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Review Article

PULSATILE DRUG DELIVERY SYSTEMS THE NOVEL APPROACH

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ABSTRACT

Oral pulsatile drug delivery systems (PDDS) are intended to induce programmable lag phases before a quick and quantifiable, repeated, or prolonged medication release. As a result, they are gaining popularity due to their inherent suitability for achieving chronotherapeutic goals, which have just been highlighted concerning several prevalent chronic illnesses characterized by typical night or early-morning recurring symptoms (e. g. bronchial asthma, heart attack, rheumatoid arthritis, early-morningawakening). Furthermore, time-based colonic release is possible when pulsatile delivery devices are correctly modified to overcome unexpected gastric emptying and give delay periods that roughly match the small intestine transit time. Oral pulsatile administration is accomplished using several release platforms, including reservoir, capsular, and osmotic devices.

The current review article addressed the topics that followed: the reason pulsatile drug delivery systems have been invented; diseases for which pulsatile release is necessary; classification, advantages and disadvantages; methods used in the current systems; the situation nowadays and its potential for the future; recent advancements, and especially, the previous five to ten years of research on pulsatile drug delivery conducted by researchers using a variety of drugs for a variety of diseases.

Keywords: Circadian rhythm, Lag time, Ph, Pulsatile, Remotely controlled

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INTRODUCTION

The drug delivery system allows the active ingredient in the medication to be released to produce the desired therapeutic response [1, 2]. Traditional drug delivery systems (tablets, capsules, syrups, ointments, etc.) have poor bioavailability and fluctuating plasma drug levels, making them incapable of achieving sustained release. Without an effective delivery method, the entire therapeutic procedure may be rendered ineffective. Furthermore, the medicine must be administered at a precise, controlled rate and at the target spot to provide optimal efficacy and safety [3, 4]. Pulsatile medication delivery devices were created to address the issues associated with traditional drug delivery. Pulsatile medication delivery has progressed significantly. Pulsatile, also known as targeted medication delivery, provides action at a precise time or after a time lag [5-7].

Solid oral dosage forms of drugs are now widely employed and make up the majority of the whole system of drug delivery due to their more convenient method of administration and better patient convenience. The majority of oral drug delivery systems have a specific drug-releasing pattern, and the concentration of the drug is kept within the therapeutic range [8-10]. Pulsatile pharmaceutical delivery methods are becoming highly important as well as popular for targeted delivery systems based on drug design as technology advances. It keeps the disease conditions' circadian rhythms and lowers the drug's negative effects. As a result, the primary function of pulsatile drug delivery systems is to administer the drug at the appropriate time, location target, and quantity [11]. The medication is released using the sigmoid al-release pattern, which is distinguished by a period of little or no release (lag time). These systems release or distribute the medicine at a specified moment, dependent on the pathophysiological demand of the disease. As a result, it increases therapeutic efficacy and patient compliance and reduces dose frequency [12-14].

Pulsatile Drug Delivery Systems (PDDS) are gaining popularity because they give the medicine at the correct place, at the right time, and in the right amount, offering spatial, temporal, and smart distribution and enhancing patient compliance [15]. Where steady medication release is not desired, pulsatile drug release is preferable. A pulse must be produced so that a complete and fast medication release is accomplished after the lag time chance to coordinate with the body's circadian rhythm [16]. These systems are characterized by two release phases. A first phase during which little drug is released, followed by a second phase, during which the drug is released completely within a short period after a lag time. Most PDDSs are repository gadgets coated by a barrier polymeric coating. The coating prevents drug release from the core until the polymeric shell is completely dissolved, eroded, or ruptured during/after a certain lag time. After this, the drug is released rapidly from the inner reservoir core. Pulsatile release tablet formulation generally consists of a rapid-release core tablet encased in a barrier layer either formed by press coating, liquid coating, or a combination of both [17]. Pulsatile drug delivery is thus one technology that holds out significant promises of assistance to patients suffering from chronic conditions, which include joint inflammation, asthma, ulcers, and hypertension by providing medicine at the right time, in the right place, and the right amounts [18]. PDDSs feature an unusual method for promptly and thoroughly releasing the medication after a lag time or a period with no drug release [19, 20]. Pulsatile release is the name given to such a pattern of release [21, 22].

PDDS shows different types of drug release patterns as per shown in fig. 1 given below (A) sigmoidal release after lag time, (B) delayed release after lag time, (C) sustained release after lag time and (D) extended-release without lag time [1, 6].

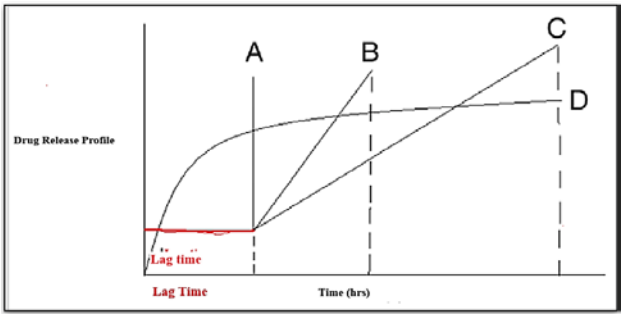

Fig. 1: Drug release profile [1, 6]

Circadian rhythm

Circadian rhythms are 24 h cycles of changes in behaviours, thoughts, and body. The majority of living things, including plants, animals, and microbes, are impacted by these natural processes, which are primarily sensitive to light and darkness. The research into the mechanism of circadian rhythms is called chronobiology [23, 24]. A light-related circadian rhythm can be exemplified by sleeping at night and waking up during the day. The picture on the [fig. 2] a typical teen's circadian rhythm cycle [25, 26].

Fig. 2: Circadian rhythm cycle [24]

Need of pulsatile

There are some Rational or reasons for developing pulsatile drug delivery that convert into needs for better patient compliance. Some needs are listed below in [fig. 3] [3, 4].

Advantages

Increase the absorption and bioavailability than conventional immediate-release or sustained-release drugs because of their capacity to deliver the medication in a burst way at the objective site of assimilation [1, 6]. Site targeting permits the delivery of poorly bioavailable medications that would get destroyed in a higher GIT climate, for example, (peptide and protein molecules) [14]. Minimizes the medication's dosage without sacrificing its therapeutic effect. Decreasing the adverse effect. and drug interaction because of the lower cytochrome P450 isoenzymes. With Improved patient compliance. Chronotherapy-modified delayed discharge gives an ideal treatment for the disease. and Pulse discharge allows various dosing in a single dosage form. Broadened daytime or night-time activity and Minimize cost to the patient because fewer dosage units are needed by the patient in treatment. Medication adjusts to suit the circadian rhythms of the body. and preserves mucosa from drugs that irritate or damage it. Medication loss is prevented by first-pass metabolism. and No danger of dose dumping, they avoid Plasma Peak Concentration variations (Fluctuations) and administer medication at the site of movement at constant levels [16]. It will improve the absorption and bioavailability at the intended site of absorption due to its burst delivery mechanism. Keep biological tolerance out of sight [19, 28].

Disadvantages

It has limited drug load capacity and drug arrival fragmentation. Increased production costs. An abundance of process variables. Lack of repeatability and viability in assembly [21].

To begin constructing the pulsatile drug delivery system, an in-depth understanding of the disease's physiology is necessary [27]. In a condition where the body's circadian rhythms are crucial, the drugs' pharmacokinetics and/or pharmacodynamics fluctuate over a day [28, 29]. A list of diseases exhibiting this kind of chronological pattern can be found in [table 1]. One such condition where a pulsatile drug delivery system may be helpful is asthma. Normal lung function exhibits circadian fluctuations, peaking in the wee hours of the morning. Numerous cardiovascular system functions, including blood flow, cardiac output, stroke volume, heartbeat, and blood pressure, are influenced by circadian rhythms in the event of cardiovascular disease.

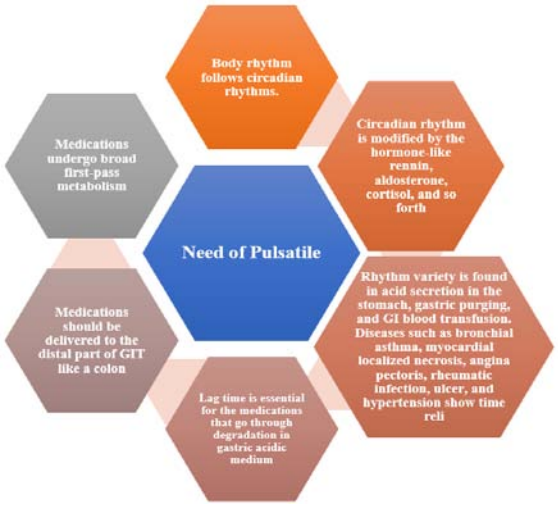

Fig. 3: Need of pulsatile [3, 6]

Table 1: Some important diseases that required pulsatile drug delivery

Disease	Chronological behavior	Drugs investigated
Asthma [30]	Asthma is an ongoing inflammatory condition of the lungs. Chronic inflammation is linked to airway hyperresponsiveness (an exaggerated airway-narrowing response to specific triggers such as viruses, allergens, and exercise), which results in recurrent episodes of wheezing, breathlessness, chest tightness, and/or coughing that can vary in intensity over time and over time. Symptom episodes are commonly linked with widespread but varying airflow blockage inside the lungs, which is usually reversible either on its own or with proper asthma medication, such as a fast-acting bronchodilator [30].	Salbutamol Sulphate [31] (Pulsatile Pellets) Theophylline [32]
Peptic ulcer	A peptic ulcer is a characteristic breakdown in the mucous membrane of the stomach (gastric ulcer) or the first section of the small intestine (duodenal ulcer) that is exceedingly painful and caused by the acute effects of acid pepsin in the lumen. One of the most frequent causes of peptic ulcers is Helicobacter pylori. Acid secretion symptoms appear after midnight (2 to 4 a. m.) [34].	Ranitidine Hydrochloride [34, 35] (Floating pulsatile tablet), Famotidine [36, 37] (Osmotic tablet)]
Cardiovascular disorders	A cardiovascular disorder is characterized by abnormal heart or blood vessel function. Blood clots (thrombosis) and plaque development in artery walls can limit blood flow to the brain, heart, or body, resulting in artery hardening and constriction. Platelet agreeability rises along with nocturnal hypertension in the early morning [39].	Lisinopril (Osmotic pulsatile tablet) [38], Amlodipine Besylate (Pulsatile tablet) [40], Felodipine (Pulsatile tablet)
Diabetes mellitus	A group of metabolic disorders in which the person has high glucose levels in the blood can be termed diabetes mellitus. The reasons behind the increased glucose level in the blood are either because of inadequate insulin production or because the body's cells do not respond properly to insulin [41, 42].	Glibenclamide [43] (Pulsincap micro-sponges, Glipizide [44] (Pulsatile Pellets), Insulin (Pulsatile Liposomal system) [45]
Arthritis [46]	Arthritis is a type of joint illness that causes inflammation in several joints. The most frequent kind is osteoarthritis, which causes joint stress and infection. In osteoarthritis, cartilage loses its flexibility and becomes destroyed, causing fibrous tissue and ligaments to stretch and the bones to scrape against each other, producing excruciating agony [46, 47].	Aceclofenac (Floating pulsatile microspheres) [48], Celecoxib (Osmotic tablets) [49], Diclofenac [50] (Pulsatile microcapsules)
Hypercholesterolemia	Hypercholesterolemia is defined as an increase in blood cholesterol levels and an increase in cholesterol synthesis during the night. Cholesterol levels are said to be lowest between 2 and 6 p. m. and highest at 6 am. [51, 52]. For hypercholesterolemia, chronotherapy can be performed by scheduling the medicine following the circadian cycle. These drugs work better in the evening than in the morning [53, 54].	Simvastatin (Pulsatile micro-spheres) [55]
Cancer	Many clock genes are activated transcriptionally and post-transcriptionally, and regulatory loops are inhibited to induce circadian oscillation in the cells of mammals [56, 57]. The anomaly in the circadian oscillations appears in the early morning, and different medications were studied to lengthen gastric residence time to target stomach cancer and boost drug absorption [58].	5-Fluorouracil (Pulsincap) [59]
Hormone secretion [60]	A hormone is a type of regulatory molecule generated by glands throughout all multicellular animals and carried to a target organ by the circulatory system to control its physiology and behavior. Hormones control a wide range of physiological and behavioral processes, including digestion, stress, respiration, tissue function, lactation, growth, and reproduction. Growth hormone and melatonin are created at night, whereas testosterone or cortisol are produced in the morning [61, 62].	Budesonide (Micro-particles) [63, 64], Fluticasone furoate (Nasal spray) [64]

Asthma

Asthma is a long-term lung illness that affects people of all ages. It is caused by inflammation and muscle stiffness around the airways, making breathing difficult. Coughing, wheezing, shortness of breath, and chest tightness are some of the symptoms. These signs might be moderate or severe, and they can appear and disappear over a while. However, asthma can be a serious condition, it is treatable with the appropriate medication. People who have asthma symptoms should consult a doctor. In paediatric practice, bronchial asthma is among the most prevalent chronic pathologies. In the European Union, it affects about 5.5 million children, with an average prevalence of 10% across all member states. Asthma-related mortality and morbidity have been rising over the past few decades despite advances in our understanding of the condition and the creation of new treatment approaches [67, 68]. Even though it's crucial, giving kids with asthma the best care possible presents several difficulties, from making the right diagnosis to starting treatment early and adjusting it as needed [69-71].

Asthma is the most frequent chronic disease among children and is a major noncommunicable disease (NCD) that affects both children and adults. Asthma symptoms are caused by irritation and narrowing of the small passageways in the lungs, which can include any combination of coughing, wheezing, shortness of breath, and chest tightness. In 2019, asthma affected around 262 million people (1) and killed 455,000 people [72, 73].

In the case of moderate types of the disease that previously only advantaged from bronchodilator therapy, when necessary, recent evidence points to significant benefits from anti-inflammatory medication use. In addition, studies have demonstrated the beneficial effects of bronchodilator medication when used in conjunction with inhaled corticosteroids [73, 74]. A new treatment option for moderate disease is called "single maintenance and reliever therapy," or "SMART" for short. It is now successfully incorporated into the present guidelines. In steps 3 and 4 of asthma management, the Global Initiative for Asthma (GINA) and the National Asthma Education and Prevention Program Coordinating Committee (NAEPP) both advise using a single inhaler that combines an inhaled corticosteroid (ICS) with a particular fast-acting bronchodilator (FABA), formoterol, for both maintenance and rapid relief therapy [75].

Classification of pulsatile drug delivery system

PDDS are classified as time-controlled systems, in which the drug release is primarily controlled by the delivery system; stimuli-induced, in which release is controlled by stimuli such as pH or enzymes present in the intestinal tract or enzymes present in the drug delivery system and externally regulated systems, in which release is programmed by external stimuli such as magnetism, ultrasound, electrical effect, and irradiation [76].

Mechanisms of drug release by pulsatile drug delivery

Generally, pulsatile drug delivery shows drug delivery mainly such as Diffusion, Erosion, and Osmosis, which are explained in the following [fig. 6].

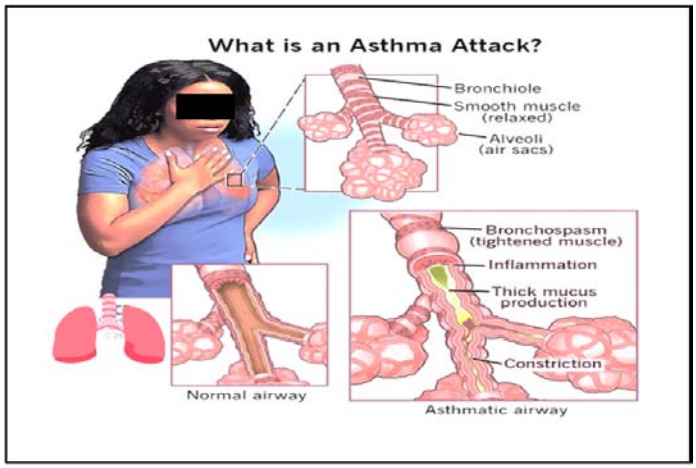

Fig. 4: Asthma condition [76]

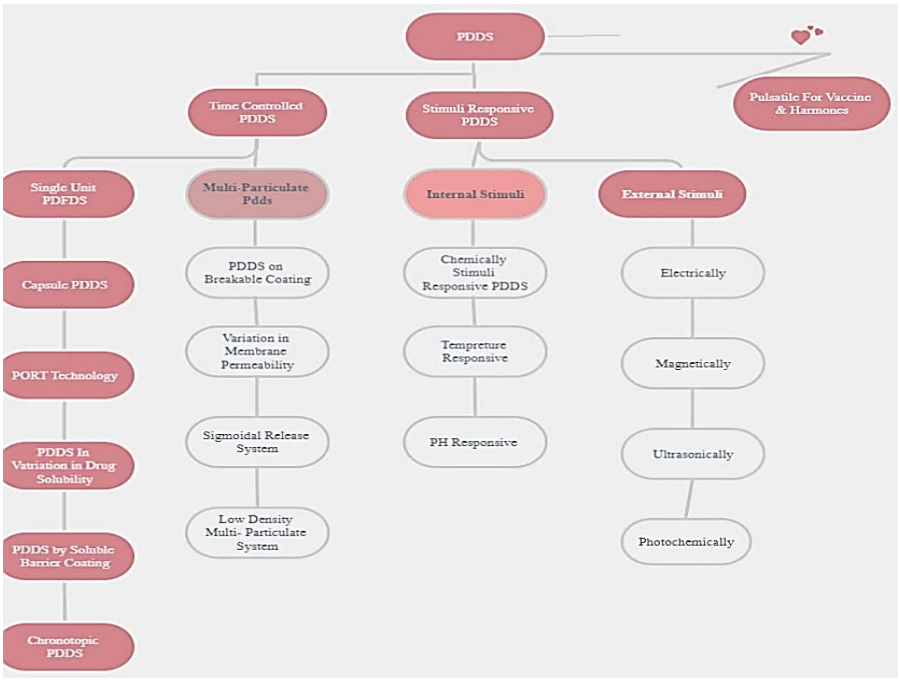

Fig. 5: Classification of pulsatile drug delivery system [1, 6, 76]

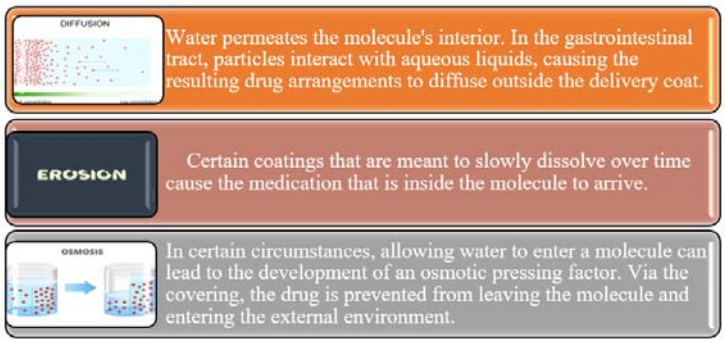

Fig. 6: Mechanisms of drug release by pulsatile drug delivery [1, 6, 13, 77]

Marketed technologies for PDDS

For pulsatile drug delivery, several commercially available technologies have been developed, including Pulsincap ™, PORT ®, Uniphyl®, and Opana® ER.48–50, CODAS®, OROS®, IPDAS®, GEOCLOCK®, and Pulsincap ™ [78, 79].

A few of them are talked about below [table 2].

Table 2: Some marketed technologies done by pulsatile drug delivery [78]

Technology	Description	API	Proprietary name	Disease	Manufacturer
PULSINCAP ™	The medication solution is poured into a water-insoluble capsule body. Swellable hydrogel plug closes open end. When it comes into touch with GI fluid, the polymer expands and pushes itself out of the capsule after a little delay, followed by rapid release [80, 81].	Dofetilide	Pulsincap™	Anti-arrhythmic	Developed by R. P. Scherer International Corporation, Michigan, USA
PULSYS™	A novel pulsatile release technology that consists of one immediate-release and two delayed-release components with the use of soluble and insoluble coatings [82].	Amoxicillin	Moxatag™	Antibiotic therapy	Middlebrook Pharmaceuticals, Westlake, Texas, USA
DIFFUCAPS ™	Multiparticulate system that gives medication release profiles from single drugs or drug combinations. Customized drug release profiles are developed by stacking active drug from aqueous or solvent-based drug solutions onto a neutral core (such as cellulose spheres), then covering with one or more rate regulating membranes [83].	Propranolol HCl	Innopran ® XL tablets	Hypertension	Eurand Pharmaceuticals, LTD, Dayton, Ohio, USA
CODAS™	Multiparticulate pH-dependent release system. This capsule contains many pellets having an inner core surrounded by drug and water-soluble and water insoluble polymers. The drug releases through pores of the polymer coating.	Verapamil HCl	Verelan® P M	Hypertension	Elan Drug Technologies, San Francisco, CA, USA
OROS®	Osmotically controlled single-unit system. The first semipermeable membrane prevents the absorption of water into to tablet and second layer delays the regulation of water into the inner core and the third layer provides the extended release.	Verapamil	Covera-HS	Hypertension	Alza corporation, Mountain view, CA, USA
PORT ®	The capsule is coated with a semipermeable membrane, and the plug contains osmotically active chemicals and the medication formulation. When it comes into contact with GI fluid, it permits water penetration and pressure to develop, and the insoluble plug is evacuated after a lag period, which varies depending on the length of the hydrogel plug [84].	Methylpheni-date	Ritalin	CNS Stimulants	Therapeutic System Research Laboratory, Michigan, USA
IPDAS ®	The technology consists of multiple high-density controlled-release beads compressed into a tablet form. The active ingredient is released from the multi-particulate by diffusion via the polymeric membrane and/or the micro matrix. This method ensures that irritating drugs are distributed widely throughout the GI tract.	Naproxen sodium	Naprelan®	NSAID	Elan Pharmaceuticals LTD, USA
CONTIN®	Release by pulse manner at the time of asthmatic attack in morning h.	Theophylline	Uniphyl ®	Nocturnal Asthma	Purdue Frederick, Nor-folk, CT, USA
CEFROM ®	Biodegradable polymers/bio-actives are subjected to varying temperatures, thermal gradients, and flow processes to produce microspheres of uniform size and shape [85].	Diltiazem	Cardizem® LM	Hypertension	Fuisz Technologies, Chantilly, VA, USA
GEOMATRIX ®	The release is controlled by constructing a multilayered tablet made of hydrophilic polymers and surface-controlling barrier layers. The drug release is controlled by barrier layers when exposed to fluid.	Molsidomine	Coruno®	Angina Pectoris	Skye Pharma, Muttenz, Switzerland
GEOCLOCK ®	The press-coated tablets have an active drug inside and outer layer consisting of a mixture of hydrophobic wax to obtain a pH-pH-independent lag time prior to delivering the drug at a predetermined release rate [86].	Prednisone	LODOTRA TM	Rheumatoid arthritis	Skye Pharma
OBREXA®	Controlled size and density beads using granulation, spheronization, and extrusion technique	-	-	-	Eurand Pharmaceuticals, LTD, Dayton, Ohio, USA
SODAS®	Production of spherical beads of drug and excipients having 1-2 mm diameter and coated with product-specific release controlling polymers	-	-	-	Elan Pharmaceuticals LTD, USA
SyncroDose ®	A tablet containing an inner drug core, surrounded by compression coating of two polysaccharides, xanthan gum, and locust bean gum	-	-	-	Penwest (WO2005027843)
OSDrC ®	OSDrC® technology permits the location of cores of any shape into the tablet just where they need to be positioned for optimal delivery of the drug. Accurate positioning allows scientists to control the release of the drug by varying the thickness of the coating.	-	-	-	WO2005046978 A1 WO2006022290 A1

Advances in remotely controlled delivery systems

Externally regulated delivery systems have the delivery intended to be dependent on an external stimulus that can be remotely managed, for example, by a smart device. In this article, we will examine some of the most recent advancements in remotely controlled delivery systems, such as wireless controlled implantable systems, electro-responsive, light-responsive, ultrasound-responsive, and magnetically induced pulsatile systems, as well as wireless controlled implantable systems [87].

Wirelessly controlled pulsatile drug delivery systems

Wirelessly controlled drug delivery systems are intended for pulsatile and on-demand medication delivery. With the proliferation of smart devices, medication delivery device control has become simpler, more versatile, and more user-friendly. The adoption of a safety processor system, which allows better precision and safety of the program, along with controlling medical instruments with a remote-control device, which includes a mobile phone, had previously been recommended [87]. A safety processor acts as a connection device between the mobile phone and the medical equipment, retrieving communications from the phone before they are sent to the medical device. It provides a secure and dependable connection between the mobile phone and the medical device, and it may also check to see if the operational command typed into the mobile phone is within acceptable bounds [88].

Wirelessly controlled implanted system for secure and comfortable on-demand and pulsatile insulin administration. It consists of a magnetic-driven pump, an external control device, and a mobile application. The smartphone program may release a precise amount of the medicine and alter it wirelessly. [88, 89]. The mobile application gives safety constraints since it is programmed to fix a dosage frequency and dose limit to eliminate the possibility of dosing error. Furthermore, the mobile application may be managed via Bluetooth, allowing for on-demand administrations [90, 91]. If the patient is predicted to suffer hypoglycemia at any moment, it may also prevent all commands from being processed. All administration history will be maintained on the mobile device as well [92].

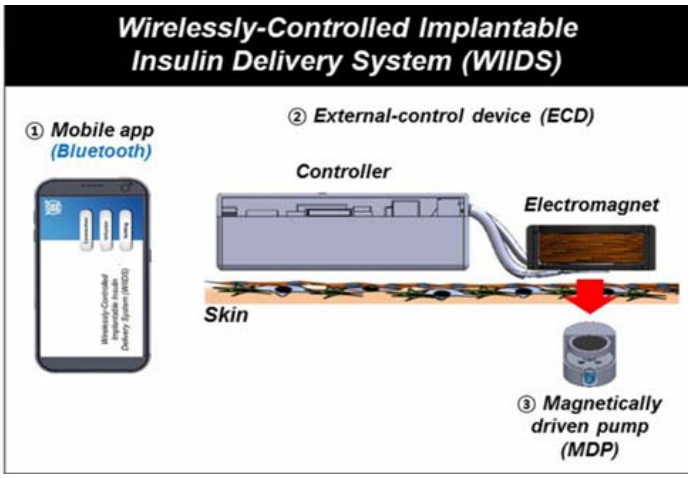

Fig. 7: Wirelessly controlled implantable insulin delivery system [90]

Electrically stimulated pulsatile drug delivery systems

Electrically responsive delivery systems are widely employed to administer drugs to precise locations and times using implantable polymers or electronic devices and external electrical fields [93]. The voltage might be precisely controlled by modern equipment, allowing for precise medication release. This technique has numerous advantages, but at greater voltages, there is undesirable tissue damage and a low penetration depth, which is a serious issue. Biocompatible polyelectrolytes such as carbomer, xanthan gum, agarose, calcium alginate, and acrylate-methacrylate derivatives can be used to create electrically stimulated systems [94].

Kwon *et al.* investigated the ejection of insulin via methacrylate hydrogels in the presence of an electrical field. The release of hydroxyl ions at the cathode elevated local pH in the presence of a modest electric field. This disrupted the hydrogen bonding in the solid state of polymers, causing the polymers to liquefy and release the medication. The release of the ionic medicines cefazolin and theophylline through a hydrogel in an electrical field was studied. by Kim and Lee [95].

Neumann *et al.* developed a bioresorbable nanocomposite film-based electro-responsive drug delivery device. The electrochemical stimulation caused local pH changes at the electrode surface, resulting in the dissolution of the carrier, which is made of a pH-sensitive polymer [96]. Another work used sodium alginate and graphene oxide crosslinked with Ca2+to create an electro-responsive drug carrier. The electrical conductivity of graphene oxide enabled the electrically triggered release of methotrexate to be successful. In recent times, electro-responsive chitosan/magnetic nanoparticles Composite Microbeads containing vancomycins were created. Furthermore, a transdermal drug delivery technique based on poly (2-ethylaniline) dextran was developed for electrically regulated diclofenac drug release. When an electrical stimulus is applied, medication is released by Fickian diffusion in conjunction with matrix swelling [97].

Light-responsive pulsatile drug delivery system

Because of their non-invasive nature, temporal control, convenience, and ease of use, light-responsive delivery systems are advantageous. Photo-chemically triggered release, photo-isomerization, and photo-thermal release are three key advancements in light-responsive drug release [98].

Light-responsive delivery technologies in clinical trials include heat-sensitive liposomes and iron oxide nanoparticles. Light irradiation causes covalent bond cleavage and subsequent drug release in the photochemically triggered release. O-nitrobenzyl, coumarin, and pyrene derivatives are examples of photoresponsive moieties used in sunlight-triggered drug delivery systems [99, 100]. The photo-isomerization activation method includes a reversible conformational change caused by ultraviolet (UV) and visible light irradiation. Azobenzenes are most typically used in this process [100]. The photo-thermal activation method employs a chromophore, which converts the energy of light into thermal energy upon photo-stimulation. The produced heat will then excite a thermally sensitive carrier, resulting in medication release [101]. Gold nanoparticles and NiPA Am hydrogels are examples of commonly used materials [102].

Ultrasound pulsatile drug delivery systems

In recent decades, ultrasound has become one of the modalities employed in the medical field for diagnostic imaging. The concept of combining ultrasound with medications has sparked attention in a variety of clinical sectors. It was used in cancer treatments, where it was known as "sonodynamic therapy," as well as diabetic treatment. Sound waves will be employed to accelerate the release of drugs from carriers and increase vascular permeability during drug delivery. Corrosion of the matrix of polymers could result in pulsed drug release [103, 104]. When ultrasound is applied to bodily tissues, it stimulates medication release by a variety of mechanisms, including pressure fluctuation, acoustic fluid streaming, cavitation, and local hyperthermia [105].

The movement of pressure waves through the body at changing frequencies and amplitudes is the basis for pressure fluctuation. For cavitation, compressible items such as small bubbles that expand and contract to pass sonic waves are utilized [106]. As a result, these oscillations will facilitate drug release and boost drug absorption [107, 108]. Acoustic streaming is made up of regional particle moves and fluid currents caused by radiation forces that are reflected and scattered in the ultrasonic field [109]. The sonic flow propels particles into target tissues while destabilizing medication transporters [110, 111].

The numerous advantages of pulsatile drug delivery systems (PDDS) over traditional dosage forms have drawn attention. They provide more benefits than conventional dosages and improve patient compliance by delivering the medication at the appropriate time, site of action, and amount. Some of the prior five to seven published studies on pulsatile delivery tablets are listed in the table below.

Table 3: Pulsatile drug delivery formulations research has been done by some listed researchers in the last 5-7 y

Drug name	Disease	Preparation methods	References
Paracetamol and felodipine [113]	Heart attacks and strokes (hypertension). Angina	3D printing method, Arburg Plastic Free forming (APF)	[113]
Febuxostat.	Gout, an inflammatory arthritis	Pulsincap technology	[114]
Flurbiprofen	Osteoarthritis (arthritis caused by a breakdown of the lining of the joints) and rheumatoid arthritis	Direct compression method	[115]
Aceclofenac	Arthritis	Press Coating Method,	[116]
Methylphenidate hydrochloride	Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric problem,	Core Press coat	[117]
Valsartan	Antihypertensive	Minitablets	[118]
Verapamil Hydrochloride	Hypertension and angina	3D-printed core-shell pulsatile tablets	[119]
Sulfasalazine and Caffeine	Crohn's disease	Colo Pulse coating has not been used for multi-particulate pellets	[120]
Ramipril	Heart attack, sudden cardiac death, stroke and myocardial infarction	Multiparticulate (e. g. mini tablets)	[121]
Propranolol hydrochloride	Hemorrhagic stroke and cardiac death	Tablets in Capsule system (TCS) using response surface methodology	[122]
Theophylline	COPD Diseases like asthma	Fused deposition modeling (FDM) 3D printing	[123]
Lisinopril	Hypertension, congestive heart failure, and heart attack.	Press coating Method.	[124]
PVA	Multipurpose drug release	3D Printing	[125]
Paracetamol	Inflammatory bowel disease (IBD,	Direct compression with soluble layer	[125]
Celecoxib	Inflammatory bowel disease	Pulsnicap	[126]
Zopiclone	Insomnia	Compression coated	[127]
Trimetazidine dihydrochloride	Angina	Compression coated	[128]
Clopidogrel	Heart attack	Multiparticulate Pulsatile	[129]
Prednisone	Asthma, arthritis, inflammatory bowel disease	compression-coated tablet	[130, 131]
Propranolol hydrochloride	Hemorrhagic stroke and cardiac death [132]	3D Printing	[133, 134]
Ketorolac	Rheumatoid arthritis and colonic inflammation	Double-compression coating method.	[136]
Carvedilol	Hypertension and heart disease. heart attacks	Compression coated	[137]
Omeprazole	Peptic ulcer	Multiparticulates in pellet form	[137]
Nicorandil	Angina Pectoris	Pulsnicap	[138]

CONCLUSION

There has been significant progress in the creation of a pulsatile delivery system that can successfully treat illnesses requiring non-constant dosage therapy. Chrono medication is required for asthma, hypertension, osteoarthritis, peptic ulcer, and other circadian diseases. Pulsatile drug delivery can efficiently solve this problem because it is adjusted by the body's circadian clock, resulting in drug release after a predetermined lag period. These systems deliver the drug at the right time, place, and amount in the patient's body. Sustained, controlled drug delivery systems have shown remarkable efficacy in medication delivery but failed in drug delivery due to illness circadian behaviour. As a result, pulsatile systems are extremely advantageous, increasing the therapeutic efficiency of medication and improving patient compliance in chronic disorders. Pharmaceutical technology has advanced dramatically in recent decades, and with the introduction of pulsatile drug delivery, which delivers the correct drug to the right patient at the right time, one can be confident that the goal of safe and efficient therapy will be realized. Further advancements in the field of drug delivery resulted in the discovery of remotely administered drug delivery systems, which give significant therapeutic benefits. Some novel technologies have recently been developed that are responsive to light, ultrasound, magnetic fields, electrical stimulation, and wirelessly driven implantable systems.

ABBREVIATIONS

Pulsatile drug delivery systems (PDDS)

FUNDING

Nil

AUTHORS CONTRIBUTIONS

Dr. Mohan Kale and Dr. Bharat W. Tekade Gave guidance to Vishal Bodke to Write the manuscript; Ruchita Badekar made a Diagrammatic and tabular data collection with Vishal Bodke, Swapnil D Phalak Ensure the data and Arranged serially. All authors

read the manuscript and are Ready for Publication. All authors have contributed equally.

CONFLICTS OF INTERESTS

The authors declare no conflicts of interest.

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