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Implantable Drug Delivery System: An Overview

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ABSTRACT

Traditional drug delivery systems have very less or we can say no control of the drug release pattern and also on the absorption of drug concentration at the site of action. A very common and noticeable problem with the conventional dosage form is an undefined concentration of drug in plasma. 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. And the advancement in the NDDS leads to the development of an Implantable drug delivery system (IDDS). Implantable drug delivery system is a type of novel drug delivery system in this system the controlled delivery of the drug is provided at the specific site where the implant is implanted. This study deals with the formulation, preparation evaluation parameters, and the future aspects of the implantable drug delivery system.

1. INTRODUCTION:

Most of the drugs about 90% are given through the oral route of drug administration but the oral drug delivery of the drugs the unpredictable plasma concentration in the human body, some drugs also get degraded in the acidic pH of the stomach, some drugs irritate of the gastrointestinal tract and these drugs also show first order and also the first-pass metabolism of the drug takes place that leads to the reduce drug concentration in the blood (1). Because the oral route of drug administration having disadvantages and difficulties also thus to overcome these problems like several drugs cannot be administered through the oral route of administration it may be due to the degradation of the drug either at acidic or alkaline pH also and may also be degraded by the gastric juice or gastric enzymes (2). A wide range of experiments and research is going on across the world to access the best system for drug delivery in the human body. It is important the find out the system of drug delivery that has controlled and sustained release of the drug in plasma and at the site of action/target site (3). Novel drug delivery system comes in the advancement at national and international levels by the researchers in the field of drug delivery system to deliver the drug in a safe and efficacious manner in the human body and that particular system can deliver a drug in such a manner that can overcome the problems of the traditional or conventional drug delivery system (4). The novel drug delivery system is designed in such a way that helps to deliver the drug at the targeted site or organ where localization of action is required (5). Implantable drug delivery system come in trend in 1938 by the two scientists named Deansby and Parkes, they implanted a compressed pellet by subcutaneous route of drug administration. An implantable drug delivery system is defined as a system in which the implant is inserted into the body by surgery. IDDS has emerged as a medical accomplishment that aims to maximize the medication's beneficial quality thereby reduce the risk of life-threatening conditions such as a tumor, ischemic heart attack, brain stroke, aids (6). For the number of medications that cannot be delivered by the oral administration, IDDS seems to be a very stronger drug delivery system, medications that are less bioavailable by the digestive tract. Antibiotics, including NSAIDS, are mostly contraceptives, etc. (7). There is a large population of people and animals who would greatly benefit from the ability to have an implanted drug delivery device. Several delivery systems have also been created; however, several have seen common medical applications due to the broad-scale needed. Drug delivery systems have long be utilized to supply patients with sufficient drug dosing over prolonged periods. Implantable

devices have the benefit of ensuring consistency with treatment response and precision of delivery, and also the ability to produce high local medicament quantities such as those occurring with chemotherapeutic drugs. These advantages make local, implantable drug delivery the most effective treatment for many therapeutic regimens. Implants are sterile medical devices that are inserted into human tissue for drug delivery and release of the drug over a long period (8). Nevertheless, it also has a variety of problems that prohibit it from being the perfect path for drug distribution. The basic characteristics of a few pharmaceutical substances are according to low molecular weight; a value of Log P between 1 as well as 3; strong solubility; as well as high partition coefficient. (9). A controlled drug action may be achieved by either chemically modifying the drug moiety or by formulating it in a specific way to control its release. The major downside of the modified release treatment method is the long travel period of about 12 hours via the GIT. If the medication could not be delivered orally, an option is an intravenous injection path. Oral controlled formulations do provide effectiveness for around 24 hours. In the case of topical drug administration, the percutaneous absorption of most drugs is limited due to the physiological characteristics of the drugs and the presence of highly impermeable stratum cornea (10). IDDS lacks the above-mentioned drawbacks associated with oral, injectable, topical drug therapy by subcutaneous injection IDDS. The amount of additives is also utilized for the introduction of a variety of therapeutic substances with distinct physical & chemical characteristics and also for greater management of release profile. These systems are available in a variety of sizes and shapes (11).

1.1 Ideal properties of implantable devices:

- The dosing frequency should be reduced to increase patient compliance and should release the drug during the entire treatment period.
- The implant should be easy to develop and should not be expensive.
- The implant should be easily removable by medical personnel to discontinue treatment.
- The implant should release the drug in a zero-order manner or in a controlled manner that leads to effective treatment and reduced side effects.
- The implantable device should be easy to sterile.
- The implant should be safe, stable, and effective and should have enough mechanical strength.

- The implant should be easy to administer and would not require any special procedure for application.
- The implant should free from any potential problem (12-14).

1.2 Advantages of the implantable drug delivery system:

- Zero-order release of medication for an extended period.
- Improved patient compliance due to a decrease in dose frequency.
- Targeted drug delivery can be achieved by the implantable drug delivery system.
- Avoid the first-pass metabolism.
- Decreased side effects.
- Improved stability of drugs.
- Improved bioavailability of drugs.
- Termination of therapy when required.
- Safe during breastfeeding.

1.3 Disadvantages of implantable drug delivery system:

- Surgery is needed for large size implants thus painful procedure.
- Therapy cannot be simply discontinued.
- Reactions between host and implant.
- Inadequate release of active pharmaceutical ingredient (API) (15, 16).

2. APPROACHES IN IMPLANTABLE DRUG DELIVERY SYSTEM

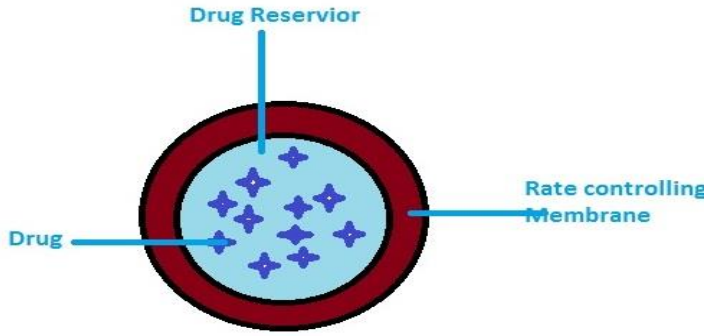
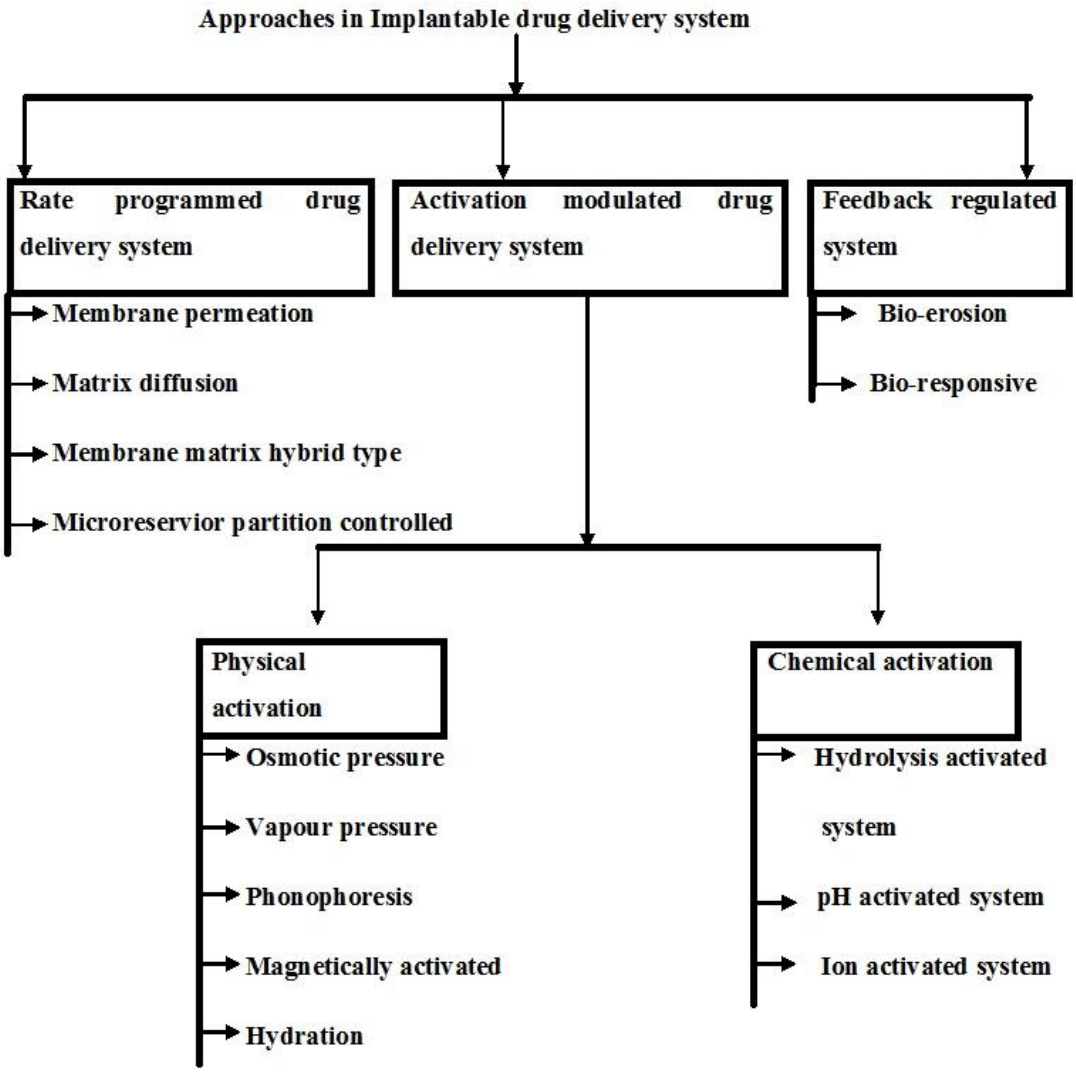


Figure No. 1: Rate programmed drug delivery system.



2.1. Rate programmed drug delivery system:

In such kind, the controlled or rate programmed devices, the release of drugs from the system is designed with a certain rate period. This is accomplished 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 (17).

2.2. 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 (18, 19).

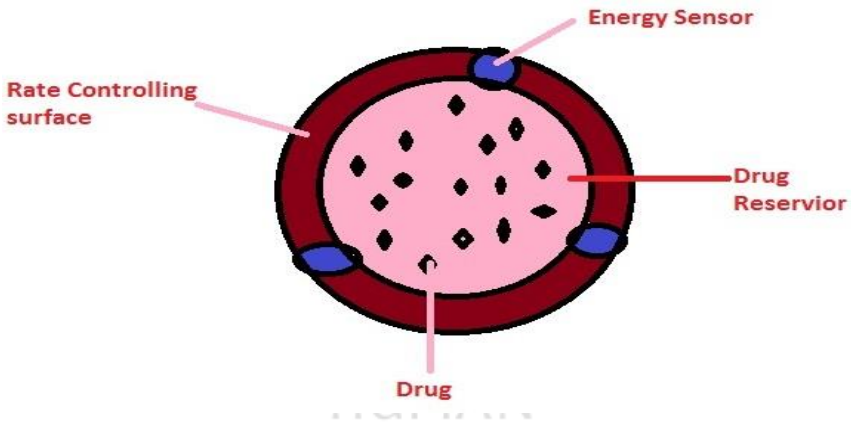


Figure No. 2: Activated modulated drug delivery system.

2.3. 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 (20).

3. IMPLANTABLE POLYMERIC SYSTEM CLASSIFICATION:

IDDS classification is a complicated process however the IDDS is separated into different kinds of active and passive implantable devices. While the passive implantable device is again broadly divided into two, the non-biodegradable device as well as the biodegradable process, since the passive diffusion releasing method is used by both the non-biodegradable

and the biodegradable device, whereas the active system needs some energy to release the drug.

3.1. Passive implants

Passive implants appear to be fairly plain, homogeneous & singular implants, usually consisting of simple drug.

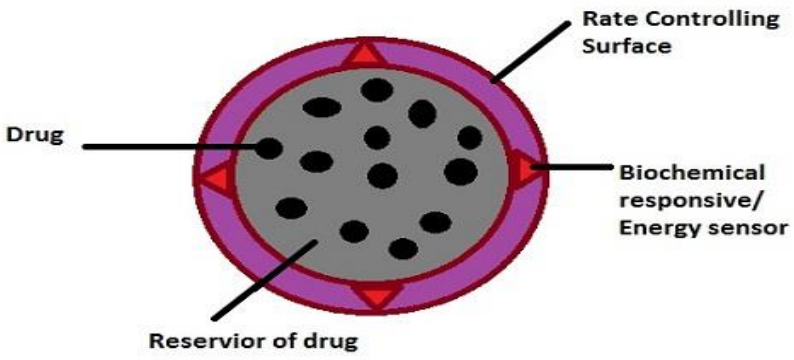


Figure No. 3: Feedback regulated drug delivery system.

Packing in a substance or composite that is biocompatible. They do not involve 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.

3.1.1. Non-Biodegradable Polymeric Implantable Systems

Polymers like silicones, polyurethanes, poly(acrylates), or copolymers like poly(ethylene vinyl acetate) are widely used to manufacture non-biodegradable devices (21-24). As can be seen in Figure No. 4, this form of the implant may be a monolithic or reservoir-type device. Implants of the monolithic form are produced from a polymer matrix wherein the medication is distributed uniformly (25). 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 (26).

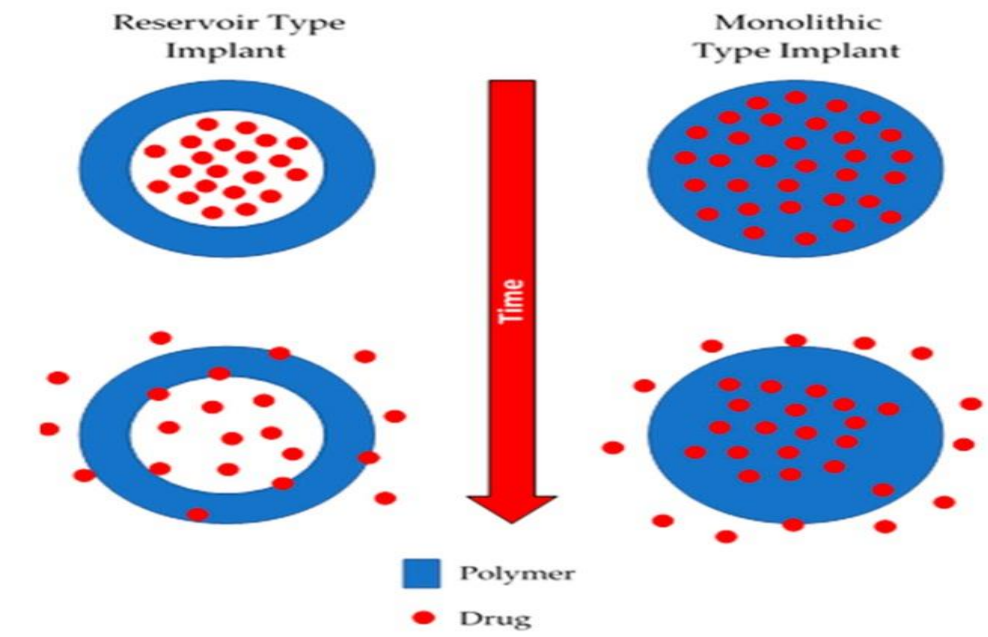


Figure No. 4: An illustration of the reservoir and monolithic type implants.

For contraceptive treatment, non-biodegradable implantable drug delivery systems have been widely utilized. Throughout the lifespan, such devices are architecturally robust even durable. Correctly, the key downside of non-biodegradable devices is that they'll need to be replaced after draining their medication load. The substances utilized to manufacture such devices demonstrate good biocompatibility over a lengthy period, and they can also lead to infection, harm to the tissues, or cosmetic deformity (27). Consequently, after all the medication has also been discharged, it is usually removed to avoid any negative impacts.

3.1.2. 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. 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. The number of potential substances which may be utilized is limited, and as the substance would

be leaving over in the body, the regulatory standards are tighter. Eventually, the primary driving force for the release of the drug is the degradation of the polymeric matrix. It can, therefore, be extremely variable in each individual (28, 29).

3.2. Dynamic or Active Polymeric Implants

There is a positive driving force for such forms of devices to regulate the discharge of medications from the implant. They thus show a higher degree of medication discharge regulation. However, they present greater design prices related to sophistication. Electronic structures made of metallic materials are the plurality of the devices in this class. Even so, just polymeric devices will be mentioned to stay within the range of this report. Pump form devices are essentially interactive delivery systems devices. Osmotic pumping is the principal type of polymeric effective device. As seen in Figure No. 5, such kind of system is mainly made up of a semi-permeable layer that covers a medication reservoir. There should be an orifice on the membrane which will enable medication discharge. In the implant, osmotic patterns will enable a steady inflow of liquid. This phase will result in a rise in the pressure inside the device which will cause the orifice to discharge drugs. This design enables the continuous release of drugs (zero-order kinetics). This type of system permits a favorable rate of release, but there is minimal medication loading.

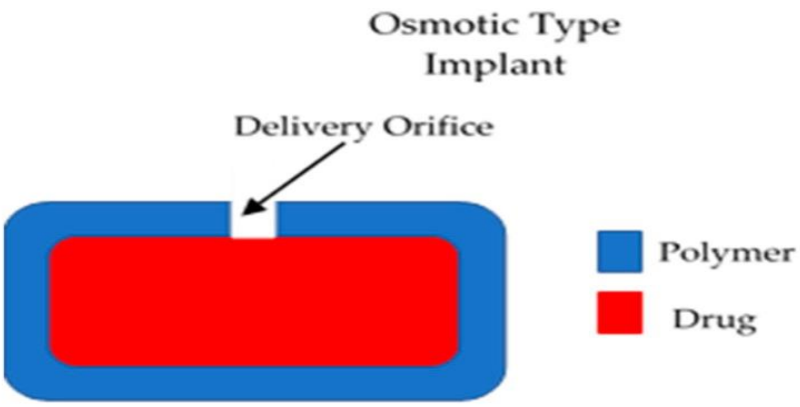


Figure No. 5: An illustration of osmotic implantable drug delivery systems.

4. POLYMERS

Polymers are the backbone of the novel drug delivery system because in the novel drug delivery system sustained or controlled release of drug is necessary that only can be achieved by the use of polymers in the system. Huge numbers of polymers are used in the controlled release formulation as a rate-limiting membrane in the system, some polymers are also used

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 (30). 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:

4.1. Non-biodegradable polymers:

Such polymers are not degraded by the natural biological process in the host body, but the implants consisting of non-biodegradable require minor or small surgery for the removal of the implanted device from the body this is a major disadvantage of the implant with non-biodegradable polymers. Non-biodegradable polymers are widely used in the preparation of contraceptive implantable devices. The implants comprise such polymers that are robust over the lifetime, sometimes these polymers cause infections, tissue injury, and cosmetic disfigurement (31). Non-biodegradable polymers are more commonly used in the preparation of diffusion-controlled implantable drug delivery systems. USFDA approves the non-biodegradable polymers as these are safe for the human body and can be used in the preparation of the implants. The release of the drug will depend on the thickness, polymer permeability, on-site release, and solubility of the drug (32, 33).

Examples: Linear high-density polyethylene (HDPE), Branched low-density polyethylene (LDPE), Ultra-high molecular weight polyethylene (UHMWPE), **Poly (tetrafluoroethylene) (PTFE) (Teflon), Silicones, polyacrylates, and polyurethanes (34-37).**

4.2 .Biodegradable polymers:

These polymers have been developed to eliminate the disadvantages of non-biodegradable polymers. The polymers are obtained either naturally or prepared in the laboratory synthetically. Such polymers degrade inside the host body by a natural biological process that leads to a very important significance is that by using biodegradable polymers eliminating step or removal of the implant is not required. Most of the polymers are degraded by the process of hydrolysis of the polymer chain. In the case of polyanhydrides and polyorthoesters, the degradation of the polymer occurs at only the surface of the polymer that leads to the release rate of the drug from the controlled system because the release of the drug is proportional to the surface area of the system or implant (38, 39). Biodegradable polymers including advantages that are nontoxic, biocompatible, and can easily be purified in a large

quantity. The synthetic biodegradable polymers having advantages over the conventional is that these are compatible with body tissue, and metabolites of these polymers are biocompatible and get easily eliminated from the body. When such biodegradable polymers are used in the drug delivery system the release rate of the drug depends on the degradation of polymer (40).

Table No. 1. Examples of Biodegradable polymers	
Family	**Type**
Polyesters	Polylactic acid, Polyvinyloxyalkonates.
Proteins	Silk, Soy protein, Corn protein.
Polysaccharides	Starch, Cellulose, Xanthan.
Polyphenols	Lignin, Tannin, Humic acid.
Lipids	Waxes, Surfactants.
Specialty polymers	Shellac, Natural rubber, Nylon (from castor oil).

5. 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.

Solvent penetration into the device's matrix controls the speed of discharge for systems dependent on regulated swelling. This is typically much weaker than drug diffusion, which would thus contribute to a slower rate of discharge. Even though diffusion from swollen matrices is primarily liable for the discharge of drugs, depletion of the matrix could also lead to the efficacy of these devices. (41).

On the other hand, osmotic pumping and passive diffusion mechanisms of drug delivery are the most promising for linear delivery of drugs. In this case, the amount of released drug is proportional to the square root of the release time.

Osmosis is the overall movement of water from a dilute solution to a more concentrated solution through a partially permeable membrane, and it causes a hydrostatic pressure difference between the two compartments (42). 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 (43).

Diffusion is a mechanism by which that substance randomly migrates to balance chemical potential or thermodynamic activity through one area to the next. Moving substances are commonly referred to as the diffusants or permeants in this process, and the membrane or matrix in that the diffusant migrates is referred to as the diffusional barrier. Also, the external stage is called the medium. The concentration gradient or diffuser profile inside the diffusional barrier is the driving force of this medication release mechanism (44). The release kinetics of medications will rely on important components in drug delivery systems induced by swelling, osmotic pressure, or passive diffusion, like the molecule's solubility and diffusion coefficient in the polymer; the medication load; as well as the polymer's *in vivo* degradation rate (45).

6. METHODS OF PREPARATION OF IMPLANTS: There are mainly three methods for the preparation of implants that are discussed below:

6.1. Extrusion method: 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^{o}C (46).

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 a 1mm diameter cylindrical punches set.

6.3. 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 100-120^{o} C (47).

7. EVALUATION PARAMETERS OF IMPLANT:

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.

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

B. 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 (48, 49).

C. 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 calculated. Of 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 (50).

D. % 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 (51). % swelling index was determined by the following formula:

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

W2 and W1 are the weight of the implant after 1 hour and in the dry state respectively.

E. *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 the vessel and the optimum temperature and rpm were set, after put the implant in the vessel and start rotating the paddle and then take the sample after

time 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 (52).

F. Stability studies: The purpose of stability testing (the International Conference on Harmonization [ICH], 2004) is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, enabling recommended storage conditions, retest periods, and shelf lives.

Table No. 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

G. 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.

8. CONCLUSION:

The drug can be administered by various routes like oral drug delivery, transdermal, and implant, etc. the majority of medicines are responsible for all the drug delivery systems. An implantable drug delivery system is an efficient and good drug delivery system and releases the drug over a long period. Implantable drug delivery system shows controlled or zero-order release of the drug, and also used for targeted drug delivery system like contraceptive implants that are used to prevent pregnancy set up in uterus such implants are placed into the uterus by small surgery and these implant release the drugs over period up to 10 years.

Implantable drug delivery system having a wide range of advancements like zero-order release, reduced toxicity, targeted drug delivery system, less amount of drug required, enhance individual compliance. Sometimes implants also lead to fewer hospitalizations that develop novel areas in healthcare professions. In this study, it is also described how the implant releases the drug from it and 4 methods of the drug release are also mentioned in the above study. This study will help in a future study on the implantable drug delivery system. This study will also help in the selection of a suitable polymer for implant preparation as the two types of polymers are used that is biodegradable and non-biodegradable polymers. Non-biodegradable polymers are most commonly used in diffusion-controlled implantable systems. This study includes the approaches in the implantable drug delivery system, formulation and preparation of implants, and also the evaluation parameters.

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