Review Article

Pulsatile Drug Delivery System (PDDS): A Cronotherapeutic Approach for Optimum Therapy

ABSTRACT:
Now a day's PDDS are gaining more attraction and importance especially for the disease follow circadian rhythms. Some chronic disease like rheumatoid arthritis, asthma, hypercholesterolemia, hyper acidity and cardio vascular diseases where peak symptoms tends to follow a 24 hour cycle called circadian rhythms. Optimum therapy of these diseases demands a drug delivery system where C_{max} of the drug achieve exactly at the time of peak of the disease. This is only possible by chronotherapeutic approach i.e pulsatile drug delivery system. This delivery system not only releases the right amount of drug at the right time but also overcome the other challenges like drug tolerance and over dose associated with traditional sustained or extended release drug delivery system. Drugs under goes extensive first pass metabolism, degradation in gastric acid medium, having biological tolerance and targeted to distal parts of GIT are suitable candidates for PDDS. It has many advantages like pre-programmed delayed-release, multiple dosing option, reduce drug loss, less drug interaction and improve patient compliance etc There are various technologies of PDDS like C O D A S ®,O R O S ®, DIFFUCAPS ®,3D Printing, PULSINCAP™ are already available in the market. The current work is focused on the requirements, advantages, disadvantages and a review on various drugs and polymers used to develop PDDS in current & past decades. The study revealed that, PDDS has a tremendous scope and can play a vital role in the optimum treatment of many chronic diseases which follows circadian rhythm .

KEYWORDS: Pulsatile Drug Delivery System(PDDS), Chrono therapeutic Drug Delivery System, Chrono pharmacology, Circadian Rhythm.

1. INTRODUCTION:

Pulsatile Drug Delivery System (PDDS) provides more benefits by releasing the right amount of the drug, at the right site of action, at the right time as compared to conventional dosage forms. Nowadays researchers are turned towards a controlled released drug delivery system which is nothing but a modified drug delivery system of the drugs which already exist. A pulsatile drug delivery system provides more efficacious drug release. Modified controlled drug delivery systems have great importance in this regard. Such a system controls the pattern of release of the drug. The amount of dug to be released and the rate of drug to be delivered can be modified in this system by changing the number and the thickness of the layer. PDDS follow the pre-programmed pattern for delivery of the drug. There are various techniques available for pulsatile drug delivery in the market such as pH-dependent system, micro-flora activated system, time-dependent system, etc. which can be designed according to the

physiology of the disease and properties of the drug molecule.The “Chrono therapeutic" is made up of two words Chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms of the body and their mechanisms. [1-4].

In the human body, there are three types of mechanical rhythms. They are:

1.1 Ultradian Rhythms:
Shorter duration oscillations are termed as Ultradian Rhythms (more than one cycle per 24 hrs.) E. g. 90 minutes sleeps cycle [5].

1.2 Infradian Rhythms:
Oscillation duration longer than 24 hrs. Are termed as Infradian Rhythms (less than one cycle per 24 hrs.) E. g. Monthly Menstruation [6].

1.3 Circadian Rhythms:
Circadian Rhythms are self-sustaining, an endogenous oscillation that occurs with a periodicity of about 24 hrs. Control release drug delivery systems for 12 or 24 hrs. Drug release is not suitable for disease, which follows circadian variation and, in such condition, there is the requirement for time or pulsatile drug delivery system. Research scholars also found that some medications may work better if their administration is coordinated with daynight patterns and biological rhythms of the human body. Human circadian rhythms are based on the sleep activity cycle which can be influenced by our genetic and hence affect the bodies functions day and night. In 1729 the first known experiment that exists on biological rhythms was conducted by French astronomer Jean Jacques d'ortousdeMairan. Biological rhythms not only impact on functions of physiology but also affect the pathophysiology of the diseases in the human body[7, 8].

In the recent work , a review has been made about requirement of pulsatile drug delivery system, it’s merits demerits, various techniques, some past works and future prospect of pulsatile drug delivery system

2. NEED OF NOVEL PULSATILE DRUG DELIVERY SYSTEM

- Acid secretion in the stomach, gastrointestinal blood transfusion, gastric emptying and cholesterol synthesis follows circadian rhythm .
- Disease like bronchal asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension follows circadian rhythm.
- Drug which undergo degradation in gastric acidic medium, example, peptides drugs.
- Drugs to targets colon.
- Timed fluctuation in secretion of hormones like rennin, aldosterone, and cortisol.
- Drugs that shows extensive first pass metabolism.
- Drugs where over exposure leads to biological tolerance. [9,10]

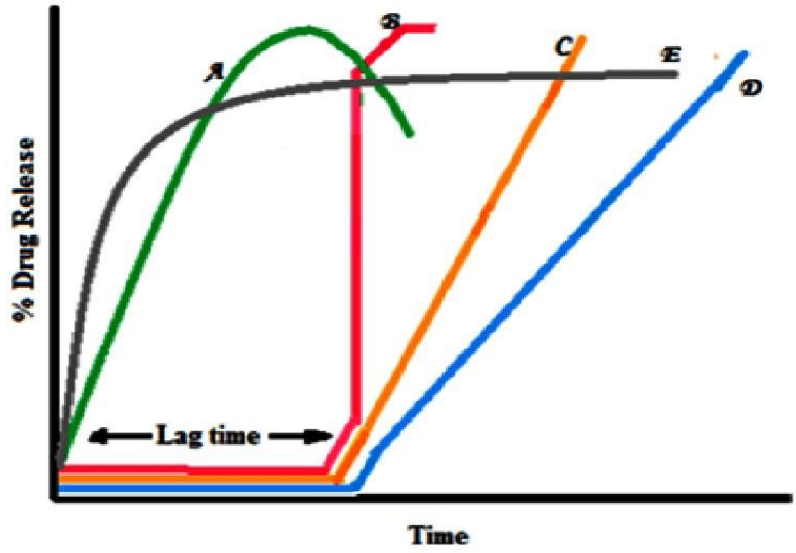

Fig.1: Drug release profile from PDDS vs conventional vs delayed release

Where,

A = Conventional release profile.

B = Burst release of drug after a lag time.

C = Delayed release of drug after a lag time.

D = Constant release profile in a prolonged period after a lag time. E = Extended release of the drug without a lag time.

3. ADVANTAGES OF PULSATILE DRUG DELIVERY SYSTEM [2, 11]

There are many advantages of Pulsatile Drug Delivery System over conventional dosage form:

- Chronotherapy, the pre-programmed delayed-release provides optimal treatment of diseases.
- Multiple dosing is allowed in a single dosage form as the system releases the drug as a pulse.
- Local treatment of the disease is allowed as the system is a site-specific drug delivery system.
- PDDS Reduce dose frequency and risk of dose dumping, dose cost, dose size and ultimately reduce the side effect and improve the patient compliance.
- Decrease side effects.
- This system increases absorption and bioavailability of the drug as compared to conventional immediate release or sustained release drug as this system release the drug in a burst manner at the target site of the drug absorption.
- Drug interaction is less due to cytochrome P450 isoenzymes.
- As this system is a target-specific release system it allows poorly bioavailable drugs that may get destroyed in the GI Tract.
- It decreases food effect when the drug is given with food.
- It improves patient compliance.
- The release of the drug in this system is not affected by the change in pH of the GI Tract, the viscosity of lumen contents, and the agitation rate of the GI Tract.

- This system can be used in different solid dosage forms, such as microspheres, granules, tablets, pallets, capsules, etc.

4. **LIMITATIONS:** [2,11]

- In vivo variability in single unit pulsatile drug delivery system.
- Production cost is very high.
- IVIVC is unpredictable.

5. RESULTS OBTAINED FOR VARIOUS TYPESS OF PDDS DEVELOPED SPECIALLY FOR CHRONIC DISEASES LIKE CARDIOVASCULAR DISEASES, ARTHRITIS, AND ASTHMA

Cardiovascular diseases:

Several functions such as Blood Pressure, Heart Rate, Stroke Volume, Cardiac output, Blood Flow of cardiovascular systems are subjected to circadian rhythms. For cardiovascular diseases, several drugs like Nitroglycerine, Calcium Channel Blockers, ACE Inhibitors, etc. are used in different dosage forms of the pulsatile drug delivery system. **[12]**

Bajpai **et al** developed the compression coated pulsatile release tablets of Losartan Potassium for the treatment of cardiovascular disease (hypertension). The prepared formulation contains a core tablet that is coated with a versatile polymer like Hydroxypropyl methylcellulose. Hydroxypropyl cellulose, Sodium Carboxy Methylcellulose is used along with the effervescent agent to produce burst release after predetermined lag-time. The results revealed that the objective of producing pre-patterned lag-time of 6-7 hours and then a fast release of drugs was achieved. [13]

Rao **et al** formulated a Pulsatile Release form Tablet and Capsule Dosage forms of Metoprolol Tartrate which are used in the treatment of hypertension and myocardial infarction. It was concluded that the capsule dosage form showed a lag-time by the better pulsatile release of drug whereas, the tablet dosage form showed a lag-time in which 10-20% of the drug was released during the lag-time followed by pulsatile release. [14]

Borgaonkar **et a**l prepared a Pulsatile Drug Delivery System of Metoprolol Tartrate using Core in Cup Tablet. The core of the table contains metoprolol tartrate and Cellulose Acetate Propionate which is used as an impermeable membrane for the drug and Sodium Alginate 500 cps and sodium alginate 2000 cps used as a soluble hydrophilic polymer layer. The result showed after a Pre-Planned lag-time of about 5 hrs. thus it is suggesting that this system (pulsatile drug delivery system) can be prepared to increase the therapeutic effectiveness of the drug. [15]

Latha **et al** developed optimized Losartan Potassium Press-coated Tablets for pulsatile release of Drug. The inner core of the tablet was prepared by compression-coating with HPMC 100 KM along and admixed with MCC as the outer layer in different ratios with the lag-time was from 0.5 to 18.5hrs **[**16].

***Archana* et a**l developed a Pre-Programmable „Tablet in Capsule" Drug Delivery device for Oral administration of Propranolol Hydrochloride using a swellable hydrophilic polymer Hydroxypropyl Methylcellulose K15 (HPMC K15) as a plug material for Pulsatile Drug Delivery for the Treatment of Hypertension. The results showed that this device can be used for chronotherapeutic drug delivery of propranolol hydrochloride for preventing early morning heart stroke in the human body [17].

***Patil* et al** prepared time-controlled pulsatile drug release of Linsopriil tablets based on a press coated table, where a core tablet is surrounded by different coating materials. The coating materials contain hydrophobic polymer of ethyl cellulose and hydrophilic materials (HPMC 15 CPS) were used in different concentrations and layers. The results show that it is a promising formulation technique for chronotherapeutic management of cardiovascular disease (hypertension). [18]

***Jagdale* et al** have designed an Enteric Press-Coated Tablet for Pulsatile Drug Delivery of Atenolol. A novel colon targeted tablet formulation was prepared by press coating which is a rapidly disintegrating tablet of Atenolol with guar gum and Eudragit L-100 as a barrier layer. Different ratios of polymers were selected to achieve suitable lag time for the treatment of angina pectoris i.e. A Cardiovascular Disease. [19]

***Jain* et al** developed a Pulsatile Drug Releasing System Containing Losartan Potassium and Hydrochlorothiazide. The results revealed that presscoated tablets achieve a burst release after 4 h of pre-Patterned lag time which is an applicable pulsatile drug delivery system for hypertension. [20]

***Patil* et al** designed a Chrono modulated pulsatile drug releasing system of captopril which is used in the treatment of Cardiovascular Disease (hypertension). The core of the formulation consists of bioactive compound captopril which was prepared by direct compression method and then coated sequentially with an inner swelling layer containing hydrocolloid HPMC E5 and an outer rupturable layer of the formulation containing Eudragit RL/RS (1:1). The system was found to be satisfactory in terms of the release of the drug after a Pre-Patterned lag time of 6 hours. [21]

***Gohel* et al** have prepared a Pulsatile Drug Delivery System of Diltiazem hydrochloride release from a novel „tablet in capsule system" containing an effervescent blend. Drug release having a Pre-Planned lag time of 4 hours was achieved through the system. [22]

Arthritis:

Arthritis is defined as the Inflammation of one or more joints, which causes pain and stiffness and may increase with the age. There are three most common Arthritis are Osteoarthritis, Rheumatoid Arthritis, and Psoriatic Arthritis.In arthritis, there is a circadian rhythm in the plasma concentration of C- reactive protein and interleukin-6 of patients with rheumatoid arthritis **[20].**Chronobiological patterns associated with arthritis have been observed with

morning stiffness and arthritic pain in patients. The people who suffer from osteoarthritis tend to have less pain in the morning time and feel more pain at night whereas rheumatoid arthritis patients feel the pain mostly increases in the morning time and decreases later as the day goes on. The new cyclooxygenase-2inhibitors effectively reduced the osteoarthritis symptoms when taken the drug in the morning time and shows better results are in rheumatoid arthritis when a small amount of the dose is taken in the evening**.** [23].

Chauhan **et al** developed a pulsatile drug delivery system of Aceclofenac for treatment of rheumatoid arthritis, with the combination of Eudragit L-100 and S-100 in the core. The concentration of the plugging material was found sufficient to maintain the Pre-Patterned lag-time for a minimum period of 4 hrs. [24]

Patel **et al** had developed a formulation of chronotherapeutics drug release of Aceclofenac. The formulation achieved the desired pulsed release profile after a PreProgrammed lag time. [25]

Kausalya **et al** prepared a Pulsatile Drug Delivery system of Flurbiprofen microspheres for the treatment of Arthritis. This system consists of drug-loaded cellulose acetate cores which are encapsulated within Eudragit S-100 microspheres. The formulation showed drug release after a Pre-Planned lag-time of 12 hours. [26]

Moon **et al** had developed press-coated Pulsatile Drug Delivery tablets of Indomethacin for the treatment of Arthritis. The press-coated tablet releases the drug after a Pre-Patterned lag-time of around 4-8 hrs. followed by a rapid and complete release phase of the drug. [27]

Jain **et al** had designed and developed a floating pulsatile drug delivery system of lornoxicam for chronotherapy treatment of rheumatoid arthritis. The system consisted of drug-containing core tablets, which are surrounded by pH-dependent polymer Eudragit S100 and the outer layer contains an effervescent layer of polymers. The formulation had shown its results followed by rapid and burst release of drug from Floating Pulsatile Tablets. with no drug release before the Pre-Patterned lag-time of about 6-7 hrs. [28]

Sharma **et al** designed and developed a low-density multiparticulate system for pulsatile drug delivery system of Meloxicam, sodium alginate, and porous calcium silicate (Florite RE®), for time and site-specific release of drug from the formulation. Formulations show a lag period ranging from 1.9 to 7.8 hrs. in acidic medium followed by a rapid release of meloxicam in simulated intestinal fluid in the human body. [29]

Li, **et al** have formulated a three-pulse based Pulsatile Drug Release of Diclofenac Sodium based on "tablets in capsule" device for the treatment of arthritis such as rheumatoid arthritis. hydroxy-propyl methylcellulose (HPMC E5) and Sodium alginate were used as the candidate modulating barrier material. The lag time of 7 hours was observed with about 60% sodium alginate concentration. [30]

***Meena* et** al have formulated a Pulsatile drug delivery system of Lornoxicam for the treatment of Rheumatoid Arthritis. Lornoxicam microcapsules were formulated by the solvent evaporation method by using Eudragit L/S 100. The system was found promising effectiveness for the chronotherapy of rheumatoid arthritis. [31]

Asthma:

Asthma is a chronic inflammatory disease of the airways, characterized by hyperresponsiveness to a variety of stimuli **[31]**. Disease like Asthma results in increased airway responsiveness & worsening the functions of the lungs. From extensive studies, it has been founded and concluded by the research scholars that the role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients, and later decreases to a low point in the early morning hours. These symptoms typically occur between midnight & especially around 4 am in the early morning time. [32,33]

***Padmaxi* et al** had prepared One-Pulse Drug Delivery System based on a presscoated tablet preparation of Montelukast sodium for the treatment of asthma. The PreProgrammable time-controlled release was obtained from a press-coated tablet over a PrePlanned lag-time of 5 hrs. and burst release was achieved after a lag time, which is consistent with the demands of chronotherapeutic drug delivery. [34]

***Sadaphal* et al** have designed and developed a pulsatile drug Releasing system of Theophylline for the treatment of Asthma. A drug consisted of Isopropyl Alcohol (70%) and Acetone (30%) which was used as a solvent for Eudragit S100 coating. The system releases the drug which was after a predetermined lag time of 6 h and thus the dosage forms can be taken at bedtime so that the content will be released in the early morning hours. [35]

***Ali* et al** have prepared a Chrono modulated Drug Releasing System of Salbutamol Sulphate for the Treatment of Nocturnal Asthma. They have designed and developed a rupturable pulsatile drug delivery system that consisted of a core that contains microcrystalline cellulose, sodium chloride, an inner or intermediate swelling layer, hydroxypropyl methylcellulose (HPMC E5), and an outer layer which is water-insoluble but permeable coating. The system was found to be satisfactory in terms of release of the drug after a Pre-Patterned lag time of 6 hrs. [36]

***Kadam* et al** had designed and developed a colon-targeted multiparticulate pulsatile drug delivery system of Theophylline for the treatment of Nocturnal Asthma. Formulation of Fast release enteric-coated pellets of theophylline was prepared for a pulsatile drug delivery system. A Pre-Patterned lag phase of 5 h was seen in the formulation. [37]

***Mahajan* et al** had designed and developed a timed delayed capsule device for chronotherapeutic delivery of Terbutaline sulphate for the therapy of asthma the lag time criterion of 5 hrs. was achieved. [38]

***Janugade* et al** have designed and developed a formulation of press-coated Montelukast sodium tablets for Pulsatile Drug Delivery System. The tablets were formulated by both dry granulation method and wet granulation methods. As compared to the dry mixed blend method wet granulation method gives less lag time to the Pulsatile Drug Delivery System. [39]

TABLE 1: Classes of drugs used in various diseases follows chronotherapeutic behaviour [3, 40,41,42]

S. NO.	DISEASES	CHRONOTHERAPEUTIC BEHAVIOR	DRUG USED
1.	Peptic Ulcer	Acid secretion s high in the afternoon and at night	H_2 blockers
2.	Asthma	Precipitation of attacks during the night or at the early morning hour	$\beta_2$agonist, Antihistaminic
3.	Cardiovascular Diseases	BP is at its lowest level during the sleep cycle and rises steeply during the early morning awakening period	Nitroglycerin, Calcium channel blocker, ACE inhibitors, etc.
4.	Arthritis	Pain occurs in the morning and more pain at night	NSAIDs, Glucocorticoids
5.	Diabetes Mellitus	Increase in the blood sugar level after a meal	Sulfonylurea, insulin, Biguanide
6.	Attention Deficit Syndrome	Increase in DOPA level in the afternoon	Methylphenidate
7.	Hypercholesterolemia	Cholesterol synthesis occurs generally higher during the night than day time	HMG CoA reductase inhibitors

TABLE 2: Different Technologies of Pulsatile Drug Delivery System are available in the market: [3, 40, 41,42]

S. NO.	TECHNOLOGY	MECHANISM	PROPRIETORY NAME AND DOSAGE FORMS	API	DISEASE
1	C O D A S ®	Multiparticular pH-Dependent System	Verelanr® PM; XL Release Capsule	Verapamil HCL	Hypertension

2.	O R O S ®	Osmotic Mechanism	Cover-HS®; XL Tablet	Verapamil HCL	Hypertension
3	DIFFUCAPS ®	Multiparticulate System	Innopran®; XL Tablets	Verapamil HCL, Propanolol HCL	Hypertension
4	ThreeDimensional Printing	Externally Regulated System	TheirForm®	Diclofenac Sodium	Inflammation
5	PULSINCAP™	Rupturable System	Pulsincap™	Dofetilide	Hypertension

Table 3: Some current and past decades development of PDDS

S. No.	Year	Formulation	Api	Ingredients [Polymers &Excepients]	Disease [In Use]	Ref
1	2009	Press Coated Tablet	Ketoprofen	EC(10cP,45cP, 100cP), SA, MS, GH.	Rheumatoid Arthritis	43
2	2009	Press Coated Tablet	Montelucast Sodium	MCC, Avicel ph-102, CCS, MS, ER, EC, L-HPC LH-31, PVP,K90, SLS	Asthma	39
3	2010	Pulsincap	Trimetadizine Hydrochloridw	ES-100, EL-100, CAP, HPMC, XG, GG, EC, Acetone, Methanol, Ethanol, LP, S-80, PE, SHP, PDP, PC, HCL	Angina	44
4	2011	Press Coated Tablet	Montelucast Sodium	CP, SSG, Mannitol, MCC, SS, Flavour, SLS,Talc, MS	Asthma & Allergic rhinitis	45
5	2011	Press Coated Tablet	Indometha cin	MCC Avicel PH-102, MS, Starch, CCS, PVP, K90, HPMC K4M, EC	Arthritis (Osteoarthriti s)	46
6	2012	Pulsincap	Metoprolo l Succinate	GG, ES, PVP, Methanol, PDHOP, SH, Talc, MS,	Hypertension	47
7	2013	Pulsincap	Ibuprofen	HPMC K100M, PEO, Formaldehyde, MS	Arthritis	48
8	2014	Pulsincap	Losartan potassium	SA, GG, XG, $BaCO_3$	Hypertension	49

9	2014	Pulsincap	Rizatriptan Benzoate	HPMC K4M, Methanol, PVPK30, Talc, MS	Migraine	50
10	2014	PulsinCap	Lansoprazole	HPMC K 100 M, PVP K30, Lactose, MS, Talc, XG, GK	Ulcer	51
11	2014	Pulsincap	Salbutaml Sulphate	MCC Avicel PH101, ES100, EL100, SA, HPMC, PO, EC, Acetonitrile, Methanol	Asthma	52

S. No.	Year	Formulation	Api	Ingredients [Polymers &Excepients]	Disease [In Use]	Ref
12	2015	Press Coated Tablet	Ketoprofen	HPMC K4M & K100M, ES100 & EL100, SSG, MCC, Lactose, MS, Talc, CP, CCS, SSG, PGS	Rheumaatoid Arthhhritis	53
13	2015	Press Coated Tablet	Salbutamol Sulphate	SSG, CCS, MCC, DCP, MS, Talc, HPMC K15M, EC, ES100 & EL100	Asthma	54
14	2015	Pulsincap	Lovastatin	ERS100, GG, XG, KG, GK	Cholesrterol (CVD)	55
15	2016	Pulsincap	Captopril HCL	HPMC K4M, CCS, GG, XG, SA, MS, MCC Avicel 581	Hypertension	56
16	2016	Pulsincap	Amlodipine Besylate	HPMC, Sodium CMC, Carbopol 971, XG	Hypertension	57
17	2016	Pulsincap	Glipizide	EC, CCS, ES-100, EL-100, DHP, PDP, PE, n-Hexane, GG, PVP, CAP, SH, MS, SC, S-80, T-80	Type-II Diabetes Mellitus	58
18	2016	Pulsincap	Melatonin	DCM, Lactose, PEG, EC, NaCMC, Hard gelatin Capsule, Formaldehyde,	Insomnia	59
19	2016	Tablet in Capsule	Nicorandil	ES-100, EL-100, MCC, PVP, SSG, MS, Lactose	Angina Pectoris	60
20	2016	Pulsincap	Fluvastatin Sodium	EC, XG, GG, KG, GK, Span80, Tween-80	Cholesterol (CVD)	61
21	2016	Press Coated Tablet	Pregabalin	PVP, Lactose, DCP, EC, IPA	Anticonvulsant	62

22	2016	Press Coated Tablet	Diltiazem Hydrochlorid e	MCC Avicel PH102, CCS, MS, Klucel HF, HXF, ERSPO,	Hypertensio n	63
23	2017	Press Coated Tablet	Propranolol Hydrochlorid e	HPMC K4M, EC, CCS, MCC, MS, Talc	Hypertensio n	64
24	2017	PulsinCap	Terbutalin Sulphate	SSG, SBC, Vivapur 302, EC, HPMC K100M, GG,	Bronchial Asthma	65

S. No.	Year	Formulation	Api	Ingredients [Polymers &Excepients]	Disease [In Use]	Ref
25	2018	Pulsincap	Ketoprofen	AA, CAP, HPMC, PDHOP, BC, UDCM, EC, ERS 100,	Rheumatoid Arthritis	66
26	2018	Microcapsul e	Montelucast Sodium	ES100, EL100, XG, GG,CAP, LP, S-80, DP, Acetone, PE	Nocturnal Asthma	67
27	2018	Pulsincap	Budesonide	HPMC K4M, EL100, EC, PVP K30, Talc, MS, LSA, GG, HPMC K15M,	Asthma	68
28	2018	Pulsincap	Valsartan	HPMC K4M, EC, PVP, Talc, MS,	Hypertension	69
29	2018	Press Coated Tablet	Salbutamol Sulphate	EC 20, HPMC k4M, L HPMC LH11, SSG, CCS, CP, PVP k30, MCC PH 102, MS, LMH	Asthma	70
30	2018	Pulsincap	Irbesartan	HPMC K4M, EC, PVP	Hypertension	71
31	2019	Pulsincap	Lisinopril	EA, HPMC K4M, SSG, MCC, PVP K30	Hypertension	72
32	2019	Pulsincap	Atrovastatin	BC, HPMC, MC, SA, EC, XG,	Hypercholestrolemia	73
33	2020	Pulsincap	Rivaroxaban	SSG, CCS, HCL, Methanol, MCC, MS, Talc, EC, HPMC, Formaldehyde, PP, PDP, SHP,	Hypercholestrolemia	74
34	2020	Pulsincap	Montlucast Sodium	Starch MCC, CCS, SA, PVP k30, HPMC, XG, ES-100, MS, Formaldehyde, NaOH, HCL, PP, Ethanol,	Nocturnal Asthma	75

35	2021	Press Coated Tablet	Losartan Potassium	HPMC K4M, HPMC K100M, HPMC 50CPS, MCC Avicel PH 102, EC, Talc, MS, Colour	Hypertension	76

6. THE MECHANISM FOR DRUG RELEASE OF PULSATILE DRUG DELIVERY SYSTEM: [1]

There is mainly 3 mechanism of drug-releasing from a Pulsatile Drug Delivery System. They are:

Diffusion:
When water diffuses inside the particle of the drug when the particle comes in contact with the fluid of the gastrointestinal tract, that results from the drug solutions diffused from inside to outside.

Osmosis:
When water allows entering into the inside of the drug particle, an osmotic pressure can b built up inside under the right circumstances. The inside pressure forced the drug to outside through the coating.

Erosion:
Some coating of the formulations designed to erode gradually with time, which result in the drug release contained within the particle

7. VARIOUS MODIFIED RELEASE DRUG PRODUCTS: [39]

- **Extended-Release:** It leads to two-fold reductions in dosing frequency compared to immediate release dosage forms.
- **Controlled release**: This system allows the release of the drug gradually over an extended period but not at a predetermined rate.
- **Sustained-release:** This system delivers drugs at a Pre-Planned rate over a long period.
- **Delayed Release:** This dosage form releases the drug at a time other than immediately after administration.

- **Targeted Release:** These delivery systems deliver the drug at or near the specific site of action and may have extended-release characteristics.

- **Repeated Action:** This product is designed to release the first dose initially, followed by a second dose of the drug at a later time.

- **Prolonged Action:** This dosage form releases the drug slowly and provides a continuous supply of the drug over an extended period.

8. DIFFERENT METHODS FOR PULSATILE DRUG DELIVERY SYSTEM: [1,77-80]

Methodologies for Pulsatile Drug Delivery System can be classified into:

8.1 Time Controlled:

8.1.1 Pulsatile Drug delivery by Erosion of layer:

This release system of the drug contains a reservoir device coated by an outer barrier layer. This consists core containing drug reservoir which is coated by hydrophilic polymer HPMC. The release of the drug can be controlled by modifying the thickness and viscosity of the outer layer.

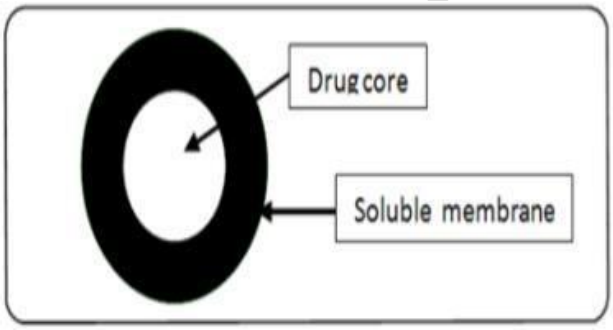

Fig.2: Pulsatile Drug delivery by Erosion of layer

8.1.2 Pulsatile Delivery of drug by Rupturable Membrane:

This system of drug delivery contains an outer layer that is water-insoluble but permeable coating with rupture phenomenon. The pressure is necessary for the rupture of the outer coating which is obtained by Effervescent or swelling agents. The lag-time can be Preplanned by changes in the thickness of the rupturable layer.

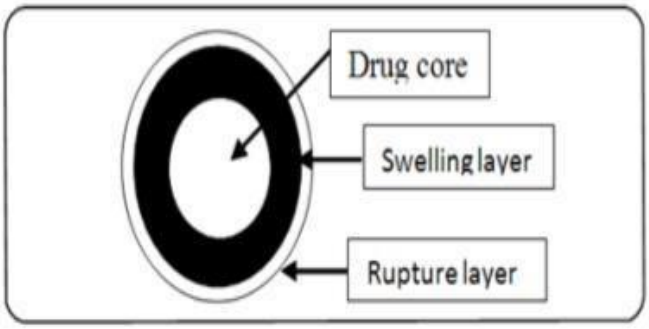

Fig.3: Pulsatile Delivery of drug by Rupturable Membrane

8.1.3 Pulsatile Drug Delivery System based on Capsule Shaped:

This system of Pulsatile Drug delivery contains a water-insoluble body of the capsule with the water-soluble cap on one end of the capsule and a plug is attached to the capsule body. The capsule body contains active pharmaceutical ingredients. After detecting the lag time the water-soluble cap is removed when it comes in contact with GI fluid and the plug is detached by swelling or erosion only in higher pH of the small intestine.

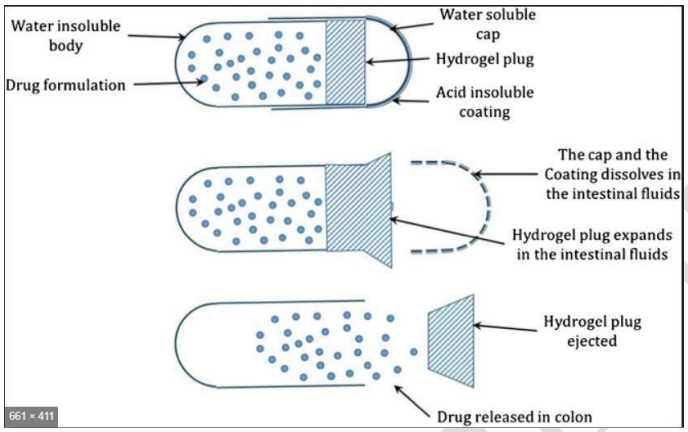

Fig.4: Pulsatile Drug Delivery System based on Capsule Shaped

8.1.4 Osmosis based Pulsatile Drug Delivery System:

In this system of drug delivery, the core containing the drug is coated with a semipermeable membrane which produces swelling and osmotic effect. In this system, the capsule is divided into 2 parts one of which contains the active pharmaceutical ingredient and another part contains an osmotically active agent. When water diffuses inside of the membrane, it raises the pressure inside, results in the plug is detached after a predetermined lag time which can be controlled by changes in the thickness of the layer.

8.2 Internally Stimuli Controlled:

8.2.1 Pulsatile Drug Release Induced by Temperature:

Temperature is most widely used as the triggering signal for triggered drug delivery system or pulsatile drug delivery system. There are many Thermo-Responsive agents used in the Pulsatile Drug Delivery System which triggered the release of active pharmaceutical ingredients. In this system of drug delivery the thermoresponsive polymer swells up and deswells in response to the temperature which modulates the release of the drug in a swollen state.

8.2.2 Hydrogel system:

These are also known as thermosensitive gel which changes their volume in response to change in temperature. In this system, the thermosensitive hydrogel swells up when the temperature i.e.32^{o}C and deswells when the temperature will rise.

8.3 **Pulsatile Drug release by Chemical Stimuli:**

8.3.1 Glucose Responsive Insulin Release System:

This device for the release of drugs is responsive to change in glucose levels in the blood. When blood glucose concentration increases glucose, oxidase is changed into gluconic acid which affects the pH of the system. When the pH of the system change, that results in the release of insulin. This device also has pH-sensitive hydrogel.

8.3.2 pH-sensitive Pulsatile Drug Delivery system:

This system is mostly used in the pH-dependent system. The device used in this drug delivery system has two compartments, one of which is immediate release and another one is based on pulse release which releases the active ingredient in the device when there are changes occur in the pH of the system. a pH-dependent polymer such as acetate phthalate, sodium carboxymethyl cellulose is used for the release of the drug at any specific site which can be predetermined.

8.3.3 Pulsatile Drug Release induced By Inflammation:

Any kind of stress either physical or chemical like injury, fracture, etc. can cause inflammation at the site of injury occurs. There are some inflame responsive cells that produce hydroxyl radicals in the body. This system of drug delivery responds to hydroxyl radicals and releases the drug in a predetermined manner in the body. This system is mostly used in inflammatory diseases such as rheumatoid arthritis.

8.3.4 Intelligent gel responding to antibody concentration Drug release system:

There are various kinds of bioactive compounds present in the human body. If any changes occur in the concentration in these bioactive compounds the system detected the changes and gets activated and releases the drug in a pre-planned manner.

8.4 Externally regulated:

For releasing the drug in a controlled pulsatile manner, the other option to adopt is an externally induced drug releasing system such as: magnetically, ultrasound, electric field, or light source.

8.4.1 Pulsatile Drug Release by Magnetic field:

In this system of drug delivery, magnetic beads are implanted in the body to release the drug, which can be controlled externally. This system reduces the movement of the drug by oral route and increases patient compliance. This system can also use for site-specific drug release in the body.

8.4.2 Pulsatile release by Ultrasound:

Pulsatile Drug Delivery System by ultrasound method is better for releasing the drug in the body parts such as skin, lungs, intestinal controlled drug delivery system through the biological barrier. A research scholar Miyazaki et al found that Ultrasound can be obtained up

to a 27-folds increase in the release of 5-fluorouracil from an ethylene and vinyl acetate (EVAc) matrix.

8.4.3 Pulsatile drug release by Electric Field:

PDDS electric field has some advantages like the availability of equipment as external stimuli. These technologies also include iontophoresis, infusion pumps, etc. electric fields influence the release of the drug from the hydrogel-containing drug into the body.

8.4.4 Pulsatile Drug Release by Light:

This system of delivery works and is regulated by the interaction between light and material which can be achieved by combining a martial which absorbs light of desired wavelength and the material used that absorbed energy to release the drug from the device.

9. CURRENT SCENARIO:

Now a day's, most of the drug delivery systems are focused on the potential of the drug delivery systems which can release or deliver the drug after a particular modified lag time i.e. pulsatile mode. This system of drug delivery reduces the frequency of dose and also there is no risk of dose dumping.

10. FUTURE SCOPE:

The pulsatile drug delivery system is the current as well as future drug delivery system for certain diseases. The pulsatile drug delivery system is quite promising as compared to the zero or first order drug delivery system.
Pulsatile release of drug is achieved and can be modified by using a different coating of the polymer and by changing the thickness of the coating in the drug.

11. CONCLUSION:

Nowadays controlled drug delivery systems and sustained drug releasing system has gained a lot of success in the field of Pharmacy, but these systems are not able to deliver or release the drug according to o circadian rhythm of the body. The pulsatile drug delivery system gained attraction in this regard to deliver the drug in circadian rhythm. The pulsatile drug delivery system has reduced the dose dumping as well as dose frequency and delivers the desired efficiency and also reduces the risk of adverse effect as compared to other controlled or sustained drug delivery system. There are many techniques in the market such as rupturable

coating layer, erodible coating layers, externally regulated system, stimuli induced PDDS, temperature and chemical-induced PDDS are useful in the treatment of various disease and Pulsatile Drug Delivery system should promising in the future for the treatment of the patient.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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