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Review Article

PULSATILE DRUG DELIVERY: A STRATEGY FOR TREATING CHRONOTHERAPEUTIC AILMENTS

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ABSTRACT

Modern drug delivery systems have been promoted to a unique notion of chronopharmacology, i.e., the ability to provide the medicament to a patient in a staggered profile, as the discipline of chronobiology has advanced. The main disadvantage of developing such a delivery system that fits the circadian cycle is the lack of accurate technology (Pulsatile drug delivery system, PDDS). Pulsatile devices are gaining popularity because they deliver the medicine to the correct region of action at the correct time, allowing for spatial and temporal dosing and compliance among patients. These technologies are meant to work with the body's natural circadian cycle. The circadian rhythm affects various biological systems in humans, including metabolism, physiology, behaviour, sleep patterns, hormone synthesis, and so on. This article addresses several methods, such as osmotic systems, capsular systems, single and multiple-unit programable devices that rely on soluble or erodible polymer coatings, and the usage of rupturable membranes. The present review covered the rationale for the creation of pulsatile drug delivery systems, benefits, limitations the types of diseases that require pulsatile release, categorization, and assessments of pulsatile system of drug delivery.

Keywords: Pulsatile system of drug delivery, Chronotherapeutic ailments, Circadian cycle

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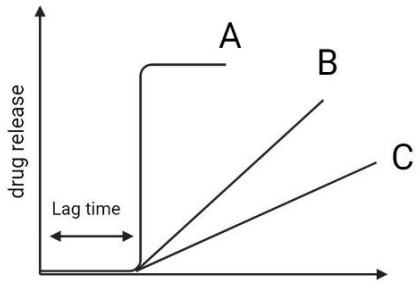
INTRODUCTION

The majority of the drug delivery market is comprised of the cargo-targeted delivery of drugs. The concentration of drug release in the therapeutic range is maintained in the oral controlled-release systems for a longer period, ensuring sustained therapeutic benefits. Some illnesses demand that medicine be delivered after a time delay, and this type of release is inefficient. Pulsatile medication is a process in which the medicine is released suddenly after a specified significant delay or time gap under the clinical conditions' biological clocks. This is true when drugs, such as proteins and peptides, are subjected to extensive metabolic breakdown. In the case of long-term therapy, drug resistance might develop and have negative consequences. Chances are lower in this case since the required concentration of medication at a certain time point is accessible. The pulsatile/delayed release process can be initiated in response to external signals (e. g., chemical, thermal, electric, and magnetic stimuli) it can be controlled by inherent mechanism, ie., devices that are intended to function consistently despite significant physiological parameters (temperature, pH, ionic strength). Due to gastrointestinal transit constraints, the only feasible targets for orally administered pulsatile delivery devices are circadian or ultradian variation patterns of disease symptoms. Indeed, they might be useful in the treatment of illnesses that appear mostly at early morning or night, such as cardiovascular disease, bronchial asthma, rheumatoid arthritis, and sleep problems. In these cases, pulsatile-release drugs might give a prompt pharmacological response following the nighttime dosage regimen without needing either an unnecessary protracted exposure of the patient to the drug molecule or disrupting normal sleep patterns, which would reduce compliance. The figure depicts a typical PDDS graph that departs from a controlled release [1-5].

Why is chronotherapeutic medication administration required? [5-7]

Biological tolerance

After administration, drugs like nitroglycerine and salbutamol sulfate have demonstrated biological tolerance since they tend to linger on the specific site and sustain a continuous plasma drug-release profile. As a result, it will decrease the biological activity of the medications.



A-release of drug as a pulse after a lag time
B-delivery of the drug rapidly and completely after the lag time
C-constant drug release over a prolonged period of time

Fig. 1: Depicts a typical PDDS graph that departs from a controlled release

First pass metabolism

To improve oral bioavailability of drugs like salicylamide and beta blockers which undergoes predominant first pass metabolism, it is required to reduce the pre-systemic metabolism of drugs.

GI irritation and drug instability in gastric fluid

Medications such as peptides are susceptible to stomach acid breakdown; PDDS protects these drugs from the stomach, and medications that induce stomach mucosal irritation (e. g., NSAIDs) or nausea and vomiting are also suited for distribution via time control systems.

Local therapeutic requirements

In order to achieve high therapeutic benefits with minimal side effects in a few particular disorders, such as inflammatory bowel disease, local therapy is necessary. PDDS can meet th

Conditions associated with chronotherapy

Several biological processes and the activity of numerous organs are time-linked and exhibit the circadian cycle. It also influences other

bodily activities like acid secretion in stomach and hormonal secretions. Investigators have also discovered that many diseases are time-dependent. for example, asthma and anginal attacks becomes severe most frequently in the morning.

The perks of a pulsatile drug delivery systems [8, 9]

- The pulsatile dosage form has several advantages over the traditional dosage;
- The use of chronotherapy or controlled delayed release, allows for the most effective treatment of diseases.
- In comparison to conventional immediate and sustained release medications, it has better absorption and bioavailability due to its ability of burst release of medication at the target site.
- Pulse release technology enables multiple dosing of drugs from a single dosage form. Multiple dosing in a single dose form is possible with pulse release.
- Allows for disease-specific release for local therapy. Changes in the pH, lumen viscosity, or rate of GIT agitation have little impact on drug release.
- Site targeting enables the administration of less bioavailable medications that would degrade in the environment of upper GI tract, for example (protein and peptide molecules).
- Maintains therapeutic effects even in the low dose of drugs.
- Increased patient compliance.
- Drug interactions are reduced because of decreased cytochrome P450 isoenzymes.
- Drug loss due to high first-pass metabolism is avoided.
- They provide constant drug levels at the site of action and prevent peak-to-valley fluctuations.

The pulsatile drug delivery system's limitations [10]

- A multi-particulate pulsatile system of drug delivery device is made using several manufacturing processes.
- The drug load is minimal.
- The release is incomplete.

The drug release mechanism of a PDDS [11]

Diffusion

Water diffuses into the interior of particles when they come into contact with aqueous fluids in the gastrointestinal (GI) system, and drug solutions diffuse to the exterior over the release coat.

Erosion

Certain coatings have been designed to release medication as they slowly degrade over time.

Osmosis

The interior of the particle can develop an osmotic pressure when water enters it under the right circumstances. The coating causes the medication to be forced out of the particle.

Different forms of pdds development and its outcomes

The respiratory system

Circadian rhythms have an impact on lung function as well. Lung function in healthy persons is impaired in the early morning. This alteration, however, is more evident in in individuals suffering from asthma. It is possible that function of lung may have decreased in the range of 25% to 50% [12]. Padmaxideveloped a One-Pulse drug delivery system for the treatment of asthma based on a press-coated tablet formulation of Montelukast sodium. The pre-programmable time-controlled release was acquired from a press-coated tablet after a 5-hour lag period, and burst release was accomplished after a lag time, which is commensurate with the needs of chronotherapeutic drug delivery [13]. Qureshihas designed a Chrono-modulated Salbutamol Sulphate drug delivery System for the Treatment of Nocturnal Asthma. They developed a rupturable, pulsatile drug delivery system made of an inner or intermediate swelling layer of hydroxypropyl methylcellulose (HPMC E5), a reservoir containing drugs, a water-insoluble but permeable outer covering, and a core made of microcrystalline cellulose and sodium chloride. After a 6-hour delay, the method was deemed sufficient for drug release [14]. Mahajan had devised and developed a timed delayed capsule device for the chronotherapeutic release of Terbutaline sulphate for the treatment of asthma, and a lag time of 5 h was attained [15]. Sadaphalhad devised and constructed a pulsatile medication release device for theophylline for the treatment of asthma. A medication made from Isopropyl alcohol (70%) and acetone (30%) was chosen as solvents for the EudragitS100 coating. The device delivers the medicine after a specified lag period of 6 h, allowing dosage forms to be administered before night and the payload to be delivered in the early morning hours [16].

Skeletal system

Rheumatoid arthritis and osteoarthritis both have a 24-hour cycle. Patients with rheumatoid arthritis are more likely to experience pain complaints in the morning. Moreover, the levels of C-reactive proteinand interleukin-6 also follow a daily cycle. Rheumatoid arthritis patients exhibit circadian cycles in joint pain and finger edema. These incapacitating symptoms correspond to pain's circadian patterns [17]. The novel cyclo-oxygenase-2 inhibitors efficiently decreased osteoarthritis symptoms when taken in the morning and showed superior outcomes in rheumatoid arthritis when a small quantity of the dosage was given in the evening [18]. Moon have created press-coated pulsatile system drug delivery tablets of Indomethacin for the treatment of arthritis. The press-coated formulation releases the medicine after a pre-programmed lag time of 4–8 h, followed by a quick and rapid drug release phase [19]. Jain conceived and developed a floating pulsatile lornoxicam medication delivery device for rheumatoid arthritis chronotherapy treatment. The system consists of a drug-containing core tablet surrounded by the pH-dependent polymer EudragitS100 and an effervescent polymer layer on the outside. The formulation's results were followed by quick and burst drug release from floating pulsatile tablets with no drug release before the pre-planned lag period of approximately 6-7 h [20]. Meenadeveloped a lornoxicam pulsatile medication delivery device for the treatment of rheumatoid arthritis. Lornoxicam microcapsules were made utilizing the solvent evaporation process and Eudragit L/S 100. The technique was proven to be successful in the chronotherapy of rheumatoid arthritis [21]. Meloxicam, sodium alginate, and porous calcium silicate (Florite RE®) were combined in a low-density multi particulate system by Sharma to formulate a pulsatile drug delivery system that enables for site-and temporal-specific drug release. Formulations in acidic environments show a lag period of between 1.9 and 7.8 h, followed by a fast release of meloxicam into the simulated human intestinal fluid [22]. Chauhan created a pulsatile drug delivery system of Aceclofenac for the treatment of rheumatoid arthritis, with the combination of Eudragit L-100 and S-100 in the core. The plugging material concentration was determined to be sufficient to sustain the pre-planned lag time for at least 4 h [23]. Kausalya had prepared a pulsatile system of drug delivery of flurbiprofen in the form of microspheres for arthritis treatment. This system consists of drug-loaded cellulose acetate cores that are encapsulated within Eudragit S-100 microspheres. The formulation showed drug release after a pre-planned lag time of 12 h [24]. Patel *et al.* developed a formulation for the controlled release of Aceclofenac. The formulation achieved the desired pulsed-release profile after a pre-programmed lag time [25]. Li formulated a three-pulse-based pulsatile drug release of diclofenac sodium device based on "tablets in capsules" for the treatment of rheumatoid arthritis. The suggested modifying barrier materials were hydroxypropyl methylcellulose (HPMCE5) and sodium alginate. With a 60% sodium alginate concentration, a lag time of 7 h was found [26].

The cardiovascular system

In people with cardiovascular disease, capillary resistance and vascular reactivity are higher in the morning and decline over the

day. In the morning, platelet agreeability increases while fibrinolytic activity decreases, resulting in hypercoagulable blood. As a result, the occurrence of myocardial infarction and sudden cardiac death is higher from morning to midday [27]. Bajpai developed the pulsatile release tablets of losartan potassium, which are compression coated for the treatment of hypertension and have a core tablet covered with a versatile polymer such as hydroxypropyl methylcellulose. To create a burst release after a predetermined lag period, hydroxypropyl cellulose and sodium carboxymethylcellulose are combined with the effervescent ingredient. The results showed that the goal of establishing a preplanned lag period of 6-7 h followed by a quick medication release was met [28]. Borgoankarcreated a pulsatile metoprolol tartrate system of drug delivery utilizing a core in a cup tablet. The table's core comprises metoprolol tartrate and cellulose acetate propionate, which serve as an impermeable barrier for the medication, as well as sodium alginate 500 cps and sodium alginate 2000 cps, which serve as a soluble hydrophilic polymer layer. The result was obtained after a pre-planned lag time of around 5 h, implying that this system (pulsatile drug delivery system) can be constructed to boost the therapeutic efficacy of the medication [29]. Rao has produced a Pulsatile Release form Tablet and Capsule Dosage forms of Metoprolol Tartrate which are used in the treatment of myocardial infarction and hypertension. It was established that the capsule dosage form exhibited a lag-time due to superior pulsatile drug release, whereas the tablet dosage form exhibited a lag-time during which 10-20% of the medication was released followed by pulsatile release [30]. Gohel have developed a pulsatile drug delivery method for the release of diltiazem hydrochloride from a novel tablet in a capsule system incorporating an effervescent mix. The technology enabled drug release with a pre-planned lag period of 4 h [31]. Patil has created a press-coated tablet with a core tablet surrounded by multiple coating materials for the time-controlled pulsatile drug release of Linsopril tablets. In varied concentrations and thicknesses, coating materials such as ethyl cellulose (EC) a hydrophobic polymer, and HPMC 15 CPS a hydrophilic polymer (HPMC 15 CPS) were utilized. The findings indicate that it is a potent formulation strategy for cardiovascular disease chronotherapeutic treatment (hypertension) [32]. Latha had optimized Losartan Potassium Press-Coated Tablets for pulsatile drug release. The inner core of the tablet was created by compression-coating HPMC 100 KM coupled with microcrystalline cellulose as the exterior layer in various ratios with lag times ranging from 0.5 to 18.5 h [33]. Jagdale have developed an enteric-press-coated atenolol tablet for pulsatile method of drug delivery. Press coating was used to create a unique colon-focused tablet formulation, which is a quickly dissolving tablet of atenolol with guar gum and Eudragit L-100 as a barrier layer. Different polymer ratios were used to provide an appropriate lag time for the treatment of angina pectoris [34]. Patil created a chrono-regulated pulsatile drug delivery system for captopril, which is used to treat cardiovascular disease (hypertension). The potent bioactive captopril, which was formulated by direct compression synthesis, is at the centre of the formulation. It is gradually covered with hydrocolloid HPMC E5 in the inner swelling layer and Eudragit RL/RS in the outer rupturable layer (1:1). After a 6-hour pre-programmed lag period, it was determined that the system was adequate for releasing medication [35].

The gastrointestinal system

A circadian cycle can also affect how the digestive system functions. The output of the stomach rises at night, while the motility of the stomach and intestines falls. In a previous study, it was discovered that meals around 20:00 had stomach emptying rates that were, on average, 50% slower than those at 08:00 [36]. This resulted in consequences for the pharmacokinetics of medicines taken orally. During the night, drug breakdown, solubility, and absorption may be delayed. Furthermore, increased acid secretion may aggravate duodenal ulcers in afflicted patients. As a result of this circadian cycle, a once-daily dose in the evening has been recommended [37]. Ashish Kumar invented pulsatile drug delivery for a preparation containing rabeprazole sodium. The suggested formulation consists of a core tablet containing rabeprazole sodium and a super disintegrant with an erodible polymer outer coating layer to create an instantaneous pulse of drug release. Furthermore, the compression coating of the core tablet was done with cellulosic polymers to create a lag time where no medication is released. In order to overcome the challenge of quick medication release, the proposed delivery method aims to achieve rapid drug release (a sinusoidal drug release curve) shortly after a lag time [38]. The pulsincap technology was created by Indira for the pulsatile drug delivery of lansoprazole. The body of an insoluble capsule is filled with a Lansoprazole matrix tablet, which is then plug-sealed with HPMC K 100. The Lansoprazole matrix tablets were made using the wet granulation process. Then, plugs made by direct compression that varied in thickness and hardness were used to seal the capsule's opening. The medication will be administered at the ideal time thanks to the drug delivery system (during the night) [39]. Daisy created an optimized pantoprazole sodium press-coated pulsatile release formulation. To improve the lag time, press-coated tablets were made with varying concentrations of coating material, namely hydroxypropyl methylcellulose (HPMC) K4 M and ethyl cellulose. The 40:60 ratio of HPMC and ethyl cellulose demonstrated the predicted lag period of around 3 h, followed by burst instantaneous release with the best dissolving rate [40].

Hypercholesterolemia

During cholesterol production, a circadian pattern is seen. In general, cholesterol production is higher at night than during the day. It might vary depending on the individual. The maximum production happens early in the morning, 12 h after the previous meal. Evening dosage with 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors exhibited higher effectiveness than morning dosage. The activity of the rate-limiting enzyme HMG-CoA is greater at night [41]. Chandra Sekar had developed a modified pulsincapsystem for the delivery of atorvastatin. The system comprises of an insoluble capsule body made using formaldehyde vapours and a hydrogel plug placed at the opening of the insoluble capsule body to attain the predefined lag period of 5 h [42]. Using the press-coated approach, Sri Lekha created a pulsatile release of rosuvastatin, a hyperlipidaemic medication. The tablet's core contains rosuvastatin, anhydrous lactose, and various ratios of super disintegrants such as croscarmellose sodium and sodium starch glycolate. To restrict medication release in stomach and intestinal fluids, the quickly dissolving inner core tablets comprising rosuvastatin and other excipients were press coated with a coating material constituted of a combination of varying weight proportions of hydrophobic polymer (ethylcellulose) and hydrophilic polymer (HPMC K4M). HPMC K4M was preferred for its swelling and erodibility, whereas ethyl cellulose was chosen for its rupturable characteristics. The 10-hour lag period for medication release is determined by the impact of the polymer composition [43]. Jithendra created a pulsincap device for pulsatile lovastatin administration to the colon. The capsule bodies were formaldehyde-treated and filled with lovastatin microspheres; the aperture was closed with a hydrogel plug, and the bodies were capped with an untreated capsule cap. To prevent unpredictable stomach emptying, the sealed capsules were completely coated with 5% cellulose acetate phthalate using a dip coating process. The drug release took place 5 h later [44].

Table 1: Diseases that require pulsatile release

Disease	Peptic ulcer	Asthma	Hypercholesterolemia	Cardiovascular	Arthritis
Chronological behavior	The afternoon and night are when acid secretion is highest.	Attack occurrence during the early hours of the morning or during the night.	Cholesterol synthesis is generally high during the night.	During sleep, blood pressure is at its lowest; it is highest in the morning.	Morning pain that gets worse at night.
Drugs used	H_2 Blocker [45]	β_2 agonist, antihistamine [46, 47]	HMG COA reductase inhibitors [48].	Nitro-glycerine, Calcium channel blockers, and ACE inhibitors [49, 50]	NSAIDS, Glucocorticoids [51]

Classification of pulsatile drug delivery system

I. Time-controlled pulsatile drug delivery

- Single-Unit Pulsatile Systems
  - Capsular-Based System
  - Capsular Systems Based on Osmosis
- System with Erodible or Soluble Coating
- System with Rupturable Layers or Membrane

II. Stimuli-induced pulsatile drug delivery system

- Temperature-Induced Systems
- Chemical Stimuli Induced Pulsatile Systems
- Glucose-Responsive Insulin-Releasing System
- PH Sensitive Drug Delivery
- Inflammation-Induced Pulsatile Delivery
- Drug Release from Smart Gel Responding to Antibody Concentration

III. Externally regulated pulsatile drug delivery

- Pulsatile Drug Release by Magnetic Field
- Pulsatile Drug Release by Ultrasound
- Pulsatile Drug Release by Electric Field

I. Time-controlled pulsatile drug delivery [52]

In order to replicate biological time, the pulsatile mode of release is produced after a predetermined interval in the time-controlled format. Two main components make up a pulsatile drug delivery system: one is an immediate-release, and the other is a pulsed-release type

A. Single-unit pulsatile systems

Capsular-based system

The Pulsincap® system has become one of the most popular utilised capsule-based pulsatile devices. R. P. Scherer International Corporation in Michigan, United States, designed it [53]. The system is made up of an insoluble capsule body that holds the drug reservoir. Swellable hydrogel plugs are utilized to encapsulate the medicinal content inside the capsule body. Hydrogel plugs of various viscosities are made using polymers like HPMC, PMA, PVA, and PEO. The length of the plug determines the lag time. The soluble cap of the capsule shell, which deteriorates in the vicinity of dissolution or gastric juice, secures the entire system [54].

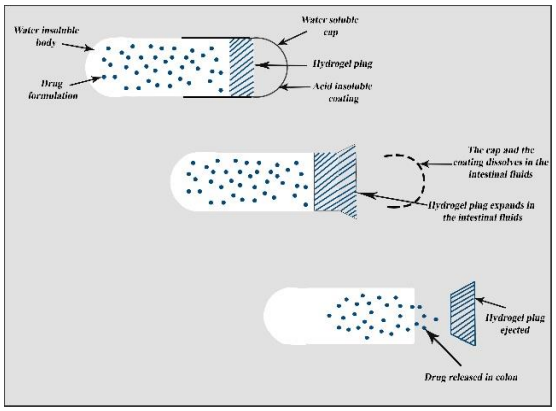


Fig. 2: Capsular-based system

Capsular systems based on osmosis

The therapeutic system research laboratory in Ann Arbor, Michigan, USA, devised the Port system, which comprises a capsule dosage form covered with a semipermeable membrane [55]. A capsule covered with a semipermeable membrane is used in the osmotic system. An insoluble plug containing an osmotically active ingredient and the medication formulation are contained within the capsule [56]. The semipermeable membrane of the capsule allows water to enter when it comes in contact with the dissolving fluid, which increases pressure and eventually causes the insoluble plug to expel out of the capsule over time [55].

B. System with erodible or soluble coating [57]

Most of the pulsatile drug delivery devices use barrier-coated reservoirs. In such systems, drug release is regulated by controlling the breakdown or deterioration of the external layer after a particular period. By adjusting the outer coat thickness, the active component is often released in a time-dependent manner.

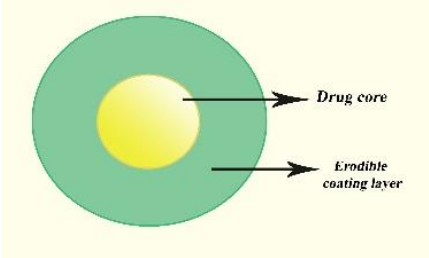


Fig. 3: System with erodible or soluble coating

C. System with rupturable layers or membrane [58]

The foundation for rupturable systems is a reservoir system protected by a rupturable membrane. The pressure produced by effervescent or swelling agents causes the outer membrane to burst. The hard gelatin capsules that contain the medication have a pulsatile system and a rupturable coating. The capsules had an initial coating of swelling material, which was followed by an outer layer that was insoluble but permeable to water. These coated capsules could continuously absorb the dissolution medium when submerged in it until the pressure from the swelling layer caused the outer coating to rupture.

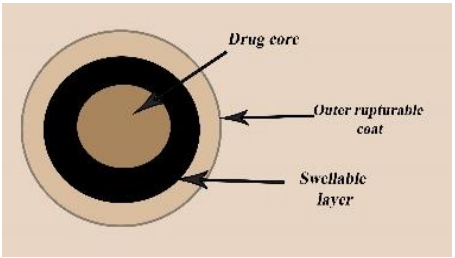


Fig. 4: System with rupturable layers or membrane

D. Stimuli-induced pulsatile drug delivery system [59]

Stimuli-based drug delivery systems deliver drugs a result of stimulation caused by the biological environment. The drug release from those systems occurs in response to stimulus-induced changes in the gels or micelles, which swell or erode in reaction to the corresponding stimuli. The medicine is released in these systems following activation by any biological influence, such as temperature or another chemical stimulus.

II. Chemical stimuli induced pulsatile systems

A. Temperature-induced systems [60]

For pulsatile release, thermo-responsive hydrogel systems were created. The polymer in these systems undergoes a de-swelling or

swelling phase in response to temperature, which controls the release of drugs when the polymer is swollen.

B. pH sensitive drug delivery [60]

This sort of pulsatile drug delivery system has two components: immediate release and pulsed release, which release the medication in reaction to pH changes. A pH-dependent system has benefited from the fact that varied pH conditions exist in various gastrointestinal tract areas. By selecting pH-dependent polymers, drug release can be targeted to a specific location. N, N-dimethyl aminoethyl methacrylate, and chitosan are examples of pH-sensitive polymers.

C. Glucose-responsive insulin-releasing system [61]

When blood glucose levels rise, like after eating, glucose oxidation to gluconic acid, mediated by the glucose oxidase enzyme, can reduce pH to about 5.8. This pH change promotes polymer swelling, which leads to the release of insulin. When insulin lowers blood sugar levels, gluconic acid levels fall as well, and the system changes to a deswelling mode, resulting in less insulin release.

D. Inflammation-induced pulsatile delivery [62]

Hydroxyl radicals (OH) are created by inflammation-responsive cells during inflammation. Yui and colleagues employed hyaluronic acid, a linear mucopolysaccharide consisting of repeated N-acetyl-D-glucosamine and D-guluronic acid disaccharide subunits. HA is mostly destroyed in the body by either a specialised enzyme, hydroxyl radicals, or hyaluronidase. When a person is healthy, hyaluronidase degrades only a small amount of hyaluronic acid. When hyaluronic acid is delivered into inflammatory sites, hydroxyl radicals are generally prominent and rapidly degraded.

E. Drug release from smart gel responding to antibody concentration [63]

There are different types of bioactive substances in the body. Recently, unique gels were developed that changed their swelling or shrinking features in response to variations in bioactive chemical concentration.

III. Externally regulated pulsatile drug delivery [64]

When external stimuli such as ultrasonic, electric effect, radiation, and magnetic field are given to a system that is sensitized to induce drug release, in addition to when the external stimuli are removed from the system, the release process from the device is terminated. Recent improvements in regulated systems have resulted in a variety of externally regulated systems. It was created to efficiently target the treatment to the site of action while reducing the likelihood of adverse effects by administering the drug at the appropriate dosage.

A. Pulsatile drug release by a magnetic field [65]

A polymer matrix can be implanted with magnetic steel beads holding a model medication. When subjected to a magnetic field, the beads shake within the matrix, causing tensile and compressive stresses. This, in turn, acts as a pump, ejecting additional drug molecules from the matrix. Magnetic particles such as iron, cobalt, nickel, steel, and magnetite create the magnetic response.

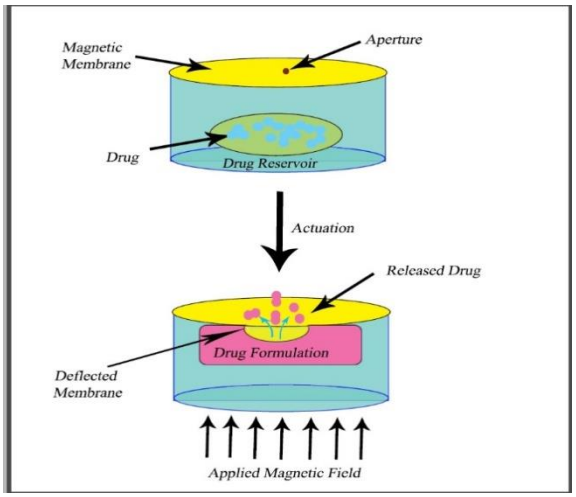


Fig. 5: Pulsatile drug release by magnetic field

B. Pulsatile drug release by ultrasound [10]

Ultrasound Interaction improves drug penetration across biological barriers such as skin. Non-cavitational phenomena like radiation pressure, radiation torque, and acoustic streaming are caused by the absorption of acoustic energy by fluids or tissues as well as oscillating bubbles.

C. Pulsatile drug release by electric field [66]

The system is made of polyelectrolytes. These polyelectrolytes include a large number of ionizable groups as well as a backbone chain. As a result, it is both electro-and pH-responsive. Electromagnetism operates under the influence of an electric field. In general, responsive hydrogels de swell, swell, or erode. The initiation of polymer erosion and the release of drugs from the polymer matrix happens as a result of a change in local pH caused by the absence or presence of an electric field.

Table 2: Patents for PDDS

S. No.	Patent title	Type of formulation	Active agent	Patent number	References
1	Implantable electro-mechanically driven device	Implant	Digoxin	US 4003379	[67]
2	Erosion-Dependent Systems	Coated tablet	Propranolol-HCl	US 5229131	[68]
3	Multiparticulate pulsatile drug delivery system	Pellets	Diltiazem HCl	US5,260,068	[69]
4	Multiparticulate pulsatile drug delivery system	Pellets	Diltiazem HCl	US5,508,040A	[70]
5	The implantable electro-mechanically delivery system	Implant	Peptide	US7917208 B2	[71]
6	Pulsatile drug delivery	Three layered pellets	Diltiazem HCl	US 6635277 B2	[72]
7	Time-controlled or position-controlled drug delivery system	Tablet in capsule	Sotalol HCl	US 7048945	[73]
8	Gastro retentive Pulsatile drug delivery	-	Valsartan	US20110189286 A1	[74]
9	Pulsatile tablet	Film-coated tablet	Diclofenac K	US 7972625 B2	[75]
10	Pulsatile technology	Multiple pulse amphetamine salt	Amphetamine	US 6605300	[76]
11	Timed pulsatile drug delivery system	Multicoated beads	Sotalol HCl	US 6627223B2	[77]
12	Pulsatile release	Capsule or like	H2 antagonist	US6663888	[78]
13	Pulsatile technology	Beads	Diltiazem HCl	US5914134A	[79]
14	Pulsatile release dosage form	Coated tablet or capsule	-	WO 2015028972 A1	[80]

Table 3: Evaluation of PDDS [5, 10]

S. No.	Name of the test	Method to perform the test and its significance
1	Tablet thickness and diameter	The purpose of the test is to determine the thickness and diameter of a tablet. This is done by using vernier calliper. The two components were used to measure the uniformity of the tablets overall structure.
2	Hardness test	The hardness of the tablet is also determined to determine if it can with stand the effects of handling and storage. six tablets were randomly chosen for the hardness test. The meter used by Monsanto measures the hardness of a material by weight per square centimetre.
3	Friability	The test was performed using the Friabilator of Roche. The percentage change in friability or weight was calculated by taking into account the various factors that affect its stability and hardness. F= (1-W/Wo) × 100, F=friability Wo denote the original weight. W denotes the final weight.
4	Content uniformity	The API weight is checked to ensure that it stays within the prescribed range according to the Indian Pharmacopoeia. The procedure involved randomly selecting 20 pills and weighing them. A batch of powdered pills was then dissolved in a volumetric flask containing 0.1 N HCl. The absorbance was then measured using a set wavelength.
5	Weight variation	The procedure involves randomly selecting 20 pills and then measuring them, which will determine the average weight. This test ensures that the pills stay within the prescribed range.
6	*In vitro* buoyancy determination	The floating characteristics of the tablet in the gastro-floating drug delivery system have a significant impact on the *in vivo* behaviour of the medication. As a result, it is necessary to identify the dosage form's floating mechanism.
7	Floating lag time	The amount of time it takes for the tablet to rise to the top of the liquid after being added to the dissolving media at a pH of 1.2, a temperature of 37 0.5 °C, and a paddle rotation speed of 50 revolutions per minute.
8	Total floating time	The amount of time it takes for the tablet to continuously float on top of the gastric fluid when there is no pepsin present, at a pH of 1.2, a temperature of 37 °C, and paddles rotating at 50 rpm.
9	*In vitro* dissolution	The various dosage forms under consideration will be tested using various USP dissolution tools. The entire experiment will be carried out in a particular medium with a particular pH range. A UV double-beam spectrophotometer is used following the regular collection of samples for analysis.
10	Swelling index	Each pill was weighed out precisely before being dissolved in 50 millilitres of double-distilled water. The pills were carefully taken out after 60 min, cleaned with filter paper to remove any water that had accumulated on the surface, and then precisely weighed. The formula used to calculate the percentage swelling index (SI) was SI = (wet weight-dry weight/dry weight)*100.
11	Rupture test	The rupture test on coated tablets was carried out using the USP paddle apparatus. The *In vitro* Dissolution Method's other variables were identical to those for that method. Lag time is the period of time after which the outer coating layer starts to crack. The Rupture test was used to prove this.

CONCLUSION

Controlled and sustained delivery methods keep *in vivo* drug concentrations within therapeutic levels for extended periods, which is necessary but not enough for treating circadian rhythm illnesses. There is a constant demand for innovative, brand-new delivery methods to enhance patients' therapeutic advantages. PDDS is one such technology that holds out great hope for individuals suffering from chronic ailments. The primary advantage of this method of medication administration is that the medicine is only delivered when necessary. It is possible to conclude that the pulsatile drug delivery method offers superior administration of medications with chrono-pharmacological behaviour, significant first-pass metabolism, the requirement for nighttime dosage, or an absorption window in the GIT. Pulsatile drug delivery methods will show promise in the near future.

ABBREVIATIONS

PDDS-Pulsatile drug delivery system

NSAIDs-Non-steroidal anti-inflammatory drugs

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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