Sibi S Mathew et al /J. Pharm. Sci. & Res. Vol. 12(10), 2020, 1336-1340

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Recent Technologies in Pulsatile Drug Delivery: A Review

Sibi S Mathew*, Mathan S, Meenu Sreekumar, Shaiju S Dharan
Ezhuthachan College of Pharmaceutical sciences,
Marayamuttom, Neyyattinkara Pin: 695124, Trivandrum, Kerala, India.

Abstract:
Pulsatile drug delivery system are gaining importance in the field of pharmaceutical technology as these system deliver drug at right dose at specific time at a specific site. They have more multiple benefits over than the conventional dosage form. These systems are designed by circadian rhythm of the body, and the drug is rapidly and completely as a pulse after a lag time. Recent trends include multi particulate drug delivery systems that are especially suitable for achieving controlled or delayed release oral formulation s with low risk of dose dumping, flexibility of blending to attain different release pattern as well as reproducible and short gastric residence time. Various methods and marketed technologies are available like Pulsincap TM, Diffucap, CODAS, OROS, and PULSYSTM.

Key Words: Circadian rhythm, pulsatile drug delivery, cardiovascular disease

INTRODUCTION:

Recently most convient method is oral controlled or programmed drug release. In these method programmed drug release ie.,pulse pattern are followed. PDDS providing special and temporal delivery and also increasing patient compliance. They have multiple benefits over the conventional dosage form. These system are designed according to the circadian rhythm of the body, and the drug is released rapidly and completely as a pulse after a lagtime.

PDDS(s) are designed as timely delivery systems for drugs. These systems are designed as body's circadian rhythm to accomplish time-specific and site-specific delivery of drugs. Pulsatile systems mostly as chronopharmacological behavioral of drugs.The drug release as a pulse after a lag time (a time interval without release of the drug) should be programmed in which that a fast and complete release of the drug follows the lag time as shown in Figure 1[1]

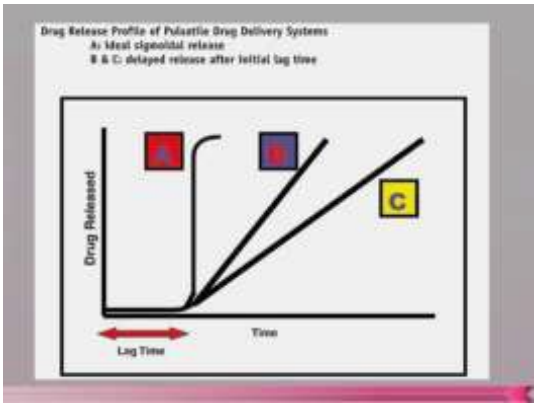


Fig no: 1

PULSATILE DRUG DELIVERY SYSTEM:

Pulsatile drug delivery system, which release the drug rapidly and completely after a lag time ,thus provide spatial and temporal delivery and increasing patient compliance and also increase patient interest.[2]

ADVANTAGES:

- These systems can be used for extended day time or night time activity.
- They reduce the dose frequency, dose size and cost, which ultimately reduces side effects, thereby improving patient compliance.
- Drug adapts to suit circadian rhythms of body functions or diseases.
- Drug targeting to specific site like colon can be achived.
- They also protect mucosa from irritating drugs.
- Drug loss by extensive first pass metabolism is prevented.
- They provide constant drug levels at the site of action and prevent the peak-valley fluctuations.

DISADVANTAGES:

- Low drug loading capacity and incomplete release of drug.
- Multiple manufacturing steps.[3]

DISEASE REQUIRED:

DISEASE	CHRONOLOGICAL BEHAVIOR	DRUGS USED
Asthma	Exacerbation more common during the sleep period & attacks after midnight or at early morning hours	β2 agonist, Antihistamines
Allergic rhinitis	Worse in the morning/uponrising	Antihistamines
Cancer	The blood flow to tumors is threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase	Vinca alkaloids, Taxanes
Duodenal ulcer	Gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are all slower at night.	Proton pump inhibitors

DISEASE	CHRONOLOGICAL BEHAVIOR	DRUGS USED
Neurological disorders	The central pathophysiology of epilepsy and the behavioralclassification of convulsive events.	MAO-B inhibitor
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than day time.	HMG CoA reductase Inhibitors
Diabetes mellitus.	Increase in the blood sugar level after meal	Sulfonylurea, Insulin
Arthritis.	Level of pain increases at night	NSAIDs, Glucocorticoids
Cardiovascular diseases.	BP is at its lowest during the sleep cycle and rises steeply during the early morning	Nitroglycerin, calcium channel, blocker, ACE inhibitors
Attention deficit syndrome	Increase in DOPA level in afternoon.	Methylphenidate

Methodologies for PDDS

Methodologies for PDDS can be briefly classified into 4 classes,

- Time controlled Pulsatile Release
- Single Unit System
- Multi Particulate System
- Stimuli – induced
- Thermo – responsive pulsatile release
- Chemical stimuli induced Pulsatile systems
- External stimuli pulsatile release

Time controlled Pulsatile Release System

The time controlled systems can be classified as single unit (e.g. tablets and capsules) or multiple unit systems.

➢ **Single unit Systems**

- **Capsular Systems**

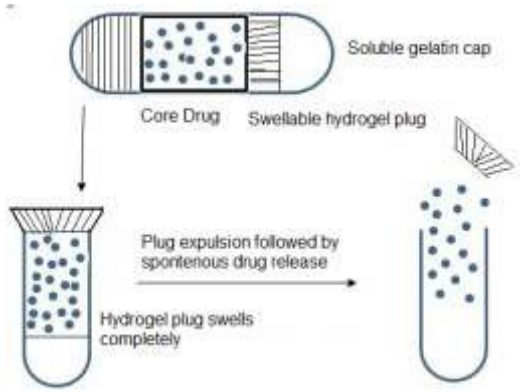


FIG NO : 2 CAPSULAR SYSTEM

These systems consists of an insoluble capsule body containing drug and a plug. This plug is removed off after a pre- determined lag time due to swelling, erosion or dissolution.

These system consists a water – insoluble body filled with drug formulation. The body contains closed and an open- end closed with a swellable hydrogel plug. This plug contact with fluids or medium, gets swollen up, and pushes itself out of the capsule after a time lag. The time lag can be programmed by the dimensions and position of the plug.

- **Port Systems**

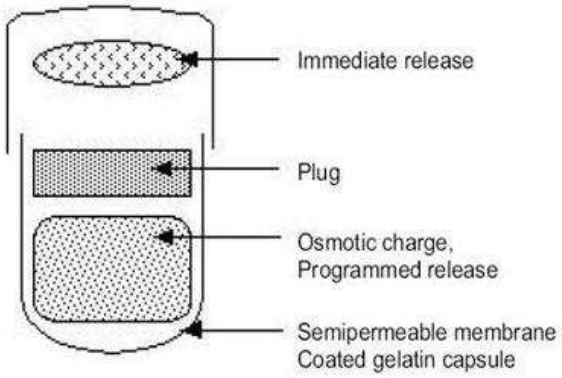


Fig no; 3 port system

In this system consists of gelatin capsule coated body with a semi – permeable membrane a with an insoluble plug and also they contain an osmotically active agent along. In presence of medium, the water diffuses and they create a inner pressure and they eject the plug after a pre determined time lag. The time management can be carried out by increasing the thickness of the membrane.

The liquid drug that spontaneously absorbs the highly porous particle and these particles release through an orifice of semi-permeable capsule coated with expanding osmotic layer. The wall is made up of elastic material, and contain an orifice. Due to osmotic pressure develops and stretch the wall and drug releases.

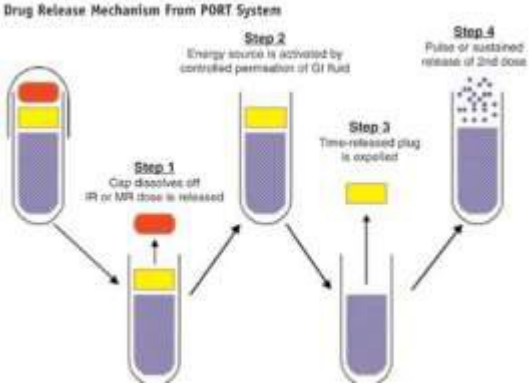


Fig no : 4 port system mechanism

- **Multi – particulate Systems**

➢ **Advantages over single – unit systems**

- They have small size and there is no risk of dose dumping.
- There is less inter and intra subject variability in gastro–intestinal transit time.
- There are less adverse effects and also improved

tolerability.

- There is flexibility in design and stability also.

➢ **Disadvantages**

- Lack of manufacturing reproducibility
- High production cost
- Multiple formulation steps
- Need of advanced technologies.[4]

DELIVERY SYSTEMS PROVIDED WITH RUPTURABLE COATING LAYERS

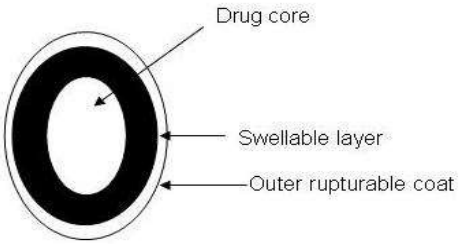


Fig no: 5 rupturable coating layer

It contains an outer release controlling water insoluble but they coat with permeable coating that may induce rupture of the body. Now days a hard gelatin capsules are used along with inner swell able and outer rupturable layer. The film rupture may induced by swelling, osmotic pressure. The drug release can be attained by specific time interval. [5]

DELIVERY SYSTEMS PROVIDED WITH ERODIBLE COATING LAYERS

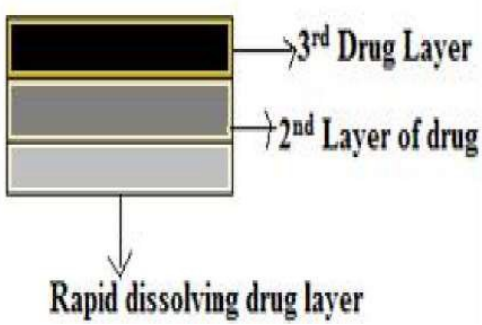
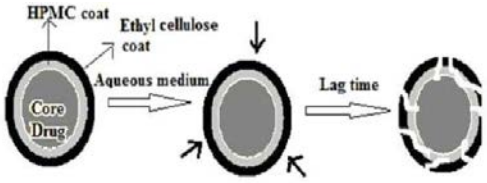


Fig no: 6 erodible coating layer

It is made up of reservoir device coated with a barrier layer. The barrier layer erodes then the drug get release after a predetermined time lag. The time lag can be controlled by thickness of the coating layer and viscosity grade of HPMC layer. PDDS is designed to achieve the time controlled drug delivery. When they contact with medium, it swells and drug is released by a lag time.

They made up of three layer tablet that consist of two layers of drug and separated by a drug free gellable polymeric barrier layer. The three layer tablet coated with impermeable coating and the top side of the tablet contact with dissolution medium, the intial dose in the top most layer was release rapid and the second layer dissolves or eroded from the bottom layer at after the gelled barrier layer dissolves. [6]



Figno:7 mechanism of erodible coating layer

STIMULI INDUCED PULSATILE RELEASE SYSTEM

- **Temperature induced systems:**

The thermo- responsible hydrogel methods are mostly used in pulsatile drug delivery system. These method develops the pulsatile drug delivery system. At the specific temperature the polymer will affect the temperature they swells or de-swells and they cause release of the drug. Eg: designed pulsatile indomethacin release patterns by use reversible swelling characteristics of butyryl acryl amide and iso-propyl-acryl amide co-polymers

- **Inflammation-induced Pulsatile Release:**

When the inflammation occurs at the injured region they produce hydroxyl radical from the inflammation responsive cells. Inflammatory cells produced hydroxyl radical and developing a drug delivery system and drug release in s specific manner. This mostly used in inflammatory disease like Rheumatoid arthritis.

- **pH Sensitive Drug Delivery Systems:**

In this method the drug are divided into two parts immediate release and pulsed release which release the drug according due to pH change. The pH in the different area of GIT , they different pH in different areas of GIT so the change in the pH helps the release of the drug.

- **Antibody dependent release**

Intelligent gels were developed to release the drug in response to antibody concentration. They are able to change their swelling/de-swelling properties by which drug permeation changes. The basic design is to incorporate polymerized antigen-antibody complex in the gel network, and in the presence of the same free antigen, the antibody in the antigen-antibody complex will bind to the free antigen leading to gel swelling and subsequently drug release.

Externally regulated systems [7]

The main advantage of this method is maintain the dose, duration and maintain the dose. It includes electric field, magnetic field, ultrasound.

➢ **Electric field**

In this technique usually contain poly electrolytes, so they are responding to pH changes and electric field. On application of external electric field to a hydro gel that contains poly- electrolytes, hydroxyl ions will be generated at the cathode, and the local pH will increase. This leads to hydro gel erosion and drug release.

➢ **Magnetic field**

In this method magnetic beads are incorporated in a dosage form and external magnetic field. The mechanism of this method is to control the movement of drug through the GI tract by the presence of magnetic attraction.

- **Ultrasound**

Ultra sound technique improves the absorption of oral, inhaled and topical application. They also improves the drug release from the dosage form. It is mainly used cancer treatment by using ethylene and vinyl acetate matrix that contain 5-flurouracil that may help to interfere with DNA synthesis and treat the solid cancer. It is reported that the release of 5-flurouracil from the matrix is 27 hold higher than conventional dosage form.

RECENT TECHNOLOGIES[8]

- **DIFFUCAPS**

In the GI tract that contain varies pH range that may inhibit or the drug absorption, dissolution and absorption. The intestinal pH is most suitable for absorption, dissolution and drug release. To overcome these problems Eurand company develops the Diffucaps technology. In this they incorporates an acid or crystallization inhibiting polymer on an innercore. The usage of the incorporated acid are to maintain the soluble form of the basic drug. The outer layer consist layered beads and the entire preparation is coated with a functional polymer and filled in a capsule or compressed into a tablet. ARMIX is a preparation that was developed using Diffucaps technology

- **OROS®technology**

OROS technology is mainly used to enhance the absorption of poorly water soluble drugs. It consists of a two or three layer core comprising of one push layer in addition to one or more drug layers. The main components of the push layer include an osmotic agent and water swellable polymers. The drug layer mainly consists of the poorly water soluble drug, a suspending agent and an osmotic agent. This two or three layer core is surrounded by a semi-permeable film. As fluids from the GI tract enter this preparation, a suspension that contains the drug, GI fluids and the suspending agent will be formed in the core. In addition, the push layer will swell to push the suspension outside the dosage form after a pre-determined time. Many preparations, such as Procar-dia XL®, Ditropan XL® and Concerta® have been developed by applying OROS® technology

- **The intestinal protective drug absorption system (IPDAS®)**

NSAIDs may cause GI irritation. To avoid this prob-lem, IPDAS® has been recently developed as a tablet containing beads that are coated with a controlled release polymer system. After tablet ingestion, the beads will disperse widely in the stomach, and the drug will be released slowly by virtue of the con-trolled release polymers. This tablet protects the GI tract from irritant drugs by the wide dispersion of the drug containing beads, instead of local accumulation of drug molecules.

The basic concept of IPDAS® was extended and modulated by Elan Drug Technology Company to formulate Naprelan®, which contains naproxen as the active ingredient. The intention was to administer naproxen once daily, so it will be released over an extended period. In addition to extended release, an immediate release was desired for pain relief within30 min. This system was well-tolerated by patients and successfully studied and tested to achieve a biphasic release profile.

- **Geoclock® technology**

Geoclock® technology produces compressed tab-lets. The core contains the active ingredient, and the outer film is made up of wax with brittle mate-rial to provide a pH-independent lag time. In addi-tion to time-controlled release, this basic design was utilized to produce tablets that target the co-lon. Geoclock® technology was applied on predni-sone to formulate LodotraTM tablets in order to control rheumatoid arthritis. These tablets are tak-en at night before sleeping, and the active compo-nent will be released after 4-6 h, which is the opti-mal timing to relieve sharp morning pain.

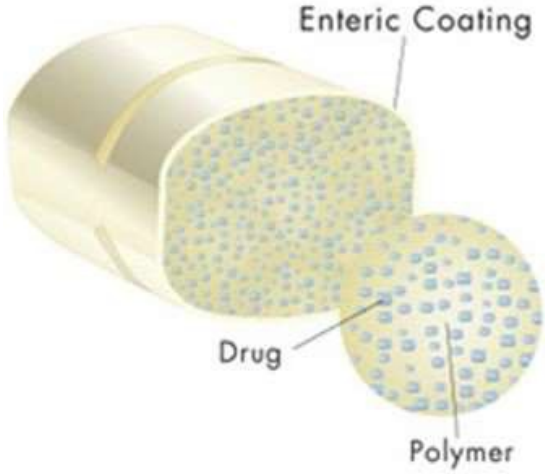
- **Controlled-onset-extended-release (COER-24TM) technology [9]**

One of the currently approved preparations to control hypertension and angina pectoris is Covera-HS tab-let, which contains verapamil hydrochloride as the active ingredient. This unique tablet was made by using COER-24TMtechnology to mimic circadian fluctuations in heart rate and blood pressure.Covera-HS tablet is taken at night to achieve the peak plasma concentration in the early morning hours for the pur-pose of targeting the highest blood pressure and heart rate during that time.

- **Diffutab® technology**

Diffutab®

This allows control of the time and site of drug release. High doses of a drug can be incorporated into the core of the preparation, and it is covered by a combination of hydrophilic and hydrophobic polymers to control drug release. The whole preparation can be covered by an enteric coat. Erosion of the polymers and diffusion of the active ingredient allow once-a-day dosing.



- **Chronotherapeutic oral drug absorption system[10]**

The main advantages of Chronotherapeutic oral drug absorption system (CODAS) technology are food and pH independent drug release, extended release pattern after a lag time and site-specific drug release.

This technology was applied on verapamil to produce a preparation named Verelan®PM taken at bedtime to be released 4-5 h after ingestion to target the highest blood

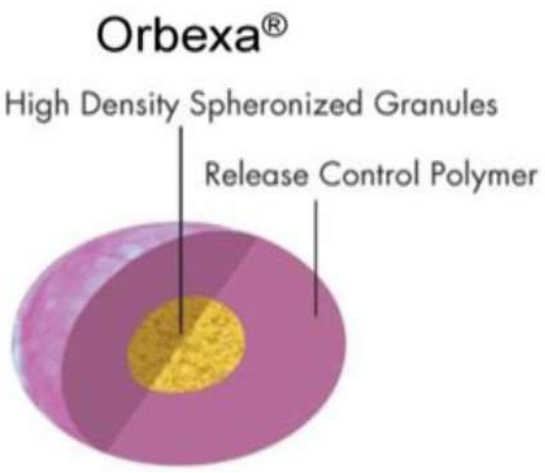
pressure during the day, which is usually early morning. In order to achieve this delay in drug release, a combination of water soluble and insoluble polymers were used to coat drug-loaded beads that were filled in a capsule. In the presence of GI fluids, the water soluble polymers will dissolve gradually to form pores through which the active ingredient will be released over an extended period. The rate of ve-rapamil release has been shown to be independent of pH, food and GI motility .

- **Covera-HS [11]**

One of the currently approved preparations to con-trol hypertension and angina pectoris is Covera- HS. This unique tablet was made by using COER-24TM technology to mimic circadian fluctuation in heart rate and blood pressure .

- **Orbexa® technology**

For high-dose products, Orbexa technology can be used. It is a multi-particulate system used to pro- duce special beads with specific size and density, and these beads are filled in a capsule or single- dose sachets. Orbexa technology can be useful in achieving time-controlled, site-specific or sus- tained drug release .



- **Minitabs®**

Minitab® is a capsule containing minute cylindrical tablets of one or more active ingredients. Each small tablet is coated with one or more membranes to control drug release rate. In addition, gel forming excipients or a matrix can be added inside each tablet in order to control medication release rate.

CONCLUSION

The pulsatile drug delivery system is a good approach to improve drug efficacy and safety and also improve patient compliance. This system help to target the drug to particular site and also they can be achieve pulse form of dose. PDDS can be programmed or controlled the dose release and reduce the toxic effect. These system deliver the drug at right place,right time, right dose and right site.

Significant modification and designing of the conventional delivery system in the form of pulsatile drug delivery system ensure time-controlled pulsatile release of active ingredient. For the successful development of chronotherapeutics dosage form , knowing the circadian rhythm of disease may helps to improve the particular disease. So there is a significant progress in the development of pulsatile drug delivery that can effectively used to treatbthe disease with non- constant dosing therapy.

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