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Pulsatile Drug Delivery: Harmonizing Therapeutics With The Body's Clock

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ABSTRACT

Circadian rhythms govern critical physiological functions, influencing disease progression and therapeutic outcomes. Pulsatile Drug Delivery Systems (PDDS) have emerged as a groundbreaking approach in drug delivery, releasing therapeutic agents in a time-aligned manner to match the body's inherent rhythms. This review explores the mechanistic basis, classification, and applications of PDDS, including time-controlled, stimuli-responsive, and osmotic systems. Special focus is given to aligning drug delivery with circadian oscillations in diseases such as asthma, arthritis, diabetes, and cancer. Recent research into enzyme, pH, glucose, and temperature-responsive platforms is discussed, highlighting clinical potential and translational barriers. This paper underscores the role of PDDS in optimizing drug efficacy, minimizing toxicity, and advancing circadian-based pharmacotherapy.

Keywords: *Chronotherapy, Pulsatile Drug Delivery System (PDDS), Circadian Rhythm, Smart Polymers, Lag time and Chronopharmacology*

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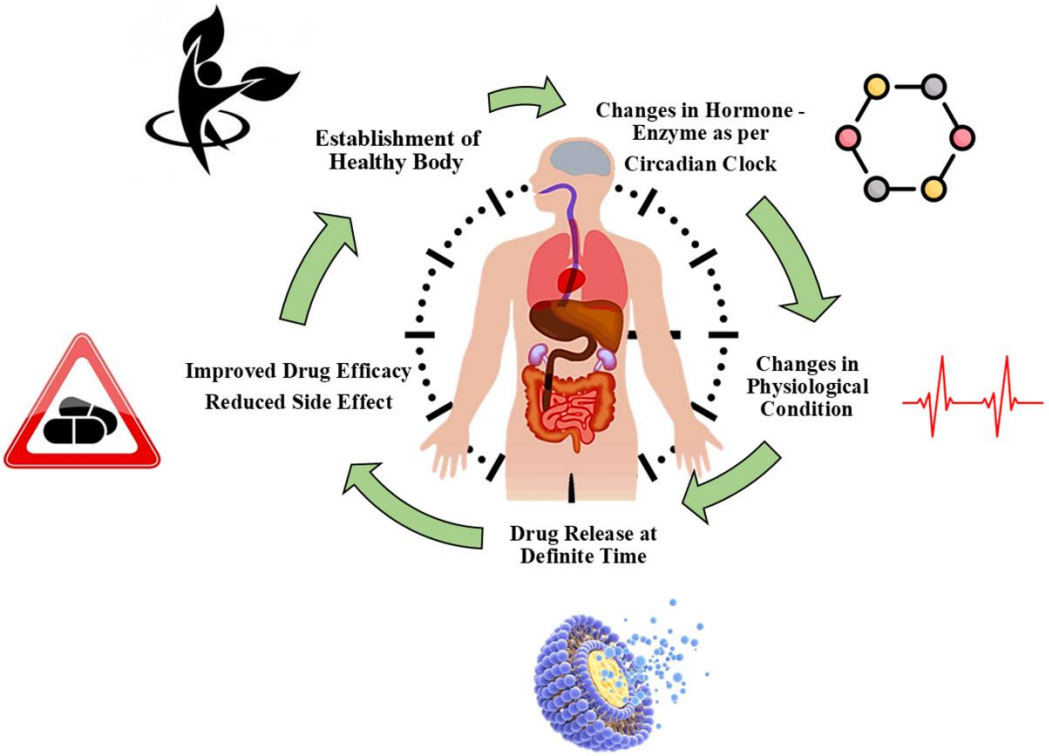
1. INTRODUCTION

Imagine a world where body's natural clock governs every physiological function from the rise and fall of hormones to the timing of peak organ function. This internal clock, known as the circadian rhythm, orchestrates various biological processes in a 24-hour cycle, regulating sleep, metabolism, immune responses, and cognitive function. The synchronization of these rhythms with external cues, such as light and food intake, is crucial to maintaining optimal health and well-being. However, modern lifestyles, including erratic sleep patterns, night shifts, jet lag, and exposure to artificial light, disrupt this delicate balance, leading to disturbances in circadian rhythm[1].

Chronotherapy refers to the alignment of medical treatment with body's circadian rhythms in order to maximize therapeutic action and minimize side effects. When disrupted, this delicate synchronization can contribute to the onset of several diseases, including metabolic disorders (e.g., diabetes and obesity), cardiovascular diseases (e.g., hypertension and myocardial infarction), and neurodegenerative conditions (e.g., Alzheimer's and Parkinson's disease)[2].

For instance, individuals working night shifts or suffering from chronic sleep deprivation often exhibit altered hormonal secretion, increased oxidative stress, and a heightened inflammatory response, which significantly impact overall health[3]. To address these challenges, Pulsatile Drug Delivery Systems (PDDS) have emerged as a revolutionary approach in pharmacotherapy.

GRAPHICAL ABSTRACT



1.1 Pulsatile Drug Delivery System

The Pulsatile Drug Delivery System (PDDS) is an advanced drug delivery method intended to distribute medications in a site-specific, time-dependent, and regulated manner[4]. In contrast to traditional sustained-release systems, which administer medication frequently, PDDS distributes the medicine in a burst (pulse) at a predetermined time to correspond with the symptoms of the disease or the body's biological rhythms (chronotherapy).

PDDS ensure that drugs are administered precisely when the body needs them the most, mimicking natural biological rhythms. This approach is particularly beneficial for diseases with time-dependent symptom patterns[5].

Consider a patient with asthma who experiences peak symptoms during the early morning hours due to circadian variations in airway resistance and inflammatory mediator levels. A standard medication may not provide adequate relief due to its uniform release pattern, whereas a pulsatile system can be programmed to release the drug just before symptoms intensify, ensuring effective control[6]. Similarly, patients with rheumatoid arthritis often suffer from severe morning stiffness due to elevated inflammatory cytokines overnight. A PDDS can ensure that anti-inflammatory drugs are released in the early morning hours, improving mobility and reducing discomfort.

The significance of PDDS lies in its ability to align drug administration with the body's natural rhythms, optimizing therapeutic efficacy while minimizing side effects. By targeting the exact time of need, these systems enhance patient compliance, reduce drug resistance, and improve overall treatment outcomes[7]. The following sections delve deeper into the mechanisms, formulation strategies, and advancements in PDDS, highlighting its transformative role in modern medicine.

Certain diseases exhibit circadian rhythms where symptoms worsen at specific times of the day. PDDS are crucial for treating these conditions efficiently, ensuring optimal drug levels at the time of greatest need.

2. CIRCADIAN RHYTHM: BODY'S INTERNAL CLOCK

2.1 The 24-Hour Symphony

Our bodies are intricately designed to function in harmony with the Earth's rotation. This internal synchronization is orchestrated by the circadian rhythm, a complex biological process that regulates various physiological functions over a 24-hour cycle (fig. 1) depicts bodies cyclic rhythm showing some important physiological events taking place at specific time. Melatonin, a key hormone produced by the pineal gland plays a role in regulating the body's circadian rhythm that is

the sleep-wake cycle[8]. The secretion of this hormone is highly influenced by light. The gland starts producing melatonin, in response of darkness in the evening, this peaking during the night and tapering off towards morning. This hormone is also involved in temperature regulation. As melatonin levels rise in the evening, the body's temperature drops, contributing to the feeling of sleepiness. Body's blood pressure naturally decreases during the night as the body enters a state of rest and recovery, with the lowest levels around 2-4 AM and further it rises gradually after waking, peaking by 10-12 PM, and stays elevated throughout the day[9,10]. Decline again, reaching a lower point in the evening before bedtime. Maintaining optimum health and well-being requires that these cycles be in synchronization with outside stimuli, such as light and food consumption[11].

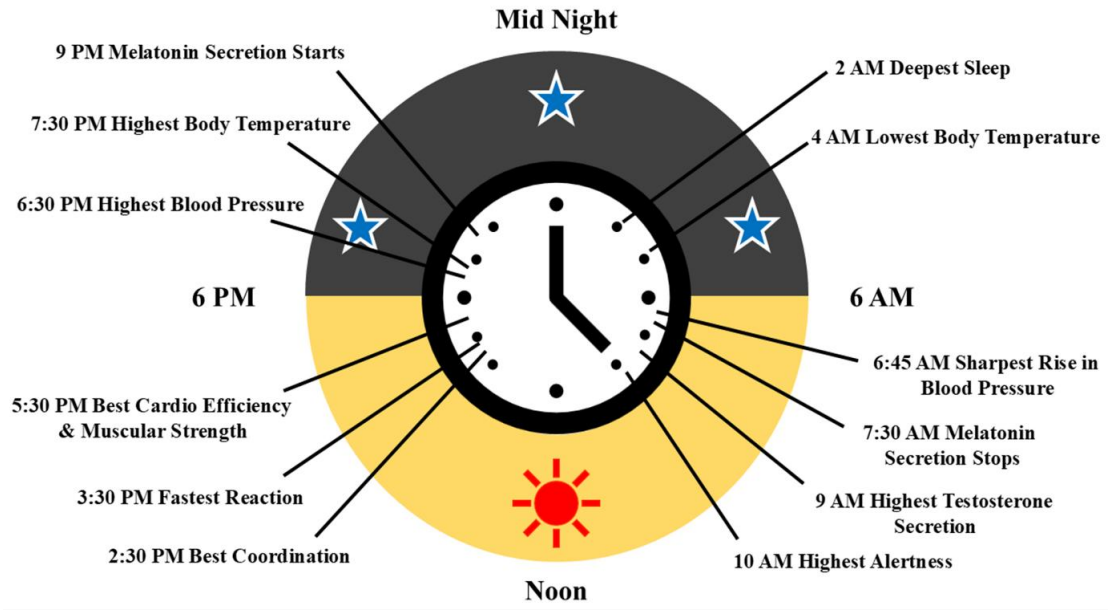


Figure 1. Body's Circadian Rhythm

2.2 The Master Clock

The primary conductor of this biological orchestra is the suprachiasmatic nucleus (SCN), a tiny cluster of neurons located in the hypothalamus as illustrated in (fig.2). This region of the brain receives light signals from the retina and uses this information to synchronize the body's internal clock with the external environment[12].

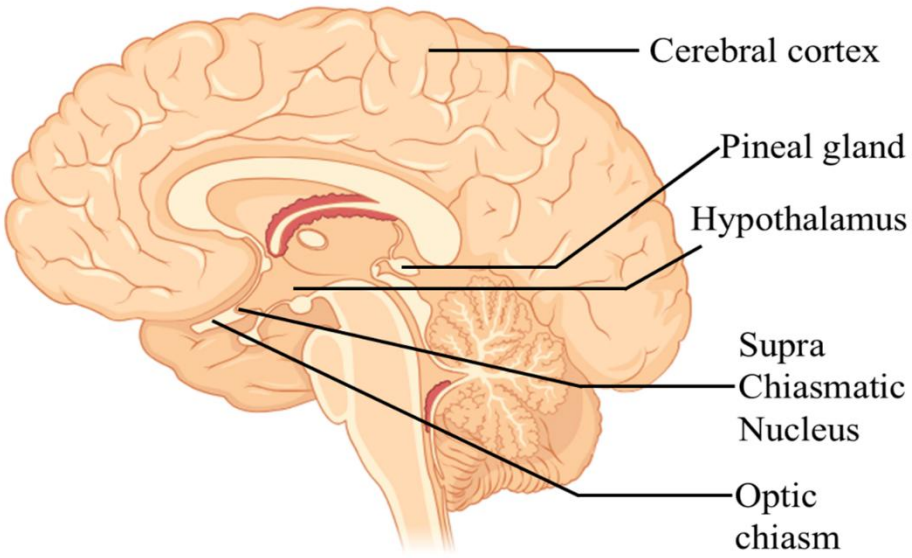


Figure 2. Diagram of Human Suprachiasmatic Nucleus

2.3 The Rhythm of Life

The circadian rhythm is crucial for regulating many physiological processes. It controls the sleep-wake cycle, promoting daytime alertness and nighttime sleepiness. The suprachiasmatic nucleus (SCN) orchestrates this by regulating hormone release, including melatonin, cortisol, and growth hormone, which affect numerous bodily functions. Body temperature also follows this daily rhythm, peaking in the late afternoon or early evening. The circadian rhythm further influences digestion by regulating appetite, digestion itself, and nutrient absorption. Finally, cognitive functions like attention, memory, and problem-solving are significantly influenced by this daily cycle[13].

Several factors influence body's circadian rhythm. Light exposure, particularly natural sunlight, is a powerful cue for synchronizing our internal clock. Consistent sleep and meal schedules are also essential for maintaining a healthy rhythm. Regular physical activity further stabilizes this internal clock and improves sleep quality. Conversely, chronic stress, certain medications, and social/work routines, along with other environmental factors, can disrupt the sleep-wake cycle and interfere with proper circadian function[14].

2.5 PDDS for Circadian Disorders

Circadian disorders occur due to disruptions in the body's biological clock (circadian rhythm), which regulates essential physiological functions such as hormone release, sleep-wake cycles, and metabolism. Several diseases, including hypertension, asthma, arthritis, diabetes, and peptic ulcers, exhibit time-dependent symptoms that require drug release at specific periods for effective management[15]. Pulsatile Drug Delivery Systems (PDDS) are designed to synchronize drug release with the body's circadian rhythm, ensuring optimal therapeutic effects while minimizing side effects. Since the circadian rhythm follows a 24-hour cycle, it significantly influences disease symptoms and drug metabolism. For instance, blood pressure peaks in the early morning in hypertension, asthma symptoms worsen at night and early morning, rheumatoid arthritis causes the highest joint stiffness in the morning, and blood glucose levels fluctuate throughout the day in diabetes. As constant drug release may not be ideal for such conditions, PDDS ensures that drugs are delivered at the right time, enhancing efficacy and reducing adverse effects[16]. In diabetes insulin therapy aims to mimic the body's natural insulin secretion pattern continuous basal secretion and meal-stimulated boluses. Circadian rhythm-influenced glucose and insulin fluctuations in diabetic patients, understanding this pattern is crucial for effective insulin replacement therapy, especially in Type 1 diabetes. Proteins and peptides, like insulin, can be susceptible to degradation by proteolytic enzymes in the upper gastrointestinal tract[17]. To ensure their stability and absorption, the colon, with its relatively lower enzyme activity, emerges as a preferred site for drug delivery. PDDS can achieve this targeted colon delivery. By incorporating a lag time of approximately 5 hours, these systems can bypass the stomach and small intestine, releasing the drug specifically in the colon[18]. This time-dependent release mechanism aligns with the transit time of the formulation through the upper GI tract. Pulsatile Drug Delivery Systems (PDDS) have shown significant potential in managing various diseases by delivering medications in a time-specific manner. Conditions such as hypertension, asthma, arthritis, and peptic ulcers often exhibit circadian rhythm-dependent symptoms, making PDDS an ideal therapeutic approach. By ensuring drug release at precise intervals, PDDS enhances treatment efficacy, minimizes side effects, and aligns with the body's natural biological clock. This targeted approach has revolutionized therapies for conditions requiring optimal drug concentration at specific times, improving patient outcomes as shown in table 1.

Table 1. Application of PDDS therapy for several disease

Disease	Circadian rhythm of disease	Category of drug used	Example	References
Cardiovascular Diseases	Blood pressure typically drops during sleep and experiences a sharp increase upon waking	a) Calcium channel blockers b) ACE inhibitors c) Nitroglycerine	a) Dilitiazem, Amlodipine b) Lisinopril, Enalapril c) Nitroglycerine	[74–76]
Arthritis	Pain in the morning and it intensify at night	a) NSAIDs b) Glucocorticoids	a) Ibuprofen, Diclofenac b) Exogenous glucocorticoids like prednisone in low dose	[77–79]

Asthma	Attacks tend to occur at night or in the early morning	a) β2agonist, b) Anti-histamines	a) Albuterol Terbutaline b) Fexofenadine, cetirizine, Loratidine	[80,81]
Peptic ulcer	Acid production peaks in the afternoon and evening	a) H2 blockers	a) Cimetidine, famotidine	[82,83]
Cancer	*Blood flow to the tumor is significantly higher during periods of daily activity compared to rest*	a) Alkylating agents b) Antimetabolites c) Antimicrotubular agents	a) Nitrosoureas, platinum analogs like cisplatin b) Folate antagonists like methotrexate c) Vinca alkaloids like vincristine, vinblastine	[84]
Neurological disorder	*The underlying mechanisms of epilepsy and the characteristics of seizures*	a) MAO-B inhibitor	a) Selegiline, Rasagiline	[85]
Diabetes mellitus	*Blood sugar rises after eating*	a) Sulfonylurea, b) Insulin, c) Biguanides	a) Glipizide, glimepiride b) Insulin c) metformin	[86–88]

3. ADVANTAGES OF PDDS

Improved therapeutic efficacy can be achieved by delivering the drug at the right time, maximizing its impact on the target site and mimicking the body's natural rhythms to optimize drug action. This approach also leads to reduced side effects by minimizing exposure to high drug concentrations, thus lowering the risk of adverse reactions. Additionally, it allows for targeted drug delivery, which helps decrease systemic side effects. Enhanced patient compliance is another benefit, as it simplifies dosing regimens, making it easier for patients to adhere to their treatment plans. This method reduces the frequency of dosing, improving convenience and patient satisfaction. Targeted drug delivery ensures that the drug is delivered to specific sites of action, further increasing therapeutic efficacy and reducing side effects. The concept of chrono-pharmacology leverages the body's circadian rhythms to optimize drug delivery and overall effectiveness[19].

4. DISADVANTAGES OF PDDS

The development of complex drug delivery systems (PDDS) comes with several challenges. Designing and manufacturing these systems is intricate and requires specialized techniques, with precise control of drug release kinetics often being difficult to achieve[20]. Additionally, variability in drug release can be influenced by factors like gastric emptying time and other physiological conditions, which may affect the therapeutic efficacy and safety of the drug. Not all drugs are suitable for PDDS, as they may require specific physicochemical properties that not all medications possess. The higher cost of PDDS is another consideration, as the complex formulation and manufacturing processes tend to increase expenses compared to conventional dosage forms. Moreover, there is a potential for dose dumping, where rapid drug release could lead to high peak plasma concentrations, raising the risk of side effects[21].

5. CLASSIFICATION OF PDDS

Pulsatile Drug Delivery Systems (PDDS) are designed to release the drug in a specific, controlled manner, often in bursts or pulses, rather than continuously. These systems can be used for conditions where a rapid or time-sensitive release is required, such as in circadian rhythm-based treatments or for drugs that require targeted delivery at specific times. Here's an overview of the different classifications of Pulsatile Drug Delivery Systems as shown in (fig. 3).

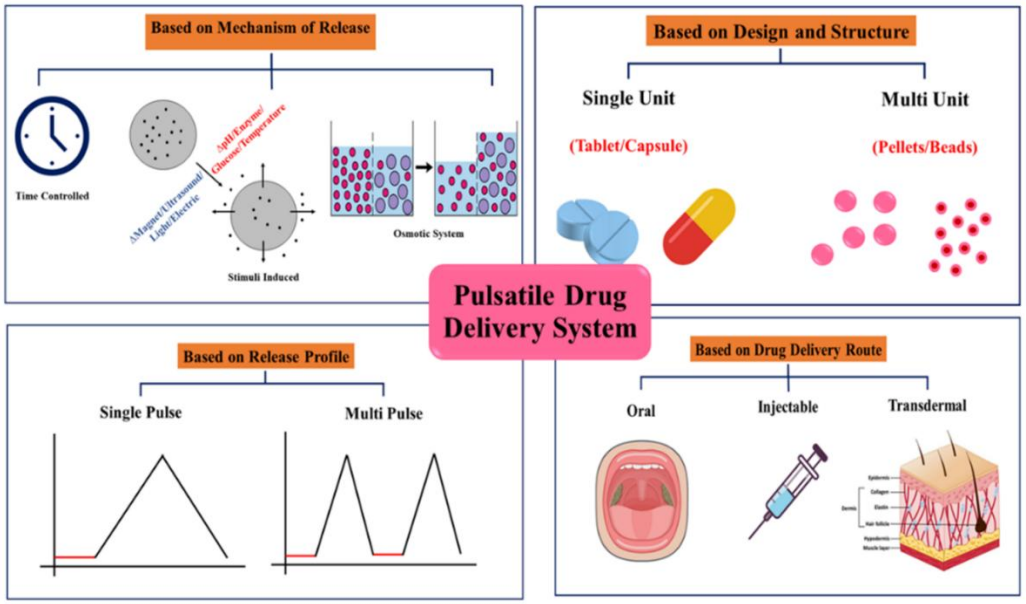


Figure 3. Classification of Pulsatile Drug Delivery System

5.1 PDDS Based on Mechanism of Release

Based on the mechanism of release of drug, the pulsatile drug delivery system is mainly classified into three broad categories which are time controlled, stimuli induced and Osmotic system which are further classified into sub categories as shown in (fig.4).

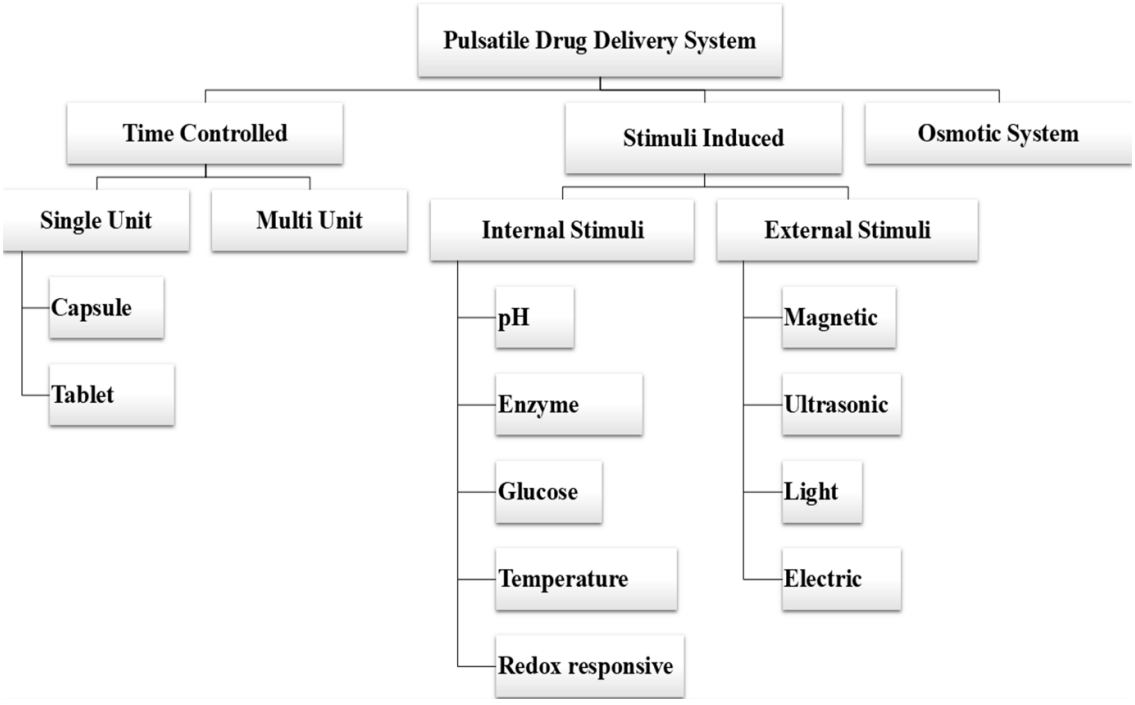


Figure 4. Classification of PDDS based on mechanism of release

5.1.1 TIME CONTROLLED PDDS

A Time-Controlled Pulsatile Drug Delivery System (TCPDDS) is designed to release drugs in controlled bursts after a predetermined lag period, mimicking the body's natural rhythms. It is particularly useful for diseases with predictable patterns, such as asthma, arthritis, and cardiovascular conditions. The system consists of a drug core surrounded by a release-controlling barrier, which delays drug release until it ruptures or erodes, ensuring enhanced therapeutic efficacy with minimized side effects.

5.1.1.1 SINGLE UNIT TIME CONTROLLED PULSATILE DRUG DELIVERY SYSTEM

A Single Unit Time-Controlled Pulsatile Drug Delivery System is an advanced mechanism that releases drugs at specific intervals in a pulsatile manner. Unlike continuous drug release, it delivers therapeutic agents at predetermined times, improving efficacy, patient compliance, and reducing side effects. Typically formulated as tablets or capsules, it consists of a drug core surrounded by a release-modulating barrier. Capsule-based systems use a rupturable or dissolvable polymer plug that controls the lag time before drug release. In tablet-based systems, hydrophilic or erodible polymers gradually dissolve, exposing the core drug for controlled, time-specific release.

A. Capsular system

A plug and an insoluble capsule body that contains a medication make up a capsular system. Following a certain lag period, the plug is extracted due to dissolution, erosion, or enlargement[22]. The medicine is released as a pulse from the insoluble capsule body after a plug that has been pushed away by erosion or swelling continues the lag time. One type of capsular system is the Pulsincap system, which consists of a medication formulation inside a water-insoluble capsule body. A swellable hydrogel plug is used to seal the body's open end[23]. The mechanism of drug release from pulsincap system as depicted in (fig.5), is when the pulsincap system contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a particular lag time[24]. This step is followed by a rapid release of drug. The lag time is controlled by plug which pushed away by swelling, erosion, or dissolution. Manipulating the dimension and the position of the plug can control the lag time[25]. For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants. Various materials used for formulation of swellable plug which include hydroxypropyl methyl cellulose, poly vinyl acetate and poly vinyl alcohol, polyethylene oxide and enzymatically controlled erodible polymer such as pectin. The length and thickness of the plug decides the lag time[26].

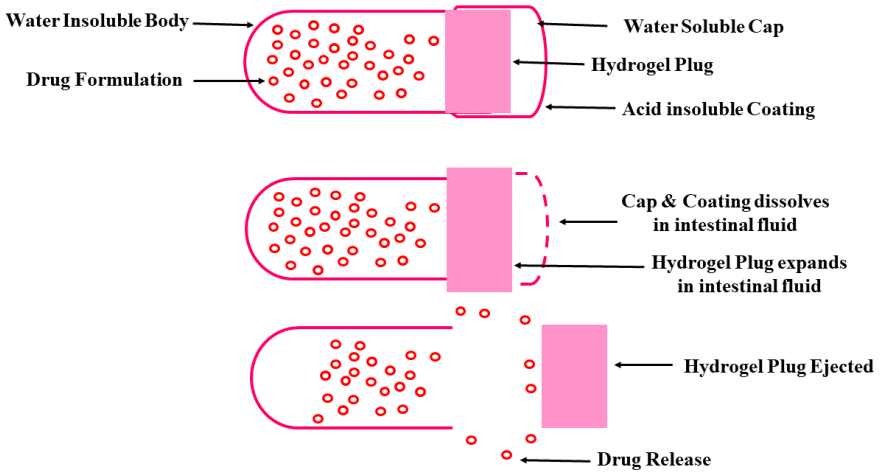


Figure 5. Pulsincap System

B. Tablet system

The tablet system for single-unit pulsatile drug delivery is designed to provide a time-controlled release of the drug in a single pulse or multi-pulse release after a predetermined lag time. These systems typically consist of a core drug surrounded by a release-controlling barrier made of hydrophilic, hydrophobic, or pH-sensitive polymers[27]. The outer barrier remains intact during the initial period, preventing drug release and ensuring the desired lag time. After the lag phase, the barrier either swells or erodes, allowing the rapid release of the drug. This system is particularly beneficial for diseases that follow circadian rhythms or require medication at specific times, such as asthma or arthritis[28]. The lag time can be adjusted by modifying the thickness or composition of the outer coating, providing flexibility to meet various therapeutic needs. Additionally, these systems improve patient compliance by offering controlled and precise drug delivery without the need for multiple doses[29]. A barrier-coated reservoir device makes up the majority of pulsatile drug delivery systems. The medicine is then quickly released from the reservoir core when this barrier erodes or dissolves after a certain amount of

time[30]. The thickness of the coating layer affects the lag time.

B.1 Compressed Coated Tablet

By directly compressing the core and the coat, compression coating eliminates the requirement for a separate coating procedure and coating solutions. The inner layer of the compression-coated tablet is made up of ingredients that are insoluble in gastric media but released in the intestinal environment, while the outer layer delivers the first dosage and quickly dissolves in the stomach as displayed in (fig.6). It is possible to employ materials like hydrophilic cellulose derivatives. On a laboratory scale, compression is simple. The technique's main shortcomings are the difficulty of properly positioning the cores and the comparatively high volume of coating ingredients required[31].

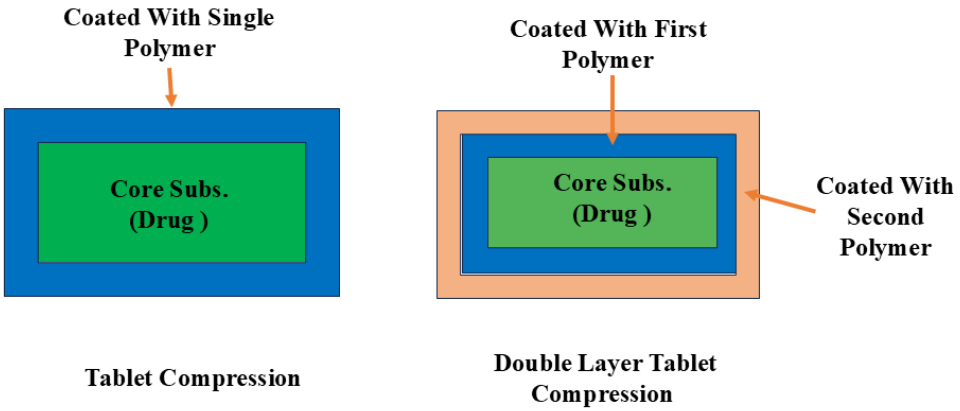


Figure 6. Compressed Coated Tablet

B.2 Multi Layered Systems

Both sides of the core have one or two impermeable polymeric coatings (compressed or films) applied to them. A tablet device with three layers to enable multi medication release. A medication dosage is included in both layers. The drug dose that is instantly available is found in the outer drug layers. The drug layers are separated by a swellable polymer-based intermediary layer. The layer with the other dosage of medication is covered with an impermeable polymer film. In order to provide delayed (5 h) medication absorption, the first layer may also include a drug-free hydrophilic polymer barrier[32]. It consists of a hydrophilic matrix core containing the drug dose as in (fig.7). This kind of three-layer device has been used in the treatment of Parkinsonian patients using L-dopa/benserazide. Night-time problems and early-morning symptoms of Parkinsonism can be avoided by using a dual-release Geomatrix formulation, which allows daily doses of drug to be reduced and leads to extent of bioavailability 40 % greater than when a traditional controlled release formulation is employed[33].

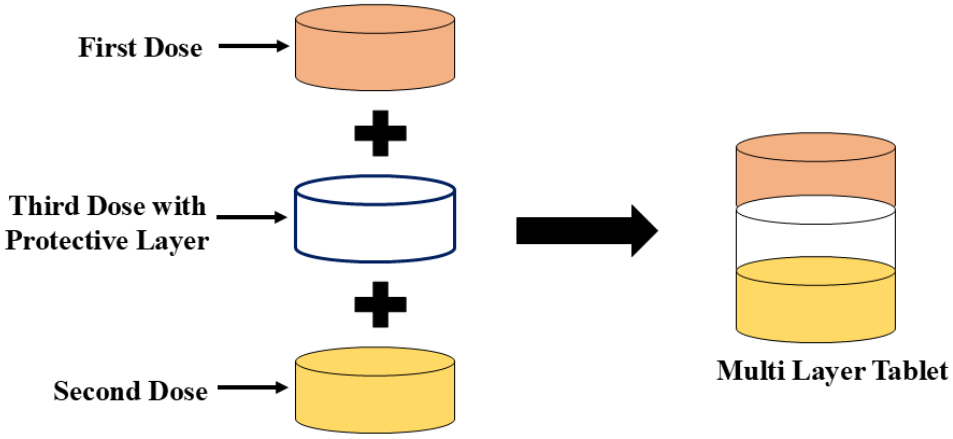


Figure 7. Multi-Layered Tablet

5.1.1.2 MULTI UNIT TIME-CONTROLLED PULSATILE DRUG DELIVERY SYSTEM

A multiple-unit time-controlled pulsatile drug delivery system consists of several small, individual units, such as pellets or beads, that are designed to release a drug in a controlled, pulsatile manner. Each unit is coated with a barrier layer that can be designed to rupture or alter permeability after a predefined lag time, thus allowing for precise drug release at specific

intervals as depicted in (fig.8). These systems offer several advantages over single-unit systems, including reduced risk of dose dumping, better reproducibility in drug release, and the flexibility to blend units with different release profiles[34]. Furthermore, they exhibit a more predictable gastric residence time, which enhances the uniformity of drug release. The lag time between pulses can be adjusted by varying the thickness of the coating. This system's primary drawback is that it has a lesser drug-carrying capacity since there are more excipients present. These systems are always reservoirs with a covering of altered permeability or rupturable material. The many kinds of multi-unit systems are listed and described below[35].

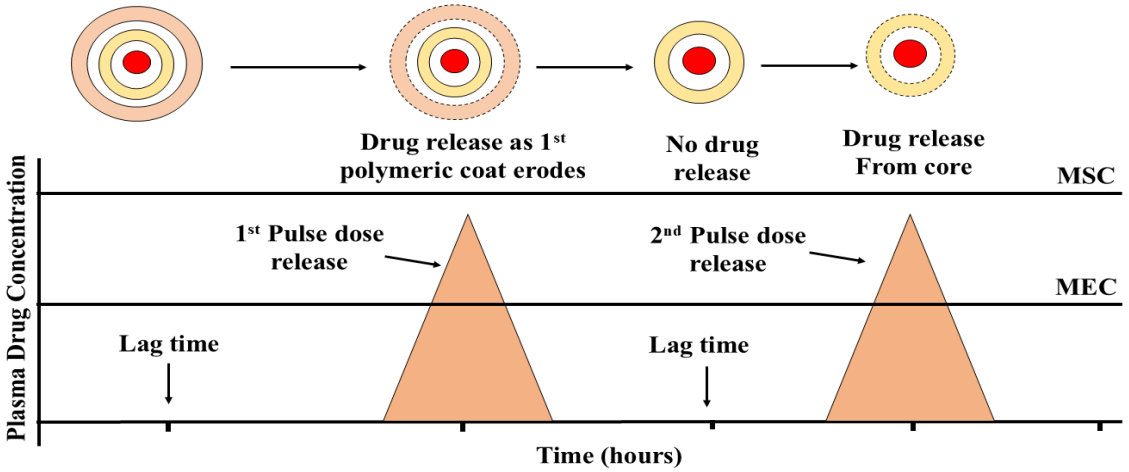


Figure 8. Multi Unit System

5.1.2 STIMULI-INDUCED PULSATILE DRUG DELIVERY SYSTEMS

Stimuli-induced pulsatile drug delivery system enables controlled, on-demand drug release, improving therapeutic outcomes and reducing side effects. They are particularly beneficial for managing conditions that follow circadian patterns or require precise drug administration, such as asthma, arthritis, or cardiovascular diseases. Stimuli-induced pulsatile systems offer a more personalized approach to treatment by ensuring that drugs are delivered when and where they are needed most.

5.1.2.1 INTERNAL RESPONSIVE PDDS

Internal stimuli-induced pulsatile drug delivery systems rely on biological or chemical signals within the body to trigger drug release. Common internal stimuli include pH, enzymes, and redox conditions, which enable site-specific and controlled drug delivery. pH-sensitive systems use materials like Eudragit polymers that dissolve at specific pH levels, ensuring targeted release in the stomach or intestines. Enzyme-responsive systems rely on specific enzymes, such as proteases or amylases, to degrade the polymeric coating and release the drug at desired sites like the colon or tumors. Redox-responsive systems exploit the reducing environment in inflamed tissues or cancer cells, breaking disulfide bonds in the carrier material to enhance therapeutic precision and minimize side effects.

5.1.2.1.1 pH Responsive PDDS

The pH-responsive pulsatile drug delivery system is a specialized approach designed to release drugs at specific intervals in response to pH changes in the gastrointestinal tract. It uses materials that are sensitive to pH variations, allowing controlled drug release as shown in (fig.9), based on the acidic or basic environment of different regions in the body[36].

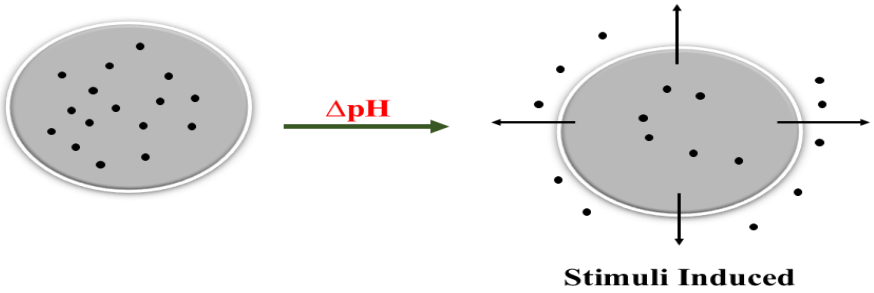


Figure 9. pH responsive PDDS

Typically, the drug is encased in a polymeric coating that remains intact under normal conditions but dissolves or swells when the pH reaches a threshold, such as in the stomach or intestines, triggering drug release. This system is ideal for conditions that follow circadian patterns, where timed drug release enhances therapeutic efficacy. pH-sensitive polymers like chitosan, eudragit, and poly (acrylic acid) are commonly used, as they undergo structural changes, such as swelling or solubility alterations, at specific pH levels. This makes the system suitable for drug administration to regions like the stomach (acidic), intestines (neutral to basic), or inflammatory sites with acidic microenvironments. pH-responsive systems are particularly beneficial for diseases such as cancer, diabetes, respiratory conditions, and gastrointestinal disorders, where pH changes can act as endogenous triggers[37]. Normal cells (Extracellular pH: Around 7.4, Intracellular pH: Around 7.2) have a higher extracellular pH than cancer cells (Extracellular pH: Around 6.7-7.1, Intracellular pH: Around 7.4), and normal cells have a lower intracellular pH than cancer cells as illustrated in (fig.10). For instance, during asthma attacks, or in cancer pH changes due to inflammation and mucus production can trigger targeted drug release. These technologies enhance patient compliance, reduce side effects, and improve treatment efficacy through precise, site-specific, and time-specific drug delivery.

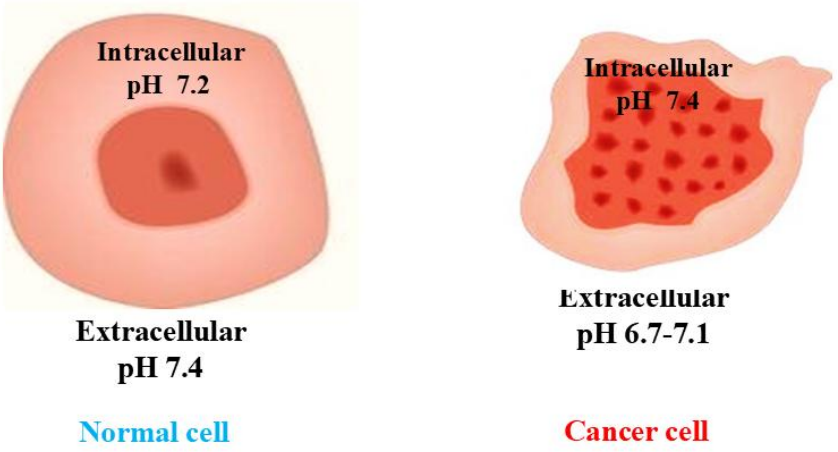


Figure 10. Normal and Cancerous Cell pH

Dalvadi et al., explores the design and testing of a drug delivery system that releases medication in response to specific pH conditions, mimicking the body's natural circadian rhythms. The system utilizes pH-sensitive hydrogels that swell or shrink in response to changes in pH, allowing for the controlled release of drugs at predetermined times[38]. pH-sensitive polymers are very important for pulsatile drug delivery systems due to the fact that they facilitate site-specific and time-controlled release of the drug. They are so-called "smart" polymers since they respond to pH change in the body by altering structure, thereby providing targeted drug delivery at the desired site. They provide improved therapeutic efficacy with reduced side effects. Some of the most commonly used are polyacrylic acid, Eudragit, and chitosan-based systems. Their application is from oral drug delivery to colon-targeted and anticancer therapy as shown in table 2.

Table 2. pH responsive polymer for PDDS

Polymer Name	Cancer Type	Cancer Cell pH	Mechanism of Action	Reference
Carboxymethyl Cellulose (CMC) Nanogel	Breast Cancer	pH 6.5	CMC **swells in acidic tumor environments**, releasing **quercetin** for enhanced anticancer effects.	[89]
Sericin-Coated Magnetic Nanoparticles (MSN-PTA)	Breast Cancer	pH 5.5-6.8	pH-dependent **sericin degradation** enables controlled **drug release**, targeting MCF-7 cells.	[90]
Poly(lactic-co-glycolic acid)	Colon Cancer	pH 6.0-7.0	PLGA-PEG **breaks down in acidic conditions**, allowing **drug penetration in tumors**.	[91]

(PLGA)-PEG Micelles				
Diketo-Tautomer-Entrapped 5-Fluorouracil (5-FU) Nanoparticles	Colorectal Cancer	pH 5.5-6.5	pH-sensitive **5-FU activation** improves **bioavailability and controlled drug release**.	[92]

5.1.2.1.2 Enzyme Responsive PDDS

Enzyme-sensitive pulsatile drug delivery systems (PDDS) release drugs in response to specific enzymatic activity in the body. These systems utilize polymeric materials or coatings that degrade or undergo structural changes when exposed to target enzymes, enabling precise drug release as illustrated in (fig.11). Enzymes regulate drug release at specific sites, making these systems effective for targeted and time-controlled medication delivery. For example, enzymes overexpressed in the colon or cancerous tissues trigger drug release, ensuring site-specific delivery while minimizing systemic side effects. This approach is particularly useful for treating conditions such as inflammatory bowel disease (IBD), colon cancer, and infections, where enzyme activity is heightened. The release mechanism relies on enzyme-cleavable linkers, such as peptide sequences (e.g., Gly-Ser, Gly-Pro) or ester bonds, which enzymes like trypsin or lipase can break. Polymeric carriers like poly(ethylene glycol) (PEG), poly(lactic-co-glycolic acid) (PLGA), chitosan, and glucose oxidase are commonly used, allowing controlled drug release at target sites for enhanced therapeutic efficacy and reduced side effects.

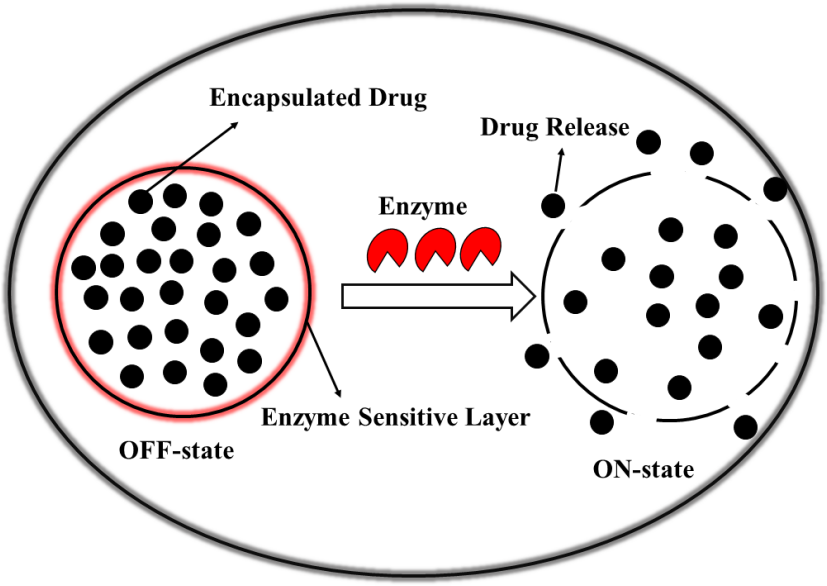


Figure 11. Enzyme Responsive PDDS

Enzyme-responsive polymers play a vital role in pulsatile drug delivery systems, ensuring site-specific and time-controlled release of the drug. Smart polymers modify their structure in response to specific enzymes to deliver the drug in a targeted and efficient manner. The systems optimize therapeutic efficacy at minimum side effects. They have unique applications in chronotherapy, where the drug release is synchronized with the biological rhythm of the body. Polymer design has evolved, enhancing responsiveness, thus they are potential candidates for precision medicine as shown in table 3.

Table 3. Enzyme responsive polymer for PDD System

Enzyme	Polymer	Functional Group	Disease	Role in Therapy	Reference
Lipase	PLGA (Poly Lactic-co-Glycolic Acid)	Ester (-COO-)	Inflammation	Controlled drug release for anti-inflammatory therapy	[93]

Trypsin	PEGylated Liposomes	Hydroxyl (-OH)	Cancer	Enhances drug solubility and stability in chemotherapy	[94]
Superoxide Dismutase (SOD)	Hyaluronic Acid	Carboxyl (-COOH), Hydroxyl (-OH)	Cancer	Reduces oxidative stress in cancer cells	[95]
Pyroglutamyl Aminopeptidase 1 (PGP-1)	Polycarbonates	Carbonyl (-C=O)	Inflammation	Targeted enzymatic therapy for inflammation	[96]

Singh et al., investigates the design and testing of drug delivery systems that utilize enzymes as triggers for pulsatile drug release. The system involves enzyme-responsive hydrogels that degrade or change structure in response to specific enzymes, allowing for the controlled release of drugs at predetermined times[39].

5.1.2.1.3 Glucose Responsive PDDS

Glucose-sensitive pulsatile drug delivery systems (PDDS) are specialized drug delivery systems designed to release drugs, typically insulin, in response to changes in blood glucose levels. These systems utilize glucose-sensitive materials or enzymes, such as glucose oxidase, to detect fluctuations in glucose concentrations and trigger drug release accordingly as shown in (fig.12). When blood glucose levels rise, glucose oxidase converts glucose into gluconic acid, leading to pH changes or swelling of glucose-responsive polymers[40]. This triggers the release of the drug, helping regulate blood sugar levels in a timely manner. Glucose-sensitive PDDS offers a promising approach for managing diabetes, as it provides an on-demand, self-regulated drug release system that mimics the body's natural insulin response. By ensuring precise, glucose-dependent drug delivery, these systems improve glycaemic control, reduce the risk of hypoglycemia, and enhance patient compliance with fewer dosing interventions.

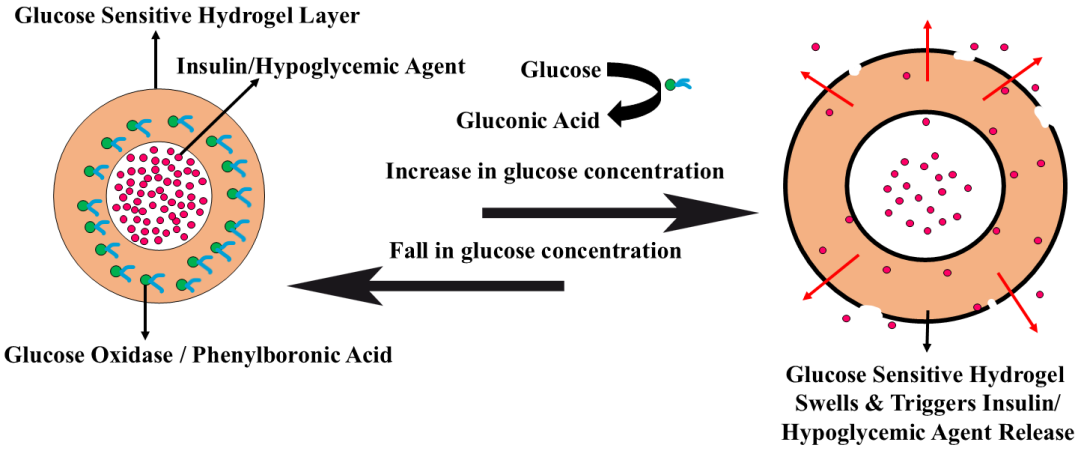


Figure 12. Glucose Responsive PDDS

Glucose-sensitive drug delivery systems often use polymeric hydrogels that contain glucose-responsive materials, such as boronic acids or glucose-binding proteins. A common approach involves incorporating boronic acid derivatives into hydrogels, which interact with glucose to form reversible boronate esters. When blood glucose levels rise, glucose binds to the boronic acid groups, causing the polymer to swell and create pores in the gel. These pores allow the encapsulated drug to be released. When glucose levels drop, the hydrogel shrinks, reducing the pore size and stopping further drug release. Polymers like polyethylene glycol (PEG) [41], poly(N-isopropylacrylamide) (PNIPAM) [42], and polyvinyl alcohol (PVA) [43] are commonly used in these systems, often modified with glucose-binding agents like phenylboronic acid (PBA). In these systems, the binding of glucose to the phenylboronic acid causes changes in the hydrogel's structure, triggering the release of the drug in response to glucose fluctuations.

5.1.2.1.4 Temperature Responsive PDDS

Temperature-induced pulsatile drug delivery systems (PDDS) are advanced drug delivery mechanisms that release drugs in response to temperature fluctuations. These systems utilize temperature-sensitive polymers, such as poly(N-isopropylacrylamide) (PNIPAM) or poloxamers, which undergo phase transitions at specific temperatures. When the temperature crosses a critical threshold, these polymers either swell or shrink, triggering drug release. For example, at higher temperatures, the polymers may collapse, squeezing out the drug, while at lower temperatures, they may swell, creating pores for drug diffusion, as illustrated in (fig.13). Temperature-induced PDDS is particularly beneficial for localized therapies, such as cancer treatment, where tumor site temperatures can be selectively elevated to induce drug release [44]. These systems offer precise drug delivery control, minimize side effects, and enhance therapeutic outcomes by ensuring drug release occurs only when needed and at the desired site. The core mechanism of these systems relies on thermoresponsive materials that undergo phase transitions, such as gelation or sol-gel transformation, in response to temperature changes. Hydrogels or nanogels made from polymers like PNIPAM, poly(ethylene glycol) (PEG), and poly(vinyl alcohol) (PVA) exhibit amphiphilic properties, shifting between hydrophilic and hydrophobic states at specific temperatures. Most of these systems have a lower critical solution temperature (LCST), above which the polymer becomes hydrophobic and releases the drug. This change regulates drug release based on the swelling or deswelling of the polymer network. When the temperature exceeds the LCST, the polymer shrinks, expelling the drug, whereas cooling restores the hydrophilic state, stopping further release. These temperature-sensitive systems enable precise, on-demand drug release, making them highly effective for various therapeutic applications.

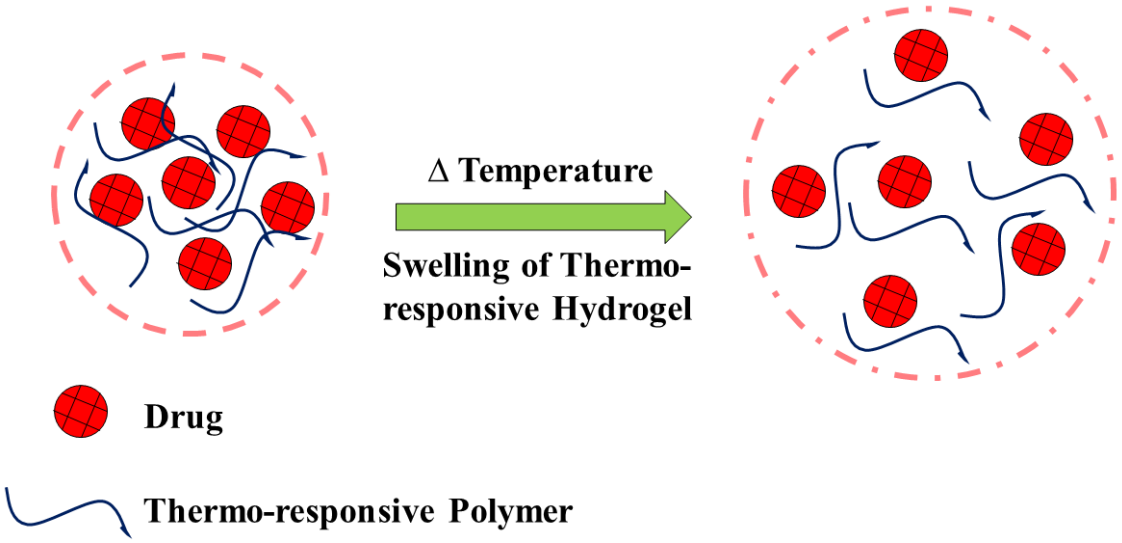


Figure 13. Temperature Responsive PDDS

Thermoresponsive polymers can deliver controlled, demand-based drug release at a certain physiological temperature and thus enhance the effectiveness of drugs. Lower critical solution temperature (LCST) or upper critical solution temperature (UCST) mechanisms lead to their action. Some of the common examples include poly(N-isopropylacrylamide) (PNIPAAm) and copolymers thereof. These kinds of systems lead to patient compliance, minimization of side effects, and targeted therapy with precision as shown in table 4.

Table 4. Thermoresponsive polymers for PDDS

Polymer Name	Cancer Type	Cancer Cell Temperature	Mechanism of Action	Reference
Poly(N-isopropylacrylamide) (PNIPAAm) Hydrogel	Breast Cancer	40-42°C	PNIPAAm undergoes **thermo-induced gelation**, controlling **drug release** at **hyperthermic tumor sites**.	[97]

PNIPAAm-Coated Gold Nanorods	Breast Cancer	42-45°C	Gold nanorods absorb **near-infrared (NIR) light**, generating **heat-triggered drug release**.	[98]
Temperature-Responsive Polymersome (PNIPAAm-DOX Conjugate)	Lung Cancer	39-42°C	**Dual drug delivery system** reverses **cancer drug resistance** under **elevated temperature**.	[99]
Poly(N-isopropylacrylamide) (PNIPAAm) Nanoparticles	Thyroid Cancer	41-43°C	**Temperature-responsive polymer shrinks**, squeezing out **loaded drug** at **tumor sites**.	[100]

5.1.2.1.5 Redox responsive PDDS

Redox-responsive pulsatile drug delivery systems (PDDS) are designed to respond to distinct redox environments for controlled drug release. These systems exploit variations in cellular redox states or reactive oxygen species (ROS) levels, particularly in pathological conditions like cancer. Elevated ROS levels in tumor cells trigger drug release at the target site, enhancing therapeutic precision. Redox-responsive PDDS are gaining attention for their ability to achieve precise, on-demand drug delivery by leveraging redox potential differences between normal and diseased tissues. For instance, tumors exhibit elevated glutathione (GSH) levels, which can break redox-sensitive linkers, such as disulfide bonds, leading to localized drug release. These bonds remain stable in healthy tissues but degrade in high-redox environments, ensuring targeted and rapid drug delivery. This strategy minimizes systemic side effects while enhancing therapeutic efficacy. When integrated into PDDS, redox-responsive systems can synchronize drug release with circadian rhythms or disease progression, offering significant advantages for time-sensitive or site-specific therapy. Furthermore, redox-responsive drug delivery systems enhance tumor targeting by exploiting the tumor microenvironment's distinct redox properties. The selective cleavage of redox-sensitive bonds in tumor cells improves drug efficacy while minimizing off-target effects. Some advanced redox-responsive PDDS integrate dual-stimuli mechanisms, combining redox sensitivity with pH or enzymatic triggers for improved precision. These strategies enhance drug stability in circulation, promote tumor-specific accumulation through the enhanced permeability and retention (EPR) effect, and reduce systemic toxicity, making them a promising approach for advanced cancer therapy [45–47].

5.1.2.2 EXTERNAL STIMULI RESPONSIVE PDDS

External stimuli responsive delivery systems (PDDS) are advanced drug delivery mechanisms that release drugs in response to external triggers such as light, magnetic fields, ultrasound, or electrical signals. These systems utilize specialized materials that undergo structural or chemical changes when exposed to external stimuli, triggering drug release. For example, light-sensitive systems use photosensitive polymers or nanoparticles that degrade or swell upon light exposure, releasing the drug. Magnetic field-responsive systems incorporate magnetic nanoparticles that heat up or move when exposed to a magnetic field, leading to drug release[48]. Ultrasound-responsive systems use sound waves to create mechanical vibrations or cavitation, disrupting the polymer matrix and releasing the encapsulated drug. Electrical stimuli can also induce drug release by causing the swelling or shrinking of electrically responsive hydrogels. These external stimuli PDDS offer precise control over drug delivery, enabling site-specific and time-specific release, making them particularly useful for cancer treatment, pain management, and other conditions requiring on-demand drug release.

5.1.2.2.1 Magnetically Responsive PDDS

Magnetically responsive pulsatile drug delivery systems (PDDS) use external magnetic fields to control drug release at a targeted site. Magnetic nanoparticles (MNPs) or materials like iron oxide (Fe_3O_4 or Fe_2O_3) encapsulate drugs and can be guided by an external magnetic field for precise delivery. Once positioned, the system utilizes magnetic forces to trigger drug release at the designated location. In this type of system, drugs are often dispersed in a polymer matrix, which releases macromolecular drugs at a slow rate. This rate can be enhanced by incorporating an electromagnetically triggered vibration mechanism within the polymeric delivery device [49]. A subdermally implantable magnetic device is created by embedding a small magnet ring in the core of a hemispherical drug-dispersing polymer, with a drug-impermeable coating except for a single cavity. Positioned above the magnet, this cavity allows controlled drug release, as illustrated in (fig.14). Under normal conditions, the drug diffuses slowly, but when the magnet is activated by an electromagnetic field, vibrations

increase drug release speed significantly.

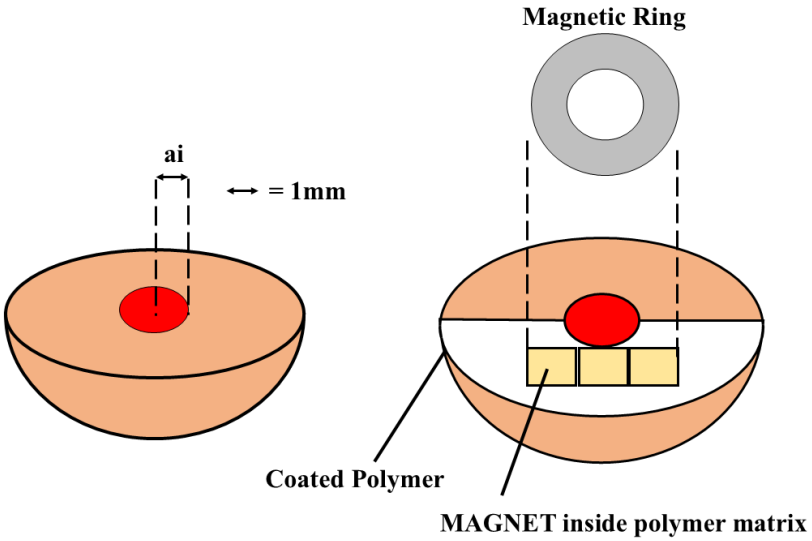


Figure 14. Magnetically Responsive PDDS

Surwase et al. explores the design and testing of drug delivery systems that utilize magnetic fields to induce pulsatile drug release. The system involves magnetic nanoparticles integrated into hydrogels or liposomes, which change structure or release drugs in response to magnetic fields, allowing for controlled release at specific times[50].

5.1.2.2.2 Ultrasound-Responsive PDDS

An ultrasonically stimulated pulsatile drug delivery system uses ultrasound waves to trigger the release of a drug in a controlled, pulsatile manner. This system typically involves a drug-loaded carrier, such as a capsule or gel, that contains materials sensitive to ultrasound waves. When exposed to ultrasound, the sound waves cause physical changes in the system, such as the expansion or rupture of the carrier, allowing the drug to be released in pulses[51]. It permits precise drug penetration through the colon, lungs, blood vessels, and skin. When pulsatile formulations came into contact with ultrasonic waves, the polymer degraded, improving drug release through both initial bursts and sustained release. Additionally, the pulsatile drug distribution from the polymer-based compositions is facilitated by the cavitation process caused by ultrasound radiation[52]. When exposed to ultrasonic waves, polymers degrade, making it easier for the drug molecules inside the device to be delivered. This method is especially utilized to increase the drug's absorption across biological barriers such as vascular channels, respiratory organs, and skin. These ultrasonic waves control the drug's release from the device by starting to erode the polymeric matrix[53].

5.1.2.2.3 Light-Responsive PDDS

Light-responsive pulsatile drug delivery systems (PDDS) are advanced platforms that release drugs upon exposure to specific light wavelengths. These systems incorporate light-sensitive materials, such as photosensitive polymers or nanoparticles, which undergo structural or chemical changes upon irradiation. Light exposure can trigger material degradation, swelling, or permeability changes, leading to controlled drug release [54]. For instance, azobenzene derivatives and spiropyran undergo reversible structural transformations under UV light, facilitating drug release. Near-infrared (NIR) light is particularly advantageous for deep tissue applications due to its superior penetration and minimal damage to surrounding cells. Light-responsive PDDS enable precise, non-invasive, and on-demand drug delivery, making them highly suitable for cancer therapy, wound healing, and localized treatments [55]. These systems operate through three primary mechanisms: photochemical release, photo-isomerization, and photo-thermal release. Photochemical release involves breaking covalent bonds upon light exposure, commonly using materials like o-nitro benzyl, coumarin, and pyrene derivatives [56]. Photo-isomerization utilizes UV or visible light to induce reversible structural changes, often employing azobenzenes. Photo-thermal release relies on heat generation from light-absorbing materials like gold nanoparticles or PNIPAAm hydrogels, which trigger drug release from thermosensitive carriers. Advanced technologies, including heat-sensitive liposomes and iron oxide nanoparticles, are already undergoing clinical evaluation, highlighting the potential of light-responsive PDDS in modern medicine.

5.1.2.2.4 Electrical Stimulation-Responsive PDDS

Electrical stimulation-responsive pulsatile drug delivery systems (PDDS) are designed to release drugs in response to external electrical stimuli. These systems typically use electrically sensitive polymers or hydrogels that change their properties when exposed to an electric field. When an electrical current is applied, these materials may swell, shrink, or alter their permeability, triggering the release of the encapsulated drug[57]. For example, polyelectrolyte hydrogels, such

as poly (ethylene glycol) (PEG) or poly (vinyl alcohol) (PVA), can respond to changes in electric fields, causing the hydrogel to expand or contract and release the drug. Conductive polymers, like polypyrrole and polyaniline, can also be used to control drug release by responding to electric signals. These systems offer precise, on-demand drug release, making them ideal for targeted therapies such as wound healing, pain management, and cancer treatment. Additionally, they can be used for localized drug delivery where the electrical stimulus can be applied directly to the treatment area, enhancing efficacy and reducing side effects[58].

5.1.3 OSMOTIC SYSTEM

An osmotic system for pulsatile drug delivery utilizes the principle of osmosis to release drugs at specific time intervals. This system typically consists of a semi-permeable membrane, a drug reservoir, and an osmotic agent. When the system is exposed to bodily fluids, water permeates through the membrane, causing the osmotic agent to swell and generate pressure. This pressure then pushes the drug out of the reservoir at a controlled, pulsatile rate. The design ensures that the drug is released at predetermined intervals, making it ideal for drugs requiring controlled release or those designed to act at specific times within the body.

5.1.3.1 Port System

The Port System is designed as a gelatin capsule that is coated with a semipermeable membrane, such as cellulose acetate. Within the capsule, there is an insoluble plug made up of an osmotically active agent combined with the drug formulation as shown in (fig.15). The drug release mechanism operates on the principle that when the capsule comes into contact with an aqueous environment, water molecules diffuse through the semipermeable membrane. This influx of water increases the internal pressure, ultimately leading to the ejection of the plug after a predetermined lag time[59]. The lag time itself can be precisely controlled by varying the thickness of the coating. Notably, the system has demonstrated a strong correlation between the lag times observed in in-vitro studies and those recorded in in-vivo experiments involving human subjects. This consistency highlights the reliability of the Port System in controlled drug delivery.

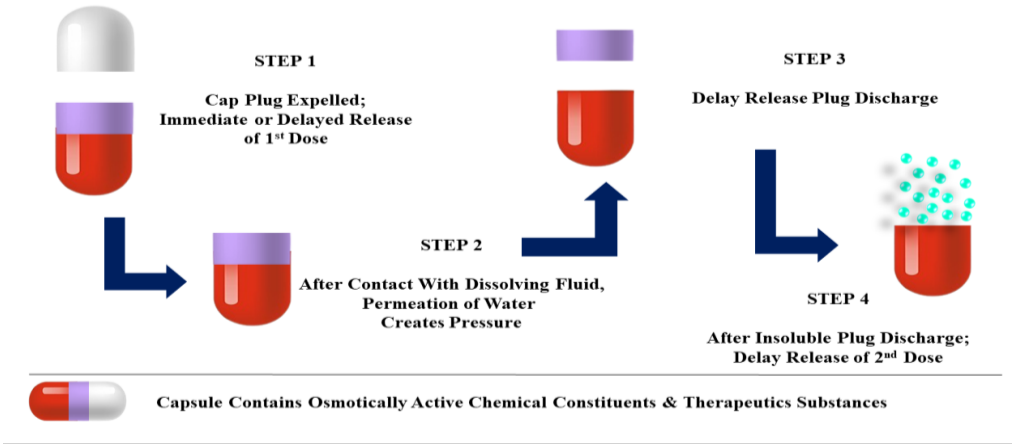


Figure 15. Port System

5.2 PDDS Based on the Release Profile

The pulsatile drug delivery system is classified based on its release profile into single-pulsatile and multiple-pulsatile systems as displayed in (fig.16), ensuring time-specific drug administration. The single-pulsatile system delivers the drug as a single burst after a predetermined lag time, making it suitable for chronotherapeutic diseases. In contrast, the multiple-pulsatile release system provides successive drug pulses at scheduled intervals, enhancing therapeutic efficacy in conditions requiring repeated dosing. These systems are crucial for optimizing drug bioavailability while minimizing side effects.

Figure 16. Classification of PDDS based on release profile

In the context of pulsatile drug delivery systems (PDDS), the single pulse and multi-pulse systems are two distinct approaches designed to release a drug at specific time intervals, mimicking the natural release patterns of certain biological substances as shown in (fig.17). A single pulse system is designed to release the entire dose of a drug in one distinct, controlled burst after a predetermined lag time[60]. The drug is typically encapsulated in a system that prevents release until a specific trigger, such as an environmental change or a specific time, initiates the drug's release. This type of system is often used when a rapid onset of action is needed, or when the therapeutic effect of the drug requires a sudden release at a particular point in time, for example, in the case of drugs that need to act quickly in response to an acute event. In contrast, a multi-pulse system is designed to release the drug in multiple discrete pulses over an extended period. Each pulse is separated by a predetermined interval, providing periodic drug delivery that can better match the circadian rhythms or the fluctuating needs of the body. The multi-pulse system may rely on several mechanisms such as swelling, erosion, or osmotic pressure changes to trigger each individual pulse[61]. This type of system is particularly beneficial when sustained, but not continuous, drug delivery is desired. It allows for periodic peaks of drug concentration in the bloodstream, which is ideal for medications that target diseases or conditions requiring multiple therapeutic interventions over time, like chronic conditions. Both systems aim to improve therapeutic outcomes by providing a controlled release profile, reducing side effects, and enhancing patient compliance.

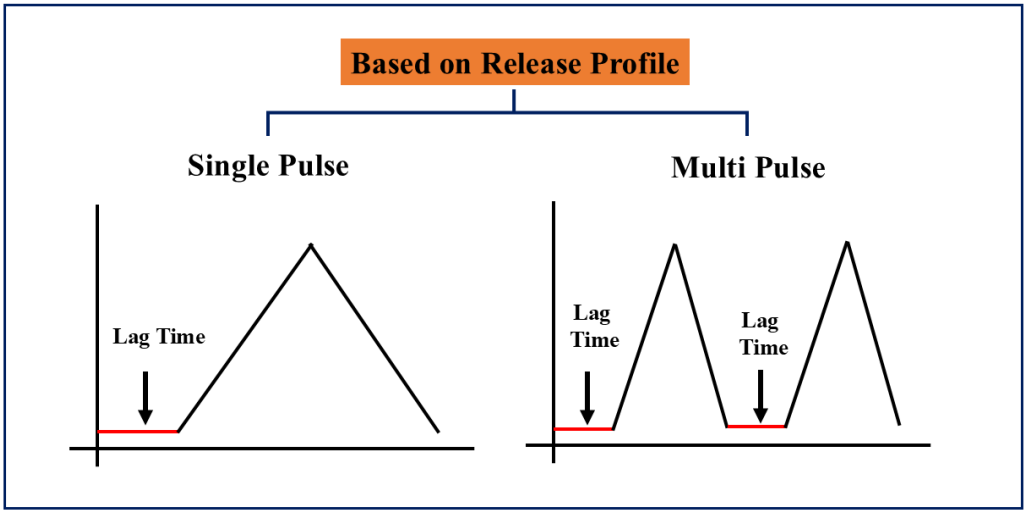


Figure 17. Single and Multi-Pulse Release System

5.3 PDDS Based on Design and Structure

The pulsatile drug delivery system is categorized into single-unit and multi-unit systems, designed to release drugs in a programmed manner for enhanced therapeutic efficacy as shown in (fig.18). Single-unit systems, such as coated capsules and tablets, rely on specific formulation strategies to achieve delayed drug release[62]. In contrast, multi-unit systems, including multi-particulate formulations, provide greater flexibility, uniform drug distribution, and reduced interpatient variability[63]. These designs are particularly beneficial for conditions requiring time-specific drug administration, aligning with the body's biological rhythms.

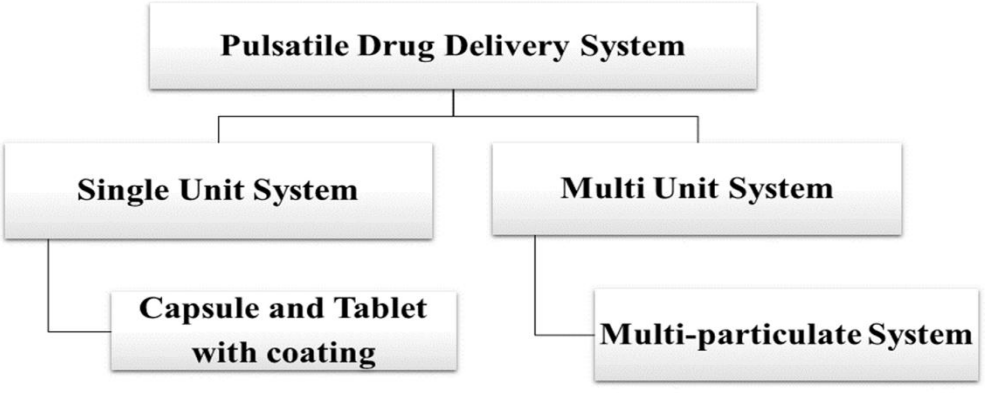
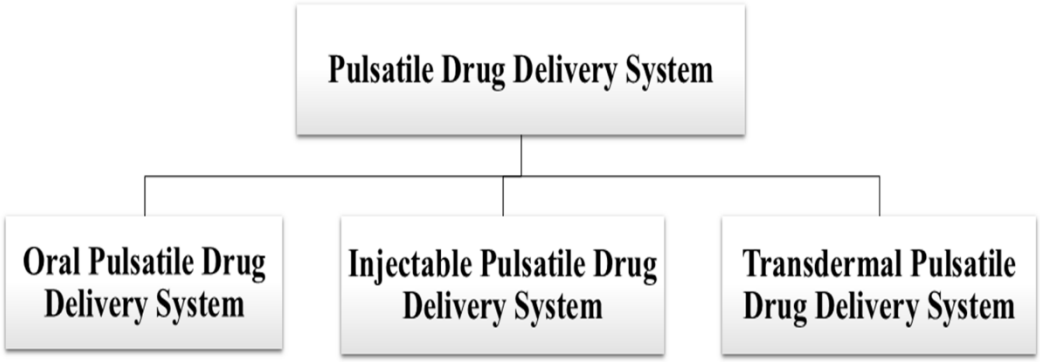


Figure 18. Classification of PDDS based on design and structure

5.4 PDDS Based on the Type of Drug Delivery Route

Based on the route of drug delivery the pulsatile drug delivery system is classified into broadly into 3 categories that is oral, injectable and transdermal system as displayed in (fig.19).



5.4.1 Oral Pulsatile Drug Delivery System

Oral pulsatile drug delivery systems are designed to release drugs at specific times, synchronizing with circadian rhythms or disease symptoms for optimal therapeutic benefits. Unlike conventional sustained- or immediate-release formulations, these systems introduce a predetermined lag phase before drug release. This strategy is particularly useful for conditions like asthma, arthritis, cardiovascular diseases, and sleep disorders, where symptoms follow predictable patterns. By utilizing technologies such as swellable polymers, erodible coatings, or osmotic pumps, these systems ensure precise drug release, enhancing bioavailability while minimizing side effects. The goal of oral pulsatile drug delivery is to improve patient adherence, optimize drug efficacy, and provide personalized treatment for chronic or time-sensitive conditions [64]. Research by Kadam D. Vinayak et al. focused on developing pulsatile tablets for colonic drug release using time- and pH-dependent polymers. Theophylline was chosen as the model drug, with Eudragit RL100 and S100 as key polymer components. Formulations coated with a 60:40 ratio of these polymers achieved controlled pulsatile release after a five-hour lag phase. In vitro studies confirmed that drug release was effectively delayed until colonic pH conditions were met, highlighting the potential of this system for chronopharmaceutical drug delivery, especially in asthma management [65].

5.4.2 Injectable Pulsatile Drug Delivery System

An injectable pulsatile drug delivery system is an advanced medical technology designed to release drugs in a controlled, periodic manner, mimicking the body's natural rhythms, such as hormone secretion. Administered via injection, this system employs mechanisms like programmable pumps or bioresponsive materials to ensure precise, time-dependent drug release [66]. By maintaining drug concentrations within an optimal therapeutic window, it prevents under- or over-medication, improving treatment outcomes [67]. This approach is particularly beneficial for conditions requiring timed drug delivery, such as hormone replacement therapy, cancer treatment, and chronic pain management. Research by Fujioka Yuri et al. explored the use of VP-R8, a D-octaarginine-linked co-polymer, to enhance dendritic cell-based vaccines. Using the murine dendritic cell line DC2.4 and the T-cell lymphoma line EL4, they demonstrated that VP-R8 significantly increa sed antigen uptake and presentation [68]. In vivo studies revealed that VP-R8-pulsed dendritic cells effectively suppressed tumor growth and enhanced tumor-infiltrating CD8 T-cell responses. These findings highlight VP-R8's potential in improving dendritic cell-based immunotherapy for cancer treatment [69].

5.4.3 Transdermal Pulsatile Drug Delivery System

Transdermal drug delivery offers a non-invasive alternative to parenteral administration, bypassing the harsh gastrointestinal environment and enhancing patient compliance. However, the skin's barrier properties limit the absorption of molecules larger than 500 Da, particularly hydrophilic ones[70]. To overcome this, both active and passive delivery methods are employed as depicted in (fig.20). Active approaches, such as microneedle technology, create micron-sized pores in the skin to facilitate drug permeation[71]. Passive strategies involve chemical enhancers and nanocarriers to improve drug absorption. Microneedles offer a promising approach by creating micro-sized pores in the skin to enhance transdermal drug delivery without stimulating pain receptors, thus improving patient compliance[72].

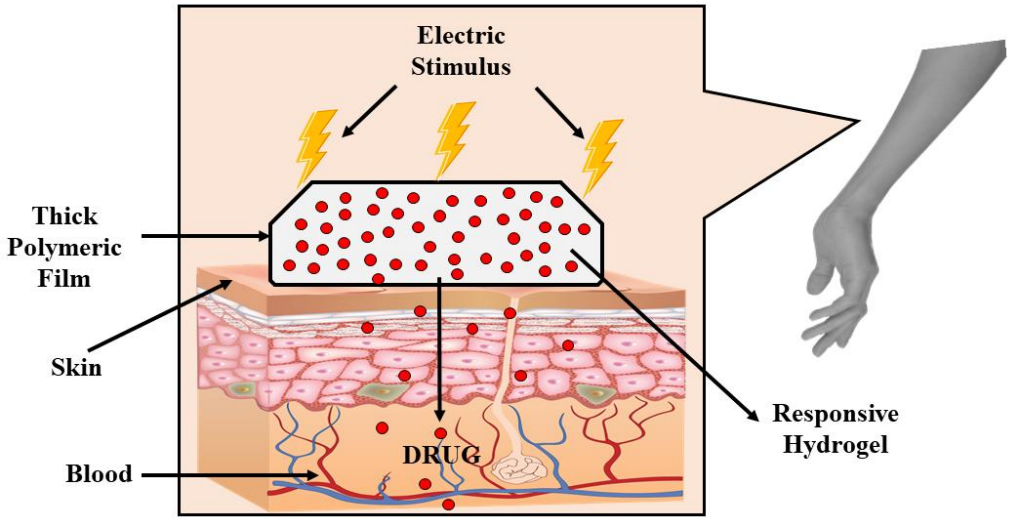


Figure 20. Transdermal System

Vaseem Sheikh Rifath et al., employed to enhance transdermal drug delivery, highlighting the significance of overcoming the skin's barrier properties. It discusses advanced techniques such as iontophoresis, electrophoresis, ultrasound, and microneedle systems that utilize mechanical, chemical, and electrical energy to facilitate drug permeation. The materials explored include reservoir-type transdermal patches with magnetic enhancements and dissolving microneedle arrays designed for effective drug delivery. Results indicate improved dermal bioavailability when compared to conventional methods, emphasizing the advantages of these innovative strategies[73]

6. MARKETED FORMULATIONS OF PDDS

Marketed formulations of pulsatile drug delivery systems, highlighting their composition, release mechanisms, therapeutic applications, and advantages. The table 5 provides an overview of commercially available products designed for chronotherapeutic drug release, ensuring optimal therapeutic outcomes. Various formulations utilize technologies such as time controlled, stimuli-induced, and multiparticulate systems. The listed products demonstrate the significance of pulsatile delivery in conditions like hypertension, asthma, and arthritis. This compilation aids in understanding advancements and trends in pulsatile drug delivery for improved patient compliance.

Table 5. Marketed Formulations of PDDS

Technology	Key Features	API	Disease	Manufacturer	References
PULSYS	Multiple drug-containing pellets with different coatings for staged release	Amoxicillin	Antibiotic therapy	Middlebrook Pharmaceuticals, Westlake, Texas, USA	[101]
DIFFUCAPS	Drug layered with polymers that erode at different rates, causing bursts of release	Propranolol HCl	Hypertension	Eurand Pharmaceuticals, LTD, Dayton, Ohio, USA	[102]
PORT	Non-eroding implant that releases drug	Methylphenidate	CNS Stimulants	Therapeutic System Research Laboratory,	[103]

	at a controlled rate			Michigan, USA	
IPDAS	Can be designed for single or multiple pulses, or sustained release	Naproxen sodium	NSAID	Elan Pharmaceuticals LTD, USA	[104]
CONTIN	Matrix system that slowly erodes to release drug	Theophylline	Nocturnal Asthma	Purdue Frederick, Nor-folk, CT, USA	[105]

7. RECENT RESEARCH DONE ON PULSATILE DRUG DELIVERY SYSTEM

Pulsatile drug delivery systems (PDDS) have attracted considerable attention in pharmaceuticals and medicine due to their ability to deliver drugs in controlled bursts at specific times. This approach is particularly beneficial for managing diseases requiring drug release patterns that mirror the body's natural rhythms, such as diabetes mellitus and cancer. PubMed data on publications across various disease categories from 2019 to 2024 offers insights into the growing interest in and diverse applications of PDDS as shown in (fig.21, 22).

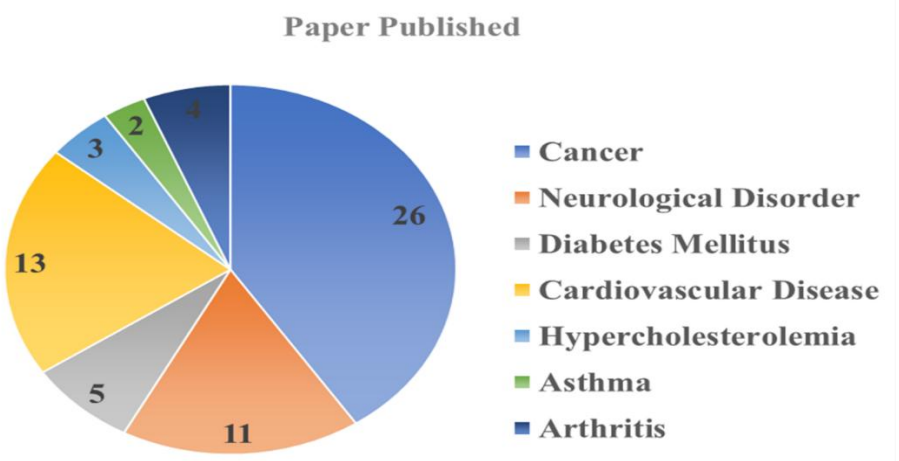


Figure 21. Paper published with respect to disease

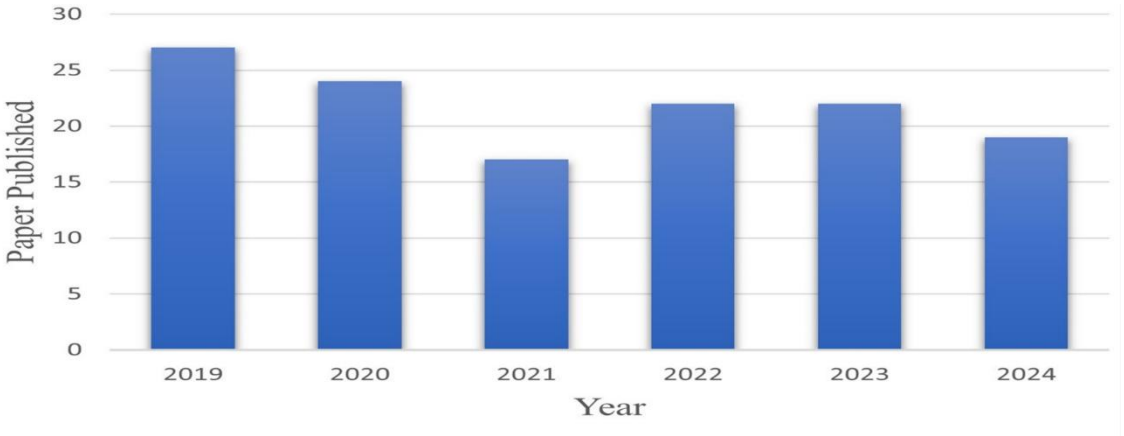


Figure 22. Paper published on PDDS over the years

7.1 Emerging Trends in Disease-Specific Research

Cancer: With the most publications (26), cancer is a primary focus for PDDS. These systems are crucial in chemotherapy for delivering precise drug doses at specific times, minimizing side effects while maximizing therapeutic effects. This targeted approach addresses the critical time-sensitive nature of drug release in cancer therapies.

Neurological Disorders: The second-highest number of publications (11) focuses on neurological disorders like epilepsy and Parkinson's disease. These conditions often require precise, time-dependent drug release to maintain therapeutic brain levels, making PDDS a promising approach for improved symptom management.

Diabetes Mellitus: With five publications, diabetes research demonstrates ongoing interest in PDDS. These systems could improve insulin control by mimicking physiological blood glucose fluctuations, providing a more natural and sustained delivery compared to traditional injections.

Cardiovascular Diseases: Thirteen publications highlight the demand for controlled, pulsatile drug release in managing conditions like hypertension, arrhythmia, and atherosclerosis. This approach could improve treatment effectiveness, particularly in preventing toxicity and ensuring optimal therapeutic response.

7.2 Therapeutic Areas with Limited Research Focus

Hypercholesterolemia, Asthma, and Arthritis: With relatively few publications (3, 2, and 4, respectively), these conditions represent potential areas for further PDDS research, especially for long-term treatments requiring intermittent drug release and tailored release profiles.

7.3 Trends in Publication Over Time

The publication data reveals fluctuating interest in PDDS between 2019 and 2024, peaking in 2019 with 27 papers. Despite these fluctuations, publication numbers have remained relatively consistent, indicating sustained, though slightly moderated, interest. This suggests that the initial surge in PDDS research, likely driven by novelty, has now stabilized, with a greater emphasis on refining existing technologies and targeting specific disease applications.

8. CONCLUSION

Pulsatile Drug Delivery Systems (PDDS) represent a paradigm shift in pharmacotherapy by offering time-controlled drug release tailored to the body's circadian rhythms. This approach enhances therapeutic efficacy, minimizes adverse effects, and improves patient compliance. The versatility of PDDS allows for applications across multiple disease domains, including cardiovascular disorders, diabetes, asthma, and cancer. Advances in polymeric coatings, osmotic systems, and stimuli-responsive mechanisms have further expanded the possibilities of achieving precise, site-specific, and time-dependent drug delivery. However, challenges such as formulation complexity, variability in drug absorption, and cost implications remain hurdles to widespread clinical adoption. Future research should focus on refining PDDS technologies, integrating smart drug delivery approaches, and exploring novel biomaterials to enhance drug stability and controlled release. With continued advancements in chronopharmacology and personalized medicine, PDDS holds significant promise in optimizing therapeutic outcomes and revolutionizing drug delivery systems for improved patient care.

9. CONSENT FOR PUBLICATION

Not applicable.

10. FUNDING

None.

11. CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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