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PULSATILE DRUG DELIVERY SYSTEM-A NOVEL APPROACH

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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. Pulsatile drug delivery aims to release drugs on a programmed pattern i.e.: at appropriate time and/or at appropriate site of action. Pulsatile drug delivery systems administered via the oral route could be divided into two distinct types, the time controlled delivery systems and the site-specific delivery systems. These systems are designed according to the circadian rhythm of the body. According to Latin literature *Circa*means Day and *Dian* means night. This drug delivery system is programmed drug delivery system in harmonization with body clock. Pulsatile drug delivery system divided into 2 types preplanned systems and stimulus induced system. basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastro-intestinal motility, etc. The simplest pulsatile formulation is a two layer press coated tablet consisted of polymers with different dissolution rates. Homogenicity of the coated barrier is mandatory in order to assure the predictability of the lag time. Diseases wherein PDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, and attention deficit syndrome in children, cancer, diabetes, and hypercholesterolemia. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.

INTRODUCTION

Over the last 30 years the pharmaceutical market has been demonstrated increasing preferably for controlled and targeted drug delivery system.(1) Such systems have been focused on constant, variable; sustain drug release and/or targeting the therapeutic agent to a specific site/tissue/ organ.(2) However, recently there are certain conditions for which such release pattern is not suitable. Such conditions that lead to the requirements of a time programmed therapeutic system, which capable of releasing drug after predetermined time delay and maintain constant drug levels throught the day.(3).Nowadays, concept of chronopharmaceutics has emerged, wherein, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy(5) Diseases where a constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of "Pulsatile Drug Delivery Systems . In these systems, there is rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off release period. Various techniques are available for the pulsatiledelivery like pH dependent systems, time dependent systems, micro-flora activated systems, etc. which can be designed as per the physiology of disease and properties of the drug molecule.These dosage forms have to be administered repetitively to maintain the drug concentration within therapeutically effective range. This repeated administration may result in fluctuating drug levels in the plasma. Controlled drug delivery systems have been introduced to overcome this drawback of fluctuating drug levels associated with conventional dosage forms.(6)

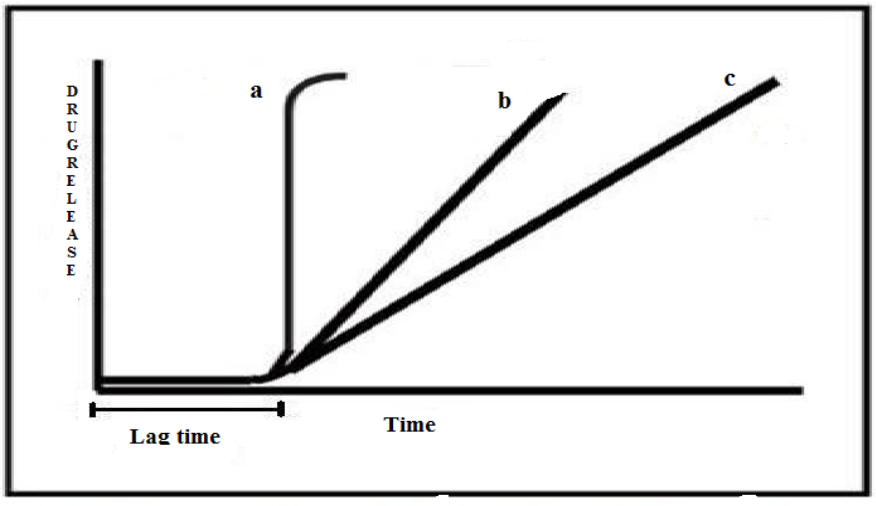

Figure 1:Drug release(a) pulsatile,(b)&(c) conventional

There are three types of mechanical rhythms in our body(7)

They are:

i. Circadian

ii. Ultradian

iii. Infradian

Circadian: This word comes from Latin word "circa" means about and "dies" means day

Ultrdian: Oscillation of shorter duration are termed as ultradian (more than 1 cycle per 24 h)

Infradian: Oscillations that are longer than 24 h (less than one cycle per day)Diseases where a constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of "Pulsatile Drug Delivery Systems"

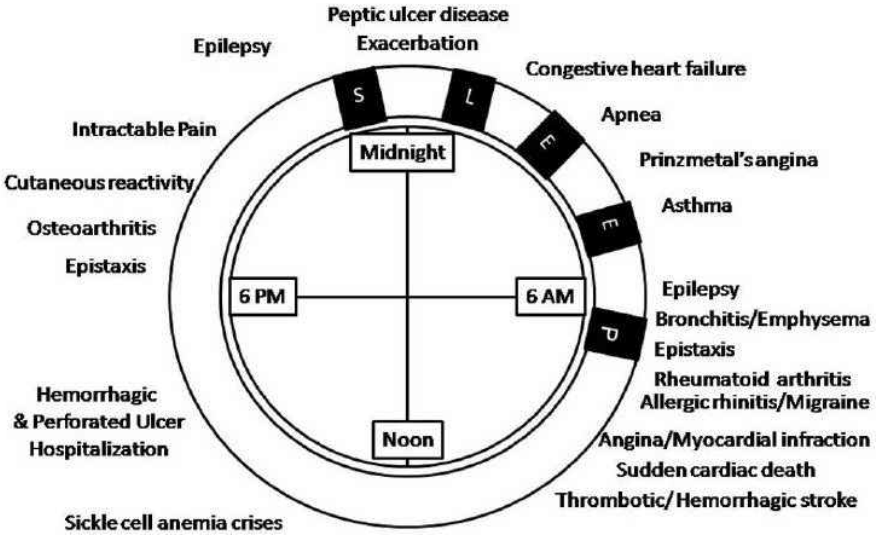

Figure. 2: Cycle of circadian rhythm

Advantages and drawbacks of pulsatile drug delivery systems:

Advantages:

- Predictable, reproducible and short gastricresidence time
- Less inter- and intra-subject variability
- Improve bioavailability
- Reduced adverse effects and improved tolerability
- Limited risk of local irritation
- No risk of dose dumping
- Flexibility in design
- Improve stability
- Improve patient comfort and compliance

Drawbacks:

- Lack of manufacturing reproducibility and efficacy
- Large number of process variables
- Multiple formulation steps
- Higher cost of production
- Need of advanced technology
- Trained/skilled personal needed for manufacturing

Mechanism of drug release from pulsatile drug delivery system

The mechanism of drug release from PDDS can be occurring in the following ways:

Diffusion

Water diffuses into the interior of the particle when particle come in contact with aqueous fluids in thegastrointestinal tract and resultant drug solutions diffuse across the release coat to the exterior.

Erosion

Some coatings designed to erode gradually with time, result in the release of drug contained within theparticle.

Osmosis

An osmotic pressure can be built up within the interior of the particle when water allows entering under the right circumstances. The drug is forced out of the particle into the exterior through the coating

Diseases requiring pulsatile drug delivery:

A disease where rhythmic circadian organization of the body plays an important role, pharmacokinetics and/or pharmacodynamics of the drugs is not constant within 24 h. Asthma is one such disease where pulsatile drug delivery system can be useful. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. In case of cardiovascular diseases, several functions (e.g. BP, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood.(8) Circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance in case of insulin substitution in type 1 diabetes has been well exploited. Furthermore diverse

directions of circadian changes in lipid fractions in patients and normal subjects may contribute to alteration in the rhythmicity of other metabolisms and in the blood coagulation system, thus leading to various complications. A circadian rhythm occurs during hepatic cholesterol synthesis. In case of arthritis there is a circadian rhythm in the plasma concentration of C- reactive protein and interleukin-6 of patients with rheumatoid arthritis.

1. Peptic ulcer: Acid secretion is high in the afternoon and at night.
2. Asthma: Precipitation of attacks during night or at early morning hour
3. Cardiovascular diseases: BP is at its lowest during the sleep cycle and rises steeply during the early morning period.
4. Arthritis: Pain in the morning and more pain at night
5. Diabetes mellitus: Increase in the blood sugar level after meal
6. Attention deficit syndrome: Increase in DOPA level in afternoon

CURRENTLY AVAILABLE SYSTEMS

Pulsatile systems are basically time controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes & gastric motility.

Classification of pulsatile drug delivery system (9)

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 particular time interval in order to mimic the circadian rhythm. Such type of pulsatile drug delivery system contains two gears: one is of immediate release type and other one is a pulsed release type. Various methodologies for time controlled pulsatile release systems are discussed in following section.

1.1. Delivery systems with rupturable coating layer.

In this system, outer release controlling water insoluble but permeable coating and based on mechanically induced rupture phenomenon. In recent times different systems based on hard gelatin capsules and tablet core were illustrated, all coated by outer rupturable layer and inner swellable. The film rupture may be attained by swelling, osmotic or effervescent additives in

the reservoir. By optimizing the system, drug release can be obtained at specific time Interval **(fig 3)**. Sungthongjeen et al developed a tablet system consisting of core coated with two layers of swelling and rupturable coatings where in they used spray dried lactose and microcrystalline cellulose in drug core and then core was coated with swelling polymer croscarmellose sodium and an outer rupturable layer of ethyl cellulose

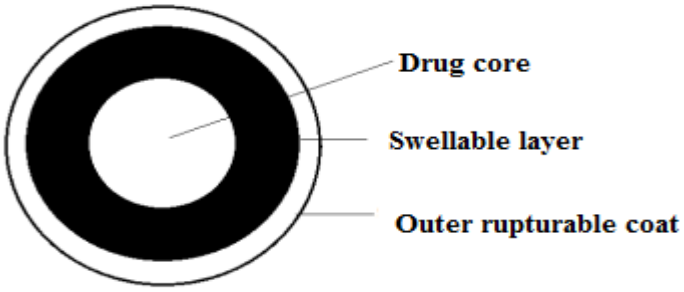

Fig. 3. Schematic diagram of Deliver systems with rupturable coating layer

1.2. Capsule shaped system provided with release controlling plug.(10)

Capsule-based system consists of pulsincap system, R. R. Scherer (International Corporation, Michigan, US) developed Pulsincap. This system comprises of a water-insoluble capsule enclosing the drug reservoir. Seal the drug contents into the capsule body, a swell able hydrogel plug was used. It swelled, when this capsule came in contact with the dissolution fluid and after a lag time, the plug pushed itself outside the capsule and rapidly released the drug which consists of an insoluble capsule body and swellable and degradable plugs made hydrophilic polymers or lipids .The lag time is controlled by plug, which is pushed away by swelling or erosion and drug is released as a pulse from the insoluble capsule, i.e.,Pulsincap®(fig.4).The composition and thickness of the polymeric membranes determine lag time of plug. A swellable hydrogel plug seals the drug contents into capsule body. When this capsule body get in touch with dissolution medium, the hydrogel plug swells, and after the lag time, the plug pushes itself outside the capsule and rapidly releases the drug. Various types of polymer used for formulation of swellable plug include hydroxyl propyl methyl cellulose (HPMC), polyvinyl acetate and polyethylene oxide.

1.3. Delivery systems provided with erodible coating layers.

In such systems generally comprise reservoir device coated with a barrier layer. The barrier erodes after a specific lag time, after which the drug is released rapidly from the reservoir(fig 5). Time dependent release of the active ingredient can be controlled by thickness and viscosity of the outer coat .(11)Sangalli et al. developed an oral dosage form devised to

release drugs following a programmed time period after administration based on this concept. System is composed of a drug-containing core and swellable polymeric coating of HPMC which is capable of delaying drug release through slow interaction with aqueous fluids (12)

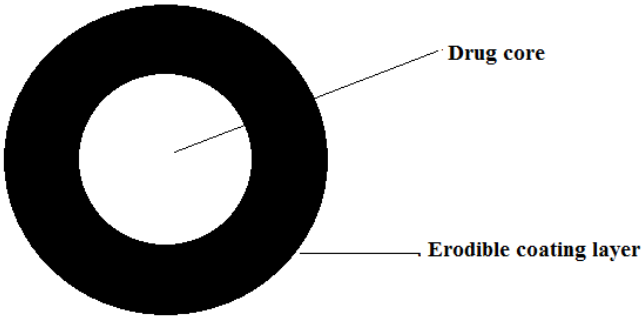

Fig. 5.Schematic diagram of Delivery systems with erodible coating layers.

2) Stimuli induced pulsatile systems

In these systems release of the drug is followed by any biological stimulation like temperature,pH, any other chemical.

2.1. Temperature induced systems

Temperature is most widely used triggering signal for a variety of pulsatile drug delivery system. Temperature as a signal has been justified by the fact the body temperature often deviates from the physiological temperature (37ºc) in the presence of pathogens. This deviation sometimes used for the stimulation and release of active therapeutic agents from various temperatureresponsive drug delivery systems. Thermo-responsive hydrogel systems have been developed for pulsatile release. Hydrogel that undergo reversible volume changes in temperature are known as thermo-responsive hydrogel. This gel shrinks at a transition temperature that is related to the lower critical solution temperature of the linear polymer from which the gel is made. Thermoresponsive hydrogel have a certain attraction for water, and thus swell at temperatures below the transition temperature, whereas they expel water and thus shrink or “Deswell” at temperature above the trasition temperature. Of the many thermo-responsive polymer , poly(*N*-isopropyl acrylamide) (PIPAAm) is probably the most widely used.(13)

2.2. Chemical stimuli induced pulsatile systems(15)

2.2.1. Glucose-responsive insulin release devices

In case of diabetes mellitus patients there is rhythmic increase in the levels of glucose in the body requiring injection of the insulin at proper time. Several systems have been investigated which are able to respond to changes in glucose concentration. One such system includes pH

sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. Glucose oxidase catalyses oxidation of glucose to gluconic acid which changes the pH of the system. This pH changes can be used to drive the swelling of pH dependent membrane and resulting into release of insulin. A double membrane system was formed. In first membrane, glucose oxidase was immobilized on cross linked polymer like polyacrylamide and this was referred to as glucose sensing membrane. Second membrane system, co-polymer membrane made up of *N*,*N*dimethylaminoethyl methacrylate or chitosan or polyol etc., which is pH sensitive and worked as an interface between insulin reservoir and sensing membrane(14) Relesase Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased, the pH of the barrier membrane increased and it returned to the deswelling mode thereby decreasing the insulin release. In this way, this system controlled the rhythmic changes in glucose level in blood and maintained in normal range

2.2.2. 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 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 include cellulose acetate phthalate, polyacrylates, sodium carboxy methylcellulose,

3) Externally regulated systems (15)

For releasing the drug in a pulsatile manner, another way can be used in which drug release is obtained by external stimuli like magnetism, ultrasound, electrical effect and irradiation. Magnetically regulated system contain magnetic beads in the implant like magnetite, iron , cobalt ,nickel etc. On external application of the magnetic field, drug release occurs because of magnetic beads.

3.1 Magnetic induces release:

Magnetically regulated system contains magnetic beads in the implant. Magnetic steel beads wereengrafted in an ethylene and vinyl acetate (EVAc) copolymer matrix that was loaded with bovine serumalbumin as a model drug. The beads oscillate within the matrix on exposure to the magnetic field,alternatively creating compressive and tensile forces.This in turn acts as a pump to push more amount ofthe active solute out of the matrix

3.2 Ultrasound induces release:

Ultrasound is used as an enhancer for the improvement of drug permeation through a biological barrier, such as skin, lungs, intestinal controlled drug delivery

3.3 Electric field induces release:

As these devices use polyelectrolyte thus are pHresponsive as well as electro responsive. Polyelectrolyte contains polymers with comparatively high concentration of ionisable groups along the backbone chain. For chronotherapy, several technologies are required such as microelectronics and micromachining and potential etc. These technologies also include iontophoresis, iontophoresis and infusion pumps. Under theinfluence of electric field, electro-responsive hydro gels generally bend, depending on the shape of thegel which lies parallel to electrodes whereas deswelling occurs when the hydro gel lies perpendicular to the electrodes.

3.4 Light induces release:

In this system drug delivery is regulated by the interaction between light and material and can be achieved by combining a material that absorbs light at a desired wavelength and a material that uses energy from the absorbed light to regulate drug delivery. A new class of optically active nanoparticles is developed such as Gold nanoshells which comprise of a thin layer of gold surrounding a core. Required composite material can be obtained by implanting the nano shells in a NIPAAm-co-AAM hydro gel. nanoshell when absorb the near-infrared light and convert it to heat and then temperature of composite hydro gel is raised above its lower critical solution temperature (LCST). Finally, hydro gel collapses and these results in an enhanced rate of release of soluble drug held within the matrix

Recent advances in the pulsatile drug delivery system(16,17,18,19)

At present, pulsatile drug delivery systems have great importance in various disease conditions specifically in diabetes where dose is suggested at different time intervals. The sub-systems, multi-particulate systems (e.g. pellets) offer various advantages over single unit. The release profile of pellets can be of any type like time dependent, pH dependent, micro flora activated system. Great interest is taken in site and time specific oral drug delivery to improve therapeutic efficacy. Gastro retentive drug delivery system is a suggestion to prolong gastric residence time, thereby targeting site-specific drug release in upper gastrointestinal (GI) tract. Floating drug delivery system (FDDS) and bio adhesive drug delivery are widely used techniques for gastro retention. Various pulsatile technologies have beendeveloped on the basis of methodologies as discussedpreviously.

1. ACCU-BREAK Technology

This technology is designed to easily divisible tablets in exact smaller doses, thus dosage adjustment become easy. In ACCU-T-CR Trilayer tablets, tablet contains a controlled-release (CR) medication and/orimmediate release (IR) component. It gets separated by a drug-free break layer which allows the CR dose to be divided into exact half doses

2. TMDS Technology

The Time Multiple Action Delivery System provides control release rate of multiple ingredients within a single tablet

3. GEOCLOCK Technology

In this technology, chronotherapy focused presscoated tablets are used in which an active drugremain surrounded by an outer tablet layer consists of a mixture of hydrophobic wax and brittle material.In this way a pH independent lag time is obtained.

4. DUREDAS Technology (Dual Release Drug Absorption System)

In this technology, a bilayer tablet was manufactured. One layer of the tablets provided with immediate release action and second layer with sustained release action

5. KV/24

In this technology, one or more drug compounds remain encapsulated to express release of drug in a pre-determined fashion. Prior to coating with one or more polymers, a neutral core is coated with a drug substance to achieve a once-a day release profile. The drug can be combined in two ways, one with the neutral core second incorporated into the coating process

6. INNOHERB

In this technology, pellets are coated inside of the capsule. Desired active herbal compound converted into micro pellets or small beads. The coating of these carried out by semi permeable membrane to improve stability and mask taste/smell

7. IPDAS Technology (Intestinal Protective Drug Absorption System)

In this, the beads with high density drug are compressed to form controlled release tablets. It is particularly suitable for tablet that cause gastroirritation and disintegrates rapidly. The release is controlled by the nature of the drug-containing bead matrix or its semi-permeable membrane coating. It is extruded and spheronisedMultiparticulate based technology. Initially, it was developed for a proprietary formulation of naproxen with fast onset of action to relief pain over a 24-hour period which is marketed in the US and Canada under the trade name Naprelan.

8. ORBEXA Technology

In this multi particulate system, high drug is loadedand product is subjected to granulation. Aftergranulation/extrusion and spheronization, functional polymer membranes are used to coat the resultant beads for additional release rate control and may be filled into capsules. This technology can be used for sensitive drugs such as protein

Drugs Formulated As Pulsatile Drug Delivery System (20-28)

Table 1: Drugs Formulated As Pulsatile Drug Delivery System

Sr no.	Drug	Dosage form
1	Diclofenac sodium	Pulsatile Tablet
2	Ranitidine hydrochloride	Floating pulsatile tablet
3	Aceclofenac	Floating pulsatile tablet
4	Theophylline	Pellets
5	Meloxicam	Multiparticulate System for Pulsatile delivery
6	Salbutamol sulphate	Pulsatile tablet
7	Verapamil HCL	Floating pulsatile tablet

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