Review Article

A Review on Novel Approach Pulsatile Drug Delivery System

Nayana D.Patil[1], M.M.Bari[1], S.D.Barhate[1]
[1]Department of Pharmaceutics, Shree Sureshdada Jain Institute of Pharmaceutical Education & Research, Jamner, Dist- Jalgaon (M.S), India.
***Corresponding author's E-mail:** sulkan.21@rediffmail.com

Accepted on: 20-04-2013; **Finalized on:** 30-06-2013.

ABSTRACT

Pulsatile drug delivery which releases drug in a programmed pattern i.e. at appropriate time and/or at appropriate site of action. It refers to treatment method in which drug in vivo bioavailability is matches with rhythms of disease, in order to optimize therapeutic outcomes and minimise side effects. Currently, it is gaining increasing attention as it offers a more sophisticated approach to the traditional sustained drug delivery system i.e. a constant amount of drug released per unit time. Pulsatile drug delivery system (PDDS) delivers the drug at specific time as per the patho-physiological need of the disease, resulting in improved therapeutic efficacy and patient compliance. Diseases wherein PDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children, and hypercholesterolemia. Various technologies such as time-controlled, pulsed, triggered and programmed drug delivery devices have been developed and extensively studied in recent years for chronopharmaceutical drug delivery. Various types of formulation such as bilayer tablet, coated tablet, pellets, tablet in capsule can be prepared to deliver drug in a pulsatile manner.

Keywords: classification, diseases, Pulsatile drug delivery system, rhythm of disease, technologies, types of formulation.

INTRODUCTION

The newer technologies are developing in pharmaceutical field. The most efficacious dosage forms are generated on already existing molecules because many hurdles occur during discovery of the new molecules.[1] In traditional days, drug delivery has meant for getting a simple chemical absorbed predictably from the gut or from the site of injection. A second generation drug delivery goal has been the perfection of continuous, constant rate delivery of bioactive agents. However, living organisms are not ''zero-order'' in their requirement or response to drugs. They are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle which will maximize desired and minimize undesired drug effects.[2] The oral route of drug delivery is most favoured and the most user friendly Means of drug administration having the highest degree of patient compliance, as a result of which much effort are aimed to identify orally active candidates that would provide reproducible and effective plasma concentrations *in vivo*.[3] The drug delivery system on constant/sustained drug output with the objective of minimizing peaks and valleys of drug concentrations in the body to optimize drug efficacy and to reduce adverse effects. A reduced dosing frequency and improved patient compliance can also be expected for the controlled / sustained release drug delivery systems, compared to immediate release preparations.[4]

Biological rhythm

A biological rhythm is a self-sustaining process inside the human body. It is defined as the process that occurs periodically in an organism in conjugation with and often in response to periodic changes in environmental condition. Our bodies' rhythm, also known as our biological clock, and the rhythm of the solar system that change night to day and lead one season into another. Our internal clocks are also dictated by our genetic makeup.[5]

There are 4 types of rhythms in our body

Ultradian: Which are cycles shorter than a day

E.g. Milliseconds take for a neuron to fire or a 90- minute sleep cycle.

Circadian: Which last about 24 hours

E.g. Sleeping and Waking patterns.

Infradian: It is referring to cycles longer than 24 hours.

Seasonal: Seasonal affective disorder (SAD), which causes depression in susceptible people during the short days of winter.

Circadian rhythm

Biological rhythm within a single day is termed as circadian rhythm. Here, the oscillation time is 24 hours. Human circadian rhythm is based on sleep -activity cycle, is influenced by our genetic makeup and hence, affects the body's function day and night (24-Hrs period).[6] The dependence of body's functions in certain disease states on circadian rhythm is well known. Chronobiological studies have established circadian rhythm for almost all body functions, e.g. Heart rate, blood pressure, body temperature, plasma concentration of various hormones, gastric pH and renal function.[7]

Generation of circadian rhythm

The circadian rhythm is first coined by Halberg and Stephens in 1959.[8] The human circadian time structure

presents peaks of actions directly related to the daily routine of most human beings. As human physiology and biochemistry predictably vary during 24 hour period. It is easy to understand that some medical conditions present prevalence at certain periods of the day.

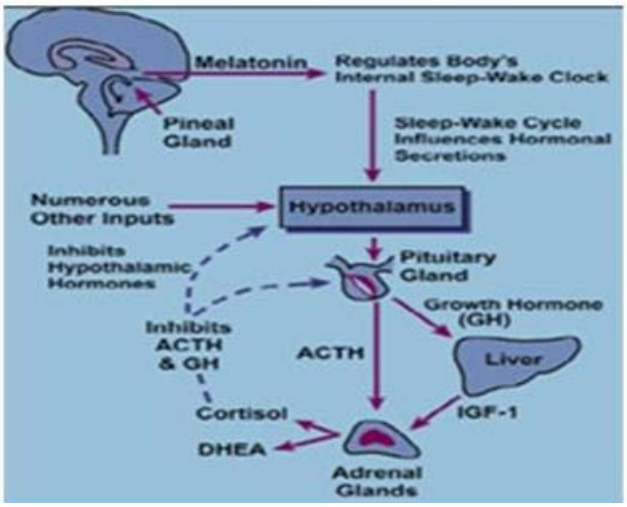

Figure 1: Generation of circadian rhythm

Figure 1 represents suprachiasmatic nucleus present in brain (SCN). It acts as biological clock and generate biological rhythm by control of clock genes. The rhythm cycle is generated by SCN and it calibrated by alternation of dark and brightness both through melatonin secretion through penal gland. Secretion of various hormones like aldosteron, rennin, and cortisol is fluctuated in blood levels.[9] PDDS is mainly observed in pH, acid secretion, gastric emptying, cholesterol synthesis, and gastrointestinal blood transfusion.[10]

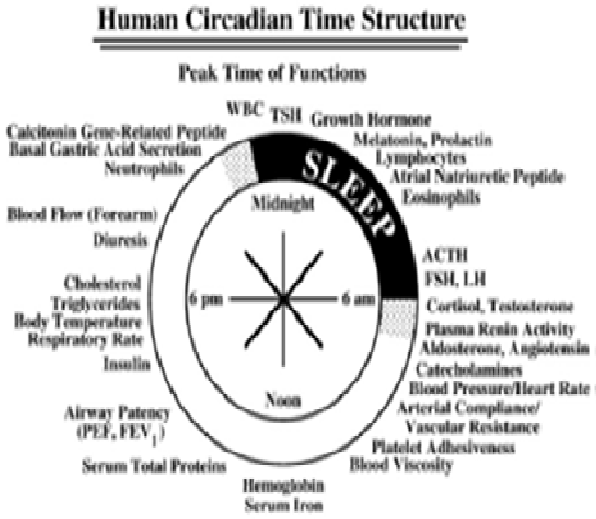

Figure 2: Human circadian time structure

Figure 2 that illustrating the human circadian time structure is to depict the peak time of 24-h.Rhythms on a clock--like diagram like that shown in Figure 2.[11-13] This figure shows the peak time of a select number of human circadian rhythms in relation to the typical synchronizer routine of most human beings.

Need of PDDS[14-16]

- Many body functions follow circadian rhythm, i.e., their activity increases or decreases with time. A number of hormones like rennin, aldosteron, and cortisol show daily as well as timely fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion.
- Acid secretion, gastric emptying, cholesterol synthesis, and gastrointestinal blood transfusion may alter with circadian rhythm.
- Chronopharmacotherapy of diseases which shows circadian rhythms in their path physiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension.
- Lag time is essential for those drugs undergo acidic degradation (e.g. peptide drugs) that irritate the gastric mucosa or induce nausea and vomiting.
- Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon the drug release should be prevented in the upper two-third portion of the GIT.
- Drugs undergoes extensive first pass metabolism that easily given by pulsatile drug delivery system.
- Drugs that produce biological tolerance due to continuous exposure of drug in body. This system tolerance by giving lag time.

Advantages of PDDS[17, 18]

- Extended day time or night time activity.
- Reduced side effects.
- Reduced dose size and dosing frequency.
- Improved patient compliance.
- Daily fewer dosage units are required by patients in the therapy and hence daily cost is lowered.
- Drug adapts to suit circadian rhythms of body functions or diseases.
- Drug targeting to specific site like colon.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism e.g. proteins and peptide.
- Avoid biological tolerance (e.g. Tran dermal nitro-glycerine).

Disadvantages of PDDS

- Difficult to manufacture and it is costly.

Conventional sustained release approach to modern chronopharmaceutical delivery of drugs

The shift from conventional sustained release approach to modern chronopharmaceutical delivery of drugs can be credited to the following reason(s).

First pass metabolism

Some drugs, like beta blockers, and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize pre-systemic metabolism. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability.[19]

Biological tolerance

Continuous release drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug. e.g. Biological tolerance of transdermal nitro-glycerine.

Special chronopharmacological needs

Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of 24 hour a day. e.g. Asthma and angina pectoris attacks are most frequently in the morning hours.

Local therapeutic need

For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

Gastric irritation or drug instability in gastric fluid

For compounds with gastric irritation or chemical instability in gastric fluid, the use of a sustained release preparation may exacerbate gastric irritation and chemical instability in gastric fluid.

Drug absorption differences in various gastro-intestinal segments

In general, drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine. Compensation for changing absorption characteristics in the gastrointestinal tract may be important for some drugs.

Table 1: Circadian rhythm and the manifestation of clinical disease

Disease	Chronological behavior	Drug used
Asthma	Exacerbation more common during the sleep period & attacks after midnight or at early morning hours	β2 agonist, Antihistamines
Allergic rhinitis	Worse in the morning/upon rising	Antihistamines
Hormone secretion	Growth hormone and melatonin produced at night testosterone and cortisol in morning hr	Corticosteroids
Rheumatoid arthritis	Morning pain at night	NSAIDs, Glucocorticoids
Osteoarthritis	Symptoms worse in the middle/later portion of the day	NSAIDs
Angina Pectoris	Chest pain and ECG changes more common in early morning	Anti anginal drugs
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than day time	HMG CoA reductase inhibitors
Myocardial Infraction	Incidence higher in the early morning	Cardiovascular agents
Stroke	Incidence higher in the morning	-
Sudden cardiac death	Incidence higher in the morning after awakening	-
Diabetes mellitus	Increased blood sugar level after meal	Sulfonylurea, Insulin
Peptic ulcer disease	Acid secretion high in afternoon and at night	H2 blockers

The disease recently targeted for pulsatile drug delivery are those which have enough scientific background to justify chronopharmaceutical drug delivery system compared to conventional drug delivery system.[21]

Bronchial Asthma

It is characterizes by airway inflammation resulting in hyper responsiveness of lower respiratory tract to various environmental stimuli.[22] Airway resistance increases progressively at night in asthmatic patient. This asthma is called as nocturnal asthma. It is an exacerbation of asthma with increase in symptoms, airway responsiveness and/or lung function.[23] The majority of bronchospastic attacks occur in early morning -2 am and 6 am each day.[24] The agents are designed to release the active drug at the time of attack. e.g., i) In one study used time release formulation of theophylline (Theo-24) achieved therapeutic drug concentration during night and avoid the toxic level during the day when the dose is ingested at 3 pm.[25] ii) A single daily dose of inhaled corticosteroids, when administered at 5:30 pm rather than 8 a.m. was nearly as effective as four doses a day.

Allergic rhinitis

Common symptoms of allergic rhinitis are sneezing, nasal rhinorrhea, red itchy eyes, nasal pruritus and nasal congestion. Each of the symptoms was found to occur most frequently before breakfast and in the morning and least frequently in the middle of the day. There are two phases of occurrence of allergic rhinitis i.e. early phase (developing within minutes) and late phase (manifesting after 12–16 hrs). The early phase happens due to release of histamine, prostaglandins, cytokines, TNF-α, chemotactic factors etc resulting in sneezing, nasal itch, rhinorrhea. On the other hand late phase is shown due to

elaboration, adhesion and infiltration of circulating leukocytes, T cells and eosinophils evoking nasal congestion, obstruction due to the exacerbation of inflammation of the nasal, sinus and other tissue of the upper airway.

Pain

Pain control is one of the most important therapeutic priorities.[26] The pain is generally occurs in arthritis. In arthritis there is circadian rhythm in the plasma concentration of C - reactive protein and interleukin-6 of patient with rheumatoid arthritis.[27] The different opoid peptides like 5-hydroxytryptamine, bradykinin, glutamate, NO, substance P, cytokines and prostanoids are involved in the activation of nociceptors. Patients with osteoarthritis tend to have less pain in the morning and more at night. While patients with rheumatoid arthritis have pain that usually peaks in the morning and decreases throughout day. The symptoms are swelling of finger and pain at joint.[28]

Renal colic shows morning peak independent of gender and presence or absence of visible kidney stones. The various analgesics are administered on the basis of nature and duration of pain.

E.g. Aspirin, paracetamol, NSAIDs and morphinomimetics are indicated against nociceptive pain, while anticonvulsants, tricyclic antidepressants and local anaesthetics are used against neurogenic pain

Duodenal ulcer

Generally gastric acid secretion is highest in the evening in duodenal ulcer patients and decreases in the early morning.[29] Duodenal perforations showed highest incidence in the afternoon, while gastric perforations showed a major peak around noon and a secondary peak near midnight.

Neurological disorders

Epilepsy

The circadian rhythm is involved in epilepsy.[30] The effect of biological clock on seizure is studied by experimental model. Behavioural chronobiology provides the detection of probable new regulation processes concerning the central mechanisms of epilepsy.[31] Because of this fact, the circadian psycho physiological patterns of epilepsy show dynamic biological systems which recommend some intermodulating endogenous processes between observation and seizure susceptibility.

New regulation processes regarding the central mechanisms of epilepsy in chronobiology is invented by physiology and medical research[32] Chronophysiology investigations considered at a rhythm metric level of resolution suggest several heuristic perspectives regarding, (a) the central pathophysiology of epilepsy, (b) the behavioural classification of convulsive events. It is also well known that the brain area with the highest concentration in noradrenergic nerve terminals and noradrenalin (NA) have a circadian rhythm in their content of NA. A breakthrough chronopharmaceutical formulation against insomnia that plagues many people would be one that addresses the entire oscillatory cycle of human sleeping process.[33, 34]

Alzheimer's disease

Change of circadian rhythm is also seen in patients with Alzheimer's disease.[35] Alzheimer's disease leads to pathological changes in the suprachiasmatic nucleus and thus it disrupts circadian rhythms of the brain's function. The circadian abnormalities are seen together with cognitive and functional deterioration in this disease

Parkinson's disease

Alterations in circadian rhythm of blood pressure, amplified diurnal blood pressure variability and postprandial hypotension.[36] Clinical data shows daily fluctuations of motor activity pattern but the effect of the phase of the disease and the subsequent roles of drugs are difficult to estimate.

Cancer

There are many clock genes involved in transcriptional and post transcriptional activation and inhibition of regulatory loops that produce circadian oscillation in mammalian cells.[37] Generally CLOCK: BMAL1 or NPAS2:BMAL1 protein dimmers are responsible for activation of the transcription of the clock genes per and cry. The clock genes related rhythm alterations at the tissue level may be seen due to the desynchronization of the individual cancer cells that form into a solid tumour. The difference of minutes or hours of internal rhythm in each cell from that of its neighbours leads to such condition. A change in the molecular clock of human tumours is further supported by decreased expressions of the Per1, Per2 or Per3 genes at a single time point in comparison with reference tissues. In addition, the blood flow to affected area is higher in cancer patients than the other parts of the body. Another group of authors has compared the effect of continuous infusion of 5-fluorouracil (5-FU) with circadian patterns of 5-FU administration which shows peak value at 4 a.m., 10 a.m., 4 p.m. or 10 p.m.[38,39] The study indicates that the cytotoxic effect of 5 FU minimum for the circadian delivery.

Diabetes

The circadian variations of glucose and insulin occur in diabetes.[40] The goal of insulin therapy is to mimic the normal physiologic pattern of endogenous insulin secretion in healthy individuals, with continuous basal secretion as well as meal stimulated secretion. Providing basal insulin exogenously to patients with diabetes inhibits hepatic glucose production.[41, 42]

Hypercholesterolemia

A circadian rhythm occurs during hepatic cholesterol synthesis. This rhythm varies according to individuals.

Indeed, there is a large variation in plasma mevalonate concentrations between individuals. Therefore cholesterol synthesis is generally higher during the night than during daylight, and diurnal synthesis may represent up to 30%–40% of daily cholesterol synthesis[43]. Many individuals display a paradoxical synthesis, with an inverted diurnal cholesterol synthesis. The maximal production occurs early in the morning, i.e. 12 h after the last meal. Studies with HMG COA reductase inhibitors have suggested that evening dosing was more effective than morning dosing[44].

Blood complications

Coagulation disorder and thrombosis

The fluidity and retention of the blood within the circulatory system is essential for the life[45]. Circadian rhythm has been found in many components of circulatory and haemostatic systems such as muscle cells, aorta, peripheral vascular muscle and endothelium. Alterations in the time structure of circadian rhythms may lead to hypercoagulability and thrombosis or hypocoagulabity and haemorrhage. The vasomotor tone of the coronary and peripheral arteries and the vasoconstrictor response to adrenaline are greater in the morning than in the afternoon. β-thromboglobulin also shows peak concentration around 6 a.m. and low values between noon and midnight. Factor VII demonstrates prominent circadian variation with highest values between 8 a.m. The peak time of Factor IX is also reported to be around 9 a.m. The peak concentration of natural coagulation inhibitors like protein C, protein S and anti thrombin occurs at 6 a.m. and lowest values occur between noon and midnight.

Infectious diseases

The elevation of body temperature, fever due to bacterial infections is higher in the evening while that due to viral infections is more likely in the morning. e.g. Influenza is epidemic in the winter season.[46]

The centre of disease control of the US publishes prominent patterns of infectious diseases as given below-

I. Meningococcal meningitis- January Peak
II. Mumps- April Peak
III. Pertusis- August Peak
IV. Varicella- April Peak
V. Typhoid- August Peak

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEMS[47]

Pulsatile drug delivery system is classified into four classes

A. Time controlled pulsatile release

I. **Single unit system**
   i. Capsular system
   ii. Port system
   iii. Delivery by solubility modulation
   iv. Delivery by reservoir systems with erodible or soluble barrier coatings

II. **Multi-particulate system**
   i. Pulsatile system based on rupturable coating
   ii. Time controlled expulsion system
   iii. Pulsatile delivery by change in membrane permeability
   iv. Sigmoidal release system
   v. Low density floating multiparticulate pulsatile systems

B. Stimuli induced :

I. **Internal stimuli induced Pulsatile system**
   i. Temperature induced system
   ii. Chemical stimuli induced system
   iii. pH sensitive drug delivery system

II. **External stimuli induced system**
   i. Electrically stimulates Pulsatile system
   ii. Magnetically stimulated Pulsatile system
   iii. Ultrasonically stimulated Pulsatile system
   iv. Photo chemically stimulated Pulsatile system

A. Time controlled Pulsatile release

I. Single unit system

i. Capsular system

A capsular system consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined lag time owing to swelling, erosion, or dissolution. The lag time is continued by a plug that gets pushed away by swelling or erosion, releasing the drug as a pulse from the insoluble capsule body. The system is comprised of a water insoluble capsule enclosing the drug reservoir. A swellable hydrogel plug was used to seal the drug contents into the capsule body. When the capsule comes in contact with dissolution fluid, the plug gets swells, and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug. The length of the plug and its point of insertion into the capsule controlled the lag time.[48] The pulsincap® system (Fig- 3) is developed by R.P. Scherer International Corporation, Michigan.[49, 50] It is made up of a water insoluble capsule body filled with drug formulation. The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or Gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a lag time. This is followed by a rapid drug release. Manipulating the dimension and the position of the plug can control the lag time.

For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymers (e.g., polymethacrylates), erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), and congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (e.g. pectin). This formulation does not cause GI irritation and some time it is overcome by enteric coating.[51, 52]

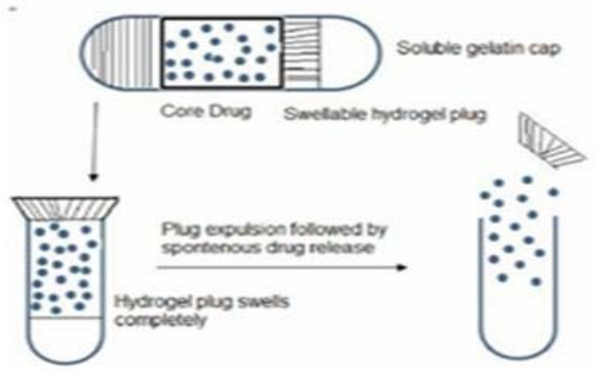

Figure 3: Schematic diagram capsular system

ii. Port system (Programmable oral release technology)

Port® system consist of a gelatin capsule coated with a semi permeable membrane (e.g., cellulose acetate) housing an insoluble plug (e.g. lipidic) and an osmotically active agent along with the drug formulation (Figure 4). When in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. Coating thickness controls the lag time. The system was proposed to deliver methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in school-age children. Such a system avoids a second daily dose that otherwise would have been administered by a nurse during school hours.[53]

It is further classified as -

Based on expandable delivery orifices

It is used to delivers the drug in liquid dosage form. Osmotic pressure develops on the drug reservoir and drug release occurs through delivery orifices. The lag time is modified by changing the Thickness of barrier membrane.[54]

Delivery by series of stops

It is for implantable capsule. It contains a drug and water absorptive osmotic engine placed in compartments separated by movable partition. Pulsatile drug delivery is achieved by series of stops. The number and frequency of stops and longitudinal placements of stop along with length of movable partition.[55] Pulsatile drug delivery is achieved by series of stops. The number and frequency of stops and longitudinal placements of stop along with length.

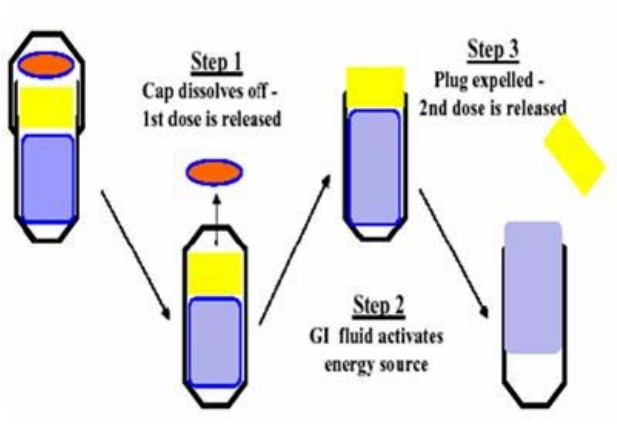

Figure 4: Port system

iii. Pulsatile drug delivery by modulating solubility

Magruder developed system consist of various solubility modulators. The system is used for anti-histaminic drug like salbutamol sulphate. Composition contains salbutamol sulphate and modulating agent sodium chloride. The amount of sodium chloride required is less than the amount needed to maintain the saturation fluid enters in osmotic device. It gives pulse release.

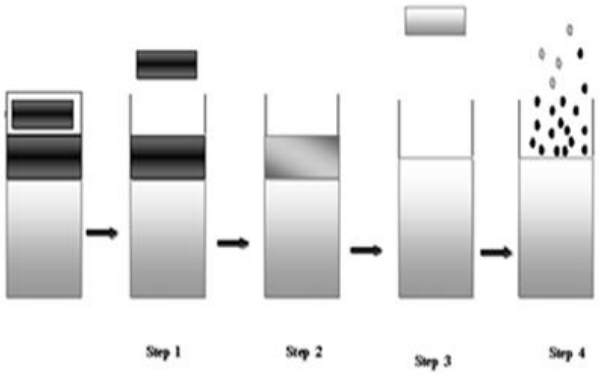

Figure 5: Drug release mechanism from port capsule

Figure 5 shows Step 1: Caps dissolves immediatly & modified release dose is released. Step 2: Energy source is activated by controlled permeation of GI fluide. Step 3: Time release plug is expelled. Step 4: Pulse or sustained release of second dose.

iv. Delivery by reservoir systems with erodible or soluble barrier coatings

The drug reservoir is coated with soluble erodible barrier. After its dissolution or erosion of that barrier drug is released from the reservoir.

Delivery systems with rupturable coating layer

These systems consist of an outer release controlling water insoluble but permeable coating layer which produces mechanically induced rupturing. The film rupture may be attained by including swelling, osmotic or

effervescent additives in the reservoir. By optimizing the system, drug release can be obtained at specific time interval.

Delivery system with erodible coating layer

In these systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing drug. Time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer coat.[56]

e.g. i) Time clock® system: (West Pharmaceutical Services Drug Delivery and Clinical Research Centre) consist of solid dosage form coated with lipidic barrier containing carnauba wax and bees wax, along with surfactant like polyethylene sorbitan monooleate. The coat erodes or emulsifies in the aqueous environment. The thickness of coat is directly proportional to the time required to release the drug. The lag time is increase with increase in thickness of the coating.[57] This type of system is suitable for water soluble drugs. The main advantage of this system is to formulate without any special equipment. The premature drug release occurs and it will dissolve with dissolution medium and release with sustained manner without complete erosion their by it retard the release in pulsatile manner. ii) Chronotropic® system: It is based on a drug reservoir coated with soluble barrier coating of hydroxy propyl methyl cellulose (HPMC).This barrier layer erodes or dissolved after predetermined lag time. The lag time is depending upon the thickness of coating and use of viscosity grade HPMC. The coating helps to overcome variability in gastric emptying and colon specific release can be obtained.[58] This system is suitable for both tablet and capsules. Multiparticulate formulations are beneficial for oral bioavailability of peptides and proteins.

II. Multi-particulate system

The designing multiparticulate dosage form has more advantageous than single unit dosage form. The mechanism by which the drug is released from pellets depends on the type of coating, insoluble coating under all physiological conditions, pH-dependent coating whose solubility changes dramatically at some point in GI tract and slowly erodes coating. The method of preparation and processing parameters are affected on pellets preparation.

i. Reservoir systems with rupturable polymeric coating

Most multiparticulate pulsatile delivery systems are reservoir devices coated with a rupturable polymeric layer. Upon water ingress, drug is released from the core after rupturing of the surrounding polymer layer, due to pressure build-up within the system. The pressure necessary to rupture the coating can be achieved with swelling agents, gas-producing effervescent excipients or increased osmotic pressure. Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time. Water soluble drugs are mainly released by diffusion; and water insoluble drug, the release is dependent on dissolution of drug.[59, 60] In time-controlled explosion systems (TES), where drug is released by a quite novel mechanism which is neither diffusion control nor dissolution control, but by explosion of the outer membrane.

TES were developed for both single and multiple unit dosage forms. In both cases, a core contains drug plus an inert osmotic agent and suitable disintegrants. Individual units can be coated by a protective layer and then by a semi permeable layer, which is the rate controlling membrane for the influx of water into the osmotic core. Osmotic pressure is exerted and delivery of drug occurs.

A four layered time-controlled explosion system was developed where, drug was layered on an inner core (polystyrene balls or non-pareil sucrose beads), followed by a swellable layer (e.g., hydroxypropyl cellulose) and an insoluble polymeric top layer (e.g., ethylcellulose). Advantage of this system is to release the drug completely, independent of the environmental pH and drug solubility.[61, 62]

ii. Time controlled expulsion system

This system is based on a combination of osmotic and swelling effects. The core contains the drug, a low bulk density solid and/or liquid lipid material (e.g. mineral oil) and a disintegrants. The core is further coated with cellulose acetate. After immersion in aqueous medium, water penetrates the core displacing the lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of the coating material.[63] Another system is based on a capsule or tablet composed of a large number of pellets consisting of two or more pellets or part.[64]

iii. Pulsatile delivery by change in membrane permeability

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium. Several delivery systems based on this ion exchange have been developed. Eudragit RS 30D is reported to be a polymer of choice for this purpose.[65] Typically contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions. The ammonium group being hydrophilic it facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner.

iv. Sigmoidal release system

Sigmoidal release pattern is therapeutically beneficial for timed release and colonic drug delivery, and observed in coated systems. A sigmoidal release pattern is reported based on the permeability and water uptake of Eudragit RS or RL, influenced by the presence of different counter-ions in the release medium. Pulse release depending on the change in diffusion properties of Eudragit RS. A core

of theophylline coated with Eudragit RS showed very slow release rates in pure water but significant increase in the release rate was found when the microcapsules were immersed in an organic acid solution containing succinic, acetic, glutaric, tartaric, malic, or citric acid.[66] Because the higher hydration of the film containing quaternary ammonium groups on interaction with the acids.

v. Low density floating multiparticulate pulsatile systems

Low density floating multiparticulate pulsatile dosage forms reside in stomach only and not affected by variability of pH, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach. In short multiparticulate pulsatile release dosage forms possessing gastric retention capabilities. Multiparticulate floating-pulsatile drug delivery system was developed using porous calcium silicate (Florite RE) and sodium alginate, for time and site specific drug release of meloxicam for chronopharmacotherapy of rheumatoid arthritis.[67]

B. Stimuli induced

This system is based on various physicochemical process occurs in our body. It is site specific drug delivery system because of induction of stimuli at specific site. Biological stimuli like release of enzymes, temperature of the site, hormones, antibodies, pH of the site, presence of certain cells, concentration of biomolecules (glucose, neurotransmitters, inflammatory mediators)etc acts as stimuli to trigger the drug release.[68,69]

I. Internal stimuli induced pulsatile system

i. Temperature induced system

The temperature is important for pulsatile drug delivery. The temperature is rises above the physiological body temperature (37°c) in presence of pyrogens. This deviation is important in various temperature responsive drug deliveries to release drug from temperature sensitive polymer in the disease occupying fever. The thermal stimuli induced pulsatile drug delivery systems like hydrogels and micelles were developed.[70]

In this system polymer undergoes swelling or deswelling phase in response to temperature which modulate release in swollen state. The thermosensitive polymeric micelles as a drug carrier were developed for the treatment of cancer. The end functionalized poly (N-Isopropyl acrylamide) to prepare corona of micelles which shows dehydration and rehydration with change in temperature.[71] Sudden increase in temperature above transition temperature of gel results in formation of dense, shrunken layer on the gel surface (skin layer) which hinders the water permeation from inside the gel into the environment. The drug release from hydrogel below 32°c was govern by diffusion, and above this temperature the release was stopped completely because skin layer is formed on hydrogel surface (on- off drug release regulation).

ii. Chemical stimuli induced system

a) Glucose-responsive insulin release devices

In case of diabetes mellitus there is rhythmic increase in the levels of glucose in the body requiring injection of the insulin at proper time. Many systems are developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release. Insulin reduces the blood glucose level and after decreasing concentration of gluconic acid system goes to deswelling mode.

e.g. pH sensitive polymers includes N,N dimethylaminoethyl methacrylate, chitosan, polyol etc. Obaidat and Park prepared a copolymer of acryl amide and allyl glucose. The side chain of glucose unit in copolymer was bound to concanavalin A.[72] These hydrogels showed a glucose-responsive, sol–gel phase transition dependent upon the external glucose concentration. Okano developed the system based upon the fact that boronic acid moiety forms reversible bonds with polyol compounds including glucose. They used water soluble copolymers, containing phenylboronic acid side chains which showed formation of a reversible complex gels with polyol compounds such as poly(vinyl alcohol) (PVA).[73] Such complexes dissociated after the addition of glucose in a concentration dependent manner.

b) Inflammation-induced pulsatile release

When any physical and chemical stress such as injury, broken bones etc occurs the various inflammatory reactions takes place at injury site. At inflammatory sites phagocytic cells like macrophages and polymorphonuclear cells, play role in healing process. During inflammation hydroxy radicals (OH) are generated from inflammation responsive cells. Yui and co-workers focused on the inflammatory-induced hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner. They used hyaluronic acid (HA) which is specifically degraded by the hyaluronidase or free radicals. Degradation of HA via the hyaluronidase is very low in a normal state of health. Degradation via hydroxyl radicals however, is usually dominant and rapid when HA is injected at inflammatory sites. Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated HA gels as new implantable drug delivery systems.[74]

C) Drug release from intelligent gels responding to antibody concentration

Many bioactive compounds are present in body. Novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/deswelling characteristics. Special attention was given to antigen-antibody complex formation as the cross-linking units in the gel, since such interactions are very specific. Utilizing the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/deswelling and drug permeation changes occurs.[75]

iii) pH sensitive drug delivery system

The versatile approach to design chronotropic system to attain specified lag time prior to drug release by using pH dependent polymers. These can be single unit or multiparticulate dosage forms with reliable and predictable drug release profile. This system having advantage to exist in different pH environment at different parts of gastrointestinal tract. So that pH dependent system is targeting at specific site of gastrointestinal tract is possible as well as a desired lag time can be achieve due to dependency of polymer solubility only at particular pH of gastrointestinal tract. e.g of pH dependent polymers include copolymers of methacrylic acid(variuse grades of eudragit), phthalates, carboxy methyl cellulose etc.[76] These polymers are used for enteric coating to protect the drug from degradation in GIT & attain release in specific part of intestine. (According to solubility of polymers at specified pH and specific site of intestine). The number of chronotherapeutic system have been develops and marketed for chronotherapy utilizing pH dependent polymers for asthma, angina pectoris, rheumatoid arthritis, cancer, diabetes, ulcer etc.[77]

a. pH dependent colonic DDS

The pH of stomach is 2-3(higher after eating), 6.5-7 in the small intestine and 7-8 in the large intestine. pH sensitive polymers those contains carboxy group which make them insoluble at low pH values soluble at higher pH values are used for colon targeting of drug. E.g. Eudragit L (soluble at pH greater than 6).and Eudragit S and FS (soluble in pH greater than 7).

b. pH and time dependent colonic system

Combination of two or more polymers with delayed release competent that realize on the passage of time, leads to feasibility of targeted delivery in terminal ileum and colon e.g. Eudragit L, S or FS gives transit from stomach and small intestine. A second barrier of coating with pH independent polymer like Eudragit RS or ethyl cellulose which gives delayed release for several hrs.

c. pH and bacterial enzymes dependent colonic DDS

It combines enzyme degraded polysaccharides and pH dependant polymers is CODES system. Outer coating consist of Eudragit polymer which dissolves after transit of dosage form into small intestine and expose to undercoating layer of Eudragit E (acid soluble). This layer does not dissolve. Undercoating permits lactulose to release the environment adjacent to the tablet. These disaccharides metabolized and lower the pH to produce Eudragit E dissolves and release the drug.

II. External stimuli induced system

These types of open-loop systems are not self-regulated. But for delivery of the drug in pulse manner another way in which drug release in programmed pattern can be the external regulated system. These systems are magnetically stimulated, ultrasonically modulated and photo stimulated.

i. Electro responsive pulsatile release

This system provides the drug release by action of applied electric field on rate limiting membrane and/ or directly on solute, thus controls it transport across the membrane. The polymer has two redox states, only one of which is suitable for ion binding. Drug ions are bound in redox state and release. The mechanism of drug transport of proteins and natural solutes across hydrogel membranes. electrically induced swelling of membrane to alter effective pore size and permeability. Electrophoretic and electroosmotic agumentation of solute flux within a membrane. Electrostatics partitioning of charged solutes in charged membrane.

***ii.* Magnetically stimulated pulsatile system**

In this system magnetic steel beads can be embedded in a polymer matrix with model drug. During exposure to the magnetic field, the beads oscillate within the matrix, alternatively creating compressive and tensile forces. This in turn acts as a pump to push an increased amount of the drug molecule out the matrix. Magnetic response comes from incorporated magnetic particle like magnetite, iron, nickel, cobalt and steel.

Langer developed one system of polymeric matrix containing dispersed drug along with magnetic beads.[78] Generally ethylene-vinyl acetate copolymer is used for this purpose. An oscillating magnetic field is generated to trigger the release of drug. Saslawski applied an oscillating magnetic field to trigger the release of insulin in pulsatile manner from alginated microspheres.[86] Here ferrite micro particles and insulin were dispersed in sodium alginate aqueous solution. This suspension was added to calcium chloride solution which causing formation of cross-linked alginate spheres. These spheres were again cross-linked with aqueous solution of poly (L-lysine) or poly (ethylene imine). The release rate was improved in absence of a magnetic field.

Table 2: Advanced technologies and marketed formulations of Pulsatile drug delivery system

Technology	Description	API	Proprietary Name	Make
COER-24 ™	Controlled onset and extended release. It is osmotically controlled single unit system. Semipermiable membrane prevents that regulates absortion of water into the tablet. The second layer delay the passage of water into inner core. The third layer gives extended release. This system contains verapamil which maintain blood pressure for 24 hrs.	Verapamil	Covera-HS	Alza
CODAS™	Chronotherpeutics oral drug absorption system.It gives 4-5 hrs delay in drug delivery by an extended drug release with peak plasma concentration occurring approximately 11hr after administration. This capsule contains many pellets having inner core, surrounded by drug and water soluble and water insoluble polymers. Drug releases through pores of polymer coating.	Verapamil	Verelan®p M	Schwarz Pharma, USA
Diffucaps ™	Multiparticulate system that provides drug release profile from either single drug or combination of drugs. Customized drug release profile are created by first layering with active drug from aqueous or solvent based drug solutions onto a neutral core (such as cellulose spheres) followed by coating with one or more rate controlling membrane.	Propranolol	InnoPran ® XL	Reliant Pharmaceuticals
Pulsincap ™	Water insoluble capsule body filled drug solution. The capsule body closed at open end with swelleble hydrogel plug. When it contact with GI fluid polymer swells and pushing itself out of the capsule after lag time followed by rapid release.	Dofetilide	-	Develops by RPSIC, Michigan, US
Port® system	Programmable oral drug delivery system. Capsule coated with semi permeable membrane. Inside the plug consisting of osmotically active agents and the drug formulation. When it contact with GI fluid then it allows water penetration and pressure to develop and the insoluble plug expelled after lag time, which controls coating thickness.	Methylphenidate	-	Develops by TSRL, Michigan USA
Egalet® Technology	It is delayed burst release system. It uses erosion rather than diffusion as a method of drug delivery. It consists of two impermeable plugs and the middle portion in which active agents are enclosed. The matrix errodes upon contact with water. Plug consist of ethyl cellulose, cetosteroyl alcohol and polyethylene oxide. It gives zero order performance after lag time	-	Egalet®	Egalet Denmark
SyncroDose ™ Technology	It utilises agglomerated hydrophilic matrix system in compression coating combine with active and various other excipients in the core. The lag Time is controlled by xanthan gum, locus bean gum and two polysaccharides[90].	-	TIMERx ™	Penvest Pharmaceutical
Geminex™ Technology	It release drug by two different release profiles (Immediate release and controlled release. Matrix consists of gum and polymers which when contacted with aqueous environment to form tight gel and slowly eroding the core.	-	-	Penvest Pharmaceutical
Qtrol ™ Technology	It allows the formation of tailored dosage forms and particularly trilayer coating for time dependant release. It is used for congenital hyperplasia, Addisons disease and hypo-pitutorysm by utilizing its patented technology delivers the corticosteroid and hydrocortisone.	Cortisol	-	-
Lip'ral™ SSR	Synchronise solubilizer release. Synchronise release of insoluble drug and solublizers and ideally suited for solubilisation for drugs that require solubilisation and controlled release. The release profile can be modulated for delayed, pulsatile or sustained release for targeted site absorption.	-	Lip'ral ™	Lipocin, Inc

Table 3: Advanced technologies and marketed formulations of Pulsatile drug delivery system (Continued...)

Technology	Description	API	Proprietary Name	Make
TES™	Time controlled explosion system contains both single and multi particulate system. The core contains drug, inner osmotic agent and suitable disintegrants. Individual units can be coated by protective layer and then semi permeable membrane which is rate controlling membrane. As water reaches to core and it develops osmotic pressure and gives immediate release of drug.	-	-	Fujisawa pharmaceutical
Ticking Capsule	The device that employs electrical means of controlling pulsatile drug release couple with electronic timing.	-	-	-
ChronoDose™	Time and dosage controlled administration of drugs, non-invasively through skin. It worn like wristwatch can be pre-programmed to administered the drug dose into body automatically. It delivers the dose during 24-72 hrs in an on/ off fashion.	-	ChronoDose™	
Smartcoat™ Technology	It develops very high potency, controlled release tablets, allowing for smaller size tablets while controlling the release over a 24 hrs period. "Chronotabs" were developed for bedtime administration using smart coat technology.	-	chronotabs	Biovail
CEFORM technology	This technology used for treatment of hypertension and gives pulse release	Diltiazem HCl	Cardizem®LA	-
API modification	Physico-chemical modification of the API. It will releases the drug in the intestine	Famotidine	Pepcid®	-
API modification	Physico-chemical modification of the API	Simvastatin	Lipovas®	-
CONTIN technology	Release by pulse manner at the time of asthmatic attack in morning hrs	Theophylline	Uniphyl®	

Table 4: Patents on Pulsatile drug delivery system

Name of Topic	Active agent	Type of Formulation	Patent Number	Date of patent filling	Reference
Time controlled or position controlled drug delivery system	Sotalol HCl	Tablet in capsule	US 7048945	2003	81-82
Pulsatile technology	Amphetamine	Multiple pulse amphetamine salt	US 6605300,6322819	27/11/2001	83
Implantable electro-mechanically driven device	-	Implant	US 4003379	24/9/1975	84
Pulsatile technology	Dilitazem HCl.		US 5914134		85
Pulsatile drug delivery system	Ivermectin	Bilayer Tablet	EP0246813B1	1/5/ 1987	86
Controlled release article with pulsatile release	-	Multi-layered article	5213808		
Pulsatile drug delivery system	Ivermectin		4,723,958	9/2/1988	
Pulsatile drug delivery system	Propranolol	Coated Tablet	5,229,131	20/7/1993	87
Multiparticulate pulsatile drug delivery system	-	Pellets	5,508,040	16/4/1993	
Pulsatile drug delivery system	Nifedipin Diltiazem	Spherical particle	5,840,329	24/11/1998	

iii. Ultrasonically stimulated pulsatile system

Pulsed drug delivery can be achieved by the on–off application of ultrasound. During polymer degradation incorporated drug molecules are released by repeated ultrasonic exposure. It can be used for the augmentation of drug permeation through biological barriers such as skin, lungs, intestinal wall and blood vessels. Ultrasonic waves cause the erosion of the polymeric matrix thereby modulating drug release. Miyazaki and co-worker, (1998), evaluated the effect of ultrasound (1 MHz) on the release rates of bovine insulin from ethylenevinyl alcohol copolymer matrices and reservoir-type drug delivery systems in which they found sharp drop in blood glucose levels after application of ultrasonic waves.[78] The cavitations is responsible for degradation and release from bioerrodible polymers

iv. Photo chemically stimulated pulsatile system

In this system the interaction between light and the material can be used for modulating the drug delivery

system. The study material should absorbs the light at desired wavelength and material uses energy from the absorb light. e.g Gold nanoshell (a thin layer of gold surrounding a core of active nano particle). Embedding the nanoshells in a NIPAAm-co-AAM hydrogel formed the required composite material. When exposed to near-infrared light, nanoshells absorb the light and convert it to heat, raising the temperature of composite hydrogel above its LCST. That's result in the increase of release rate of the drug from the matrix system.[79]

Photo responsive gels reversibly change their physical or chemical properties upon photo radiation.

CONCLUSION

Different technologies have been applied to develop time controlled, pulsed, triggered & programmed drug delivery devices in recent years.

The timing of drug administration in disease therapy has significant impact upon treatment success. Pulsatile drug delivery systems that effectively treat various disease such as asthma, peptic ulcer, cardiovascular disease, arthritis, hypercholesteromia etc. Pulsatile drug delivery system is most suitable for time specific and site specific delivery of drugs. Numbers of patents are filed by various companies recently. PDDS has good future.

REFERENCES

1. Survase S, Kumar N, Pulsatile drug delivery: current scenario, Current Research & Information on Pharmaceutical Sciences, 8, 2007, 27-33.
2. Youan B J, Pulsatile drug delivery, Journal of Controlled Release, 98, 2004, 337-353.
3. Charman S, Charman W, Oral modified-release delivery systems, In: Modified Release Drug Delivery Technology, New York, Marcel Dekker, 2003, 1-11.
4. Burnside B, Guo X, Fiske K, Couch R, Treacy D, Chang, R, Guinness Mc, Rudnic C, E : US20036605300 2003.
5. Sudhamani T, Radhakrishanan M, Deepthlakshmi M, Gansean V, Chronotherapeutic fioating pulsatile drug delivery: An Approch for time specific and site specification absorption of drugs, Research Journal of Pharmaceutical Technology, 4(5), 2011, 685-690.
6. Evans RM, Marain C, Taking Your Medication: A Question of timing. American Medical Asssociation: 1996, 3-8. Marain C, editors,eds. Taking Your Medication : A Question of timing, Chicago,IL: American Medical Asssociation; 1996, 3-8.
7. Li, JJ, Circardian variation in myocardial ischemia: the possible mechanisms involving in this phenomenon. Med Hypotheses 61(2), 2003, 240-243.
8. Halbeg F, Stephens A, susceptibility to auabain and physiological circadian periodicity, Proc Minn Acsd sci, 27, 1959, 139-43.
9. Gunny.R, Junginger H E, Peppas N, Pulsatile drug delivery system: current applications and future trends, stuftgart, Germany, wissenchtflich, velagsggels, 1993.
10. Goo,R, Moore J, Greenbergh E, Alazraki N, Circadian variation in gastric emptying of meal in humans. Gastroenterol, 93(3), 1987, 515-518.
11. Rathee P, Hooda A, Rathee, S, Kumar V, Jain M, A Biological rhythm-guided approach to drug delivery: Chronopharmaceutics, International Journal of Institutional Pharmacy and Life sciences, 1(2), 2011.
12. Awasthi R, Kumar P, Chronotherapy: Science and technology of drug scheduling on basis of biological rhythm, Journal of Chronotherapy and Drug Delivery, 1(1), 2010, 9 -18.
13. Devdhawala M, Seth A, Current status of chronotherapeutic drug delivery system: An overview, J. Chem. Pharm. Res, 2(3), 2010, 312-328.
14. Vinupama s, Shwetha S, Kamath. K, S. Keerthi, senthil kumar, Pulsatile drug delivery system: a review, International Bulletin of Drug Research., 1(1): 19-31.
15. Leemer, B, Chronopharmacokinetic: Implication for drug treatment, Journal of Pharmacy & Pharmcology, 51, 1999, 887-890.
16. Rubinstein A, Tirosh B, Baluom M, Nassar T, David A, The rationale for peptide drug delivery to the colon and the potential of polymeric carriers as effective tools, Journal Of Controlled Release, 46, 1995, 59-73.
17. Rompicharla.B, Suria P, A comprehensive review of pulsatile drug delivery system, International Journal of Pharmacy Research, 3(3), 2012, 106-108.
18. Prasanth V, Mitesh P, Modi, Sam T, Pulsatile: a tool for circardian rhythm - A review, Journal of Drug delivery and Therapeutics, 2(1), 2012, 58-65.
19. Sajan J, Cinu, TA, Chacko AJ, Litty J, Jaseeda T, Chronotherapeutics and Chronotherapeutic Drug Delivery Systems, Tropical Journal of Pharmaceutical Research, 8 (5), 2009, 467-475.
20. Reddy R, Jyothsna M, Mod S, Chetty C, Review on Pulsatile drug delivery system, Journal of Pharmaceutical Science and Research, 1(4), 2009, 109-115.
21. Belgamwar V, Gaikvad M, Patil G, Surana S, Pulsatile drug delivery system, Asian Journal Pharmacy, 2008, 141-145.
22. Smolensky M, Lemmer B, Renberg A, Chronobiology and chronotherapy of allergic rhinitis and bronchial asthma , Adv Dali.Rev., 59, 2007, 852-882.
23. Martin R, Banks-Schlegel, Chronobiology of asthma, Respir.Crit. Care. Med., 158, 1998, 1002-1007.
24. Dethlefsen U, Repges R, Ein neues Therapieprinzip bei nachtlichen Asthma. Med. Kli., 80, 1985, 44-47.
25. Mandal A, Biswas N, Karim K, Chatterjee S, Drug delivery system based on chronobiology- A review, Journal of Controlled Release, 147, 2010, 314-325.
26. Bruguerolle B, Labrecque G, Rhythmic pattern in pain and their chronotherapy, Adv. Drug Deliv. Rev., 59, 2007, 883–895.
27. Saitohl T, Watanabe Y, Kubo Y, Shinagawa M, Otsuka K, Ohkawa S, Watanabe T, Intragastric acidity and circadian rhythm, Biomed. Pharmacotherapy, 55, 2000, s138–s141.
28. Khan Z, Pillay V, Choonara Y E, du Toit L C , Drug delivery technologies for Chronotherpeutics applications, Pharm. Dev. Technol., 14, 2009, 602–612.
29. Moore G , Halberg F, Circadian rhythm of gastric acid secretion in men with active duodenal ulcer, Dig. Dis. Sci., 31, 1986, 1185–1191.
30. Hofstra W, de Weerd A, How to assess circadian rhythm in humans: A review of literature, Epilepsy Behav. 13, 2008, 438–444.

31. Poirel C, Ennaji M, Circadian aspects of epileptic behaviour in comparative psychophysiology, Psychol. Rep., 68, 1991, 783–801.
32. Poirel C, Ennaji M, Chronobiological paradigms of mental life and clinical neurosciences. Encephalopahy, 26, 2000, 57– 66.
33. Ziegler M, Lake C, Wood J, Ebert M, Circadian rhythm in cerebrospinal fluid nor adrenaline of man and monkey' Nature, 264, 1976, 656– 658.
34. Czeisler C, Weitzman E, Moore-Ede M, Zimmerman J, Knauer R, Human sleep: its duration and organization depend on its circadian phase science, 210, 1980, 1264–1267.
35. Volicer L, Harper D, Manning B C, Goldstein R, Satlin A, Sundowning and circadian rhythms in Alzheimer's disease, Am. J. Psychiatry, 158, 2001, 704–711.
36. Bruguerolle B, Simon N, Biologic rhythms and Parkinson's disease: a chronopharmacologic approach to considering fluctuations in function, Clin. Neuropharmacol., 25, 2002, 194–201.
37. Levi F, Focan C, A. Karaboue, V. de la Valette, D. Focan-Henrard, B. Baron, F. Kreutz, S. Giacchetti, Implications of circadian clocks for the rhythmic delivery of cancer therapeutics, Adv. Drug Delivery Rev., 59, 2007, 1015–1035.
38. Youan B, Chronopharmaceutical drug delivery systems: Hurdles, hype or hope, Adv. Drug Delivery Rev., 62, 2010, 898–903.
39. Altinok A, Levi F, Goldbeter A, A cell cycle automation model for probing circadian patterns of anticancer drug delivery, Adv. Drug Deliv. Rev., 59, 2007.
40. Singh D, Poddar A, Nigade S, Poddar S, Pulsatile Drug Delivery System: An Overview, IJCPRR, 2(2), 2011.
41. Moore J., Englert J, Circadian rhythm of gastric acid secretion in man, Nature, 1970, 1261–1262.
42. Cincotta A, Meier A, Circadian rhythms of lipogenic and hypoglycaemic responses to insulin in the golden hamster (Mesocricetus auratus), J. Endocrinol, 103, 1984, 141– 146.
43. Mayer D, The circadian rhythm of synthesis and catabolism of cholesterol, Arch. Toxicol, 36, 1976, 267–276.
44. Goff W, Guerin M., Chapman J, Bruckert E, Circadian and interindividual variations of cholesterol synthesis, Sang Thromb. Vaiss, 13, 2001, 461– 467.
45. Haus E, Chronobiology of hemostasis and inferences for the chronotherapy of coagulation disorders and thrombosis prevention, Adv. Drug Deliv. Rev., 59, 2007, 966–984.
46. Beauchamp D, Labrecque G, Chronobiology and chronotoxicology of antibiotics and aminoglycosides, Adv. Drug Deliv. Rev., 59, 2007, 896–903.
47. Suthar M, Patel H, Patel U, Brahmbhatt T, Bhatt S, Kadikar H, Pulsatile drug delivery: A review, International journal of pharmaceutical research, 1(1), 2012.
48. Jain D, Raturi R, Jain V, Bansl P, Singh R, Recent technologies in pulsatile drug delivery systems, Biomatter, 11, 2011, 57-65.
49. Kumar M, Ali A, Kaldhone P, Shirode A, Kadam VJ, Platform technologies for colon targeted drug delivery system: A Review Article. J Pharm Res, 3, 2010, 543-547.
50. Hebden J, Wilson C, Spiller R, GilChrist P, BlackShaw P, Frier M, Perkins AC, Regional differences in quinine absorption from the undisturbed human colon assessed using a timed release delivery system, Pharm Res, 16, 1999, 1087-92.
51. Gothoskar AV, Joshi AM, Joshi NH, Pulsatile drug delivery systems: a review, Drug Delivery Technology, 4(5), 2004, 1-11.
52. Shivakumar HG, Pramod kumar TM, Kashppa GD: Pulsatile drug delivery system, Indian J Pham Educ, 37(3), 2003, 125.
53. Therapeutic System Research Laboratory (TSRL Inc), PORT Technologies act sheet, Sep-2004.
54. Czeisler C.A., Weitzman E, Moore-Ede M.C., Zimmerman J.C., Knauer R.S Human sleep: its duration and organization depend on its circadian phase, Science, 210, 1980, 1264–1267.
55. Parmar R, Parikh R, Vidyasagar G, Patel D, Patel C, Birju D, Pulsatile drug delivery system : An overview, IJPSN, 2(3), 2009, 605-613.
56. Gazzaniga A, Paluga L, Foppoli A, Eur. J. Pharm. and Biopharm, 2007 (In Press).
57. Patel j, Patel D, Vachhani S, Prajapati S T, Patel C N, Current status of Technologies and Devices for chronotherapeutics Drug delivery systems, Research Journal Pharmaceutical Technology, 3(2), 2010, 344-352.
58. Sangalli M, Maroni A, Zema L, Busetti Z, Giordano F, Gazzaniga A, In vitro and in vivo evaluation of an oral system for time and/or site-specific drug delivery, Journal Of Controlled Release 73 ,2001, 103–110.
59. Ueda Y, Hata T, Hisami Y, Ueda S, Kodani M, Time Controlled Explosion Systems and Process for Preparing the Same U.S. Patent 4871549 October 3, 1989.
60. Ueda S, Yamaguchi H, Kotani M, Kimura S, Tokunaga Y, Kagayama A, Hata T, Development of a novel drug release system, time-controlled explosion system (TES): III. Relation between lag time and membrane thickness, Chem. Pharm. Bull., 42 (2), 1994, 364–367.
61. C.M. Chen, Pulsatile particles Drug Delivery System, U.S. patent 5472708, December 16, 1995.
62. C.M. Chen, Pulsatile particles Drug Delivery System, U.S. patent 5260069, November 9, 1993.
63. Chen C M, Multiparticulate Pulsatile Drug Delivery System, US Patent No 5508040, 1996.
64. Bodmeier R, Guo X, Sarabia RE, Skultety P, The influence of buffer species and strength on diltiazem HCl release from beads coated with aqueous cationic polymer dispersions,Eudragit RS, RL 30D. Pharm Res, 13(1), 1996, 52-56.
65. Narisawa S, Nagata M, Danyoshi C, Yoshino H, Murata K, Hirakawa Y, Noda K, An organic acid-induced sigmoidal release system for oral controlled-release preparations, Pharm Res, 11(1), 1994, 111-116.
66. Narisawa S, Nagata M, Danyoshi C, Yoshino H, Murata K, Hirakawa Y, Noda K, An organic acid induced sigmoidal release system for oral controlled release preparation, Pharm. Res, 11 (1), 1993, 111–116.
67. Sharma S, Pawar A, Low density multiparticulate system for pulsatile release of meloxicam, Int. J. Pharm, 313 (1–2), 2006, 150–158.
68. Akhgari A, Garekani A, Sadghi F, Azimale M, Statistical optimization of indomethacin pellets coated with Ph dependant methacrylic polymers for possible colonic drug delivery, Inst. J. Pharm, 30, 2005, 22-30.
69. Arora G, Singh I, Nagpal M, Arora S, Recent advances in stimuli induced pulsatile drug delivery system: - A Review, RJPT, 4(5), 2011.

70. Okano T, Yuim N, Yokoyam M, Yoshida R, Advances in polymeric system for drug delivery, Gordon and Breach, Yverdon, Switzerland, 1994.

71. Avani S, Doshi N, Patel D, Badmanban R, Patel CN, Footstep of pulsatile drug delivery system in pharmaceutical sciences, Research Journal of Pharmaceutical Technology, 3(2), 2010.

72. Obaidat A A, Park K, Polymeric Biomaterials: Medicinal and Pharmaceutical Applications, Pharm. Res, 13, 1996, 989-995.

73. Obaidat AA and Park K, Biomedical Applications of Hydrogels Handbook, Biomaterials, 18, 1997, 801-806.

74. Yui N, Okano T, Sakurai Y, Journal of Controlled Release, 22, 1992, 105-116.

75. Miyata T, Asami N, Uragami T, life chemistry, Nature, 399, 1999, 766-769.

76. Sudhamni. T, Radhakishan. M, Mallela. D, Ganesan. V, Chrotherapeutic floating pulsatile drug delivery: An approach for time specific and site absorption of drug, Research Journal of Pharmaceutical Technology, 4(5), 2011.

77. Miyata T, Asami N, Uragami T, A reversibly antigen sensitive hydrogel antigen- antibody bindings macromolecules, 32, 1999, 2082-84.

78. R Langer, Polymer systems for controlled release of macromolecules, immobilized enzyme medical bioreactors, and tissue engineering, in: J. Wei, J.L. Anderson, K.B. Bischoff, M.M. Denn, J.H. Seinfeld, G. Stephanopoulos (Eds.), Advances in Chemical Engineering, Academic Press Limited, 24-28 Oval Road. London NW1 7DX, 1994.

79. Averitt R, Sarkar D, Halas N, "Plasmon Resonance Shifts of Au-Coated Au2S Nanoshells: Insight into Multicomponent Nanoparticle Growth" Phys. Rev. Lett, 78, 1997, 4217-4220.

80. Shigehiro OHDO, Chronopharmaceutics: Pharmaceutics Focused on Biological Rhythm. Biol. Pharm. Bull, 33(2), 2010, 159 - 167.

81. Gohel MC, Sumitra M, Modulation of active pharmaceutical ingredient release from a novel tablet in capsule system containing an effervescent blend, Journal of Control Release, 79, 2002; 157-164.

82. Percel P, Vishnupad KS, Venkatesh GM, Lee DY: US20037048945, 2003.

83. Burnside B.A, Guo X., Fiske K., Couch R.A, Chang R.K, Rudnic E.M: US6322819, Pulsatile technology, 1998.

84. Ellinwood, Jr, Everett H, US4003379, Implantable electro-mechanically driven device, 1977.

85. Sharma VK: US5914134, Pulsatile technology, 1999.

86. Pope, Devid, EU 0246819B1, Pulsatile drug delivery system, 1987.

87. Amidone, US 5229131, Pulsatile drug delivery system, 1993.

Source of Support: Nil, **Conflict of Interest:** None.