurethanes, poly acrylates, or copolymers like poly ethylene vinyl acetate. This sort of implant could be a monolithic or reservoir-type device.Monolithic implants are made from a polymer matrix in which the medication is evenly distributed.(10) But on the other side, a lightweight medication core protected by a porous non-biodegradable layer is found in reservoir-type devices. The thickness of the membranes as well as the permeability of the medication via the membrane will control the release kinetics .Non-biodegradable implanted medication delivery methods have been widely used for contraceptive therapy. Such devices have sturdy architecture and are even long-lasting.True, the main drawback of non-biodegradable products is that replacement is required.Once their pharmaceutical load has been depleted. The materials used to make such devices exhibit good biocompatibility over time, but they can also cause infection, tissue damage, or cosmetic deformity. In order to prevent any negative effects, the medication is typically removed after all of the patients have been discharged. (11)

Biodegradable Polymeric Implants: To address the disadvantages of non-biodegradable devices, biodegradable implants have been made. Such devices are manufactured utilizing polymers or block copolymers which can be split apart into small pieces which are exhaled or absorbed by the body afterward. Polymers like poly caprolactone (PCL), poly lactic acid (PLA) or poly lactic-co-glycolic acid are usually used (PLGA). To change the rate of drug release, such substances have been thoroughly examined & their deterioration kinetics could be easily tuned. (12) The key benefit of the strategic implant is that it is not possible to remove them after implantation, as the person's body would destroy them. The same models previously mentioned may be used to construct them: monolithic devices & reservoir-type implants. One downside of this unique type of system is that it is more difficult to produce than non-biodegradable devices. (13)

Dynamic or Active Polymeric Implants: Such technologies to control the release of drugs from the implant are being driven positively. They exhibit more drug discharge regulation as a result. They do, however, provide more expensive designs that are associated to refinement. Electronic .The majority of the devices in this class are built of metallic constructions. Even though, in order to stay within the scope of this report, only polymeric devices will be described. In essence, interactive delivery system devices come in pump form. The most common kind of polymeric effective device is osmotic pumping. Such a system is primarily composed of a semi-permeable membrane that covers a drug reservoir. (14) Osmotic patterns within the implant will permit a constant influx of liquid. During this stage, the device's internal pressure will increase, which will cause the orifice to release medication. This layout allows the Continuous medication release (zero-order kinetics). Although there is little medication loading with this type of system, it allows for a favourable rate of release.

Polymers : Because a sustained or controlled release of the drug is required in a novel drug delivery system and can only be accomplished by the use of polymers in the system, polymers serve as the system's structural foundation.Huge numbers of polymers are used in the controlled in the implants as a rate-limiting membrane in the system but the selected polymer should also be compatible with the host and easy to sterilize. (15) Release formulation as a rate-limiting membrane in the system, some polymers are also used Various other components are used in the implants like fatty materials (cholesterol) and metals (titanium, stainless steel 316) also in the special implantable devices.The polymers used in the implants are of mainly two types that are as follows:

A . Non-biodegradable polymers

B. Biodegradable polymers

Table 1. Some of the implantable polymeric drug delivery devices and classification

Product name	Implant type	Material	Drug delivered	Indication
Norplant	Sub cutaneous	silicone	Levonorgestrel	Contraceptiom
Jadelle	Sub cutaneous	silicone	Levonorgestrel	Contraceptiom
Estring	Intra veginal	silicone	Estradiol	Menopausal symptoms
Nuvaring	Intra vaginal	PEVA	Etonogestrel ,ethinyl estradiol	Contraception
Implanon	Sub cutaneous	PEVA	Etonogestrel	Contraception
Nexplanon	Sub cutaneous	PEVA	Etonogestrel	Contraception

3. Mechanism of drug release from implantable polymeric drug delivery system

For the implantable polymeric drug delivery, there have been primarily four medication releases, which are

matrix depletion; regulated swelling; osmotic pumping; & passive diffusion. (16)

For systems depending on controlled swelling, solvent penetration into the device's matrix regulates how quickly the device discharges. It would result in a slower rate of discharge because this is normally much weaker than drug diffusion. Diffusion from swollen tissuesAlthough matrices are primarily responsible for the release of drugs, their depletion may also affect the effectiveness of these devices. (17)

The most promising drug delivery methods for linear delivery, however, are osmotic pumping and passive diffusion. The quantity of medication released in this instance is inversely related to the square root of the release time.

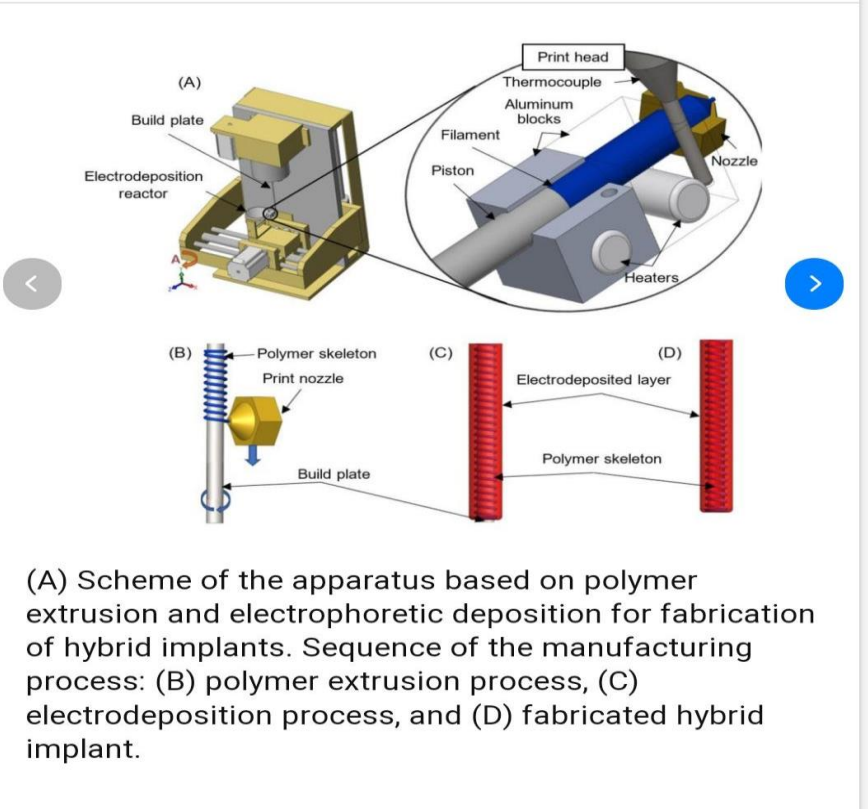
Osmosis is the general passage of water through a partially permeable membrane from a diluted solution to a more concentrated solution, and it creates a hydrostatic pressure difference between the two compartments. Osmotic pumping is a phenomenon that utilizes the abovementioned concept to adjust the delivery rate of drugs in defined conditions. In this case, osmotic pressure, caused by water absorption, drives the transport of the drug. Moreover, implantable drug delivery devices based on this phenomenon will demonstrate a constant release rate. (18)

Diffusion is a mechanism by which that substance randomly moves from one location to another to balance chemical potential or thermodynamic activity. In this process, moving materials are generally referred to as diffusants or permeants, and the membrane orThe diffusional barrier isthe matrix through which the diffusant migrates. The external stage is often referred to as the medium.This medicine release mechanism is driven by the concentration gradient or diffuser profile inside the diffusional barrier. (19) Medication release kinetics will be dependent on crucial elements in drug delivery systems that are induced The molecule's solubility and diffusion coefficient in the polymer, the medication load, and the polymer's in vivo degradation rate, as well as swelling, osmotic pressure, or passive diffusion.

4. Methods of preparation of implants

There are mainly three methods for the preparation of implants that are discussed below:

Extrusion method: To create a solution, a chosen medicine is first dissolved in an appropriate solvent system. After that, the polymer is gradually added to the solution and left to stand for 10 to 15 minutes to soak. The developed swelling material had been mixed.consistently until a dough-like substance forms. The dough was inserted into the extruder cylinder and extruded by the aid nozzle into the shape of long rods. The implants were first cut into the ideal size and dried at 40°C after drying all night at room temperature. (20)



(A) Scheme of the apparatus based on polymer extrusion and electrophoretic deposition for fabrication of hybrid implants. Sequence of the manufacturing process: (B) polymer extrusion process, (C) electrodeposition process, and (D) fabricated hybrid implant.

Figure 4. Extrution method

Compression Method: The solution was created by dissolving the medication and polymer.To make a consistent cake, the resulting solution underwent freeze-drying. Compression of the cake allowed for the formation of the implant. implanted devicesconstructed using a stainless steel system created for this purpose and a set of 1mm diameter cylindrical punches, under pressure of 1 metric tonne from a Carver hydraulic press. (21)

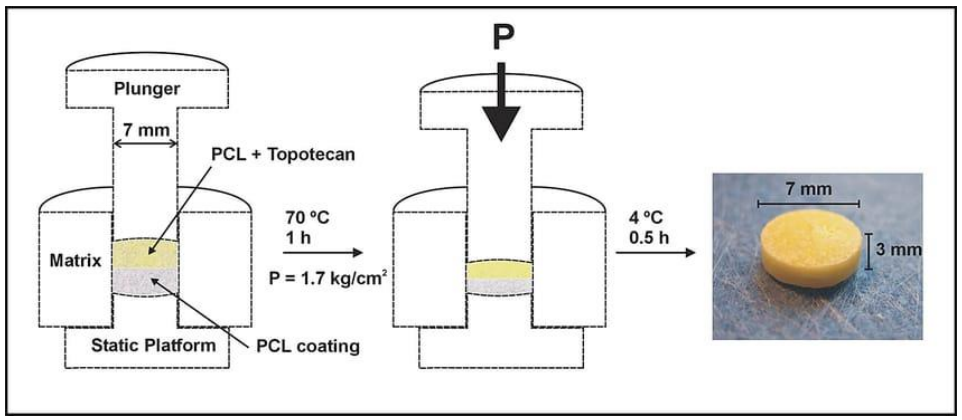


Figure 5. Melt molding compression technique

Molding 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 100-120o C. (22)

5. Evaluation patameters for implants

After the preparation by any suitable method, an implant is subjected to the evaluation that is Shape and size, Uniformity of thickness, Weight variation, and stability studies also.

Size and shape: Implants are evaluated under light and the size of the implant was determined with the help of Vernier Caliper.

Uniformity of thickness: Implants are separately subjected to determine the thickness With the help of Vernier Calipers, which gives a precise reading of thickness and tells about the difference in the thickness of every implant. Minimum three samples should be evaluated to get the mean value

Uniformity of weight: This test is also known as the weight variation test. It is performed to determine the uniformity of the weight of every implant. Take 20 implants randomly and Weighed mean weight was calculatedOf 20 implants two implants should not be more in Weight than the mean weight and none of the implants should be the double weight of Average weight. (23)

% Swelling Index: Prepared implants had been dipped into the swelling medium at neutral pH and left at room temperature for an hour. After that implant was weighed, the free solution was removed by tapping the surface with the dry filter paper. (24)

***In-vitro* dissolution studies**: In-vitro dissolution studies are important to determine the drug release and the stability of drug products. In-vitro dissolution study is carried out with the help of the rotating paddle, the method comes under the category of apparatus 2. The dissolution medium was filled in thtime intervals of the predetermined time. And the collected samples were examined under a UV visible spectrophotometer at a specified wavelength. The dissolution study performs a minimum of three times, and the average observation was taken. (25)

Stability studies: According to the International Conference on Harmonization (ICH), stability testing's goal is to provide proof of how a drug substance's or drug product's quality changes over time under the influence of various environmental factors like temperature, humidity, and light, allowing for the recommendation of storage conditions, retest intervals, and shelf lives.

Table 2. ICH guidelines for stability studies

Case	Study type	Storage condition	Duration
General	Long term	25ºC±2ºC/60%±5% or 30ºC±2ºC/65%±5%	12 months
	Intermediate	30ºC±2ºC/65%±5%	6 months
	Accelerated	40ºC±2ºC/75%±5%	6 months
Stored in refrigerator	Long term	5ºC±3ºC	12 months
	Intermediate	25ºC±2ºC/60%±5%	6 months
Stored in freeze	Long term	-20ºC±5ºC	12 months

Drug and polymer interaction study: Infrared spectroscopy of API/drug and polymers was done by the FTIR. After the preparation implant was also subjected to FTIR analysis to check the compatibility of the drug with additives.

6. Implantable drug delivery devises

Field of Controlled Drug Delivery

Implantable controlled drug delivery techniques can also be used to administer medication to organs like the cornea that are immunologically remote and inaccessible by other means. Today, the field of controlled drug delivery makes use of techniques including microencapsulation, polymer implants, bioadhesive systems, and transdermal patches. (26)

Transdermal Patches

In order to distribute the medicine below the skin, transdermal patches often feature hollow microneedles composed of a biocompatible polymer. Transdermal patches provide many benefits over conventional drug delivery methods, including the fact that the medications are not broken down in the gastrointestinal tract (GIT), they are painless, and they supply a steady dosage without the requirement for patient compliance. The nicotine patch is a well-known illustration of a transdermal patch.

Polymer Implants

Biodegradable polymers filled with medicinal molecules are called polymer implants. When the polymer interacts with bodily fluids, it breaks down, releasing medication molecules in the process. By changing the characteristics of the polymers, the rate of the polymer's degradation and, consequently, the drug release, can be optimised. Polyglycolic acid (PGA), Polylactic acid (PLA), polyurethane, and mixtures of these in various ratios are among the polymer materials that are most frequently employed for these applications. (27)

Bioadhesives

Bioadhesives are chemicals that bind to biological surfaces and establish bonds. Polymer hydrogels are the most often utilised materials here. In that they are also laden with medications and release those drugs at a predetermined pace when in contact with bodily fluids, the concept of operation is similar to that of polymer implants. Water-swollen polymer networks are known as hydrogels. Physical or covalent cross-links may be used to hold the polymer chains together. The components of the hydrogel can be made to respond to their chemical or physical surroundings by design. Due to a change in the equilibrium of solution and hydrophobic forces as the temperature is elevated, it collapses into a denser, more compact form at 35–40 ^{o}C.

Microencapsulation

For the medicine to stay in a viable state and be released when it reaches its target, the drug molecule must be covered with a substance that will delay the time until it is resorbed. This process is known as microencapsulation. Microencapsulation can be done in a variety of ways. Some of them make use of nanoparticles, liposomes, polymer microspheres, etc. The aforementioned gadgets, known as "passive devices," precisely and progressively dispense the medicine in extremely small doses. However, they are unable to provide the medication "on demand" or in a non-linear manner. They are unable to be programmed to only give drugs when necessary. (28)

7. Implantable infusion pumps (29,30)

Vapour pressured powered devices

It consists of first and second chamber. Basic principle at a given temperature, a liquid is in equilibrium with its vapour phase exerts a constant pressure refilling is done for every three months with helIt consists of flexible tube, housing, and rollers with help of roller the lumen of tube compresses, which causes flow of fluid towards the exit with help of roller the lumen of tube compresses which causes flow of fluid towards the exit.

Figure 6. Vapour pressured powered device

Solenoid pump: It consists of implantable infusion devices ,an external physician cansole hand held unit with which patient can initate programmed doses of drug it uses a solenoid derivenreciprocating to move infusate from reservoir out through the deliver cathet.

Command system: Operate from a radio signal originating in a physician console.Command system is used to change basal delivery rate ,to turn the device on and off and to set limits on medication usage.

Telemetry system: It involves transmission of data from a remote location. Used for confirmation of battery voltage and rate of infusing medication.

Power system: It must be small in size and long lasting, contains rechargeable Ni Cadmium cells to store energy and operate the system between recharges.

Figure 7. Solinoid pump

8. Conclusion

One of the innovative components that is sometimes overlooked in the advancement of new medicine delivery through formulation, research, and development in many pharmaceuticals is implantable drug delivery. Currently, there is a lot of research being done on implanted medication delivery devices. Utilizing novel types of extended medication delivery systems will eliminate the requirement for multiple dosing. The introduction of novel implantable frameworks is anticipated to lower drug treatment costs, increase the efficacy of medications, increase patient compliance, and expand medication adequacy in the next years.Implanted drug delivery systems can provide a substance in a tailored manner while reducing the frequency of patient-driven dosage.Implantable drug delivery devices are devoid of limitations associated with oral, Intravenous, topical drug administration.

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Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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