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PULSATILE DRUG DELIVERY SYSTEM: A PROMISING DELIVERY SYSTEM FOR CONTROLLED DRUG RELEASE

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ABSTRACT

Pulsatile drug delivery system is the most interesting, time and site specific system. This system is designed for chronopharmacotherapy which is based on the circardian rhythm. The present study is aiming at the development of chronotherapy, designed according to the chronological behavior of body. Although oral delivery has become a widely accepted route of administration of therapeutic drugs, the gastrointestinal tract presents several formidable barriers to drug delivery. PDDS can be classified into time controlled systems wherein the drug release is controlled primarily by the delivery system; stimuli induced PDDS in which release is controlled by the stimuli, like the pH or enzymes present in the intestinal tract or enzymes present in the drug delivery system and externally regulated system where release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. Thus it is important to develop new drug delivery systems to achieve pulsed delivery of a certain amount of drugs in order to mimic the function of the living systems, while minimizing undesired side effects. Therefore Pulsatile drug delivery is one such systems that, by delivering drug at the right time, right place and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension.

KEY WORDS: Pulsatile drug delivery, chronotherapy, lag time, Circadian rhythm.

INTRODUCTION[1]

Pulsatile system is amongst one of the time and site specific systems and gaining a lot of interest as it is increasing patient compliance by means of providing time- and site-specific drug delivery system, thus providing spacial and temporal delivery. A pharmaceutical dosage

form such as a capsule capable of delivering therapeutic agents into the body in a time-controlled or position controlled pulsatile release fashion, is composed of a multitude of multicoated particulates (beads, pellets, granules, etc.) made of one or more populations of beads.

In which cases or circumstance pulsatile drug delivery is used they are listed below

1) Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology.
2) Avoiding the first pass metabolism e.g. protein and peptides
3) For which the tolerance rapidly exists
4) For targeting specific site in intestine e.g. colon
5) For time programmed administration of hormones and drugs
6) For drugs having short half life.

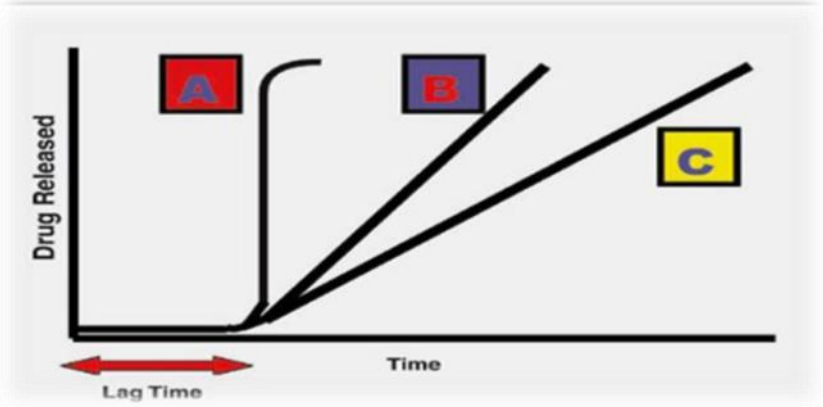

Figure 1: Drug release profile of pulsatile drug delivery systems. A - Ideal sigmoidal release; B & C – Delayed release after initial lag time

Chronopharmacotherapy

Recent studies show that diseased have predictable cyclic rhythms and the timing of medication regimens can improve outcome in selected chronic conditions. "Chronopharmaceutics" consist of two words Chronobiology and Pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. There are three types of mechanical rhythms in our body, they are

- Circadian
- Ultradian
- Infradian

Circadian: "Circa" means about and "dies" means day.

Ultradian: Oscillation of shorter duration are termed as Ultradian (more than one cycle per 24h)

Infradian: Oscillations that are longer than 24 h (less than one cycle per day)[2].

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

1. **First pass metabolism:** Some drugs, such as 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.

2. **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 nitroglycerin.

3. **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 the 24 hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours.

4. **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.

5. **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.

6. **Drug absorption differences in various gastrointestinal 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. For example, it is rational for a delivery system to pump out the drug much faster when the system reaches the distal segment of the intestine, to avoid the entombment of the drug in the feaces (Burnside et al., 2003).

Advantages of Pulsatile Drug Delivery System

1. Extended day time or night time activity.
2. Reduced side effects.
3. Reduced dosing frequency.
4. Reduction in dose size.
5. Improved patient compliance.
6. Lower daily cost to patient because fewer dosage units are required by the patient in therapy.
7. Drug adapts to suit circadian rhythms of body function or disease.
8. Drug targeting specific site like colon.

Disadvantage of Pulsatile Drug Delivery System

1. Lack of manufacturing reproducibility and efficacy.
2. Large number of process variables.
3. Batch manufacturing process.

Classification of Pulsatile Drug Delivery System

The pulsatile drug delivery systems are of two types:

1. Single unit system
2. Multiparticulate/Multiple unit system.

1. Single Unit System

❖ **Capsular System:** This system consists of insoluble capsule body housing, a drug and a plug (Figure 2). After a predetermined lag-time plug is removed because it undergoes swelling, erosion or dissolution.

Example- Pulsincap system, in this system a water insoluble body containing the formulation, system is closed with a swellable hydro gel which is plugged at open end. Upon contact with gastro-intestinal fluid or dissolution medium the plug swells pushing itself out of the capsule after lag-time. Position and dimension of plug control lag-time. For rapid release of water insoluble drug effervescent or disintegrating agents are added. No gastrointestinal irritation can be observed in both human and animal. Plug material is generally made up of following-

- Swell able materials coated with insoluble but permeable polymer (polymethacryates).
- Erodible compressed polymer (HPMC, polyvinyl alcohol, polyethylene oxide)
- Congealed melted polymer (glyceryl monopleate).

- Enzymatically controlled erodible polymer (pectin).

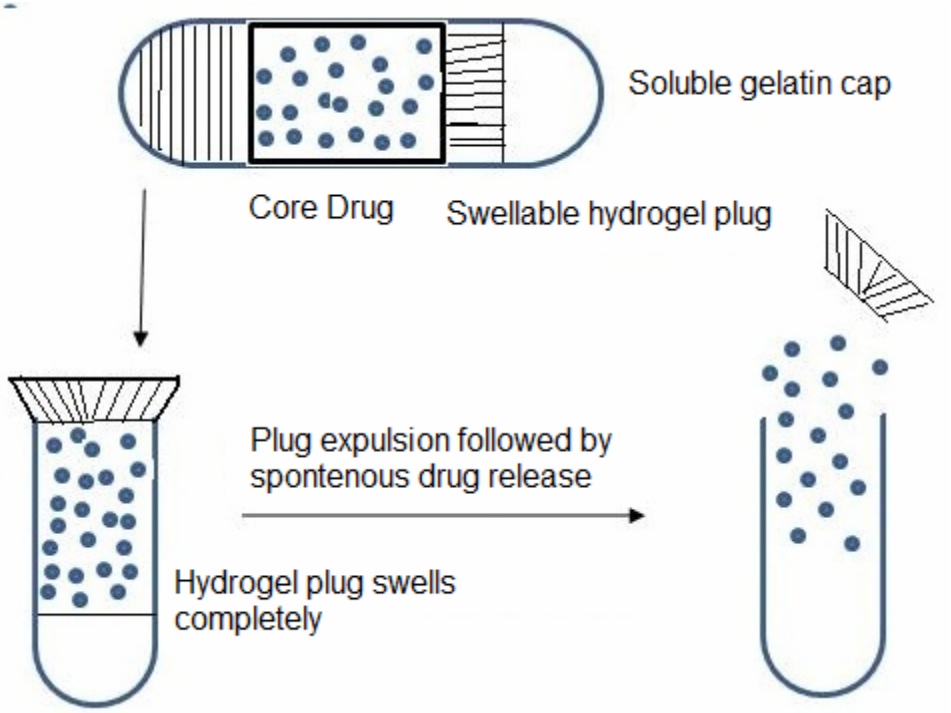

Figure 2: capsular system

❖ **Pulsatile Delivery by Osmosis: -** The port® system consists of gelatin shell filled with somatically active ingredient along with drug and also having an insoluble lipoid plug. Shell is coated with semi permeable membrane then plugged with insoluble plug. When system comes in contact with aqueous medium the water move across semi-permeable membrane and exerts pressure which removes the plug after lag-time. Drug release through orifice of a semi-permeable capsule supported by an expending osmotic layer after the barrier layer is dissolved. Still another system is based on delivery by a series of stop. In this system the capsule contain a drug and water absorptive water engine that is placed in compartment separated by a movable partition. These stops obstruct the movement of partition but are overcome in succession when osmotic pressure rises above there hold level.

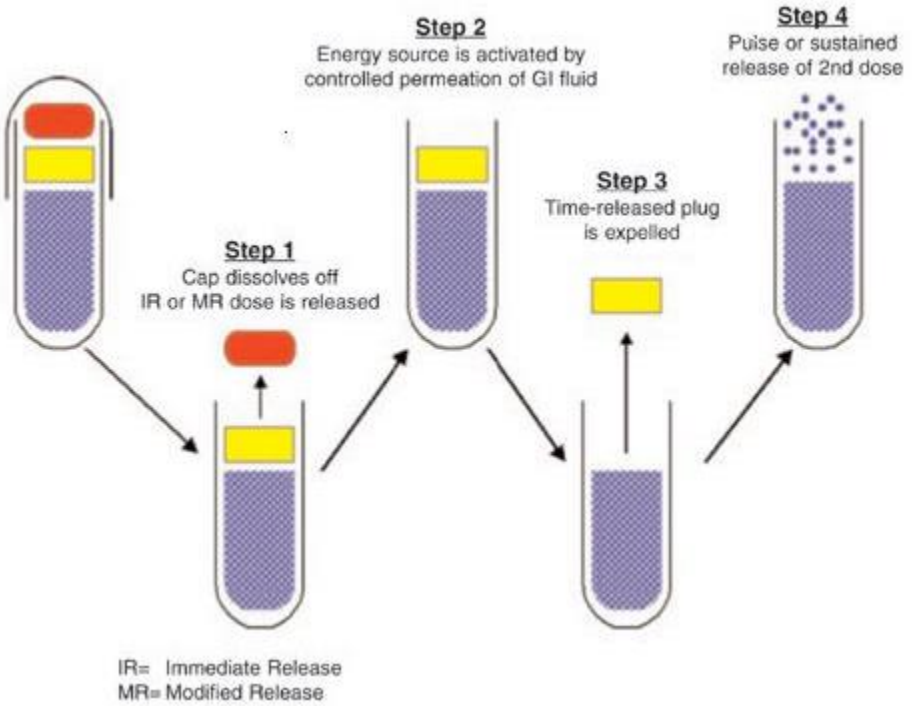

Figure 3: Drug Release Mechanism from PORT System[3]

❖ **Pulsatile Delivery by Erosion or Solublization of Coating:** Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after specific lag period and drug is subsequently released rapidly. The lag time depends on the thickness of the coating layer.

Example: The time clock system consists of solid dosage form coated with lipid barriers such as carnauba wax and beeswax along with surfactant like polyoxyetylen esorbitan monopleate. When this system comes in contact with the aqueous medium the coat emulsifies or erodes after the lag-time depending on the thickness of coat. The lag time of system is independent of the gastrointestinal motility, pH, enzyme and gastric residence time.

❖ **Pulsatile delivery by rupture of membrane:-** the other class of the reservoir type pulsatile system is based on rupturable coating. The drug release from the occurs when surrounding polymeric membrane undergo ruptured due to in built pressure within system. The effervescent excipients produces gas or osmotic agent produce osmotic pressure or swelling agent cause swelling, one of these is necessary for rupture of coating. Citric acid and sodium bicarbonate is incorporated as effervescent mixture in tablet core coated with ethyl cellulose, when system comes in contact with water it produces carbon dioxide gas which exerts pressure and after lag time rupture the membrane and rapid release of drug occurs. A

reservoir system with a semi permeable coating is proposed especially with drug with high first pass effect in order to obtain in-vivo drug pattern similar to the administration of several immediate release doses Croscarmellose sodium starch glycol late or low substituted hydroxypropyl cellulose were used as swelling substances, which resulted in composition of outer polymeric membrane.

2. Multiparticulate system: Multiparticulate systems are reservoir type of devices with a coating, which either rupture or change its permeability. Drug is coated over sugar seed. These granules may then be packaged in a capsule or compressed with additional excipients to form a tablet. The active pharmaceutical ingredient may also be blended or granulated with polymer before coating to provide an additional level of control. However, drug loading in this type of system is low due to higher need of excipients.

❖ **Pulsatile release by rupturing of membrane:** In these multiparticulate system drug is coated on sugar seed and then coated with insoluble and swell able top layer. The swelling agent includes superdisintegrant like car boxy methylcellulose, sodium starch glucollate, L-hydroxyl propyl cellulose. Polymer like polyacrlic acid, polyethylene glycol etc. Alternatively comprising of a mixture of tartaric acid and sodium bicarbonate that is used as an effervescent agent. Water ingress to system cause the coating to swell, rupture and release of drug occurs. Release of drug is independent of pH or solubility of drug. Lag-time can be varied by varying thickness of coating or by changing amount of plasticizers in the outermost layer. If concentration of osmotic agent increases rapid release of drug after lag-time can be observed.

❖ **Rupturable Coating With Osmosis: -** These systems contain core having drug (low bulk density solid or liquid lipid material) and disintegrate. Core is coated with cellulose acetate polymer. System is combination of swelling and osmotic effect, upon immersion in aqueous medium, water penetrates the core, displace the lipid materials, after depletion of lipid material internal pressure increase until a critical stress is reached, which cause rupture of coating. Another type of system is one in which tablet or capsule is composed of large number of pellets. Single pellets of these systems contain drug plus osmotic agent and coated with water preamble, water insoluble polymer. In film hydrophobic agent is incorporated which alter permeability. The rate of water influx and drug efflux cause the film coating of each population to differ from any other pellet coating in the dosage form. Pellet gets swelled

due to dissolution of osmotic agent as it comes in contact with water resulting in regulation of diffusion and release of drug content from pellet.

❖ **Change in Membrane Permeability Based Pulsatile Release:** The permeability and water uptake of acrylic polymer with quaternary ammonium groups can be influenced by the presence of different counter ions. The ammonium group is hydrophilic which cause interaction with water and change in permeability of it in controlled manner. In these system cores containing drug and sodium acetate coated with four different layer of Eudragit RS30D. Small amount of sodium of sodium acetate dramatically change the permeability of Eudragit film. After lag time permeability increases due to increase in interaction between Eudragit and acetate, resulting in entire drug release within few minutes. Increase in lag-time occurs as thickness increase but it has no effect on release. Sigmoid release system consist of drug and succinic acid core coated with ammonio-methacrylate copolymer USP/NF TYPE B. the lag-time is controlled by the rate of water influx through polymer membrane. Succinic acids dissolve by the water cause increase in permeability of hydrated polymer film that increases free volume. These finding were used to design acid containing core that is coated by polymeric membrane.[4-8]

Diseases Requiring Pulsatile Drug Delivery

Disease	Chronological Behavior	Drug Used
Asthma	Precipitation of attack during night or at early morning.	Antihistamines, B2 agonist.
Attention deficit syndrome	Increase in DOPA level in afternoon.	Methylphenidate.
Arthritis	Pain increases in early morning caused by the marked release of inflammatory cytokines, including interleukin-6 in the early hours of the morning.	NSAIDs, glucocorticoid.
Cancer	Blood flow to tumor is three fold greater during each daily activity phase of the circadian cycle then during the daily rest phase.	Vinca alkaloids, Texans.
Duodenal ulcer	Gastric acid secretion is highest at night; bowel motility and gastric empting are slower at night.	Proton pump inhibitors.
Peptic ulcers	Acid secretion is high in after noon and at night.	H2 blokers.
Hyperchole sterolemia	Cholesterol synthesis is generally higher during night than day time.	HMG CoA reductase inhibitor.
Diabetes	Increase in blood sugar level after meal.	Sulfonylurea, insulin

mellitus		
Neurological disorder	Central path physiological of epilepsy.	MAO-B inhibitor.
Cardiovascular disease	BP is at its lowest during sleep cycle.	Nitroglycerine, CCBs, ACE inhibitors.

Methodologies of Pulsatile Drug Delivery

Methodologies for the pulsatile drug delivery system can be broadly classified into three classes:-

1. Time controlled pulsatile system
2. Chemical stimuli induced pulsatile system
3. Externally regulated pulsatile system

1). Time controlled release system:- in time controlled drug delivery system pulsatile release is obtained after a specific time interval in order to mimic the circadian rhythm. Such type of pulsatile drug delivery system contains two components- one is of immediate release type and other one is a pulsed release type.

a) Delivery system with rupturable coating layer: - these systems consist of an outer release controlling water insoluble but permeable coating subject to mechanically induce rupture phenomenon. Recently different systems based on hard gelatin capsule and tablet core were described, all coated by inner swell able and outer rupturable layer. The film rupture may be attained by swelling, osmotic or effervescent additives in the reservoir [9]**.** By optimizing the system, drug release can be obtained at specific time interval.

b) Delivery system provided with erodible coating layer: - in such system 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.

2. Chemical stimuli induced pulsatile system

a) Glucose-responsive insulin release devices:- in case of diabetes mellitus there is rhythmic in the level of glucose in the body requiring injection of insulin at proper time. When glucose concentration in the blood increase glucose oxidase converts glucose into gluconic acid which change 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

desewlling mode thereby decreasing the insulin release. Examples of the pH sensitive polymer include N, N dimethyaminoethyl methacrlate, chitosan etc.

b) Inflammation-induced pulsatile release: - on receiving any physical or chemical stress, such as injury, fracture etc. inflammation take place at the injured sits. During inflammation, hydroxyl radicals are produced from these inflammation responsive cells.

c) Drug release from intelligent gel responding to antibody concentration: - these are numerous kinds of bioactive compound which exits in the body. Recently, novel gel were developed which responded to the change in concentration of bioactive compound to alter their swelling/ desewlling characteristics. Special attention was given it anti-antibody complex formation as the cross-linking units in the gel, since such interactions are very specific. Utilization the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigen, reversible gel swelling/ desewlling and drug permeation change occurs.

d) 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 release the drug in responses to change in pH. In case of pH dependent system advantage has been taken of the fact that there exits different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymer drug release at specific location can be obtained. An example of pH dependent polymer includes cellulose acetate phthalate, polyacrylates and sodium carboxymethycellulose. These polymers are used as enteric coating materials so as provide release of drug in the small intestine.

4. Externally regulated system

For releasing the drug in a pulsatile manner, another way can be the externally regulated system in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads.[10,11]

Recent Advances in the Pulsatile Drug Delivery[12, 13]

Now day pulsatile drug delivery systems are gaining importance in various disease condition. Among these systems, multi-particulate systems offer various advantage over single unit which include no risk of dose dumping, flexibility of blending unit with different release patterns, as well as short and reproducible gastric residence time. Multiparticulate system

consist pellets of different release profile which can be of any type like time dependent, pH dependent, micro flora activated system as discussed in the previous section. Site and time specific oral drug delivery have recently been of great interest in pharmaceutical field to achieve improved therapeutics efficacy. Gastro retentive drug delivery system is an approach to prolong gastric residence time, there by targeting site specific drug release in upper gastrointestinal (GI) tract. Various pulsatile technologies have been developed on the basis of methodologies as discussed previously. These includes OROS® technology, CODAS® technology, CEFORM® technology, three dimensional printing®, timerx® etc.

CONCLUSION

Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. Circadian disorders such as hypertension, osteoarthritis, Asthma etc., which require chronopharmacotherapy. PDDS can effectively tackle this problem as it is modulated according to body's circadian clock giving release of drug after a specified time lag. Pulsatile release systems should be promising in the future.

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