

PULSATILE DRUG DELIVERY SYSTEM: A REVIEW**Swati B. Rathod*, Manoj M. Bari, Dr. Shashikant D. Barhate.**

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ABSTRACT

Pulsatile drug delivery systems are developed to deliver drug in a programmed pattern i.e. at an appropriate time and/or appropriate site of action. The rapid and complete drug release occurs after predetermined lag time. The principle rationale for the use of pulsatile release of the drugs where a constant drug release is not desired. Diseases wherein PDDS are promising include cardiovascular diseases, arthritis, asthma, cancer, hypercholesterolemia, peptic ulcer, neurological disorder, diabetes. The current article focuses on the diseases requiring PDDS methodologies involved for the existing system, recent advances in PDDS, technologies, PDDS product currently available in the market.

KEYWORDS: Pulsatile drug delivery, lag time, circadian rhythm, classification, technologies.

INTRODUCTION

Oral controlled drug delivery system represent the most popular form of controlled drug delivery system for the obvious advantages of oral route of drug administration over the conventional dosage form. Such system release the drug with constant or variable release rates. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance. The oral controlled release system shows the typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), there by sustained therapeutic action.

However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern can be achieved by modulating the chronomodulated system.^[1]

Chronomodulated system is also known as pulsatile system or sigmoidal release system or programmed release system or time controlled release system.

Pulsatile drug delivery system (PDDS) which releases drug in a programmed pattern i.e. at an appropriate time and/or appropriate site of action.^[2] The rapid and complete drug release occurs after predetermined lag time. It delivers the drug at right time, right place and in right amount.^[3] Pulsatile drug delivery system delivers the drug at specific time as per the pathophysiological need of the disease resulting in improved patient compliance and therapeutic efficacy.

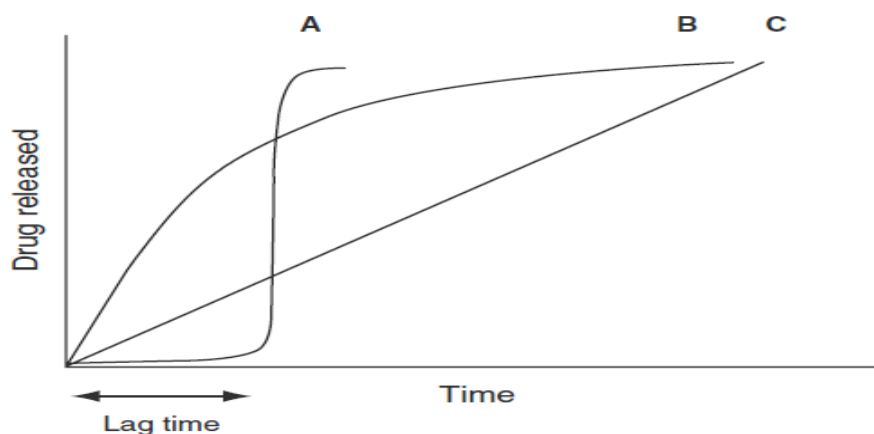


Fig. 1: Drug release profiles: (A) pulsatile, (B) and (C) conventional extended release.^[4]

Many diseases are affected by the biological rhythm and show circadian rhythm intensity. Various terminologies related to rhythm of life is as follows-

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.

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 pattern.

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.^[2]

Generation of circadian rhythm

“ Circadian rhythm “ was first described by Halberg and Stephens in 1959. Suprachiasmatic nucleus (SCN), present in brain act as a biological clock which creates biological rhythm under the control of clock genes and coordinate peripheral oscillation for functions including cell proliferation and cellular metabolism. The cycle duration generated at the SCN is calibrated by the alteration of light/ darkness, both directly and through melatonin secretion by the pineal body. Many body functions that follow circadian rhythm, i.e. their activity waxes and wanes with time. A number of hormones like renin, aldosterone and cortisol shows daily fluctuations in their blood levels. Circadian effect are also observed in case of pH and acid secretion in stomach, gastric emptying and gastrointestinal blood transfusion.^[5] Circadian rhythm regulates many body functions in humans, viz. metabolism, physiology, behavior, sleep pattern, hormone production etc.^[6]

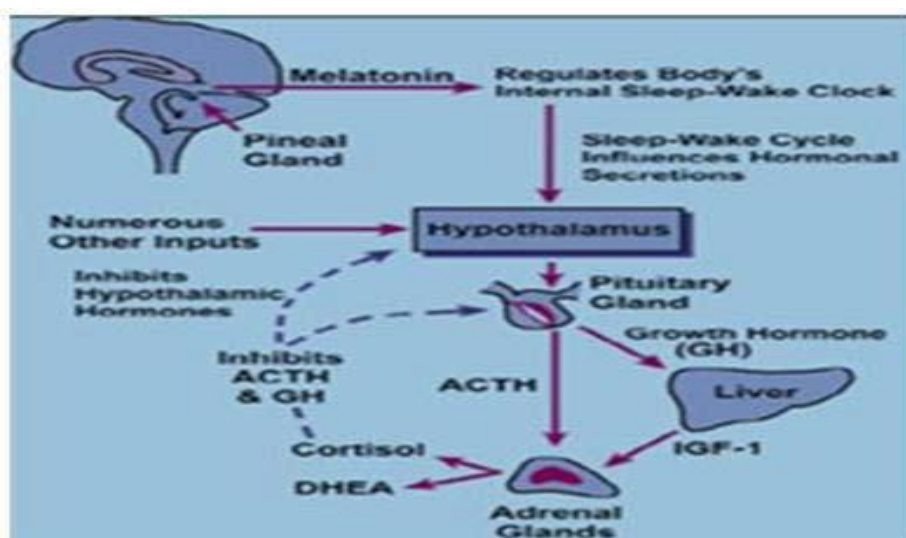


Fig. 2: Generation of circadian rhythm

Circadian Variation

Many common diseases also display a marked circadian variation during onset or exacerbation of symptoms, as shown in Fig. 3. Since the circadian rhythm influences normal biological processes, the occurrence or intensity of symptoms of these diseases is not constant throughout the day. Several diseases including arthritis, asthma, allergies, peptic ulcer, dyslipidemia and cancer exhibit predictable circadian variation. Medications and treatments given at the appropriate time according to the body's circadian rhythms will result in more favorable outcomes.^[7]

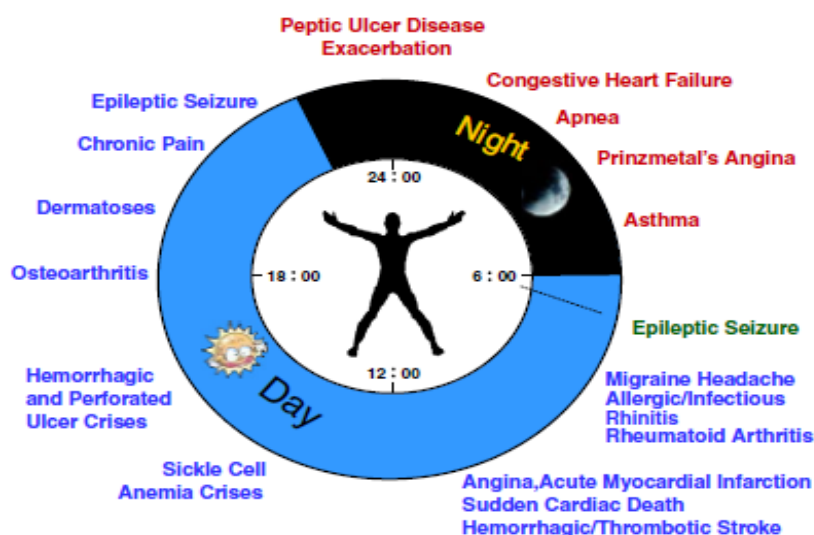


Fig. 3: The circadian pattern of disease

Advantages of PDDS

1. Extended daytime or night time activity.
2. Reduced side effects.
3. Reduced dosage frequency.
4. Reduction in dose size.
5. Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
6. Drug adapts to suit circadian rhythm of body functions or diseases.
7. Drug targeting to specific site like colon.
8. Protection of mucosa from irritating drugs.
9. Drug loss is prevented by extensive first pass metabolism.
10. Patient comfort and compliance.

Disadvantages of PDDS

1. Lack of manufacturing reproducibility and efficacy.
2. Large number of process variables.
3. Multiple formulation steps.
4. Higher cost of production.
5. Need of advanced technology.
6. Trained / skilled personal needed for manufacturing.^[8]

Need of PDDS

1. Many body functions that follow circadian rhythm e.g. secretion of hormones, acid secretion in stomach, gastric emptying and gastrointestinal blood transfusion.
2. Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic diseases, ulcer and hypertension.
3. Drugs that produce biological tolerance demand for a system that will prevent their continuous presence at the biophase as this tends to reduce their therapeutic effect.
4. Lag time is essential for those drugs undergo acidic degradation (e.g. peptide drugs) that irritate the gastric mucosa or induce nausea and vomiting.
5. 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.
6. Drugs undergoes extensive first pass metabolism that easily given by pulsatile drug delivery system.^[2]

Table. 1: Diseases requiring pulsatile drug delivery ^[2, 10]

| Disease | Chronological behavior | Drugs used |
|----------------------------|--|------------------------------------|
| Asthma | Precipitation of attacks during night or at early morning hour | β_2 agonist, Antihistaminics |
| Peptic ulcer | Acid secretion is high in the afternoon and at night | H2 blockers |
| Arthritis | Pain in the morning and more pain at night | NSAIDs, Glucocorticoids |
| Diabetes mellitus | Increased blood sugar level after meal | Sulfonylurea, Insulin, Biguanide |
| 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 | Incidences higher in the early morning | Cardiovascular agent |
| Attention deficit syndrome | Increase in DOPA level in afternoon | Methylphenidate |
| Allergic rhinitis | Worse in the morning/upon rising | Antihistamines |

Diseases Currently On Target For Chronopharmaceutical Formulations

All functions in human are highly organized in the time as biological rhythms of diverse periods, both in health and disease conditions. This represents a challenge for those involved in the development of drug delivery system to make possible the treatment of illness according to these physiological rhythms as a means of improving therapeutic outcomes. Some diseases currently on target for chronopharmaceutical formulations include: ^[11]

Bronchial asthma

It is characterized by airway inflammation resulting in hyper responsiveness of lower respiratory tract to various environmental stimuli. Airway resistance increases progressively at night in asthmatic patient. The asthma is called nocturnal asthma. It is an exacerbation of asthma with increase in symptoms, airway responsiveness and/or lung function. The majority of bronchospastic attacks occur in early morning-2 am and 6 am each day. 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. ii) a single daily dose of inhaled corticosteroid, when administered at 5:30 pm rather than 8 am was nearly 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 (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. ^[2]

Arthritis

The chronobiology, chronopharmacology and chronopharmaceutics and pain have been extensively reviewed. For instance, there is a circadian rhythm in the plasma concentration of c-reactive protein and interleukin-6 of patient with rheumatoid arthritis. Increasingly, the arthritides have shown statistically quantifiable rhythmic parameters. Included in the latter

group are joint pain and joint size. In addition, a number of drugs used to treat rheumatic diseases have varying therapeutic and toxic effects based on the time of day of administration. Patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day. Chronotherapy for all forms of arthritis using NSAIDs such as ibuprofen should be timed to ensure that the highest blood levels of the drug coincide with peak pain. For osteoarthritis sufferers, the optimal time for a nonsteroidal anti-inflammatory drug such as ibuprofen would be around noon or mid-afternoon. The same drug would be more effective for people with rheumatoid arthritis when taken after the evening meal. The exact dose would depend on the severity of the patient's pain and his or her individual physiology.^[12]

Ulcers

It is well known that patients with peptic ulcer disease normally experience maximal acid secretion and pain near the time they go to bed, since the rate of stomach acid secretion is highest at night. Hence, most ulcer medications are administered at night to enhanced therapeutic effect.^[11]

Diabetes

There circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance in case of insulin substitution in type 1 diabetes have been previously discussed. 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. Exogenous administration of mealtime doses promotes peripheral glucose uptake (i.e. it prevents postprandial increases in blood glucose concentration) as well as reducing hepatic glucose release.^[12]

Cardiovascular diseases

Several functions (e.g. BP, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. It was postulated that modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac

events. Cardiac events also occur with a circadian pattern. Numerous studies have shown an increase in the incidence of early-morning myocardial infarction, sudden cardiac death, stroke, and episodes of ischemia. The circadian pattern of BP has been well documented. BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period. Most patients with essential hypertension have a similar circadian rhythm of BP as do normotensive persons, although hypertensive patients have an upward shift in the profile.^[12]

Hypercholesterolemia

A circadian rhythm occurs during hepatic cholesterol synthesis. This rhythm varies according to individuals. Indeed, there is a large variation in plasma 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. 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.^[12]

Cancer

Human and animal studies suggest that chemotherapy may be more effective and less toxic if cancer drugs are administered at carefully selected times that take advantage of tumor cell cycles while less toxic to normal tissue. The rhythmic circadian changes in tumor blood flow and cancer growth are relevant both when tumors are small and growing most rapidly and when they are larger and growing more slowly. The blood flow to tumors and tumor growth rate are each up to threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase. Clinical studies testing whether circadian chemotherapy timing meaningfully affects drug toxicity patterns and severity, maximum tolerated dose, average dose intensity, tumor response quality and frequency and the survival of patients with cancer, have been indicated since the pioneer work of Haus *et al.* on leukemic mice. The chronotherapy concept offers further promise for improving current cancer-treatment options, as well as for optimizing the development of new anticancer or supportive agents.^[12]

Neurological disorders

Epilepsy – The circadian rhythm is involved in epilepsy. 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. 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 mechanism of epilepsy in chronobiology is invented by physiology and medical research. 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.

Alzheimer's disease - Change of circadian rhythm is also seen in patients with Alzheimer's disease. 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. 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.^[2]

Mechanism of Drug Release From Pulsatile Drug Delivery System

The mechanism of drug release from PDDS can be occurring in the following ways-

Diffusion - Water diffuses into the interior of the particle when particle come in contact with aqueous fluids in the gastrointestinal tract and resultant drug solutions diffuse across the release coat to the exterior.

Erosion - Some coatings designed to erode gradually with time, result in the release of drug contained within the particle.

Osmosis - An osmotic pressure can be built up within the interior of the particle when water allows entering under the right circumstances. The drug is forced out of the particle into the exterior through the coating.^[13]

Table. 2: Polymers employed in PDDS ^[14]

| Synthetic | Natural |
|-----------------------------|-----------------|
| HPMC K4M | Sodium alginate |
| HPMC K15M | Pectin |
| HPMC K100M | Karaya gum |
| Eudragit | Gelatin |
| Ethyl cellulose | Xanthan gum |
| Cellulose acetate phthalate | Chitosan |
| Polymethacrylic acid | Guar gum |

Classification of pulsatile drug delivery system ^[2, 15, 16]

Pulsatile drug delivery system is classified into four classes

A. Time controlled pulsatile release**I. Single unit system**

1. Capsular system
2. Port system
3. Delivery by solubility modulation
4. Delivery by reservoir systems with erodible or soluble barrier coatings

II. Multi-particulate system

1. Pulsatile system based on rupturable coating
2. Time controlled expulsion system
3. Pulsatile delivery by change in membrane permeability
4. Sigmoidal release system
5. Low density floating multiparticulate pulsatile systems

B. Stimuli induced**I. Internal stimuli induced Pulsatile system**

1. Temperature induced system
2. Chemical stimuli induced system
3. pH sensitive drug delivery system

II. External stimuli induced system

1. Electrically stimulates Pulsatile system
2. Magnetically stimulated Pulsatile system
3. Ultrasonically stimulated Pulsatile system
4. Photo chemically stimulated Pulsatile system

A. Time controlled pulsatile release

I. Single unit system

1. 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. The pulsincap® system (Fig- 4) is developed by R.P. Scherer International Corporation, Michigan. 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.

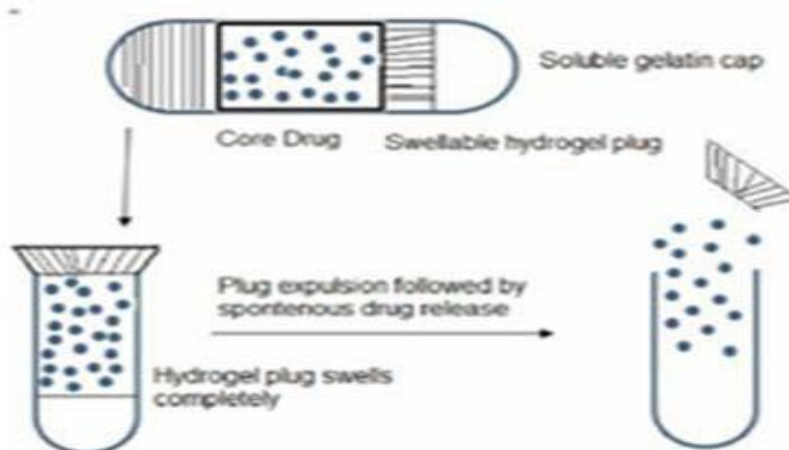


Fig. 4: Schematic diagram capsular system

2. 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 (Fig 5). 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.^[2]

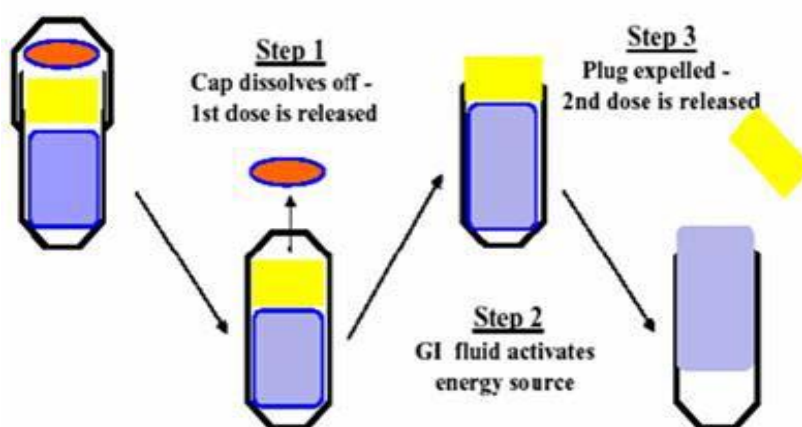


Fig. 5: Port system

3. Pulsatile drug delivery by modulating solubility

These system contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of antiasthmatic drugs like salbutamol sulphate. The compositions contain the drug and a modulating agent, sodium chloride (NaCl). The amount of NaCl was such that it was less than the amount needed to maintain saturation in a fluid that enters the osmotic device. The pulsed delivery is based on drug solubility.

4. 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.

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. 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. 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.

1. 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. 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.

2. 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. Another system is based on a capsule or tablet composed of a large number of pellets consisting of two or more pellets or part.

3. 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. It 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 facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to

permeate the active core in a controlled manner. This property is essential to achieve a precisely defined lag time.

4. 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 counterions 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. Because the higher hydration of the film containing quaternary ammonium groups on interaction with the acids.

5. Low density floating multiparticulate pulsatile system

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 floatingpulsatile 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.

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.

I. Internal stimuli induced pulsatile system

1. 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. 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 (NIsopropyl acrylamide) to prepare corona of micelles which shows dehydration and rehydration with change in temperature. 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 governed by diffusion, and above this temperature the release was stopped completely because skin layer is formed on hydrogel surface (on-off drug release regulation).

2. 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. Several systems have been 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 by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release. Examples of the pH sensitive polymers include N, N-dimethylaminoethyl methacrylate, chitosan, polyol etc.

b) Inflammation-induced pulsatile release

When any physical and chemical stress such as injury, broken bones etc occurs the various inflammatory reactions take place at injury site. At inflammatory sites phagocytic cells like macrophages and polymorphonuclear cells, play role in healing process. During inflammation hydroxyl radicals (OH) are generated from inflammation responsive cells. Yui and co-workers focused on the inflammation-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.

3. pH sensitive drug delivery system

Such type of pulsatile drug delivery system contains two components one is of immediate release type and other one is pulsed release which releases the drug in response to change in pH. In case of pH dependent system advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained. An example of pH dependent polymers includes cellulose acetate phthalate, polyacrylates, and sodium carboxy methyl cellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine.

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.

1. 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 its 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 augmentation of solute flux within a membrane. Electrostatics partitioning of charged solutes in charged membrane.

2. 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. 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 alginate microspheres. 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 (Llysine) or poly (ethylene imine). The release rate was improved in absence of a magnetic field.

3. 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. The cavitations is responsible for degradation and release from bioerrodible polymers.

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

Table. 3: Recent technologies based on chronomodulation ^[17]

| Technology | Rationale | Developed by | Marketed formulation |
|---|---|---|---|
| SODAS [®] (Spheroidal Oral Drug Absorption System) | System is a mixture of immediate and delayed and/or sustained release coated non peril seeds. | Elan Pharmaceuti-cals | Avinza [™] , Ritalin [®] LA and Focalin [®] XR. |
| IPDAS [®] (Intestinal Protective Drug Absorption System) | Gastro-retentive high density multiparticulate system. | Elan | Naprelan [®] |
| CODAS [™] Chronotherapeutic Oral Drug Absorption System | System ensures a lag time in drug release hence maximum amount is attained at the time required long after the formulation administration. | Elan | Verelan [®] PM |
| PRODAS [®] Programmable Oral Drug Absorption System | System consists of multiparticulates (minitabs) able to release the drug at different time intervals and different release rates and/or mechanisms | - | - |
| Geoclock [®] | Compression coated controlled dosage form containing coat of a wax material to ensure pH independent erosion along with superdisintegrant to ensure complete release. | SkyePharma | Lodotra [™] |
| Geomatrix [™] | Multilayered matrix tablet having mixutre of hydrophilic and hydrophobic polymers in a suitable ratio to ensure | | Sular [®] , ZYFLO CR [™] , Coruno [®] , diclofenac-ratiopharm [®] Madopar DR [®] |
| PULSYST [™] | Multiparticulate system in a tablet dosage form. Minitabs with different release patterns are compressed into a single tablet | MiddleBrook [™] Pharmaceuticals | Moxatag [™] |
| OSDrC [®] (one step dry coating Technology) | Tablet with in tablet for pulsatile or controlled release pattern | - | - |
| Hypermatrix [™] [66] | A drug matrix assembly is defined as five dimensional in nature: length, height, width, space, and time. The understanding and controlling of properties associated with these dimensions facilitates responses to the multivariate external environment of the Gastro-Intestinal Tract (GIT) resulting in time-release delivery of a wide range of pharmaceuticals | IntelliPharmaceti cal | - |

| | | | |
|-----------------------------|---|--|-----------------------------|
| IntelliMatrix™ | Matrix prepared by intelligent polymers like hydroxyethyl cellulose as matrix former and lactose as channelling agent | IntelliPharmaceutical | - |
| Eurand Minitabs® technology | Cylindrical minitabs containing drug mixed in controlled release polymer with an optional controlled release coating Supplied in capsule. | Aptalis Pharmaceutical (formerly Eunard Pharmaceuticals) | - |
| Diffucaps® multiparticulate | Drug layering on sugar pellets or cellulose spheres followed by release controlling polymer coating. It is able to provide a lag time of 4-5 hrs. | Aptalis Pharmaceutical (formerly Eunard Pharmaceuticals) | Innopran® XL tablet |
| Diffutab® technology | Produces a once daily dosage regimen with the help of mixtures of hydrophilic polymers allowing diffusion of drug in controlled fashion | Aptalis Pharmaceutical (formerly Eunard Pharmaceuticals) | - |
| Orbexa® technology | Multiparticulate system based on extrusion-spheronization for sensitive drugs like proteins. Spheroids are coated with release controlling polymer. Helps in incorporating high dose in a single dosage form as compared to diffucaps | Aptalis Pharmaceutical (formerly Eunard Pharmaceuticals) | - |
| OROS | Dosage form consisting of drug and osmotically active compound enclosed in a polymeric membrane with one minute orifice. | Alza corporation | Chronset™, INVEGA, CONCERTA |
| Port | Combination of immediate and delayed release components. Device enclosed in a housing sequencing IR component, polymeric plug, delayed component, osmotic agent. The cap of device dissolves immediately after administration and releases the IR component. With span of time osmotic agent pushes the plug to release the delayed component | - | - |

Table. 4: Chronopharmaceutical systems approved by US-FDA ^[18]

| Indication/rationale for chronotherapy | Chronopharmaceutical technology | Proprietary Name; Dosage Form | API | Date of FDA approval |
|---|---------------------------------|-------------------------------------|--------------|----------------------|
| Asthma/increased bronchoconstriction in morning | CONTIN | Uniphyll®; extended release tablets | Theophylline | Sept 01, 1982 |

| | | | | |
|--|--------------------------------------|--|----------------------------------|--------------|
| Ulcer/increased gastric acid secretion in evening | Physico-chemical modification of API | Pepcid® tablets | Famotidine | Oct 15, 1986 |
| Hypercholesterolemia/increased cholesterol synthesis overnight | Physico-chemical modification of API | Zocor® tablets | Simvastatin | Dec 23, 1991 |
| Hypertension increased BP in early morning | OROS | Covera HS; extended release tablets | Verapamil HCl | Feb 26, 1996 |
| Hypertension | CODAS | Verelan® PM; extended release capsules | Verapamil HCl | Nov 25, 1998 |
| Anti-psychotic | OROS | Concerta® tablet | Methylphenidate HCl | Aug 1, 2000 |
| Hypertension | CEFORM | Cardizem LA; Extended release tablets | Diltiazem HCl Verapamil HCl | Feb 06, 2003 |
| Hypertension | DIFFUCAPS | Innopran XL; extended release capsules | Propranolol HCl Verapamil HCl | Mar 12, 2003 |
| Schizophrenia | OROS | Invega | Paliperidone | Dec 19, 2006 |

CONCLUSION

Sustained drug delivery system is not beneficial particularly in case of treating diseases which follows circadian rhythms but in case of pulsatile drug delivery system is very much useful. For determining optimum need of drug in the body, circadian rhythm of the body is an important concept. Pulsatile drug delivery system (PDDS) releases drug at right time, right amount and at right site. PDDS that can effectively treat diseases with non-constant dosing therapies and hence, enhance patient compliance, optimal delivery of the drug to the site of target while minimizing the undesired effects. Pulsatile release systems should be promising in the future.

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