REVIEW ARTICLE

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PULSATILE DRUG DELIVERY: A REVIEW

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Abstract: Pulsatile drug delivery systems are gaining a lot of interest now days. These systems are designed according to the circadian rhythm of the body. These systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient compliance and therapeutic efficacy. Pulsatile delivery, which is meant as the liberation of drugs following programmed lag phases, has drawn increasing interest, especially in view of emerging chronotherapeutic approaches. Pulsatile drug delivery shows potential benefits for the diseases which show circadian rhythms like rheumatoid arthritis, cardiovascular diseases, asthma, peptic ulcer, allergic rhinitis.

Key Words: Pulsatile drug delivery system, Circadian rhythm, Chronotherapeutics

INTRODUCTION TO PULSATILE DRUG DELIVERY SYSTEM: [1, 2]

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems 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.

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 is known as pulsatile release.

A pulsatile drug delivery system is characterized by a lag time that is an interval of no drug release followed by rapid drug release.

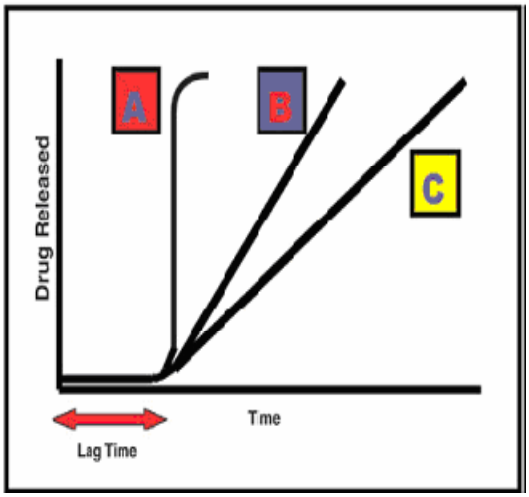


Figure 1 Drug release profile of pulsatile drug delivery system[1, 2]

A: Ideal sigmoidal release

B & C: Delayed release after initial lag time

Chronotherapy:[3]

Co-ordination of biological rhythms and medical treatment is called chronotherapy.

Chronotherapeutics:[3]

Chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. It is becoming increasingly more evident that the specific time that patients take their medication may be even more significant than was recognized in the past. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hour period, may be changing as researcher's report

that some medications may work better if their administration is coordinated with day night patterns and biological rhythms.

Biological rhythms:[3]

1. Ultradian Rhythms:

Oscillations of shorter duration are termed Ultradian Rhythms (more than one cycle per 24 h). E.g.90 minutes sleep cycle.

2. Infradian Rhythms:

Oscillations that are longer than 24 hours are termed as Infradian Rhythms (less than one cycle per 24hours). E.g.Monthly Menstruation.

3. Circadian rhythms:

Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 Hours. Interestingly, the term circadian is derived from the Latin circa which means "about" and dies which can be defined as "a day". Normally, circadian rhythms are synchronized according to internal biologic clocks related to the sleep-wake cycle. Our circadian rhythm is based on sleep-activity cycle and is influenced by our genetic makeup and thereby affects our bodies' function throughout day and night (24-hour period).Circadian rhythm regulates many body functions in humans like metabolism, physiology, behavior, sleep pattern, hormone production. There are number of conditions which show circadian pattern and advantage could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease.

The first pulsed delivery formulation that released the active substance at a precisely defined time point was developed in the early 1990s. In this context, the aim of the research was to achieve a so-called sigmoidal release pattern (pattern A in Figure 1). The characteristic feature of the formulation was a defined lag time followed by a drug pulse with the enclosed active quantity being released at once. Thus, the major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time. Often, the drug is released over an extended period of time (patterns B & C in Figure 1). This following reviews the various pulsatile drug delivery systems that are reported.

In chronopharmacotherapy (timed drug therapy) drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. By basing drug delivery on circadian patterns of diseases drug effect can be optimized and side effects can be reduced. If symptoms occur at daytime a conventional dosage form can be administered just prior the symptoms are worsening. If symptoms of a

disease became worse during the night or in the early morning the timing of drug administration and nature of the drug delivery system need careful consideration.[4, 5]

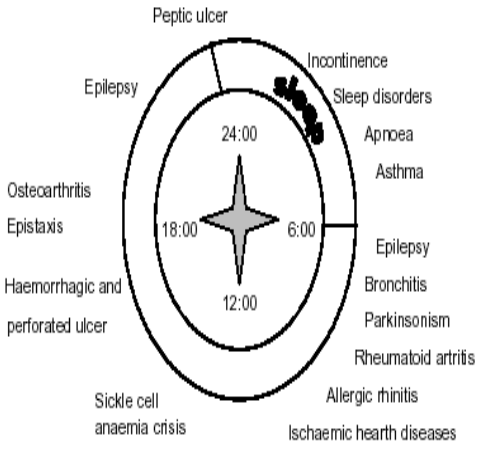


Figure 2 24-hr clock diagram of the peak time of selected human circadian Rhythm with reference to the day-night cycle[4, 5]

Control release systems for 12 or 24 hr drug release are not suitable for diseases, which follow circadian variation. In that condition there is requirement for time or pulsatile drug delivery system.

Advantages: [1, 2]

1.Many body functions that follow circadian rhythm. A number of hormones like rennin, aldosterone, and cortisol show daily 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.

2.Diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension display time dependence. Sharp increase in asthmatic attacks during early morning hours. Such a condition demands considerations of diurnal progress of the disease rather than maintaining constant plasma drug level. A drug delivery system administered at bedtime, but releasing drug well after the time of administration (during morning hours), would be ideal in this case. It is true for preventing heart attacks in the middle of the night and the morning stiffness typical of people suffering from arthritis.

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.The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g., peptide drugs) irritate the gastric mucosa or induce nausea and vomiting. These conditions can be satisfactorily handled by enteric coating, and in this sense, enteric coating can be considered as a pulsatile drug delivery system.

5.Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon requires that the drug release be prevented in the upper two-third portion of the GIT.

6.The drugs that undergo extensive first-pass metabolism (b-blockers) and those that are characterized by idiosyncratic pharmacokinetics or pharmacodynamics resulting in reduced bioavailability, altered drug/metabolite ratios, altered steady state levels of drug and metabolite, and potential food-drug interactions require delayed release of the drug to the extent possible

DISEASES REQUIRING PDDS. [6]

Sr. No	Diseases	Chronopharmacological behaviour	Drugs used
1	Peptic ulcer	Acid secretion is high in afternoon and in night	H_2 blockers
2	Asthma	Precipitation of attacks during night or at early morning hour	B_2 agonist, Antihistaminic
3	Cardiovascular diseases	Blood pressure is at its lowest during the sleep and rises steeply during the early morning awakening period	Nitroglycerin, Calcium channel blockers, ACE inhibitors
4	Arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
5	Diabetes mellitus	Increase in blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
6	Attention deficit syndrome	Increase in DOPA level in afternoon	Methyl phenidate
7	Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time	HMG CoA reductase inhibitors.

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEMS: [1, 2]

Pulsatile drug delivery systems (PDDS) can be classified in site-specific and time-controlled systems. Drug release from site-specific systems depends on the environment in the gastro intestinal track, e.g., on pH, presence of enzymes, and the pressure in the gastro intestinal track. In contrast, time-controlled DDS are independent of the biological environment. The drug release is controlled only by the system. Time-controlled pulsatile delivery has been achieved mainly with drug containing cores, which are covered with release-controlling layers.

Single unit system:

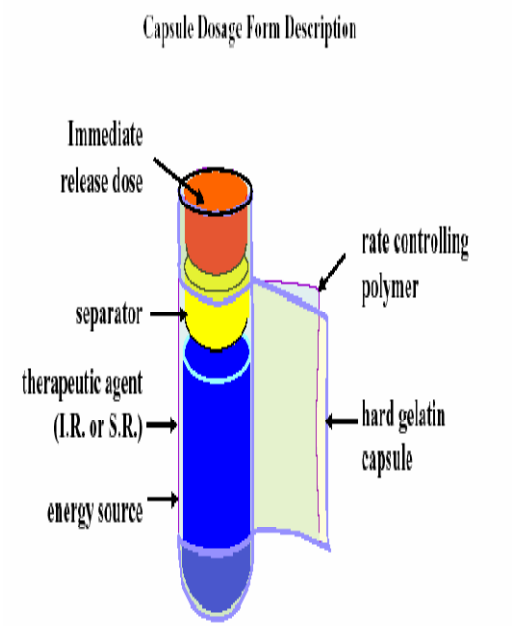
Capsular system:

Different single-unit capsular pulsatile drug delivery systems have been developed. A general architecture of such systems 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 Pulsincap® system is an example of such a system that 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). These formulations were well tolerated in animals and healthy Volunteers, and there were no reports of gastro-intestinal irritation. However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine.[1, 2, 7-9]

The Port® System[1, 2, 10] consists of a gelatin capsule coated with a

semipermeable membrane (eg, cellulose acetate) housing an insoluble plug (eg, lipidic) and an osmotically active agent along with the drug formulation (Figure No. 3). When in contact with the aqueous medium, water diffuses across the semipermeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. Coating thickness controls the lag time. The system showed good correlation in lag times of in vitro and in vivo experiments in humans. 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.



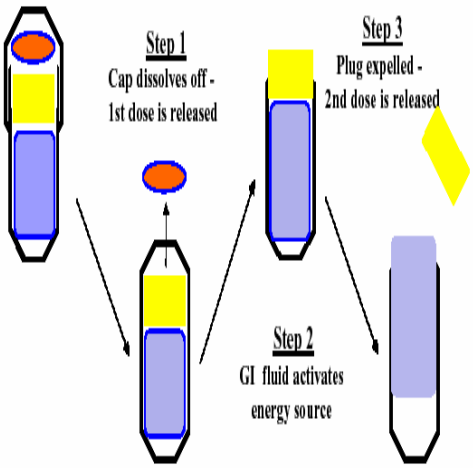


Figure No. 3: Drug release mechanism from PORT system[10]

Tablets system:[1, 11]

Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly. The lag time depends on the thickness of the coating layer.

The Time Clock® system consists of a solid dosage form coated with lipidic barriers containing carnauba wax and bees wax along with surfactants, such as polyoxyethylene sorbitan monooleate. This coat erodes or emulsifies in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion. In a study with human

Volunteers, it was shown that the lag time was independent of gastric residence time, and the hydrophobic film redispersion did not appear to be influenced by the presence of intestinal enzymes or mechanical action of stomach or gastro-intestinal pH. The lag time increased with increasing coating thickness. Such systems are better suited for water-soluble drugs.

The major advantage of this system is its ease of manufacturing without any need of special equipment. However, such lipid-based systems may have high in-vivo variability (e.g., food effects).

The possible problems of erosion-controlled systems include a premature drug release when the penetrating water dissolves the drug, which diffuses out through the barrier layers, and sustained release after the lag phase when the barrier layer is not eroded or dissolved completely, thereby retarding the drug release.

The Chronotropic® system consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of release. In addition, through the application of an outer gastric-resistant enteric film, the variability in gastric emptying time can be overcome, and a colon-specific release can be obtained, relying on the relative reproducibility of small intestinal transit time. The lag time is controlled by the thickness and the viscosity grades of HPMC. The cores containing Antipyrine as the model drug were prepared by tableting and retarding, and enteric coats were applied in a fluidized bed coater. The in vitro release curves displayed a lag phase preceding drug release, and the in vivo pharmacokinetic data showed a lag time prior to presence of detectable amounts of drug in saliva. Both in vitro and in vivo lag times correlate well with the applied amount of the hydrophilic retarding polymer. The system is suitable for both tablets and capsules.

Multiparticulate systems:[1, 11]

Multiparticualte systems (e.g., pellets) offer various advantages over single unit systems. These include no risk of dose dumping, flexibility of blending units with different release patterns, and reproducible and short gastric residence time. But the drug-carrying capacity of multiparticulate systems is lower due to presence of higher quantity of excipients. Such systems are invariably a reservoir type with either rupturable or altered permeability coating.

Pulsatile system based on rupturable coating:[1, 12]

Time-Controlled Explosion System: This is a multiparticulate system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer. The swelling agents use include superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose, polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc. Alternatively, an effervescent system comprising a mixture of tartaric acid and sodium bicarbonate may also be used. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The release is independent of environmental factors like pH and drug solubility. Varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer can vary the lag time. A rapid release after the lag phase was achieved with increased concentration of osmotic agent. In vivo studies of time controlled explosion system (TCES) with an in-vitro lag time of three hr showed appearance of drug in blood after 3 hr, and maximum blood levels after 5 hr.

Osmotic-based rupturable coating systems:[1, 12]

Permeability Controlled System: This system is based on a combination of osmotic and swelling effects. The core containing the drug, a low bulk density solid and/or liquid lipid material (e.g., mineral oil) and a disintegrant were prepared. This core was then coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of coating.

Another system is based on a capsule or tablet composed of a large number of pellets consisting of two or more pellets or parts (i.e., populations). Each pellet has a core that contains the therapeutic drug and a water-soluble osmotic agent. Water permeable, water-insoluble polymer film encloses each core. A hydrophobic, water insoluble agent that alters permeability (e.g., a fatty acid, wax, or a salt of fatty acid) is incorporated into the polymer film. The rate of water influx and drug efflux causes the film coating of each population to differ from any other pellet coating in the dosage form. The osmotic agents dissolve in the water causing the pellets to swell, thereby regulating the rate of drug diffusion. The effect of each pellet population releasing its drug content sequentially provides a series of pulses of drug from a single dosage form. The coating thickness can be varied amongst

the pellets. This system was used for the delivery of antihypertensive drug, diltiazem. Schultz and Kleinebudde reported the use of osmotically active agents that do not undergo swelling. The pellet cores consisted of drug and sodium chloride. These were coated with a semipermeable cellulose acetate polymer. This polymer is selectively permeable to water and is impermeable to the drug. The lag time increased with increase in the coating thickness and with higher amounts of talc or lipophilic plasticizer in the coating. The sodium chloride facilitated the desired fast release of drug. In absence of sodium chloride, a sustained release was obtained after the lag time due to a lower degree of core swelling that resulted in generation of small fissures.

Pulsatile delivery by change in membrane permeability:[1, 12]

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. The cores were prepared using Theophylline as model drug and sodium acetate. These pellets were coated using Eudragit RS 30D (10% to 40% weight gain) in four different layer thicknesses. A correlation between film thickness and lag time was observed. It was found that even a small amount of sodium acetate in the pellet core had a dramatic effect on the drug permeability of the Eudragit film. After the lag time, interaction between the acetate and polymer increases the permeability of the coating so significantly that the entire active dose is liberated within a few minutes. The lag time increases with increasing thickness of the coat, but the release of the drug was found to be independent of this thickness.

Stimuli induced pulsatile systems:[3]

In these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli. These systems are further classified in to temperature induced systems and chemical stimuli induced system, on the basis of stimulus.

1. Temperature induced systems[3]

Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state.

2. Chemical stimuli induced system[3, 11]

Chemical stress is one of the most widely utilized triggering signals for a variety of triggered or PDDS. A biochemical change in the physiology of human beings is utilized as a stimulus for triggering drug release from the pulsatile system. They further classified into:

a) Glucose-responsive insulin release devices
b) Inflammation-induced pulsatile release
c) Drug release from intelligent gels responding to antibody concentration
d) pH sensitive drug delivery system

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.

Inflammation-induced pulsatile release:

On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation- responsive cells.

Drug release from intelligent gels responding to antibody concentration:

There are numerous kinds of bioactive compounds which exist in the body. Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/reselling characteristics. Special attention was given to antigen-antibody complex formation as the cross-linking units in the gel, since such interactions are very specific.

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 the case of pHdependent system advantage has been taken of the fact that there exists a different pH environment at different parts of the GI tract. Thus, by selecting the pHdependent polymers, drug release at specific locations can be obtained. Such a type of PDDS contains two components; one is of immediate release type and the other one is pulse released, which releases the drug in response to change in pH.

Examples of pH-dependent Polymers include Cellulose acetate phthalate, Eudragit L100, Eudragit S100, HPMC phthalate, HPMC trimellitate, HPMC acetate maleate, polyvinyl acetate phthalate, and Shellac. These polymers are used as enteric-coating materials so as to provide release of drug in the small intestine.

Externally regulated pulsatile drug delivery[3]

For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation.

MARKETED TECHNOLOGIES OF PDDS: [11]

Technology	Proprietary name and dosage form	API	Indications
OROS	Covera-HS; extended release tablets	Verapamil HCl	Hypertension/increased BP in early morning
CODAS	Verelan PM; extended release capsules	Verapamil HCl	Hypertension
CEFORM	Cardizem LA; extended Release tablets	Diltiazem HCl,Verapamil HCl	Hypertension
DIFFUCAPS	InnoPran XL extended release capsules	Propranolol HCl	Hypertension
PULSYS	Moxatag tablet	Amoxicillin	Infection
Three-dimensional printing	Theirform	Diclofenac Sodium	
PULSINCAP	Pulsincap	Dofetilide	Hypertension

DRUGS FORMULATED AS PULSATILE DRUG DELIVERY SYSTEM:

Sr. No	Drug	Dosage form
1	Diclofenac sodium[13]	Pulsatile Tablet
2	Ranitidine HCL[14]	Floating Pulsatile Tablet
3	Aceclofenac[15]	Floating Pulsatile Tablet
4	Aceclofenac[16]	Floating Pulsatile Multiparticulate System
5	Theophylline[17]	Pellets
6	Meloxicam[18]	Multiparticulate System For Pulsatile Release
7	Theophylline[19]	Pulsatile Tablet
8	Salbutamol Sulphate[20]	Pulsatile Tablet
9	Verapamil HCL[21]	Floating Pulsatile Tablet
10	Metoprolol Tartarate[22]	Floating Pulsatile Tablet
11	Propranolol[23]	Time Controlled Pulsatile Release Tablet
12	Atenolol[24]	Enteric Press Coated Tablet For Pulsatile Delivery
13	Nizatidine[25]	Floating Pulsatile Tablet

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