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Implantable Drug Delivery Systems: Recent Advances and Future Directions

Farheen Anjum V. Shaikh[1], Zishan K. Momin[2], Nusrat K. Shaikh[3], Jitendra O. Bhangale[4]
[1]Student, Smt. N. M. Padalia Pharmacy College, Navapura, Ahmedabad, Gujarat, India 382210
[2]Student, Smt. N. M. Padalia Pharmacy College, Navapura, Ahmedabad, Gujarat, India 382210
[3]Associate Professor, Smt. N. M. Padalia Pharmacy College, Ahmedabad, Gujarat, 382210, India
[4]Professor and Principal, Smt. N. M. Padalia Pharmacy College, Ahmedabad, Gujarat, 382210, India
Corresponding Author Email id: **jitu2586@gmail.com**

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ABSTRACT:
Medication must be delivered precisely to certain structures in order for therapy to be effective and safe. Ordinary medication administration frequently results in undesired off-target effects and must overcome a variety of transportation challenges in order to acquire and sustain a given drug concentration. One of these challenges is ensuring that patients follow their treatment plan. Implanted drug delivery systems, or IDDSs, offer a solution to these issues. The implanted medication delivery system is a form of new drug delivery method that precisely delivers medication to the implant under controlled conditions. This study addresses the development, advanced assessment criteria, classification, kinds, therapeutic applications, various advantages, current situations, and future prospects of the implanted drug delivery system. Numerous implanted technologies are now being employed for a wide range of medical applications, including birth control, dentistry, ophthalmology, and cancer. However, the high cost of this newly discovered medication delivery technique prevents widespread adoption. Furthermore, extensive scientific studies must be conducted to confirm that the newly produced gadgets meet their requirements for development before they are widely used in populations. In this study, we look at several typical systems that respond to endogenous (e.g., pH, reactive oxygen species, and proteins) and exogenous (e.g., light, sound, electricity, and magnetism) stimuli. Furthermore, a variety of newly described IDDS varieties are investigated, such as "closed-loop" IDDS, radio frequency-controlled IDDS, and self-powered IDDS, as well as other stimulus-responsive systems based on the ideas. The benefits and downsides of various IDDS, bottleneck issues, and potential remedies are ultimately explored to provide guidance for future study. To meet the demand, we finished this study and assessed the clinical situation of the FDA-approved IDDS's prospective uses for foreign body outcomes, which are required for implant and tissue insertion..

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1.0 INTRODUCTION:

Deans by and Parkes' 1938 research on the effects of compressing and subcutaneously (SC) implanting crystalline hormone pellets in castrated male chickens is where implant drug delivery systems (IDDSs) in modern medicine first originated. Folkman and long developed implantable formulations in the 1960s whose drug release rates are regulated by a polymeric membrane (Kumar et al., 2018). [1] They investigated the possible long-term systemic drug delivery advantages of silicone rubber, or Silastic. In 1861, Lafarge originally developed the proposal of an implanted device for the delivery of medicament with sustained release. In the beginning, solid implants carrying steroid hormones had been manufactured as injectable systems for long-term distribution [2].

Subcutaneous drug delivery devices are inserted beneath the skin to allow drugs to enter the bloodstream without the need for further needle jabs. For internal implantations, a sterile drug delivery device with two rod-shaped ends and an extended body can be used. It has also been able to spread drugs steadily at a controlled rate. [3] Surgical procedures, needles, or specialized implantation instruments are frequently utilized for implantation of subcutaneous or intramuscular tissue. Subcutaneous and intramuscular tissues are ideal for implanting drug-depot devices because of their high fat content, which allows for low innervation, restricted innervation, greater hemoperfusion, and delayed drug absorption. [4]

IDDSs are of significant importance to many pharmaceutical types, particularly those that are site-specific, have problematic gastrointestinal absorption, or cannot be taken orally. Some examples include birth control methods like biologics such as insulin or heparin, steroid chemotherapy, antibiotics, and analgesics. Rate-regulated release of substances, environmental stability, biological suitability, rapid sterilization, quickness of manufacture & comparative cheapness, robustness, and a difficult surgical procedure are all requirements for implantable drug delivery in order to promote patient compliance by minimizing the frequency of medicament administration throughout the course of treatment.

Introduced therapeutic devices are primarily used for long-term, continuous pharmaceutical delivery and controlled release.[5] The optimal implanted drug delivery system must be hygienic, biocompatible, and environmentally stable, as well as increase patient acceptability by reducing the frequency of medicine administration during therapy. Release the medicine in a rate-controlled way that improves performance while minimizing side effects; it is simple to give and inexpensive, and medical providers may easily withdraw it to discontinue therapy. [6]

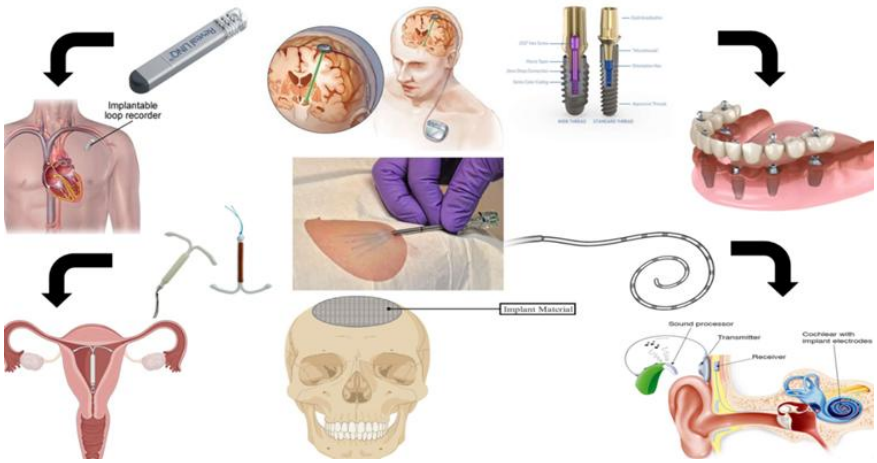

Figure 1: An subcutaneous drug delivery gadget.

1.1. DIVISION OF IMPLANTABLE POLYMERIC MEDICATION DELIVERY GADGET SYSTEMS

Polymers are an important component of installation systems because they provide enhanced and sustained medication release. They function as a rate-limiting barrier in implant systems, and cleanliness and biological biocompatibility must be considered when proposing one. [7]
Two unique categories could be used to classify the substances used for implants.

1.1.1. Inactive Polymeric Implants are:

These are simple, uniform, single-dose devices that are mostly filled with a basic drug in a matrix that is biocompatible. They don't have any mobile parts or methods; instead, they rely on passive diffusion to release the pharmacological dosage. Passive devices belong to two subcategories: biodegradable and non-biodegradable. [8]

A. Not biodegradable polymer implant systems:

Membrane-capped reservoirs and matrix-controlled or polymeric structures are the most common commercial options. Some of the most often used polymers are silicones, polyurethanes, polyacrylates, and heteropolymers such as polyethylene vinyl acetate (PEVA). The medication is distributed equally across the base in a matrix-controlled manner. The medicine that has been implanted progressively releases itself from the delivery process. The dynamics of the drug's evacuation and release rate may change depending on the base's constituent materials. In a reservoir-type device, a non-biodegradable porous layer whose breadth and penetrability parameters interact shields the compact medication from release kinetics. [9, 10]

Given their long lifespan, these instruments should be removed after the medicinal substance load has been completed to minimize any unpleasant side effects, such as infection, tissue deterioration, and cosmetic defects. These types of systems are commonly utilized in contraception. Norplant was among the first reservoir implants to be widely used [11].

B. Biodegradable Polymer Implant Systems:

In addition to the various advantages these systems have over biodegradable ones, their popularity is growing. Synthetic polymers, including polylactic acid (PLA), polycaprolactone (PCL), and polylactic-co-glycolic acid (PLGA), are commonly used in formulation. The inclusion of inert polymers, which break down into little bits and travel through internal absorption and elimination, is its most favorable feature. This improves patient acceptability and compliance by eliminating the need for an incision while removing the device. However, before the medicine can be released from these systems, the polymer's base must break down. This approach varies widely from person to person and is influenced by a number of variables, including fluctuations in body pH and temperature. (See Table 1). [12, 13]

These are also more difficult to manufacture than non-biodegradable materials. Many things were considered when designing them. The immune system's polymer base dissolution profile must be consistent for long-term drug release. A one-order profile with a flattening slab-type construction that does not erode the edges is favored for more equal and consistent medication release. [14]

There are two major groups of biodegradable devices. Figure 2 shows reservoir systems and solid forms. Reservoir systems are similar to non-biodegradable systems in terms of composition and drug release mechanism. However, in physiologically disintegrating systems, the dispersion of chemicals over the membrane breaks faster than the polymers outside the membrane layer. As a result, the barrier stays intact, but the medicine behind it is promptly released. Eventually, this unbroken membrane degrades within the body and is expelled. Another form is unbreakable, in which the medication bonds to a polymeric material before gradually eroding and releasing throughout the body. [15]

Table 1: Biodegradable polymeric examples

Class	Example
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

1.1.2. Dynamic or active polymer implants:

Through established propulsion, this kind of implant controls the drug's release throughout the device. Consequently, it offers a higher standard for medication administration. They use several kinds of energy-dependent positive impulse mechanisms for regulating discharge. Energy can come from hundreds of sources, including osmotic pressure gradients and electromechanical forces. [16]

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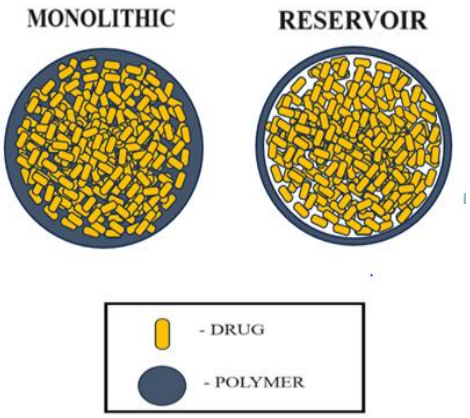

Figure 2: Types of implants are dynamic or active.

2.0 The Present State Of Implantable Drug Delivery System Development:

2.1. Endogenous, Responsive Stimulus Idds:

People's tissues might have different physiological states depending on whether they are healthy or unwell. For example, normal tissues contain a pH around 7.4, whereas cancers have a pH ranging from 5.0 to 6.5. Furthermore, the malignant tissues had four times more GSH than the normal tissue. [17] Furthermore, the development and course of disease is frequently associated with abnormal expression of biomarkers, including proteins, enzymes, & cytokines. To achieve precise regulated release, it is advantageous to induce drug release in an atypical physiological condition or in response to disease indications.

A. Acid-Sensing Drug Release:

Acid-resistant IDDSs often have acid-dependent interactions with conjugate medicines and/or carriers, such as acetals and Schiff bases, along with ortho esters (Figures 3 & 4). Sarmah et al. created a pH-sensitive hydrogel by combining dialdehyde-containing starch derivatives with the mutated amino acid "chitosan," employing dynamic Schiff-based linkages as a pH-sensitive linker. The quantity of ampicillin released was determined by the pH level of the hydrogel; the antibiotic was most active at pH 1.2 and decreased as the pH increased. Bacteriostatic studies revealed that the ampicillin-containing hydrogels remained very effective toward the bacterial strains under study. (18) To create a hydrogel by dynamical acylhydrazone covalent bonds, the intermediate was cross-linked using adipic acid dihydrazide. Diacetone-acrylamide, di (ethyleneglycol) ethyl ether acrylate, and oligo (ethyleneglycol) methyl ether acrylate were the basic components required to make the intermediate.

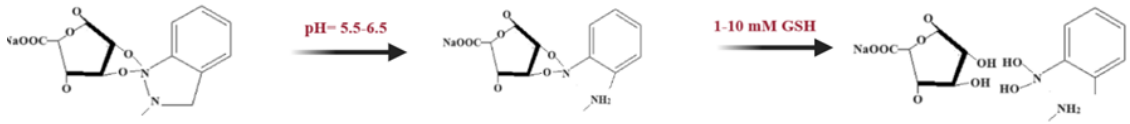

Figure 3: Drug carriers utilize a dual-responsive redox/pH mechanism.

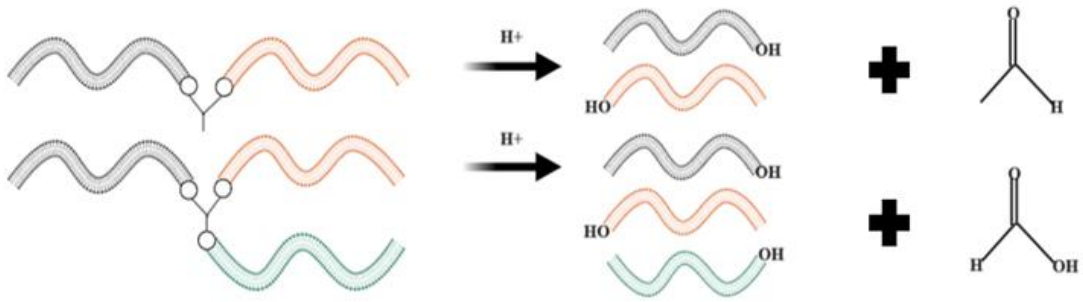

Figure 4: The crystal structure of ortho esters and pH-sensitive acetals.

Because the hydrazone bonds are highly sensitive to pH changes, even a small pH decrease (from 7.4 to 6.8) may lead to a noticeable change in release sequences. The hydrogels released equivalent amounts of both bovine serum albumin and glucose oxidase. At pH 7.4, only around 33% of the glucose oxidase was released in 7 days. However, at a pH of 6.0, the release reached 60% on the first day. (19) Another method for initiating medication release is through acid-catalyzed reactions. Wang et al. developed an implanted chemotherapeutic platform (FeMSN@PG fiber) by combining FeMSNs with PCL-gelatin fibers and injecting Fe_0 nanocrystals into the tiny pores of membrane-like silica nanoparticles (FeMSNs) (Figure 5). After replacing FeMSNs with H+ at the tumor site, they interacted with oxygen to generate H_2O_2. H_2O_2 produced hydroxyl free radicals, which were employed to destroy cancer cells. [20]

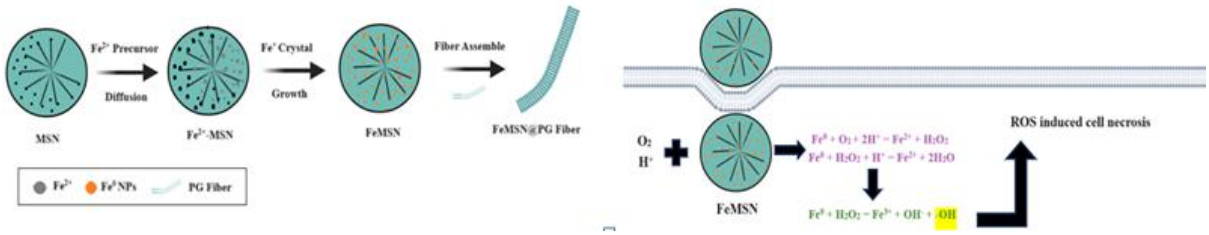

Figure 5: The inserted anticancer platform FeMSN@PG fiber, embedded with Fe_0 nanocrystals, has a cell-killing mechanism as seen in the diagram. Used with permission.

B. ROS- Sensing Drug Released:

The most common types of highly reactive bonds in redox-responsive structures are thioethers, disulfide linkers, and diselenide bonds (Figures 6 & 7). [21-22] The aberrant physiological environment in diseased tissues, such as increased GSH and H_2O_2 levels, can readily reduce or oxidize chemical bonds. ROS include hydrogen peroxide (H_2O_2), superoxide ($\bullet O_2^-$), and singlet oxygen ($^1O_2$), along with hydroxyl radical (•OH). The aberrant generation of ROS is a common characteristic of many diseases. ROS thus serve as effective mediators for initiating the delivery of certain medicines. ROS-sensitive systems, like pH-sensitive systems, use redox-sensitive interactions to link medicines, drugs, or carrier monomers together. ROS-sensitive DDSs can be delivered directly at the site of injury as bulk materials such as hydrogels and polymer patches, enhancing therapy accumulation. Yao et al. fused thioketal linkages into elastic polyurethane (PUTK), which they then electrospun into fiber polyurethane patches. Thioketal connections can be disrupted by ROS, which is overexpressed in myocardial infarction. Methylprednisolone (MP), a load glucocorticoid, gets released as the PUTK structure is destroyed. The PUTK/MP patch dramatically increased angiogenesis, enhanced cardiac function, and scavenged over 60 percent of free radicals in only six hours after 28 days of therapy. [23]

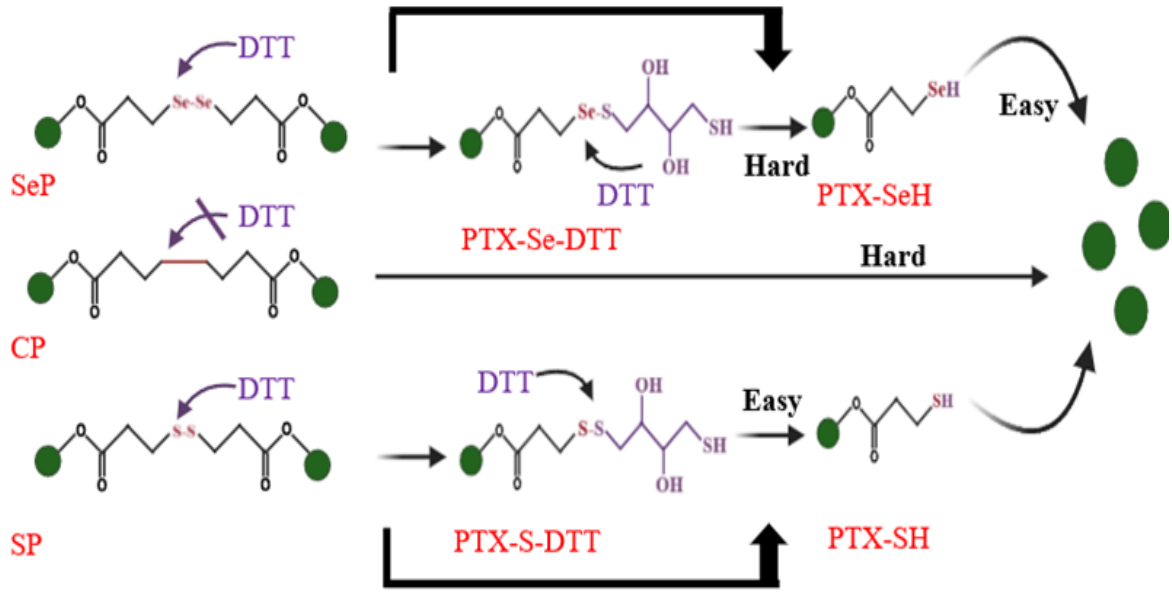

Figure 6: Dithiothreitol (DTT) reduces disulfide and selenide linkages. Used by permission

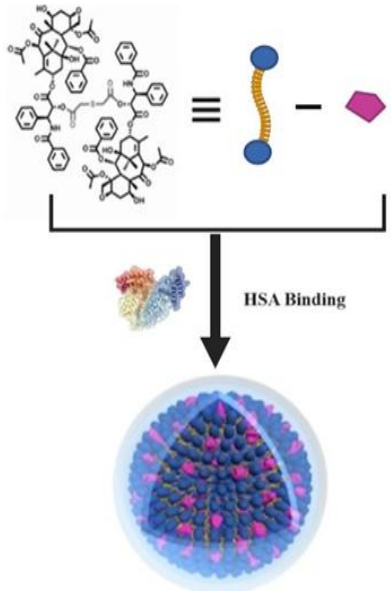

Figure 7: Diagram showing the arrangement of thioether linkages in paclitaxel dimer prodrug PTX2-S and albumin nanoparticles loaded with IR780. Used by permission.

C. Biomolecule-Sensing Drug Release:

Diseases are frequently accompanied by metabolic abnormalities and malfunctions in cells, which cause inappropriate physiological reactions such as protein and enzyme overproduction. Improper physiological activity is an effective approach to induce drug release. Fu et al., for example, used hyaluronic acid-acrylate hydrogel to encapsulate sunitinib nanodrugs, resulting in a matrix of metalloproteinase-responsive hydrogel. While matrix metalloproteinases are significantly expressed in tumor locations, they can contribute to tumor growth by breaking down the normal extracellular matrix and basement membrane. The water-soluble gel structure was cross-linked by sensitivity peptides that matrix metalloproteinases might degrade, causing the hydrogel to collapse and release the sunlight-sensitive nanodrugs it contained. [24] Lu et al. use microfluidic technology to combine hydrogel microspheres coated with vancomycin and calcium phosphate (CaP) nanosheets to create a combined hydrogel for treating bone problems. The hydrogels and vancomycin are covalently bonded by oligonucleotide linkers, which have antibacterial properties and can be precisely destroyed by the microbial nuclease and Ca^{2+} at the site of infection to release vancomycin. Concurrently, calcium phosphate nanosheets were released from its gel-like pores, accelerating bone repair. [25]

2.2. Exogenous Responsive Stimulus Idds:

IDDS that responds to endogenous activation can precisely regulate the release of drugs at the site of injury. However, these methods are unsuitable for purposes where the physiological environment does not very much, such as cancer diagnosis and immunization. Furthermore, endogenous impulses can cause irreversible damage to the carrier material, making "on-off" regulated absorption difficult. The contents of the medication load and the carriers must be carefully regulated to avoid excessively high or low drug levels at the implant site.

Exogenous stimulus-sensitive devices have the ability to release burdens in response to a variety of signals, such as radiation, magnetism, electricity, or ultrasound. Because of their little influence on biological tissues and lack of connections with the cellular signaling system, these signals may improve the spatiotemporal precision of medicine administration while causing minimum harm. [26] Exogenous stimulation-responsive drug delivery systems that can accurately change the position, strength, and duration of the signal application to ensure particular site activation and cargo release have been created via intensive research and development within this concept.

A. Photosensitive IDDS:

As an external stimuli signal, light has several advantages, including non-invasiveness, high spatiotemporal precision, and low cost. When light reaches an item via radio frequency, it can change its condition and cause greater temperatures, breaking down chemical bonds. Thus, light may be used to effectively manage IDDS. Several photosensitive medicine delivery methods have been developed to improve delivery efficacy.

Photosensitive systems require careful wavelength selection. UV radiation, which has a wavelength ranging from 100 to 400 nm, can cause severe damage to tissues and proteins through oxidation and strong bond breakage. Certain polymers and photosensitive small molecules, such as trithiocarbonate, vitamin B12 metabolites, and ruthenium complexes, show potential as alternates to UV-responsive systems since they may detect visible light (400-750 nm). [26] However, the limited rate of penetration of photo-responsive IDDS remains a difficulty. The photosensitive spectral range will be expanded to the near-infrared (NIR I: 700-1000 nm, NIR II: 1000-1700 nm) window, enhancing the possible uses of photo-responsive IDDS. In contrast to light in the UV-visible window, the radiation from the NIR window has a greater capacity to permeate tissue and causes less harm from photosynthesis. [27]

Based on how the response mechanisms organize themselves, two types of photosensitive IDDS might be determined:

1. Light directly activates drug release in direct photoresponsive systems, such as photocleavage, photoisomerization, or photothermal-induced drug release. [28]
2. Light-induced intermediate reaction molecules, including ROS, are commonly used in indirect photo-responsive devices to release loaded medicine. Photosensitizers, which act as ROS makers and relieve load by cleaving ROS-sensitive links, are commonly found in these systems.

B. Ultrasound-sensitive IDDS:

Ultrasound is a nontoxic signal that may infiltrate tissues without causing damage. Hydrogels are widely employed in ultrasound-sensitive implants. Ultrasound extracts medicines from hydrogels, mostly by mechanical and thermal reactions. The principal factors driving drug release are localized high temperatures and the shear stress caused by ultrasonic movement. [29] Although mechanical hits cause permanent flaws in the hydrogel, they cannot give switching control over drug release. Following ultrasonic therapy, self-healing hydrogels may revert to their original state and stop releasing drugs. Furthermore, the use of nanoparticles to isolate the hydrogel from the ultrasonic reaction element is an approach for preventing irreparable damage. The release rate may be regulated by adjusting the ultrasonic energy, frequency, exposure length, and other parameters to offer medication administration on demand.

C. Magnetically sensitive IDDS:

The natural magnetic inertia of biological tissues, which remains unaffected by phototoxicity or penetration depth and is not responsible for tissue damage, is the primary benefit of magnetically sensitive IDDS in the field of biomedicine. The strong magnetic field's little interaction with biological tissue shouldn't harm the biological barrier. Additionally, studies demonstrate that when cells internalize magnetic nanoparticles (MNPs), external magnetic fields can temporarily interrupt endothelial adhesion connections, activate the bypass transport pathway of vascular endothelial cells, raise vascular endothelial permeability, and facilitate the entry of drugs into tissues. [30]

MNPs are essential for magnetic triggering because of their significant magnetic moments and quick response to variations in an external magnetic field. When magnetic triggering occurs depends on how magnetic components respond to external magnetic fields. The two activation mechanisms are magnetic deformation and the magnetothermal effect. High-frequency alternating magnetic fields (AMFs) are usually utilized to thermally deposit MNPs, changing their composition and delivering the cargo. A low-energy AMF or a static magnetic field can flip the MNPs' magnetic moment, disrupting the MNPs and causing their carriers to shift and the cargo to fall out.[31]

D. Radio frequency (RF) field-controlled IDDS:

Radio frequency (RF) is a high-frequency fluctuating electromagnetic wave that can penetrate through biological tissues noninvasively and raise body temperature by speeding up the relative motion of molecules. This influence led to the ejection of the implanted device. Lee et al. created a radio-frequency field-controlled IDDS that includes a wireless temperature sensor for temperature regulation, an oxidizing starch patch (OST) for DOX insertion, and an ultrathin magnesium electronic gadget for heating (Figure 8). To initiate DOX release and promote DOX penetration into brain tissue, the temperature of the IDDS in mice following intracranial implantation was wirelessly regulated by an external alternate radio frequency field. Intracranial insertion allows medications to pass straight across the blood-brain barrier, promoting drug accumulation at injury sites. [32] Radio frequency can be used to transmit commands that control the functioning of implanted devices or to power

them. In an emergency, Joo et al. created a soft implanted medicine delivery device that may be used to treat epilepsy. Wireless voltage induction might be utilized to start subcutaneous medication release, and it could be linked remotely to wearable electronics. The gadget consists of three parts: an electrophysiological sensor, a transmitter, and an implanted drug reservoir. A watch-like power transmitter was worn above the implant site to allow wireless communication, while the drug transmitter was placed beneath the wrist skin. For tracking his physiological status, the patient wore an electrical monitor on his head. When the individual suffers a severe seizure, the sensor detects an aberrant signal and instructs the radio transmitter to wirelessly trigger the implanted drug reservoir, therefore initiating drug release [33].

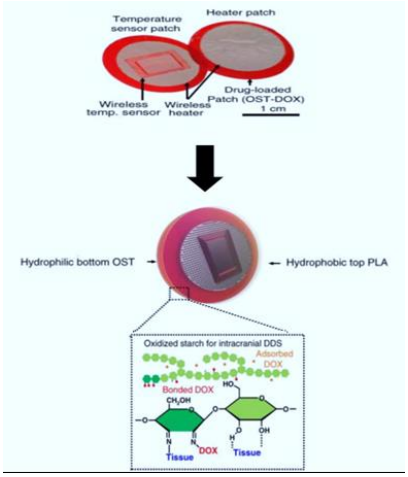

Figure 8: Schematic representation of the drug's molecular structure and the BEP that contains oxidized starch (OST).

E. Electro-sensitive IDDS:

Electro-responsive IDDSs offer distinct advantages that improve the precision and dependability of the drug-releasing system because programming allows for the rapid and exact adjustment of power supply, direction, and other parameters. Furthermore, by integrating the power management system into a microchip and combining it with smart materials, a closed-loop micro-DDS with a sensing function that can interact with patients via electromagnetic signals to change the release mode based on their physiological status, drug dosage, and other parameters can be created. This lays the framework for precision healthcare. An electro-responsive IDDS consists of two basic components: drug loading and power supply. Metal nanoparticles, carbon-based nanomaterials, conductive hydrogels, and conductive polymers are common components of drug delivery systems.[34] The most typically used materials are conductive hydrogels and polymers. Conductive polymers are polymeric compounds that exhibit high electrical conductivity and biocompatibility. Conductive substances have been studied as possible drug delivery methods since Zinger and Miller revealed in the 1980s that a voltage could be used to free ferrocyanide and glutamate from polypyrrole layers. [35] Polyacetylene was the first conductive plastic found, and over 40 years of development and study have resulted in over 25 conductive polymers being employed in drug delivery. [36] The most often utilized materials are polypyrrole (PPy), poly(3,4-ethylenedioxythiophene) (PEDOT), and polyaniline (Figure 9). The previously polyheterocyclic family of conducting polymers, which includes PEDOT and PPy, has been shown to be safe for fibroblasts, endothelial cells, and mesenchymal stem cells. Their biocompatibility is exceptional. [37] Polyaniline- and oligo-aniline-based biomaterials (leucoemeraldine, emeraldine, and pernigraniline bases) have electrical response properties that are influenced by their convertible oxidation patterns (Figure 10). Furthermore, polyaniline and oligo-aniline trap bacteria and liberate acidic ions via electrostatic interactions. Its naturally inherent antibacterial properties make it useful for wound repair and other applications. [38]

Hydrogel polymers may stretch and absorb large amounts of water due to their three-dimensional (3D) network architecture. Hydrogels are widely used in the biomedical disciplines of biologic delivery, tissue engineering, and biosensors due to their extracellular matrix-like properties.[39] However, the low electrical conductivity and dynamic robustness of natural hydrogels restrict their use. By integrating conducting elements into a pure hydrogel, conductive hydrogels could be created, combining the benefits of conductive polymers and hydrogels. These conductive materials may include conductive polymers, metal nanoparticles, and carbon nanomaterials. (40) Introducing conductive components to hydrogels greatly broadens their range of uses by increasing their

conductivity and bestowing additional features such as strong mechanical qualities, stimulus responsiveness, and self-repairing capabilities.

Electrically responsive DDSs are released by the carrier's reversible redox reactions, pH shifts caused by water electrolysis, or changes in the hydrophilic/hydrophobic phase or carrier pore size triggered by electrical stimulation. Because the releasing process involves numerous interlinked processes, it is difficult to pinpoint the primary one. To clarify the major processes, a few case examples were chosen.

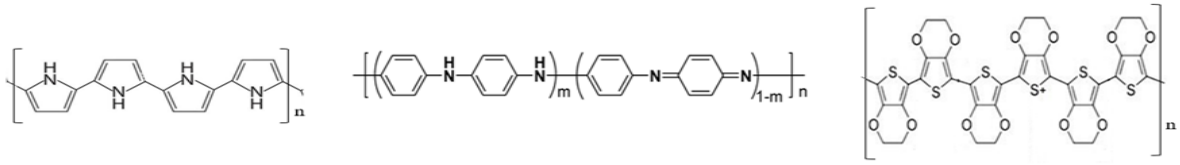

Figure 9:) polypyrrole, polyaniline, and poly (3,4-ethylenedioxythiophene) (PEDOT (PPy) structures.

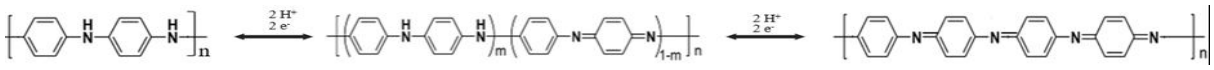

Figure 10: Change from one PANI oxidation state to another.

F. Self-powered IDDS:

As previously stated, electro-responsive IDDS provide a variety of benefits that lead to better regulated release performance. However, one significant problem with electro-responsive IDDS is energy supply. Standard batteries have limitations in terms of battery capacity and possible biosafety risks, putting patients at risk of leaks and necessitating regular battery changes for implanted electronic devices. According to sources, new self-powered technologies, such as triboelectric nanogenerators (TENG) and enzyme biofuel cells (EBFC), have recently been used to power IDDS.

G. Closed-loop design IDDS:

"Closed-loop" IDDSs can self-regulate the release of drugs. They can autonomously administer the proper medicine dosage after detecting aberrant physiological indications in the body. A "closed-loop" DDS is generally made up of three key components: detectors, control algorithms, and medication delivery systems. Sensors recorded physiological signals, which were subsequently transmitted to the monitoring system. When the control system determined that the signal exceeded a typical threshold, it directed the drug delivery system to disperse the medicine. For example, Lee et al. created a "closed-loop" microbubble-boosted focused ultrasound device as an adjuvant therapy for brain cancer. This method comprises two phases: imaging and therapy. When the visual mode is engaged, the microbubbles' location may be tracked via ultrasound imaging. When microbubbles enter the brain, the device detects increased echo signals and promptly changes to therapeutic mode, adjusting the power of the acoustic emission, breaking the blood-brain barrier, and allowing the immune adjuvant to enter the brain tumor. [41]

It is critical to note that "closed-loop" DDS are only appropriate for conditions like diabetes, which produce an elevation in blood glucose levels and have a clear, identifiable biomarker. Similarly, the symptoms, subdivisions, and clinical features of many disorders, such as seizure disorders and Parkinson's disease, are numerous and intricate, with no widely agreed way of determining their degree of severity. As a result, the clinical diagnosis is extremely individualized, making it impossible to verify whether the illness is caused by a set of predetermined control algorithms. [42] Today, "closed-loop" DDS systems are primarily utilized to treat diabetes. While hybrid "closed-loop" systems, such as Insulet's Omnipod 5, Tandem's t:slim X2 pump with Control-IQTM, and Medtronic's 670G, are already on the market, fully computerized "closed-loop" DDS are being researched. (43) In a pilot research, randomly selected teenagers with type 1 diabetes were treated with the Medtronic 670G for more than six months. When compared to the standard therapy group, patients treated with the combined closed-loop approach had significantly lower blood glucose change indicators and hyperglycemia. Their assessments of brain development were also more similar to those of healthy persons. [44]

3.0. Recent Therapeutic Application:

Implantable drug delivery devices can be beneficial for a wide range of therapeutic applications, including women's health, tumors, ophthalmic ailments, pain management, infectious diseases, and disorders of the central nervous system [45, 46].

A few examples of IDDD for any of these classifications are shown in Tables 2–5. IDDD has had a significant impact on women's health, notably the usage of contraception. Norplant was the first implantable contraception technique approved in 1990. Implantable long-acting contraception has been found to be one of the most effective kinds of contraception, with an annual pregnancy incidence of less than one percent for women using these procedures [47, 48].

Table 2: Here are some examples of implanted medicine delivery devices for women's health.

Product Name	Implant Type	Material	Drug Delivered	Indication	References
Norplant®	Sub-cutaneous	Silicone	Levonorgestrel	Contraception	49,50
Jadelle®					
Estring®	Intra-vaginal	Silicone	Estradiol	Menopausal symptoms	51
Nuvaring®	Intra-vaginal	PEVA	Etonogestrel, Ethinylestradiol	Contraception	52,53
Implanon®	Sub-cutaneous	PEVA	Etonogestrel	Contraception	54,55
Nexplanon®					

Systemic distribution is the most common method for administering chemotherapy medicines. However, it frequently entails administering drugs at the maximum permissible dose, which can result in serious side effects such as neutropenia and cardiomyopathy. [56] Systemic exposure can be decreased by implanting a drug delivery device at the site of action, which minimizes harm to healthy tissue. Table 3 shows some instances of implanted drug delivery devices used to treat cancer.

Table 3: Here are some examples of implanted medicine delivery devices used to treat cancer. ND stands for "not revealed."

Product Name	Implant Type	Material	Drug Delivered	Indication	References
Zoladex®	Sub-cutaneous	PLGA	Goserelin	Prostate cancer	57
Prostap®SR	Sub-cutaneous	PLGA	Leuprolide	Prostate cancer	58
Gliadel Wafers®	Intra-tumoral	Silicone	Carmustine (BCNU)	Primary malignant glioma	59,60
Oncogel®	Intra-tumoral	PLGA-PEG-PLGA	Paclitaxel	Oesophageal cancer	61
Vantas®	Sub-cutaneous	Methacrylate basedhydrogel	Histrelin	Prostate cancer	62, 63
GemRIS®	Intra-tumoral	ND	Gemcitabine	Non-muscleinvasive BladderCancer	64

Delivery of medication to the forward area of the eye is challenging due to the ocular environment's specific anatomical and physiological obstacles [65]. To properly treat ocular disorders, the therapeutic ingredient or medication dose must be given to the site of action and maintained there for the length of the therapy. This is especially difficult due to inadequate medicine penetration and retention in the eye via lacrimation, tear dilution, or tear turnover [66]. These problems are exacerbated by challenging device use associated with ocular disorders and low patient compliance [66, 67]. Implantable drug delivery devices alleviate some of these delivery issues by reducing the total number of therapy administrations necessary. They do, however, have several drawbacks, including burst release, poor absorption, and the likelihood of dose dumping [66].

Table 4: Several instances of producing implantable ocular implants are displayed.

Product Name	Implant Type	Material	Drug Delivered	Indication	Reference
Ocusert®	Intra-ocular	PEVA	Pilocarpine, Alginicacid	Open angle glaucoma	68
Retisert®	Intra-ocular	Microcrystalline cellulose, PVA, Magnesium stearate	Fluocinolone	Non-infectious uveitis	69
Vitrasert®	Intra-ocular	PVA, PEVA	Ganciclovir	CMV retinitis in AIDS patients	70

The application of implanted medication delivery systems to treat pain looks to be a viable approach. Chronic pain is not only difficult to manage, but it also increases the risk of addiction, overdose, and death. Implantable medication delivery devices might be effective in the treatment of infectious diseases like tuberculosis (TB). Treatment for TB is long-term, and the medications used may have adverse consequences. These variables contribute to patients' poor adherence to the recommended course of care, which frequently leads to treatment failure and resistance development. An implanted medication delivery device is the best option in this scenario for ensuring patient compliance and treatment completion. When patients do not take antipsychotic medicine as

prescribed, they are more likely to be hospitalized again and have other negative effects. [71] According to estimates, half of those with schizophrenia are missing their medications as recommended [72]. Parenteral administration of antipsychotics has several advantages, including lower drug serum levels, increased bioavailability, and lower drug plasma level volatility. [72] Aside from these benefits, a long-acting implanted medication delivery system would assure full patient compliance. Table 5 illustrates several implanted medication delivery devices used to treat pain, bacterial diseases, and central nervous system problems.

Table 5: lists several implantable medication delivery systems for the treatment of infectious diseases, pain, and abnormalities of the central nervous system. ND=Not disclosed

Therapeutic Indication	Product Name	Implant Type	Material	Drug Delivered	Indication	References
Pain	ND (Axxia Pharmaceuticals)	Sub-cutaneous	PU, PEG/PPG/ PTMEG	Hydromorphine	Chronic neuropathic pain	73
	LiRIS®	Intra-vesical	Silicone	Lidocaine	Interstitial cystitis/bladder pain syndrome	74, 75
	Probuphine®	Sub-cutaneous	PEVA	Buprenorphine	Opioid abuse	76
Infectious Diseases	ND	ND	PLGA	Isoniazid	TB	77
	ND	ND	PLGA	Isoniazid, Pyrazinamide	TB	78
Central Nervous System disorders	Med-Launch	Sub-cutaneous	PLGA	Risperidone	Schizophrenia	79 80
	ND	Sub-cutaneous	PU	Risperidone	Schizophrenia	81
	Risperdal consta®	Sub-cutaneous	PLGA	Risperidone	Schizophrenia	82

4.0 THE FUTURE PROSPECTS FOR IMPLANTABLE DRUG DELIVERY SYSTEMS:

Implantable devices provide several benefits for medicine administration. There are many different types of systems, and technology is always evolving. There are now gene therapy inserts and bioresponsive implantable devices available for study and development. Despite remarkable advances in this sector, implanted devices will always have limitations due to the invasive nature of the therapy. [83]

Numerous investigations are now being undertaken in the field of implanted pharmaceutical delivery devices. However, before most of these preparations can be deployed, much more research is needed in the fields of drug release kinetics, recyclable and biocompatible materials, and system enhancement. According to the article, experts believe that a number of these systems may be tweaked over long periods of time to produce superior negative-order release kinetics profiles in vivo. They will enable long-term use and planning. Proteins and peptides, which are exceedingly unstable when taken orally, are being employed to manufacture an increasing number of these medications. New extended-release delivery methods will allow for the constant distribution of such a treatment over a long period of time, eliminating the need for several dosages. In the next years, it is envisaged that advances in new implanted systems will assist in lowering medication therapy costs, boost medicine effectiveness, and improve patient adherence [84, 85].

This is a very tough topic to tackle because of numerous substantial challenges with sensor technology, such as electrode drift, homogeneity issues with wholly implanted devices, and changes in sensor performance caused by tissue cell overgrowth. Most importantly, these prospective implanted delivery devices might improve the patient's standard of life and independence. [84]

5.0 CONCLUSION:

This article discussed the evolution of implanted controlled-release devices. Smart materials with stimulus-responsive characteristics, including optical, ultrasonic, electric, and magnetic responses, have been used to make films, patches, or micro- and nano-drug storage arrays in order to develop IDDSs. Furthermore, well-designed implanted drug-delivery microelectromechanical devices have been developed, allowing patients to manipulate the pattern of medicine release through contact. Without requiring human assistance, "closed-loop" control IDDSs may independently identify abnormal physiological signals and deliver medicine thanks to integrated sensor and control algorithms. This enables patients to live ordinary lives without being reliant on regular injections, drugs, and tests—especially those with chronic diseases. Self-powered devices, which circumvent the limitations of lithium batteries while boosting their safety and reliability, further address the problem of the supply of energy for implanted devices.

Implantable drug delivery is a unique component that is sometimes disregarded in the manufacture, research, and development of revolutionary medication administration systems in numerous treatments. Numerous investigations are being undertaken on implanted medicine delivery systems. Advanced extended medicine delivery technology will eliminate the need for several doses. In the coming years, the development of innovative implantable frameworks is predicted to reduce drug treatment costs, boost pharmaceutical efficacy, improve patient compliance, and promote medication adequacy. Implanted medication delivery devices can eliminate the need for patient-driven dosage adjustments and administer a substance in a more tailored manner. There are no limits to using implanted pharmaceutical delivery devices compared to oral, intravenous, or topical drug administration.

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