



A REVIEW ON IMPLANTABLE DRUG DELIVERY SYSTEM

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Abstract:

Drug delivery of therapeutics to the target structures is essential for treatment efficiency and safety. Patients' compliance with the treatment schedule remains another challenge. Implantable drug delivery systems (IDDSs) provide a way to solve these problems. IDDSs are bioengineering devices surgically placed inside the patient's tissues to avoid first-pass metabolism and reduce the systemic toxicity of the drug by eluting the therapeutic payload in the vicinity of the target tissues. IDDSs present an impressive example of successful translation of the research and engineering findings to the patient's bedside. It is envisaged that the IDDS technologies will grow exponentially in the coming years. However, to pave the way for this progress, it is essential to learn lessons from the past and present of IDDSs clinical applications.

Keywords: Implantable drug delivery systems, Brain Tumor, Glioma, Radiation Therapy, Chemotherapy, Radiosurgery.

INTRODUCTION

Nicolaus Steno's profound quote, "The Brain, the masterpiece of creation, is almost unknown to us" (1669), echoes the enduring enigma surrounding the intricacies of this remarkably complex organ. Centuries have elapsed, yet the mysteries of the brain continue to captivate the scientific community, beckoning further exploration. Historical traces of the term 'brain' can be traced back to the ancient Egyptian medical text known as the Edwin Smith Papyrus, which dates back to 1500 years before the Christian era. This significant document hails from the 16th and 17th dynasties of the second intermediate period in ancient Egypt. Remarkably, within this papyrus, the earliest known description of the Central Nervous System (CNS) can be found, representing a significant milestone in the history of neuroscience.¹ The human brain ranks among the preeminent and intricate organs in the human body, comprising an impressive array of over 100 billion neurons, intricately interconnected via an extensive network of trillions of synapses. The central nervous system (CNS) comprises both the brain and the spinal cord. CNS is the foundation of our being, intelligence, personality, memories, ideas, speech, and comprehension, as well as our fundamental bodily processes and how we interact with the world around us, are all under its control.² The brain stem, cerebellum, and cerebrum are the three primary areas of the human brain that can be distinguished

despite its enormous interconnections. In addition to linking the brain with the spinal cord and the rest of the body, the brainstem, which is made up of the, midbrain, pons, and medulla, regulates respiration, heart rate, digestion, and other autonomic functions. The cerebellum is crucial for balance and motor control, but it also plays a part in some cognitive processes including attention and language, as well as emotional processes (such as controlling the fear and pleasure responses) and the processing of procedural information.

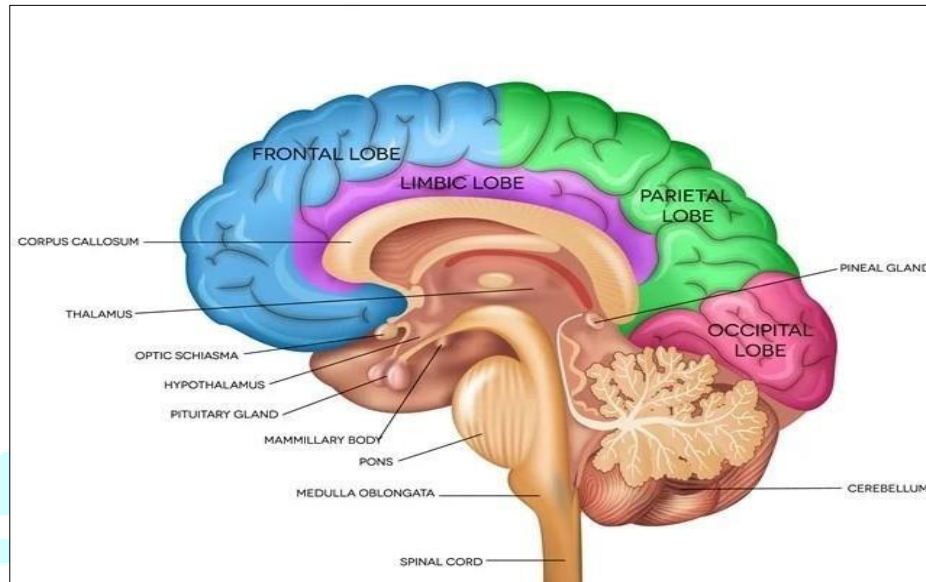


Fig 1. Anatomy of Human brain

Brain tumor

When abnormal cells develop within the brain, a tumor is created. Malignant or cancerous tumors and benign tumors are the two basic categories of tumors. Primary tumors, which begin within the brain, can be distinguished from secondary tumors, also referred to as brain metastasis tumors, which are cancerous growths that have spread from another location.³

In general, there are two types of brain tumors:

1. Primary brain tumor
2. Secondary brain tumor

1. Primary brain tumor

Brains are the origin of primary brain tumors. Any area of the brain or associated structures can become a tumor. The main portion of the brain known as the cerebrum is where the majority of adult brain tumors begin. 24 percent of tumors (or 24%) begin in the meninges. These are the layers of tissue that cover and shield the spinal cord and brain. Approximately one in ten (10%) cancers begin in a brain gland, such as the pituitary or pineal. Gliomas, the most prevalent type of brain tumor, start in the glial (supporting) tissue. Gliomas are classified into numerous categories depending upon the cell that they are thought to have originated from. It also includes oligodendrogliomas, ependymomas, mixed gliomas, and astrocytic tumors (astrocytoma, glioblastoma and anaplastic astrocytoma). Astrocytoma is a member of the glioma tumor category, which makes up 27% of all cancers and 80% of malignant tumors.

Secondary brain tumor

These tumors differ from primary brain tumors in several ways. Secondary brain tumors are tumors brought on by cancer that has its origins elsewhere in the body.⁴ Lung, kidney, breast, stomach, colon, and carcinoma skin cancer are among the cancers that can travel to the brain. This occurs as a result of cancer cells separating from the main malignancy and migrating through the bloodstream to colonize the brain. They may start to develop into new tumors there.⁵ Metastasis is the medical term for the proliferation of cancer within the body. The disease and term for cancer that has spread to the brain are the same as those for the primary (original) malignancy. Brain metastases can occur in up to 30% of persons with initial malignancies in organs other than the brain. Every year, secondary brain cancer cases are at least two times more common than malignant original brain cancer.



Fig. 2. Representation of Brain Tumor

Glioma

Glial cells, which serve to maintain and protect the neurons, proliferate unchecked to become gliomas, which are benign brain tumors. The term "glioma" is used to refer to all neoplasms that develop from the brain's glial cells, which also include astrocytes, oligodendrocytes, and ependymal cells. Nearly 50% of initial brain tumors are caused by it. Brain cancers called gliomas are hypothesized to develop from neuroglial stem or progenitor cells. They have historically been categorized as astrocytic, oligodendroglial, or ependymal tumors according to their histological appearance. According to cell origin and behavior, brain tumors are categorized by the WHO from less invasive (benign) to most aggressive (malignant). Tumors are characterized by giving them a grade, which describes the pace of growth and ranges from Grade I (least harmful) to Grade IV (most harmful). According to WHO classification, Grade IV signifies the prevailing and highly aggressive manifestation of brain tumor pathology, i.e., Glioblastoma Multiforme.

Epidemiology of Glioma:

According to Global Cancer Statistics 2020, there were 308,102 new cases of brain and nervous system malignancies diagnosed in 2020, and there were 251,329 fatalities. Astrocytic (WHO grades I–IV) tumors are prevalent in adults aged 75–84, while oligodendroglial (WHO grades II–III) tumors are prevalent in people aged 34–44. These intracranial tumors are categorized based on WHO classification. The two types of brain tumors that affect adults the most frequently are these two. Pilocytic astrocytoma, in contrast, is the most

frequent malignancy in children (0–14 years old). Glioblastoma has a relatively poor prognosis compared to other intracranial tumors, with a five-year survival rate of less than 3% of patients.⁵

Brain cancer scenario in India

The National Cancer Registry is kept up to date at all tertiary level hospitals by our country's national regulatory organization, the Indian Council for Medical Research (ICMR). A 2007 study by Jalali et al. examined patients who had been enrolled in the neurooncology clinic at Tata Memorial hospital for a year. They discovered 580 primary brain tumor cases and 78 incidences of brain metastasis. 238 of the primary tumor patients appeared between the ages of 19 and 40, while 43 instances were younger than six years. Only 9% of all cases were older than 60. The median age at which benign, malignant, and metastatic tumors presented was 34, 37, and 49.5 years, respectively. Similar occurrences were seen at ages 29, 63, and 61, meaning they occurred at least a generation earlier than the statistics from wealthy countries. There have been observations regarding diversity in histology, assertiveness, and subsequent clinical outcomes in addition to the variance in median age.⁶

Brain Tumor Classification according to GRADE

Brain tumors are classified in the medical community according to their Grade. The conduct of a tumor under microscopic inspection helps determine its Grade.

GRADE I: The term "benign" refers to these tumors. They resemble normal brain cells almost exactly, and they grow more slowly than other grades. The initial stage of a tumor is this.

GRADE II: These tumors are classified as malignant GRADE I tumors and as low-grade GRADE II tumors.

GRADE III: High grade tumors are those with a GRADE of III or IV. Their behavior differs greatly from that of normal cells, necessitating immediate medical attention.

GRADE IV: Such tumor types develop the fastest and exhibit the most aberrant behavior compared to other grades.⁷

Current methodology for treatment of brain tumors

Adult patients who have tumors of the brain or spinal cord might get a variety of treatments. There are four common therapy types:

Watchful waiting

A patient's status is carefully monitored as they wait for symptoms to develop or alter before starting any treatment.

Surgery

The surgeon will work to remove as much of the brain tumor as feasible throughout the procedure, focusing on areas that are accessible and can be safely operated upon. There are dangers associated with brain tumor surgery, including bleeding and infection. Depending on whatever area of the brain the tumor is in, there may be additional hazards. For instance, there may be a risk of loss of vision following surgery on a tumor close to the nerves that control the eyes.

Radiation Therapy

Radiation therapy uses X-rays or photons characterized as high-energy beams, for eradicating tumor cells through targeted and controlled means. As an aspect of brachytherapy, radiation may occasionally be administered into the body close to the brain tumor or it may come through an instrument outside the body. Either the entire brain will receive the external beam radiotherapy, or limited to the region affected by the tumor within the brain. Malignant tumor that has progressed towards the brain via another anatomical region is most frequently treated with whole brain radiation. Depending on the radiation type and dosage, radiation therapy side effects can vary. Generally speaking, it may result in weariness, headaches, and irritated scalp.⁸

Radiosurgery

In a traditional sense, stereotactic radiation therapy is not a form of surgery. Instead, radiosurgery, which delivers a highly targeted form of radiation treatment using multiple radiation beams, kills the malignant cells in a very tiny region. The brain tumor is exposed to an extremely high dose, at the point where all the radiation beams arrive together, which kills the tumor cells even though each radiation beam isn't especially potent. In most situations, radiosurgery is performed in a single session, and the patient is able to return home the same day. There may be negative consequences like fatigue, headaches, and nausea.⁹

Chemotherapy

This process employs certain drugs with intent to destroy cancer cells. Both intravenously and orally administered chemotherapy drugs are available. Temozolomide (Temodar) stands as the foremost chemotherapy agent typically employed in the treatment of brain tumors, administered through both oral tablet and injectable routes. Depending upon the type of cancer, there are numerous more chemotherapy medications that can be employed. A new type of chemotherapy may be given during surgery. After completely or partially removing the brain tumor, the surgeon may place a couple of disk-shaped wafers inside the area left by the tumor. Over the following few days, these wafers gradually release the medication. The type and dosage of medications the patient takes during chemotherapy affect the adverse effects. Chemotherapy can result in hair loss, nausea, and vomiting.¹⁰

Currently used chemotherapeutic medicines for brain tumors

Carmustine (BCNU)

Cisplatin

Irinotecan

Lomustine (CCNU)

Procarbazine

Temozolomide

Vincristine

Chemotherapeutic medication side effects

The most harmful side effect of chemotherapy is the total destruction of the immune system. Hair loss is a typical side effect. Additionally, chemotherapy damages the cells that line the digestive tract, leading to unpleasant side effects such as nausea, anorexia, diarrhea, vomiting, and lip and mouth sores. Additionally, the skin may thin. Depression of the bone marrow, light-headedness, pain in the body, fever, a general feeling of melancholy, and exhaustion. Certain chemotherapy medications have the potential to harm nerve and muscle tissue, which could lead to unpleasant symptoms such as difficulties walking, loss of balance, vision issues, clumsiness, brain fog, hearing loss, trembling, tremors, and burning or tingling sensation. In female such therapy can harm the female genital system, including the ovaries, leading to either temporary or permanent infertility.¹⁰

Limitations of systemic chemotherapy for brain tumors

Chemotherapeutic chemicals are administered directly or permitted to enter the blood stream when using a systemic chemotherapy method. The BBB is the most significant physiological barrier in the brain and places restrictions on the unrestricted entry of tiny compounds and chemotherapeutics into the brain. Passive diffusion of exogenous chemicals into the brain is restricted by the BBB, which serves as a physical and functional barrier.¹¹ A significant barrier to the effective transport of CNS medicines to the brain is the BBB's distinct vasculature compared to blood arteries in the rest of the body. The protective covering of endothelial cells lining the tiny blood veins within the brain parenchyma makes up the majority of the BBB. Tight junctions that prevent free movement of chemicals and ions between cells across the endothelium layer connect these cells to one another. The transfer of substances via the cells is a prerequisite for substances that must pass through the barrier to enter or exit the brain. Non-fenestrated brain capillary endothelial cells with tight connections are the primary structural element of the BBB. Pericytes and astrocytes, which help to stabilize vessel walls and control vessel development, support these endothelial cells.¹²

There are two strategies being developed at the moment to enhance the cancer treatments already available. The development of NDDS, which aims to deliver medications specifically to cancer cells and avoid the source of toxicity as well as help retain medications at therapeutic concentrations for long periods of time, is the other approach. One approach involves using proteomics and genomics research to identify new tumor-specific molecular targets. In this context, the idea of nanomedicine—using drug delivery systems that are nanosized (1–1000 nm) to target tumors—has shown a lot of potential. When referring to medications that contain many components, the word "nanomedicines" is frequently used as a general phrase for referring to nano-sized pharmaceuticals and drug delivery systems. These polymer-based nanoparticles, which can be either natural or synthetic, are used to create medications that are better targeted and released under regulated conditions. For localized drug delivery and regulated drug release over time, entrapped drug with biodegradable polymers can be injected into the body.¹³ For instance, leuprolide (Lupron depot) and small polymer rods called goserelin (Zoladex) that contain analogues of luteinizing hormone-releasing hormone (LHRH) are frequently used to treat prostate cancer. Therapy is particularly convenient for patients to utilize since dosages of the anti-tumor peptide remain constant for approximately three months as the polymer progressively degrades. Carmustine (Gliadel), a different biodegradable polymeric implant for brain cancer (glioblastoma multiforme), carries the alkylating compound bis (2-chloroethyl)nitrosourea (BCNU) in tiny polymer discs made of a biodegradable polyanhydride polymer. After the tumor has been surgically removed, these discs are inserted into the brain. They gradually disintegrate to distribute the medication locally and stop the growth of tumors. It has

taken a lot of work to transform them into nanoscale vectors that can be targeted more precisely at the tumor.¹⁴

Targeted drug therapy

Targeted drugs are focused on specific abnormalities that are prevalent in cancer cells, allowing pharmacological therapies to effectively eliminate cancer cells by impeding these aberrant processes.¹⁵ Bevacizumab (Avastin), a targeted medication therapy, is used to treat glioblastoma, a specific type of brain cancer. This medication, administered intravenously (via a vein), inhibits the formation of new blood vessels, leading to the deprivation of blood supply to the tumor, subsequently resulting in the eradication of tumor cells. A benign (noncancerous) brain tumor that develops in persons with the hereditary condition tuberous sclerosis is treated with everolimus (Afinitor). Everolimus inhibits a body enzyme involved in the development of cancer cells. The The blood-brain barrier (BBB) acts as a hindrance to the diffusion of certain medication molecules into brain tumors, thereby restricting their ability to traverse the brain tissue effectively.

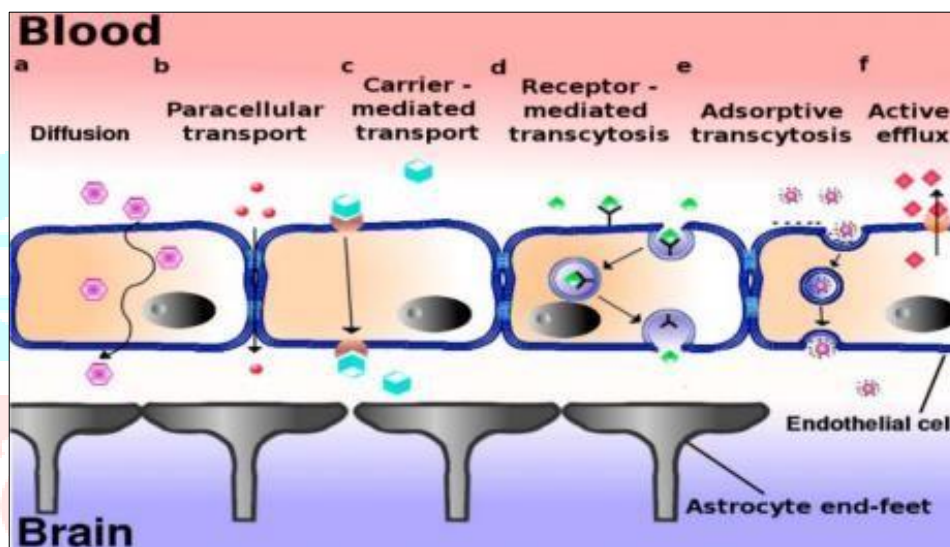


Fig.3. Blood Brain Barrier

Implantable drug delivery system

90% of medications are administered orally, but oral drug delivery of the medications results in unreliable plasma concentration in the circulatory system, some medications degrade in the stomach's acidic pH, some medications irritate the GI tract, and these medications also exhibit first order and also the initial metabolism of the medication, which reduces the medication's concentration in the blood. Since the ingestion method of drug administration has drawbacks and difficulties, it is necessary to find solutions to these issues. For example, certain medications cannot be administered via the oral route during administration because they degrade at acidic or alkaline pH levels and/or by digestive juices or digestive enzymes. In order to find the most effective method for delivering drugs into the human body, several trials and research projects are being conducted worldwide.¹⁶

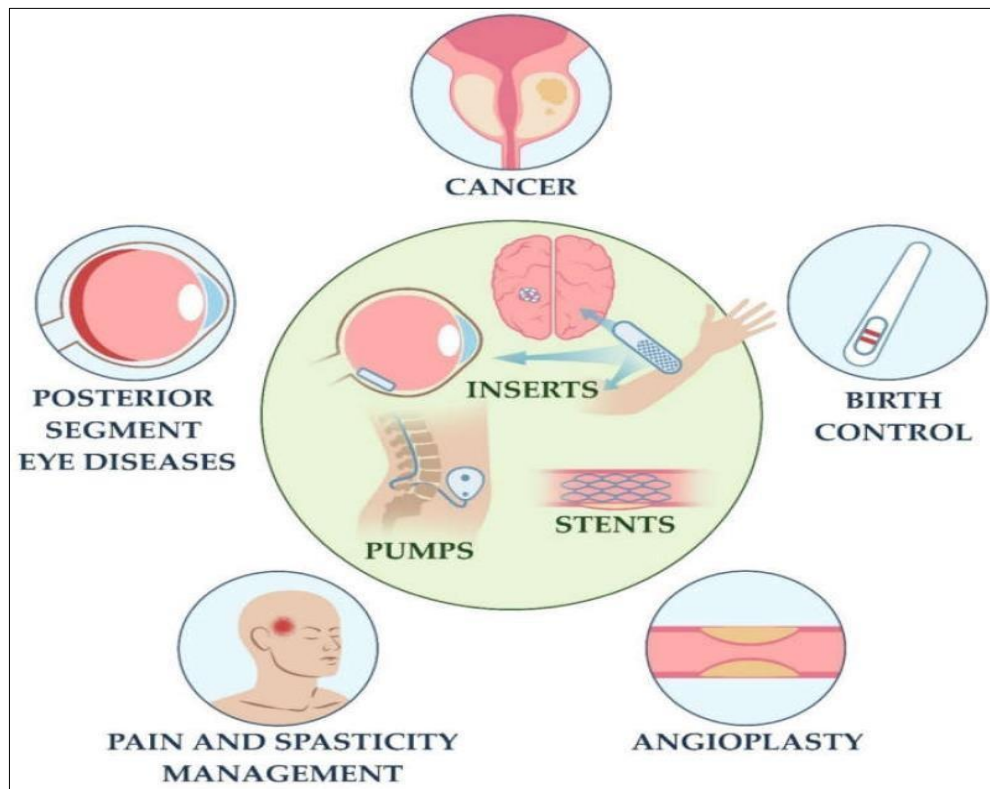


Fig.4. Commercially available IDDSs and their applications

IDEAL PROPERTIES OF IMPLANTABLE DEVICES

To enhance patient adherence and compliance, the dosing frequency should be decreased, and the medication should be released consistently during the course of treatment.

The implant needs to be inexpensive and simple to develop.

Medical professionals should be able to remove the implant with ease to stop treatment.

They should exhibit controlled or zero-order drug release kinetics, thereby ensuring efficacious treatment outcomes and mitigating the incidence of side effects.

It should be simple to sterilize the implantable device.

Merits of the IDDM

Sustained zero-order drug release over a prolonged duration.

Better patient compliance as a result of a reduction in dose frequency.

The implanted medication delivery device can provide targeted drug delivery.

Bypass the first-pass effect.

Safe, effective and decreased side effects.

Enhanced stability of drugs.

Enhanced drug bioavailability.

Ease in discontinuation of therapy when required.

Demerits of IDDM

Large-sized implants necessitate surgical intervention, entailing a potentially painful procedure.

Discontinuation of the therapy is not amenable to a straightforward approach.

Interactions between the host organism and the implant.

Insufficient release of the active pharmaceutical ingredient(API).



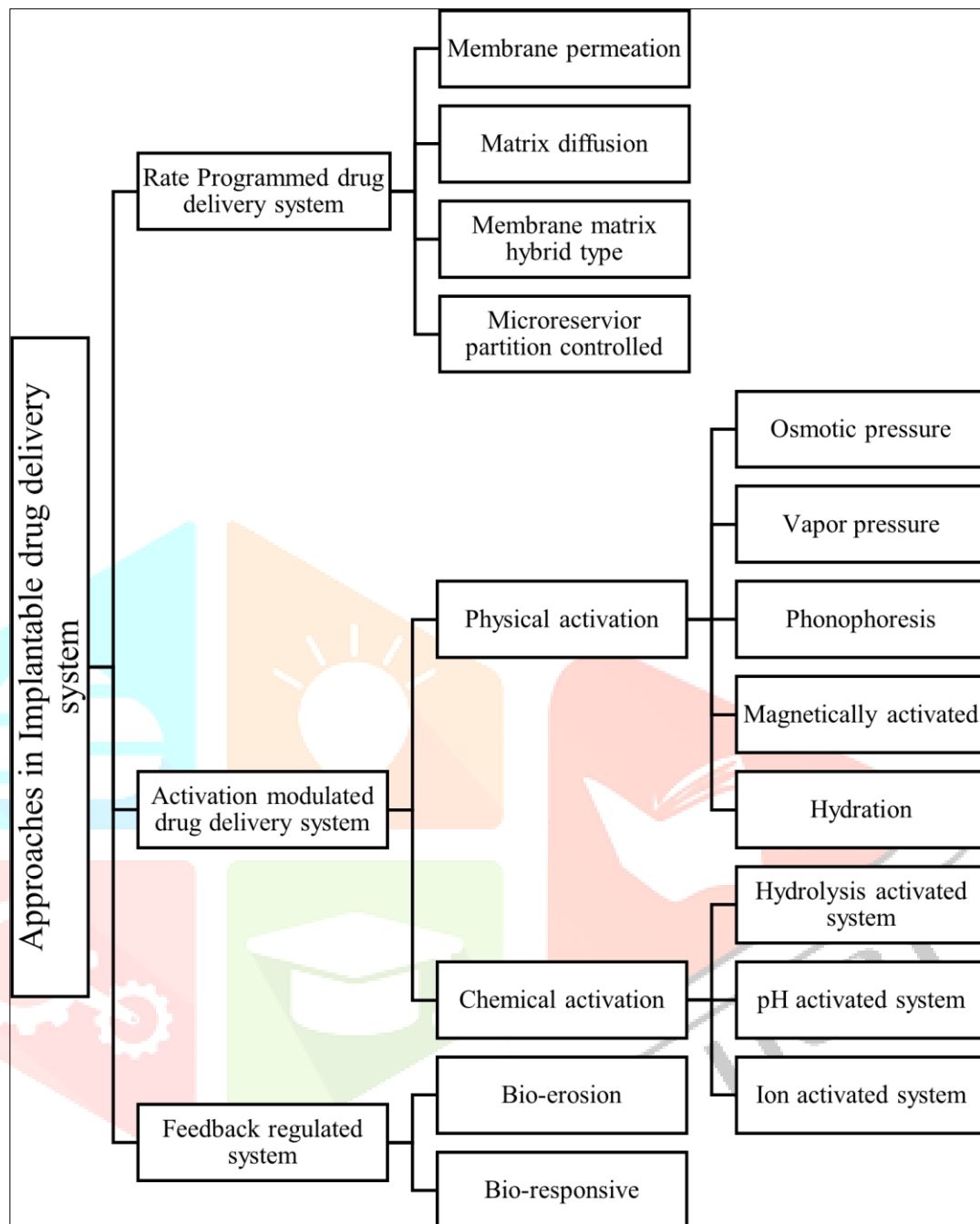


Fig. 5. Approaches in Implantable drug delivery system

Implantable Polymeric System Classification:

Although classifying the IDDS is a difficult task, it is divided into many both active and passive implantable device types. Since both the non- biodegradable and biologically degradable processes use the passive diffusion releasing method, the passive implantable instrument is again broadly divided into these two categories. In contrast, the active system requires energy to release the drug.¹⁷

Passive implants

Passive implants often consist of easy medications and appear to be rather simple, uniform, and single implants. incorporating a biocompatible material or composite. According to their description, they don't use any mechanical components and instead rely on a passive, diffusion-mediated method to slow down drug release.¹⁸ Treatment kinetic studies are relatively customizable due to the medicine choice, dosage, overall device structure, polymer matrix, and surface characteristics.¹⁹

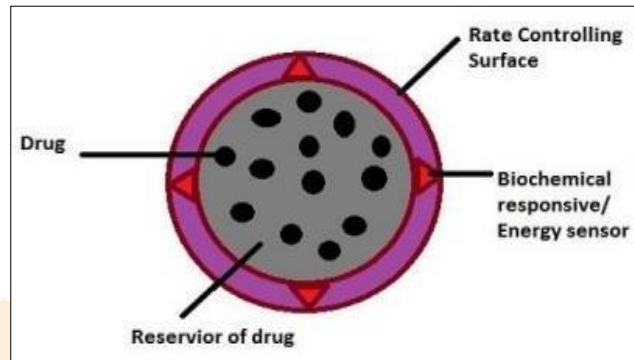


Fig. 6. Feedback regulated drug delivery system

Non-Biodegradable Polymeric Implantable Systems

Polymers like poly(acrylates), polyurethanes, silicones, or copolymers like poly (ethylene vinyl acetate) are frequently used in the production of non- biodegradable devices. Fig. 7 illustrates a reservoir- or monolithic-type implant of this type. A polymer matrix is used to create monolithic implants, and the medication is equally distributed throughout. Reservoir-type devices, on the other hand, contain a porous, non-biodegradable coating over a light pharmaceutical core. The release kinetics will be controlled by the drug's capacity to pass through the membrane and the thickness of its outer layer.

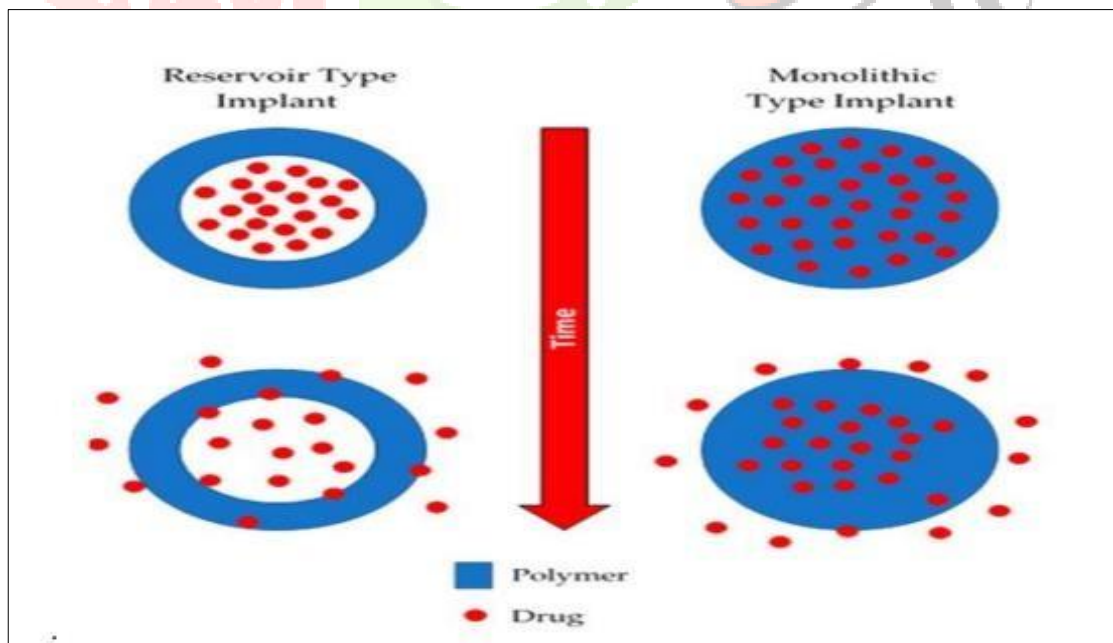


Fig. 7. An illustration of the reservoir and monolithic type implants

Biodegradable Polymeric Implants

Implants made of biodegradable materials were initially created to address the problems with non-biodegradable technologies.²⁰ These gadgets are constructed of polymers or block copolymers that can be disassembled into minute pieces and either breathed or absorbed by the body. Commonly utilized polymers include poly(caprolactone), poly(lactic acid), and poly(lactic-co-glycolic acid). Such compounds have been carefully researched and their degradation kinetics could be easily modified to change the rate of medication release. The shortcomings of non-biodegradable technology have been addressed by the development of implants that naturally disintegrate.²¹ These gadgets are constructed from polymers or block copolymers, which can be broken down into tiny pieces and inhaled or absorbed by the body. Commonly used polymers include poly(lacticacid), poly(caprolactone), and poly(lactic-co-glycolic acid) (PLGA). Such compounds have undergone extensive examination, and their kinetics of deterioration could be easily modified to alter the pace of drug release.²²

Active or Dynamic Polymeric Implants

Positive forces are driving the development of such technology to regulate drug release from the implant. As a result, they display increased drug discharge regulation. They do offer more pricey designs, though, which are linked to elegance. The majority of the devices in this class are electronic structures based on metallic materials.²³ Even though only polymeric devices will be covered in order to stay within the purview of this report. Devices for interactive delivery systems resemble pumps in essence. Osmotic pumping is the most prevalent type of polymeric functional device. As seen in Fig. the main component of such a system is a membrane that is semi-permeable that protects a drug reservoir. A hole that can be utilized for dispensing medication should be present in the membrane. The implant's osmotic patterns will allow for a continuous flow of fluids. The device's pressure within will rise during this phase, which will cause the incision to release medication. Drugs can be continually delivered because of the zero-order kinetics of this architecture.²⁴

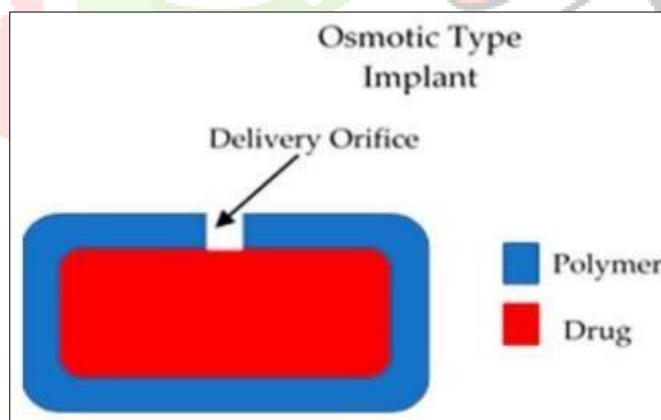


Fig. 8. A representation of osmotic IDDM

IMPLANTS' PREPARATION TECHNIQUES:

Extrusion method:

A selected medication is first dissolved in the proper solvent system to produce a solution. The polymer is then gradually added to the mixture and allowed to soak for 10 to 15 minutes. A consistent mixture of the created swelling material resulted in a product that resembled dough. The dough was placed inside the compressor cylinder and extruded into the form of long rods using the assist nozzle. The implants were initially sized properly and dried at 40 degrees Celsius after spending the previous night at room temperature.²⁵

Advantages

Continuous manufacturing process allows for high throughput.

Precise control over implant shape and size.

Suitable for a wide range of materials, including metals and polymers.

Compression Method

The medicine and polymer were dissolved to produce the solution. The resulting solution underwent freeze-drying to produce a uniform cake. The cake's compression made it possible for the implant to develop. Implants have been produced utilizing a Carver hydraulic press at a pressure of 1 metric ton using a stainless-steel system designed for such purposes and a set of 1mm diameter cylindrical punches.

Advantages

Well-suited for large-scale production of implants.

Lower processing temperatures compared to extrusion, reducing material degradation risks.

Enables the fabrication of intricate implant shapes.

Molding Method

The polymer-drug solution was initially formulated using an appropriate solvent system, followed by subjecting it to lyophilization, resulting in the formation of a homogeneous cake. Subsequently, the prepared cake was molded into rods using a Teflon sheet heated on a hot plate at temperatures ranging from 100 to 120°C.

Advantages

Low-cost technique suitable for mass production.

Versatile for producing implants of various shapes and sizes.

Reduced risk of material degradation compared to high-temperature processes.

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