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INNOVATIVE APPROACHES FOR PULSATILE DRUG DELIVERY SYSTEM

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Abstract:

With the advancement of the technologies in the pharmaceutical field, drug delivery systems have drawn an increasing interest over the last few years. Nowadays, the importance of pharmaceutical galenic research is turned towards Chronopharmaceutical drug delivery systems (CDDS) as they deliver the drug at the right site of action at the right time and in the right amount based on circadian rhythms, thus providing spatial and temporal delivery and increasing patient compliance. Sustained and controlled drug delivery system release the drug at a substantially steady rate of release per unit of time. However, there are instances where maintaining a constant blood level of a drug is not desirable. In such cases a pulsatile drug delivery may be more advantageous. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the lag time. The aim of this current review is to describe, the diseases requiring CDDS, methodologies involved for the existing systems and more focus on the time induced and stimuli induced methodologies, recent update and CDDS product currently available in the market.

Keywords: *Pulsatile, lag time, circadian rhythm, time induced, stimuli induced*

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INTRODUCTION:

The term "Chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Researchers have recently concluded that both disease states and drug therapy are affected by a multitude of rhythmic changes that occur within the human body [1]. Pulsatile drug delivery systems are gaining a lot of interest and attention these days. These systems have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release."[2] Though most delivery systems are designed for constant drug release over a prolonged period, pulsatile delivery systems are characterized by a programmed drug release, as constant blood levels of a drug may not always be desirable [Fig - 1]. However, only a few such orally applicable pulsatile release systems are available due to potential limitations of the dosage form size, and/or polymeric materials and their compositions used for producing such dosage forms [3]. Such a novel drug delivery has been attempted for the following diseases listed in [Table 1][4].

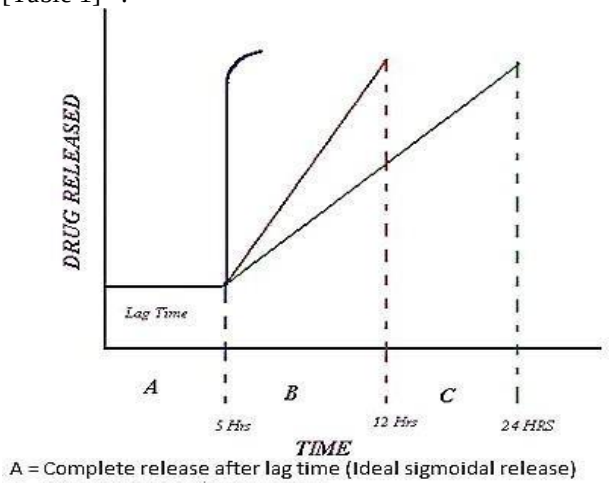

Fig: 1.1Drug Release Profile of Pulsatile Drug Delivery System

Pulsatile devices may have many applications in areas of other medicine where a constant rate of drug release does not match the physiological requirements of the body. This is often the case when treatments involve hormone-based drugs. Secretion of many hormones exhibits pulsatile patterns comprising frequent pulses over periods from hours to weeks [5], so it is more effective to mimic this with a synthetic delivery system. Current research in the field of drug delivery devices, by which triggered and/or pulsatile release is achieved, has been intensified.

Need for chrono pharmaceutical drug delivery system [6]

There are many conditions and diseases where sustained release formulations don't show good efficacy.

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

- First pass metabolism
- Biological tolerance
- Special chronopharmacological needs
- Local therapeutic need
- Gastric irritation or drug instability in gastric fluid
- Drug absorption differences in various gastrointestinal segments

Table 1: Diseases requiring Pulsatile Drug Delivery

Disease	Chronological behaviour	Drugs used
Arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
Asthma	Precipitation of attacks during night or at early morning hour	β2agonist, Antihistaminics
Attention deficit syndrome	Increase in DOPA level in afternoon	Methylphenidate
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period	Nitroglycerin, Calcium channel blocker, ACE inhibitors etc.
Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
Peptic ulcer	Acid secretion is high in the afternoon and at night	H_2 blocker
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time	HMG CoA reductase inhibitors
Antiretroviral therapy	Protecting the drug from degradation in regions of gastric or upper intestinal mucosa or drugs with extensive first pass metabolism	Acyclovir , Ritonovir

METHODOLOGIES FOR PULSATILE DRUG DELIVERY

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

1. Time controlled
2. Stimuli induced
3. Externally regulated

1.Time controlled pulsatile release system

In time controlled drug delivery systems, 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.

Various methodologies that can be used for time controlled pulsatile release systems are following

1. Pulsatile system based on Osmosis
2. Capsule shaped system provided with release controlling plug
3. Delivery systems with rupturable coating layer
4. Delivery system with erodible coating layers

1.Pulsatile system based on Osmosis[7]

Osmotic system consists of capsule coated with the semipermeable membrane. Inside the capsule was an insoluble plug consisting of osmatically active agent and the drug formulation. When this capsule came in contact with the dissolution fluid, the semipermeable membrane allowed the entry of water, which caused the pressure to develop and the insoluble plug expelled after a lag time. Such a system was utilized to deliver methylphenidate used in the treatment of attention deficit hyper activity disorder as the pulsatile port system.[8,9]

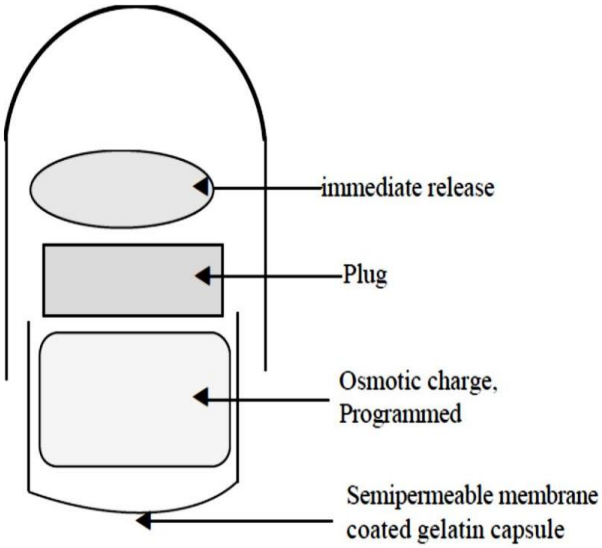

Fig.2 Schematic diagram of osmosis system

Capsule shaped system provided with release controlling plug[10]

- Single-unit systems are mostly developed in capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion, and the drug is released as a "pulse" from the insoluble capsule form the capsule body.
- This dosage form consists of an insoluble capsule body containing a drug and swellable

and degradable plugs made of substances such as hydrophilic polymers or lipids.

- The lag time can be controlled by manipulating the dimension and the position of the plug.
- Polymers used for designing of the hydro gel plug includes:
- Insoluble but permeable and swellable polymers(eg:polymethacrylate)
- Erodible compressed polymers(eg: hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide)
- Congealed melted polymers(eg: saturated polyglycolated glycerides, glyceryl monooleate)
- Enzymatically controlled erodible polymer (eg: pectin**)**

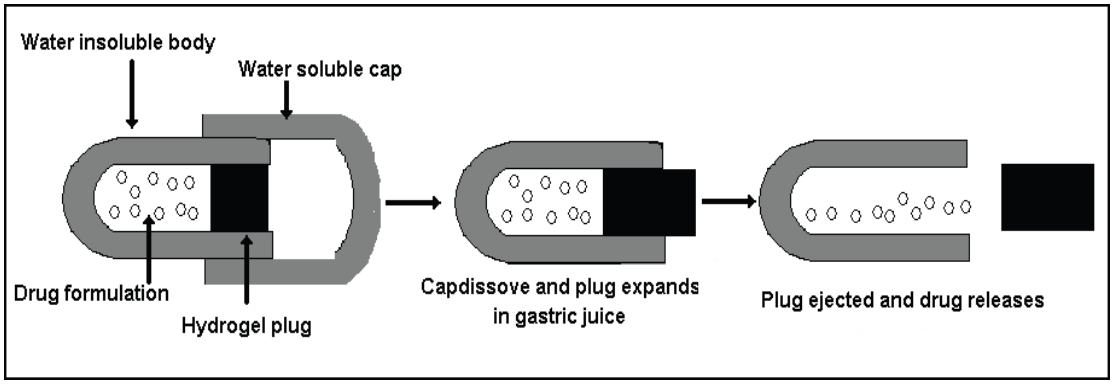

Fig:3 Schematic diagram of release of drug from capsule

Delivery systems with rupturable coating layer [11]

Factors in place of swelling or eroding, these systems are dependent on the disintegration of the coating for the release of drug. The pressure necessary for the rupture of the coating be achieved by the swelling, disintegrants, effervescent, excipients, or osmotic pressure. Water permeation and mechanical resistance of the membrane are major affecting the lag time.

Eg: BuflomediHcl is used for treatment of peripheral.

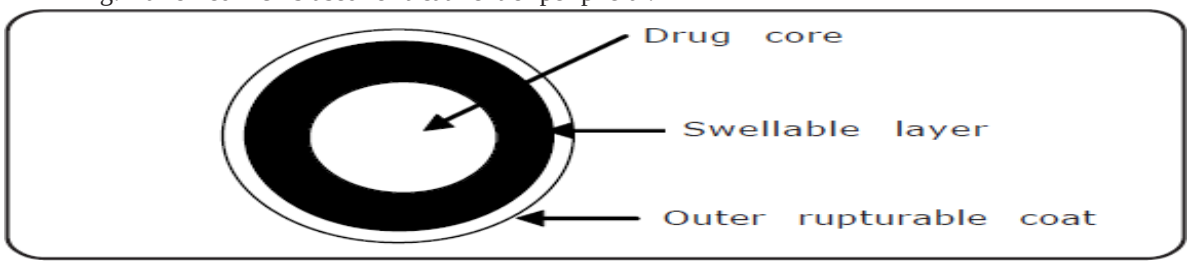

Fig:4-Schematic diagram of drug delivery with rupturable coating layer

Delivery system with erodible coating layers[12]

In such systems, the core containing drug is coated with the soluble or erodible polymer as outer coat and the drug release is controlled by the dissolution or erosion of the outer coat.

Time dependent release of the drug can be obtained by optimizing the thickness of the outer coat as shown in fig 5.

Ex: The time clock system and the chronotropic system.

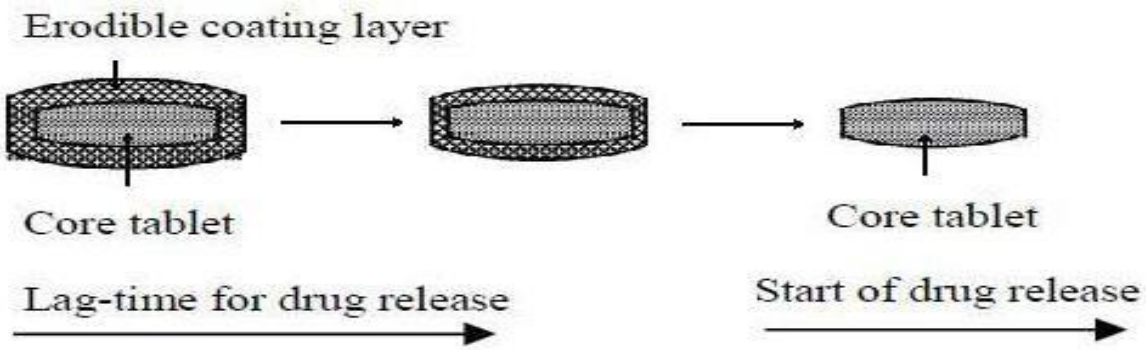

Fig:5 Schematic diagram of drug delivery with erodible coating layer

2. Stimuli induced pulsatile release system [13]

In these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli [14]. These systems are further classified as:

Temperature induced systems:

The temperature induced pulsatile/triggered drug delivery systems utilize various polymer properties, including the thermally reversible coil/globule transition of polymer molecules swelling change of networks, glass transition and crystalline melting [15].

Thermo responsive hydrogel and polymer systems

Thermally responsive hydrogels and membranes have been extensively exploited as platforms for the pulsatile drug delivery.

In these systems the polymer undergoes swelling or de-swelling phase in response to the temperature which modulate drug release in swollen state [16].

Eg: Y.H. Bae et al developed indomethacin pulsatile release pattern in the temperature ranges between 200C and 300C by using reversible swelling properties of copolymers of N-isopropyl acrylamide and butyryl acrylamide [17].

Chemical stimuli induced pulsatile system

Glucose-responsive release devices [18]

In a glucose-rich environment, such as the blood stream after a meal, the oxidation of glucose to gluconic acid catalysed by glucose oxidase can lower the pH to approximately 5.8. This pH change includes 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-Dimethylaminoethylmethacrylate, chitosan, polyol etc.

Inflammation-induced pulsatile release

During inflammation, hydroxyl radicals are produced from these information-responsive cells. Degradation via hydroxyl radicals however, is usually predominant and rapid when hyaluronic acid gel 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 [19].

Drug release from intelligent gels responding to antibody concentration

There are great in number 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/deswelling characteristics. Special attention was given to antigen-antibody complex formation as the cross-linking units in the gel, since such interaction is very specific [20]. Utilising the difference in association constant's between polymerised antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/deswelling and drug permeation changes occurs [21].

pH sensitive drug delivery system

This type of PDDS contains two components. The first is fast release type while the other 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 [22]. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetatephthalate, poly acrylates, sodium carboxy methyl cellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine. Eg: Eudragit in colon target systems .

3. Externally regulated systems

The externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation in order to release the drug in a pulsatile manner [23].

Advantages of chronopharmaceutical drug delivery system [24]

- Predictable, reproducible and short gastric residence time.
- Bioavailability is increased.
- Not only less inter but also intra-subject availability.
- Reduce side effects, reduced dosage frequency, Reduction in dose size and patient compliance.
- Increases absorption and bioavailability than conventional immediate release or sustained released drugs.
- Lower daily cost to patient due to fewer dosage unit are required.
- Drug adapts to suit cardiac rhythms to body function or disease.

Limitations of chronopharmaceutical drug delivery system [25]

- Lack of manufacturing reproducibility and efficacy.
- Technologies employed and the equipment's used are complicated.
- Multiple manufacturing steps and large number of process variables.
- In vivo variability in single unit pulsatile drug delivery system.
- Homogeneity coated barrier is mandatory to assure the predictability of lag time.
- Higher cost of production as need of advanced technology.
- Immediate withdrawal of drug is not possible.

CONCLUSION:

It can be concluded that there is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Chronopharmaceutical drug delivery system offers a solution for delivery of drugs exhibiting chronopharmacological behavior, extensive first pass metabolism, necessity of night time dosing at right time, right place and in right amounts. These systems can effectively treat diseases with non-constant drug therapies such as diabetes, asthma, arthritis etc. These considerations should ensure that the current high level of interest in this area would stretch well in to future and ensure in the betterment of quality of life.

List of the marketed pulsatile drug delivery technologies used:

S.No	Registered trademak ®	Drug	Chrono pharmaceutical technology®	Indications for chronotheraphy	References
1	Sanctura XR	Trospium chloride	Pellet coating technology	Overactive bladder (OAB) symptom	Chancellor M *et al*[26]
2	Invega	Paliperidone	OROS technology	Schizophrenia	Pani L *et al*[27]
3	Cardizem LA	DilitiazemHCl	CEFORM microsphere technology	Hypertension	Ezeugo,U *et al*[28]
4	Seroquel XR	Quetiapinefu m arate	Hydrophilic matrix technology	Depressive Disorder	Weisler R *et al*[29]
5	Glumetza	Metformin HCl	AcuForm technology	Type II diabetes	Schwartz SL *et al*[30]
6	Cystrin CR	Oxybutynin HCl	TIMERx technology	Urinary incontinence	Julian F. Guest *et al*[31]
7	Ritalin LA	Methylphenid ate HCl	SODAS technology B	Attention deficit hyperactivity disorder	Biederman J *et al*[32]
8	Coruno	Molsidomine	Geomatrix technology	Chronic angina pectoris	André Herchuel z *et al*[33]
9	Covera-HS	Verapamil HCl	OROS technology	Hypertensio	Smith DH *et al*[34]

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