AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

A Review On Pulsatile Drug Delivery System

Mangesh A. Bhutkar[1], Swapna R. Khochage[1]*, Indryani Raut[1], Snehal D. Mali[1], Supriya K. Patil[1], Pallavi P. Navale[1]
1.Rajarambapu college of Pharmacy, kasegaon, Sangli

ABSTRACT

Modified release dosage forms have acquired a great importance in the current pharmaceutical research. It denotes a formulation of a medicinal agent that releases the active ingredients over several hours, in order to maintain a relatively constant plasma concentration of the drug. In addition, sustained and controlled release devices are not applicable in some cases like time-programmed administration of hormones and many drugs. The living systems are predictable dynamic resonating systems which require different amounts of drug at expected times within the circadian cycle. Pulsatile drug delivery system has fulfilled this requirement. This system is such a system where drug is released suddenly after well-defined lag time or time gap according to circadian rhythm of disease states. No drug is released from the device within this lag time. This method is good for the drugs with extensive first pass metabolism and targeted to specific site in the intestinal tract. Pulsatile drug delivery system classified as time controlled pulsatile release, stimuli induced, chemical stimuli induced pulsatile systems, external stimuli pulsatile release etc.

Keywords - lag time, pulsatile, time controlled, first pass metabolism, stimuli induced

*Corresponding Author Email: swapnark123@gmail.com
Received 26 July 2013, Accepted 13 August 2013

Please cite this article in press as: Khochage S *et al* . A Review On Pulsatile Drug Delivery System American Journal of PharmTech Research 2013.

INTRODUCTION

Daily rhythms in plants and animals have been observed since early times. As early as the fourth century BC, Alexander the Great's scribe Androsthenes noted that the leaves of certain trees opened during the day and closed at night showing a clear rhythmicity. In 1729, the French astronomer Jean Jacques d'Ortous deMairan conducted the first known experiment on biological rhythms. Since then, it has been proven that insects use photoperiodic information to bring their growth and dormant periods into harmony with seasons. Circadian rhythms of behavior in mammals are known to be robust and precise. The effectiveness and toxicity of many drugs vary depending on the relationship between the dosing schedule and the 24-h rhythms of biochemical, physiological and behavioral processes.

Worldwide several researches are going on for the development of new drug delivery system. In conventional therapy drug is released immediately after medication. So, the drug concentration in the plasma is raised. The target of drug discovery is to obtain maximum drug efficacy and minimum side effect. With the advancement of technologies in the pharmaceutical field drug therapy has changed its path. In addition, sustained and controlled release devices are not applicable in some cases like time-programmed administration of hormones and many drugs. The living systems are predictable dynamic resonating systems which require different amounts of drug at expected times within the circadian cycle. Pulsatile drug delivery system has fulfilled this requirement. Pulsatile drug release is such a system where drug is released suddenly after well-defined lag time or time gap according to circadian rhythm of disease states. No drug is released from the device within this lag time.

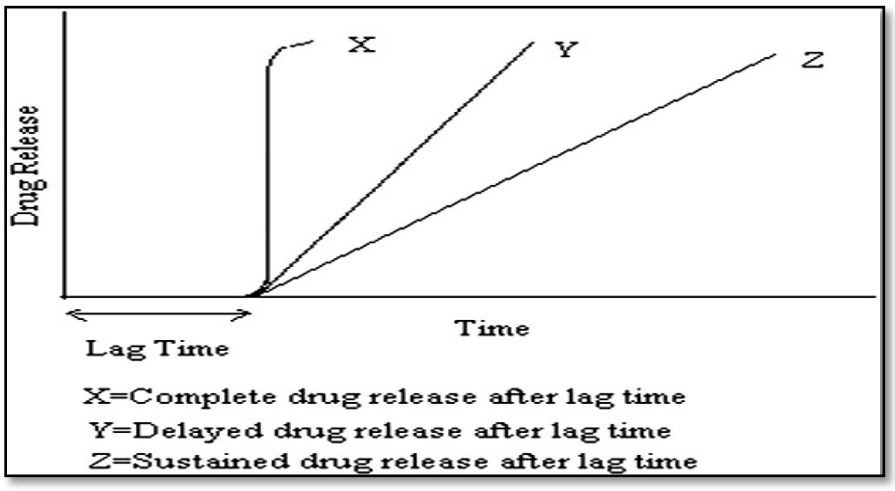

Figure 1: Drug release profile of pulsatile drug delivery system; A: Ideal sigmoidal release, B & C: Delayed release after initial lag time

This method is good for the drugs with extensive first pass metabolism and targeted to specific site in the intestinal tract. Drug release pattern from the device with pulsatile effect is shown in Figure. 1. This delivery is gaining lots of interest and attention because time specific and site-specific delivery of drug with actual amount is obtained from this device. Here release of drug can be controlled by circadian rhythm which regulates many body functions in human beings. Pulsatile drug delivery system is defined 'as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined off – release period, i.e., lag time'

Pulsatile drug delivery systems, which release the drug rapidly and completely after a lag time, thus provide spatial and temporal delivery and increasing patient compliance, have generated increasing interest during recent years for a number of diseases and therapies.

Biological rhythms

There are three types of Biological rhythms in our body. They are: [1, 3]

i. Circadian

ii. Ultradian

iii. Infradian

i. Circadian

The term 'circadian' was coined by Franz Halberg from the Latin circa, meaning about, and dies, meaning day.

ii. Ultradian

Oscillation of shorter duration are termed as ultradian. (More than one cycle per 24 hrs)

iii. Infradian

Oscillations that are longer than 24 h (less than one cycle per day)

Ultradian, circadian, and infradian rhythms coexist at all levels of biologic organization

What is a circadian clock? [2, 5, 6]

Much of the behavior, physiology, and biochemistry of organisms changes rhythmically over the course of each day. Circadian rhythms are generated by "clock genes", which encode genetic instructions that produce certain proteins whose levels oscillate during the course of the day. These oscillating biochemical signals control various functions, such as sleep/waking cycles in other words; they constitute our "internal biological clock", which adapts to the daily cycle of day and night.

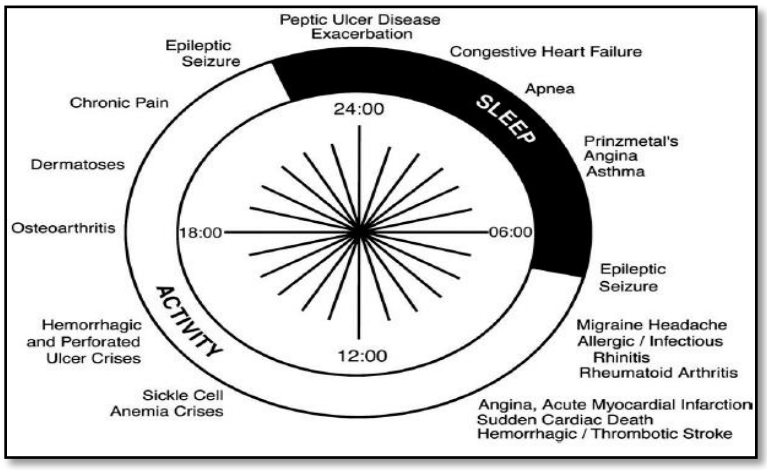

Figure 2: Human circadian rhythm showing diseases require PDDS

The synchronizer routine of most human beings is sleep in darkness from ~10–30 p.m. to ~6–30 a.m. and activity started from ~6–30 a.m. to ~10–30 p.m.

Some of these changes occur only in response to environmental stimuli such as light:dark (LD) cycles, whereas other rhythms persist even in the absence of environmental changes. Rhythms that occur with a periodicity roughly matching that of the earth's rotation on its axis and that continue in the absence of external stimuli are termed circadian. There are many types of circadian rhythms, ranging from the subtle (such as rhythms in photosynthetic activity in cyanobacteria) to the obvious (such as activity rhythms in animals. Circadian rhythms are controlled by an endogenous oscillator, the circadian clock. The circadian clock allows organisms to anticipate rhythmic changes in the environment and accordingly change their physiological state. Circadian clocks respond to changes in the environment. Such resetting of the clock so that internal time matches local time (entrainment) can be accomplished by signals (called zeitgebers, meaning time-givers) such as changes in light, temperature, activity, and nutrient availability. In addition, circadian rhythmicity arises as a cell-autonomous trait even in multicellular organisms. A consequence is that multicellular organisms have functional clocks in many different cell types. These traits common to circadian clocks in all organisms underlie an impressive variety of clock outputs. In mammals, processes influenced by the circadian clock include digestion, regulation of body temperature, hormone secretion, and behaviors such as time of sleep onset.

Classification

Methodologies for the PDDS can be broadly classified into four classes;

I. Time controlled pulsatile release

A. Single unit system

B. Multi-particulate system

II. Stimuli induced

A. Inflammation-induced Pulsatile Release

B. Temperature induced systems

C. pH Sensitive Drug Delivery System

III. Chemical stimuli induced pulsatile systems

A. Glucose-responsive Insulin Release Devices

B. Drug release from intelligent gels responding to antibody concentration

IV. External stimuli pulsatile release

A. Micro Electro Mechanical Systems (MEMS)

B. Electro responsive pulsatile release

C. Magnetically induced pulsatile release

I. Time controlled pulsatile release system

These time-controlled systems can be classified as single unit (e.g., tablet or capsule) or multiple unit systems.

A) Single Unit System

Capsular Systems [7, 8]

Different single unit capsular PDDS have been developed. A general design of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined time lag due to swelling, erosion, or dissolution.

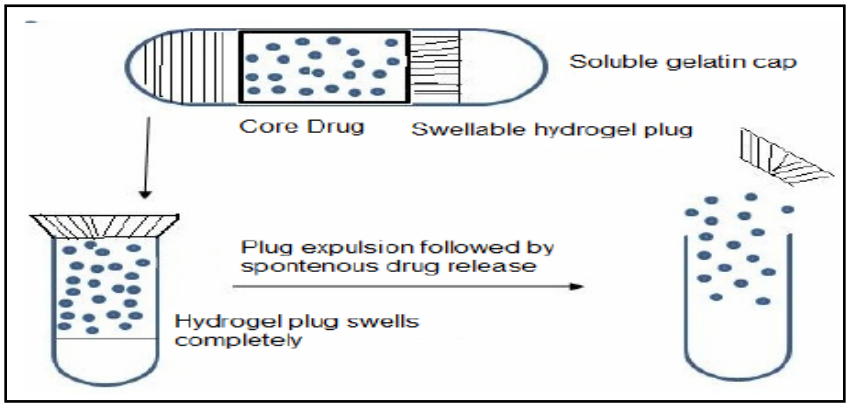

Figure 3: Diagrammatic representation for pulsincap.

The Pulsincap system is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation. The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a time lag. This is followed by a spontaneous release of the

drug. The time lag can be controlled by manipulating the dimension and the position of the plug. The plug material consists of insoluble but permeable and swellable polymers e.g.: polymethacrylates, erodible compressed polymers (e.g: hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g: saturated polyglycolated glycerides, glycerylmonoole and enzymatically controlled erodible polymer e.g: pectin. These formulations are well tolerated in animals and healthy volunteers, and there have been no reports of gastro-intestinal irritation. However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine.

Pulsatile System Based On Osmosis

- **Port Systems** [9,10]

This system consists of a gelatin capsule coated with a semi permeable membrane (e.g: cellulose acetate) housing an insoluble plug (e.g: lipidic) and an osmotically active agent along with the drug formulation. When it comes in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after lag time. The time lag is controlled by the thickness of semi permeable membrane. In order to deliver drug in liquid form, an osmotically driven capsular system was developed. In this system, liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved.

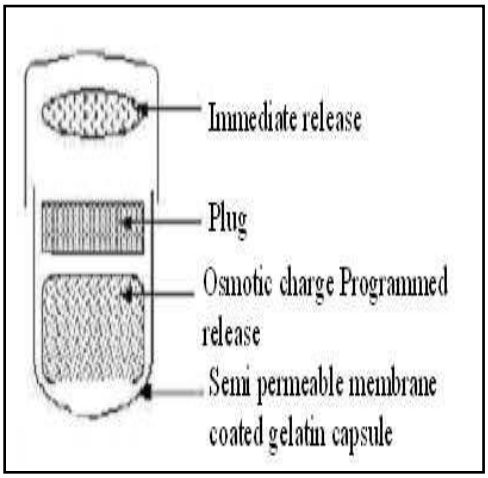

Figure 4: Diagrammatic representation for Port Systems

- **Delivery by a Series of Stops** [11]

This system is described for implantable capsules. The osmotically driven delivery capsule contains therapeutically active agent and water-absorptive osmotic engine separated by a

slider partition to deliver the drug in a pulsatile manner through the orifice. The lag time needed for pulsatile delivery is achieved by a Series of stops placed along the inner wall of capsule which obstruct its movement. As the hydrostatic pressure rises above the threshold level the partition is forced to deliver the next batch of drug. The pulse intensity is controlled by the number of stops and their position along the longitudinal axis.

- **Single Unit Systems Delivery by Solubility Modulation** [12]

  These systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was developed for delivery of salbutamol sulphate The compositions contain the drug (salbutamol sulphate) and a modulating agent, sodium chloride (NaCl). The amount of NaCl was such that it was less than the amount needed to maintain saturation in a fluid that enters the osmotic device. The pulsed delivery is based on drug solubility. The modulating agent can be a solid organic acid, inorganic salt, or organic salt.

- **A System Based on Expandable Orifice:** [8]

  This device is in the form of capsule from which the drug is delivered by the capsule's osmotic infusion of moisture from the body. There is an orifice consisting of elastic material on the capsule's wall. It is so small that under relaxed condition flow of the drug through the orifice is nearly zero. When the pressure is developed inside the shell elastic wall is stretched. Consequently the orifice expands sufficiently from time to time to allow the release of drug in pulsatile manner.

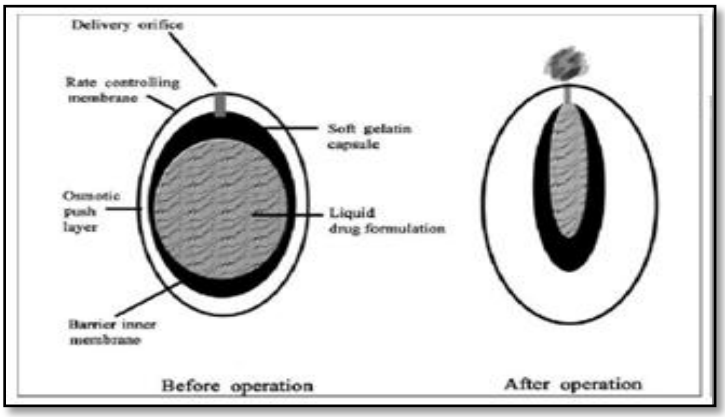

Figure.5: Diagrammatic representation for System Based on Expandable Orifice

Delivery by Reservoir Systems with Erodible or Soluble Barrier Coatings [13, 9]

In such systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing drug. Time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer.

These systems are another class of reservoir type pulsatile systems with a barrier layer, which

dissolves or erodes after a specific ag time followed by burst release of drug from the reservoir core. Generally in these , the lag time is controlled by thickness of coating layer. For instance, a chronotropic system which consists of a drug containing core layered with HPMC and a top layer of enteric coating, the lag time before drug release will be dependent upon the thickness and viscosity grade of HPMC layer. Since drug release mechanism in these types of systems is dissolution, that's why, a high degree of drug solubility relative to dose of drug is essential for rapid release of drug after the lag period. Various grades of hydroxyl propyl methyl cellulose and Eudragit (acrylate) polymers have been studied to in an attempt to deliver drugs to various sites in gastrointestinal tract due to their solubility and eroding properties.

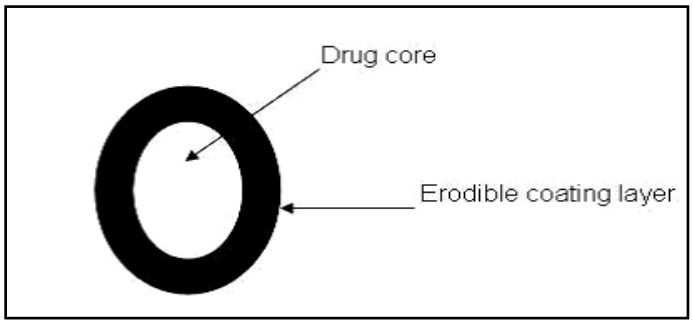

Figure.6: Diagrammatic representation for Systems with Erodible Coatings

Formulations dependent on slow dissolution behavior of high viscosity polymers. It consists of mini tablets with therein dispersed a drug substance which is coated with a high viscosity polymer (HPMC 40000) and an outer enteric coating . The outer film protects the system from fluid in the stomach and dissolves upon entering in small intestine. HPMC layer delays the drug release for 3-4 hours when the system is transported through small intestine. Expected behavior and release profile of swellable/erodible reservoir systems for oral pulsatile delivery.

B) Multiparticulate Systems: [14]

Multiparticulate systems are reservoir type of devices with a coating, which either ruptures or changes its permeability. Drug is coated over sugar seeds these granules may then be packaged in a capsule or compressed with additional excipients to form a tablet. The active pharmaceutical ingredient may also be blended or granulated with polymers before coating to provide an additional level of control. However, drug loading in this type of system is low due to higher need of excipients.

Pulsatile Delivery by Change in Membrane Permeability [15]

These systems are designed when a sigmoidal release pattern is desired, therapeutically beneficial for timed release and colonic drug delivery. Drug release is achieved by change in

permeability of polymeric coating layer in presence of certain counter ions of surrounding media, based on this Narisawa et al, developed a device capable of pulse-release depending on the change in diffusion properties of Eudragit RS. They analyzed that core of theophylline coated with Eudragit RS showed very slow release in pure water but significant increase in release rate was found when the microcapsules were immersed in an organic acid solution containing succinic acid, glutaric acid, tartaric acid, malic acid or citric acid. The reason behind that was higher hydration of film containing quaternary ammonium groups in the polymer chain, were not affected by succinic acid, suggesting that the quaternary ammonium groups of Eudragit RS are essential to produce unique drug release profile. The release profile of systems based on permeability changes depend strongly on physicochemical properties of the drug and its interaction with membrane. Therefore, with this system a pulsatile release profile may be obtained for some particular drug molecules in a specific form but cannot be generally applied to all drugs.

Pulsatile System Based on Rupturable Coating [16,17]

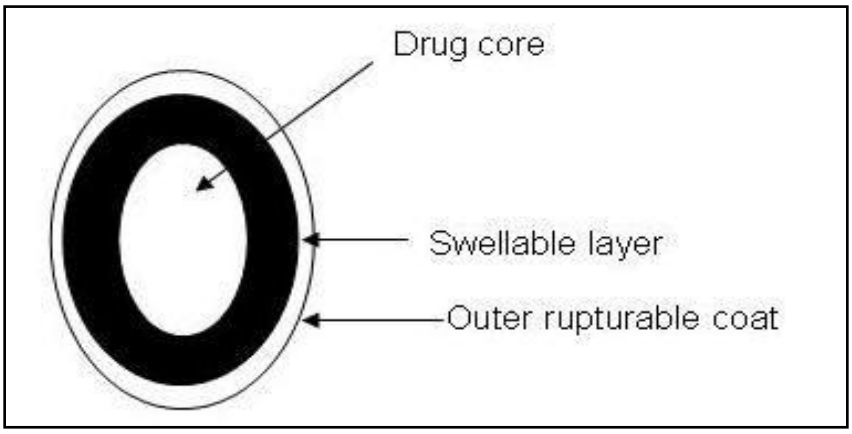

Figure.7: Diagrammatic representation for Pulsatile System Based on Rupturable Coating

These systems consist of an outer release controlling water insoluble but permeable coating subject to mechanically induced rupture phenomenon. Recently different systems based on hard gelatin capsules and tablet core were described, all coated by inner swellable and outer rutpurable layer. The film rupture may be attained by including swelling, osmotic or effervescent additives in the reservoir.

Bussemer et al. worked on a pulsatile system with rupturable coating on drug present in hard gelatin capsules. These capsules were first coated with a swelling layer and then with an insoluble but water-permeable outer coating. These coated capsules when immersed in the release media could take up the media at a constant rate up to a point when the outer coating

would rupture because of the pressure caused by the swelling layer. It could be concluded that by increasing the swelling layer, the lag time could be shortened. However, by increasing the outer coating, the lag time could be prolonged. It was also observed that addition of HPMC to the outer coating shortens the lag time. A pharmaceutical implant was developed for biologically active material, an excipient comprising at least one water soluble material and above which polymer film coating adapted to rupture at predetermined period of time after implantation. In one form, a bilayer film coating forms an impermeable barrier to the drug. An insoluble outer film controls the degree of access of physiological film to the inner film. A film coating comprising a mixture of ethyl cellulose and a copolymer of glycolic and lactic acids is used. As ethyl cellulose is an insoluble polymer, when the polylactic glycolic acid (PLGA) polymer in the film hydrolyses, the film becomes porous and allows release of the drug. The rate of hydrolysis of the PLGA depends on the ratio of the lactic acid to glycolic acid in the polymer

II. **Stimuli induced pulsatile release system**

A. Inflammation-induced Pulsatile Release [18]

Inflammation takes place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells .Yui and co-workers focused on the inflammatory induced hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner. They used hyaluronic acid (HA) which is specifically degraded by the hyaluronidase or free radicals. Degradation of HA via the hyaluronidase is very low in a normal state of health. Degradation via hydroxyl radicals however, is usually dominant and rapid when H 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.

B. Temperature induced systems 19, 20

Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state. Y.H. Bae et al developed indomethacin pulsatile release pattern in the temperature ranges between 20^0C and 30^0C by using reversible swelling properties of copolymers of N-isopropylacrylamide and butyrylacrylamide.

C. pH Sensitive Drug Delivery System [21]

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, Eudragit E-100.

III. Chemical stimuli induced pulsatile systems

This system was divided into three subparts and is discussed below,

A. Glucose-responsive Insulin Release Devices [22]

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 enzyme, pH or any other chemical stimuli. This novel type of glyco-sensitive gel may have potential utilities in self-regulated drug-releasing systems as well as in other applications such as actuators, regulators, and separation systems with glyco-sensitivity. The fabrication of insulin delivery systems for the treatment of diabetic patients. Delivering insulin is different from delivering other drugs, since insulin has to be delivered in an exact amount at the exact time of need. Many devices have been developed for this purpose and all of them have a glucose sensor built into the system. In a glucose-rich environment, such as the bloodstream after a meal, the oxidation of glucose to gluconic acid catalysed by glucose oxidase can lower the pH to approximately 5.8. This enzyme is probably the most widely used in glucose sensing, and makes possible to apply different types of pH-sensitive hydrogels for modulated insulin delivery. This pHchange induces 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.

B. Drug release from intelligent gels responding to antibody concentration [23]

There are numerous kinds 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. Utilizing the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens,

reversible gel swelling/deswelling and drug permeation changes occurs.

IV. External stimuli Pulsatile release

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

A. Micro Electro Mechanical Systems (MEMS) [7]

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 in an 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.

B. Magnetically Induced Pulsatile Release [25]

Use of an oscillating magnetic to regulate the drug delivery from a polymer matrix was one of the first methodologies investigated to develop an externally controlled drug delivery system. Magnetic carriers receive a 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. Basically the mechanistic approach behind the strategy is based on the slowing down the movement of oral drugs in the gastrointestinal system through magnetic attraction. 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 intestine

C. Electro Responsive Pulsatile Release [25]

The combination of developments in several technologies, such as microelectronics and micromachin ing, as well as the potential need for chronotherapy, have currently assisted the development of electronically assisted drug delivery technologies. These technologies include iontophoresis, infusion pumps, and sonophoresis. Several approaches have also been presented in the literature describing the preparation of electric stimuli-responsive drug delivery systems using hydrogels. Kishi et al. developed an electric stimuli induced drug release system using the electrically stimulated swelling /deswelling characteristics of polyelectrolyte hydrogels. They utilized a chemomechanical system, which contained a drug model within the polyelectrolyte gel structure. These gels exhibited reversible swelling / shrinking behavior in response to on–off switching of an electric stimulus. Thus, drug molecules within the polyelectrolyte gels might be squeezed out from the electric stimuli-induced gel contraction along with the solvent flow. To realize this mechanism, poly (sodium acrylate) microparticulate gels containing pilocarpine as a model drug were prepared.

4. Disease Which Require Pulsatile Drug Delivery System wih their Proprietary Product

Table 1: Disease which require pulsatile drug delivery system with their proprietary product

Diseases	Chronological behavior	Drugs used	Proprietary name dosages form	Proprietary chronopharmace-utical technology	Ref.
Duodenal ulcer	Acid secretion is high in the noon and at night	H2 blockers	Gaster® tablets, Pepcid® Tablets	Physico-chemical modification of API	27
Bronchial asthma	Precipitation of attacks during night or at early morning hours	B2 agonist, Antihistaminics	Uniphyl® extended release tablets (Theophylline), Hokunalin, (Tulobuterol)	CONTIN® (Transdermal chrono delivery System)	26, 28, 27
Cardiovascular diseases	BP is at its lowest during sleep cycle and rises in early morning	Nitroglycerin, Calcium channel blocker, ACE inhibitors etc	Covera-HS® extended release tablet (Verapamil HCl),	OROS®	29, 30, 27
			Verelan®PM extended release capsules (Verapamil HCl),	CODAS®	
			Cardi zem® LA extended release tablets(Diltiazem HCl),	CEFORM®	
			InnoPran® XL (Propranolol HCl)	DIFFUCAPS	
Arthritis	Pain in the morning & more pain in the night	NSAIDs, Glucocorticoids	TheirForm®	Three dimensional Printing	31, 32
			Lodotra Prednisone	GeoClock (Geomatrix) technologY	
Diabetes mellitus	Increase In blood sugar level after meal	Sulfonylurea,Insuli n, Gliclazide Biguanide	Diamicron MR (Gliclazide)	Hydrophilic matrix	2
			Glumetza Metformin HCl	AcuForm technology	8,34
Hyperlip-idemia	Cholesterol synthesis is generally higher during night than day	HMG CoA reductase Inhibitors	Lipovas® tablets, Zocor® tablets	Physico-chemical modification of API	8, 27

Allergic rhinitis	sneezing,nasal rhinorrhea, red itchy eyes, nasal pruritus and nasal congestion	Montelukast sodium , olopatadine HCL, l-	-	-	33
Sleep disorder	show complex time structure with rhythm and pulsatile variations in multiple frequencies.		-	-	8
Parkinson's disease	alterations in circadian rhythm of blood pressure, amplified diurnal blood pressure variability and postprandial hypotension	Levodopa/ Benserazide HCl	Madopar DR Levodopa/ Benserazide HCl	Geomatrix technology	8
Attention deficit Syndrome	Increase in DOPA level in afternoon	methylphenidate HCl	Concerta® tablet	OROS®	2
Schizophrenia	Breakdown of thought processes and by a deficit of typical emotional respons-es.	Paliperidone	Invega™	OROS®	2
Antibiotic	-	Amoxicillin	MOXATAG®:extended-release tablets	PULSYSTM	35

CURRENT & FUTURE DEVELOPMENTS

The future of chronotherapeutics seem to be quite promising as in certain disease states pulsatile release exhibit several advantages over the conventional drug delivery mechanisms. Pulsatile drug delivery systems can be either time controlled or site-specific, single or multiple units. At the moment pulsatile release (site or time specific) most often is achieve by using different polymers in coating layers or by changing the coating thickness.

Currently pharmaceutical company focused on developing and commercializing pulsatile drug products that fulfill unmet medical needs in the treatment of various diseases For several diseases (e.g. bronchial asthma, rheumatic disease, myocardial infarction etc) as well for control of body functions (blood pressure, levels of many hormones e.g. aldosterone, rennin, and cortisol) influenced by circadian rhythms, delayed or pulsatile drug release could be an optimal approach. The prime advantage in this drug delivery is that drug is released when necessity comes. These drugs give hazardous problems in conventional and sustained release therapies. Now many FDA approved chronotherapeutics drugs are

available in the market (Table no.1). Key point of development of this formulation is to find out circadian rhythm i.e. suitable indicator which will trigger the release of drug from the device.

Examples of technologies that may be used for parenteral routes in chronotherapy include chrono modulating infusion pumps (i.e. Melodie™, Panomat™ V5, Synchromed™, Rhythmic™) and controlled release microchip strategies. Examples of technologies intended for oral administration include Contin®, Chronset®, Codas®, Ceform®, Diffucaps®, TIMERx®, Chronotopic™, Egalet™, GeoClock™, Port™, Three-dimensional printing (3DP)™, methods involving physicochemical modification of the active pharmaceutical ingredient and/or the use of controlled release erodible polymer.

CONCLUSIONS

It can be concluded that pulsatile drug delivery systems offer a key for delivery of drugs exhibiting chronopharmacological behavior, necessity of night time dosing, etc. If symptoms of a disease display circadian variation, drug release should also vary over time. Since it is seems that timing of drug administration in disease therapy has significant impact upon treatment success. There is a need for new delivery systems that can provide increased therapeutic benefits to the patients to match with circadian rhythm of body. Various methodologies are employed for developing pulsatile drug delivery like time controlled, stimuli induced, externally regulated system and multiparticulate drug delivery system. pulsatile drug delivery systems ensure the current high level of interest in this area with improved quality of life of patient.

ABBRIVTIONS

PDDS -Pulsatile drug delivery system
LD Cycles -light:dark cycles
PLGA -Polylactic glycolic acid
HA -Hyaluronic acid
MEMS -Micro Electro Mechanical Systems
3DP -Three-dimensional printing

REFERENCE

1- Bi-Botti C. Youan. Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery. J Controlled Release 2004; 98: 337– 353.
2- A.S. Mandal et. al. Drug delivery system based on chronobiology-A review. J Controlled Release 2010; 147:314–325.
3- Nitin. D. Gajbhiye et al. Pulsatile drug delivery system. J Pharm Res 2013; (1):120-123.
4- Ramesh D. Parmar et. al. Pulsatile drug delivery systems: an overview. Int J Pharma Sci

Nanotechnol 2009; 2(3): 605-614.

5- Shatam Agarwal, Jaijeet Roychowdhury. Efficient multiscale simulation of circadian rhythms using automated phase macro modelling techniques. Pacific symposium on bio computing 2008; 13: 402-413.

6- Stacey L. Harmer et. al. Molecular bases of circadian rhythms. Rev. cell dev. Boil 2001; 17; 215–53.

7- Vinupama et.al. Pulsatile drug delivery system: A Review. Int bulletin of drug research; 1(1): 19-31.

8- Ketousetuo Kuotsu et.al. Drug delivery system based on chronobiology-A review. J Controlled Release 2010; 147: 314–325.

9- Gupta Anujet.al. Review on recent advances in pulsatile drug delivery systems: A vision for better future for treatment of diseases. Int Pharma Sci. 2012; 2 (2): 71-77.

10- V.N.L.Sirishaet.al. Pulsatile drug delivery system-a review. Int J Pharma Res Allied Sci 2012;1(3): 13-23.

11- Dubal Ashwini et al. Chronotherapy: a novel drug delivery system. Int J Res Ayurveda Pharm 2011; 2 (6): 1692-1700.

12- Sutar K.P. et. al. Use of chronotherapeutics in design of pulsatile delivery systems-a review. J Pharma Scientific Innovation 2012; 1(2): 50-55.

13- Meenu Rajput et. al. Pulsatile drug delivery system: a review. Int J Res Pharm Biomedical Sci 2012; 3 (1): 118-124.

14- Ravikumar Reddy J. et al. Review on: pulsatile drug delivery systems. J Pharma. Sci Res2009;1(4): 109-115.

15- Chopra et al. Chronotropic systems: an emerging trend in drug delivery for pulsed release in chrono pharmacotherapy. Int J Pharma Clinical Res 2010; 2(1): 10-19.

16- Jigar D. Patel et. al. Pulsatile drug delivery system: an "user-friendly" dosage form. J Pharma Res Health 2010; 2(2): 204-215.

17- Bussemer T. et. al. A pulsatile drug delivery system based on rupturable coated hard gelatin capsules. J Controlled Release 2003; 93: 331-339.

18- Yui N, Okano T et. al. Inflammation responsive degradation of cross linked hyaluronic acid gels. J Controlled Release 1992; 22: 105-116.

19- Sharma Ritika et.al. Pulsatile drug delivery system: a review. Int Res J Pharm 2013; 3(7): 103-107.

20- Bae YH, Okano T, Hsu R, et al. Thermo-sensitive polymers as on–off switches for drug

release. Makromol.Chem1987; 8: 481-485.

21- Patel Pavan Kumar et. al. Pulsatile drug delivery system an overview. Asian J Pharma Sci Clinical Res 2011; 1(1): 44-51.

22- Hitesh Dalvadia, , Jayvadan K P. at.el. Chronpharmaceutics pulsatile drug delivery system as current trend. Asian J Pharma Sci 2010; 5 (5): 207-230.

23- Srikanth M.V. et.al. Recent trends in pulsatile drug delivery systems - A review. Int J Drug Delivery 2010; 2: 200-212.

24- Vikas Jain et. al. Recent technologies in pulsatile drug delivery. Biomatter 2011; 1(1): 1-9.

25- Patel Vipul P. et.al. Pulsatile drug delivery system for treatment of various inflammatory disorders: a review. Int J Drug Develop Res 2012; 4 (3): 67- 87.

26- Nidhi Nainwal et.al. Chronotherapeutics - A chronopharmaceutical approach to drug delivery in the treatment of asthma. J Controlled Release 2012; 163:353-360.

27- N.L. Prasanthi et.al. Chronotherapeutics: a new vista in novel drug delivery system. Int J Pharma Sciences Review Res 2011; 6(2): 99-75.

28- Nandvishal V. Deore et. al. Formulation and evaluation of Terbutaline sulphate pulsatile drug delivery system. J Pharm Pharma Sci; 1(3):1004-10015.

29- Kumar, Rajyalakshmi et.al. Formulation and evaluation of metoprolol succinate pulsatile drug delivery system for chrono biological disorder: anti hypertension. Indian J Pharma Sci Res 2012; 3(10): 4004-4009.

30- M Bajpai, D.C.P. Singh, A Bhattacharya. Design and in vitro evaluation of compression-coated pulsatile release tablets of Losartan potassium. Indian J Pharma Sci 2012; 74 (20): 101-106.

31- M. Najmuddin et.al. Development and evaluation of pulsatile drug delivery system of Flurbiprofen. R J Pharma Biological Chemical Sci 2010; 1(2): 284-290.

32- J.B.Naik, S.P.Zineet et.al. Development of single unit floating-pulsatile specific drug delivery system for chronotherapeutic release of Aceclofenac, Int J Applied Biology Pharma Technol 2011; 2 (2): 339-348.

33- Janugade B. U. et al. Formulation and evaluation of press-coated Montelukast sodium tablets for pulsatile drug delivery system. Int J Chem. Tech Res 2009; 1(3): 690-691.

34- S.-Y. Lin, Y. Kawashima et.al. Current status and approaches to developing press-coated chronodelivery drug systems. J Controlled Release 2012; 331–353.

35- Supriya. Shidhaye et.al. Technologies in pulsatile drug delivery system. Int J Advances in pharmacy, biology and chemistry 1(4); 438-455.