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A Comprehensive Review of Pulsatile Drug Delivery System

Grover Chandani*[I], Bhatt Ganesh[1], Kothiyal Preeti[1]

1. Division of Pharmaceutical Sciences, S.G.R.R.I.T.S. Patel Nagar, Dehradun, Uttarakhand, India

Novel Oral Drug Delivery technologies have emerged and expanded into different drug delivery system with different drug release mechanisms.Sophisticated instrumentation,modern mathematical models and computation power have advanced the concept of drug delivery from a simple pill to a programmable time controlled smart system Pulsatile drug delivery system (PDDS) is the most interesting time - and site-specific system as per the patho-physiological need of the disease. This system is receiving increasing interest for the development of drugs for which conventional controlled drug release system with continuous release are not ideal. These drugs are having high first –pass effect or special chronopharmological needs. Pulsatile drug release profile is characterized by time period of no release (lag time) followed by a rapid and complete drug release. Diseases requiring PDDS includes asthma, peptic ulcers, cardiovascular diseases, arthritis, attention deficit syndrome in children and hypercholesterolemia. PDDS can be classified into: a) time controlled systems wherein the release of drug being controlled by the system itself (b) stimuli induced PDDS in which release is controlled by the stimuli like the pH or enzymes present in the intestinal tract or enzyme present in the drug delivery system (c) Externally regulated system in which the drug is handled and controlled by external stimuli like magnetism, irradiation, electric effect and ultrasound. Various systems like capsular systems, osmotic systems based on the use of erodible polymer or soluble coating, use of ruputurable membranes.

Keyword: Pulsatile Release,Chronotherapeutics,,Time Controlled System, pH Targeted Release.

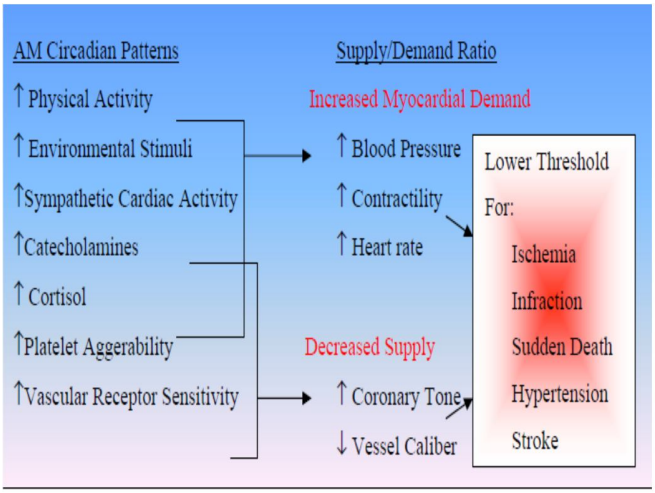
INTRODUCTION Controlled drug delivery systems aim to maintain plasma concentration of drugs within the therapeutic window for longer period of time, thereby to ensure sustained therapeutic action and for that reason an increasing interest in their development exist.

Corresponding Author's Contact information:
Grover Chandani *
Department of Pharmaceutical Sciences, S.G.R.R.I.T.S., Patel Nagar, Dehradun, India.
E-mail: chandanigrover@gmail.com

Several disease states have been proven to follow biological rhythms, expressed by short-, intermediate, and long-period oscillations. Circadian (24-h) time structure is most studied and rather the most common oscillation in a

number of pathological cases such as asthma where the crisis are mostly happening late at night, osteoarthritis where the pain is more intense again during night, rheumatoid arthritis where the pain peaks at the morning, duodenal ulcer where the highest gastric secretion is happening in the night times, neurological disorders such as epilepsy where the oscillations are following melatonin secretion, hypercholesterolemia where the cholesterol synthesis is higher during the night and several cardiovascular diseases such as cardiac and/or platelet aggregation. Diseases with time structures other than circadian rhythm are also possible, for example,diabetes is following the secretion of insulin stimulated by meal, or tumour growth in cancer states that follows body changes in blood flow. Menstrual cycle and the corresponding
hormonal flux are also following cyclic patterns.Pulsatile delivery systems aim to deliver a drug via theoral route at a rate different than constant, (i.e. zero order Pulsatile Release).[1-6]

Fig 1 : Possible Causes of Morning Increase In the Incidence of Coronary:



Pulsatile Drug Delivery System are gaining a lot of significance as the drug is released completely after defined lag time. Pulsatile Delivery provides special and temporal relief increasing patient compliance.[7]

PDDS is being defined as the rapid and transient release of certain amount of molecules within short time period after a predetermined lag phase.[8]

PDDS gaining importance / relevance in following situations:

1. Avoidance of the degradation in upper GIT e.g. – proteins and peptides.
2. Chronopharmacotherapy of diseases showing circadian rhythms in their pathophysiology.[9]
3. For drugs which exhibit biological tolerance (which can't be delivered at a constant rate since, the drug effect decreases with time of constant drug level) For drugs with extensive first-pass metabolism.
4. For time-programmed / dependent administration of harmones and many drugs such as isosorbide dinitrate .[10]

ADVANTAGES of PDDS:

1. Nearly constant drug levels at the site of action.
2. Avoidance of undesirable side effects.
3. Reduced dose.
4. Improved patience compliance.
5. Used for drugs with chronopharmacologcal behavior.
6. No risk of dose dumping.
7. Improved bioavailability,tolerability and reduces side effects.[11]

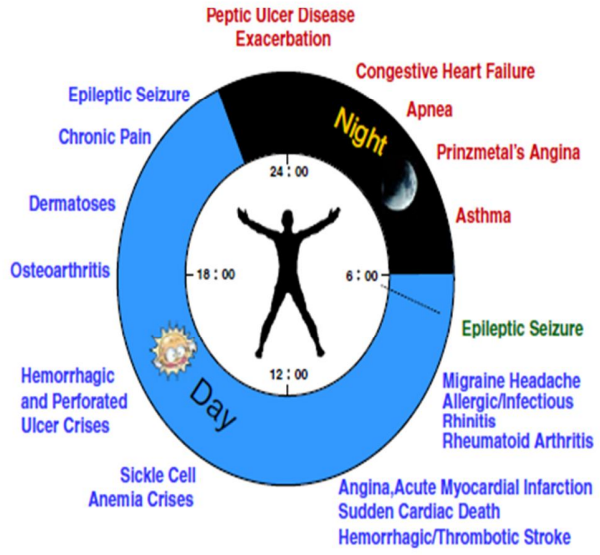
LIMITATION:

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.

Circardian Rhythm and Manifestation of Clinical Disease:fig 1,2 :

Diseases	Circardian Rhythmicity	Drug Used
Peptic Ulcer	Acid secretion is high in the afternoon and at night	H_2 Blockers
Arthritis	Pain in the morning and more pain at night.	NSAIDS, Glucocorticoids
Diabetes mellitus	Cholesterol synthesis is during night than during day time	Biguanide. HMGCOA reductose inhibitors
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during early morning awakening period	Nitroglycerine, Calcium+ channel blockers, ACE inhibitors
Attention deficit syndrome	Increase in PUPA level in the afternoon	Methyl phenidate
Asthma	Precipitation of attacks during night or at early morning hours.	B2agonist, antihistaminics

Fig 2 :Clinical Rhythm and Manifestation of Clinical Diseases:



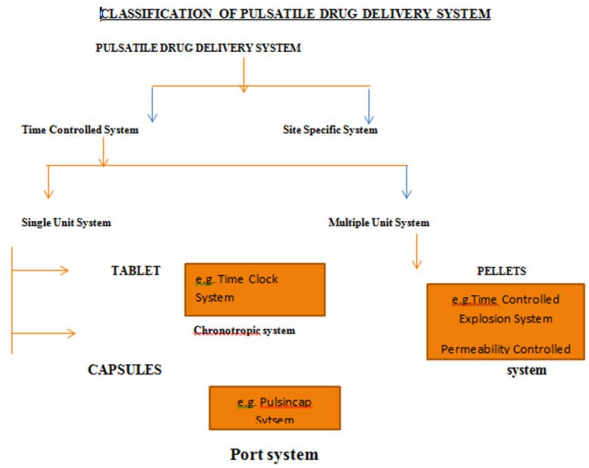
METHODS OF DEVELOPMENT OF PULSATILE DRUG DELIVERY SYSTEM:[12,13]

Different approaches of Pulsatile system

- **Time Controlled system**
- **Internally stimuli induced system**
- **Externally Regulated System**
- **Multiparticulate System**

Summarization of Methods:

1.Time controlled pulsatile release system.: fig 3



In time controlled drug delivery systems pulsatile release is obtained after 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. Various methodologies that can used for time controlled pulsatile release systems are discussed in following section[13]

- **By Solubilization or Erosion of Layer**:In such section,the core containing drug is coated is coated with erosion or soluble polymers and drug released is controlled by dissolution or erosion of outer coat.Time dependent release of drug can

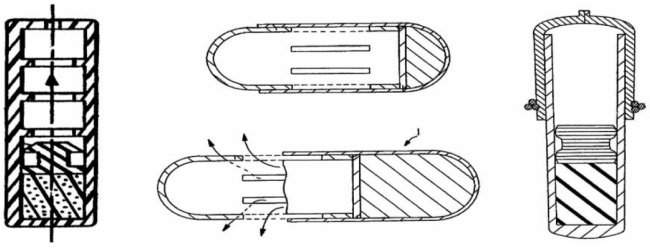
be obtained by obtimizing the thickness of outer coat.[14]

- **Pulsatile Delivery By Rupturing of membrane:**These system are dependent on disintegration of coating for release of drug.The pressure necessary for rupturable for coating can be achieved by swelling,disintegration,effervescent excipients, or osmotic pressure.Water permeation and mechanical resistance of the outer membrane are two important factors affecting the lag time.[15,16]

- **Capsule Shaped System provided with Release Controlling Plug:**These system contains the release controlling plug between immediate release compartment and pulse release compartment.On contact with aqueous fluids, the cap rapidly dissolves thereby releasing the immediate release component followed by pulsed release component.[18,19]

- **Pulsatile System Based on Osmosis:** Osmotic System contains a capsule coated with semipermeable membrane.Inside the capsule there is an insoluble plug consisting of osmotically active agent and the drug formulation.shown in fig 4.

Fig 4 : Osmotic Pumps Used In Pulsatile Drug Delivery System: mechanism by Osmosis

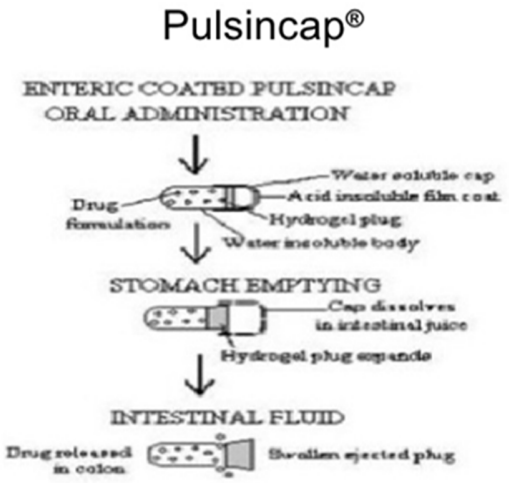


2.Stimuli Induced System:

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 system and chemical stimuli induced system, on the basis of stimulus.fig 5

In these system there is a release of drug after stimularion by any biological factor like temperature or any other chemical stimuli These system are further classified into Temperature Induced system and chemical stimulated Induced system on the basis of stimulus.These are of following types.[20,21]

- Temperature induced Pulsatile Release
- Themoresponsive hydrogel system
- Thermoresponsive polymeric micelle system
- Glucose responsive insulin release Devices lik Pulsincap system
- pH sensitive Drug delivery system
- Inflammation induced Pulsatile release



- **pH Dependent 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. Examples of pH dependent polymers includes cellulose acetate phthalate,polyacrylates, sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine.

➢ Externally Regulated System

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. Magnetically regulated system contain magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads. In case of ultrasonically modulated systems, ultrasonic waves causes the erosion of the polymeric matrix thereby modulating drug release**.**It includes**:**

Magnetic induces release
Light induces release
Electric induces release
Ultrasound induces release

- **Magnetically Induced System:**

Magnetically regulated system contain magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads. Saslawski et al. developed different formulation for in vitro magnetically triggered delivery of insulin based on alginate spheres.

- **Ultrasonically Induced System**:
  Ultrasound is mostly used as an enhancer for the improvement of drug permeation through a biological barrier, such as skin, lungs, intestinal controlled drug delivery. Kost and coworkers depicted anultrasound-enhanced polymer. Miyazaki et al. used ultrasound to achieve up to a 27-fold increase in the release of 5-fluorouracil from an ethylene and vinyl acetate (EVAc) matrix. Increasing the strength of the ultrasound resulted in a proportional increase in the amount of 5-fluorouracil released.

4.Multiparticulate System:

These system are reservoir type system with either rupturable or altered permeability coating and generally housed in Capsular body.A rupturable pulsate,e drug delivery system consist of (a) drug core (b) swelling layer comprising of a superdisintegrant and a binder (c) an insoluble water permeable polymeric coating.

RECENTLY AVAILABLE CHRONOPHARMACEUTICAL TECHNOLOGIES:

- OROS TECHNOLOGY based on osmotic mechanism
- CEFORM TECHNOLOGY
- CONTINR TECHNOLOGY
- DIFFUCAPS TECHNOLOGY- Multiparticulate system
- CHRONOTOPIC TECHNOLOGY
- Time RX TECHNOLOGY- TIME CONTROLLED SYSTEM
- PULSINCAP-Rupturable system

COMMERCIAL PRODUCTS:

1. Pulsys-amoxycillin-Advancis Pharm Corp.
2. Uniphyl-Theophylline-Purdue Pharm Pdts
3. Ritalin β-methylphenidate-Novartis
4. CODAS-Verapamil HCL
5. TIMER X- Oxymorphone
6. Pulsincap TM-Dofetililde

CONCLUSION

It can be concluded that Pulsatile drug delivery system offers better delivery of drugs possessing chronopharmacological behaviour,extensive first pass metabolism, necessity of night time dosing,or absorption window in GIT.Pulsatile drug delivery system shall be promising in future.

CURRENT AND FUTURE DEVELOPMENT:

The future of chronotherapeutics and more specifically the future of delivering drugs in a pulsatile manner seems to be quite promising as in certain diseases states pulsatile release exhibit several advantages over the traditional zero or first order drug delivery mechanism.

Pulsatile drug delivery system can either be time controlled or site specific single or multiple units. At a moment pulsatile release (site or time specific) most often is achieved by using different polymers in coating layers or by changing the coating thickness.

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