Heliyon 10 (2024) e29064

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

# A current era in pulsatile drug delivery system: Drug journey based on chronobiology

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ARTICLE INFO

*Keywords:*
Novel dosage forms
Pulsatile drug delivery
Dosing time
Extended time frame
Release period

ABSTRACT

Almost all biological processes in the human body are regulated by circadian rhythm, which results in drastically different biochemical and physiological conditions throughout a 24 h period. Hence, suitable drug delivery systems should be efficiently monitored to attain the required therapeutic plasma concentration and therapeutic drug responses when needed as per chrono pharmacological concepts. "Chronotherapy" is the fast and transient release of a particular quantity of drug substance post a predetermined off-release period, termed as 'lag time'. Due to rhythmic variations, it is typically unnecessary to administer a medicine drug in an unhealthy condition constantly. Pulsatile drug delivery systems have received a lot of attention in pharmaceutical development because they give a quick or rate-controlled drug release after administration, followed by an anticipated lag period. Patients with various illnesses, such as asthma, hypertension, joint inflammation, and ulcers, can benefit from a pulsatile drug delivery system. Thus, a pulsatile drug delivery system may be a potential system for managing different diseases. This review mainly focuses on pulsatile drug delivery systems. It reviews and discusses the rationale, drug release mechanism, need, and system classification. In addition, it covers mainly externally regulated pulsatile drug delivery systems and recent advances in pulsatile systems like artificial intelligence and 3D printing. It also covers the ethical issues associated with pulsatile drug delivery systems.

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https://doi.org/10.1016/j.heliyon.2024.e29064
Received 7 January 2024; Received in revised form 15 March 2024; Accepted 29 March 2024
Available online 4 April 2024

## 1. Introduction

Several global pharmaceutical industries have researched and discovered drugs to treat various ailments that affect the population.

**List of abbreviations**

| | |
|---|---|
| 3DP | Three-Dimensional Printing |
| ACE | Angiotensin-converting enzyme |
| ADHD | Attention Deficit Hyperactivity Disorders |
| API | Active Pharmaceutical Ingredients |
| BCS | Biopharmaceutical Classification System |
| CODAS | Chronotherapeutic Oral Drug Absorption System |
| DDS | Drug delivery system |
| DOPA | Dihyroxyphenylalanine |
| DOX | Doxorubicin |
| EC | Ethyl Cellulose |
| FDM | Fused deposition modeling |
| HMG | Human menopausal gonadotropin |
| HPC | Hydroxyl Propyl Cellulose |
| HPMC | Hydroxy Propyl Methyl Cellulose |
| LCST | Lower Critical Solution Temperature |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| OSDRC | One-Step Dry -Coated Tablet System |
| PDMAPAA | Poly (Dimethylaminopropyl acrylamide) |
| PEO | Polyethylene oxide |
| PIPAAm | Poly (N-isopropyl acrylamide) |
| PLGA | Poly (lactic-*co*-glycolic acid) |
| PMMA | Polymethyl methacrylates |
| pMWNT | Pristine Multi-Walled Carbon Nanotubes |
| PPDS | Pulsatile drug delivery system |
| PVA | Polyvinyl acetate |
| RP | Rapid Prototype |
| SSM | Single-cavity microcapsules |
| Sodium CMC | Carboxymethyl cellulose sodium |
| SSG | Sodium starch glycolate |
| TCES | Time-controlled explosion system |
| TB | Terbutaline sulfate |
| QPVP | Quaternized poly(4-vinyl pyridine) |

Developing a new drug for the market needs substantial financial investment and a long duration [1,2]. Over the past few years, efforts have been made to cut the cost and risk involved in drug development by focusing on formulating novel dosage forms. In practice, the classical drug delivery system has been made for prolong drug release to attain therapeutic benefits for a more extended [3,4].

Targeted therapy improves therapeutic potential and reduces systemic toxicity by releasing a controlled amount of the drug into the body [5]. Drug delivery systems (DDS) use advanced techniques developed in the modern era. The different endogenous physico-chemical factors like enzyme content, pH, and redox gradients control the drug delivery [6].

The development of "smart" delivery systems, which try to mimic physiological processes or respond to specific stimuli, have advanced significantly compared to classical DDS [7–9]. This smart DDS manufactured using, intelligent materials could be improved by continuously administering the drug using a pulsatile system [10–12]. This smart DDS can distribute drugs according to physiological requirements and have the potential to deliver drugs on time, on-site, and in appropriate quantities. This type of DDS is known as the “Pulsatile Drug Delivery System (PDDS).” Based on the circadian cycle of the human body, PDDS is created to deliver drugs at the ideal time, place, and quantity [13]. As a result, synchronizing drug treatment with biological cycles may result in significant health advantages and less harm to the patient. "Chronotherapy" is the medical term used for this type of treatment. The key benefits of chronotherapy have been determined for several conditions known as chronotherapeutic disorders, which are characterized by the emergence of symptoms at a particular time of the day. These diseases have a biological rhythm and affect multiple physiological systems, including the digestive, circulatory, respiratory, and skeletal systems, as well as processes like inflammatory processes [14, 15].

PDDS is described as the rapid release of a certain quantity of drug components over a short period following a predefined off-release delay, also known as lag time. Hence, these conditions promote the development of delayed fast-release systems, i.e.,

pulsatile release systems [16]. Many PDDSs are storage devices with polymeric barrier coatings on them. The coating and delays drug release from the core until the polymer has entirely corroded, broken down, or burst during or after a lag period. After that, the inner reservoir core rapidly releases the drug [17]. Asthma, hypertension, joint inflammation, and ulcer patients may benefit from pulsatile drug delivery [18].

## 2. Rationale for the use of a pulsatile drug delivery system

### 2.1. Advantages

Several controlled and sustained-release formulations have been developed and commercialized in the past few decades to treat various illnesses and disorders [4,19,20]. PDDS offers the release of one or more drug pulses at a desired time or location post-programmed lag time. Thus, it improves patient compliance [21]. It gives continuous drug levels at the action site and avoids fluctuations in plasma-drug concentration [22]. PDDS also provides immediate or extended drug release [23]. As for immediate drug release, PDDS possesses faster and transitory drug release within a short span immediately after predetermined release time. Moreover, extended-release forms permit sustained drug release after a lag [24].

### 2.2. Dis-advantages

PDDS, as studied, resulted in low drug loading and needed a higher proportion of the excipients. It suffers from a lack of manufacturing reproducibility and efficiency due to increase in process variables. The cost of production of PDDS is high as it requires technical skills and trained personnel to manufacture it. The preparation of PDDS comprises of multiple formulation steps. It also requires advanced technology for its manufacturing [22,25].

### 2.3. Drug administration in co-ordination with the circadian rhythm

The numerous research studies have shown that circadian rhythms are unstable and vary with time. The circadian rhythm can impact various physiological activities, and its anomalies are commonly linked to disease [26–28]. Only a few conditions have been demonstrated to have symptoms and onset depending on the 24 h clock [26,28,29]. For example, the symptoms of an asthma attack can worsen overnight, and myocardial infarctions frequently happens in the morning [30,31]. Most importantly the variations in the hormonal levels in the 24 h day-night cycle is maintained by the circadian clock and wake/sleep cycles, as shown in Fig. 1.

To get the medication at the target site of action, chronopharmaceutical drug delivery devices have been created with a pulsatile release pattern based on the disease conditions [32,33]. PDDS is based on the circadian cycle of the human body, and the medication is promptly release as a pulse following a lag time, thus improving at drug therapy. The drug delivery is synchronized with circadian dependent therapy [34]. PDDS can alter the time of scheduled pharmacological ingredients to fit circadian cycles, resulting in better drug treatment for various conditions [35].

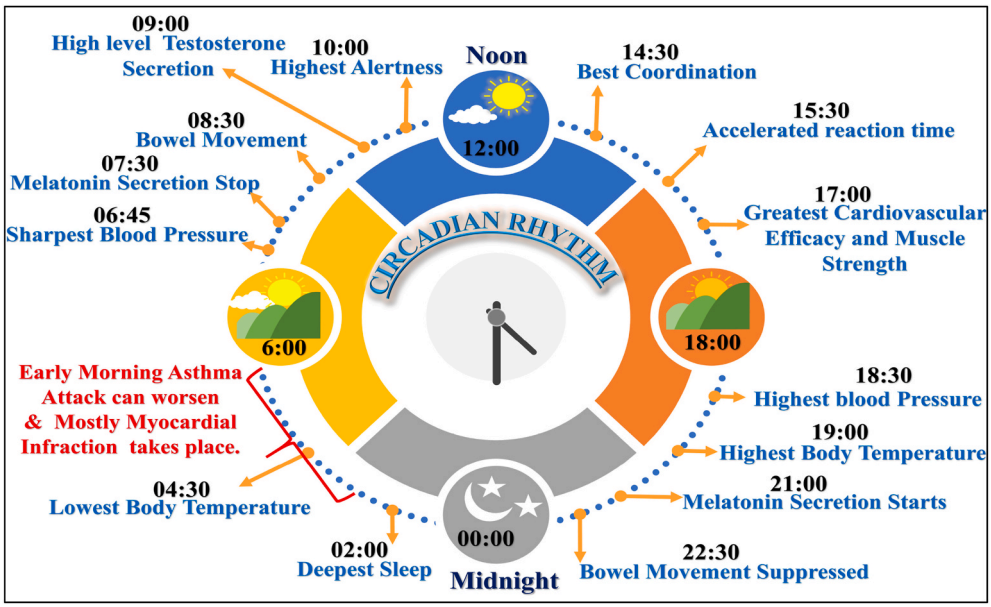


**Fig. 1.** Cycle for circadian rhythm.

## 3. Drug release mechanism of pulsatile drug delivery system

The drug release from PDDS (Fig. 2) takes place in the following ways.

### 3.1. Osmosis

When water enters specific conditions, an osmotic pressure can be built inside the drug molecule [36,37]. There is a difference in the concentration of the solute across the semi-permeable membrane, which is responsible for creating pressure. Water is permitted to pass via semi-permeable, and solute substances are mainly not permitted due to the selective nature of the membrane. The pressure subjected to the more-solute amount side to prevent solvent flow is known as "osmotic pressure [38]. Thus, osmosis is defined as water migration from a higher concentration area to a lower concentration via a semi-permeable membrane [39].

### 3.2. Diffusion

The diffusion of water takes place into the drug molecule. The drug substance diffuses outside through the delivery coat after interacting with the liquids of the gastrointestinal system.

### 3.3. Erosion

Fewer coatings suggest that they will disintegrate more slowly over time, allowing the active to be released [40]. There are two erosion mechanisms of drug release from pulsatile drug delivery systems. Surface erosion happens where the polymer meets water directly, where erosion and hydrolytic breakdown take place. Furthermore, as is frequently the case with hydrolytically degradable polymers, the rate of water diffusion exceeds the rate of hydrolytic destruction. In that case, the bulk of the polymer membrane will rapidly come in contact with moisture and start degrading [41]. In contrast to a solid polymer membrane, which gets thinner over time, the barrier maintains its dimensions while gradually losing solidity until it completely disintegrates. It is mostly seen in acid-catalyzed polymers, where autocatalysis-based degradation effectively breaks down the polymer from the inside out due to acid degradation products trapped within the polymer's bulk [17]. The thickness of the membrane plays a critical role in the behavior of erosion because it determines the amount of water and autocatalytic chemicals that are present in the membrane interior [42].

## 4. Need for pulsatile drug delivery

PDDS is required in conditions involving the body's circadian rhythm or when a drug breakdown takes the gastric region; hence, the lag time in the release becomes crucial. In addition, PDDS is required for targeted delivery to the specific site in the GIT (Gastro intestinal Tract) to deliver a drug that undergoes degradation via the first-pass effect and localized drug delivery to attain the desired therapeutic response. PDDS is shown to be having a promising advantage to patients impacted with time-dependent diseases where the amount of the drug is vital during a specific time, like angina pectoris, cancer, arthritis, gastric ulcers, asthma, and myocardial

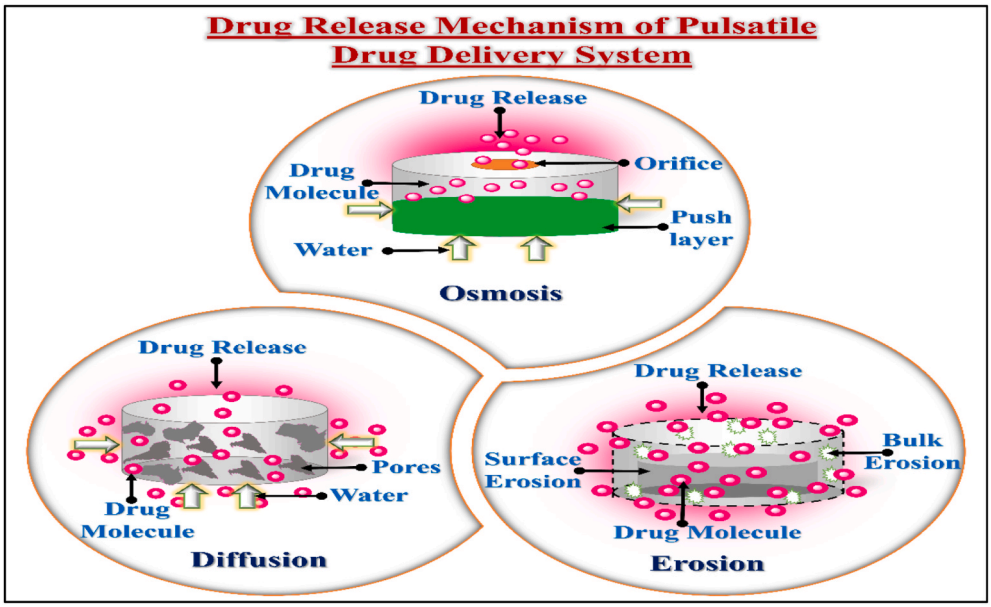


**Fig. 2.** Representation of pulsatile drug delivery system with a drug release mechanism.

infarction [43,44]. Table 1 represents the pulsatile drug delivery system in managing different diseases.

## 5. Classification of pulsatile drug delivery

### 5.1. Stimuli-responsive pulsatile drug delivery

The stimuli-responsive systems aid in the distribution of drugs due to the response to biologically produced impulses. The drug is discharged in these systems after being promoted by biological factors like heat and physiological response. There is an interest in designing a stimuli-sensitive administration mechanism that releases the therapeutic compound when specific enzymes are present. Hence, stimuli-responsive pulsatile drug delivery is a potential choice because it can be used as needed. Furthermore, they are classified as follows [46,47].

#### 5.1.1. Chemical stimuli-induced pulsatile release

The pH-responsive intelligent bio-materials could be developed, that adapt to ecological factors changes. It allows local therapeutic administration when the environment's pH seems alternatively basic or acidic [48–53].

Qu et al. studied N-carboxyethyl chitosan plus dibenzaldehyde-terminated poly (ethylene glycol) enclosed in doxorubicin like an intravenous hydrogel for liver fibrosis treatment in the latest report [51]. This investigation illustrated the pH fluctuations lead to physicochemical changes that allow this polymer's framework to expand and release the encapsulated drug.

Li et al. generated a familiar idea for developing boronate, fluorescent nanostructures contained in doxorubicin for internal visualization and inhibition of the cancerous cell line [54]. The pH adjustment from 5.4 to 7.4, the biopolymers demonstrated a quick-tempered emission of doxorubicin following a limited release [55]. An alternative method was used by a group investigating sodium bicarbonate within PLGA empty microspheres [56]. Under lower pH, bicarbonate forms carbon dioxide and water through carbonic acid breakdown, increasing gas pressure to breach the PLGA cover and expose the enclosed antibiotics. Further study has concentrated on the vulnerable implications of rising pH and has been used to target tissues, including the small intestines.

Pafiti et al. developed hydrogels containing blank particles trapped inside a poly (acrylamide), disintegrating and releasing the drug at pH 8.0 [57]. As the collide particles were dissolved at elevated pH, such pH-sensitive substance could retain its natural structural properties at pH 4 of the stomach and promoted the drug release. Moreover, the ability to produce polymeric biomaterials in various shapes and forms enables these systems to supply via several routes, including parenteral, intracoronary, intramuscular, oral, and epidermal. When pH-sensitive devices are used during installation or distribution, they are prone to off-delivery. Addressing such limitations while improving on the present benefits enables further discovery, innovation, and advancements in pH-responsive polymers, allowing the delivery of drugs [58].

#### 5.1.2. Thermo-responsive pulsatile discharge

The trigger signal frequently used for pulsatile discharge is temperature. The body temperature commonly deviates from the physical temperature (37 °C) when diseases or pyrogens are present. This variation from the typical range functions as a stimulus, causing therapeutic chemicals to be release from numerous temperature-responsive systems.

*5.1.2.1. Thermo-responsive hydro gel systems.* Thermo-sensitive gels undergo changeable volume transitions due to temperature variations. These gel contracts at a linear polymer's lower critical solution temperature (LCST). Since it changes volume, this property can produce a squeezing hydrogel by encapsulating the hydrogel inside a rigid capsule. For example, temperature-sensitive hydro gel's reversible volume change allows for on and off-release. PIPAAm cross-linked gels show thermo-responsive, intermittent swelling and deswelling phases; below 32 °C, they expand and shrink above this point. The end-functionalized PIPAAm was developed into block copolymers with lipophilic polymers. In aquatic solution, block composites generated micellar structures (with central shell structure) below the PIPAAm transformation temperature. This technique releases medication when the polymer enters an expanding or non-

**Table 1**
Pulsatile drug delivery system in the management of different diseases [45].

| Drug Used | Disease state | Chronological behavior |
|---|---|---|
| $B_2$ agonist, Antihistamines | Asthma | Precipitation of attacks in the early morning and night |
| Glucocorticoids, NSAIDs | Arthritis | The intensity of pain increases at night |
| Methylphenidate | Attention deficit syndrome | Enhancement in the DOPA level in the noon |
| Taxanes, Vinca alkaloids | Cancer | The bold flow to tumors is three times greater during each daily exercise. |
| Calcium channel blockers, Nitroglycerin, ACE inhibitors | Cardiovascular diseases | Blood pressure is lowest during the sleep cycle and steadily increases early in the morning. |
| Sulfonylurea, Insulin | Diabetes mellitus | Enhancement in blood sugar level post-meal |
| Proton pump inhibitors | Duodenal ulcer | Small bowel motility and gastric emptying are slower at night; gastric acid secretion is at its maximum. |
| HMG CoA reductase | Hypercholesterolemia | Cholesterol synthesis usually is higher during the night than day time |
| $B_2$ blockers | Peptic ulcer | Secretion of acid is maximum at noon and night. |
| MAO B inhibitors | Neurological diseases | Central pathophysiology of epilepsy and behavioral classification of convulsion actions |

expanding phase due to chemical interaction with the membrane, a pH change, or the induction of inflammation [36,59–61].

### 5.2. Time-controlled pulsatile discharge systems

A time-depending system is designed to discharge their pharmacological effects after a set time. To ensure drug discharge independence from the environment, the delivery mechanism must predominantly control the delay before drug discharge [62]. Most polymers with regulated drug discharge via surface deterioration of multilayer gadgets [63,64]. The time-controlled explosion system is shown in Fig. 3.

#### 5.2.1. Single unit pulsatile system

*5.2.1.1. Osmosis-based capsular structure.* The semi-permeable membrane-enclosed capsule that makes up the osmotic process. The capsule contained the drug formulation, an osmotically active ingredient, and an indissoluble stopper. The semi-permeable membrane of this capsule allowed water to enter when it came into contact with body fluids causing pressure to build-up and the indissoluble plug to be evacuated owing to pressure after some lag time [65]. A capsule covered with a semipermeable membrane is used in this method. When the capsule shell is delivered to be in contact with gastrointestinal fluids, the semipermeable barrier permits gastric fluid to enter. The plug expands and resulting in osmotic stress. The membrane explodes when the strain exceeds its tensile strength, and the time taken for the membrane to tear is called lag time. The plug is ejected after a little delay, releasing the medicine. Paracetamol, sugar (sorbitol), an osmotic regulator, and sodium dodecyl sulfate, a releasing accelerator, are included in a tough gelatin capsule developed by Barzegar-Jalali colleagues [66].

*5.2.1.1.1. Expandable orifice-based system.* An osmotically controlled capsular technology was devised to distribute the liquid drug. The liquid drug is soaked up into high porosity molecules, which discharge the medication via an orifice of a semi-penetrable compartment backed by a growing osmotic coat just after the barrier coat is dispersed in the liquid. This approach combines the advantages of prolonged discharge and a long half-life. Liquid drug delivery is appropriate for indissoluble medicines, polypeptides, and polysaccharides [67]. The stress within the capsule develops as osmosis proceeds, forcing the extension of the wall. Thus, when the flexible walls are stretched beyond a certain point the opening extends to the correct size, releasing the substance at the specified rate. Elastomers, including styrene-butadiene copolymer, have strongly been proposed. Depending on the thicknesses of the semi-permeable membrane and the barrier layer, pulsatile discharge happens after lag times of 1–10 h [68].

*5.2.1.1.2. PORT system.* The capsule comprises the drug and an insoluble plug carrying an osmotically active compound (Fig. 4). When the dissolving agent comes into contact with this capsule, the semi-permeable barrier permitted water to enter, creating stress that eventually lead to the discharge of the indissoluble drug. Such a device was used to dispense methylphenidate, which is used to treat attention deficit hyperactivity disorders (ADHD), through a method known as the pulsatile port system [69].

*5.2.1.2. Pulsatile system with soluble or erodible barrier coatings*

*5.2.1.2.1. Tablets.* The inner body and the top coat are directly compressed in a compressed layer, eliminating the need for coating solutions. At the same time, the inner body is prepared with ingredients that are insoluble in the gastric medium but are discharged into the intestinal area. To achieve this objective, a cellulose derivative could be employed. The advantages of press-layered pulsatile drug delivery systems include the ability to preserve acid-labile drugs and the low cost of manufacture. This technology's main disadvantage is that a huge volume of coating substances is needed appropriately [70,71].

*5.2.1.2.2. Multi-layered tablet.* A tri-coated tablet featuring two drug-carrying coats split by a drug-free gellable polymeric obstacle

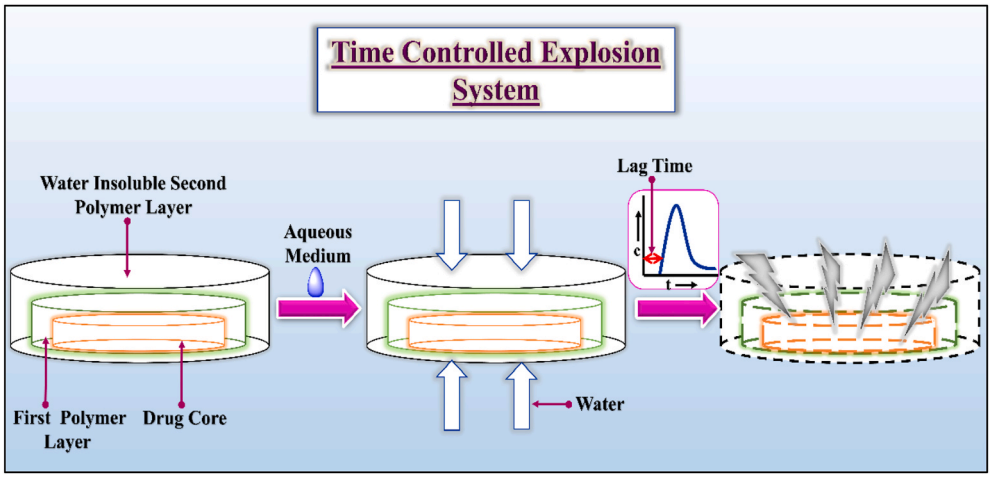


**Fig. 3.** Time-controlled explosion system.

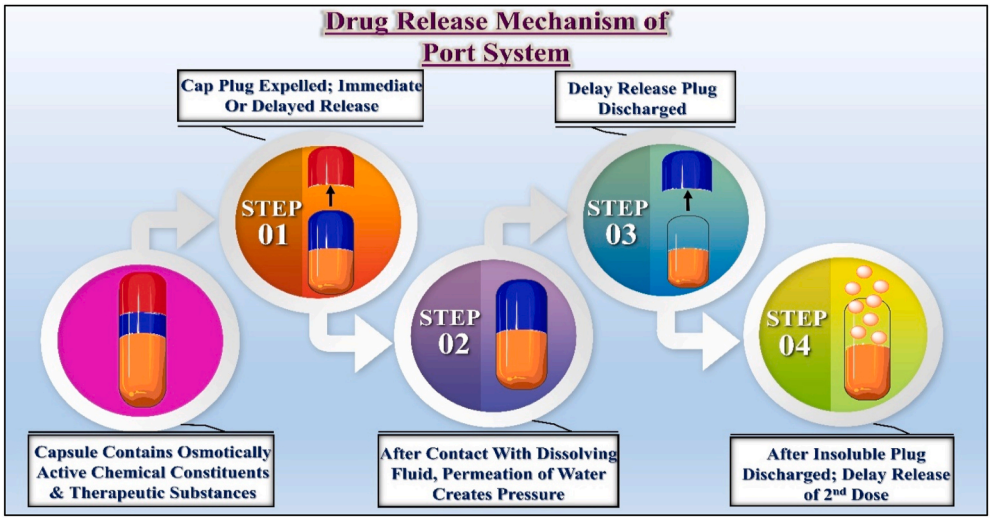


**Fig. 4.** Drug release mechanism of the PORT system.

coat can produce two pulses. These three coated tablets are impermeable ethyl cellulose layered on three sides, with the top section which is left uncoated. Upon contact with the dissolving media, the first dosage absorbed into the top coat is immediately released from the uncoated surface. The subsequent pulse is extracted from the bottom coat following the erosion and disintegration of the HPMC coat [72].

*5.2.1.2.3. Time-clock system.* The time-based system is a solid-state pharmaceutical state covered within a liquid dispersion delivery mechanism. At 75 °C, the core is covered with a water diffusion of a water-hating surfactant coat (beeswax, carnauba wax) [73]. A water-soluble coat is added to increase adherence to the core coat [74].

*5.2.1.2.4. Chronotropic system.* A drug-containing core is covered with water-loving swellable HPMC in the chronotropic system, causing a delayed release [75]. If the small intestinal transport time remains unmodified, implementing an outer enteric layer can bypass the variation in empty stomach duration and results in a colon-target discharge [76]. The HPMC thickness and viscosity grades address the delay time. Both *in-vitro* and *in-vivo* delay periods are highly associated with the quantity of hydrophilic retarding polymer used [77]. Poonuru et al. fabricated and evaluated methylphenidate hydrochloride bimodal chrono-controlled drug delivery system. The core tablets were formulated using super disintegrant Kollidon CL SF (4% and 8%) and diluents (microcrystalline cellulose PH 102, Ludipress). Among all the batches, batch F10 comprising HPMC E50 at 70% resulted in the best release, 60% slow for 4 h and 40% immediate burst release at 5 h. The best outcomes, which matched circadian differences in the disease state, were from the A1 formulation using Cellactose-80 as a diluent [78].

*5.2.1.3. Capsule-based system.* Such devices generally have an indissoluble capsule outer body that houses a medication and a plug. Due to swelling and dissolution, the plug is detached after a specific time. The Pulsincap® system (Scherer DDS, Ltd) depicted in Fig. 4 is an example of a system containing a water-indissoluble capsule outer body stuffed with drug preparation. When the plug touches dissolving media or gastrointestinal fluid, it expands and eventually pushes itself out of the capsule. A fast discharge of the medication accompanies this. The delay period can be modified by changing the plug's diameter and location [79,80].

Ye et al. self-healing microcapsules comprising single cavity microcapsules for pulsatile release of compounds. A different category of polymer-laden drug delivery systems has been studied to manage several diseases. However, the dosing frequency of many compounds like stimulators of interferon gene agonists, Covid vaccines, and protein-1 antibodies (programmed cell death) needs regular administration of intramural or intertumoral injections. This frequent administration leads to poor adherence, increased cost of therapy, and compromised therapeutic effectiveness. Hence, researchers formulated a multidose drug delivery platform using various molecular weights of polylactic-*co*-glycolic acid (PLGA) into self-self-healing single-cavity microcapsules (SSM). This strategy indicated a flexible approach to attain customized pulsatile drug release. It was 100% biodegradable with reasonable safety. Thus, single injection delivery comprising solely PLGA will have the potential for clinical translation and treatment of many diseases [81].

### *5.2.2. Multiparticulate/multiunit system*

*5.2.2.1. Pulsatile delivery by a change in membrane permeability.* The acrylic polymer containing quaternary ammonium groups associated with counterion in the release medium affects its permeability and water uptake properties. These properties are beneficial for the timed drug release in the colonic area. Eudragit RS and RL are the best choices for acrylic polymer. It contains a positively charged quaternary ammonium functional group and negatively charged hydrochloride as counterions. The water-soluble ammonium group shows that interaction with water functional groups caused polymer modification, leading to the enhancement of water permeation into the drug core and the provision of controlled delivery with the support of a definite lag time [82,83].

Ugurlu and IIhan et al. evaluated the pulsatile delivery of dexketoprofen trometamol using a combination of immediate-release and colon-targeted release mini-tablets using the wet granulation method. Eudragit polymers, namely Eudragit L100, S100, RS, 30D, and Surelease®, demonstrated good solubility at a physiological pH range of 6.0–7.4 and are used as coating polymers for colon-targeted mini tablets. Results showed that optimized immediate-release mini-tablet (F3) released ~ 90 % in 0.1 M HCL in the first 1 h, attributed to high solubility and drug permeability. The colon-targeted mini-tablet (CF2-A and CF2–B) was coated with Eudragit L100 and released the drug ~ 90% and ~80 % by the end of 3 h via the pan-assisted coating technique. It was found that the combination of both Eudragit polymers in a (3:1) ratio enhanced the drug release rate by ~ 95% within the first 6 h but did not achieve the colon target release due to premature drug release. Thus, findings concluded that the Eudragit S 100 and Surelease polymer combination has the potential to retard the drug release pattern and also maintain a deficient level for a more extended period [84].

Narisawa et al. have studied the sigmoidal time-controlled release profile of theophylline beads containing Eudragit RS 30D and NE 30D coating in the presence of succinic acid solution. Theophylline beads were formulated and coated with Eudragit RS and NE using a continuous flow granulator. A dissolution study revealed that beads coated with Eudragit RS 30D enhanced the theophylline release compared to Eudragit NE 30D coated beads in 0.5 M succinic acid aqueous solution for 12 h. The study concluded that Eudragit RS 30D enhances the permeation of theophylline via electrostatic interaction and distribution of succinic acid with the quaternary ammonium group of the polymer. Thus, it could be a promising polymer for obtaining a sigmoidal release profile of other compounds [85].

Che et al. prepared a biomimetic and bioactive scaffold loaded with teriparatide pulsatile delivery for local and systemic osteoporosis regeneration. Osteoporosis is one of the challenging problems linked to aging, leading to fractures (osteoporotic) and deaths. Hence, teriparatide is considered a crucial compound in osteoarthritis management, but adverse events restrict its clinical uses. Traditional drug delivery systems are not showing sensitive and short-term drug release. Hence, a teriparatide-loaded biomimetic and bioactive scaffold was developed for on-demand drug release. The study showed pulsatile release of the teriparatide from smart system causes of osteoporotic bone defects, also osteoporotic bone defects, and osteoporotic bone defects rejuvenation and good anti-osteoporosis activity. Finally, the study concluded that biomimetic and bioactive scaffolds loaded with teriparatide pulsatile delivery is a potential approach and may be commercialized for osteoporotic fracture management [86].

The impact of polycation coating on the extended release of the antigenic ESAT-61-20 peptide from PLGA nanoparticles was examined by Büyükbayraktar et al. The antigenic peptide epitope from the *M. tuberculosis* ESAT-6 protein was encapsulated in PLGA nanoparticles for this study with particle sizes 180–240 nm. They used quaternized poly (4-vinyl pyridine) (QPVP), a cationic polymer, to coat the nasal vaccination prototype to create a potentially positively charged system. The uncoated nanoparticles showed a 3-phase *in vitro* release with complete drug release in 4 months. Then, after 45 days, an extra 5% of the peptide was released. The coating of nanoparticles using QPVP resulted in drastic changes in the release period and peptide quantity. The antigenic peptide-laden nanoparticles coated with polycation promote more nitric oxide (NO) *in vitro* release than free and non-coated nanoparticles, proving the immunostimulant potential of fabricated nanoparticle systems. The study concluded that non-coated nanoparticles with the delayed pulsatile release of the antigenic peptide could be further studied in the production of single injection self-boosting vaccine formulations [87].

*5.2.2.2. Pulsatile system with a rupturable coating.* The pulsating system with rupturable coatings is a reservoir comprising active pharmaceutical ingredients, swelling polymer, and rupturable permeable polymer coating. This system's externally coated water-insoluble permeable polymer allows water permeation within the tablet core. In the tablet core, the permeated water swells the polymer, and buildup pressure within the system causes the polymer to rupture, leading to release from the ruptured polymer. The rapid delivery of drugs from the polymer coating depends upon pressure, and it can be achieved using swelling, gas-forming, and osmotic pressure-generating agents [25,62].

Liu et al. investigated the impact of sustained-release and pulsatile coating on iso-sorbide-5-mononitrate (5-ISMN) loaded multi-unit tablets to manage angina pectoris. An anti-anginal substance called 5-ISMN offers excellent oral absorption at various therapeutic dosages. Eudragit NE 30D was used as a coating polymer for sustained release, while HPMC E5 and Surelease® were used as swellable polymers. The study showed that 13% weight gain of Eudragit NE 30D provides ~90% of cumulative release over 240 min. The central composite optimization study revealed that a multi-unit pellet tablet containing ~2.46% weight gain of Opadry II (X1, isolation layer), ~12.33% weight gain of HPMC E5 (X2, swellable coating), and ~6.66% weight gain of Surelease® delivered the 5-ISMN within 8 h dissolution study, including ~ 4 h lag period and ~4 h sustained release period. This work concluded that multi-unit pellet tablets prepared using Opadry II, HPMC E5, and Surelease® exhibit pulsatile delivery with a lag time of 4 h [88].

Yadav et al. examined the swellable, rupturable polymer coating on glipizide-encapsulated microcrystalline cellulose. The extrusion-spheronization methodology prepared glipizide-loaded microcrystalline cellulose-based pellets (type I). Using fluidized bed coating methodology, it was coated with swellable hydroxypropyl methylcellulose polymer (HPMC E15 and K4M) and ruptured ethyl cellulose polymer (EC). This process yielded coated pellets (type II). A dissolution study on type II pellets showed that HPMC E15 with 20% coating (at the level of 5, 7.5, and 10% EC coating) achieved burst release ~ 35–50% within 1 h, formation of the lag period up to 6 h due to rupture of EC polymer and then sudden release for up to 12 h. The study results indicated a higher level of HPMC E15 and a lower level of HPMC K4M in combination with EC at all coating levels provide the glipizide pulsatile release via swelling and rupturing mechanism [89].

*5.2.2.3. Osmotic-based rupturable coating system.* The osmotic-based rupturable coating system works on the osmotic and swelling mechanisms. This system comprises a drug core, a low-density material, a disintegrating agent, and a cellulose acetate coating. The tablet coating allows water to penetrate the core and enhances internal pressure, rupturing the coating and releasing the drug [90].

Zhang et al. developed and investigated the pulse release formulations of terbutaline sulfate (TB) bilayer tablets prepared using a swellable HPMC layer and Eudragit (RS and RL) mixture as a semipermeable outer coating layer. The results demonstrated that bilayer tablets containing TB, sodium chloride (as an osmotic agent), and HPMC with a coating level of 2.5% displayed an initial lag time of ~2–4 h and then faster drug release up to 12 h compared to formula I (only sodium chloride without HPMC) and formula II (only HPMC without sodium chloride). According to the results, HPMC swelling behavior and osmotic pressure across the membrane are responsible for forming the lag phase and rapid drug release [91].

Hung et al. characterized omeprazole and propranolol hydrochloride containing multiarticulate pulsatile delivery system comprising Eudragit RS (as rupturable controlled release membrane) and sodium chloride (as osmogent). The study showed that the extrusion/spheronization technique in the presence of osmogent was the best way to make the drug/osmogent-containing pellets. The remaining two model active substances had a higher water solubility. The 4% osmogen produced a lag time of 0–12 h by controlling the membrane thickness, and the plasticizer concentration resulted in a pulsatile profile of propranolol hydrochloride. Thus, it was concluded that an osmotic pressure-activated pulsatile delivery system could also be utilized for chronotherapy in the clinic [48].

### 5.3. Externally regulated pulsatile delivery system

#### 5.3.1. Electro-responsive pulsatile delivery

One kind of remote-controlled drug delivery system is an electro-responsive pulsatile distribution device. In this system, external stimuli and triggers such as ultrasound, radiofrequency [92], magnetic field [93], electric field [94], and near infra-red illuminations are utilized as a source for drug delivery [95]. The electric field provides an accurate and effective stimulation to the delivery system by adjusting the voltage supply [95]. The hydrogel-based formulations, i.e., polymeric implants, have shown excellent biocompatibility concerning temperature, pH, and the electric field. Based on these external stimulations, the hydrogel-based polymeric implants provide a pulsatile release [96,97].

Servant et al. designed, constructed, and studied the structural integrity of electro-responsive carbon nanotube hydrogels for pulsatile delivery. An electro-responsive device was created to distribute drug molecules that pulse when electricity is on and off. PMAA-based hydrogel matrix was made by adding pristine multi-walled carbon nanotubes (pMWNTs) through *in situ* radical polymerization, causing the hydrogel more durable. PMWNTs and cross-linker concentration had a significant impact on the electrical and mechanical attributes of the hydrogel hybrids. Subsequently, the gel released 70% of the loaded drug with two short electrical stimulations. Finally, high concentration of pMWNTs and the polymer network made the hydrogel hybrids more electrically stable and increased the drug release from the gel [98].

Kagatani et al. evaluated rats' electro-responsive pulsatile insulin depot delivery from poly (dimethyl aminopropyl acrylamide) (PDMAPAA) gel. Insulin was loaded into an electro-responsive PDMAPAA gel and given to rats as a depot under the skin. The gel caused a pulsating drop in plasma glucose level under a continuous current of 1.0 mA (0.36 mA/cm$^2$). In the case of pharmacological bioavailability, it was found that the gel released 0.12% of the insulin after these two stimuli. Finally, insulin is released from the electro-responsive PDMAPAA gel when it moves through the gel network with the help of the electro-kinetic flow of solvated insulin and water molecules [99].

#### 5.3.2. Ultrasonically stimulated pulsatile release

Ultrasound stimulation acts as a permeation enhancer. It provides controlled drug permeation through the skin, blood vessels, lungs, and intestine. Ultrasonic waves in contact with pulsatile formulations caused polymer degradation, enhancing the drug release via initial burst and sustained release. The ultrasound irradiation-induced cavitation mechanism also facilitates the pulsatile drug delivery from the polymer-based formulations [45].

Emi et al. have characterized macromolecules (dextran, chemotherapeutics, and protein signaling factor) loaded calcium-crosslinked alginate hydrogel for pulsatile and sequential delivery profiles via signal and multi-pulse exposures. As a result of a single-pulsed ultrasound treatment that caused molecular release and gel erosion, it was challenging to get therapeutic delivery from the gels without destroying or overheating them. Nevertheless, multi-pulse ultrasonic exposures released more therapeutic material while maintaining gel erosion and, ensuring that temperature rises to a minimum. The study concluded that ultrasonically responsive polymeric hydrogel could control and improve complex therapeutic delivery approaches in cancer therapy [100].

#### 5.3.3. Magnetically induced pulsatile release

The magnetically induced pulsatile delivery system uses an oscillating magnetic field to control the active pharmaceutical ingredient (API) delivery from polymer-based formulations. Within the formulations, the incorporated magnetic materials, viz magnetite, nickel, iron, and cobalt, act as magnetic carriers and regulate drug delivery using polymeric pulsatile formulations. Magnetic carriers are water-soluble, biocompatible, non-immunogenic, and non-toxic to the human body. Following oral administration and under the influence of the external magnet, the magnetic carriers containing the drug slows down its transportation to the stomach and intestine, leading to a change in its drug absorption. Thus, it results provides pulsatile delivery [101–103].

Emi et al. have developed and evaluated pulsatile systems comprising chemotherapeutic compounds employing magnetically assisted hydrogel formulations. The study showed that the pulsatile pattern displayed more effective results in melanoma cells. Tests also found that parameters such as the drug length on periods, release rates, and pulse widths might be utilized to improve delivery patterns. It showed that magnetically responsive biphasic ferrogels can make pulsating mitoxantrone delivery profiles like those evaluated in the laboratory. The scheduling of pulses was managed by selecting the timing and duration of magnetic field stimulation. These findings evidenced that pulsatile-based chemotherapeutic delivery behavior could be advantageous. It also suggests that

magnetically assisted hydrogel formulations could be tools for improving pulsatile chemotherapeutic delivery patterns in the clinic [104].

## 6. Marketed techniques of the pulsatile release system

### 6.1. Pulsincap technology

The pulsincap device was created by the R.R. Scherer International Corporation in Michigan, United States. Its components include a half-capsule core (the non-dissolving section), a hydrogel plug sealed at the open end, and a water-soluble cap that may be removed with water. An enteric polymer coats the unit parts to circumvent having different gastric empty times. After some time, the plug comes out of the capsule and quickly releases the drug. An alternative way to make the drug was to create a four-layered spherical bead or granule. This structure had a drug core, sodium starch glycolate (SSG) or carboxymethyl cellulose sodium (sodium CMC) as a swelling agent and low-water soluble polymer as an outer membrane such as ethyl cellulose or Eudragit® RL. Because of the swelling, the membrane and the drugs are released quickly. Different viscosity scores of hydroxyl propyl methylcellulose (HPMC), polymethyl methacrylates (PMMA), polyvinyl acetate (PVA), and polyethylene oxide (PEO) were used to make the hydrogel plug. Another new idea was to make timed-delivery press-coated and enteric-coated solid dosage forms. It was created by combining diltiazem hydrochloride as the primary API with an enteric coating on timed-delivery press-coated pills [79,105,106].

Senthilnathan et al. evaluated the pulsatile delivery of glibenclamide using Pulsincap technology. According to the results, all dosage forms discharged their first pulse within 2 h. Then, after the hydrogel plug swells, they release their second pulse. When blood sugar levels rose after breakfast and lunch, glibenclamide in the form of a pulsing could be controlled via the first pulse post breakfast and the second pulse post lunch. Therefore, it is appropriate for people with diabetes to maintain their blood sugar levels after eating [107].

### 6.2. CODAS (chronotherapeutic oral drug absorption system)

Elan Drug Technology created the CODAS® method to deliver drugs for extended periods. The CODAS® technology has a lot of benefits, like a delivery schedule that fits with the body's natural circadian rhythm, a controlled-release, extended-release, and a pH, food, and posture-independent rate of release [108,109].

Verelan® PM is also made with CODASTM technology for bedtime dosing and has a 4–5 h delay in drug release. These pellet-filled capsules allowed the drug to stay in the body for a more extended period. Verelan® PM formulations were made to start the verapamil release up to ~ 4–5 h. The release-controlling polymer comprises polymers that can be dissolved in water and those that cannot be dissolved in water. Each day, the aqueous part from the intestines showed contact with the polymer coating on the beads. The pores allow drugs to enter and exit the polymer coating after dissolution. The low water-soluble polymer still serves as a barrier to keep the drug from being released in a controlled way. The rate at which it comes out is almost unaffected by pH, posture, or food. A system like Verelan® PM, which has a lot of different parts, doesn't have to move around in the intestine to work [110].

### 6.3. OROS® technology

The OROS systems were used for APIs that didn't dissolve in water. Bilayer and trilayer dosage cores comprise one push and an API layer. There are drugs, osmogens, and suspending agents in this layer. The push layer has osmogens and aqueous swellable polymers. A lot of different OROS® technologies (ALZA Corp.) have been made, including Concerta®, Procardia XL®, and Ditropan XL®. The new L-OROS® SOFTCAP™ system combines the parameters of a controlled profile and improved bioavailability for easier administration and effectiveness [111]. The L-OROS technology is a self-emulsifying liquid carrier-based formulation. It mainly contains the drug encapsulated in non-aqueous liquid carriers, which helps to absorb the drug from the gastrointestinal membrane and bloodstream. Following oral consumption, the formulations release the drug within the gastrointestinal tract (GIT), disperse in the G.I. fluid, enhancing the drug solubility and, thus, bioavailability [112,113].

### 6.4. OSDRC technique (one step dry coated tablet system)

Due to the time-consuming nature of the traditional technique, manufacturing costs are increased along with the chance of failure, which could result in a shortage of core tablets. The OSDRC technique was developed to tackle this problem. With the aid of a center and an outer punch, it enables the production of dry-coated tablets in a single pass. The punches are rotated on a platter, while the tablets are produced in a single step [6,71,114].

Sucrose (amorphous) and the OSDRC method were utilized by Ando et al. to evaluate a sugar-coating approach for moisture-protective tablets. The outer covering of the OSDRC tablet was composed of amorphous sucrose, a sugar coating. Researchers investigated compressed amorphous sucrose's water vapor permeability, tensile strength, disintegration time, and isothermal crystallization behavior. Amorphous tablets' crystallization behavior was affected by compression pressure, but water vapor absorption tests showed that they behaved similarly to amorphous powder. After compression at approximately 200 MPa, it was found that crystallized amorphous sucrose was less moisture-protective and had a lower water vapor permeability coefficient of about January 2000 when compared to a tablet produced with microcrystalline cellulose (MCC), lactose, hydroxypropyl methyl cellulose (HPMC) and sucrose crystal mixture. The f addition, which affects the physicochemical properties and water vapor permeability. It indicates that

the sugar-coated tablet made with OSDRC and amorphous sucrose was moisture resistant. The findings concluded that the sugar-coating technique benefited moisture-resistant manufacturing tablets [115].

### 6.5. DIFFUCAPS® technology

The solubility and absorption of certain compounds are affected by pH differences in GIT. This pH sensitivity can be problematic, especially when formulating continuous or regulated release formulations. Dipyridamole and carvedilol are soluble APIs in the stomach's acidic environment but insoluble in the intestine's alkaline environment, where active drug absorption is optimal. Weak and essential pharmacological molecules insoluble at pH $> 5$ are mainly concerned. The once or twice-daily administration of individual pharmaceuticals or drug combinations with pH-dependent solubility patterns and minimal solubility in physiological fluids can be administered with the help of Eurand's Diffucaps technology [116]. Diffucaps technology is a multi-particulate bead formulation of several coats of medication, polymer, and excipients that govern drug release. For medicines with a low solubility profile in intestine pH and physiological fluids, the beads contain a coating of alkaline buffer and organic acid to modulate drug solubility by generating an optimum pH environment. Diffucaps beads can be compressed into capsules and orally disintegrating tablets. They have a diameter of approximately 1.5 mm. Furthermore, diffuser-based capsule formulations provide a variable dosing form by allowing patients who have trouble swallowing tablets and capsules to sprinkle the contents on food. Diffucaps flexibility enables easy modification of the drug delivery pattern and dosage strength to obtain desired *in vivo* effects [117]. All the marketed technologies of PDDS are depicted in Table 2 and Fig. 5.

## 7. Artificial intelligence in PDDS

The development of implantable drug delivery systems needs to consider several parameters, such as adjustment of dose, site-specific delivery, sustained release, and smart control system [119]. The drug delivery methods include a micro pump mechanism, ultrasound, and site-specific delivery using microrobots [120–122]. The microfluidic system is the potential approach for developing a micro or nanoparticles-laden drug delivery system [123,124]. For the drug to be programmed, electronic items, wireless hardware, and power supply have been fixed in a microchip implant (MicroCHIPS, Inc.), followed by a pulsatile drug release for six months [125].

## 8. 3D printing in PDDS

Capsula r-shaped Chronocaps are based on a PDDS made using a novel 3D printing technique. The capsules of different thicknesses can be made using injection molding methods using other hydrophilic polymers that yield a variable lag time [126].

Melochhi et al. determined the effectiveness of such capsular devices formulated by injection molding and 3D printing. The developed 3D-printed devices showed a lag time before drug discharge from the device. Moreover, the morphological modifications were identical to the system fabricated by injection molding. Finally, it was concluded that 3D printing could substitute the injection molding method [127].

Dumpa et al. developed novel core-shell gastro retentive floating pulsatile drug delivery systems by combining direct compression and hot-melt extrusion-paired fused modeling (FDM) 3D printing. The polymer containing filaments [Hydroxypropyl cellulose (HPC)

**Table 2**
Marketed pulsatile drug delivery technologies.

| Marketed technology | Developed by | API | Polymer used | Working principle | References |
|---|---|---|---|---|---|
| Three-dimensional printing® (3DP) | Rapid Prototype (RP) Technology | Chlorpheniramine and Diclofenac sodium | Eudragit RL100, HPMC, lactose | Erosion-based dual release and zero order release | [45] |
| Pulsincap® | R.R. Scherer International Corporation, Michigan, US | Diltiazem HCL and Diclofenac sodium | Ethyl cellulose, Eudragit RL, HPMC, PMMA, PVA and PEO (Water insoluble polymer), Sodium starch glycolate, and sodium CMC (swelling agent) | Time and pH-dependent controlled release | [106] |
| CODAS® | Elan Drug Technology, Ireland Verelan® PM (Proprietary products) | Verapamil | Water soluble and insoluble polymer | Controlled-onset release | [110] |
| OROS® | ALZA Corporation, USA Procardia XL®, Ditropan XL®, Concerta® (Proprietary products) | Nifedipine, Paliperidone and Methylphenidate HCl | Osmotic agents and water-swellable polymer | Controlled-release and bioavailability enhanced delivery | [112] |
| OSDRC® | Sanwa Kagaku Kenkyusho Co., Ltd. Japan | Acetaminophen | HPMC and Eudragit L100 -55 | Timed and controlled release | [118] |
| DIFFUCAPS® | Eurand Pharmaceuticals, Inc., USA Innopran XL® and AMRIX (Proprietary products) | Propranolol HCL and Verapamil | Organic acid or crystallization inhibiting polymer, controlled release polymer | Controlled release | [116,117] |

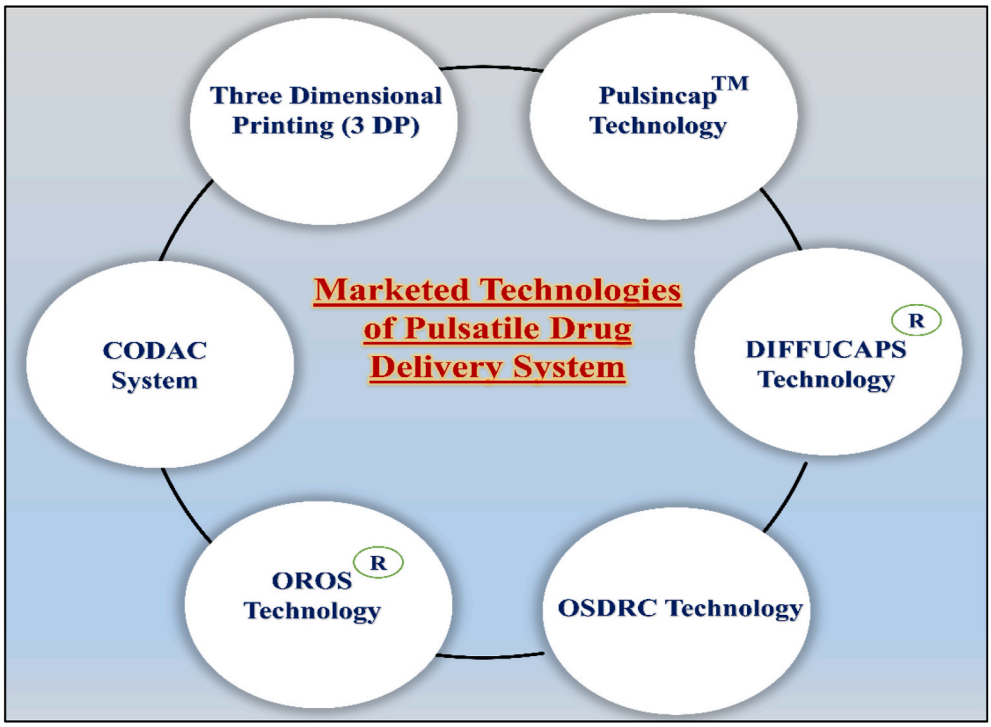


**Fig. 5.** Marketed technologies of pulsatile drug delivery system.

and ethyl cellulose (EC)] were prepared by hot-melt extrusion technique and were used as in FDM 3D printing. Theophylline tablet is the main component that has been directly compressed. The tablet shell to make pulsatile floating dosage forms with various dimensions was designed, printed, and characterized. During the study, it was observed that all core-shell tablets were floated, showing a good floating nature throughout the release study without any lag time. The lag time was 30 min to 6 h for pulsatile drug release. The filament configuration's ethyl cellulose content significantly ($p < 0.05$) affected the lag time. The formulation with a lag time of 6 h, and infill density of 100% was chosen as the optimal batch. It also contained 0.5% of ethyl cellulose. Therefore, FDM 3D printing is seen as a viable approach to develop complex, personalized drug delivery systems for pharmaceutical purposes [128].

## 9. Conclusion and future perspectives

The pulsatile drug delivery system has gained popularity recently due to its ability to discharge the drug into the patient's body at the proper time, location, and dosage. The progressive development in the design of pulsatile formulations considering circadian rhythm creates scientists' significant interest in preparing chrono pharmacotherapy-based formulations. Chrono pharmacotherapy effectively deliver drugs for the patient in a well-organized manner. The conventional formulations provide an incomplete and partial drug delivery to the site of action. Hence, the development of alternative formulation strategies, such as stimuli-responsive, single unit, rupturable membrane, and external stimulation, can advance the conventional system and organize its pulsatile release with the consideration of patient needs. According to circadian disorders, many traditional systems have been engineered into pulsatile systems to improve drug delivery. However, more comprehensive studies concerning the selection of polymer, internal/external stimulation, and drug-polymer interaction are warranted to understand better the pulsatile release mechanisms. The ethical issues pertaining to the PDDS system need to be studied in future for its better understanding. More advanced studies are needed to predict PDDS and its mechanism for managing various diseases.

## Funding

The funding is provided by Datta Meghe Institute of Higher Education and Research (DU), Sawangi (Meghe), Wardha, 442001, Maharashtra, India.

## CRediT authorship contribution statement

**Amarjitsing Rajput:** Writing – original draft, Conceptualization. **Prashant Pingale:** Writing – original draft. **Darshan Telange:** Writing – original draft. **Shubham Musale:** Writing – original draft. **Shailesh Chalikwar:** Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

This review article is a motivational compilation of our regular pulsatile drug delivery system research. The authors extend their gratitude to the Management and Principal, Dr. S. J. Surana of R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, and Principal Dr. Atmaram Pawar of Bharati Vidyapeeth (Deemed to be University), Poona College of Pharmacy, Pune for providing necessary library facilities for doing literature.

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