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# Circadian rhythms regulated pulsatile drug delivery system

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***Abstract*---**As the body works both day and night, genetics influences how effectively an organism adapts to a changing environment. During diseases, conditions like asthma, ulcers, and rheumatoid arthritis need treatment at certain times of the day. We require pulse drug delivery to avoid unwanted side effects depending on the disease condition. Its ability to prevent drug receptor downregulation and provide effective therapeutic effects has made pulsatile drug delivery a preferred method for treating diseases governed by the body's circadian cycle. The pulsatile release is used for drugs when a steady drug release (zero-order release) is undesirable. In time-controlled TCS systems, the delivery system controls the drug release. In stimulus-induced PDDS systems, the drug release is governed by stimulation factors like pH, temperature, and enzymes; external stimuli like magnetic, electric, and ultrasonic stimulation impact the drug release. The above-mentioned releasing mechanism is used by marketed technologies such as CODAS®, IPDAS®, etc. Pulsatile drug delivery systems are well suited for drugs with chronopharmacological characteristics and dose needs throughout the night. A pulsatile drug delivery system ensures that medications are administered to patients with chronic diseases such as asthma, hypertension, and rheumatoid

arthritis at the right place, right time, right location, and the right dose. The present article concentrates on the circadian rhythm regulating pulsatile drug delivery system. It includes the basic concept of the Pulsatile Drug Delivery System and different methods. PDDS-related patents are also incorporated that cover current and future developments and PDDS products already on the market.

***Keywords*---**circadian rhythm, pulsatile, pulsatile technologies, time controlled pulsatile delivery, stimuli induced pulsatile delivery, externally regulated pulsatile drug delivery.

## Introduction

In the daytime, several body functions change dramatically. These fluctuations affect the disease state and the plasma drug concentrations. Human circadian rhythms are endogenous autonomous oscillators of physiological activities on the basis of the sleeping pattern. Genetics plays an essential role in how well an organism can adapt to a changing environment because it affects how well the body operates during the day and night (the 24-hour cycle). [1] All circadian rhythms in humans, whether they are related to neurobehavioral function, hormones, physiology, or behavior, are controlled by the biological clock. [2] Biological processes, according to a significant amount of research, are not constant but change throughout time. While most drug delivery research has concentrated on constant drug release rates due to the limits of administering drugs as per the disease rhythmicity, clinical research has demonstrated that the degree of rhythmic variation may considerably predict the most morbid and fatal event occurring for 24 hours. [3] Maintaining a constant plasma drug concentration is not always beneficial. Some diseases may need pulse drug delivery to prevent undesirable side effects and drug exposure [4], Asthma, ulcers, and rheumatoid arthritis are among the disorders that are influenced by the body's circadian rhythm and need medication to be taken at certain times of the day, particularly in the early morning hours. [5] Pharmaceutical researchers are concentrating their efforts on developing more effective drug delivery methods using current molecules. In this scenario, modified release dosage forms are crucial. These systems regulate the drug's release pattern, either with constant or programmed release rates. It is possible to do this using a pulsatile drug delivery system (PDDS). [6]

A pulsatile drug delivery system (sigmoidal release system) (Fig. 1) is defined as the instant and transient release of a specified number of drug molecules during a brief time immediately after a preset off-release interval, i.e., lag time. This delivery system is designed to release the drug according to a predetermined schedule, i.e., at the proper time and site of action. A pulse must be constructed in such a way that a complete and rapid drug release occurs after the lag phase, to align the release of drugs with circadian rhythms. [7] These delivery methods rapidly release the drug after a lag time, ensuring spatial and temporal distribution and boosting patient compliance. The main reason for using pulsatile release is for drugs where a constant drug release, i.e., a zero-order release, is not

desired. As a result, these delivery methods have sparked a growing interest in various diseases and treatments in recent years. [8]

The pulsatile drug delivery system is gaining popularity for treating diseases regulated by the body's circadian cycle and its ability to avoid drug receptor downregulation and provide effective therapeutic effects. These methods are advantageous for (i) substantial first-pass metabolism and built-in resistance to certain medicines. (ii) Localization of drugs that are absorbed or operate locally in the intestine. at a specific time. and (iii) Therapeutic adjustments to accommodate the patient's unique chronopharmacological needs. [9] These systems are best suited for drugs that are metabolized into pharmacologically active molecules, There are several types of drugs: those with long half-lives in vivo (resulting in a longer duration of action), those with short half-lives (requiring an excessive amount of active ingredients in dosage form), those requiring high doses (for therapeutic effect), and those requiring extremely low doses (for therapeutic effect). Moreover, a delayed burst release can improve absorption, cut down on side effects, and increase and decrease the amount of drugs taken. [10]

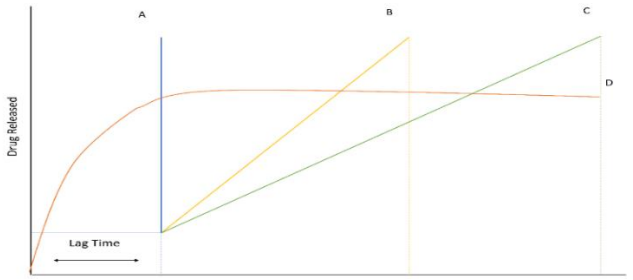



Fig.1: Drug release profiles: (a) Sigmoidal release after lag time, (b) delayed-release after lag time, (c) sustained release after lag time, and (d) extended- release without lag time

There are three main categories based on the pulse regulation of drug release:

- Time-controlled pulsatile release (one or more unit systems)
- Internal stimulus-induced pulsatile release
- External stimulus-induced pulsatile release system

**Circadian rhythms**

Circadian rhythms are self-sustaining, endogenous oscillators that enable organisms to adapt their behaviours throughout 24 hours in response to the changing environment caused by the Earth's rotation. The word "circadian" (circa dies day) is used because, under constant circumstances (i.e., not influenced by external time signals), the free-running period may be longer or shorter than, but not precisely, 24 hours. [11] (Fig. 2) An organism may anticipate and prepare for regular changes in the environment using these rhythms. The body's internal temperature, brain wave activity, hormone synthesis, and other biological functions are all tied to this cycle in some way. [12] The body's biological rhythms may be influenced by a variety of outside influences, including sunlight exposure and the use of certain drugs like coffee. Biological rhythms are classified into

ultradian, circadian, and infradian. Ultradian rhythms are shorter-duration rhythms that are typically less than a day, such as a 90-minute sleep cycle. [13] Suprachiasmatic nuclei in the hypothalamus and pineal gland are primarily responsible for our body's circadian rhythm. [14]

The circadian rhythm regulates several human physiological activities, including metabolic rate, pathophysiology, sleep cycle, and hormone synthesis. It has been stated that morning hours saw a higher rate of shocks and heart attacks. [15] Cortisol levels are higher in the morning, and its release is said to decrease during the day progressively. Blood pressure is also said to be high in the morning until late afternoon, then declines throughout the evening. [16] Gastric acid secretion typically follows a circadian rhythm, with a substantial spike of acidity occurring when the gastric pH level falls below 4 for at least 1 hour at midnight. [17] Osteoarthritis patients have less morning pain than rheumatoid arthritis patients, while individuals with rheumatoid arthritis report higher morning discomfort. The circadian rhythm of asthma has been associated with increased airway permeability and decreased lung function in patients with nocturnal asthma. Symptoms usually appear between the hours of 2:00 a.m. and 8:00 a.m., with the peak time being around 4:00 a.m. [18]. In general, cholesterol synthesis occurs more efficiently at night than throughout the day. Maximum production occurs in the early morning, around 12 hours after the last meal. Evening dosage with inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG CoA) reductase was shown to be more effective than the morning dose in several studies. [19] Insulin, for example, is a hormone that is released in response to a trigger in the body. Basal insulin release increases protein and glycogen synthesis in muscle and adipose tissue. To keep blood sugar levels stable, a triggered release of insulin happens both during and after the consumption of meals. [20]

Circadian rhythm oscillations progressively diminish with age in humans and rats. Still, it is unclear if this age-related decline is due to a malfunctioning core clock or inadequate ambient entrainment. Numerous environmental parameters may influence CR. Any imbalance in these parameters may result in circadian disturbances, which may lead to various diseases through a range of signaling pathways and physiological processes. [21]

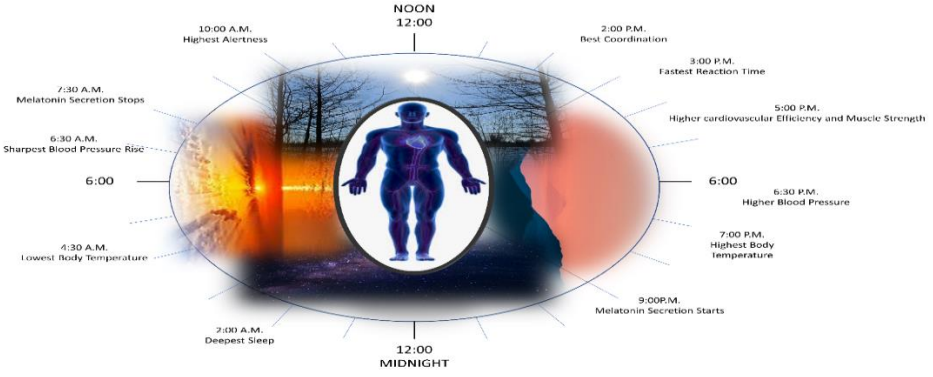



Fig.2: Circadian rhythms are endogenous oscillations that occur on a 24-hour cycle and exhibit distinct patterns of core body temperature, hormone synthesis, and other biological functions

**Established circadian rhythms diseases**

According to several studies, circadian alterations have been linked to a wide range of diseases, including cancer, dysplasia, cardiovascular disease, obesity, diabetes, and sleep disorders. When the circadian rhythm malfunctions, it affects organ development, causing problems to the brain and bones, resulting in dysplasia. In order for the brain to grow properly, it needs CR. A population with interrupted CR has a higher incidence of brain conditions such as sleep disorders and depression. Physiological processes such as cell proliferation, differentiation, oxidative stress, inflammation, synthesis, and cellular metabolism, all controlled by the circadian clock, might be the cause of these associations. as mentioned in Table: 1**.** [22]

Table No.1: Enumerates various diseases with their chronological behavior and symptoms. [23]

| Disease | Chronological behavior and symptom | Drugs Used |
|---|---|---|
| Diabetes mellitus | having an abnormally high level of sugar in the circulation following a meal, Frequent Urination, | Sulfonylurea, insulin, Meglitinide Analogues |
| Arthritis | C-reactive protein (CRP) is an inflammatory indicator. The blood levels of C-reactive protein (CRP) and interleukin-6 (IL-6) have increased. Pain in the early morning. | NSAIDs, corticosteroids, (DMARDs) |
| Cardiovascular drugs | BP increases quickly in the early morning, falls steadily in the late evening, and is at its lowest during sleep. | Nitro-glycerine, calcium channel blockers |
| Asthma | The lungs' tiny airways are inflamed and narrowed. Late night or early morning attacks are prone to occur. | Beta-agonist, antihistaminic |
| Hormone secretion | Melatonin and growth hormone are secreted at night, whereas testosterone and cortisol are secreted in the morning. | Budesonide (Micro-particles), Fluticasone furoate (Nasal spray) |
| Peptic Ulcer | The lining of the stomach, lower esophagus, or small intestine might develop sores. Acid secretion increases at night and day. | Proton-pump blockers |
| Attention-deficit syndrome | DOPA levels increase in the afternoon. | methylphenidate, amphetamine, atomoxetine |
| Hypercholes- terolemia | Night-time cholesterol synthesis is higher than daytime cholesterol synthesis. | HMG CoA reductase inhibitors |
| Cancer | Tumour blood flow is three times larger during daily activity phase than during daily rest phase. | Vinca, alkaloids, Taxanes |

**Various terminologies describe this method of delivering drugs at a specified time**

Chronotherapeutics: Chronotherapeutics is the study of drug distribution depending on the physiological behaviors of a disease throughout a specific time. It is becoming more apparent that the precise moment of drug delivery to patients maybe even more critical. Certain pharmaceuticals may perform better if they are administered at regular intervals throughout the day to maintain stable drug levels over the whole 24-hour period, according to the practice of administering medication at regular intervals. [24][25]

Chronopharmacology: Chronopharmacology is a branch of pharmacology that studies the effects of different drugs on the body throughout the day. [26]

Chronopharmacokinetic: The study of drug absorption, distribution, metabolism, and excretion over time is referred to as chronopharmacokinetics. Pharmacokinetic parameters, which are often thought to be time-invariant, are impacted by many physiological processes that exhibit a circadian rhythm. Gastric acid production, gastrointestinal movement, blood flow, drug-protein binding, liver enzyme activity, and renal blood flow all play a role in time-dependent fluctuations in drug plasma concentrations. The term chronotherapy refers to the synchronization of circadian with medicinal treatment. [27]

**Need of pulsatile drug delivery**

Some of the essential benefits of pulsatile vs traditional medication administration are listed below.

- First pass metabolism: Drugs like salicylamide and beta-blockers are subject to substantial first-pass metabolism. As a result, pulsatile drug delivery methods are preferable to traditional or sustained drug administration dosage forms to prevent first-pass metabolism. [28]
- Biological tolerance: Pharmacotherapeutic efficacy may be significantly reduced by continuous drug plasma profiles, such as the development of biological resistance to transdermal nitro-glycerine. [29]
- Special Chrono pharmacological needs: Circadian rhythms are well established in several physiological processes. Numerous symptoms and development of the disease have been observed to occur throughout specific times of the 24-hour day. For example, asthma attacks and angina pectoris episodes occur more commonly in the early hours. [30]
- Gastric irritation or drug instability in gastric juice: In the case of chemically unstable drugs in gastric juice and causing gastric irritation, the administration of a sustained-release formulation may worsen gastric irritation and chemical instability in gastric juice.
- Drug absorption differences in various gastrointestinal segments: Generally, drug absorption in the stomach is slightly slow, rapid in the small intestine, and significantly decreasing in the large intestine. Some drugs may need compensation for varying absorption properties in the gastrointestinal system. For example, in order to avoid the excretion of the drug in feces, the

delivery system should pump the drug out considerably more quickly when it reaches the distal part of the intestine.

- Local therapeutic need: The delivery of active substances to the site of inflammation without loss owing to absorption in Ultradian Rhythm to treat local diseases such as inflammatory bowel disease (IBD): Ultradian rhythms (therapeutic efficacy and minimizing side effects) may be achieved with shorter small intestine oscillations.
- Minimize drug-drug interaction: Delayed-release dosage forms have been suggested to avoid probable drug-drug interactions without modifying the distribution frequency of combination drugs, which could have a negative effect on several consecutive days of taking the same medications together. Their research also looked at how well the patients kept their word as part of their research. [31]

**These dosage formulations have several benefits, including**

- Avoiding unwanted side effects.
- The dosage has been reduced.
- Drug levels at the action site are almost constant.
- Minor Threat to dose dumping.
- Flexibility in Drug Delivery System Design.
- Not only less inter- but also intra-subject variability.
- Patient compliance has been increased.
- They are employed for drugs that have a strong first-pass effect and have a chronopharmacological action. [32]

**Some of the conditions that necessitate pulsatile release**

- Biological processes have a circadian rhythm, which fluctuates over time. Hormones, for instance.
- Lag time is critical for medications undergoing degradation in gastric acidic media, irritate the stomach mucosa, or provoke nausea and vomiting.
- BioPhase-intolerant drugs need a method to avoid their persistent presence in the biophase, limiting their therapeutic impact.
- Targeting GIT distant organs such as the colon necessitates blocking drug release in the top two-thirds of the digestive tract.
- Bronchial asthma, myocardial infarction, angina pectoris, rheumatoid illnesses, ulcers, and hypertension are examples of time-dependent diseases.
- Circadian rhythms may affect acid secretion, stomach emptying, cholesterol production, and gastrointestinal blood transfusion. [33]

**Disadvantages of pdds**

- Unreliable manufacturing and therapeutic efficacy.
- High production costs
- Manufacturing requires advanced technology.
- Experts needed for production.
- Many process variables.

- Multi-step formulation
- Inadequate drug loading ability
- Unpredictable in vitro-in vivo correlation. [34]

**Classification of pulsatile drug delivery system**

Various strategies have been developed and employed to create chronotropic systems for pulsatile drug release. For the most part, these techniques may be divided into three broad groups, as shown below in (Fig. 3).

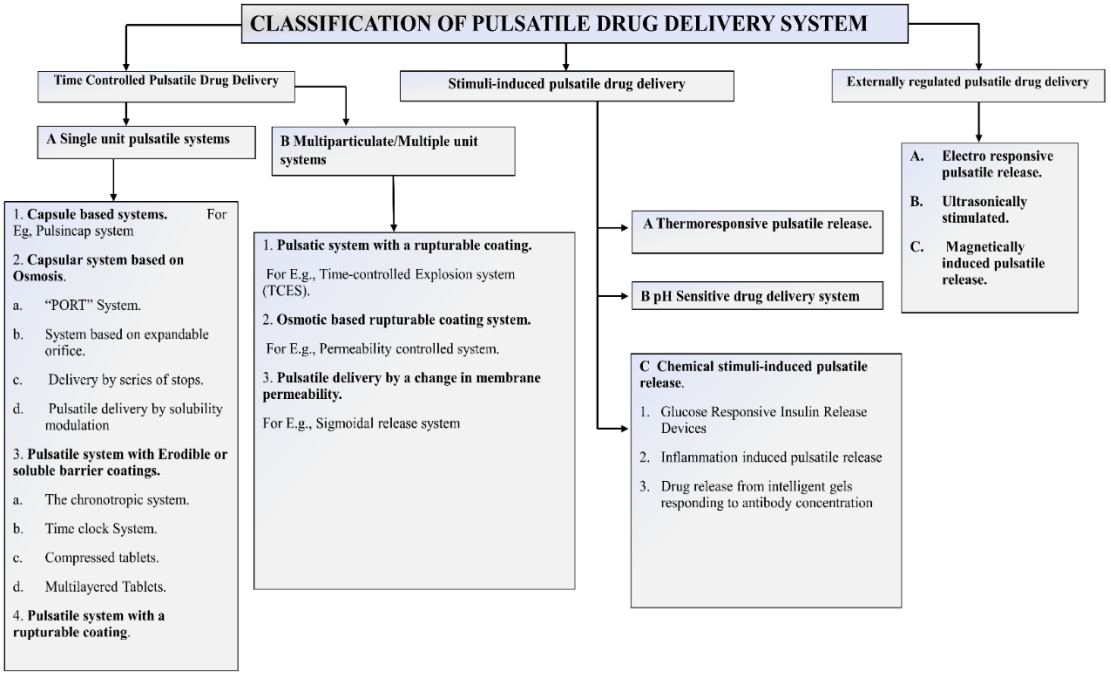



Fig.3: Classification of Pulsatile Drug Delivery System

**Time controlled pulsatile drug delivery**

The drug is released rapidly after a specified off-release period in time-controlled drug delivery systems. This kind of PDDS typically comprises the drug in two components: an immediate-release type and a pulse release type. These systems are categorized further into single-unit (e.g., tablets or capsule) and multiple-unit systems. [35]

**Single-unit**

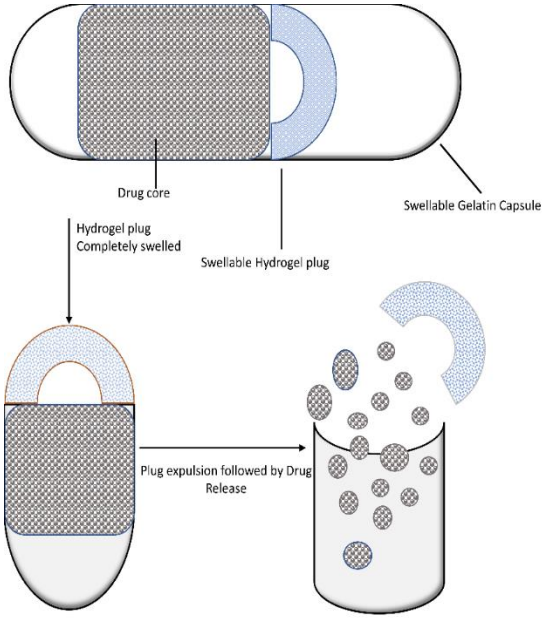
**Capsule-based systems**

Single-unit systems are often designed as capsules. The lag time is regulated by a plug that is pushed away by swelling or erosion, and the drug is released from the insoluble capsule body as a "pulse." The lag time may be achieved by altering the plug's dimensions and location. E.g., the Pulsincap system, (Fig. 4) R. P. Scherer

International Corporation, MI, USA, invented the Pulsincap® system in 1990. The system consists of a gelatin capsule body that has been impermeably coated with ethyl cellulose. The medication contents were sealed inside the capsule body using the molded hydrogel plug. [36]

**Capsular system based on osmosis**

This method encapsulates a medication and an osmotic agent capable of absorbing water in compartments separated by a movable barrier. The pulsatile delivery is achieved by a succession of stops along the capsule's inner wall. Such stops restrict the mobility of the partition but are overcome in sequence once the osmotic pressure exceeds a particular level. Osmotic delivery capsules ("osmotic pumps") (Fig. 5) work by allowing water to enter the capsule reservoir selectively. The capsule absorbs water through these walls due to a water-attracting chemical inside the capsule, which causes osmotic pressure across the capsule wall. For. ex: - PORT" The system is built on an expanding orifice, and the distribution is accomplished by a series of stops. By modulating the solubility, pulsatile delivery may be achieved. [37]



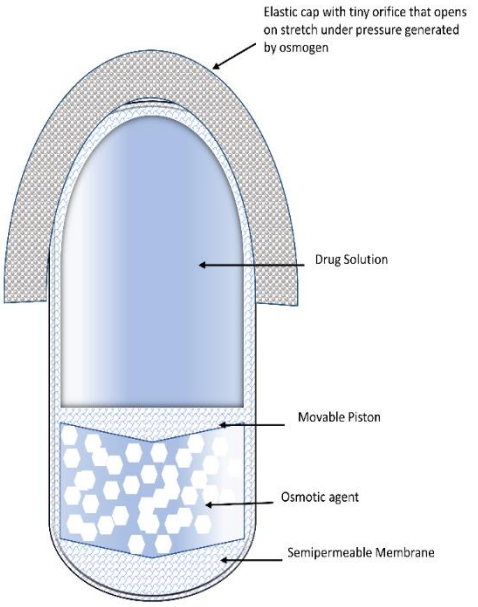




Fig4: Pulsincap system

Figure 5: Capsular system based on osmosis

**A pulsatile system with soluble or erodible or soluble barrier coatings**

A barrier layer is used in most pulsatile drug delivery systems. This barrier melts or corrodes after a certain amount of time, allowing the drug to be released from the reservoir core. Lag time varies based on the coating layer's thickness. [38] The chronotropic system contains a core containing a drug reservoir coated with HPMC. Outside this layer is an enteric-coated film to overcome intrasubject

variability in stomach emptying rates. The HPMC thickness and viscosity grade determine the lag period and onset of action. [39]

**A pulsatile system rupturable coating**

For drug release, these systems depend on coat disintegration. Effervescent excipients, swelling agents, or osmotic pressure are used to provide the pressure required for coating rupture. A citric acid and sodium bicarbonate effervescent combination incorporated into an ethylcellulose tablet core coat produces carbon dioxide after water penetration into the core, leading to pulsatile drug release upon coat rupture. [38]

**Multiparticulate/ multiple unit system**

Multi-particulate drug delivery systems use rupturable polymer coatings, soluble or eroding polymer materials to produce controlled and delayed release. As shown in (Fig. 6), for minimal dumping, short stomach residence duration, and precise release patterns.

**A pulsatile system rupturable coating**

For example, Time controlled Explosion system (TCES) (Fig. 7)
A swellable layer sits on top of the nonpareil sugar-coated sugar seeds as part of this multiparticle system. Swelling agents include sodium carboxymethyl cellulose, sodium starch glycollate, and L-hydroxypropyl cellulose. Polyvinyl acetate, polyacrylic acid, and polyethylene glycol are examples of this polymer group. [40]

**Osmotic based rupturable coating system**

The osmotic-based rupturable coating technique utilizes the interaction of osmotic and swelling effects. The core was made using the drug, a low-mass solid or perhaps fluid lipid material (e.g., mineral oil), and disintegrant. Following that, the core was covered with a cellulose acetic acid derivative. Lipid material is displaced when water enters the core when immersed in an aqueous medium. After the lipid material is depleted, the internal pressure rises until the essential pressure is achieved, resulting in a coating rupture. [40]

**Pulsatile delivery by a change in membrane permeability**

There are a variety of pharmacological formulations that have a delayed release for oral administration. As previously said, drug release must be regulated based on the active component's therapeutic goal and pharmacological properties. As a result, maintaining stable blood levels is not always ideal. On the contrary, to avoid habituation, the plasmatic rate should follow the patient's metabolic rhythm and the patient's individual demands at certain times and reduce the adverse effects caused by the active component. [41]

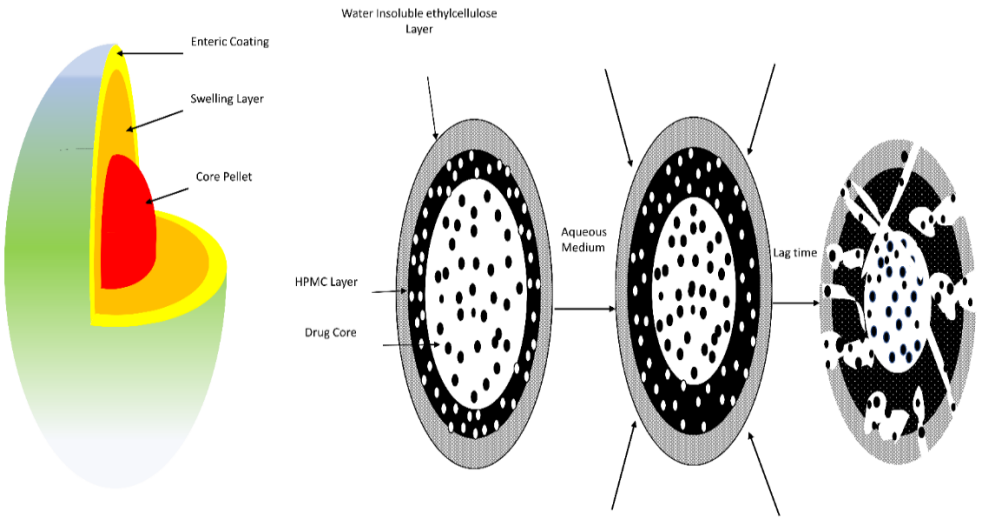



Figure 6: Multi-particulate drug delivery system & Figure7: Time –controlled explosion system (TCES)

**Stimuli induced pulsatile drug delivery system**

After stimulation by any biological factor, such as temperature or other chemical stimuli in these systems, the drug is released. Temperature-induced systems and chemical stimulus-induced systems are further subdivided based on the stimulus.

**Thermoresponsive pulsatile release**

Temperature variations are frequently used as a trigger to enhance the release of therapeutic drugs from numerous reactive drug delivery systems for disorders that evoke a rise in body temperature or fever. Methods for pulsatile drug release from thermoresponsive hydrogels have been developed. Thermoresponsive hydrogels have been used to create methods for pulsatile drug release. In such methods, the polymer swells or de-swells in response to a certain temperature, thus managing the drug's release state. Y.H. Bae et al. used the reversible swelling capabilities of butyryl acrylamide and iso-propyl-acrylamide copolymers to create pulsatile indomethacin release patterns. [42][43]

**Ph-sensitive drug delivery system**

A pulsatile drug delivery system consists of two parts: an immediate release component and a pulsed release component that delivers the drug in response to a change in ph. One of the advantages of a pH-dependent system is that multiple pH conditions are found throughout the digestive tract. With the help of pH-dependent polymers, it is possible to deliver drugs precisely where they are needed. Sodium carboxymethylcellulose, polyacrylate, and Eudragit E-100 are all

examples of pH-dependent polymers. Use these polymers as enteric coatings so that the drug may enter the small intestine more easily. [44]

**Chemical stimuli induced pulsatile release**

Chemical stimuli are among the most extensively studied stimuli for drug release on a pulsatile basis. Human metabolic changes may be employed as stimuli to promote drug release from PDDS. They may be further subdivided into insulin release devices that respond to blood glucose levels, inflammation-responsive pulsatile release devices, and intelligent gel release systems. [45]

**Glucose responsive insulin release devices**

Diabetes mellitus causes a rhythmic spike in blood sugar, requiring insulin administration at the appropriate time. Numerous methods capable of responding to variations in glucose levels have been created. A pH-sensitive hydrogel containing glucose oxidase immobilized in the hydrogel is one such system. When the blood glucose level rises, glucose oxidase converts glucose to gluconic acid, altering the system's pH. This pH shift causes the polymer to expand, resulting in insulin release. N, N-dimethylamino-ethyl methacrylate, chitosan, and polyol are all examples of pH-sensitive polymers. [46]

**Inflammation-induced pulsatile release**

Inflammation occurs at wounded location when subjected to physical or chemical stress. These inflammatory cells create hydroxyl radicals during inflammation. Yui et al. created drug delivery devices that reacted with hydroxyl radicals and degraded limitedly. Hyaluronic acid (HA) is destroyed by hyaluronidase or free radicals. In a healthy condition, hyaluronidase gradually degrades HA over time. When HA is injected into inflammatory areas, it is rapidly degraded by hydroxyl radicals. Thus, anti-inflammatory HA gels as potential implantable drug delivery devices may treat patients with inflammatory disorders like rheumatoid arthritis. [47]

**Drug release from the intelligent gels responding to antibody concentration**

Drugs are released from intelligent gels in reaction to antibody concentrations. Bioactive components come in a variety of forms throughout the body. Novel gels have recently been developed that vary their swelling and deswelling capabilities in response to variations in bioactive component concentrations. Antigen-antibody complex formation as cross-linking units in the gel is given special attention since such interactions are very precise. [48]

**Externally regulated pulsatile drug delivery**

**Electro responsive pulsatile release**

This technique uses polymers with high ionizable group concentrations and pH responsiveness to allow for swelling and deswelling depending on the hydrogel's proximity to the electrode. Polyelectrolytes (polymers with high ionizable group

concentrations throughout the backbone chain) are both pH and electro-sensitive. Xanthan gum, calcium alginate, and carbomer are all naturally occurring polymers. Methacrylate or acrylate derivatives, such as polyacrylamide and N-(3-(Dimethylamino)propyl) acrylamide, are common synthetic polymers. [48] Servant et al. Engineered A pulsatile drug delivery device controlled by an electric voltage on/off application. In situ radical polymerization was used to insert pristine multiwalled carbon nanotubes (pMWNTs) into a polymethacrylic acid (PMAA)-based hydrogel matrix. The addition of pMWNTs to the polymeric network improved the electrical characteristics of the hydrogel hybrids, and drug release from the gels was dramatically increased at high pMWNT concentrations, reaching 70% of the loaded dosage after two brief electrical stimulations. [49]

**Ultrasonically stimulated**

Skin, lungs, intestinal wall, and blood vessel permeability are all improved by ultrasound. In controlled drug delivery, ultrasonography has been described multiple times. Kost et al. [50] showed an ultrasound-enhanced polymer. Miyazaki et al. employed ultrasound to boost 5-fluorouracil release from an EVAc matrix up to 27-fold. The amount of 5-fluorouracil release increased with the power of ultrasound. [51]

**Magnetically induced pulsatile release**

One of the older methods was to utilize an oscillating magnetic field to regulate drug release rates from a polymer matrix. Magnetic carriers get their magnetic response to a magnetic field from integrated materials like magnetite, iron, nickel, cobalt, and so on. Magnetic carriers for biomedical applications must be water-based, biocompatible, non-toxic, and non-immunogenic. [52] This technique relies on the magnetic attraction that slows down the oral medication in the gastrointestinal system by adding an extra magnetic element to the tablets or capsules. Using an external magnet can slow food flow through the stomach and intestines in certain places. As a result, the duration and amount of drug absorbed in the GI tract can be altered. [53]

**Recently available marketed technologies for PDDS**

Cefrom®, CONTIN®, SODAS®, Egalet®, Geomatrix, GEOCLOCK®, Orbexa®, Pulsincap®, and CONTIN® are a few examples of commercially available pulsatile drug delivery technologies, and more are mentioned below in Table: 2.

Table No.2: Technologies for Pulsatile Drug Delivery

| Technology | Proprietary Name | Drugs | Mechanism | Disease | Producer | Ref No. |
|---|---|---|---|---|---|---|
| Cefrom® | Cefrom® LM | Diltiazem | It makes uniformly sized and shaped drug microspheres. Temperature, thermal gradients, mechanical forces, flow, and flow rate are applied to a solid feedstock (biodegradable polymer or bioactive agent form). | Hypertension | Fuisz Technologies Ltd | [54] |

| | | | | | | |
|---|---|---|---|---|---|---|
| Pulsincap® | Pulsincap™ | Dofetilide | Drug-loaded water-insoluble capsule with swellable hydrogel plug. It is then coated with an enteric coating that dissolves in the small digestive system, releasing the drug. The link expands and affects drug absorption. | Antiarrhythmic | Develops by R.P. Scherer International Corporation, Michigan, USA ( | [55] |
| CODAS® | Verelan® PM XL | Verapamil HCl | pH-dependent Multiparticulate release mechanism This capsule has numerous pellets with drugs and water-soluble and insoluble polymers around their inner cores. Polymer holes allow drug release. | Hypertension | Elan Drug Technologies, San Francisco, CA, USA | [56] |
| DIFFUCAP® | Innopran® XL | Propranolol HCl | Multiparticulate system that allows single or many drugs release profiles. Customized drug release profiles are established by covering a neutral core (such as cellulose spheres) with active drugs from aqueous or solvent-based drug solutions and one or more rate-regulating membranes. | Hypertension | Eurand Pharmaceuticals, LTD, Dayton, Ohio, USA | [57] |
| CONTIN® | Uniphyl® | Theophylline | Release by pulse during the time of an asthma attack in the morning. | Nocturnal Asthma | Purdue Frederick, Norfolk, CT, USA | [58] |
| IPDAS® | Naprelan® | Naproxen sodium | IPDAS uses Multiparticulate tablet technology to promote gastrointestinal tolerance to NSAIDs. Its a high-density bead controlled-release tablet. A polymeric membrane or micro matrix diffuses active components from multiarticulate. It enables drug distribution throughout the GI tract. | NSAID | Elan Pharmaceuticals LTD, USA | [59] |
| GEOCLOCK® | LODOTRA™ | Prednisone | The tablets are coated with hydrophobic wax to achieve a pH-independent lag period before delivering the drug at a preset release rate. | Rheumatoid arthritis | Skye Pharma | [60] |
| GEOMATRIX® | Coruno® | Molsidomine | The release is regulated by building a multilayered tablet with hydrophilic polymers and surface-regulating barrier layers. Barrier layers control drug release when exposed to liquid. | Angina Pectoris | Skye Pharma, Muttenz, Switzerland | [61] |
| OROS® | Covera-HS | Verapamil | It's an osmosis-based technique. A semi-permeable membrane with a delivery hole is laser cut and then formed into a tablet. This pill has two layers: the drug and an osmotically active | Hypertension | Alza corporation, CA, USA | [62] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | component. Its viscosity varies when it comes in contact with GI fluid. The osmotic pump forces the active medication out of the tube. Its often used in long-lasting pills. | | | |
| PULSYS™ | Moxatag™ | Amoxicillin | A new pulsatile release technique that uses soluble and insoluble coatings to provide one immediate release and two delayed-release components. | Antibiotic therapy | Middlebrook Pharmaceuticals, Westlake, Texas, USA | [63] |
| Egalet | Egalet® Technology | opioid products | Egalet Technology has two unique systems: continual release and delayed release. A matrix and an impermeable coat make up the continuous release mechanism. Two lag plugs in an impermeable shell constitute the delayed-release form. | - | Egalet Ltd, Denmark | [64] |
| Obrexa | Orbexa® Technology | proteins, enzymes | Using this approach and spheronization methods, one may produce controlled-sized and acceptable beads and a defined-based granulation extrusion with precise density. The beads may then be put into capsules or supplied in sachet form to manage the release rate further. | - | Aptalis Pharmaceutical Technologies | [65] |
| SODAS (Spheroidal Oral Drug Absorption System) | SODAS® | - | Multiparticulate drug delivery method using 1-2 mm spheroidal beads. The drug is applied to an inert core, then several layers of soluble and insoluble polymers are coupled with various excipients to generate the rate-controlling layer. | - | Elan Corporation LTD, USA | [66] |

**Patents on pulsatile drug delivery system**

PDDS has been the subject of several unique studies in the past, and researchers are now researching new concepts for pulsatile drug release in the current decade. From 1981 to the present, patent publications relating to pulsatile drug delivery have shown more promising systems with various breakthroughs in the drug delivery arena. The development of chronotherapeutic drugs in the future will need careful evaluation and integration with other new fields such as hydrogel and transdermal delivery technologies. The patents for PDDSS that have been applied for and awarded are listed below in Table: 3.

Table No.3: Patents on PDDS

| Patent Title | Patent Status | Outcome | Patent Number | Ref. No. |
|---|---|---|---|---|
| Programmable pharmaceutical compositions for Chrono drug release. | 26/10/2021 | *The programmable osmotic-controlled compositions of disclosure give a lag time independent of food, food type, pH, etc. The disclosed compositions may be configured to generate the desired lag period and then release the medicine at a certain rhythm.* | *US11154494B2* | *[67]* |
| Micro molded or 3-D printed pulsatile release vaccine formulations. | 28/05/2019 | *An adjuvant, a stabilizer, and release modifier are included in MM" or 3DP" formulations. An antigen is present in the formulation for the initial release, and optionally at ten to ninety-day intervals for subsequent release for ten to forty-five days following the first release.* | *US10300136B2* | *[68]* |
| Timed, pulsatile release systems | 14/02/2017 | *The dosage form includes multicoated drug particles (beads, pellets, and mini/micro tablets) with barrier and lag-time coatings. A predetermined lag time is followed by varying release characteristics for each TPR bead population.* | *US9566249B2* | *[69]* |
| Gastric release pulse system for drug delivery | 08/09/2015 | *The product is designed to provide temporary gastric retention of at least two of the first, second, and third pharmacological dose forms inside the patient's stomach or at a subsequent gastrointestinal location proximal thereto.* | *US9125803B2* | *[70]* |
| Pulsatile release of medicaments from a punctal plug | 08/09/2015 | *This invention offers techniques and equipment for delivering active agent* | *US9125715B2* | |

| | | | | |
|---|---|---|---|---|
| | | *pulsatile through a punctal plug. A tube is supplied for insertion into a punctal plug cavity. The tube has one or more pulsatile delivery units organized linearly. The pulsatile delivery units have an active agent core and an encapsulating layer surrounding them.* | | *[71]* |
| Ph-controlled pulsatile delivery system, methods for preparation and use thereof | 28/10/2015 | *In a pH-controlled pulsatile release system (PPRS), an active chemical, preferably a pharmaceutically active substance, is embedded in a pH-sensitive coating material with a swellable agent capable of taking in at least five times its weight in water.* | *EP1916995B1* | *[72]* |
| Pulsatile flux drug delivery | 16/09/2014 | The present invention relates to catheter-based drug delivery for mammals. The technique employs pulsatile flux to change the delivery geometry while limiting tissue migration away from the catheter shaft and preventing fluid backflow. In particular, the brain benefits from this kind of delivery. | *US8834446B2* | *[73]* |
| Pulsatile peri-corneal drug delivery device | 25/06/2013 | *The current invention relates to a pulsatile ophthalmic pericorneal drug delivery system with an annular body and a mechanism for delivering repeated dosages of a therapeutic composition over time.* | *US8469934B2* | *[74]* |
| Pulsatile release histamine H2 antagonist dosage form. | 16/12/2003 | *Using a unit dose, like a capsule, a drug can be delivered into the body at a set time each day. There is a 3–5-hour lag period between each bead population being released.* | *US6663888B2* | *[75]* |

| | | | | |
|---|---|---|---|---|
| | | *Each bead type has a fast or slow release.* | | |

**Conclusion**

The pulsatile drug delivery system is a modern breakthrough in the area of drug administration that is easy to formulate and has considerable therapeutic effects. These systems provide the drug at the proper time, location, and dose. Contrary to popular belief, pulsatile drug delivery systems are particularly effective in treating circadian disorders. Significant progress has been made in developing pulsatile drug delivery systems that efficiently treat diseases such as diabetes with non-constant dose regimens. Commercialization-ready products are now being designed to administer proteins, hormones, pain medicines, and other pharmacological components. Although some significant advances have been made in this area, pulsatile medication administration still has some unexplored characteristics that may open up new avenues via better engineering.

**Prospects**

The unlawful diversion of these modified formulations for profit has caused issues in the postapproval period as well as on a far broader scale. The FDA has become more reliant on creating and executing risk management plans as a mechanism for allowing a drug's approval to proceed while imposing certain conditions. Many different sorts of studies are being conducted on pulsatile drug administration to uncover circadian rhythm using appropriate technology everywhere. Due to its unique characteristics, such as the minimal risk of dosage dumping, patient compliance, and the criteria mentioned above, this delivery will be a leading technique to administer therapeutic agents in the future**.**

**Consent for publication**
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**Conflict of interest**
The authors declare no conflict of interest, financial or otherwise.

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