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PULSATILE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT:
Pulsatile Drug Delivery Systems are gaining a lot of interest as they deliver the drug at the right place at the right time and in the right amt. hence providing temporal delivery and increasing patient compliance. Pulsatile drug delivery systems are designed according to the circadian rhythm of the body. Thus the principle rationale for the use of pulsatile release of the drugs is where a constant drug release is not required. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the definite lag time. Pulsatile systems are beneficial for the drugs having chronopharmacological behavior where night time dosing is desired, such as antiasthmatic, antihypertensive and antiarhythmic. Current review article discussed the development of pulsatile drug delivery system, types of disease in which pulsatile release is required, advantages, disadvantages, classification, limitation, evaluation and work done on pulsatile drug delivery system.

Keywords: Pulsatile drug delivery, Circardian Rhythm, Chrono-pharmacological, Lag time.

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INTRODUCTION

Over the last 30 years, numerous technical advancements has occurred in the formulations, biodegradable polymers and understanding of pharmacokinetics has resulted in new techniques of drug delivery. Apart from the targeted, prolonged, controlled, sustained and targeted delivery systems, a new drug delivery systems known as pulsatile delivery system has drawn attention of the scientists, which is based on the concept of chrono-therapeutics. A pulsatile drug delivery system is one that delivers drug molecule in rapid and transient manner within a short time period immediately after a predetermined off release (lag time) period. The rationale for use of proposed system is to deliver drug at a time when disease condition is in the most morbid and mortal state during 24 hours. The particular rhythm in the onset and amount of symptoms were seen in diseases such as bronchial asthma, rheumatic disease, angina pectoris, ulcer, diabetes, hypercholesterolemia, neurological disorder and hypertension. Several pulsed release formulations have been developed, where tablets/capsules are the basis of pulsatile formulation that addresses emerging chronotherapeutic requirements. PDDS aims to release drug on programmed pattern that is at appropriate time and at appropriate site of action. The pulsatile effect, that is, the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time[1-5].

Control release systems for 12 or 24 hr drug release are not suitable for diseases, which follow circadian variation and in such conditions there is requirement for time or pulsatile drug delivery system. Long-term constant drug concentration exposed in blood and tissues may induce many problems such as tolerance of drug and activation of physiological system. These systems are beneficial for the drugs having chronopharmacological behaviour (where night time dosing is required), first pass effect and having specific site of absorption in gastro intestinal tract (GIT). Most

pulsatile drug delivery systems are reservoir devices covered with a barrier coating. The barrier may erode, dissolve or rupture during/after a certain lag time after which the drug is released quickly from the inner reservoir. The lag time prior to the rupture is mainly controlled by: (i) the permeation and mechanical properties of the polymer coating and (ii) the swelling behavior of the swelling layer. The rupturing of the barriers is induced by an expanding core upon water penetration through the barrier coating. The expansion can be caused by effervescent excipient or swelling agents. Pulsatile tablet formulations are manufactured with a rapid-release core (reservoir) encased in a barrier layer formed by rupturable press coating or liquid coating of erodible and swelling polymer. Polymers like various grades of Eudragit® or ethyl cellulose have been tested as film coating to achieve the desired lag time[6-14].

Drug release profile of pulsatile drug delivery systems is shown in fig. 1

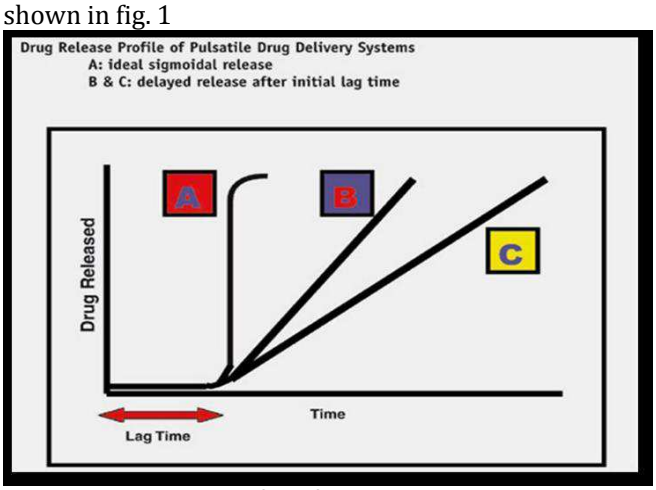

Fig 1: Drug release profile of pulsatile drug delivery systems

Advantages[15-18]

1. Extended daytime or night time activity.
2. They reduce the dose size and dose frequency, which reduces side effects and hence cost is reduced thereby improving patient compliance.
3. Drug adapts to suit circadian rhythms of body functions or diseases.
4. Drug targeting to specific site like colon.
5. Protection of mucosa from irritating drugs.
6. Drug loss is prevented by extensive first pass metabolism.
7. This system helps to prevent the continuous presence of some drugs (e.g. salbutamol sulphate) that produce biological tolerance and thus they increase their therapeutic effect.
8. They provide constant drug levels at the site of action and prevent the peak-valley fluctuation.
9. Pulse release allows multiple dosing in a single dosage form.

Disadvantages[19]

1. Lack of manufacturing reproducibility and efficacy.
2. Large number of process variables.
3. Multiple formulation steps.
4. Higher cost of production.
5. Need of advanced technology.
6. Trained/skilled personal needed for manufacturing.

Limitation[20-21]

1. Multiple manufacturing steps in case of Multiparticulate drug delivery system.
2. Low drug loading capacity and incomplete release of drug.
3. In vivo variability in single unit pulsatile drug delivery system.
4. Drug dose manipulation in case of child and elder patients is not possible.
5. Immediate withdrawal of drug is not possible.

Necessity of Pulsatile drug delivery system[22]

1. Follow Circadian rhythm
2. Protection from gastric environment
3. To achieve localized action
4. First-pass metabolism can be overcome
5. For drugs having short half life

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEM (PDDS):

(I) Time controlled pulsatile release
(A) Single unit system
1. Osmotic pressure based systems
- Based on expandable orifice
- Based on solubility modifications
- PORT systems
2. Capsular systems
3. Pulsatile system with rupturable coating
4. Pulsatile system with erodible or soluble barrier coatings

(B) Multi-particulate system
1. Time controlled explosion systems
2. Osmotic based rupturable coating system
3. Rupturable coating systems
4. Pulsatile Delivery by Change in Membrane Permeability
5. Sigmoidal release systems.

(II) Stimuli Induced
(A) Thermo-responsive pulsatile release
1. Temperature controlled systems

(B) Chemical stimuli induced pulsatile systems
1. Inflammation induced systems
2. Glucose sensitive systems
3. pH based systems
4. Gel based systems

(III) Externally regulated pulsatile release
(A) Electro responsive pulsatile release
(B) Micro electro mechanical systems (MEMS)
(C) Magnetically induced pulsatile release
(D) Ultrasounds.
(E) Mechanical force
(F) Electric field
(G) Light
(IV) Pulsatile release systems for hormone products and vaccine.

(I) **Time controlled pulsatile release:**

(A) Single unit system

1. **Capsular systems**: The general structure of this system consists of an insoluble capsule body containing a drug and a plug which is swelling, soluble or erodible after a predetermined lag time. Eg. Pulsincap system
2. **Osmosis based capsular system (PORT System):** This system consists of a gelatin capsule coated with a semi permeable membrane (eg. cellulose acetate). Inside this capsule there is an in-soluble plug, an osmotically active agent along with the drug formulation. When this cap comes in contact with the GI fluids, water diffuses across the semi permeable membrane resulting in increased pressure inside that ejects the plug after a predetermined lag time.
3. **System with erodible or soluble barrier coating:** This system consists of a reservoir device coated with a barrier layer. The barrier dissolves after a specific lag time (no drug release), after that drug was released quickly. This lag time depends on the coating layer's thickness.
4. **System with rupturable coatings:** In this system, coating disintegrates to release the drug. Pressure necessary for the rupture of the coating can be achieved by disintegrating, swelling, osmotic pressure or by effervescent excipients

(B) **Multiparticulate systems:** These systems are reservoir type of devices with a coating which either ruptures or changes its permeability. Sugar beads are coated by drug; these granules are then packaged in a capsule or compressed with additional excipients to form a tablet. The drug may also be blended or granulated with polymers before coating to provide an additional level of control. Eg: beads, pellets.

(II) **Stimuli induced:** In Pulsatile systems the drug is released after stimulation by any biological factor like temperature, or any other chemical stimuli.

(III) **Externally regulated pulsatile release:** For the drug release in a pulsatile way, the externally regulated systems in which the release of drug is programmed by external stimuli like electric effect, ultra sound, magnetism and irradiation. Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, the release of drug occurs because of the magnetic beads.

(IV) **Pulsatile release systems (PDDS) for vaccine and hormone products:** Pulsatile delivery systems offer the possibility of single shot vaccines if initial booster release of the antigen can be achieved from one system in which the timing of booster release is controlled.

Table 1: List of drugs formulated as single and multiple unit forms of PDDS[23]

Capsules	Metoprolol tartrate, Propranolol Hcl, Diclofenac sodium, Actaminophen, Ibuprofen, Metoprolol tartrate, Mesalazine, Diltiazem Hydrochloride, Nifedipine, Valsartan, Dofetilide
Pellets	Aceclofenac, Diltiazem Hcl, Indomathacin, 5-aminosalicylic acid, Propranolol Hcl, Isosorbide-5-mononitrate, Diclofenac sodium.
Microspheres	Salbutamol sulfate (pH-sensitive ion exchange resins), Theophylline, 5-aminosalicylic acid, Diltiazem hydrochloride
Films	Insulin, Diclofenac sodium
Tablets	Verapamil HCl, Propranolol HCl, Chlorpheniramine maleate, Felodipine, Salbutamol sulphate, Ranitidine HCl, Acetaminophen, Theophylline, Buflomedil hydrochloride, Isoniazid, Ketoprofen, Nifedipine, Antipyrine, Pseudoephedrine hydrochloride, Diclofenac sodium,
Beads	Meloxicam, Diclofenac sodium, Theophylline, Aceclofenac,
Micelles	Diflunisal, Doxorubicin
Thermo-responsive hydrogel	Gentamicin, Indomethacin, Sulfonamide, Diltiazem hydrochloride

Table 2: Polymers employed in PDDS[24, 25]

Synthetic	Natural
HPMC K4M	Sodium alginate
HPMC K 15M	Pectin
HPMC K100M	Karaya gum
Eudragit	Gelatin
Ethyl cellulose	Xanthan gum
Cellulose acetate phthalate	Chitosan
Polymethacylic acid	Guar gum

Table 3: Marketed Technologies of Pulsatile Delivery[26-31]

Technology	Mechanism	Proprietary name and dosage form	API	Disease
OROS*	Osmotic mechanism	Covera-H5*; XL	Verapamil	Hypertension
Three dimensional	Externally regulated system	Their Form*	Diclofenac Sodium	Inflammation
DIFFUCAPS*	Multiparticulate system	Innopran*; XL tablets	Verapamil HCL, Propranolol HCL	Hypertension
CODAS®	pH dependent system	Verelan® PM XL release capsules	Verapamil HCl	Hypertension
PULSYS™	Multiparticulate system	Moxatag™ tablets	Amoxicillin	Infection
TIMERx®	Erodible/soluble barrier coating	OPANA® ER tablets	Oxymorphone	Pain management
PulsincapTM	Rupturable system	Pulsincap TM	Dofetilide	Hypertension

Table 4: Diseases requiring PDDS [32]

Chronological behavior	Drugs used	Diseases
Acid secretion is high in afternoon and at night	H2 blockers	Peptic ulcer
Precipitation of attacks during night or at early morning	β2 agonist, Antihistamines	Asthma
BP is at its lowest during the sleep cycle and rises steeply during the early morning	calcium channel blocker, ACE inhibitors, Nitroglycerin,	Cardiovascular diseases
Pain in the morning and more pain at night	NSAIDs, Glucocorticoids	Arthritis
Increase in the blood sugar level after meal	Sulfonylurea, Insulin	Diabetes mellitus
Cholesterol synthesis is generally high during night than day time	HMG CoA reductase inhibitors	Hypercholesterolemia

EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM

1. Thickness and diameters: It is measured by using vernier calliper in mm.

2. Hardness: The hardness of tablet was measured by using monsanto hardness tester. The unit of hardness is kg/cm^2.

3. Friability: Friability of tablet was found to be USP friabilator. First of all tablet batch was weighed and placed in friabilator for 100 revolution in 4 minutes. The % friability was calculated by

$F = (Wi-Wf)/ Wi \times 100$

Where, Wi = initial weight

Wf = final weight

4. Weight variation test: The USP weight variation test was done by weighing 20 tablets individually calculating average weight and comparing the individual weight to the average.

Table No 5: Weight variation limit

S. No.	Average weight of tablet (mg)	Maximum difference
1	80mg or less	10 %
2	More than 80 mg but less than 250 mg	7.5%
3	250 mg or more	5%

5. **Lag time and Drug release:** The lag time and drug release studies was carried out in gastric and intestinal fluids at body tem. This test is performed in USP dissolution apparatus, in this test the tablet was placed in dissolution media and the sample was withdrawn at specific time interval and after that analyzed in UV spectroscopy.

6. **Rupture test**: The Rupture test on coated tablets was carried out using USP paddle apparatus. Here all other Parameters were same as In-Vitro Dissolution Method. The time at which the outer coating layer starts to rupture is called as lag time. This was determined by Rupture test.

7. **Drug content**: In this test accurately weight amount of powder was dissolved in water and filtered. After that the absorbance was measured at fixed wave length by UV spectrophotometer.

8. **Water uptake study**: The % water uptake of pulsatile release tablets was determined in medium filled container placed in a horizontal shaker (100 ml of 0.1 N Hcl, 37 ± 0.5^0C, 74 rpm n=3) at predetermined time points, the tablets were removed from the dissolution medium. They were then carefully blotted with the tissue paper to remove surface water, then weighed and then placed back in the medium up to the time when the coating of the tablet ruptured. The % water uptake update was calculated as follow:

$\%Water\ uptake = [(W_t - Wo/Wo)]\ 100$

where, Wt- weight of tablet at time t and

Wo - is weight of dry tablet

9. **Swelling index**: The individual tablets were weighed accurately and kept in 50 ml of double distilled water. Then tablets were taken out properly after 60 min., then blotted with filter paper so as to remove the water present on the surface and weighed accurately.

Percentage swelling index (SI) was calculated by using the formula

SI = (Wet weight – Dry weight / Dry weight) X 100.

CONCLUSION

Circadian rhythm of the body is an essential concept for understanding the optimum need of drug in the body. Pulsatile drug delivery is one such system that by delivering of drug at the right time, right place and in right amt., holds promising benefits for the patients suffering from chronic problems like arthritis, asthma, hypertension etc. A significant progress has been made towards designing Pulsatile drug delivery system (PDDS) that can effectively treat diseases with non-constant dosing therapies and hence, enhance patient compliance, optimal delivery of the drug to the site of target while minimizing the undesired effects. Pulsatile release systems should be promising in the future.

Work done on pulsatile drug delivery system: There are following tables no. 6 and 7 that represents the recent work done.

Table 6: Work done on pulsatile drug delivery system

S. No	Author	Drug	Method/Polymer	Inference	Ref.
1.	Zhang Z et. al. (2014)	Enalapril Maleate	Fluid bed coating technology	Drug release in pulsatile manner	33
2.	Maroni A et.al. (2013)	Acetaminophen	Spray-coating technique	Onset of release effectively delayed by coatings of reduced thickness.	34
3.	Huang H et. al. (2013)	Glipizide	wet granulation method	Peroral controlled release delivery system of water-insoluble drugs	35
4.	Sokar M.S et. al. (2013)	Valsartan	Direct compression method	Optimize the drug release after a certain lag time expecting an improvement in its bioavailability.	36
5.	Kumar S et.al.(2013)	metoprolol tartrate	Direct compression method	Prolong gastric residence time and increase the drug bioavailability	37
6.	Dandale SS et.al.(2013)	Nifedipine	Direct compression method	rapid release of the drug after a lag time	38
7.	Sandeep M et.al.(2013)	Lansoprazole	Wet granulation method.	lag time prior to drug release was highly affected by the plug position	39
8.	Prasad V et.al. (2013)	ramipril	direct compression method	Pulsatile release of the drug after a lag time	40
9.	Jain S et.al. (2012)	Lornoxicam	wet granulation method	Floating pulsatile tablets of lornoxicam effective for treatment of rheumatoid arthritis	41
10.	Patel S et.al. (2012)	Meloxicam	wet granulation method	drug can be released in upper GI tract after a lag phase	42
11.	Garg B. K et.al. (2012)	Rosuvastatin calcium	direct compression method	levels of ethylcellulose coating retarded water uptake and thus prolonged the lag time	43
12.	Patil B.S et. al.(2012)	Lisinopril dihydrate	direct compression method	Release in pulsatile manner	44
13.	Desai M et. al. (2012)	Montelukast sodium	Direct Compression method	swelling come rupturable coating approach gives desire drug release after lag time.	45
14.	Masareddy R (2011)	Diltiazem hydrochloride	direct compression method	colon specific drug release	46
15.	Patil S et.al.(2011)	Aceclofenac	direct compression method	Relief of morning stiffness in patients with rheumatoid arthritis	47
16.	Salunkhe A.K et.al.(2011)	Metoprolol tartrate	wet granulation method	F9 formulation showed compliance with chronotherapeutic objective of hypertension.	48
17.	Yadav D et. al. (2011)	Glipizide	extrusion–spheronization technique	lag time could be modified by level of swelling layer and rupturable coating	49
18.	Patil A.S et. al. (2011)	captopril	rupturable coating method	Release the drug after a desirable lag time	50
19.	Sadaphal K.P. et. al. (2011)	Theophylline	direct compression method	deliver the drug rapidly and completely after a lag time	51
20.	Rujivipat S et. al. (2010)	Acetaminophen	direct compression method	rapid release after a controllable lag time in higher pH-media.	52
21.	Tajiri S et. al. (2010)	cevimeline	fluidized hot-melt granulation method	potential for extended-release dosage forms.	53
22.	Liu F et.al. (2010)	prednisolone	wet granulation method	double-coating of Eudragit for improved pH-	54

				triggered delivery	
23.	Nayak U.Y et. al. (2009)	valsartan	hydroxypropyl cellulose (L-HPC)	Rapid release of the drug after a lag time	55
24.	Lin H.L et.al.(2008)	Doxazosin mesylate	HPMC E50	desired lag time can be adjusted by the thickness and the hydrophilicity of the coated membrane	56
25.	Qureshi J et. al. (2008)	salbutamol sulphate	direct compression method	Osmotic pumping effect eventually llead to the drug release.	57
26.	Schellekens R.C.A et. al. (2008)	Mesalazine	Eudragit S 100	Coating enables pulsatile delivery of the content to the lower parts of the intestines.	58
27.	Badve S. S et. al. (2007)	diclofenac sodium	pectin	Increase the gastric residence of the dosage form	59
28.	Ghimire M et.al. (2007)	Theophylline	glyceryl behenate(GB), L-HPC	The lag time can be modulated by varying the weight ratio of GB to L-HPC	60
29.	Sharma S et. al. (2006)	Meloxicam	ionotropic gelation method	Pulse release of drugs in upper part of small intestine	61

Table 7: Patents on PDDS

S. No.	Author	Drug	Method/polymer	Inferences	Ref.
1.	Mullen A et.al. (2013)	Active drug substances	low-substituted hydroxypropyl cellulose (L-HPC),	Delayed release of active agent followed by a pulsed delivery of the agent.	62
2.	Matharu AS et.al. (2011)	Valsartan	polymeric hydrogel	Improved residence time in the GIT and a pulsatile release profile.	63
3.	Holmlund JT et.al. (2010)	Gossypol	lyophilizing processes	inhibiting the activity of anti-apoptotic Bcl-2 family proteins.	64
4.	Muthusamy R et.al. (2010)	Active drug substances	dry granulation method	pulsatile release of the therapeutic agent after a lag time	65
5.	Gandhi AS et.al. (2008)	Valsartan	Eudragit L30	increasing the bioavailability of an ARB by administering solubilized ARB in pulses	66
6.	Dedhiya MG et.al. (2008)	Escitalopram	direct compression method	Modified and pulsatile release pharmaceutical formulations for CNS disorders	67
7.	Schellekens RCA et.al (2007)	Active drug substances	sodium starch glycolate	Pulsatile release of drug in response to a change in pH	68
8.	Hirsh J et.al. (2006)	milnacipran	wet granulation method/Cellulose acetate phthalate	releases the drug in spaced apart "pulses	69
9.	Percel PJ et.al. (2006)	Sotalol HCl	Water insoluble and enteric polymers.	Drug release in pulsatile manner	70
10.	Devane JG et.al. (2005)	Methylpheni date HCl	hydrophilic and hydrophobic polymers	Delivers drug in a pulsed or bimodal manner.	71
11.	Ting R et.al. (2004)	Isosorbide-5-mononitrate	hydrophilic and hydrophobic polymers	overcome the "first pass" effect	72
12.	Sharma VK et.al. (2003)	diltiazem HCL	Hydroxypropyl methylcellulose	Drug release in pulsatile manner	73
13.	Midha K K et.al. (2002)	methylpheni date,	Wet granulation method	release encapsulated drug in spaced apart "pulses.	74
14.	Chen et.al. (2002)	diltiazem HCL	water-permeable, film-forming, water insoluble polymer & hydrophobic agent,	release drug in a sequential, pulsatile fashion	75

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