

Pulsatile Drug Delivery System – A Novel Approach for Time and Spatial Controlled Drug Delivery

UMANG*, PRASHANT SHARMA, HITESH CHOPRA AND SANDEEP KUMAR

Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Ropar, Punjab, India

Email: umangkapila0@gmail.com

Received: November 27, 2015| Revised: January 29, 2016| Accepted: March 27, 2016

Published online: May 07, 2016

The Author(s) 2016. This article is published with open access at www.chitkara.edu.in/publications

Abstract The area of pharmaceutical research is broadened with the invention of new pharmaceutical drug delivery system. The traditional drug deliveries systems have not the way to treat or cure special disease or as well as the common disease with less side effects and maximized efficacy. ODDS have various advantages and disadvantages but their disadvantages are overcome by the CDDS. CDDS although they overcome the disadvantages of ODDS but do not handle the special pharmacological disease requirements. To overcome this PDDS is established to overcome the disadvantages of CDDS. PDDS has gained importance in the drug delivery system because of improved patient compliance, therapeutic efficacy and having fewer side effects. PDDS uses lag time for delivery of drug in body. Various systems are there in PDDS to overcome the patient's special chronopharmacological needs.

1. INTRODUCTION

Oral route is most convenient, patient friendly route of drug administration and does not require advanced technical knowledge and skills to deliver the drug as in intravenous and intramuscular routes. Another advantage of oral route is that there is no need of special device to deliver the drug to patient. Most researches are done on Oral drug delivery system (ODDS) as it is less time consuming, cheaper, and requires low cost for production as there is no sophisticated production operations involved like sterilization etc. Traditional oral drug delivery system achieves drug-plasma concentration peaks and follows bell shaped graph as first order drug release pattern. The disadvantages of traditional oral drug delivery system are overcome by controlled release drug delivery system (CDDS). The CDDS have advantages over simple

Journal of Pharmaceutical
Technology, Research and
Management
Volume 4, No. 1,
May 2016
pp. 13–29

Umang,
Sharma, P
Chopra, H
Kumar, S

uncoated ODDS as they offer less fluctuation in drug plasma peak, low dose requirement, decrease in frequency of drug administration, less side effects because of low dose, and concentration of drug lies in therapeutic window, improved patient compliances etc. But there are disadvantages with CDDS like dose dumping. To overcome this, special requirements are required which give rise to new area of research called Pulsatile drug delivery system (PDDS). There are some special conditions which require release of drug after a certain period of time called lag time to achieve optimum concentration at required time and required site. The release phase of drug is retarded in its initial phase but release is required after lag time. This type of drug formulations which have lag time and release drug after lag time are come under Pulsatile drug delivery system(PDDS). Recent studies showed that diseases which are circadian rhythm follower are overcome if medication timing is proper or optimized. The explanations of biological clock are given by three rhythms in body which are set up by the natural biological clock of the body operated by SCN present in hypothalamus gland. The three types of rhythms are:

1. Circadian rhythm: Circa means 'about' and dian means 'day'.
2. Ultradian rhythm: Oscillations of shorter duration are come under Ultradian rhythm generally oscillation or cycle of more than one in 24hrs.
3. Infradian rhythm: Oscillation longer than 24hrs generally less than one oscillation or cycle in day.

These circadian rhythms are the conceptual milestone in development and formulation of PDDS. Circadian rhythms are self sustaining, endogenous oscillations (1). These have periodicities of 24hrs or a day.

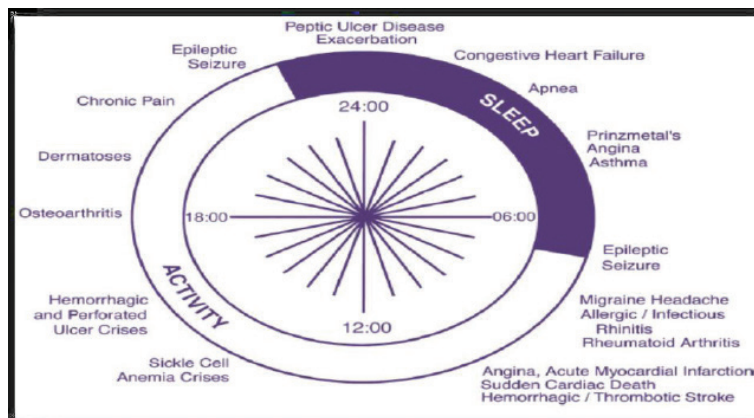


Figure 1: Circadian Rhythm Cycle and Disease Associated.

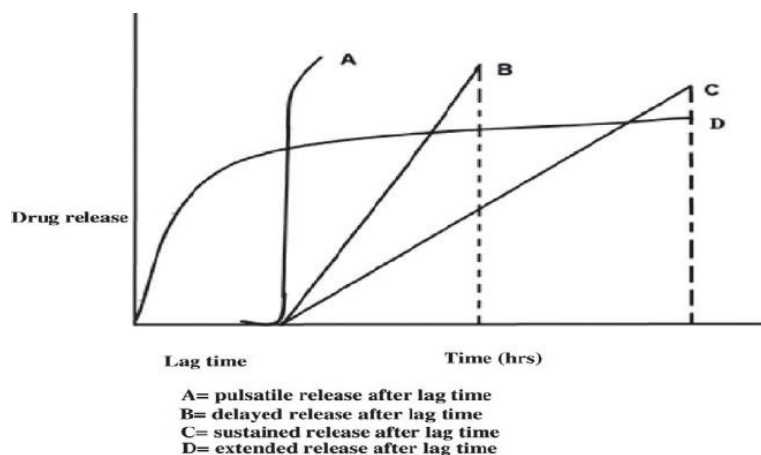


Figure 2: Graph showing pulsatile release, delayed release, sustained release and extended release.

2. REASONS TO ADOPT PDDS

1. **First pass metabolism:** The beta blockers undergo extensive first pass metabolism in intestine and liver. PDDS gives sigmoidal release which releases the drug rapidly and saturates the enzymes thus retarding rate of first pass metabolism as seen in PDDS. This results in increased oral bioavailability of beta blockers.
 2. **Special chronopharmacological needs:** Circadian rhythms are seen at specific time in 24 hrs for particular disease like asthma and angina. This potentiates to the development & role of PDDS formulations which work according to circadian rhythms.
 3. **Local therapeutic needs:** Sometimes local therapeutic effect of drug is desired as seen in inflammatory bowel disease, peptic ulcer and other targeting like colon and ileum which require release of drug after lag time along with site specific delivery.
 4. **Stability problems:** Drugs causes high git irritation and drugs which are unstable in gastric fluid are formulated by PDDS, having lag time more than the gastric residence time.
 5. **Absorption windows:** Different drugs having different absorption site at git tract. The targeting to the specific absorption window is achieved by PDDS by varying the lag time of formulation up to the desired site of absorptions.
-

Umang,
Sharma, P
Chopra, H
Kumar, S

6. **For potent drugs:** Drugs having narrow therapeutic window like digoxin and drugs having fluctuating peak plasma concentration like theophylline can be formulated in PDDS to overcome fluctuating peak plasma concentration of drug.
7. **Inter and Intra subject variability:** Inter and intra subject variability is seen for various drugs like theophylline etc which is overcome by PDDS.

Table 1: Circadian Rhythm and Manifestations of Diseases.

Disease and Syndrome	Complications seen by patients
Asthma	Complications arise during 2am-5am early morning.
Angina Pectoris	Severe pain during morning and exercise.
Hormone secretions	During night in relaxing phase eg: testosterone secretions
Myocardial infarction	During early morning.
Cardiac death	During awakening from sleep.
Peptic ulcers	Late evening and early morning symptoms are seen
Stroke	Morning time.
Allergic rhinitis	Worse symptoms are seen in morning.
Osteoarthritis	In middle of the day.

METHODOLOGIES USED IN PDDS

- 1) Time controlled PDDS
 - a) Single Unit Systems
 - i) Capsular systems
 - ii) Tablet systems
 - iii) Port systems
 - iv) Osmotic pressure systems
 - v) Based on solubility modifications.
 - vi) Reservoir system
 - b) Multi Particulate Systems.
 - i) Rupturable coating systems
 - ii) Time controlled explosion system
 - iii) Sigmoidal release systems
 - iv) Modified permeation systems
 - v) Floating delivery based systems

- 2) Stimuli Induced PDDS
 - a) Internal stimuli induced
 - i) Temperature induced
 - ii) pH based
 - iii) Glucose sensitive system
 - iv) Inflammation based
 - v) Intelligent gel based
 - vi) Enzyme based
 - b) External stimuli based
 - i) Electro responsive
 - ii) Magnetically induced
 - iii) Ultra sound induced
 - iv) Light induced
- 3) PDDS for hormones and vaccines
- 4) Recent advanced patented PDDS technologies
 - a) Spheroidal oral drug absorption system
 - b) Intestinal protective drug absorption system
 - c) Chronotherapeutic oral drug absorption system
 - d) PULSYS™ technology
 - e) EURENDS pulsatile and chrono release systems
 - f) GEOCLOCK technologies

1) TIME CONTROLLED PDDS: A) SINGLE UNIT SYSTEM

i) CAPSULAR SYSTEM

Various capsular systems have been developed now a days. The fundamental method of capsular system consists of an insoluble capsule body housing a drug and a plug in it. The body is closed at the open end with a swell able hydrogel plug. Upon contact with dissolution medium or GIT fluid the plug swells pushing itself out of the capsule body after a lag time. The lag time is controlled by manipulating the dimension and position of plug. Higher the thickness and greater the length the more will be the lag time. Another factor which decides lag time is the position of plug, the deeper the plug inserted, the more will be the lag time because when plug swells it has to travel more distance to release the drug. Water insoluble

drugs have different requirements like incorporating API along with effervescent agents and disintegrants. The plug consists of permeable and swellable polymers (polymethacrylates), erodible compressed polymers (polyvinyl alcohols, hydroxyl propyl methyl cellulose), congealed melted polymers (glycerides) and enzymatically controlled polymers (pectin).

ii) TABLET SYSTEM

In this type of drug delivery system, the lag time is controlled by the coating of erodible polymer on the core tablet containing the drug. The thickness of polymer used and type of polymer used decides the lag time of the tablet. They may be enteric coated and followed by pulse release of the drug. The choice of enteric coated polymer depends upon the pH of the delivery site of intestine (11). Examples of polymers used are Cellulose acetate phthalate (CAP), methyl cellulose phthalate etc (9).

iii) PORT SYSTEMS

Port system Consists of gelatin capsule coated with a semi permeable membrane, for example like cellulose acetate having insoluble plug (lipidic) along with osmotically active agent with drug formulation. When it comes in contact with the GIT fluid the fluid penetrates the semi permeable membrane because of osmotic pressure exerted by osmotically active agents. This forms a port to enter the liquid and drug is dissolved by this penetrated liquid. The liquid drugs can also be formulated by this method. The liquid drug is absorbed by the bigger particles which are highly porous. The capsule body is insoluble in GIT fluids but the cap of capsule is soluble in GIT fluid. The insoluble plug is fitted on the upper part of body of the capsule. The osmotic

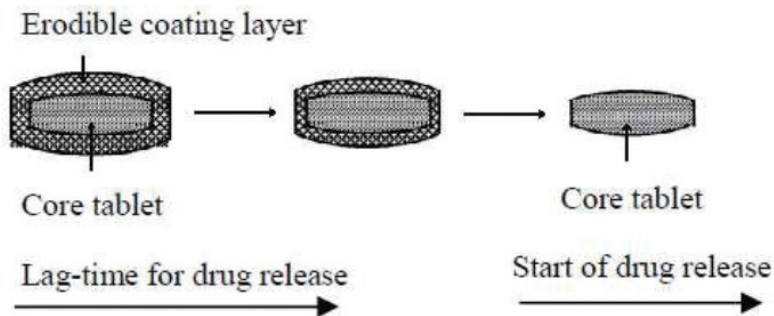


Figure 3: Tablet system showing enteric system with lag time.

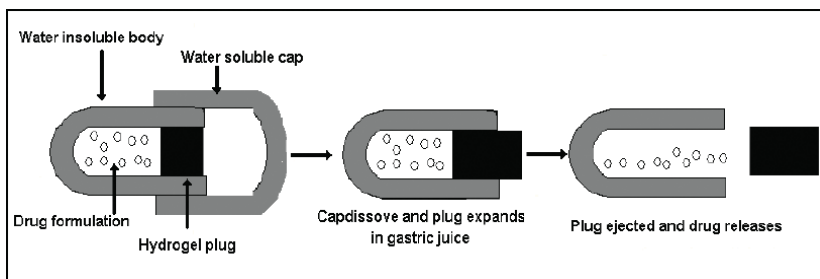


Figure 4: Capsule showing simple Port system.

agents are incorporated in the capsule (13). The capsule body or plug one of either has made up of elastic semi permeable membrane. This membrane helps the fluid for movement of liquid inside to outside and vice-versa. The osmotic active agents' creates higher osmotal pressure inside capsule which causes fluid to penetrate the semi-permeable membrane. The dissolved drug move outside from elastic plug or membrane. It may be noted that not whole drug dissolves at one time, only the fraction of drug dissolves out.

iv) OSMOTIC PRESSURE BASED SYSTEM

This system is made up of immediate release and pulsatile released part. The immediate released part may contain powdered drug, tablet, capsule and any combination of novel drug particles like liposomes, niosomes etc. This immediate release part is subjected to achieve the immediate therapeutic concentration of drug in plasma. The pulsatile release part have to achieve 'pulse' type release after immediate release to achieve and maintain therapeutic concentration thereafter immediate part. This pulsatile release part is osmotically charged or have osmotically programmed pump. Osmotic delivery is given by single osmotic pump or by series of stops separated by movable partitions. These stops obstruct the movement of partition but are overcome by liquid as osmotic pressure is there. Number of stops and longitudinal placements of stops in capsule tells the frequency and number of drug released as pulses.

v) BASED ON SOLUBILITY MODIFICATION

Solubility modification of the drug carrier like capsule housing is modified by various methods to give pulsatile release of the drug after lag time. The solubility of the capsule shell is modified by formalin. The capsule shells treated with formalin have reported time

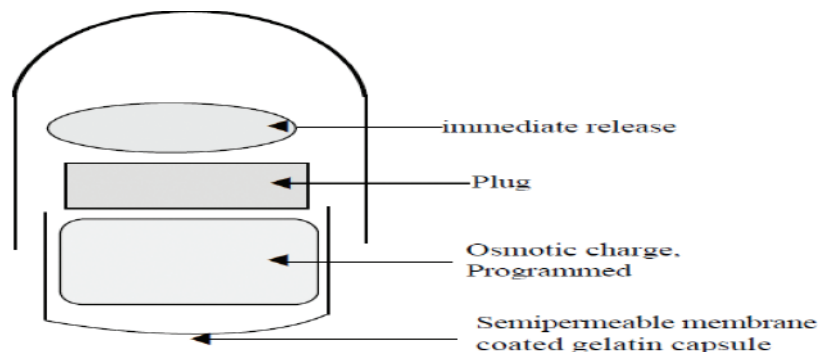


Figure 5: Capsule body having osmotically based system 3.

dependent insolubility of the 24hrs. The capsule shells placed on wire mesh which is placed on some height on desiccators. In the desiccator base formaldehyde solution is placed with small amount of potassium permanganate & then closed. The formalin vaporises evolved and get adsorbed on gelatin capsules surface and varies their solubility. In practical measure only 10 capsules are shrunk in group of 100 capsules. The drug incorporated may be tablet, pellets, niosomes, liposomes etc.

vi) RESERVOIR SYSTEMS

Reservoir system consists of the drug reservoir or 'drug depot' in capsule body or polymer layers on tablet or any other pulsatile system. Drug is released from this depot which may or may not be the control released or pulsatile released. This type of reservoir system is constructed of three parts first is core tab containing 'api', second one is erodible outer layer and last is external outer layer.

A) MULTIPARTICULATE SYSTEM

i) RUPTURABLE COATING SYSTEM

This system is based on the expansion of core which then rupture the coating to allow rapid release of the drug. This system is mostly used in floating type of pulsatile drug delivery systems. The fundamental formulation of rupturable coating system is made up of drug with effervescent material and a polymeric coating. HPMC is used as polymeric coating (7). Drug with effervescent material like sodium bicarbonate is used and gas trapped in the membrane which is made

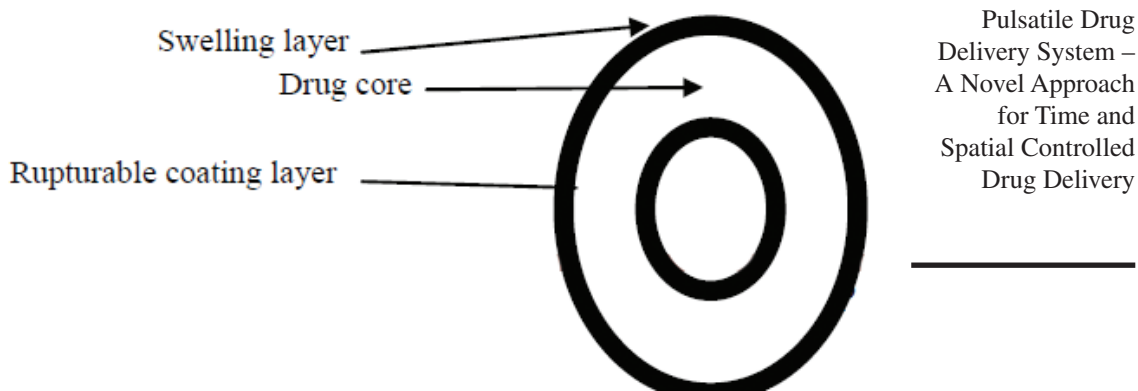


Figure 6: Rupturable system.

up of eudragit RL because Eudragit RL degrades at pH 5-6, so it will not degrade in stomach and the gas evolved lowers the density and floats in stomach fluids (6).

ii) TIME CONTROLLED EXPLOSION SYSTEM

These system consists of osmotically active layer, core pellet or core tablet and third one outermost layer is enteric coated layer. The core tablet is made up of 'api' and other excipients. The swelling layer is made up of osmotically active agent. The swelling layer consists of semi permeable membrane because of expulsion of membrane to degrade enteric coating and gives desired lag time. The concentration of enteric coated layer, osmotically active agents, and semi permeable membrane affects the lag time (14).

iii) SIGMOIDAL RELEASE SYSTEM

Sigmoidal release system is made up of core drug i.e. pellets or tablet compressed along with succinic acid. The drug and succinic acid pellets are coated with the ammonium methacrylate polymers type-b which is used as semi permeable membrane. When water comes in contact with the system drug succinic acid gets dissolved (5). The acid increases the permeability of the semi permeable membrane. Beside succinic acid other acids used are tartaric acid, acetic acid, glutaric acid, malic acid and citric acid (3).

iv) MODIFIED PERMEATION SYSTEM

The pulsatile drug delivery system is made by change in membrane permeability, has taken much interest nowadays. The change in membrane permeability acts similarly as the typical ion exchange

Umang,
Sharma, P
Chopra, H
Kumar, S

resins. An acrylic polymer with quaternary ammonium groups has been influenced by various ions in medium. Eudragit RS contains positively charged quaternary ammonium group in polymer chain (13). This ammonium group has interaction with the water there by changing the permeability. This modified permeation leads the water to penetrate and dissolves the drug.

v) **FLOATING TYPE DRUG DELIVERY**

(1) Floating type drug delivery along with pulsatile drug delivery system serving the both site specific and time specific drug delivery. Floating type drug deliveries have increased GIT resident time of drug and give site specific targeting while PDDS gives lag time like feature for time specific drug delivery¹). This consists of buoyancy layer, coating layer which is insoluble and core material. Buoyancy layer may consist of effervescent agents, low density material, gelling system which make raft like consistency on GIT fluid. Coating layer depends upon the pH of the targeted site i.e. intestine and colon hence the polymer is decided.

2) **STIMULI INDUCED PDDS**

a) **INTERNAL STIMULI INDUCED**

i) **TEMPERATURE BASED**

Temperature is mainly used as stimulus to release the drug in pulsatile manner. Temperature based polymers are used to develop temperature based PDDS. Several hydrogel based systems are used to formulate PDDS. The temperature sensitive polymers either swell or deswell during release phase in PDDS. Basically acryl amides are used in temperature sensitive PDDS. There are two types of temperature based PDDS:

- Thermo responsive hydrogel system: This type employs hydrogels in which there is volume shift i.e. swell or deswell. These hydrogel shrink at temperature, known as LCST (lower critical solution temperature) of linear polymer. This increases the miscibility of hydrogel as dispersion but when the temperature rises up to the HCST (higher critical solution temperature), this result in swelling of hydrogel and release of the drug.

- Thermo responsive polymeric micelle system: The thermo responsive micelle system is achieved by the tightly bound drug in micelles and release of drug in controlled manner which depends upon the temperature stimulus. The polymers used are poly(N-isopropyl acryl amide) i.e. [PNIPAM]-grafted polyphosphazene[PNIPAM-g-PPP] formed by co-substitution of chlorine atoms on polymeric backbones with amino terminated Nipam oligomers and ethyl glycinate.

ii) pH BASED

pH based PDDS is based on the pH sensitive polymers that are polyelectrolytes in nature. These polyelectrolytes have acidic or basic group that either accept or donate protons when pH is changed. They dissolve, swell and shrink when subjected to change of pH as a stimulus. Various polymers which are used in pH based PDDS are cellulose acetate phthalate, sodium carboxy methyl cellulose and polyacrylates. These polymers can also be used as coating to tablet, pellets, capsules, liposomes, niosomes to produce pH sensitive PDDS (13). In this case immediate release drug may or may not be loaded before pulsatile release of drug.

iii) GLUCOSE SENSITIVE SYSTEM

These types of systems are specially used in the case of Diabetes mellitus, when there is rise in the glucose concentration in the patient's blood and need insulin at that time. This is a system which respond to blood glucose i.e. pH sensitive hydrogel containing glucose oxidase immobilized enzyme in it. When glucose concentration in blood increases glucose oxidase convert glucose to gluconic acid decreases the pH toward acidic. This acidic pH cause swelling of polymer resulting in insulin release from hydrogel. Examples of polymer used are chitosan, polyol, N, N-dimethyl aminoethyl methacrylate (15).

iv) INFLAMMATION BASED

Physical or chemical stress and any injury results in release of inflammation mediators that produce hydroxyl radicals. The design of this type of drug delivery is based on the polymers which respond to the hydroxyl radicals and degraded in limited manners. Hyaluronic acid is mainly degraded either by hydroxyl

Umang,
Sharma, P
Chopra, H
Kumar, S

radicals or enzyme known as hyaluronidase. Degradation of hyaluronic acid via hyaluronidase is very low and normal state of health. But degradation by hydroxyl radical is very rapid when hyaluronic acid is injected at inflamed sites. Then it is possible to treat patients with disease like rheumatid arthritis with anti inflammatory drug and hyaluronic acid.

v) INTELLIGENT GEL BASED

There are several types of gels which respond to antigen antibody complex. There are bioactive materials present in the body like antibodies which respond to novel gels to alter their swelling and deswelling properties. These have focus on antigen antibody complex as there are specific antibodies for the specific disease. The swelling and de-swelling changes permeation to gels. This volume shift phenomenon releases the drug from gels.

vi) ENZYME BASED SYSTEM

Liposomes in combination with micro capsule of alginate beads is used as enzyme based system. Drug is loaded in liposomes by suitable methods which were loaded in microcapsules. The loaded liposomes are first coated with phospholipase A2 enzyme for PDDS. Phospholipase A2 removes the acyl group from phospholipids. These liposomes release drug molecules from them.

b) EXTERNAL STIMULI INDUCED

i) ELECTRORESPONSIVE

The electro responsive delivery systems uses polymers which have very high ionisable group in parent chains because when electric stimulus there they get ionized and release drug. Thus ionizing polymers act both as electro responsive and pH responsive polymer. Examples of polymers include agarose, xanthan gum, chitosan, carbomer, calcium alginate etc.

ii) MAGNETICALLY INDUCED

The use of external magnetic field as stimulus in magnetically induced delivery has increased because of very less side effects on human body. Oscillating magnetic field leads to the controlled release of the drug. Magnetic carriers receive magnetic response from incorporated material such as magnetite, iron,

nickel, cobalt etc. The behaviors of intelligent ferrogels were studied by Tingyu liu. The ferrogels called intelligent magnetic hydrogel, were fabricated by mixing polyvinyl alcohols hydrogel and Fe_3O_4 magnetic particles through freeze thaw cycling (2). Magnetic field is applied that attracts magnetic particle Fe_3O_4 & accumulates drug around ferrogel. When magnetic field is released rapidly. The slow release of drug can be adjusted by switching 'off' and 'on' the magnetic field. The drug release pattern depends upon the particle size of Fe_3O_4 under magnetic field. Another simple approach is by incorporating magnetic particle in capsule or tablet thus slowing down their speed by external magnetic field in GIT tract.

iii) ULTRASOUND INDUCED

Ultrasound waves are used in transdermal drug delivery as it increases the permeation of skin by physically reversible change in pore size of skin walls. But recently ultrasound waves are used in PDDS. Ultrasonic waves have been divided into two broad categories based on their effect produced: First is thermal effect producing in which fluids absorb energy and drug is released from temperature sensitive polymers (12). Second is non thermal ultrasonic waves in which oscillating bubbles and disturbances are used to fill cavities.

iv) LIGHT INDUCED

The light sensitive polymers are made with light sensitive hydrogels & used in ophthalmic deliveries. Light is used as the stimulus to release the drug. When light responsive hydrogel absorbs light there is rise in temperature and hydrogel collapse at lowest critical solution temperature and drug is released from matrices (12). The light sensitive polymers act as temperature sensitive polymers to release their drug.

3) PDDS FOR HORMONES AND VACCINES

Vaccines require initial dose of antigen with repeated booster doses to produce immunity in body. The dose regimen of the vaccine is antigen dependent. PDDS can do this job in a single administration by initially giving dose with time controlled booster doses. Vizcarra et al administered GnRh in nutritionally anoestrous cows in pulses of 2mg up to 5 min every hour for 13 days, after 13 days then the cows were given continuous infusion or pulses every 4 hrs.

Umang,
Sharma, P
Chopra, H
Kumar, S

4) RECENT ADVANCES IN PDDS:

a) SPHEROIDAL ORAL DRUG ABSORPTION SYSTEM (SODAS)

Production of controlled release beads give rise to customized dosage form that responds directly to individual drug candidate needs. Controlled release beads can be formulated with immediate release drug to achieve peak plasma concentration in body.

b) INTESTINAL PROTECTIVE DRUG ABSORPTION SYSTEM (IPDAS)

Use of high density multiparticulate tablet technology is used for GIT irritant compounds. IPDAS have number of high density controlled release beads which are compressed into tablet form. When tablet is ingested it breaks and releases the beads. Beads go to intestine and release of drug from beads is given by diffusion through polymeric membrane. Example is Naprelean® having naproxen sodium.

c) CHRONOTHERAPEUTIC ORAL DRUG ABSORPTION SYSTEM (CODAS)

CODAS is a time controlled PDDS and causes drug release after a long lag time when administered to the patient. The lag time is generally 4-5 hrs after administration of drug. A controlled release polymer is coated on the beads having combination of water soluble and insoluble polymer. Water soluble polymer slowly dissolves and drug diffuses through pores from coating, while same time water insoluble polymer continues to act as barrier maintaining controlled release of the drug.

d) GEOCLOCK TECHNOLOGY

Geoclock® tablets have been used as an API inside an outer tablet layer having mixture of hydrophobic wax with brittle material in order to obtain a pH dependent lag time. Dry coating approach is designed to allow the time release of both slow and fast release components.

e) PULSYS™ TECHNOLOGY

This technology gives once daily pulse release of drug which is actually made up of compressed tablets that contains pellets which are previously designed to release drug at different sites of GIT tract in pulsatile manner. The transit properties of pellets enhance overall absorption time and offers improved bioavailability.

Table 2: Marketed and patented technologies of PDDS.

Technology	Mechanism	Market Name	Dosage Form	API	Disease Covered
Codas®	Multiparticulate	Verelan RI® Pm	Tablets	Verapamil	Hypertension
Diffucaps®	Multiparticulate	Innopran® XI	Capsule	Verapamil and Propranolol	Hypertension
Pulsincap™	Rupturable	Pulsincap™	Capsule	Diclofenac	Inflammation
Three Dimen Externaly Their Form®	Externaly Regulated System	Theirform®		Dofetilide	Hypertension

Pulsatile Drug
Delivery System –
A Novel Approach
for Time and
Spatial Controlled
Drug Delivery

f) EURAND'S PULSATIL AND CHRONO RELEASE SYSTEM

This system is capable of providing one or more rapid release pulses at predetermined time lags. The drug pulse is given out from formulation at predetermined lag period. This increases efficiency and minimizes the side effects. Example includes propranolol hydrochloride with a 4hr delay in release after oral administration. When administered at bed time the maximum plasma level concentration of drug occur in early morning when patient have risk of cardiac problems.

ADVANTAGES OF PDDS

- Extended day and night presence of optimum drug concentration in body.
- Reduced side effects.
- Reduced dose frequency.
- Reduction of the drug used in dosage form.
- Improved patient compliance due to less dosing frequency.
- Drug targeting to colon and distinct place in git.
- Administration of gastric unstable drug is easier.
- Beneficial for the diseases which follows circadian rhythms.

DISADVANTAGES OF PDDS

- Low drug loading formulation.
- Multiple steps involved leads to variation in quality of dosage form.
- Incomplete release of the drug.

Umang,
Sharma, P
Chopra, H
Kumar, S

- Immediate withdrawal of the drug is not possible.
- Dose calculation for child and elder patient is difficult.
- In vivo variability may be seen in special cases.

CONCLUSION

There are various ways to formulate PDDS, but the design and choice of the effective method in developing of PDDS is dependent upon patients condition, drugs inherent properties, target site, lag time needed etc. The upper description of methods is based on methods established and new methods which are under development. Thus in real PDDS can take over traditional oral as well as the controlled and sustained release formulation for better efficacy. But this era is developing era of PDDS and the diseases which are controlled by circadian rhythm can be effectively managed by PDDS in future. Beside this various marketed formulation of PDDS are present in market and serving for effective disease management in recent years.

REFERENCES

- [1] Auvil-Novak SE. The chronobiology, chronopharmacology, and chronotherapeutics of pain. *Annu Rev Nurs Res.* 1999; 17: 133–153.
- [2] Balaban SM, Pike JB, Smith JP, Baile CA. Osmotically Driven Delivery Devices with Pulsatile Effect. US Patent No. 5209746; 1993.
- [3] Bodmeier R, Guo X, Sarabia RE, Skultety P. The influence of buffer species and strength on diltiazem HCl release from beads coated with aqueous cationic polymer dispersions, Eudragit RS, RL 30D. *Pharm Res* 1996; 13(1): 52–56.
<http://dx.doi.org/10.1023/A:1016021115481>
- [4] Chen CM. Multiparticulate Pulsatile Drug Delivery System. US Patent No. 5, 508,040; 1996.
- [5] Janugade B. U.1*, Patil S. S., Patil S. V.1, Lade P. D. Formulation and evaluation of press coated montelukast sodium tablet. *International Journal of Chemtech Research.* 2009.
- [6] Narisawa S, Nagata M, Hirakawa Y, Kobayashi M, Yoshino H. An organic acid-induced sigmoidal release system for oral controlled-release preparations. Part II: permeability enhancement of Eudragit RS coating led by the physicochemical interactions with organic acid. *J Pharm Sci* 1996; 85(2):184–188. <http://dx.doi.org/10.1021/js950180o>
- [7] Nitin S, Satarkar, Zach Hilt S. Magnetic hydrogel nanocomposite for remote controlled pulsatile drug release. *J Cont Relea* 2008;130:246–251.
<http://dx.doi.org/10.1016/j.jconrel.2008.06.008>
- [8] Pulsatile drug delivery release technology: An overview Suresh Rewar*, Bansal B.K., Singh C.J., Sharma A.K. 2015.
- [9] Patel PK, Patel C K, “Pulsatile Drug Delivery System”, *AJPSCR* 2012; 1: 44–51.

-
- [10] Rajput Meenu, Sharma Ritika, Kumar Sunil, Pulsatile Drug Delivery: A review. International Journal of Pharmaceutical Research and Biomedical Sciences. ISSN :2229–3701.
- [11] Rigas AN, Bittles AH, Hadden DR, Montgomery DA. Circadian variation of glucose, insulin, and free fatty acids during long-term use of oral hypoglycaemic agents in diabetes mellitus. *Br Med J* 1968; 3: 25– 28. <http://dx.doi.org/10.1136/bmj.4.5622.25>
- [12] Santini JT, Cima MJ, Langer R. A controlled-release microchip. *Nature* 1999; 335–338.
- [13] Sarawade A, Ratnaparkhi M.P., Chaudhri S., “Floating drug delivery system: An Overview”, *Int. J. Res. Dev.Pharm. L. Sci.*, 2014, **3(5)**, pp. 1106–11
- [14] Sharma GS, Srikanth MV, Uhumwangho MU, Phani Kumar KSand Ramana Murthy KV. Recent Trends in Pulsatile drug delivery: A Review. *International journal of drug delivery.* 2010.
- [15] Wilding IR, Davis SS, Pozzi F, Furlani P, Gazzaniga A. Enteric coated timed release systems for colonic targeting. *Int J Pharm* 1994; 111: 99–102. [http://dx.doi.org/10.1016/0378-5173\(94\)90406-5](http://dx.doi.org/10.1016/0378-5173(94)90406-5)

Pulsatile Drug
Delivery System –
A Novel Approach
for Time and
Spatial Controlled
Drug Delivery
