Available online at http://jddtonline.info

REVIEW ARTICLE

PULSATILE: A TOOL FOR CIRCARDIAN RHYTHM - A REVIEW

Prasanth V.V[1], Mitesh P. Modi*[1], Sam T. Mathew[2]

[1]Department of Pharmaceutics, Gautham College of Pharmacy, Bangalore-560 032, India

[2]Accenture Pharmaceutical Services, Bangalore-560 072, India

Corresponding Author's Email: miteshmodi88@gmail.com

Received 24 Nov 2011; Revised 29 Dec 2011; Accepted 03 Jan 2012, Available online 20 Jan 2012

ABSTRACT

In the field of modified release, this review covers the detail aspect of a novel pulsatile drug delivery systems (PDDS) by oral administration that aims to release drugs on a programmed pattern at specific time and specific site as per the pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. In particular, the recent literature reports on a variety of pulsatile release systems intended for the oral route, which have been recognised as potentially beneficial to the chronotherapy of widespread diseases. Asthma, peptic or deodenal ulcer, diabetes, neurological disorder, hypertension, cardiovascular diseases, arthritis, attention deficit syndrome in children, and hypercholesterolemia these kind of diseases are promising by pulsatile drug delivery. Technically, This system is designed for chronopharmacotherapy which is based on circadian rhythm and beneficial for the drugs having chronopharmacological behavior where night time dosing is required and for the drugs having high first-pass effect and specific site of absorption in gastrointestinal tract. This controlled–release system can maintain the drug concentration within the therapeutic window with a single dose, which lowers the systemic drug level and also preserves medication that rapidly destroyed by the body. Pulsatile drug delivery system is time related or site-specific related to drug released at the desired site within the intestinal tract (e.g., the colon). Pulsatile drug delivery systems are formulated when zero order drug release is not desired. Based on these premises, the aim of this review is to outline the rational and prominent design strategies behind oral pulsatile delivery. Capsular systems, osmotic systems, soluble or erodible polymer coating and rupturable membranes etc. are summarized in this pulse article. Various marketed technologies on pulsatile drug delivery like OROS, PULSINCAP, GEOCLOCK, SODAS, CODAS, etc., were launched by pharmaceutical companies.

Keywords: Circardian rhythm, Lag time, Pulsatile drug delivery, Time controlled, Site specific, Stimuli induced.

INTRODUCTION

In this time, a major goal for the drug delivery research is turned towards the development of efficacious drug delivery systems with already existing active ingredients incase of new drug discovery[1]. Many of pharmaceutical therapeutic agents are mostly effective when made available at constant rates or near to absorption sites. Much effort has been going on to develop sophisticated drug delivery systems such as osmotic devices for oral application. Oral drug delivery system is more favored on popular controlled drug delivery system in pharmaceutical research and development (R & D) business due to increase in awareness of medical and pharmaceutical community, about the importance of safe and effective use of drug. This system aims to maintain plasma drug concentration within the therapeutic window for long period of time[2]. Traditionally, it is becoming increasingly more evident with the specific time that patients have to take their medication may be even more significant than was recognized in the past. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hour period, may be changing as researcher's report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms. In the human body systems such as cardiovascular, pulmonary, hepatic and renal systems show variation in their function throughout a typical day. They are naturally followed by the internal body clocks and are controlled by the sleep wake cycle. This system focused on controlled or sustained release of drug of which has such advantages of nearly constant level of drug at site of administration, minimizing peak – valley fluctuation of drug concentration in body and avoidance of adverse effect. A

 ISSN: 2250-1177

reduction in dose, dosage frequency, patient efficacy and compliance by this delivery system can also expected[3].

However, a release pattern of drug is not suitable in certain disease condition. At that time release profile of a delivery system was characterized by lag time. In other words, the drug should not release during its initial period of administration, followed by a rapid and complete release (pulse release) of drug that is called pulsatile drug delivery system[4]. This system aims to deliver a drug via the oral route at a rate different than constant i.e., zero order release[5-10]. The lag time is the time interval between the dosage forms is placed into the aqueous environment and drug get to release from its dosage form after rupturing or eroding outer layer. The lag time between 0.5 to 4 hours is desire for upper region of gastrointestinal tract and more than 4 hours for lower portion of small intestine[11]. "Chronopharmaceutics" consist of two words chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. Mainly mechanical rhythms in our body are:

- Circadian - this word comes from Latin word "circa" means about and "dies" means day and oscillation completed in 24 hours
- Ultradian - oscillation of shorter duration(more than one cycle per 24 h)
- Infradian - oscillations that are longer than 24 h (less than one cycle per day)

Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 hours and regulate many body functions like– metabolism, sleep pattern, hormone production etc. PDDS are widely important in such wide spread disease which is mentioned in **Table-1.**

Table 1: Circadian rhythm and the manifestation of clinical diseases

SL.No	Cardiac rhythmicity	Disease or syndrome
1	Exacerbation more common during the sleep period & attacks after midnight or at early morning hours	Asthma
2	Worse in the morning/upon rising	Allergic Rhinitis
3	Growth hormone and melatonin produced at night; testosterone and cortisol in morning hr	Hormone Secretion
4	Even with constant heparin infusion rate, thromboplastin time and risk of bleeding vary significantly during the day	Blood Coagulation
5	Morning pain and more in night	Rheumatoid Arthritis
6	Symptoms worse in the middle/later portion of the day	Osteoarthritis
7	Chest pain and ECG changes more common in early morning	Angina Pectoris
8	Increased blood sugar level after meal	Diabetes mellitus
9	Incidence higher in the early morning	Myocardial Infraction
10	Incidence higher in the morning	Stroke
11	Cholesterol synthesis is generally higher during night than day time	Hypercholesterolemia
12	Incidence higher in the morning after awakening	Sudden cardiac death
13	Acid secretion high in afternoon and at night	Peptic ulcer disease
14	Increase Dopa level in afternoon	Attention deficit syndrome

The lag time is essential for those drugs that undergo degradation in gastric acidic medium like- peptide drugs, irritate the gastric mucosa or which induce nausea and vomiting. Like these conditions enteric coating providing satisfactory results[12] and also enteric coating can be considered as a pulsatile drug delivery system.

The comparison between conventional sustained release and pulsatile drug delivery system is shown in **Figure 1** and sustained release approach which shift to modern pulsatile drug delivery having certain advantages:

- Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology
- Extended day time or night time activity
- Avoiding the first pass metabolism e.g., protein and peptides[13]
- Biological tolerance **(**e.g., transdermal nitroglycerin)
- For targetting specific site in intestine e.g., colon
- For time programmed administration of hormone and drugs
- Gastric irritation or drug instability in gastric fluid
- For drugs having the short half life
- Lower daily cost to patient due to fewer dosage units are required in therapy
- Reduction in dose size and dosage frequency and also side effects

 ISSN: 2250-1177

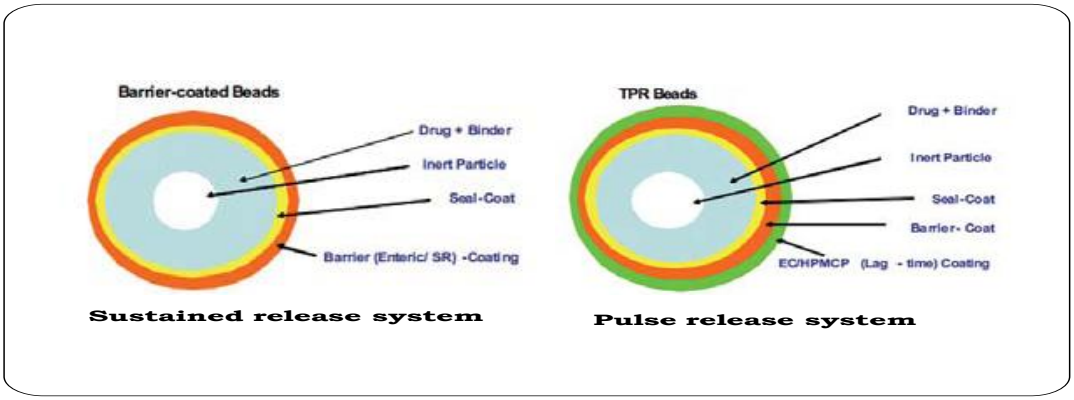

Figure 1: A comparison between sustained and pulsatile release system

PDDS increases its attention in treatment of peak symptoms in early morning and exhibit circardian rhythm. The first pulsed delivery formulation that released the active substance at a precisely defined time point was developed in the early 1990s. The different drug used for chronotherapies are shown in **Table 2.**

Table 2: Drugs developed or under development as chronotherapies

SL.NO	Class	Examples of drugs
1	Cardiovascular Drugs	Verapamil, Felodipine, Propranolol, Captopril, Metoprolol, Diltiazem, Nifedipine, Enalapril, Nitrogycerine, Dofetilide.
2	Antiasthmatic Drugs	Methylprednisolone, Prednisolone, Albuterol, Terbutaline, Theophylline, Montelukast sodium, Budesonide
3	Anticancer Drugs	Cisplatine, Oxaliplatine, Doxorubicin, 5- fluorouracil, Folinic acid, Methotrexate, Mercaptopurine
4	NSAIDs	Diclofenac sodium, Ibuprofen, ketoprofen, oxymorphone, Indomethacine, Tenoxicam, Acetylsalicylic acid,
5	Diabetes Mellitus	Sulphonylurea, insulin
6	Anti Angina Drug	Nitroglycerine
7	Anti Ulcer Drugs	Cimetidine, Ranitidine, Famotidine, Pirenzipine, Omeprazole
8	Anti Cholesterolemic Drugs	Simvastatin, Lovastatin
9	In Irritable Bowel Disease	5-amino salicylic acid
10	Others	Amoxycilline, Vitamin D_3, Dizepam, Haloperidol, Methylphenidate,

CLASSIFICATION OF PDDS

A. PRE-PROGRAMMED DELIVERY SYSTEM

1. Time controlled pulsatile drug delivery system

Principally, timed pulsatile delivery system is capable of providing one or more rapid release pulses at predetermined lag times or at specific sites, results in better absorption with effective plasma concentration-time profile for a therapeutic agent. Due to potential limitations of the dosage form size, and/or polymeric materials and their compositions, a few orally applicable pulsatile release systems are going for approach.

a. Capsular structure based system

The pharmaceutical capsular dosage form that releases its drug content at either a predetermined time or at a specific site (e.g., colon) in the gastrointestinal tract e.g., PULSINCAP[14,15]. The drug formulation consists of insoluble capsular body, swellable and degradable plugs which made up of approved substances such as hydrophilic polymers, lipids and bioactive molecules. After oral administration this capsular system came in contact with the gastrointestinal fluid than hydrogel plug swells and at preprogrammed lag time period, the plug pushes out side and rapid release the drugs. Generally to develop plug, polymeric substances used such as poly vinyl acetate, polyethylene-oxide, hydroxyl propyl cellulose etc. This delivery system has also be simplify by using erodible tablet in place of hydrogel plug. This erodible tablet is completely fit in a capsule to retard the fluid entry. Top of capsule dissolve than this tablet erodes during release of drug from mouth of capsule.

b. System based on rupturable coating

This is a reservoir-type time-controlled pulsatile release system consists of water insoluble but water permeable polymeric barrier which surrounded to the drug core subject.

 ISSN: 2250-1177

This drug core is formulated by using osmotic agents or swelling or gas producing effervescent additives. So that from the dosage form the drug is released from a core after the rupture of a surrounding polymer layer because of a hydrostatic pressure build-up within the system when it immersed into the release media. The pressure necessary to rupture the coating can be achieved with gas-producing effervescent excipients, inner osmotic pressure or swelling agents[16].

A time dependent pulsed release system of salbutamol sulfate in nocturnal asthma consisting of an effervescent core surrounded by consecutive layers of swelling and rupturable polymers was prepared and evaluated. This system prepared by direct compression method using different ratios of microcrystalline cellulose and effervescent agent and then coated sequentially with an inner swelling layer containing a hydrocolloid, hydroxypropyl methylcellulose E5 and an outer rupturable layer having Eudragit RL / RS (1:1)[17].

c. System based on solubilization or erodible membrane

These chronotropic drug delivery systems based on a drug reservoir devices coated with a soluble or erodible barrier. This barrier erodes or dissolves after and the drug is subsequently released rapidly from reservoir core after the specific preset time period that depends on the thickness of the coating layer. 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[18].

Kanakal, et al., prepared theophylline osmotic tablets for effect of coating solvent ratio on the drug release lag time. This tablets were formulated by direct compression and coated by spraying with different ratio of water-alcohol containing hydroxy propyl methyl cellulose (HPMC,5cps) as primary swelling layer and Eudragit RSPO and RLPO as porous layer. The viscosity of the coating solution was determined by using Brookfield viscometer. The optimum water/alcohol ratio (60:40) as coating solvent produced a smooth coated tablet surface texture and modulated drug release lag time of tablets[19].

The pulsatile release tablets that can suppress release of the drug in the stomach and can release the drug rapidly after a predetermined time of about 3 hours in the intestine. The system consists of a core, a swelling agent of cross-linked PVP and a coating film of ethyl cellulose / Eudragit L. But Eudragit L dissolves in an environment of pH above 6 and creates pores in the coating film. So Penetration of water molecules from the surroundings through the pores into the core causes expansion of the swelling agent, bursting the film and releasing the drug with a single pulse. Manipulation of the thickness of the coating film can control the lag time[20].

d. Osmosis based system

The principle to activate osmotically chronomodulated system for burst release of active ingredients from the delivery device must increasing the osmotic pressure inside the device that act as driving force.

In this, the PORT system is to deliver drug as an osmotically driven, capsular system was developed called the Port system **(Figure 2).** This system consists of a gelatin capsule coated with a outer semi permeable coating membrane (e.g., cellulose acetate) housing an insoluble plug (e.g., lipidic) and an osmotically active agent along with the drug formulation. When this device comes in contact with the aqueous environment, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a pre-programmed time. The time lag is controlled by the thickness of semi permeable membrane. The system showed good correlation of *in-vitro* and *in-vivo* experiments in humans and used in treatment the of Attention Deficit Hyper activity Disorder (ADHD) in school age children[21]

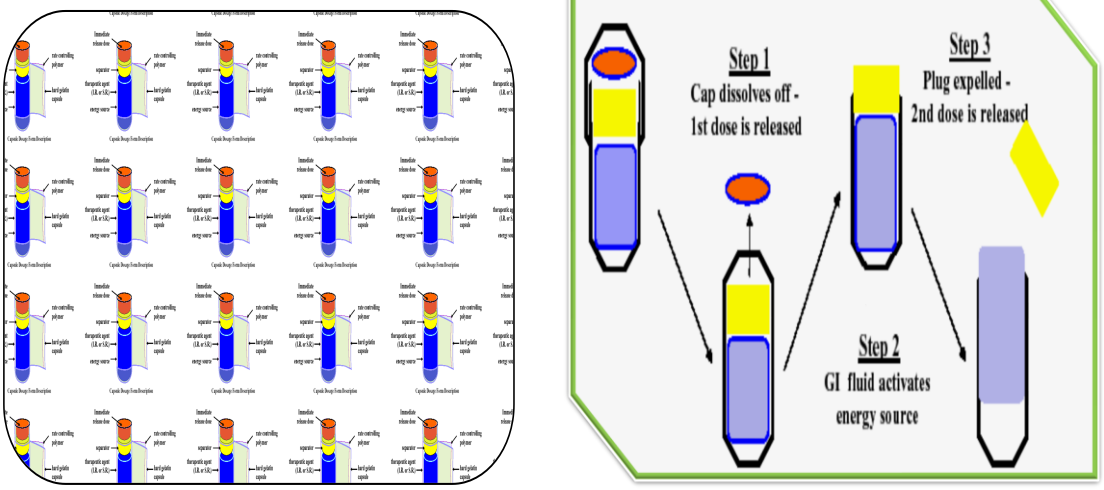

Figure 2: The PORT System (Crison et al., 1996)

But in osmotic capsular system, liquid drug is absorbed into highly porous particles. In this system the drug is deliver through an orifice of a semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved. The capsular system delivers drug by the capsule's osmotic infusion of moisture from the body. The wall of capsule created orifice is made up of an elastic material, mostly elastomer eg., styrene-butadiene copolymer which responsible to stretch the wall under a pressure differential caused by pressure rise inside the capsule[22].

2. Site specific pulsatile drug delivery system

Generally, the aim of site specific and receptor release system refers to targeting of the drug directly to a certain biological location that means the drug must release at targeted site with sufficient amount to maintain peak plasma concentration for the desired time period. Environmental factors like pH or enzymes present in the intestinal tract and also transit time control the release of a site-controlled system where as the drug release from time-controlled systems is controlled primarily by the delivery system and not by the environment. Over the past two decades the major challenge for scientist is to target the drugs specially to the colonic region of GIT. Previously colon was considered as a innocuous organ that responsible for the water absorption, electrolytes and stool storage but it's accepted as important site for the delivery of drugs.

a. pH targeted drug delivery

Induced targeted drug delivery is a targeting method that does not depend on changes in the luminal pH of the GIT, but on the pH change within the dosage form itself. Basically stomach and small intestine is the part of GIT but significant variations in the pH with values ranging from approximately 1.2 in the stomach to 6.6 in the proximal small intestine and a peak of about 7.5 in the distal small intestine followed by a sharp decline in colon where the luminal pH is below 7[23]. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, hydroxypropyl methylcellulose phthalates, sodium carboxy methyl cellulose etc. are utilized for enteric coating to avoid the degradation of drug in upper GIT and attain drug release at specific part of intestine (according to solubility of polymer at particular pH and specific site of intestine) after a predetermined lag time. Theophylline enteric-coated pellets could be successfully colon targeted by the design of pH and time-dependant modified chronopharmaceutical formulation. In conclusion, pulsatile drug release over a period of 3-12 hours is consistent with the requirements for chronopharmaceutical drug delivery. The results of serum study in New Zealand rabbits showed that the developed formulation provided a significant lag phase of 5 hours[24].

b. Enzymes present in the intestinal tract

Enzyme controlled drug release relies on the existence of enzyme producing microorganism in the colon. The bacterial degradable polymers especially azo polymers (the first coating materials to be investigated with regard to biodegradability in the colon) have been explored in order to release an orally administered drug in the colon. Actually upon passage of dosage form through the GIT, it remains intact in the stomach and small intestine where very little microbially degradable activity is present that is quiet insufficient for cleavage of polymer coating. The microflora of colon is in range of 10^{11}-10^{12} CFU / mL and the bacterial species in the colon have been estimated to be around 400 (anaerobic in nature). The colonic microflora produce variety of enzymes including β-glucoronidase, β-xylosidase, β-galactosidase, Igalactosidase, β-arabinosidase, nitroreductase, azareductase, deaminase and urea dehydroxylase. These enzymes can be exploited for colon specific drug delivery.

c. Transit time / pressure of various part of the intestine

Generally, for achieving site specific targeted delivery systems approximately 5 hours are considered sufficient with lag times of to target active pharmaceutical ingredints in colon. Basically luminal pressure is higher in the pylorus due to mechanical stress and to the colon due to reabsorption of water. So the pressure controlled colon delivery capsule as single unit utilizes the increase in pressure of the luminal contents of colon. The drug dispersed in a suppository base and coated with ethyl cellulose could take advantage of pressure differential in the GI lumen. Temperature of body is responsible for suppository base to melt and increases in volume which creates balloon of ethyl cellulose that filled with liquid. This liquid filled balloon capable to withstand small intestinal contractions (peristalsis) but ruptures in the colon when subjected to intensive contraction in colon and contents of thicker viscosity[25].

B. STIMULUS INDUCED PULSATILE DELIVERY SYSTEM

On the basis of physico-chemical processes in the body this novel stimuli induced PDDS is designed at targeted site due to physicochemaical stimuli. Examples including release of certain enzymes, hormones, antibodies, pH at specific site, presence of certain cells, biomolecules like glucose, neurotransmitter, inflammatory mediators etc. This biologiacal stimuli are responsible to trigger the release of drug from the delivery device.

a. Temperature induced PDDS

Several polymeric delivery systems undergo phase transitions and demonstrate marked swelling-deswelling phase in response to temperature which modulate release of drug in swollen state such as thermo-responsive hydrogel systems[26]. Bae et al., (1995) developed indomethacin pulsatile release pattern in the temperature ranges between 200 ^{o}C and 300 ^{o}C by using reversible swelling properties of copolymers of N-isopropylacrylamide and butyrylacrylamide[27]. Kataoka et al., (2001) developed the thermosensitive polymeric micelles as drug carrier to treat the cancer. They used end functionalized poly(*N*-isopropylacrylamide) (PIPAAm) to prepare corona of the micelle which showed both hydration and dehydration behavior with changing temperature[28].

 ISSN: 2250-1177

b. Chemically induced pulsatile drug delivery system

Mainly classified as follows

- Glucose responsive insulin release devices
- Inflammation induced

Glucose responsive insulin release devices

Particularly, the development of such delivery systems is receiving increasing interest in respond to presence of specific enzyme or protein to deliver the active pharmaceutical ingredients. Incase of diabetes-mellitus Type-1, it was depicted earlier that there is rhythmic an increase in blood glucose level in body requiring injection of the insulin at proper time. The technology has been developed for automatically release of insulin in response to change in glucose concentration. pH dependent systems for glucose sensitive hydrogel sytem based on glucose oxidase enzyme which is immobilized in hydrogel. This enzyme is responsible for catalyses oxidation of glucose into glucoronic acid as the blood concentration of glucose rises which changes the pH of system. Due to change in pH, swelling of polymer takes place and these results into insulin release. Insulin decreases the blood glucose level and consequently the gluconic acid level also declines and system turns to deswelling and hence decreasing the insulin release. Examples of such pH sensitive polymers include n-dimethyl amino ethyl methacrylate, chitosan, polyol etc[29]. Obaidat and Park prepared a copolymer of acryl amide and allyl glucose. The side chain glucose units in the copolymer were bound to concanavalin A. These hydrogels showed a glucose-responsive, sol–gel phase transition dependent upon the external glucose concentration[30].

Inflammation induced pulsatile drug delivery system

Any physical or chemical stress like-injury, fracture etc. which acts as a stimulus in the case of inflammation due to hydroxyl radicals produced from inflammation responsive cells. Yui et al., (1992), designed and prepared stimuli based inflammation responsive chronotropic system which responded to hydroxyl radicals and degraded in a limited manner. Basically with the system utilized hyaluronic acid (HA) which is specifically hydrolyzed by hyaluronidase or free radicals that present at inflammatory site. Degradation of HA via the hyaluronidase is very low in a normal state of health. Hence it became possible to treat patient with inflammatory diseases like rheumatoid arthritis, NSAIDS incorporated into hyaluronic acid gels as a new implantable drug delivery system[31].

c. Externally stimulated pulsatile drug delivery systems

These kinds of open-loop systems are not self-regulated. But for deliver the drug in pulse manner another way in which drug release in programmed pattern can be the external regulated system. These systems are magnetically stimulated, ultrasonically modulated and photo stimulated.

Magnetically stimulated system

Contain magnetic beads in implant and its approach based on magnetic attraction is the slowing down of oral drugs in the gastrointestinal system. in this drug release occurs due to magnetic beads. Magnetic carriers receive their magnetic response to magnetic field such as magnet, iron, nickel, cobalt etc. Us patent 2006997863 given one treatment method which consists of single domain magnetic particles attached to a target specific ligand for the administration of magnetic materials to the patient and the application of an alternating magnetic field to inductively heat the magnetic material composition that cause the trigger release of active agents at the targeted tumour cells. Saslawski et al., developed different formulation forin vitro magnetically triggered delivery of insulin based on alginate spheres[32].

Ultrasonically modulated system

It is mostly used as an enhancer for the improvement of drug permeation through biological barriers, such as skin, lungs, intestinal wall and blood vessels. Ultrasonic waves cause the erosion of the polymeric matrix thereby modulating drug release. Miyazaki et al., (1998), evaluated the effect of ultrasound (1 MHz) on the release rates of bovine insulin from ethylenevinyl alcohol copolymer matrices and reservoir-type drug delivery systems in which they found sharp drop in blood glucose levels after application of ultrasonic waves[33].

Photo stimulated system

In which the interaction between light and the material can be used for modulating the drug delivery system. In present study material should absorbs the light at desired wavelength and material uses energy from the absorb light. Example-Gold nanoshell (a thin layer of gold surrounding a core of active nano particle). Embedding the nanoshells in a NIPAAm-co-AAM hydrogel formed the required composite material. When exposed to near-infrared light, nanoshells absorb the light and convert it to heat, raising the temperature of composite hydrogel above its LCST. That's result in the increase rate release of the drug from matrix system[34].

Conclusion

Sustained release formulations are not efficient in treating the diseases especially with chronological pathopysiology, for which, pulsatile drug delivery is effective to tackle diseases with non constant dosing therapies such as diabetes. Circardian rhythm of body is an important concept for understanding the optimum need of drug in the body in circardian disorders. It can be concluded that PDDS offer a solution for delivery of drugs exhibiting chronopharmacological behavior, extensive first-pass metabolism, necessity of night-time dosing, or absorption window in GIT. PDDS are smart and efficient dosage forms satisfying needs of patients and offering interesting options for intelligent life cycle management. But due to lack of manufacturing reproducibility, large process variables and multiple formulation steps, these are still in limited in market. But in future due to more advancement of technology, these hurdles will be overcome and a number of

 ISSN: 2250-1177

patients will be greatly benefited by these systems. One major challenge will be to obtain a better understanding of the influence of the biological environment on the release performance of pulsatile delivery systems in order to develop simple systems based on approved excipients with a good *in vitro-in vivo* correlation. PDDS should ensure that the current high level of interest in this area would extend well in to future and result in the betterment of quality of life.

REFERENCES

1. Davis SS, Illum L, "Drug delivery systems for challenging molecules" Int. J. pharm, 1998, 176, 1-8.
2. Gennaro AR, ed. Remington. The Science and Practice of Pharmacy 20th ed. USA: Lippincott, Williams & Wilkins, 2000, 20, 903-905.
3. Burnside BA, GO X, Fiske K, Couch RA, Treacy DJ, Chang RK, Mc Guinness CM, Rudnic EM : US20036605300 2003.
4. Bussemer T, Otto I, Bodmeier R, Pulsatile drug delivery systems Crit Rev. Ther Drug Carrier Syst, 2001, 18(5), 433-458.
5. Yoshida R, Sakai K, Okano T, Sakurai Y, Pulsatile drug delivery systems using hydrogels. Adv Drug Del Rev, 1993, 11, 85-108.
6. Kikuchi A, Okano T, Pulsatile drug release control using hydrogels. Adv Drug Del Rev 2002, 54, 53-77.
7. Gazzaniga A, Maroni A, Sangalli ME, Zema L, Time-controlled oral delivery systems for colon targeting. Expt Opin Drug Del 2006, 3, 583-597.
8. Peppas NA, Leobandung W, Stimuli-sensitive hydrogels, ideal carriers for chronobiology and chronotherapy, J. Biomat Sci Polym ed. 2004, 15, 125-144.
9. Stubbe BG, De Smedt SC, Demeester J, Programmed polymeric devices for pulsed drug delivery, Pharm Res, 2004, 21, 1732-1740.
10. Gazzaniga A, Palugan L, Foppoli A, Sangalli ME, Oral pulsatile delivery systems based on swellable hydrophilic polymers, Eur J Pharm Biopharm, 2008, 68, 11-18.
11. Shiwani Sharma, Anshul Dutt Sharma, Roopa Saharawat, "Pulsatile Drug Delivery System: A Review An Advanced Approach" IJPT, June 2011, 3, 1179-1188.
12. Lachman L, Lieberman HA, Kanig JL, The Theory and Practice of Industrial Pharmacy. Verghese Publishing House, 1991, 3.
13. Rubinstein A, Tirosh B, Baluom M, Nassar T, David A, "The rationale for peptide drug delivery to the colon and the potential of polymeric carriers as effective tools" J. Controlled Release, 1995, 46, 59-73.
14. McNeil ME, Rashid A, Stevens HNE, Dispensing Device. WO Patent No. 90/09168, 1990.
15. Bussemer T, Dashevsky A, Bodmeier R.A, "Pulsatile drug delivery system based on rupturable coated hard gelatin capsules" J. Control Release, 2003, 3, 331-339.
16. Krogel I, Bodmeier R, Floating or pulsatile drug delivery systems based on coated effervescent cores, Int J Pharm, 1999, 187, 175-184.
17. Qureshi J, Amir M, Ahuja A, Baboota S, Ali J, "Chronomodulated Drug Delivery System of Salbutamol Sulphate for the Treatment of Nocturnal Asthma" Indian J Pharm Sci, 2008, 70(3), 351–356.
18. Gazzaniga A, Paluga L, Foppoli A, Maria ES, "Oral pulsatile delivery systems based on swellable hydrophilic polymers" Euro. J. Pharma. And Biopharm, 2008, 68, 11-18. Maroni A, Zema L, Cerea M, Sangalli M.E, "Oral pulsatile drug delivery systems" Exp Opin Drug Deliv, 2005, 28, 55-71.
19. Kanakal MM, Sakeena MHF, Azmin MN, Yusrida D, "Effect of Coating Solvent Ratio on the Drug Release Lag Time of Coated Theophylline Osmotic Tablets" Tropical Journal of Pharmaceutical Research, June 2009, 8 (3), 239-245.
20. Fan TY, Wei SL, Yan WW, Chen DB, Li J, An investigation of pulsatile release tablets with ethylcellulose and eudragit L as film coating materials and cross-linked polyvinylpyrrolidine in the core tablets, J Control Release 2001, 77, 245-51.
21. Crison JR, Siersma PR, Amidon GL, A novel programmable oral release technology for delivering drugs: human feasibility testing using gamma scintigraphy. Proceed Intern Symp Control Rel Bioact Mater, 1996, 23, 51-52.
22. Linkwitz A, Magruder JA, Merrill S, Osmotically driven delivery device with expandable orifice for pulsatile delivery effect, US Patent No. 5,318,558, 1994.
23. http://www.rivm.nl/bibliotheek/rapporten/623860010.pdf.
24. Kadam, Vinayak D, Gattani, Surendra G, Development of colon targeted multiparticulate pulsatile drug delivery system for treating nocturnal asthma, Drug Delivery, July 2010, 17(5), 343-351.
25. Takaya T, Ikada C, Imagawa N, Niwa K, Takada K, "Development of a colon delivery capsule and pharmacological activity of recombinant human granulocyte colony stimulating factor in beagle dogs" J. Pharm Pharmacol 1995, 47, 474-478.
26. Medlicott, NJ, Tucker IG, Pulsatile release from subcutaneous implants. Adv. Drug Del. Rev. 1999, 139-149.
27. Bae YH, Okano T, Hsu R, Kim SW, Thermo-sensitive polymers as on-off switches for drug release, Makromol, Chem. Rapid Commun, 1987, 8, 481-485.
28. Kataoka K, Harada A, Nagasaki Y, "Block copolymer micelles for drug delivery: design, characterization and

 ISSN: 2250-1177

biological significance" Adv. Drug Deliv, 2001, 47, 113-131.

29. Obaidat AA, Park K, "Characterization of protein release through glucose-sensitive hydrogel membranes" Biomaterials 1997, 18, 801-806.
30. Obaidat AA and Park K, "Characterization of protein release through glucose sensitive hydrogel membranes" Pharm. Res. 1996, 13, 989- 995.
31. Yui N, Okano T and Sakurai Y, "In flammation responsive degradation of cross linked hyaluronic acid gels" J. Control. Rel. 1992, 22, 105-116.
32. Saslawski O, Weigarten C, Beniot J.P, Couvereur P, "Magnetically responsive microspheres for the pulsed delivery of insulin" Life Sci, 1988, 42, 1521-1528.
33. Miyazaki S, Yokouchi C, Takada M, " External control of drug release: control release of insulin from a hydrophobic polymer implant by ultrasound irradiation in diabetic rats" J. Pharm. Pharmacol, 1988, 40, 716-717.
34. Averitt RD, Sarkar D and Halas NJ, "Plasmon Resonance Shifts of Au-Coated Au2S Nanoshells: Insight into Multicomponent Nanoparticle Growth" Phys. Rev. Lett, 1997, 78, 4217-4220.

 ISSN: 2250-1177