WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 11, 342-357. Review Article ISSN 2277– 7105

A REVIEW ON: PULSATILE DRUG DELIVERY SYSTEM

Akash A. Jain*[1], Sachin R. Chavhan[2], Prof. Manoj Bari[3], Dr. Surajj Sarode[4] and Dr. Shashikant Barhate[5]

Dept. of Pharmaceutics, Shree Sureshdada Jain Institute of Pharmaceutical Education & Research, Jamner (M.S), India.

Article Received on
25 July 2017,
Revised on 16 August 2017,
Accepted on 07 Sep. 2017
DOI: 10.20959/wjpr201711-9610

***Corresponding Author**
Akash A. Jain
Dept. of Pharmaceutics,
Shree Sureshdada Jain
Institute of Pharmaceutical
Education & Research,
Jamner (M.S), India.

ABSTRACT

Pulsatile Drug delivery systems are gaining a lot of interest as they deliver the drug at the right site of action, at the right time and in the right amount, as per the pathophysiological needs of the diseases, resulting in increasing patient compliance. Pulsatile Drug Delivery systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, GIT motility, etc. Various techniques are available for the pulsatile delivery like pH dependent systems, time dependent systems, etc. The major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time. A pulse has to be generated in such a way that a complete and rapid drug release is achieved after the lag time so as to match body's circadian rhythms with the release of drugs. Many of circadian dependent diseases display acute symptoms in early morning hours or in the morning at awakening. In case of cardiovascular diseases, BP is at its lowest during the sleep cycle and rises steeply during the early morning period. Pulsatile release systems can be classified in multiple-pulse and single-pulse systems. A popular class of single-pulse systems is that of rupturable dosage forms. Advantages of the pulsatile drug delivery system are reduced dose frequency; reduce side effects, drug targeting to specific site like colon and many more.

KEYWORDS: PDDS, Pulsatile Release Techniques, NDDS, Classification.

INTRODUCTION

Today, a vast amount of literature reports that biological processes are not constant but vary according to time. Although much of drug delivery research has focused on constant drug

release rate due to limitations of delivering drug according to disease rhythmicity, clinical studies show that magnitude of rhythmic differences can be to a great extent and a strong determinant of when during 24 hour most morbid and mortal event will occur. For many drugs constant release system is not suitable. Drugs not suitable for constant release are used in disease condition that exhibit rhythmic variation within a circadian cycle. For, drugs with decrease bioavailability due to first pass metabolism, gradual release of drug from constant release systems can result in greater degradation. Drugs with more toxic effects; continuous exposure may lead to increased adverse effects. For, drugs which exhibit tolerance, constant exposure decreases drug effect**.** Modified release dosage forms have acquired a great importance in the current pharmaceutical research and development field. These dosage forms show different release profiles depending on their type. This dosage form is used to describe products that alter the timing and rate of release of drug substance.

Various modified release drug products

1. Extended Release: It leads to two fold reductions in dosing frequency compared to immediate release dosage forms.
2. Controlled release: This system allows slow drug release over extended period of time but not at predetermined rate.
3. Sustained release: This system delivers drug at predetermined rate over a long period.
4. Delayed Release: This dosage form releases discrete portion of drug at a time other than readily after administration, although one portion may be released promptly after administration.
5. Targeted Release: These delivery systems deliver drug at or near the intended site of action and may have extended release characteristics.
6. Repeated Action: This product is designed to release first dose initially, followed by second dose of drug at a later time.
7. Prolonged Action: This dosage form releases drug slowly and provide continuous supply of drug over an extended period.

Pulsatile Drug Delivery Systems: A Pulsatile drug delivery system delivers drug in rapid and burst manner within a short time period immediately after a programmable lag phase. There are many situations where drug is needed to be released immediately (after bursting the delaying film coat) at specific site. These situations, therefore, compel designing a delayed fast release systems. These systems are mainly appropriate for drugs that are metabolized to

pharmacological active compounds, drugs which have long in vivo half lives showing an inherently prolonged duration of action, drugs with very short in vivo half life which require a prohibitively large amount of active ingredients in dosage form, drugs which are required in large doses for therapeutic effect and drugs which are required in very low dose. Additionally a delayed burst release can also be utilized for enhancing absorption, reducing side effects, increasing and decreasing dose.

Advantage of pulsatile drug delivery system

There are many advantages of pulsatile dosage form over conventional dosage form.

1. Increases absorption and bioavailability than conventional immediate release or sustained release drug due to its ability to release drug in a burst manner, at target site of absorption.
2. Site targeting allows delivery of poorly bioavailable drugs that would get destroyed in higher GI tract environment e.g. (peptide and protein molecules).
3. Reduces dose of drug without decrease in therapeutic effects.
4. Decreases side effects.
5. Decreases drug interaction due to lower cytochrome P450 isoenzymes.
6. Decreases food effect (change occurring in bioavailability of drug when given with food).
7. Improved compliance.
8. Chronotherapy, programmed delayed release provides optimal treatment of diseases.
9. Pulse release allows multiple dosing in a single dosage form.
10. Allows site specific release for local treatment of diseases.

Drug release profiles from pulsatile drug delivery system.

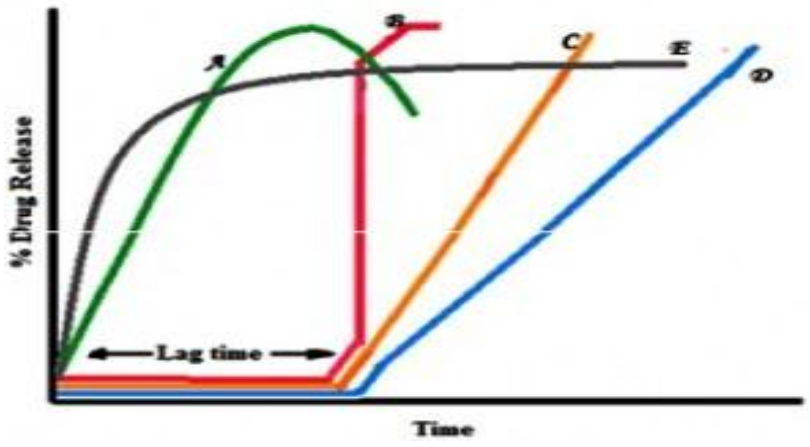


Fig. 1: **Drug release profiles from pulsatile drug delivery system.**

Where, A: Conventional release profile, B: Burst release of drug as a after a lag time, C: Delayed release profile after a lag time, D: Constant release profile in prolonged period after a lag time, E: Extended release profile without lag time.

Diseases that Require Pulsatile Technology

There are number of diseases which required to be formulated as PDDS as like: hypercholesterolemia, asthma, cancer, duodenal ulcer, arthritis, diabetes, neurological disorders, cardiovascular diseases (e.g. hypertension and acute myocardial infarction) and colonic delivery. The rationale for chronotherapy pulsatile release for each of these diseases will be briefly reviewed in tabular and text form.

Table. 1. Diseses that require pulsatile technology.

Disease	Chronological behaviour (category of drugs used)
Arthritis	Pain in the morning and more pain at night (NSAIDS, Glucocorticoids).
Asthama	Precipitation of attacks during night or at early morning hour (Antihistamines and β agonist).
Cardiovascular disease	BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period (Nitroglycerine, calcium channels blockers).
Diabetes mellitus	Increase in the blood sugar level after meal (sulfonylurea, biguanide, insulin).
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time (HMG Co-A reductase enzyme).
Peptic ulcer	Acid secretion is high (H2 blockers).

1. Lipidemic Disease: Diverse directions of circadian changes in lipid fractions in patients and normal subjects may contribute to alteration in the rhythmicity of other metabolisms and in the blood coagulation system, thus leading to various complications. A circadian rhythm occurs during hepatic cholesterol synthesis. Therefore, cholesterol synthesis is generally higher during the night than during daylight. The maximal production occurs early in the morning, i.e. 12 h after the last meal.

2. Pulmonary disease: The chronotherapy of asthma has been extensively studied. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. As bronchoconstriction and exacerbation of symptoms vary in a circadian fashion, asthma is well suited for chronotherapy.

3.Cancer: Human and animal studies suggest that chemotherapy may be more effective and less toxic if cancer drugs are administered at carefully selected times that take advantage of tumor cell cycles while less toxic to normal tissue. The blood flow to tumors was threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase. The chronotherapy concept offers further promise for improving current cancer-treatment options, as well as for optimizing the development of new anticancer or supportive agents.

4. GI Ulcer: Many of the functions of the gastrointestinal tract are subject to circadian rhythms: gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are all slower at night. During night time, when gastric motility and emptying are slower, drug disintegration, dissolution, and absorption may be slower. In peptic ulcer patients, gastric acid secretion is highest during the night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Therefore, for active duodenal ulcer, once daily at bedtime is the recommended dosage regimen for an H2 antagonist.

5. Rheumatoid Arthritis (RA): The chronobiology, chronopharmacology and chronotherapeutics of pain have been extensively reviewed. For instance, there is a circadian rhythm in the plasma concentration of C - reactive protein and interleukin of patients with rheumatoid arthritis. Patients with osteoarthritis tend to have less pain in the morning and more at night, while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day. Chronotherapy for all forms of arthritis using NSAIDs such as Ibuprofen should be timed to ensure that the highest blood levels of the drug coincide with peak pain.

6. Diabetes mellitus (DM): The circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance in case of insulin substitution in types: - I diabetes have been studied. The goal of insulin therapy is to mimic the normal physiologic pattern of endogenous insulin secretion in healthy individuals, with continuous basal secretion as well as meal-stimulated secretion.

7. CNS disorder: As an integrative discipline in physiology and medical research, chronobiology renders the discovery of new regulation processes regarding the central mechanisms of epilepsy. Chronophysiology investigations considered at a rhythmometric level of resolution suggest several heuristic perspectives regarding (i) the central pathophysiology of epilepsy and (ii) the behavioural classification of convulsive events.

8. CVS Disease: Several functions such as Blood pressure (BP), heart rate, stroke volume, cardiac output, blood flow of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregation is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. It was postulated that modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events. BP is at its lowest during the sleeping period and rises steeply during the early morning period. Most patients with essential hypertension have a similar circadian rhythm of BP as do normotensive persons, although hypertensive patients have an upward shift in the profile.

9. Colonic delivery: The colon is also seen as the preferred absorption site for oral administration of protein and peptide drugs, because of the relatively low proteolytic enzyme activities in the colon. A colon-specific drug delivery system should prevent drug release in the stomach and small intestine, and affect an abrupt onset of drug release upon entry into the colon. Time dependent delivery has also been proposed as a means of targeting the colon. Time dependent systems release their drug load after a preprogrammed time delay. To attain colonic release, the lag time should equate to the time taken for the system to reach the colon.

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEM

Pulsatile drug delivery system is classified into four classes

A. Time controlled pulsatile release

I. Single unit system

i) Capsular system. ii) Port system. iii) Delivery by solubility modulation.

iv) Delivery by reservoir systems with erodible or soluble barrier coatings.

II. Multi-particulate system

i) Pulsatile system based on rupturable coating. ii) Time controlled expulsion system.

iii) Pulsatile delivery by change in membrane permeability. iv) Sigmoidal release system.

v) Low density floating multiparticulate pulsatile systems.

B. Stimuli induced

I. Internal stimuli induced pulsatile system

i) Temperature induced system. ii) Chemical stimuli induced system.

iii) pH sensitive drug delivery system.

II. External stimuli induced system

i) Electrically stimulates pulsatile system. ii) Magnetically stimulated pulsatile system iii) Ultrasonically stimulated pulsatile system. iv) Photo chemically stimulated pulsatile system.

A. Time controlled pulsatile release

I. Single unit system

i. Capsular system: A capsular system consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined lag time owing to swelling, erosion, or dissolution. The lag time is continued by a plug that gets pushed away by swelling or erosion, releasing the drug as a pulse from the insoluble capsule body.

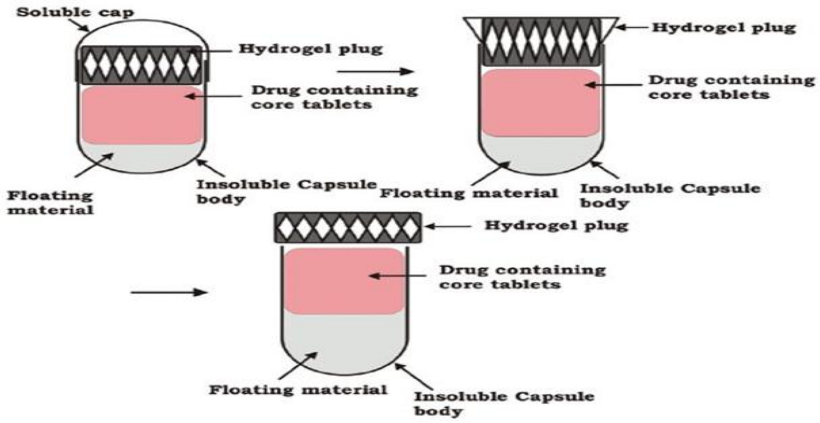


Fig. 2. Capsular System.

ii. Port system (Programmable oral release technology): Port system consist 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 (Figure 3). When in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time.

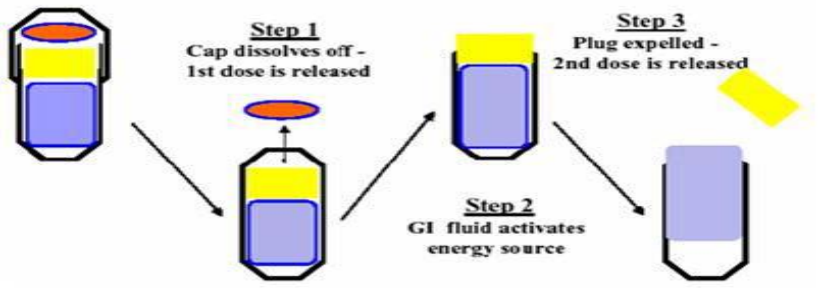


Fig. 3. Port system (Programmable oral release technology).

iii. Pulsatile drug delivery by modulating solubility

Magruder developed system consist of various solubility modulators. The system is used for anti-histaminic drug like salbutamol sulphate. Composition contains salbutamol sulphate and modulating agent sodium chloride. The amount of sodium chloride required is less than the amount needed to maintain the saturation fluid enters in osmotic device. It gives pulse release.

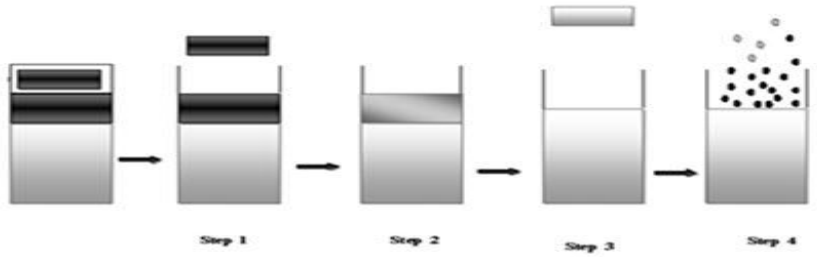


Fig. 4. Modulating solubility.

IV. Delivery by reservoir systems with erodible or soluble barrier coatings

The drug reservoir is coated with soluble erodible barrier. After its dissolution or erosion of that barrier drug is released from the reservoir.

Delivery systems with rupturable coating layer

These systems consist of an outer release controlling water insoluble but permeable coating layer which produces mechanically induced rupturing. The film rupture may be attained by including swelling, osmotic or effervescent additives in the reservoir. By optimizing the system, drug release can be obtained at specific time interval.

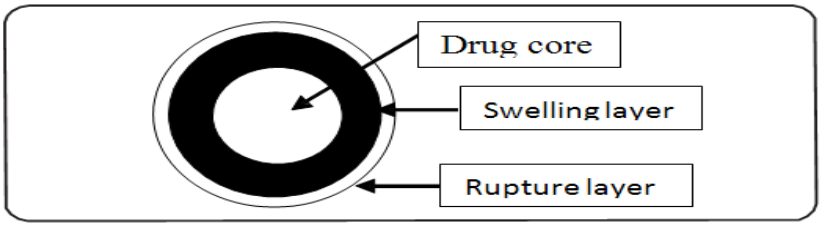


Fig. 5. Delivery systems with rupturable coating layer.

Delivery system with erodible coating layer

In these 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 ofthe active ingredient can be obtained by optimizing the thickness of the outer coat.

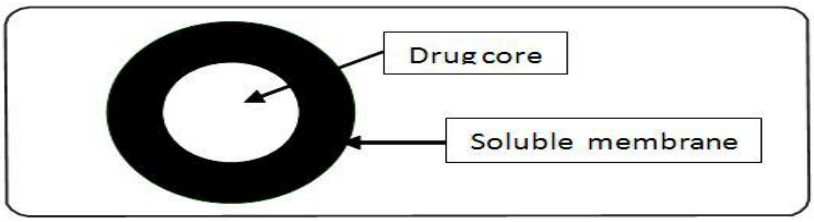


Fig. 6. Delivery system with erodible coating layer.

II. Multi-particulate system: The designing multiparticulate dosage form has more advantageous than single unit dosage form.

i. Reservoir systems with rupturable polymeric coating: Most multiparticulate pulsatile delivery systems are reservoir devices coated with a rupturable polymeric layer.

ii. Time controlled expulsion system

This system is based on a combination of osmotic and swelling effects.

iii. Pulsatile delivery by change in membrane permeability

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium. Several delivery systems based on this ion exchange have been developed.

iv. Sigmoidal release system: Sigmoidal release pattern is therapeutically beneficial for timed release and colonic drug delivery, and observed in coated systems.

v. Low density floating multiparticulate pulsatile systems: Low density floating multiparticulate pulsatile dosage forms reside in stomach only and not affected by variability of pH, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach. In short multiparticulate pulsatile release dosage forms possessing gastric retention capabilities.

I. Internal stimuli induced pulsatile system

i. Temperature induced system: The temperature is important for pulsatile drug delivery. The temperature is rises above the physiological body temperature (37°c) in presence of pyrogens. This deviation is important in various temperature responsive drug deliveries to release drug from temperature sensitive polymer in the disease occupying fever.

ii. Chemical stimuli induced system

a) Glucose-responsive insulin release devices -In case of diabetes mellitus there is rhythmic increase in the levels of glucose in the body requiring injection of the insulin at proper time. Many systems are developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel.

b) Inflammation-induced pulsatile release

When any physical and chemical stress such as injury,broken bones etc occurs the various inflammatory reactions takes place at injury site. At inflammatory sites phagocytic cells like macrophages and polymorphonuclear cells, play role in healing process.

c) Drug release from intelligent gels responding to antibody concentration

Many bioactive compounds are present in body. Novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/deswelling characteristics.

iii) PH sensitive drug delivery system

The versatile approach to design chronotropic system to attain specified lag time prior to drug release by using pH dependent polymers. These can be single unit or multiparticulate dosage forms with reliable and predictable drug release profile. This system having advantage to exist in different pH environment at different parts of gastrointestinal tract. So that pH dependent system is targeting at specific site of gastrointestinal tract is possible as well as a desired lag time can be achieve due to dependency of polymer solubility only at particular pH of gastrointestinal tract.

II. External stimuli induced system

These types of open-loop systems are not self-regulated. But for delivery of 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.

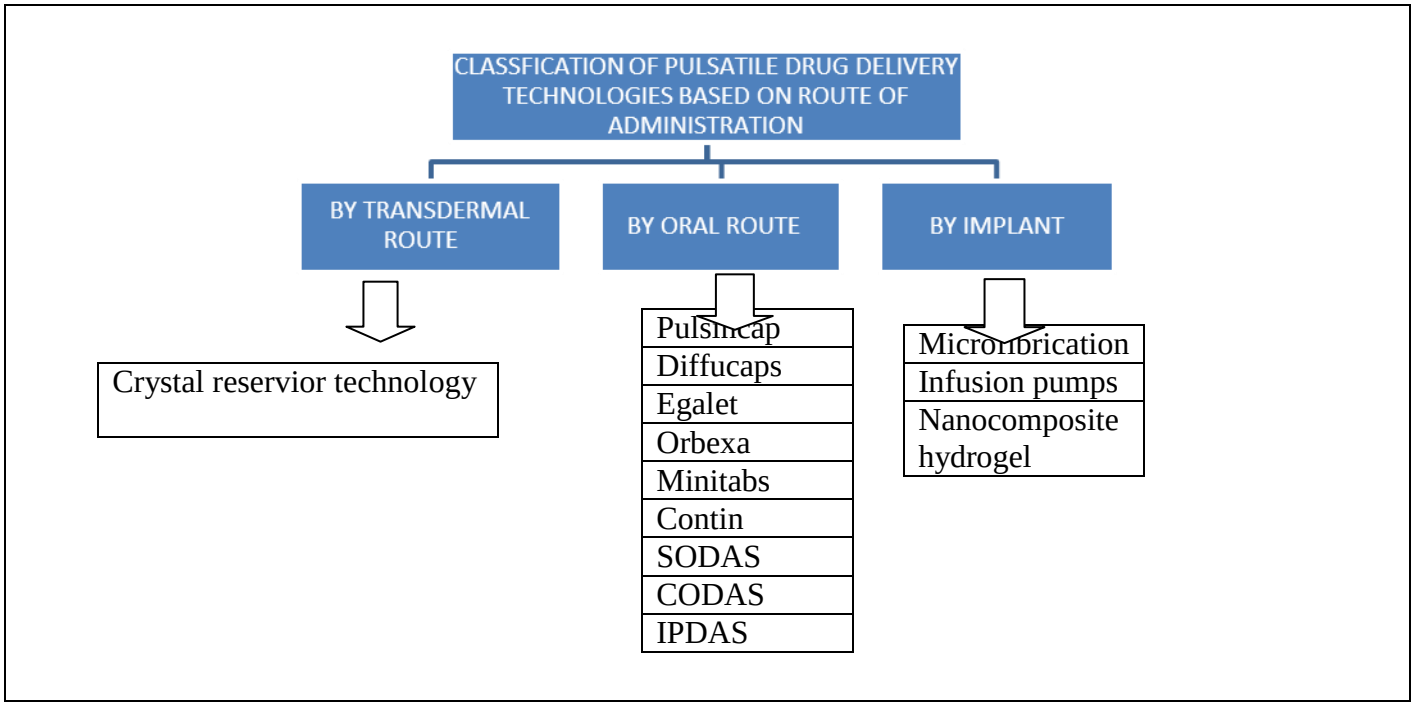
i. Electro responsive pulsatile release

This system provides the drug release by action of applied electric field on rate limiting membrane and/ or directly on solute, thus controls it transport across the membrane.

ii. Magnetically stimulated pulsatile system:- In this system magnetic steel beads can be embedded in a polymer matrix with model drug. During exposure to the magnetic field, the beads oscillate within the matrix, alternatively creating compressive and tensile forces. This in turn acts as a pump to push an increased amount of the drug molecule out the matrix.

Classification of Pulsatile Drug Technologies Based on Route of Administration

Table. 2: Classification of Pulsatile Drug Technologies Based on Route of Administration.



Chronomodulated Systems for Oral Route

Pulsincap® Technology

Pulsincap was developed by R.R.Scherer International Corporation (Michigan). This device consists of a non-disintegrating half capsule body sealed at the open end with a hydrogel plug that is covered by a water-soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When this capsule comes in contact with the dissolution fluid, it swells and after a lag time the plug pushes itself outside the capsule and rapidly releases the drug.

Diffucaps® Technology

Developed by Eurand Pharmaceuticals Ltd, USA**.** Diffucaps is a multiparticulate bead system comprised of multiple layers of drug, excipients, and functional polymer membrane to control the rate of drug release.

CONTIN ® Technology

Developed by Purdue Pharma. This technology provides for closer control over the amount of drug released to the bloodstream, and benefits patients in terms of reducing the number of doses they need to take every day, providing more effective control of their disease (particularly at night), and reducing unwanted side effect.

CODAS® (Chronotherapeutic oral drug absorption system)

Elan Corporation, USA, developed CODAS® technology. Delay is introduced by the level of non-enteric release-controlling polymer applied to drug loaded beads. The release-controlling polymer is a combination of water soluble and water insoluble polymers. As water from the gastrointestinal tract comes into contact with the polymer-coated beads, the water soluble polymer slowly dissolves, and the drug diffuses through the resulting pores in the coating.

Egalet® Technology

Developed by Egalet Ltd, Denmark. System consists of an impermeable shell with two lag plugs; active drug is sandwiched between the plugs. After the inert plugs have eroded, the drug is released, thus a lag time occurs. Time of release can be modulated by the length and composition of the plugs. This system shows erosion control drug release.

IPDAS® (Intestinal protective drug absorption system)

A new oral drug delivery approach that is applicable to gastrointestinal (GI) irritant drugs, including the non-steroidal anti-inflammatory drug (NSAID) class. The IPDAS technology is composed of numerous high-density, controlledrelease beads, which are compressed into a tablet form. Once an IPDAS tablet is ingested, it disintegrates and disperses beads containing a drug in the stomach, which subsequently passes into the duodenum and along the gastrointestinal tract in a controlled and gradual manner, independent of the feeding state.

Geoclock®

Developed by SkyePharma. It is in form of chronotherapy focused press-coated tablets. Geoclock tablets have an active drug [core] inside an outer tablet layer consisting of a mixture of hydrophobic wax and brittle material in order to obtain a pH-independent lag time prior to core drug delivery at a pre-determined release rate.

Geomatrix®

Developed by Skye Pharma Plc.USA. It is multilayered tablet which consists of a hydrophilic

matrix core, containing the active ingredient and one or two impermeable or semi-permeable polymeric coatings (films or compressed barriers) applied on one or both bases of the core which act as surface controlling barriers.

Diffutab®

This technology is useful for sustained and targeted pulsed delivery. The Diffutab technology incorporates a blend of waxes and hydrophilic polymers that control drug release through diffusion and erosion of a matrix tablet. Diffutabs are particularly useful for highdose products. This technology is applies to both soluble and insoluble products.

PulsysTM

Developed by MiddleBrook Pharmaceuticals, this enables pulsatile delivery or delivery in rapid bursts of certain drugs and provides the prolonged release and absorption of a drug. The rationale behind designing such a system is that it has been reported that antibiotics are more effective against fastgrowing bacteria.

SODAS® (spheroidal oral drug absorption system)

Developed by Elan Corporation. Multiparticulate drug delivery system, consist of uniform spheroidal beads of 1-2mm in diameter. Each bead begins as an inert core onto which the drug is applied, followed by a number of layers of soluble and insoluble polymers combined with other excipientsto produce the rate-controlling layer. Drug release from these beads occurs by a diffusion process.

Orbexa®

Developed by Aptalis Pharmaceutical Technologies**.** Orbexa technology is a multiparticulate system that enables high drug loading and is suitable for products that require granulation. This technology consists of beads of a controlled size and density using granulation/extrusion and spheronization techniques. These beads provide higher drug concentration, can be coated with functional polymer membranes for additional release rate control and can also be used for sensitive drugs such as proteins, enzymes.

Minitabs®

Developed by Aptalis Pharmaceutical Technologies. It consists of tiny (2 mm x 2 mm) cylindrical tablets coated with a functional membrane to control the rate of drug release. They contain gel-forming excipients that control drug release rate.

CHRONOMODULATED SYSTEMS FOR TRANSDERMAL ROUTE

Crystal reservoir system

Crystal Reservoir Technology is small patches, which shows controlled and sustained drug release. Release of a drug is based on the oversaturation of an adhesive polymer with drug, thus forcing a partial crystallization of the drug. The presence of both molecular solute and solid crystal forms allow for a considerably higher concentration and consistent supply of drug. As the skin absorbs the molecular solute, crystals re-dissolve to maintain maximum thermodynamic activity at the site of contact. By modifying the concentration of crystals to solute, various patterns of drug release are achieved.

Chrononomodulated delivery systems byimplant route

Chronomodulated infusion pumps

These pumps are usually characterized by a light weigh (300–500 g) for easy portability and precision in drug delivery. Implantable infusion pumps used in Insulin therapy containing a reservoir of insulin may be surgically placed within the subcutaneous tissue of the abdomen in the left upper or lower quadrant (above or below the belt).

Microfabrication

These devices contain small reservoirs loaded with drugs and separated from outside environment by thin membrane. The active silicon-based microchip membrane is thin layer of gold. In order to release the drug the voltage need to be applied**.** The release mechanism is based on the electrochemical dissolution of thin anode membranes covering microreservoirs filled with chemicals in solid, liquid or gel form. Here a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand.

Magnetic nanocomposite hydrogel

Magnetic nanocomposite of temperature responsive hydrogel was used as remote controlled pulsatile drug delivery. Nanocomposites were synthesized by incorporation of superparamagnetic Fe3O4 particles in negative temperature sensitive poly (Nisopropyl acrylamide) hydrogels along with model drug. High frequency alternating magnetic field was applied, the beads oscillate within the matrix, creating compressive and tensile forces, and hydrogel temperature increases results into accelerated collapse of gel. This in turn acts as a pump to push an increased amount of the drug molecule out the matrix to produce on demand pulsatile drug release from nanocomposite hydrogel.

REFERENCES

1. Prasanth V.V, Modi Mitesh P., and Mathew Sam T: Pulsatile: A tool for circardian rhythm - a review. Journal of Drug Delivery & Therapeutics, 2012; 2(1): 58-65.
2. Sharma Ritika, Singh Arjun, Kumar Sunil, Jamil Faraz: Pulsatile drug delivery system. International Research Journal of Pharmacy, 2012; 3(7): 103-107.
3. Vikram S. Chhabra, Shrikant K. Tilloo, Sheelpriya R., Walde, Abhay M. Ittadwar: The essentials of chronopharmacotherapeutics. International Journal of Pharmacy and Pharmaceutical Sciences, 2012; 4(3): 1-8.
4. Sirisha V.N.L, Namrata M., Sruthi B., Harika I., Kiran kumar P., Kiran Y., Kumar Rao K.Pranavi: Pulsatile Drug Delivery System-A Review. International Journal of Pharmaceutical Research & Allied Sciences, 2012; 1(3): 13-23.
5. Pandit Vinay, Sarasija Suresh: Emerging Role of Biorhythms in Optimizing Treatment of Diseases. Indian Journal of Novel Drug delivery, 2009; 1(1): 2-10.
6. Sarasija Suresh, Stutie Pathak: Chronotherapeutics Emerging Role of Biorhythms in Optimizing Drug Therapy. Indian Journal of Pharmaceutical Science, 2005; 67(2): 135-140.
7. Lemmer B. Chronopharmacokinetics: implications for drug treatment, J Pharm Pharmacology, 1999; 51: 887-890.
8. Ritschel, Forusz WA. Chronopharmacology: a review of drugs studies, Methods Find. Exp Clin Pharmacol, 1994; 16(1): 57-75.
9. Belgamwar VS, Gaikwad MV, Patil GB, Surana S, Pulsatile drug delivery system. Asian J of Pharmaceutics, 2008; 2(3): 141-145.
10. Das NG, Das SK, Controlled release of oral dosage forms, formulation, finish, and fill, Pharmtech, 2003; 10-16.
11. Stein EA, Davidson MH, Dobs AS, Schrott H, Dujovne CA, Bays H, Weiss SR, Melino MR, Mitchel ME, Mitchel YB. Efficacy and safety of simvastatin 80 mg/day in hypercholesterolemic patients, Am J Cardiol, 1998; 82: 311- 316.
12. Richard MD, Havel J, Simvastatin: a one-a-day treatment for hypercholesterolemia An Introduction. Am J Med., 1989; 87(Suppl 4): 1S– 59S.
13. Martin RJ, BanksSS. Chronobiology of asthma, Am J Respir Crit Care Med., 1998; 158: 1002– 1007.
14. Hrushesky W, Langer R, Theeuwes F, Temporal Control of Drug Delivery, Academy of Sciences, J. Controlled Release, 1987; 6: 297-305.

15. Gothoskar AV, Joshi AM, Joshi NH, Pulsatile drug delivery systems: a review, Drug Delivery Technology, 2004; 4(5): 1-11. 52.
16. Shivakumar HG, Pramod kumar TM, Kashppa GD: Pulsatile drug delivery system, Indian J Pham Educ, 2003; 37(3): 125.
17. Ramesh D Parmar, Rajesh K Parikh, Vidyasagar G, Dhaval V Patel, Chirag J Patel and Biraju D Patel. Pulsatile Drug Delivery Systems: An Overview. Int J Pharma Sci and Nanotechnology, 2009; 605-614.
18. Buchi KN, Moore JG, Hrushesky WJ, Sothern RB, Rubin NH. Circadian rhythm of cellular proliferation in the human rectal mucosa, Gastroenterology, 1991; 101: 410– 415.
19. Cloud ML, Offen WW Nizatidine versus placebo ingastroesophageal reflux disease, A6 week, multicenter, randomized, doubleblindcomparison, Nizatidin e, Gastroesophageal Relux Disease Study Group. Dig Dis Sci., 1992; 37: 865– 874.
20. Jose S, Dhanya K, Cinu TA, Litty J and Chacko A J. Colon targeted drug delivery: Different approaches. J Young Pharmacist, 2009; 1: 13-9
21. Marroum P. Development and evaluation of controlled release products with emerging technologies. Amer Pharm Rev., 2009; 147-149.