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REVIEW ARTICLE

A Recent Development of Chronotherapeutic Pulsatile Drug Delivery System for The Treatment of Cardiovascular Diseases

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ABSTRACT

Currently cardiovascular diseases (CVDs), not only the main cause of deaths in India but also are a matter of concerned throughout the world. The recent report in 11 June 2021 by World Health Organization (WHO), states that, 17.9 million peoples throughout world lost their life in 2019 due to different CVDs, which are accountable for 32% of all global deaths. 85% of it is owing to myocardial infarction and stroke. India is carrying the highest burden of CVDs among the world where every 1 out of 5 deaths is due to heart disease, specially targeting the young persons (Neo Car Diab Care in 2017 report). Heart attack cost one life every 33 second in India. The problem is that many cardiovascular events for instance sudden mount in blood pressure (BP), stroke, anginal attack, and heart attack, heart failure and cardiac arrest takes place during early morning particularly at the wake up period or last phase of the sleep which reveal towards the circadian connection of these CVDs. Hence required a deep inside view of circadian behavior of this disease for optimum therapy. Continuous extended-release dosage though had a bright past but unable to deliver the drug based on the circadian behavior. As a matter of fact, more than conventional or continuous release, a chronotherapeutic approach of pulsatile drug delivery system (PDDS) is more appropriate in this regard because it make sure its release to achieve the C max based on the circadian peak of the disease hence efficiently over comes this problem. Hence the current review is an attempt to deeply understand the connection between cardiovascular pathologies and circadian rhythm (24 hour cycle of our body) and its affect in the cardiovascular factors like fatty deposition ratio in arteries, decreased fibrinolytic activity, increased platelets aggregation, increased capillary resistance, decreased myocardial blood flow and increased level of catecholamine to set the risky platform for early morning cardiovascular events and progress in the field of PDDS as a novel chronotherapeutic approach to solve these problem including its merits, demerits, types and technologies such as EGALET®, CODAS®, TIMERx®. PORT®, CHRONOTOPIC®, CONTIN®, DIFFUCAPS®, CEFORM®, OROS® etc.

Keywords: Cardiovascular diseases (CVDs), pulsatile drug delivery system, Circadian rhythm, Chronobiology, Chronotherapectic, Chronomodulated, C max (maximum concentration in plasma)

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INTRODUCTION

Several decades of past have witnessed of growth in continuous and extended-release drug delivery systems which maintain a constant drug concentration in our body regardless the physiology of the patient. Long-term therapy using these dosage forms because many problems such as resistance, tolerability, high first pass metabolism, low oral bioavailability and drug side effects [1]. Number of widespread chronic diseases for example CVDs, hypercholesterolemia asthma, arthritis, acidity etc. shows

distinctive night-time or early morning reappearance of symptoms based on the circadian cycle (24-hour rhythm) of our living body which demands a treatment on the basis of Chrono pathological behavior of these diseases. In other word, for optimum therapy it required the timed oriented chronotherapeutic pulsatile drug delivery system (PDDS) [2,3]. PDDS is define as the quick and momentary release of fixed amount of drug molecules after a pre-determined lag time [4,5,6]. World health Organization (WHO) report says that currently cardiovascular diseases (CVDs) are the number one causes of death worldwide as well as for India. The matter of concern is that most of these cardiac events taking place at early morning when patients raise from its bed hence a deep insight view of biorhythm of this disease could play a significant role for optimum therapy**.** Keeping this in view, the current review is an attempt to underline the current scenario of CVDs, its circadian connection with early morning cardiovascular events and emerging role of PDDS as a chronotherapeutic approach to overcome such problems. It also focuses the concept advantages, disadvantages, methodologies, and various technologies involved in PDDS with an inside view of the assorted PDDS of cardiovascular drugs in last decades using various polymers and its future scope.

Current scenario of CVDs as a threat for India

The most recent report by World Health Organization (WHO) in 11 June 2021 claimed that, 17.9 million peoples of the world in 2019 lost their life due to different CVDs, are accountable for the around 32% of all global deaths and *85%* were due to heart attack and stroke among them. Currently CVDs are the number one causes of death worldwide. Based on report in 2015, around 31 % of global deaths are due to CVDs. Around 37% of total deaths in low- and middle-income countries are due to CVDs. Epidemiology studies in India indicates CVDs a serious threat for public health system. Coronary Heart Disease acts as a major cause of mortality and morbidity in India. Report of registration general shows that, in India 23% of total deaths and 32% of adult deaths is due CHD (coronary heart disease. The growth of CHD in the last 60 years in India indicates towards increasing trend of urban populations (1% to 10%) as compared to rural populations (1% to 6 %) [7]. Indians are suffered from these diseases from younger age as compared to the North American and Western Countries. It must require an urgent and sincere social, bureaucratic and political will to initiate steps in this [8] According to a report of May 19, 2016 from *IANS (India's Largest Independent Newswire),* every 33 seconds in India one person dies due to heart attack. The alarming Statistics by *Neo Car Dab Care in 2017* indicates that, India in future will be number 1 in the world in cardiovascular disease. In India around 45 million coronary artery disease patients are present. The matter of concern is that, CVDs death rate of India is 272 among one lake population, which is greater than global figure I.e. 235. Cardiac stroke and ischemic heart disease is responsible for more than 80% of these death in India [9]. *Velagaleti et al* studied the synergistic role of hypertension and coronary heart diseases leading to heart failure in the general population. Heart failure is a condition in which our heart cannot pump the required amount of blood to the tissues. In this 21stcentury, the prevention of hypertension and coronary heart disease act as a beigest challenge globally as well as for India [10].

Currently used classes of medication for cardiovascular diseases

For the management of above problems, currently different classes of medications are used i.e. Statins are used to reduce the accumulation of lipids in arteries by reducing the Low-Density Lipoprotein levels in blood, hence reduce the possibility of severe atherosclerotic. Other than statins, antihypertensive drugs like beta blockers, alpha blockers, Angiotensin receptor blockers, Angiotensin converting enzyme inhibitors, and calcium channel blockers etc are also very effective [11]. According to some recent clinical trials reports, diuretics are recommended strongly in hypertension these days [12]. Drugs like thrombolytic and aspirin, helps to dissolve clots present in arteries which prevent the possibility of new clots formation, acts as a major breakthrough to saves many lives from Myocardial infraction [13,14]. Drugs like ACE inhibitors, aldosterone antagonists and beta-adrenergic blocking agents decreases overactive compensatory mechanism in heart failure hence act as more beneficial for its management [15]. It was found that combination of several classes of drugs, for example isosorbidedinitrate (nitrates) and hydralazine (vasodilators) are proved to be more beneficial to control mortality due to heart failure [16].

Circadian connection of cardiovascular pathology and requirement of chronotherapy

Emerging role of biorhythm play a significant role in optimizing treatment of cardiovascular diseases. Circadian rhythm derived from the word "Circa" means "circle:" and "dian" means "time". It is the biorhythm where biological oscillations follow a 24 hours' cycle. Such rhythms let the living body to forecast and adapt according the precise and intermittent changes in the environment [17,18]. There are many report has been put forwarded about relationship between circadian rhythms and heart diseases. *N. Takedaetal* focused on the diurnal variations of cardiovascular tissues, vascular endothelial cells, heart

rate, blood pressure, cardiac arrhythmia, acute coronary syndrome, subarachnoid haemorrhage [19]. *C.R* Taylor 1991 et al studied 33,999 angina attacks recorded from 1022 chronic angina patient to observed the peak at morning hours [20]. James E. Muller (1999) reported a circadian peak of thrombotic process, ruptured atherosclerotic plaques, platelets activation, catecholamine and cortisol levels in the morning combines with the initiation of daily activity triggers sudden rise in blood pressure, stroke, angina, heart failure and heart attack [21]. Janie F *et al* [22] reported heightened activity of autonomic nervous system at early morning causes increase in catecholamine level which generate higher vascular tone and elevated circulating blood volume leads to sudden mount in blood pressure. M L Weisfeldt *et al* [23] warns about the higher accumulation of lipid in arteries at early morning may leads to arthrosclerosis, hypertension, angina pectoris, heart failure, stroke, heart attack and sudden cardiac arrest. William Elliott [23] analyzed the distribution of acute myocardial infarction (Figure 1), sudden cardiac death (Figure 2) and stroke (Fig 3) across 24 hours of the day including 83,929, 19,390 and 11,618 patients respectively indicate towards the 40% higher risk of heart attack, 29 % jump in sudden cardiac death and 49 % higher risk of all types of stroke in early morning period from 6 am to 12 pm [24]. According DR *Mehmet Oz*, *MD*, New York, NY *Cardiology (Cardiovascular Disease)* of Columbia University/New York Presbyterian hospital ,the probability of a heart attacks are 3 fold more at morning after awakening ,it is due to requirement of 50% extra blood supply to body from sleeping to awakening, get combined with some additional factors such as stiff blood vessels, high blood clotting, low fibrinolytic activity, plaques etcetera an additional blood pressure on the capillary walls leads to tearing of blood vessels and heart attack. Roberto Manfredini (July 2008) professor of internal medicine at the University of Ferrara in Italy, explicated that, it's not as easy as just ask patients to take a continuous release dosage form previous to bed instead of first thing in the morning, because in sleep heart rate and blood pressure normally remain low If you lower your blood pressure too much during the night, we risk dipping blood supply to the brain, and that can be risky. But peoples normally take hypertensive drugs after wake up in the morning, is already the higher-risk period. It's hard for people to accentuate the effects of their individual biological rhythms. For example, simply waking up late, we cannot keep away from morning hazard. Pandit and Suresh et al [25] studied about emerging role of biorhythms in optimizing treatment of cardio vascular diseases given in table 1.

Table 1: Circadian rhythm and manifestation of cardiovascular diseases [25]

Sudden rise in blood pressure	Cases are more in the early morning between 4-6 am.
Heart attack or myocardial infarction	Incidence are comparatively high in the early morning after awakening of patient
Strokes	Cases are comparatively more at morning after awakening
Sudden Cardiac Death	Cases are more in the morning after awakening
Angina Pectoris	Pain in the chest are more frequent in early morning after awakening

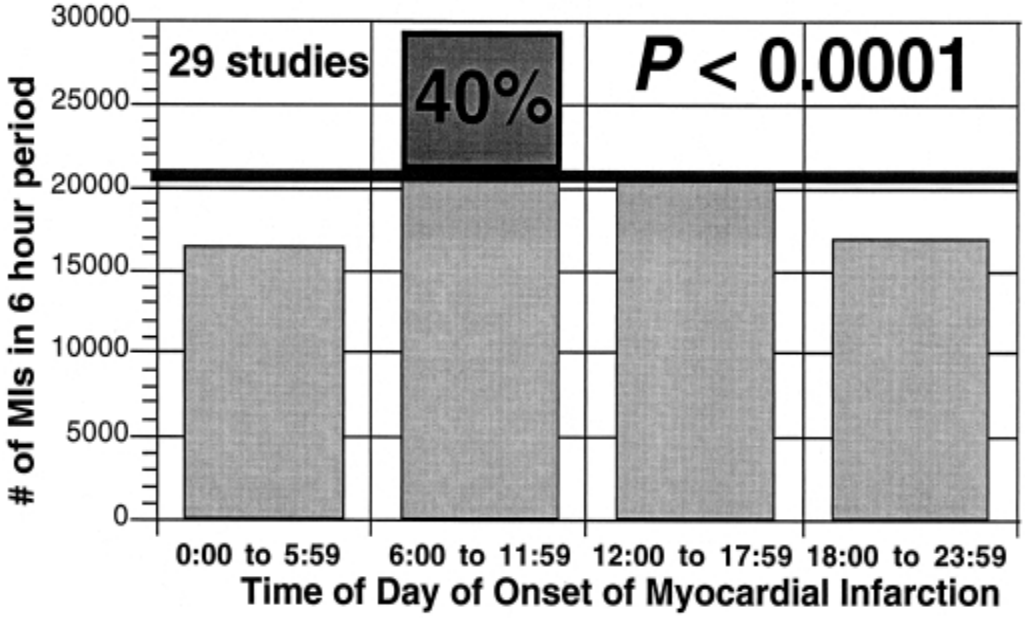

Figure 1: Frequency distribution of acute myocardial infarction for 24 h of the day in 29 studies including 83,929 patients. [23]

Horizontal deep black line at 20,982 indicates the numbers expected if heart attacks would occur randomly and evenly throughout the 24 h of the day

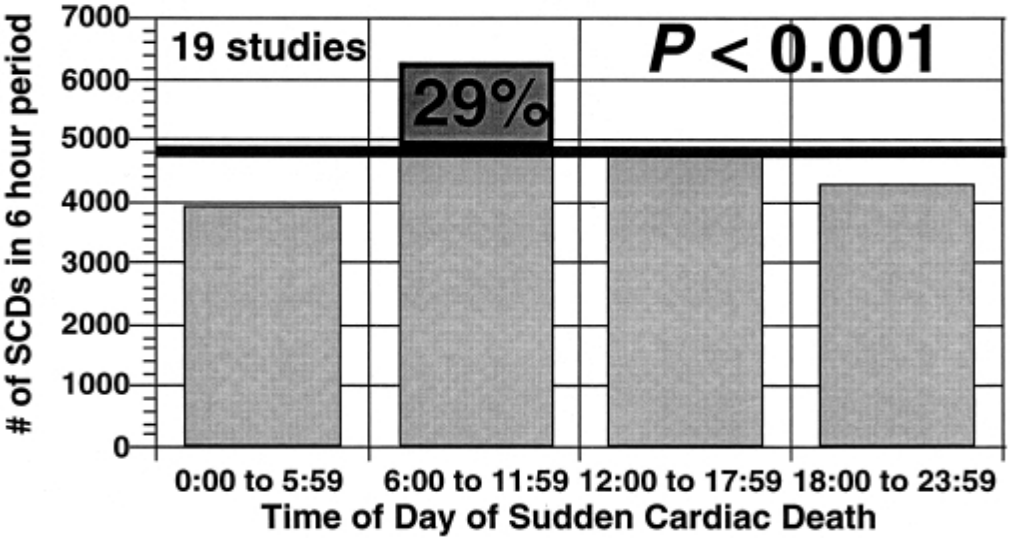

Figure 2: Distribution of sudden cardiac deaths across the 24 h of the day in 19 studies of 19,390 patients. [23]

The horizontal line at 4,848 corresponds to the number expected if sudden cardiac deaths occurred randomly and evenly throughout the 24 h of the day

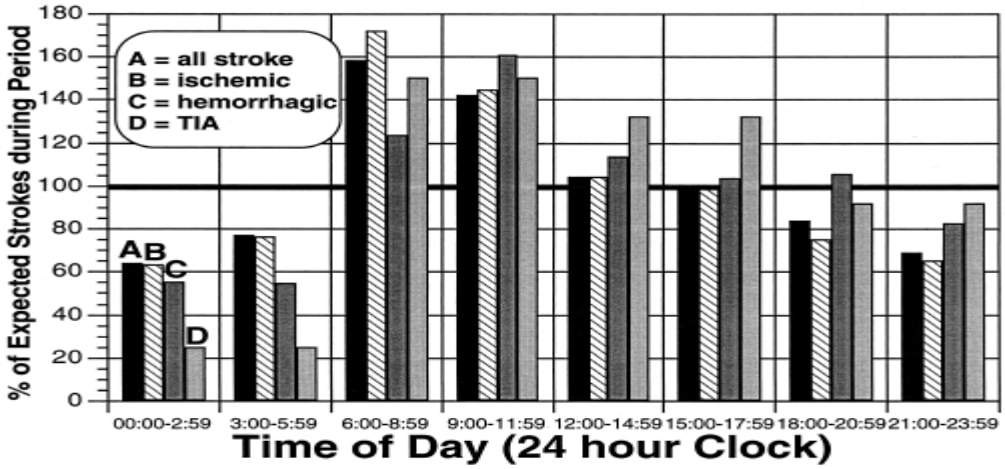

Figure 3: Distribution of various types of strokes like A-all, B- ischemic, C-hemorrhagic, D-transient ischemic attacks during the 24 h of the day of 11,618 patients. [23]

Early morning Cardiovascular conditions & requirement of PDDS

Early morning, leads to increased fatty acid deposition ratio in artery, decreased fibrinolytic activity, increased platelets aggregation which causes capillary resistance. When patient suffering from CVDs rise from its bed and get involve in daily activities its heat rate increases which leads to increase in myocardial oxygen demand which get combine with above factors leads to sudden rise in blood pressure, angina pain, heart attack, heart failure, cardiac arrest, and stroke etc. given in Figure no 4. A Chrono-modulated PDDS of cardiovascular drugs would releases the drug in such a way that the drug achieves its C max just before the rise of the patient at morning and reduces the Oxygen demand of myocardial tissues by normalizing the elevated heart rate, or reduce the blood pressure, hence play a major role in preventing this adverse cardiac event [11, 19-24].

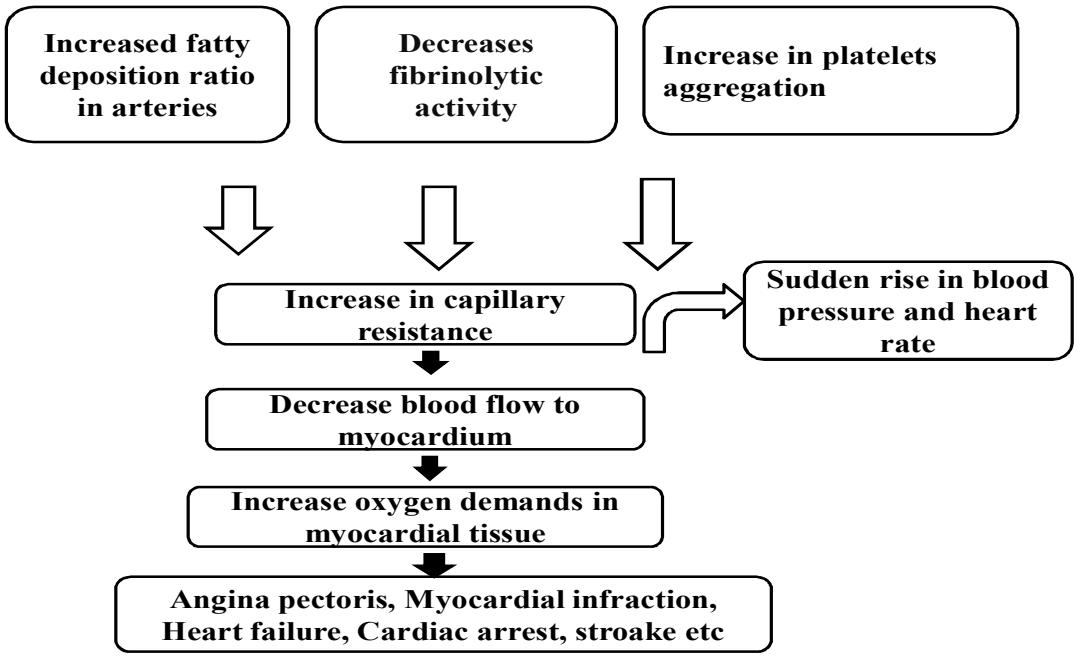

Figure 4: Factors responsible for early morning cardiac events

Pulsatile drug delivery system (PDDS) as a novel Chronotherapeutic approach for cardiovascular diseases

Oral routes are among the highest preferable route of drug administration. Usually most of the drugs are released in the conventional or extended fashion. The pharmaceutical research field is widened due to the invention of many novel drug delivery systems. [25] some diseases follow circadian rhythm where a continuous constant delivery of drug is unusual. [26] The biological functions in our body is controlled by circadian rhythm (24-hour oscillation cycle) act as the function of information circulated to different cell and tissue by Superchiasmatic nucleus of our brain, which help living being to adapt in variable environmental situation at different time. [27]. This superchiasmatic nucleus in the hypothalamus act as the epicenter of the biological clock and each cardiovascular tissue also has its own intrinsic biological rhythm. A depth understanding of these phenomena attributes towards a novel concept of chronotherapeutic drug delivery system (Table 2), which are merited to copiously explicate this orchestration of biological systems hence play a major role in treatment of cardiovascular diseases [28,29] Diseases like CVDs, Bronchial asthma, Hypercholesterolemia, Peptic ulcer, Rheumatoid arthritis and Attention deficit syndrome etc. tends to follows a pattern of 24-hour cycle (circadian rhythm) in their path physiology [27, 30, 31]. Hence, while dealing with these diseases both Circadian cycle of disease as well as time to achieve maximum plasma drug concentration (t max) of the dosage form should be taken into consideration [30, 32] These diseases required a right amount of drug delivery at a right time based on the biological requirement or circadian rhythm. In other word it required the chronotherapeutic drug delivery system to achieve this goal (Table 3) [33, 34]. Chronotherapeutic is defined as the study of providing the medicament at a 'right time" based on the circadian cycle of a disease. However, Pulsatile drug delivery system, is an emerging trend in current scenario to achieve chronotherapy of circadian based diseases. It releases the drug after a specific lag time and provides both spatial as well as temporal drug delivery hence leads to patient compliance. [4,35,36], The rational of PDDS is based on the fact that, best possible therapeutic out outcome might not be feasible with constant plasma level especially for the diseases follows circadian variation (Figure 2). PDDS is recognized to conquer the disadvantages of Controlled release drug delivery system has gained mileage as the drug delivery system due to optimum therapeutic efficacy, better patient compliance, and having fewer side effects (Figure 3). [25]. Currently Chrono pharmaceutical principle is used to targets many cardiovascular diseases such as angina, hypertension and pulmonary embolism etc. [31, 37]. The variation in blood pressure and heart rate follows circadian rhythm [31]. Most often onset of variant angina circadian rhythm, occurs between midnight to early morning hours [38]. 5 shows the basic principle of pulsatile

drug delivery system where lines “A B& C” represent the PDDS which shows quick(sigmoid), delayed release and sustained release respectively after a specific lag time of 5 hours.

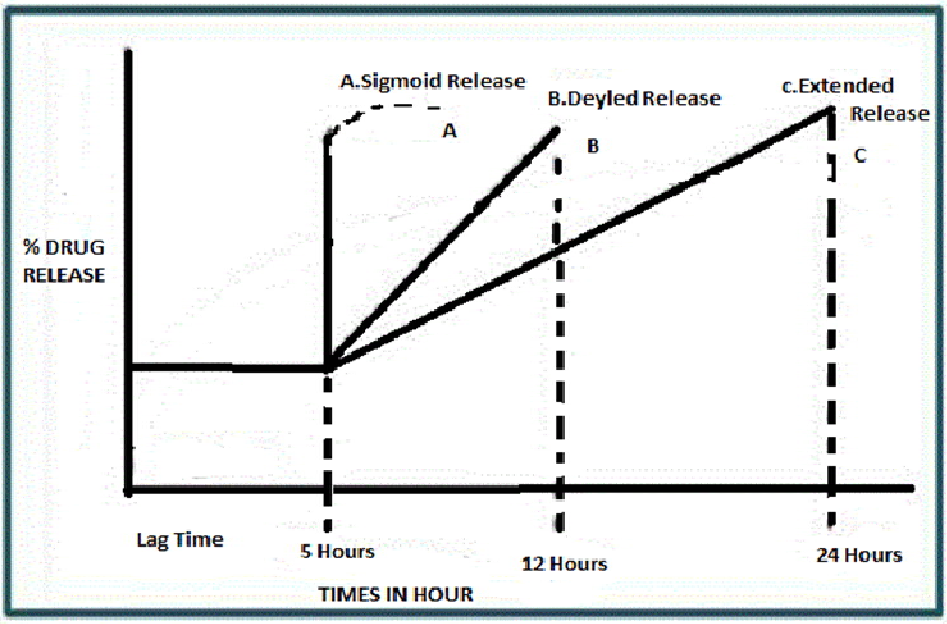

Figure 5: Graphical representation of drug release pattern of PDDS i, sigmoid release (a), delayed release (b), Sustained release (c) after 5 hours of lag times. controlled extended release without lag time(d)

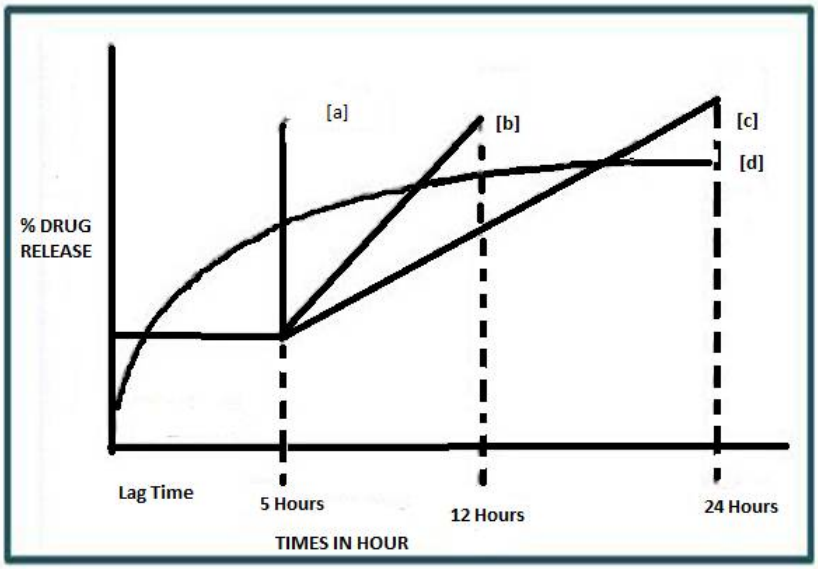

Figure 6: Graphical representation of sigmoid release (A), delayed release (B) and extended release (C) of PDDS after the lag time of 5 hours.

Table 2: Some marketed Chronotherapeutic cardiovascular Products [29]

Brand name	Generic name	Manufacturer
InnoPran XL	Propranolol	Glaxo Smith Kline, USA
Cardizem LA	Diltiazem	Biovail Corporation Mississauga on Canada
Verelan PM	Verapamil	Schams Pharma, Monhein, Germany
Covera HS	Verapamil	G.D Searle (a division of Pfizer)NY,USA

Table 3: Necessities of chronotherapeutic pulsatile drug delivery system at various condition [39.40,41].

Conditions	Overcome by Chrono therapeutic drug delivery system
Extensive first pass metabolism	**Constant or sustained release of some drugs under goes extensive first pass reduces its oral bioavailability. Chrono therapeutic drug delivery system** saturates the metabolizing enzymes by quick drug input after a predetermined lag time can enhance bioavailability.
Biological tolerance	Long terms plasma profiling of drugs leads to decline its therapeutic effect due to biological tolerance, could be overcome by Chrono therapeutic pulsatile delivery.
Special Chrono pharmacological needs	On set and symptoms of certain diseases like asthma, arthritis, cardiovascular diseases, hypercholesterolemia, acid secretion in peptic ulcer follows circadian rhythms (24 hour cycle a day) e.g., asthmatic attack and angina pain are very often occurring at the early morning hours of the day. Chrono therapeutic drug delivery system achieved the C max based on the circadian behaviour of these diseases prove to be a best approach.
Local disorder	Chrono therapeutic drug delivery system having no loss in upper part of GIT (due to lag time) releases the drug to the site of inflammation in lower part could offer a better treatment of local disorder such as inflammatory bowel disease.
Gastric irritation or drug instability in gastric fluid	Chrono therapeutic drug delivery system could be a best approach for the drugs produce Gastric irritation (NSAIDS), instable in upper GIT (protein and peptides) and induce nausea & vomiting.

Advantages of chronotherapeutic pulsatile delivery system:

- Ensures drug release in right site at right time
- Best to treat disease follows circadian rhythm
- Dose dumping could be avoided by using multiparticulate system.
- Prevent drug loss due to extensive first pass metabolism
- Improves the bioavailability and stability.
- Reduced dose frequency and dose size as compare to conventional dosage forms.
- Reduced adverse effects
- High patient compliance due to oral rout therapy as compared to conventional dosage forms
- Protect mucosal damage due to gastric irritation
- Less expensive compared to conventional controlled release system due to fewer dosage units.
- Unique pattern of drug release
- Flexibility in the designing [39.40,41].

Limitations of chronotherapeutic pulsatile drug delivery system:

- Involves more than one step in manufacturing
- The rupture time cannot be always adequately manipulated
- Drug loading is low.
- Partial release.
- In vitro, in- vivo correlation not up to the mark
- Higher production cost
- Lack of reproducibility in manufacturing
- Process variables are more
- Dosage form administration time is important [39.40,41].

Mechanism of drug release from PDDS

There are mainly three mechanism involve in the release of drug from pulsatile drug delivery system.

Erosion

In this process with respect to time the coating membrane undergoes erosion itself [42,43, 44].

Diffusion

It is the process concentration gradient is responsible for drug movement. Drug moves from higher concentration to lower concentrating. Here no energy required [44, 45].

Osmosis

In this process movement of drug occurs through a semi permeable membrane from the lower to higher side concentration. Movement of drug required external energy in the form of osmotic pressure created by osmogenes present in the formulation [42, 45].

Diseases required pulsatile drug delivery system

There are some diseases required pulsatile drug delivery system based on their chronological behavior, (table 4) [41, 46]

Table 4: Diseases required pulsatile drug delivery system

Diseases	Chronological behaviour	Time	Drug used
Cardiovascular	Blood pressure remain normal during the sleep but increased sharply at early morning while patient rise from the bed and start its daily activities	6 am	ACE Inhibitors ,Nitro-glycerine, Calcium-channel blockers, Beta blockers etc.
Hypercholesterolemia	Cholesterol synthesis is higher at night than day	8pm to 4am	HMG CoA reductase inhibitors
Peptic ulcer	Acid secretion is more in the afternoon and at the night	6 pm, 12 pm	H2 blocker
Arthritis	Pain is more at night	12 pm	NSAIDs, Glucocorticoids
Asthma	Attack occurs during night and early morning	12 am 6 pm	B2 agonist, antihistamine
Diabetes mellitus	Increase in blood after meal	----------	Insulin, Sulfonylurea

ACE – Angiotensin Converting Enzyme, NSAID-Non Steroidal Anti- inflammatory drugs

Types of chronotherapeutic pulsatile drug delivery Systems

Various methodologies are developed for the success of chronotherapeutic pulsatile drug delivery system is given below.

Timed-dependent Chronotherapeutic pulsatile drug delivery systems:

- Reservoir systems with rupturable polymer coating.
- Pulsatile delivery by solubilization or erosion of layer
- Capsular systems.
- Pulsatile System Based on Osmosis
- Chronotropic systems dependent on changed membrane permeability.
- Low density/floating systems

Stimuli Dependent Systems (pulsatile drug delivery systems):

- Temperature sensitive pulsed- release delivery systems.
- Inflammation induced systems.
- Enzyme dependent pulsatile-release systems.
- Glucose concentration dependent insulin release systems.
- Intelligent gels responding to antibody concentration.
- pH sensitive pulsatile drug delivery systems

Externally Regulated System

- Ultrasound induces system
- Electric field induces system
- Magnetic induces system
- Light induces system

Timed-release/time-dependent Chronotropic Systems

A. Pulsatile delivery by solubilisation or erosion of layer

This is most widely using system where a core tablet of drug is coated by various polymers which may or may not contain drug. When comes in contact with Gastro intestinal (GIT) fluid the outer coating layer of polymers start to erode. The lag time is achieved by time taken for erosion of coating layer. The rate of erosion of coating layers depends upon the nature and thickness of polymeric layer [47,48,49,50].

B. Reservoir systems with rupturable polymer coating

Ueda et al. patented (1989) and discovered (1994) the concept and design of a novel time-controlled explosion system, its vitro drug release properties and relation between lag time and membrane thickness. This is a single or multiple unit reservoir system where drug is present in the core surrounded by outer reputable polymeric barrier layers. Coming contact with the water the surrounding polymeric layer ruptured due to hydrostatic pressure, followed by drug release from the core. The time required for the rupture of surrounding layer depends upon the factors like thickness of the membrane, swelling agent, osmotic agents, effervescent agents etc. The lag time in drug release is the resultant of rate of

permeation of surrounding fluid and provided mechanical resistance by the outer rupturable polymeric layer. The release mechanism involves either diffusion of dissolution depends upon the nature of the drug [51-55].

C. Capsular Systems

Ross et al (2000) discovered a pulsatile capsule device (plus in cap) based on programmable erosion technique. It is consisted of an insoluble capsule body and swellable and degradable hydrogel plugs made of approved substances which seals the drug contents into the capsule body. Upon coming in contact of dissolution medium, the hydrogel plug swells and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug. It is the swelling strength and erosion rate of plug which actually decides the lag time of drug release from the device; Hydrophilic polymers like hydroxyl propyl cellulose, polyvinyl-acetate, and polyethylene-oxide etc are used for the plug [56]

D. Chrono therapeutic drug delivery system based on changed membrane permeability

Narisawa et al 1993 and 1996 developed an oral organic acid induced sigmoid or pulse release microcapsules using theophylline as core and Eudrajt RS as the polymeric coating which under goes change in permeability in presence of certain counter ions of surrounding media. Dosage form shows comparatively very slow release rate in water than solution containing glutamic acid, tartaric acid, malic acid, citric acid and succinic acid [57, 58].

E. Low density/floating pulsatile drug delivery systems

These are either single or multiple units floating pulsatile drug delivery systems found in the form of tablet, capsules, microspheres, microcapsules or beads. The dosage form not only having gastro retentive nature but also have gastro resistance polymeric coating which provide the desired lag time of drug release till the dosage form float in the stomach. Drug release from this dosage form after a specific lag time at the intestine or colon. To achieve the desired effect polysaccharides are widely accepted as the polymer. Sharma et.al. 2002 successfully designed a low density multiparticulate system for pulsatile release of meloxicam, Badve *et al 2007, developed* hollow calcium pectinate beads for floating pulsatile release of diclofenac sodium intended for chronotherapy [59, 60].

F. Pulsatile system based on osmosis

This system releases the drug based on osmotic pressure generated by osmogenes. This device is a capsule containing water insoluble polymeric plug. The capsules are coated by a semi permeable polymeric membrane. Inside of the capsule contain two parts one contain drug and other contain osmotic agent. GI (Gastro Intestinal) fluid enters in to the capsules through semipermeable membrane and come in contact of the osmotic agent to create osmotic pressure leads to removal of the in soluble plug to release active ingredients [61,62,63,64].

Stimuli Dependent Systems

These are novel targeted approaches where drug release from the dosage forms triggered by the certain physiochemical stimuli at the target site such as Temperature, pH, enzymes, hormones, antibodies, certain cells, and bimolecular concentration of glucose, inflammatory mediators, neurotransmitters etc.

A. Temperature Sensitive pulse- release delivery systems:

Physiological temperature of various types of cells inside the body is not same due to their different metabolic functions. Due to their different metabolic functions the physiological temperature of different types of cell in the body remains different. E.g. high metabolic rate of the tumor cells rises its cellular temperatures. A pulsatile drug delivery having thermos responsive hydrogel system can easily target the tumor cells based on the temperature change due to metabolic rates of tumors [65, 66].

B. Inflammation Induced pulse release systems:

Inflammatory diseases like rheumatoid arthritis releases hydroxyl radicals from inflammation responsive cells act as a stimulus to release NSAIDS from implantable dosage forms.

C. Enzyme Dependent Pulsatile-Release Systems:

Number of natural polysaccharides like pectin, guar gum, chitosan, chondroitin sulphate, dextran etc is found to have azo bond in their structure catalyzes by the enzymes produce by colonic micro flora, leads to disintegration of these polymers in colon. Applying it as a coating material in tablet or as a plugging material in capsule (pulsincap) to produce pulsatile drug delivery system releases the drug after a specific lag time used to targets colon. But lacking of good film properties and early release of drugs in GIT due to high swelling and porous nature act as the challenges to overcome while designing these dosage forms [65, 66].

D. Glucose Concentration Dependent Insulin Release Systems:

It was depicted earlier that there is a rise in blood glucose level rhythmically in Type 1 Diabetes. A number of systems were developed based on the changes in blood glucose level. Stimuli induced pH responsive hydrogel system is among one of them, which contain the enzyme “glucose-oxidase” in

immobilized form. It became active by the increase in of blood glucose level and converts the glucose in to gluconic acid. The gluconic acid changes the pH of system leads to swelling of polymer which causes release of insulin from the dosage form. Insulin decreases the glucose level in blood, as a result the gluconic acid level also declines and system turns to deswelling and hence release of insulin from the dosage form also declines. This process continues for long. Examples of some pH induced polymers are chitosan, n, n-dimethyl amino ethyl methacrylate, and polyol etc [65, 66].

E. Intelligent Gels Responding to Antibody Concentration:

Drug resistance and tolerance towards antibiotic is commonly among microbes in many infectious diseases. Hence a pulsatile drug delivery of antibiotic is must require in order to kill all microbes, both in multiplying and dormant phase. Novel gels to change their swelling/deswelling characteristics with respond to change in antibiotic concentration have been developed. Reversible swelling or deswelling of gel and changes in drug permeation based on the variation in association constants among polymerized antibody and naturally derived antibody for specific antigens [65, 66].

F. pH dependent Pulsatile Drug Delivery Systems:

Due to its reliability and optimum predictability pH dependent pulsatile drug delivery system are widely accepted in the development of chronotherapeutic system. It may be single as well as multiple unit dosage forms developed by using pH dependent polymers. These systems are based on the fact of variable pH in GIT. Desired lag time by the dosage form are achieved by enteric coating the drug to protect from the upper part of GIT and release of the drug from the dosage form depends upon the solubility of polymer at the specific site at a particular pH of intestine. Coating of polymers such as various grades of Eudrajt, Carboxy methyl cellulose, phthalates etc are used to achieve the goal. Akhgari*et.al2005 developed* Indomethacin pellets for chronotherapy of rheumatoid arthritis using various ratios of Eudragit L100 and Eudragit S100. [67] Gupta *et.al 2001* exploited various grades of Eudrajt soluble at pH more than 7 to achieve colonic delivery of 5-aminosalisylic acid for treatment of irritable bowel syndrome. Also colon targeted Chronotropic systems of nitroglycerine, verapamil, diltiazem, theophylline, budesonide, etc have been formulated to treat hypertension, angina and asthma [67, 68].

Externally regulated pulsatile drug delivery

In this system, biodegradable polymeric device contains drug implanted in the human body and timing and rate of release of drug from its dosage form is controlled by external stimuli such as ultrasound, electric, magnetic and lights etc.

A. Ultrasound induces system

In this system the ultrasound waves are used to degrade the biodegradable polymeric matrix to release the drug in a fastest rate in the body [50, 69, 70].

B. Electric field induces system

These devices contain poly electrolytic polymers having ions in their backbone which makes it as electric sensitive polymers. When exposed to external electric field these polymers alter their structure to release the drug on time [63, 70,71].

C. Magnetic induces system

These are the polymer beads containing drug and magnetic elements introduced tothe body in the form of implants. Drug release from the dosage form is controlled by exposing the implanted region to an externally controlled magnetic field.

D. Light induces system

This system prepared a mixture of drug with such materials to absorb light of specific wavelength which is the deciding factor to drug release from the matrix. E.g., light absorption by the nano shells at the infrared region generates heat which is responsible for the degeneration of the hydro gels to release drug from the polymeric matrix [70].

Dosage Form Development

Multi-Layered Tablets or Capsules

These are normally time regulated rupturable pulsatile drug delivery systems found in the form of capsules or tables. In capsules, drug packed in insoluble capsule-body. A layer of sellable polymer coating was given which was followed by an external coating of water insoluble semi permeable layer. Water ingress thorough the water insoluble semi permeable membrane and come in contact with swellable layer to swells which create hydrodynamic pressure to rupture the outer coating and permit the inner drug to release to the surrounding medium. It is the time required by the swelling layer, which decides the lag time of the drug release to achieve chronotherapy. The multilayered pulse release tablet also can be prepared by the same principle mentioned above [72].

Press Coated Tablets

These are the most highly preferred timed-release formulations due to its simple manufacturing process. It contains an inner core composed of drug and excipients encapsulated by an outer layer of polymers. The lag time of the drug release depends upon the erosion time of this outer layer. The core tablet is prepared by flat punches tableting machine then the prepared tablet is kept in between the outer layer polymers and compressed to get the pulse release tablet. The thickness of the coating membrane is the deciding factor of the lag time. Sawada *et al*. prepared timed-release compression coated tablets of nifedipine for chronotherapy of angina and compared its in-vitro-in-vivo release profile with sustained release formulation [73].

Core-Cup-Tablets

It composed of 3 parts. It's the active constituent as core, 2nd impermeable outer coating comprises of cellulose acetate propionate and 3rd the top cover gel barrier layer of hydrophilic swellable polymers like Na CMC (Sodium Carboxyl Methyl Cellulose), sodium alginate or polyethylene oxide etc. Drug release start after a predetermined time interval after the complete removal of 3rd layer i.e. top cover layer. Hence lag time is controlled by properties like swelling capacity, viscosity and thickness of the top gel layer. Release pattern of drug from this dosage form is also affected by solubility of drug [74].

Multiparticulate Systems

Various methodologies like time controlled, stimuli induced, externally regulated system has been adopted to develop multiparticulate PDDS. Dosage forms like beads, micro sponges, microspheres, granules, Pellets and nanoparticles etc are comes under the multiparticulate system. Due to their potential advantages like no dose dumping, less variability, increased bioavailability short gastric residence time, reduced local irritation, predictable and reproducible nature over single unit dosage form make it more popular choice. Numerous superior technologies have developed and many have approved by Food & Drug Administration (FDA) to design of pulse release multiparticulate drug delivery systems [75].

Pulsincap Systems

These are widely adopted pulsatile release capsules where drugs are present inside the insoluble capsule body seals by a hydrogel plug. When taken orally the water-soluble cap dissolve in gastric fluid and coming in contact of surrounding fluid the hydrogel plug starts to swell. The swollen plug is ejected after a predetermined time period to release the inside content of the capsule body. This technology can be further simplified by replacing the plug by erodible tablet [76,77].

Infusion Pumps

These are internally and externally regulated, pre-programmed systems which are sensitive to environmental pH and temperature, hydrolytic degradation, enzymatic modulation, light and mechanical stimulation, ultrasound, electric fields and magnetic fields. Some marketed "Chrono modulating infusion pumps "include "Rhythmic Pumps" "Melodie", "Panomat V5 infusion", and the "Programmable-Synchro med" etc.

Chrono Modulating-Microchips

Micro-chips are an alternative technology to attain Chrono pharmaceutical or pulsatile drug release. Santini *et al*1999 developed a solid-state silicon microchip for controlled release of single or multiple chemical substances on demand. The mechanism involved, electrochemical dissolution of thin anode membranes covering micro reservoirs filled with chemicals in solid, liquid or gel form. This technology has enough potential for the designing of Chrono therapeutic drug delivery systems with having a superior control over drug release kinetic to match biological requirement over a prolong period of time [78].

Recent techniques in the pulsatile drug delivery

OROS® technology

It is stand for "Osmotic-controlled release oral delivery system" having the brand name Chronset™, is an osmotic based Chrono modulated drug delivery device in the form of tablet, where drug is present in the core called as reservoir which is encapsulated by a semi permeable membrane having a delivery orifice created by laser drilling. The formulated tablet having two layers, one is the drug layer which is covered by the osmotic agent's layer. In GIT the fluid penetrates the semi permeable membrane comes with the contact of osmogene which changes characteristics from the non-dispensable to dispensable viscosity as a result of which creates a significant osmotic pressure to push the active constituent to pumping out through the delivery orifice in a predetermined manner. The thickness of semipermeable membrane and concentration of osmogene is the deciding factors to achieve desired rate of drug release. The device has the ability to reproducibly deliver a bolus dose in a time or site specific manner in the GIT (Gastro Intestinal Tract). Most often this technology is used for extended release drug delivery site [79].

CEFORM®

These are uniform sized microspheres of 150-180 micrometer, having better drug loading of active pharmaceuticals prepared by melt-spinning approach by using the combination of biodegradable polymers with bioactive agents applying various processing parameters like combination of thermal gradients, flow rates, mechanical forces etc during processing. The microspheres formulated in the form of tablet, capsules and suspension as a controlled release device with enteric coating or combined into a fast or slow release combination [80].

SODAS technology

It stands for Spherical oral drug absorption system are the customized drug delivery system based on the need of particular patient where pulse release of drug is achieved by coating different types of polymers to different beads.

PRODAS technology

It stands for Programmable oral drug absorption system is a capsules carrying numbers of mini tablets having drug in it compressed together to form a single unit.

DIFFUCAPS® technology

It is a capsules based system contains one or more than one drug in the forms of pellets, beads and granules etc. Each bead having the capability of deliver pre-determined drug release with or without lag time using erodible, soluble or rupturable techniques given above [81].

CONTIN® technology

This system based on the molecular complex between cellulosic polymer and a solid nonpolar aliphatic alcohol. Here cellulose polymer and a nonpolar solid aliphatic alcohol constitute molecular coordination complexes between them. The complex form has a uniform porosity make it feasible for the controlled matrix system of drug delivery in the form of tablets. This system has better controls for the drug delivery to systemic circulation [82].

CHRONOTOPIC® technology

Here generally the core containing the drug encapsulated by an outer release controlling membrane which provide the required lag time to the device. The system comes in the form of single unit tablets or multiple units' capsules containing mini tablets or pellets [82].

EGALET® technology It is a delayed release system having a water-resistant shell with double lag plugs, enfolds a plug of active constituent in the middle of the unit. The lag time is decided by the erosion time required for the plugs of the device. Shells are composed of unhurriedly bio erodible non soluble polymeric materials such as ethyl cellulose and plasticizers like cetostearyl alcohol, while polymers such as polyethylene oxide (PEO) are used as the plug matrix [83].

CODAS® technology

It is a multiparticulate system stand for "Chronotherapeutic Oral Drug Absorption System". It is planned for the bedtime dosing. Drug release delayed up to 5 hours by providing an enteric coating to the drug containing beads. The release of the drug from the dosage form is controlled by the coating material which is the mixture of both water soluble as well as water in soluble polymers. Surrounding GI fluid penetrates and solubilizes the water soluble polymer to form small pores from where drug is defused, while the water insoluble polymer remains intact and act as a barrier to maintain control release fashion from the dosage form. For example, Verelan PM XL capsule/Active Pharmaceutical Ingredient-Verapamil HCL [70, 84].

TIMERx® technology

It is a hydrogel based controlled release device which ensures zero order chronomodulated release. This system provides various kinetics of drug release by simply manipulating molecular interactions between different polymers. It is based on the principle of physical interaction between previously combined locust beanand xanthan gum mixed with dextrose, to form a strong binding gel in presence of water. The system while administered penetration of aqueous fluid from the surrounding leads to form a strong, binding gel matrix called TIMERx gum matrix, which get expands and subsequently release the drug in a programmed manner after a specific lag time [84].

PORT® technology

PORT stand for Programmable Oral Release Technologies where a single dosage form provides multiple delivery of drug a predetermined manner. It contains a core containing drug which is coated by polymeric layer of rate controlling semipermeable membrane. Drugs having poor solubility can be coated solubilizing agents to gives uniforms release from dosage form. In its capsular form a hard gelatin capsule body contain active ingredients or drug blended with osmoses plugged by water insoluble polymeric materials may contain immediate release dose of drug or not. The whole gelatin capsules are than coated by rate controlling semi permeable polymer layer [85]

ACCU-BREAK technology

Accu-Break is a patented technology where the dosage form splits itself to form small tablets of accurate dosages, which are meant for customize the treatment by dose adjustment and titration. It is Manufactured by the help of commercially found multilayered compression machine. ACCU-T- CR are the tri layered tablets which contain immediate release as well as controlled release medication [86, 87, 88].

T M D S technology

TMDS stand for (Time Multiple Action Delivery system) Technology which offer control delivery of more than one ingredient surrounded by a single tablet in predetermined programmed way. This technology allows multiple active ingredients or drug in a single tablet dosage form provides more than one release profile for an extensive period of time [89].

GEOLOCK technology

The technology imparts a compression coated table contain active ingredient which is coated or enclosed by and extra hydrophobic wax layers for programmed delivery of drug.

DUREDAS technology (Dual release drug absorption system)

It is a bilayer tablet dosage form where drug from one-layer release immediately after administrating followed by subsequent release from the next layer after a specified lag time [89,90].

K V/24

KV/24 is a multiparticulate patented, drug release technology which one or more drug compounds are encapsulated to release the drug in a pre- determined manner over a period of 24 hours after taken orally. Here a neutral core may have contained drug or coated with the drug is consequently layered by polymer to get once a day drug delivery system [88,89].

INNOHERB

These are pallets containing herbal drugs are coated with polymers and reserved in capsule shell [89, 91].

IPDAS® technology (Intestinal protective drug absorption system)

The intestinal protective drug absorption system (IPDAS) comes under the multiparticualte drug delivery system, is a novel approach of oral drug delivery to gastrointestinal (GI) irritant drugs e.g. Non-Steroidal Anti Inflammatory Drugs (NSAID). These are the compressed tablet form of numerous controlled release high density beads which are after ingestion dispersed in wide range in (Gastro Intestinal Tract) to ensure protection to the wall due to multiparticulate nature of drug release. Drug release controlled by bead matrix or bead coating technology by the help of polymers.

ORBEXA technology

It is a multiparticalate drug delivery system where product undergoes granulation process to forms multiparticulate beads containing drug which are further coated by functional polymer to achieve chronotherapy (Table 5) [89, 91].

Table 5: List of marketed pulsatile release systems using various drugs [65]

Technology	Mechanism	Brand name	Dosage form	Drug used	Disease
Pulsincap™	Rupturable system	PulsincapTM	capsule	Dofetilide	Hypertension
OROS®	Osmotically regulated	Covera-HS®;	XL tablet	Verapamil HCl	Hypertension
DIFFUCAPS®	Multiparticulate system	Innopran®;	XL tablets	Verapamil HCl Propranolol HCl	Hypertension
TIMERx®	Erodible/soluble barrier coating	OPANA®	ER tablets	oxymorphone	Pain management
PULSYS™	Multiparticulate system	Moxatag™	tablet	Amoxicillin	Infection
Covera-HS®	Osmotically regulated	Covera-HS®	ER tablets	Verapamil HCl	Hypertension
Procardia XL®	Osmotically regulated	Procardia XL	SR tablets	Nifedipine	High blood pressure and Angina
CODAS®	Multiparticulate pH dependent system	Verelan® PM	XL release capsule	Verapamil HCl	Hypertension

Pulsatile drug delivery systems using cardiovascular drugs and various polymers

A lot of development in the field of PDDS has occurred for the chronotherapy of cardiovascular diseases. Hence keeping this in view Table 6 highlights the various cardiovascular drugs, polymers and technology used in the field of chronotherapeutic pulsatile drug delivery system by the various researchers in the past and current decades.

Table 6: Assorted chronotherapeutic pulsatile drug delivery systems using cardiovascular drugs.

Drug	Technology	Principal excipients use to achieve pulse release	Lag time	Target disease	Ref
Valsartan	Nanocrystal compressed mini tablets in capsule	a. Polyxmer for nanocrystal B. Ethyl cellulose and HPMC E 5 coated mini tablets to achieve desired lag time.	Bi pulse at 5 hours gap	Early morning cardiovascular events	*[92]*
Propranolol hydrochloride	Press coated tablets in capsule	Guar gum as tablet eroding coating	Bi pulse at 5 hour gap	Hypertension, Haemorrhagic stroke, Cardiac death	*[93]*
Lisinopril	Press coated mini tablets using Rupturable polymer coating technology	Ethyl cellulose and Sodium alginate coating to maintain desired lag time	8 hours single pulse	Morning Surge of hypertension	[94]
1.Amlodipine 2.Losartan	Mini tablets in capsules	1.HPMC K4M, HPMC K15M, HPMC K100M, and PVP K 30, Avicel PH 102 for Amlodipine mini tablets 2.Eudragit S-100 used for coat mini tablets of Losartan to produce desired lag time 3.HPMC capsules	1.Amlodipine within 2 h 2. Losartan after the lag time of 6 h	Morning Surge of hypertension	*[95]*
Ramipril ‘	3 Cap pulsatile drug delivery using puls in cap technology	Isopropyl alcohol and formaldehyde 1:2 ratio vapour exposure for 60 minutes leads to cross linking of capsule produce the desired lag time.	3 pulse at 5 hours gaps	Morning Surge of hypertension	[96]
Trimetazidine HCl	Press coated tablets using Rupturable polymer coating technology	Combination of Eudragit-S 100, Eudragit-L 100 and HPMC E 50 LV as coating agents to achieve desired lag time	Single pulse after 7 hour	Chronic stable angina attack at early morning hour	[97]
1.Nebivolol Curcumin	Press coated tablets using Rupturable polymer coating technology	HPMC K100M POLYOX WSR-301	1. Nebivolol as pulse release after 8 to 8.5 hours 2. Curcumin Sustained release	Early morning hypertension	[98]
Atenolol	Press coated tablets	Saaj gum , Ethyl cellulose to control lag time	7 hours	Cardiovascular diseases	[99]
Ivabradine	Press coated tablets using Rupturable polymer coating technology	HPMC K200 M	5-6 hours	Heart failure and chest pain which are not fully managed by beta blockers	[100]
1.Amlodipine 2.Losartan	Dual drug release puls in cap	Guar gum as plug	1.Amolodipinerelease within 3 hours. 2. Losartan after a lag time of 6-7 hour.	Early morning hypertension	[101]
Irbesartan	Press coated tablets using	1.Solid dispersion of Irbesartan,	6-7 hour	Early morning hypertension	[102]

	rupturable polymer coating technology	Poloxamer-188 ratio of 1:1 to improve solubility of drug 2.HPMC K4M and Eudragit RLPO for pulsatile release		induced by excessive secretion of aldosterone	
Candesertan cilexetil	Press coated tablets using Rupturable polymer coating technology	Combination of Ethyl cellulose and Klucel EXF as erodible coating to achieve desired lag time	6 hours	Early morning hypertension	[103]
Amlodipine besylate	Modified puls in cap technology	Combination of HPMC 50cp,K100LV, Methocel K15 , sodium CMC, Carbopol 971, Xanthan gum as plugging material	7 hours	Early morning hypertension	[104]
Metoprolol tartrate	Press coated tablets using Rupturable polymer coating technology	HPMC k100 M, EC	6 hours	Early morning hypertension	[105]
Metoprolol succinate	Puls in cap technology	HPMC K100 M and lactose at 1:1 ratio us as the hydrogel plug of the capsule	5 hours	Colon specific release to treat Early morning cardiac events	[106]
Metoprolol tartrate	Puls in cap system	PMC100cps,50cps,15 cps, K4 M, 15 M, K100 M. xanthan gum, carbomer 940, carbopol 971, sodium CMC and sodium alginate of two different amounts (75mg and 100mg respectively) as hydrogel plug	5-7 hour	Early morning hypertension	[107]
Propranolol HCl	Erodible press coating technology	Tamarind gum, Okra gum and Chitosan Carbopol 940	5-7 hour	treat early morning sign in BP by colon targeting	[108]
Propranolol hydrochloride	delayed-release osmotic pump capsule having asymmetric body and impermeable of cap of different length	Glycerine and diethyl phthalate coating WSR N-10 , NaCl (osmogen) and capsule cap length decides the desired lag time in drug release	4 hour	treatment of circadian cardiovascular events	[109]
Nebivolol	Press coated tablet with erodible or rupturable coating	Hydroxyl Propyl Methyl Cellulose, HydroxyPropyl Cellulose and Sodium Carboxy Methyl Cellulose to produce burst release after predetermined lag time.	3-4 hours	Early morning hypertension	[110]
Metoprolol succinate	Modified colon targeted puls in cap	1.Kondagogu gum 2.HPMC 3000 cps as plug	6 - 6.5 (Kondagogu gum) More than 7 hour (HPMC 3000 cps)	management of Angina Pectoris	[111]
Losartan potassium	Biphasic pulsed release “tabs in cap” system	Spray dried lactose and guar gum at various ratio as plug to achieve desired lag time	6 hours	Early morning hypertensions	[112]
Carvedilol	Press coated	Eudragit L 100 and Ethyl	8 hours	Early morning	[113]

sulphate	tablet with erodible coating	cellulose		hypertension	
Atenolol	Press coated tablet with erodible or rupturable coating	Hydroxy Propel Methyl Cellulose (HPMC) K100 M, HPMC K4 M, and HPMC E15 LV in different ratios with citric acid and sodium bicarbonate as gas-forming agents	4-5 hours	Early morning hypertension, angina pectoris, arrhythmias, and myocardial infarction.	[114]
Metoprolol succinate	pulse in cap	1.Guar gum to prepare granules for colon targeting 2.HPMC as a capsules plug to achieve desired lag time	5 hours	Early morning hypertension and angina pectoris	[115]
Metoprolol tartar ate	A core in cup (three component tablet)	1.Cellulose acetate propionate as impermeable membrane surrounding the core tablet 2.Sodium alginate 500 cps and sodium alginate 2000 cps as soluble hydrophilic polymer layer to control the lag time	2.5 to 5 hours	Early morning hypertension	[116]

HPMC- Hydroxy Propel Methyl Cellulose, EC- Ethyl Cellulose, PVP-Poly Vinyl Pyrollidone

FUTURE SCOPE

Past several decades were for the development of continuous controlled release, and sustained release drug delivery system. The prospect of chronotherapeutic pulsatile delivery of drugs seems to be very optimistic in future for the treatment of CVDs and other mentioned diseases. This field still has many challenges to overcome including high production costs and in-vitro in-vivo correlation etc. Replacement of the. more expensive synthetic polymers or co- polymers by less expensive natural gums not only saves the material cost but also would enhance the biocompatibility of these dosage forms in the body, hence could play a decisive role in the future development of these dosage forms.

CONCLUSION

The challenges of CVDs across the world as well as India, threats the future generation. Many reports in the study indicates toward an apparent circadian connection of cardiovascular incidents, such as, sudden rise in blood pressure, angina, myocardial infarction, heart failure, cardiac arrest, stroke etc. Hence for an optimum therapy, it asks for a deep inside view of circadian behavior of these diseases. Rapid progress in the field of drug delivery has led to the development of PDDS is a chronotherapeutic approach to deliver right amount of drug at right time after a predetermined lag time hence achieve optimum therapy based on circadian rhythm. Since so many research works are going on to words the development of pulsatile drug delivery of many cardiovascular drugs, it may be a game changer in future in the field of CVDs.

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