Review Article **CODEN: IJPRNK** **ISSN: 2277-8713**
Patel Rajavi, IJPRBS, 2014; Volume 3(1): 138-148 **IJPRBS**

INTERNATIONAL JOURNAL OF
PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

PULSATILE DRUG DELIVERY SYSTEM: RECENT SCENARIO - A REVIEW

PATEL RAJAVI, TRIVEDI JUI, MODI DRON, PATEL VISHAL, BHIMANI BHAVIN
Department of Pharmaceutics, Arihant School of pharmacy and Bio-research institute uvarsad cross road, S.G. highway, Adalaj Dist. Gandhinagar-382421 Affiliated to Gujarat Technological University, Ahmedabad.

Accepted Date: 05/01/2014; Published Date: 27/02/2014

Abstract: Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. The release of the drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows the lag time. These systems are designed according to the circadian rhythm of the body. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired [1]. The data include rational behind the use of chronotherpeutic release of drug and application in various diseases and prerequisites of drug for pulsatile drug delivery system. Advantages, disadvantages and commercial marketed technologies of pulsatile drug delivery system launched by pharmaceutical companies is also included in data. A variety of systems like osmotic systems, capsular systems, single and multiple-unit systems based on the use of soluble or erodible polymer coating and use of reputable membranes are covered in this article. Pulsatile drug delivery systems have the potential to bring new developments in the therapy of many diseases.

Keywords: Chronotherpeutic, Erodible polymer

PAPER-QR CODE

Corresponding Author: MS. RAJAVI PATEL

Access Online On:

www.ijprbs.com

How to Cite This Article:

Patel Rajavi, IJPRBS, 2014; Volume 3(1): 138-148

INTRODUCTION

Pulsatile drug delivery system is gaining a lot of interest and attention now a day. Though most delivery system is designed for constant drug release over a prolonged period of time, PDDS are characterized by a programmed drug release, as constant blood level may not always be desirable. These systems have a typical mechanism of delivering the drug rapidly and completely after a lag time [2]. (Figure 1) Pulsed or pulsatile drug release is defined as the rapid and transient release of a certain amount of drug molecules within a short time period immediately after a predetermined off-release period.

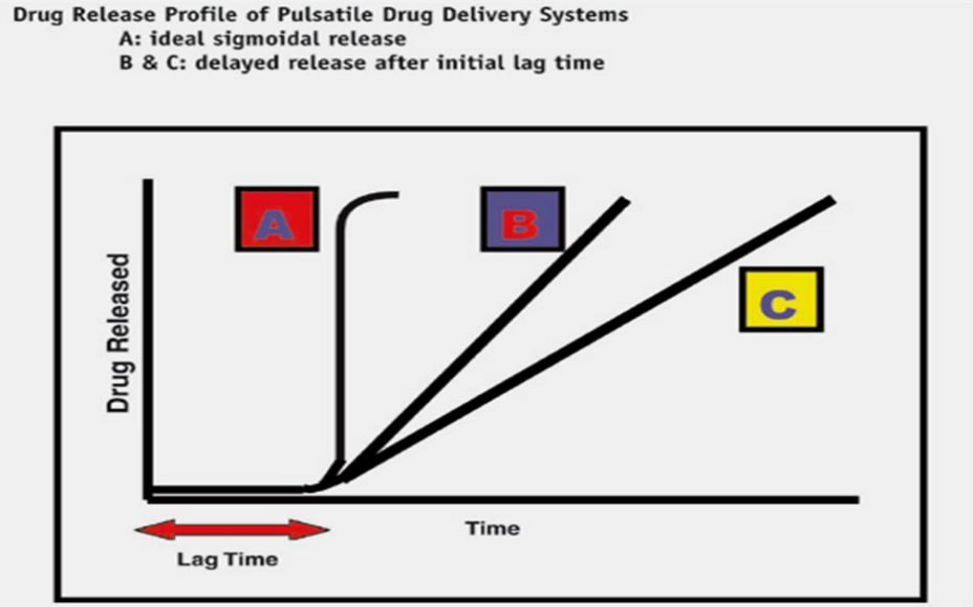


Fig 1: Drug release profile of pulsatile drug delivery systems

There are many conditions that demand pulsatile release like [3]

A) Many body functions that follow circadian rhythm. e.g.: Secretion of hormones, acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion.

B) Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic

Disease, ulcer, and hypertension.

C) Drugs that produce biological tolerance demand for a system that will prevent their continuous presence at the bio phase as this tends to reduce their therapeutic effect.

D) The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g.: peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting.

E) Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon requires that the drug release is prevented in the upper two-third portion of the GIT.

F) The drugs that undergo first-pass metabolism resulting in reduced bioavailability,

Altered steady state levels of drug and metabolite, and potential food- drug interactions.

Diseases required pulsatile delivery:

Chronological behavior	Drugs used	Diseases
Acid secretion is high in the Afternoon and at night	H2 blockers	**Peptic ulcer**
Precipitation of attacks during night or at early morning	β2 agonist, Antihistamines	**Asthma**
BP is at its lowest during the sleep cycle and rises steeply during the early morning	Nitroglycerin, calcium channel blocker, ACE inhibitors	**Cardiovascular diseases**
Pain in the morning and more pain at night	NSAIDs, Glucocorticoids	**Arthritis**
Increase in the blood sugar level after meal	Sulfonylurea, Insulin	**Diabetes mellitus**
Cholesterol synthesis generally higher during night than day time	**HMG CoA reductase Inhibitors**	**Hypercholesterolemia**

ADVANTAGES:

Predictable, reproducible and short gastric residence time

Less inter- and intra-subject variability

Improve bioavailability

Limited risk of local irritation

No risk of dose dumping

Flexibility in design

DISADVANTAGES:

Lack of manufacturing reproducibility and efficacy

Large number of process variables.

Batch manufacturing process

Higher cost of production

Trained/skilled personal needed for manufacturing.

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEM

It can be broadly classified in to 3 class:

1. Time controlled
2. Stimuli induce
3. Externally regulated
4. Multiparticulate

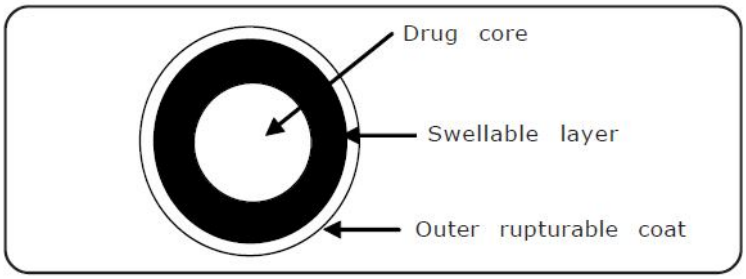
1. Time controlled

In time controlled drug delivery system, drug is released in pulsatile manner after specific time interval in order to coincide the drug with proper site, thus mimic the circadian rhythm. [4]

Pulsatile System Based on Rupturable Coating

This is a Multiparticulate system in which drug is coated on non-peril sugar seeds followed by a sellable layer and an insoluble top layer [5, 6]. The swelling agents used include superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose, etc. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The release is independent of

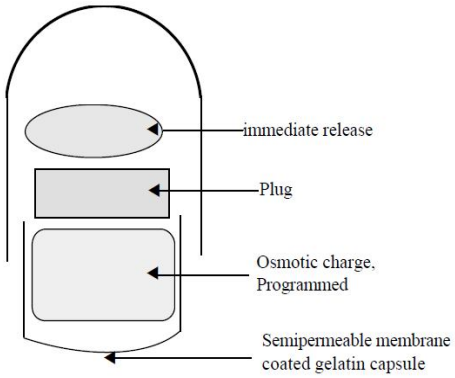
environmental factors like pH and drug solubility. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer.



Schematic diagram of drug delivery with Rupturable coating layer.

Capsule shaped system provided with release controlling plug:

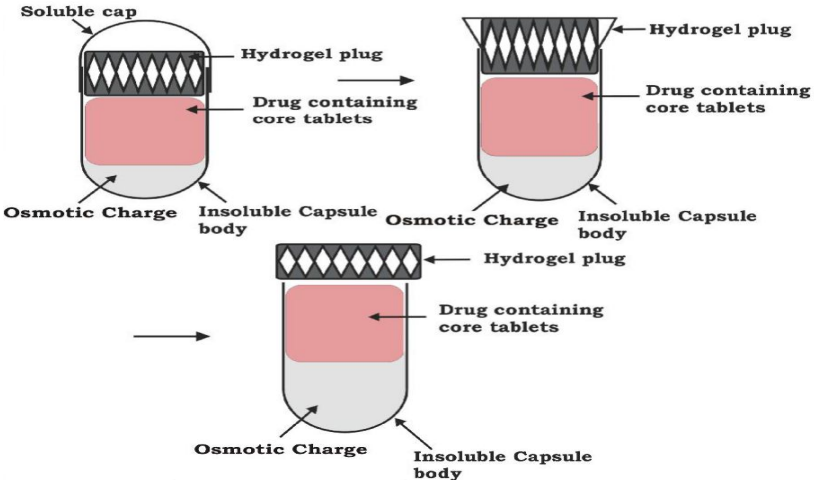
Most of the capsular body which contains the drug, and a plug, which is removed after a predetermined lag time because of swelling, erosion or dissolution.



The leg time controlled by plug, which gets pushed away by swelling or and the drug is release from the insoluble capsule body.

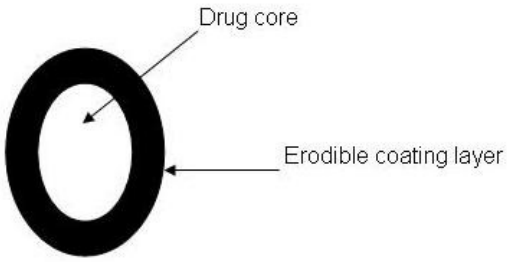
Capsule shaped system provided with release controlling plug:

Most of the capsular body which contains the drug, and a plug, which is removed after a predetermined lag time because of swelling, erosion or dissolution. The leg time controlled by plug, which gets pushed away by swelling or erosion, and the drug is release from the insoluble capsule body.



***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. Time dependent release of the active ingredient can be controlled by thickness and viscosity of the outer coat [7]. Sangallo 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 the drug release through slow interaction with aqueous fluid.



2) Stimuli induce:

Internal stimuli induced pulsatile release system

Responsive drug release from those systems results from the stimuli-induced changes in the gels or in the micelles, which may Deswell, swell, or erode in response to the respective stimuli. There has been much interest in the development of stimuli- sensitive delivery system that releases therapeutic agents in presence of specific enzyme or protein. In these systems there is release of the drug after stimulation by any biological factor like temperature or any other chemical stimuli.

Chemical Stimuli Induced Pulsatile Systems:

Inflammation-induced Pulsatile Release

On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. Degradation via hydroxyl radicals however, is usually dominant 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 [9].

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. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine [10].

Glucose-responsive Insulin Release Devices

In case of Diabetes mellitus there is rhythmic increase in the levels of glucose in the body, requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into laconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently laconic acid level also gets decreased and system turns to the dispelling mode thereby decreasing the insulin release. Examples of the pH sensitive polymers include N, N- dimethylaminoethyl methacrylate, chitosan, polyol etc. [11, 12].

3) External release pulsatile system:

This system was divided into 3 subparts and is discussed below.

Micro Electro Mechanical Systems (MEMS)

A micro fabricated device has the ability to store and release multiple chemical substances on demand by a mechanism devoid of moving its parts. The digital capabilities of MEMS may allow

greater temporal control over drug release compared to traditional polymer-based systems. Another development in MEMS technology is the microchip. The microchip consists of an array of reservoirs that extend through an electrolyte-impermeable substrate. The prototype microchip is made of silicon and contains a number of drug reservoirs; each reservoir is sealed at one end by a thin gold membrane of material that serves as an anode in an electrochemical reaction and dissolves when an electric potential is applied to it.

Electrolyte solution. The reservoirs are filled with any combination of drug or drug mixtures in any form (i.e. solid, liquid or gel). When release is desired, an electric potential is applied between an anode membrane and a cathode, the gold membrane anode dissolves within 10-20 seconds and allows the drug in the reservoir to be released. This electric potential causes oxidation of the anode material to form a soluble complex with the electrolytes which then dissolves allowing release of the drug. Complex release patterns (such as simultaneous constant and pulsatile release) can be achieved from the microchips. Microchip has the ability to control both release time and release rate.

Magnetically Induced Pulsatile Release

The use of an oscillating magnetic field to modulate the rates of drug release from polymer matrix was one of the old methodologies. Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials such as Magnetite, Iron, Nickel, Cobalt etc. For biomedical applications, magnetic carriers must be water-based, biocompatible, non-toxic and non-immunogenic mechanistic approach based on magnetic attraction is the slowing down of oral drugs in the gastrointestinal system. This is possible by filling an additional magnetic component into capsules or tablets. The speed of travel through the stomach and intestines can then be slowed down at specific positions by an external magnet, thus changing the timing and/or extent of drug absorption into stomach or intestines.

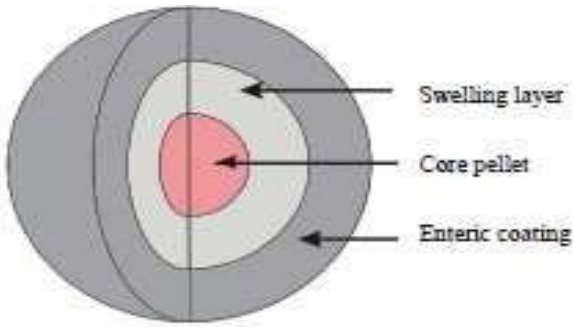
Electro Responsive Pulsatile Release

Electrically responsive delivery systems are prepared from polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH responsive as well as electro-responsive. Examples of naturally occurring polymers include hyaluronic acid, chondroitin sulphate, agarose, carbomer, xanthan gum and calcium alginate. The synthetic polymers are generally acrylate and methacrylate derivatives such as partially hydrolyzed polyacrylamide, polydimethylaminopropyl acrylamide).

4) **Multiparticulate system:**

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, in which the active substance is present as a number of small

independent subunits. They provide many advantages over single-unit systems because of their small size, less inter and intra-subject variability in gastrointestinal transit time, reduced adverse effects and improved tolerability, no risk of dose dumping, flexibility in design and finally Improve stability However, there are some draw backs in this system, which include lack of manufacturing reproducibility, high cost of production, multiple formulation steps and also the need of advanced technologies.



Pulsatile Delivery by Change in Membrane Permeability

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium. Several delivery systems based on this ion exchange have been developed. Eudragit RS 30D is reported to be a polymer of choice for this purpose [14]. It typically contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions. The ammonium group being hydrophilic it facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner.

Low Density Floating Multiparticulate Pulsatile Systems

Conventional Multiparticulate pulsatile release dosage forms mentioned above are having longer residence time in the gastrointestinal tract and due to highly variable nature of gastric emptying process may result in in vivo variability and bioavailability problems. In contrary, low density floating Multiparticulate pulsatile dosage forms reside only in stomach and not affected by variability of pH, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach [14].

RECENT ADVANCE IN THE PULSATILE DRUG DELIVERY:

Nowadays pulsatile delivery system are gaining important in various disease condition Specificity in diabetes where dose is required at different time interval .among these system, Multiparticulate system offer various advantage over single unit which include no risk of dose dumping flexibility of blending units with different release patterns, as well as short and reproducible gastric emptying time site and time specific oral drug delivery have recently been of great interest in pharmaceutical field to achieve improved therapeutic efficacy. Gastro retentive drug delivery system in as an approach to prolong gastric residence time, there by targeting site specific drug release in upper gastrointestinal tract.

REFERANCE:

1. Gahanna NP, Monica R, Sameer B, Anuradha R. Design, Evaluation and Comparative Study of Pulsatile Release from Tablet and Capsule Dosage Forms. Iranian J Pharma Sci Summer 2009; 5(3):119-128.

2. Kikuchi A, Okano T. Pulsatile drug release control using hydrogels. Adv. Drug Delivery 2002; 54:53-77.

3. J. Ravi Kumar Reddy, M. Veera Jyothsna, T. S.Mohamed Saleem2, C.Madhu Sudhana Chetty. Review On: Pulsatile Drug Delivery Systems. J. Pharm. Sci. & Res. 2009; 1(4):109-115.

4. J. Ravi Kumar Reddy, M. Veera Jyothsna, T. S.Mohamed Saleem2, C.Madhu Sudhana Chetty. Review On: Pulsatile Drug Delivery Systems. J. Pharm. Sci. & Res. 2009; 1(4):109-115.

5. Ritschel. W.A., Forusz, H., Chronopharmacology: a review of drugs studies, Methods Find. Exp. Clin. Pharmacol. 16 (1) (1994) 57-75

6. Burnside B. A., Guo X., Fiske K., Couch R. A., Treacy D. J., Chang R. K., McGuinness, C.M., Rudnic, E.M.: US20036605300, (2003).

7. Sachin Survase and Neeraj Kumar, Pulsatile drug delivery: current scenario, CRIPS, 8(2):27-33, (2007).

8. Pozzi F., Furlani P., Orale Feste Pharmazeutische, Darreichungsform Mit Programmierter Freisetzung. DE, Patent No. 4122039; (1992).

9. Wilding I. R., Davis S. S., Pozzi F., Furlani P., Gazzaniga A., Enteric coated timed release systems for colonic targeting, International Journal of Pharmaceutics, 111:99-102, (1994).

10. Gazzaniga A., Sangalli M. E., Giordano F., Oral chronotopic & Mac226: drug delivery systems: achievement of time and/or site specifity, Europian Journal of Biopharm. 40(4):246-250,(1994).

11. Gazzaniga A, Paluga L, Foppoli A, et al. (2007) Eur. J. Pharm. and Biopharm. (In Press)

12. Sangalli ME, Maroni A, Foppoli A, et al. (2004) European Journal of Pharmaceutical Sciences 22:469-476.

13. Crison J. R., Siersma P. R., Taylor M. D., Amidon G. L., and Programmable oral release technology, Port Systems & Mac226: a novel dosage form for time and site specific oral drug delivery, Proceed Intern Symp Control Rel Bioact Mater, 22:278-279, (1995).

14. Miyata T, Asami N, Uragami T. A reversibly antigen-responsive hydrogel. Nature 1999: Jun 24; 399(6738):766-69.