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Chronotherapeutic Drug Delivery Systems

Pandiyan Shanmugan and Ramu Bandameedi*

Department of Pharmacy, Mewar University, Chittorgarh, Rajasthan, India

Abstract

Recent advances in chronotherapeutics led to the development of pulsatile drug delivery systems which effectively delivered the drug at specified time. Diseases like asthma, arthritis, cancer, diabetes, hypertension, ulcer, hypercholesterolemia, congestive heart failure, stroke etc. show different day night pattern in onset and symptoms exacerbation. Pulsatile drug delivery systems deliver the drug at right time in desired levels providing the multiple benefits over the conventional dosage forms. According to the circadian rhythms of the body drug is facilitated to completely release after a lag time especially for drugs eliciting higher first pass effect and where nocturnal dosing is required these systems are highly beneficial. This review epitomizes the special focus on chronotherapeutics, various approaches in chronotherapeutic drug delivery and applications.

Keywords: Chronotherapeutics; Pulsatile drug delivery; Circadian rhythms

Introduction

Master circadian clock of the body, the suprachiasmatic nucleus regulates the endogenous circadian rhythms present inside the human body [1-3]. Major global market of drug delivery systems is occupied by the oral drug delivery systems where the drug release pattern is within the therapeutic window assures the sustained therapeutic action .some conditions demands release of drug after a lag time, i.e., a period of no drug release,where pulsatile drug delivery releases the drug completely after a lag time with increased patient compliance [4-7] shown in Figure 1. Lag time is essential for site specific drug delivery to colon requiring the prevention of drug in G.I.T excessive first pass metabolism, drug degrade in gastric acid medium in stomach, which results in bioavailability. Human body functions such as metabolism, behavior sleep patterns, hormone production regulated by circadian rhythms. Reports suggests that more chances of heart attacks in the early morning hours ,high levels of cortisol levels ,blood pressure were also high early morning than drops off in the night [8-11]. Nocturnal asthma increased responsiveness in early hours of morning, sudden surge of gastric acidity in the mid night. High cholesterol synthesis in night than in the day light all these events associated with the circadian rhythms definitely reveals the importance for designing time specific drug delivery.

Chronobiology

Study of biological rhythms and their mechanism is known as chronobiology. There are three types of mechanical rhythms in our body [12,13].

- Ultradian rhythms: generally last for shorter period less than 24 hrs.
- Infradian rhythms: have a frequency range greater than a day and last until to a week.
- Circadian rhythm: Franz Harberg coined the term circadian which mean approximately one day. The series of events usually experienced in our day to day life shown in Figure 2.

Ideal characteristics for chronotherapeutic drug delivery systems should

- Associate with real time and specific triggering biomarkers for a given disease state.
- Be biocompatible and biodegradable.
- Non-toxic with the usage of delivery systems.
- Self-regulated and adaptive capability to circadian rhythms

Advantages

- Reduced frequency in dosage schedule
- Improved patient acceptability and compliance
- Minimization of side effects
- Biological tolerance
- Protection of stomach mucosa from gastric irritation drugs
- Drugs with high first pass effects can be delivered efficiently without loss of drug
- Drug targeting to specific sites such as colon is possible

Limitations of pulsatile drug delivery system

- Multiple manufacturing steps in multiparticulate pulsatile drug delivery system.
- Low drug load.
- Incomplete release.
- *In-vivo* variability in single unit pulsatile drug delivery system.

Classification of pulsatile drug delivery systems [14]

Pulsatile drug delivery system is classified into four classes:

Time controlled pulsatile release

***Corresponding author:** Ramu Bandameedi, Department of Pharmacy, Mewar University, Chittorgarh, Rajasthan India, Tel: +919989078708; E-mail: bandameedi.ramu@gmail.com

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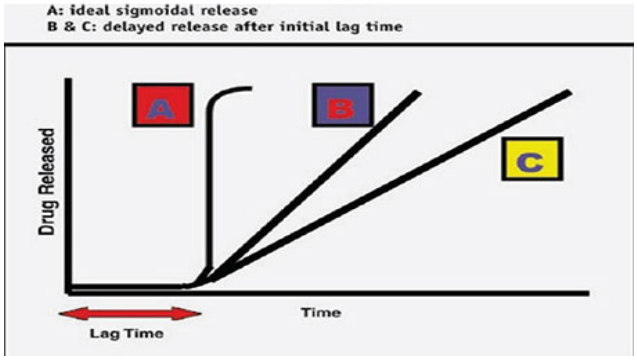

Figure 1: Drug release profile of pulsatile drug delivery systems.

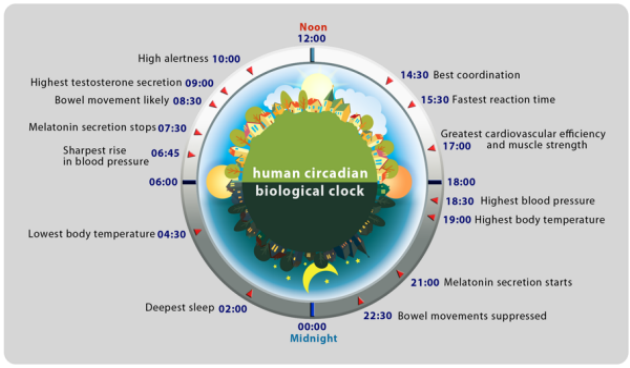

Figure 2: Human circadian biological clock.

Single unit system

i. Capsular system

ii. Port system

iii. Delivery by solubility modulation

iv. Delivery by reservoir systems

Multi-particulate system

i. Pulsatile system based on rupturable coating (Time controlled expulsion system)

ii. Pulsatile delivery by change in membrane Permeability

iii. Sigmoidal release system

iv. Low density floating multiparticulate pulsatile systems

Stimuli induced

Internal stimuli induced pulsatile system

i. Temperature induced system

ii. Chemical stimuli induced system

iii. pH sensitive drug delivery system

External stimuli induced system

i. Electrically stimulated Pulsatile system

ii. Magnetically stimulated Pulsatile system

iii. Ultrasonically stimulated Pulsatile system

Pulsicap system: It consists of a water insoluble capsule body filled with the drug and a cross-linked hydrogel plug which swells upon contact with dissolution medium or gastro intestinal fluids pushing it out of the capsules shown in Figure 3 [15,16].

Port systems: It consists of a gelatine capsule in a cellulose acetate semi permeable membrane and inside insoluble plug and osmotically active ingredient along with the drug. When it imbibes the gastric fluids resulting in increased inner pressure that ejects the plug after a lag time shown in Figure 4 [17].

Delivery by solubility modulation: Systems composites of modulated agents sodium chloride and drug, lesser amounts of NaCl is required to maintain saturated fluid entering the osmotic device which facilitates pulse release [18].

Delivery by reservoir system with erodible or soluble barrier coatings: Barrier layer was coated over to the reservoir device of pulsatile drug delivery where the barrier erodes or dissolves after a specific lag period enabling the drug to get released rapidly from the reservoir core [19].

Multiparticulate system: Drug release from these systems depends on parameters such as type of coating, pH dependent coating, insoluble coating under all physiological conditions influences the solubility changes at some point in G.I. tract and facilitates slow erosion [20].

Reservoir with rupturable polymeric coating or time controlled explosion system: Super-disintegrants incorporated in as swelling agents facilitating the time burst release of particulates upon ingress of water. Initially the drug coated on non-peril seeds followed by a swellable layer and an insoluble top layer coating [21,22]. In vitro in vivo correlation studies reported that time controlled explosion systems with a lag time of 3 hrs appearance of drug in blood and maximum release noted after 5 hrs [23].

Sigmoidal release systems: It consists pellets comprising of different acids such as succinic acid, acetic acid, glutamic acid, malic acid, citric acid, coated with ammonia methacrylate copolymer usp/nf type b. water influx turns the drug core to acid solution in turn increases the permeation of the hydrated polymer film [24].

Low density floating multiparticulte pulsatile systems: Especially for the drugs having absorption window in the stomach low density floating micro particle pulsatile dosage forms retain the drug in stomach for a longer period and not influencing by the pH fluctuations and gastric emptying [25].

Thermoresponsive pulsatile release: Hydrogels at their transient temperatures undergo substantial reversible volume changes in response to change in temperature. Among the various polymers available N-isopropylacrylamide is probably the most extensively used [26].

Chemical stimuli induced pulsatile release: Stimuli sensitive delivery systems release the drug in presence of biological factors like enzymes, pH or any other chemical stimuli example; Development of a gel composed of poly-N-isopolycrylamide with phenylboronic acid moieties that showed a remarkable change in the swelling induced by glucose [27].

pH sensitive drug delivery systems: pH dependent polymers enabled the drug to release in the desired pH range such as eudragit, pthallates, carboxy methyl cellulose, methacryllic acid especially polymers like eudragit L and S favoured the colon targeting [28,29].

Electro responsive pulsatile release: Drug release is facilitated by the action of applied electric field on rate controlling membrane containing polyelectrolytes [30-32].

Magnetically induced pulsatile system: With the incorporation of magnetic materials such as magnetite, iron, nickel, cobalt in to capsule or tablets by the external influence of magnetic field shown in Figure 5. We can position drug at a specific place or slow down its access to unwanted sites thus changing the time or extent of drug absorption in to stomach or intestine [33-35].

Ultrasonically stimulated: Interaction of Ultrasound With biological tissues, improving the drug permeation through biological barriers, such as skin. Mechanism mainly involved here is the absorption of acoustic energy by the fluids or tissues and oscillating bubbles cause non thermal effect along with the non cavitational effects such as radiation pressure, radiation torque and acoustic streaming [36] (Table 1, 2 and 3).

Evaluation of pulsatile drug delivery system

Tablet thickness and diameter: Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Vernier calipers [63,64].

Hardness: This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this six tablets were selected at random and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2 [65,66].

Friability: The friability test was carried out to evaluate the hardness and stability instantly in Roche Friabilator. The percent loss in weight or friability (F) was calculated by the formula [67,68].

$F= (1-W/Wo) \times 100$

F=friability

Wo=initial weight

W=final weight

Weight variation: This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range. This is done by sampling randomly and weighing 20 tablets and average weight is calculated.

Content uniformity: This test is performed to maintain the uniformity of weight of active ingredient in each tablet which should be in the prescribed range according to the Indian Pharmacopoeia. This test is performed by taking twenty tablets randomly, weighed and powdered. A quantity of powdered tablet was dissolved in 0.1 N HCl in 100ml volumetric flask. It was diluted and the absorbance was measured at fixed wave length using 0.1 N HCl as blank and the % drug content was estimated.

***In vitro* buoyancy determination:** The floating characteristics of the GFDDS are essential, since they influence the in vivo behaviors of the drug delivery system. However there seemed to be no threshold value for the floating system to remain afloat under a physiological condition due to the latter's complication.

Floating lag time: The time taken by the tablet to emerge onto the surface of the liquid after adding to the dissolution medium at pH 1.2, temperature 37 ± 0.5°C, paddle rotation at 50 rpm.

Total floating time: The time taken by the tablet to float constantly on the surface of the Gastric fluid without pepsin, at pH 1.2, temperature 37 ± 0.5°C, paddles rotation at 50 rpm.

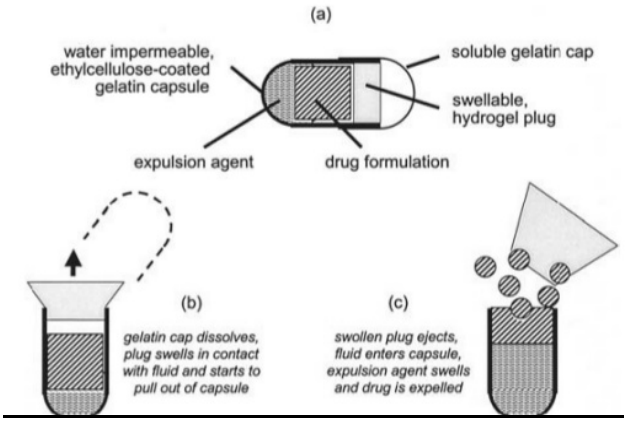

Figure 3: Pulsicap system.

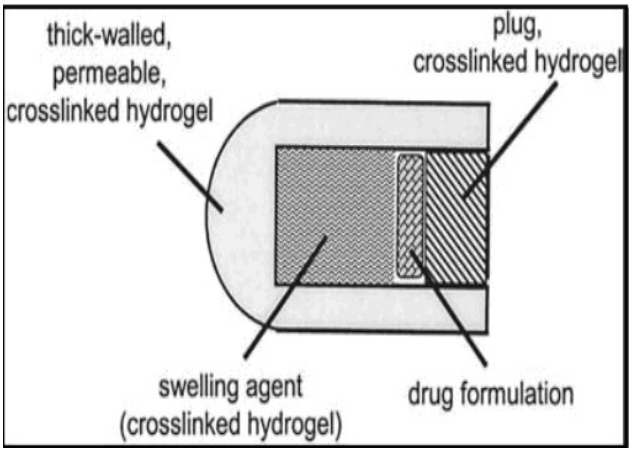

Figure 4: Port systems.

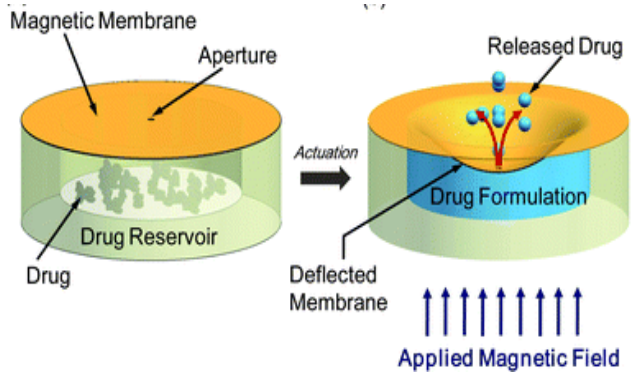

Figure 5: Drug release from magnetically induced pulsatile systems.

***In vitro* dissolution studies** [69]**:** Dissolution studies were carried out using USP XXIV dissolution apparatus (rotating paddle method-2). The collected samples were suitably diluted with dissolution fluid wherever necessary and were analyzed for the drug by using a double beam UV spectrophotometer.

Technology	Rationale	Products	Company
CONTIN®	Drug blended with hydrophilic cellulose, then hydrated with polar solvent and fixed with a higher aliphatic alcohol to produce a semi-permeable matrix with uniform porosity.	Uniphyl® once daily theophylline MS Contin® and Oxycontin® for use in pain management.	Purdue Frederick, Norfolk, CT, USA
CODAS®	Chronotherapeutical oral drug absorption system consisting of drug loaded beads that are coated with release-controlling polymer. Polymer consists of water-soluble and water-insoluble polymers to induce a lag time.	Verelan® PA containing verapamil for use in hypertension	Elan Drug Technologies, San Francisco, CA, USA
CEFORM®	Biodegradable polymers/bioactives are subjected to varying temperature, thermal gradients and flow processes to produce microspheres of uniform size and shape (150-180µm)	Cardizem® LM containing diltiazem for use in hypertension.	Fuisz Technologies, Chantilly, VA, USA
DIFFUCAPS®	A multiparticulate system consisting of an inactive core, coated with an active pharmaceutical ingredient mixed with a water-soluble composition. This may be in the form of beads, pellets or granules.	Innopran® XL containing Propranolol for use in hypertension.	Eurand Pharmaceuticals LTD, Dayton, Ohio, USA
GEOMATRIX®	The controlled release is achieved by constructing a multilayered tablet made of two basic key components; 1) hydrophilic polymers such as hydroxypropyl methycellulose (HPMC) and 2) surface controlling barrier layers. Active loaded core surface that is available for drug relase when exposed to the fluid is controlled by barrier layers.	Sular® (nisoldipine CR) and Coruno® (molsidomine)	SkyePharma, Muttenz, Switzerland
TIMERx®	A novel polysaccharide system that adopts the use of xanthan gum and locust bean gum in the presence of secondary and tertiary components, to form water-soluble granules.	'Tablet within a tablet' to obtain different chronotherapeutic profiles. Geminex® is an improvement which provides the potential for dual therapy.	Penwest Pharmaceuticals, Danbury, CT, USA
OROS®	As osmotic pump system comprising a central drug reservoir surrounded by a semi-permeable membrane, which is surrounded by osmotically active agents in tablets with a strategically laser-drilled orifice.	Covera® HS containing verapamil for use in hypertension	Alza Corporation, Mountainview, CA, USA
PULSINCAP®	Consists of a drug reservoir housed within a water-soluble capsule body. The open end is plugged with swellable polymers that are pushed out when in contact with fluid, releasing drug from the reservoir.	A versatile system that can create lag times as well as allowing tablets/ minitablets, solutions or beads to be housed within the capsule body.	R.P. Scherer International Corporation, Troy, MI, USA
PULSYSTM	A novel pulsatile release technology that consists of one immediate-release and two delayed-release components with the use of soluble and insoluble coatings.	MoxatagTM containing amoxicillin for use in antibiotic therapy.	Middlebrook Pharmaceuticals, Westlake, Texas, USA

Table 1: Marketed products of chronotherapeutic drug delivery systems [37].

Mode of drug delivery	Title (number)	Rationale for chronotherapy and features of patented systems
Oral tablet based	IR gastrointestinal drug delivery system (US6531152)	Diseases of alimentary tract, system able to release drug at specific locations within GIT [38,39].
Oral tablet based	Pulsatile particles drug delivery system (US5260069)	Hypertension, unit dosage form for delivering drugs into the body in a series of sequential, pulsatile fashion. The system can be used with drugs that cannot be released by diffusion through a porous coating such as Water-insoluble drugs [40].
Oral tablet based	Pharmaceutical compositions (US4897270)	Infection of gram-positive and gram-negative microorganisms, conventional film-coated tablets reduce the bioavailability of cefuroxime axetil and the invention overcomes this by control of the film coat rupture time and use of a tablet core, which disintegrates immediately following rupture of the film coat [41].
Oral tablet based	Pharmaceutical tablet suitable to deliver the active substance in subsequent and pre-determinable times (US6294200)	Gastroesophageal reflux disease, Pharmaceutical tablet dosage form, capable of delivering the active substance with three pulses to a pre-determinable release profile [42].
Oral tablet based	Delayed total release two pulse gastrointestinal drug delivery system (US6632451)	Analgesic and anti-inflammatory, a two pulse delivery device for delivering one or more active agents at colon [43].
Oral tablet based	Press coated pulsatile drug delivery system suitable for oral administration (US6372254)	Anti-inflammatory, a press coated pulsatile drug delivery system with an immediate release and an extended release compartment with TPR [44].
Oral tablet based	Multi-unit delivery system (US5110597)	Helminth infections, system provides pulsed delivery of a single drug or different drugs or drug formulations suited to the delivery of pharmacologically. Especially suited for active peptides and protein anabolic hormones [45].
Oral tablet based	Controlled release flutamide composition (US5162117)	Prostate cancer, invention provides controlled release form which is designed to provide an IR dose and a second pulsed delayed release dose [46].
Capsule based (delivery device with orifice)	Delivery devices with pulsatile effect (EP0627231)	Invention lies in the field of pulsatile delivery of drugs, nutrients. The pulsatile effect achieved by parameters as choice of elastic material for the band, the thickness of the band made from the elastic material, the configuration and location of the orifice, and the viscosity and surface tension of the active agent formulation [47].

Transdermal device	Pulsating transdermal drug delivery system (US5013293) Pulsating transdermal drug delivery system (US5312325)	Diabetes mellitus and cancer provide an electrophoretic/electro-osmotic transdermal drug delivery system that rhythmically delivers a therapeutic compound in response to application of current pulsations to the system [48,49].
Hydrogel system	Pulsatile drug delivery device using stimuli sensitive hydrogel (US 5226902)	Diabetes mellitus, invention relates to delivery of drug laden hydrogels which Deswell and gives pulsatile release of drugs in response to external or internal stimuli such as temperature or pH changes, or chemical reactions [50].

Table 2: Summarizes the patents the involving different types of pulsatile delivery systems with advanced formulation approaches.

Disease	Chronological behavior	Drugs used
Peptic ulcer	Acid secretion high in noon and at night	H_2 blockers [51]
Asthma	Precipitation of attacks during night or at early morning hours	B_2agonists,antihistamine [52-54]
Cardiovascular disease	BP is at its lowest during sleep cycle and rises in early morning	Nitroglycerine, Calcium channel blockers, Ace inhibitors [55-58].
Arthritis	Pain in the morning and more pain in the night	NSAIDS, glucocorticoids [59,60]
Diabetes mellitus	Increase in blood sugar level after meal	Sulfonyl urea, insulin, bioguanide [61].
Hypercholesterolemia	Cholesterol synthesis is generally high during night than day	HMG COA reductase inhibitors [62].

Table 3: Diseases requiring pulsatile drug delivery systems.

Water uptake study: The % water uptake of pulsatile release tablets was determined in medium filled container placed in a horizontal shaker (100 ml of 0.1 N HCl, 37.5°C, 74 rpm n=3) at predetermined time points, the tablets were removed from the dissolution medium. They were then carefully blotted with the tissue paper to remove surface water, then weighed and then placed back in the medium up to the time when the coating of the tablet ruptured. The % water uptake update was calculated as follow:

$$\% \text{ Water uptake} = [(Wt - Wo/Wo)] 100$$

where, Wt: Weight of tablet at time t and Wo: is weight of dry tablet.

Swelling index: The individual tablets were weighed accurately and kept in 50 ml of double distilled water. Then tablets were taken out properly after 60 min., then blotted with filter paper so as to remove the water present on the surface and weighed accurately. Percentage swelling index (SI) was calculated by using the formula

$$SI = (\text{Wet weight} - \text{Dry weight}/\text{Dry weight}) \times 100 \text{ [70]}$$

Rupture test: The Rupture test on coated tablets was carried out using USP paddle apparatus. Here all other Parameters were same as *In-Vitro* Dissolution Method. The time at which the outer coating layer starts to rupture is called as lag time. This was determined by Rupture test [71,72].

Conclusion

Rapid development in the field of drug delivery has led to the formulation of pulsatile drug delivery system, which delivers the drug at right time, place and amount in the patient's body. significant modification in the conventional delivery systems in the form of pulsatile delivery system ensures the time controlled pulsatile release of bioactive compounds which is prerequisite for chronotherapy. Sustained and controlled delivery keep the in vivo drug concentration in the therapeutic level for a prolonged period of time and this is essential but not sufficient for treatment of circadian rhythm diseases. Chronotherapy goal is to provide perfect therapy by strictly targeting the drug to specific site at most appropriate time. To correlate the biological rhythms the pulsatile drug delivery systems will play a key role by maintaining optimal concentrations at diseased state when required. Since the timing of drug administration in disease therapy has significant impact on treatment, chronopharmaceutics emerges as an important tool to overcome drug delivery problems and present a greater patient compliance.

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