ejpmr, 2021,8(8), 309-315.

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

RECENT APPROACH OF PULSATILE DRUG DELIVERY SYSTEM: AN OVERVIEW

Omkar Tipugade[4]*, Manohar Patil[1], Sayali Bhurke[2], Pallavi Chavan[3] and Shobharaj Malavi[5]

[1,4,5]Department of Pharmaceutics, Genesis Institute of Pharmacy, Radhanagari, 416212, MS, India.
[2]Department of Pharmaceutics, Shree Santkrupa College of Pharmacy, Ghogaon, Karad-415111, MS, India.
[3]Department of Pharmaceutics, Govindrao Nikam College of Pharmacy, Sawarde, 415606, MS, India.

***Corresponding Author: Omkar Tipugade**

Department of Pharmaceutics, Genesis Institute of Pharmacy, Radhanagari, 416212, MS, India.

Article Received on 16/06/2021 **Article Revised on 06/07/2021** **Article Accepted on 26/07/2021**

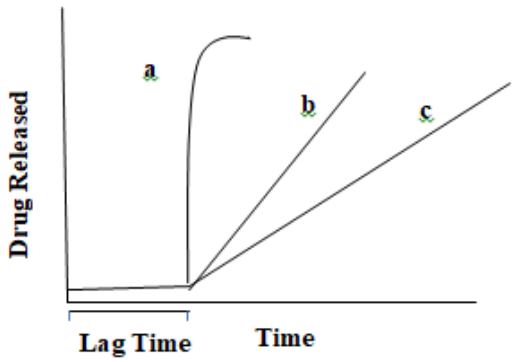
ABSTRACT

Pulsatile Drug Delivery Systems are gaining popularity because they deliver drugs at the right place, at the right time, and in the right amount, ensuring spatial, temporal, and smart delivery while also improving patient compliance. Many medications or therapies could benefit from a pulsatile drug release, in which the drug is released rapidly after a predetermined lag time. A pulse must be designed in such a way that after the lag time, a complete and rapid drug release is achieved, matching the body's circadian rhythms with the drug release, increasing the efficacy and safety of drugs by proportioning their peak plasma concentrations during the 24 hours in synchrony with biological rhythm. In recent years, various technologies for chronopharmaceutical drug delivery have been developed and thoroughly explored, including time-controlled, pulsed, triggered, and programmed drug delivery systems. To administer medicine in a pulsatile way, many types of formulations such as bilayer tablets, coated tablets, pellets, and tablet in capsule can be developed.

KEYWORDS: Pulsatile Drug Delivery System, Chronopharmaceutics, Rhythm of Disease, Technologies, Future aspects.

INTRODUCTION

The largest and oldest segment of the total medication delivery market is oral drug delivery. It is the most used and fastest-growing method of medication administration. The best dose regimen for various disease states is one that achieves an appropriate therapeutic concentration of medicine at the site(s) of action quickly and then maintains it for the duration of treatment.[1] In the pharmaceutical industry, fresh technologies are being developed. Because there are so many obstacles to overcome during the discovery of new compounds, the most effective dosage forms are created from existing molecules. Though most delivery systems are designed for steady drug release over time, PDDS are distinguished by a scheduled drug release, as maintaining a constant blood level is not always desirable. After a lag time, these systems have a common mechanism for delivering the drug quickly and thoroughly.[2] These days, pulsatile drug delivery systems (PDDS) are attracting a lot of attention and interest. After a "lag time," or a period of "no drug release," these devices feature a unique mechanism for promptly and thoroughly releasing the drug. Though most delivery systems are designed for continuous drug release over time, pulsatile delivery systems are distinguished by a scheduled drug release, as constant blood levels of a medicine are not always desirable.[10]



Advatages[2-5]

- An activity that lasts for several hours during the day or night.
- There are less adverse effects.
- Smaller doses and more frequent administration.
- Patient compliance has improved.
- Patients in the therapy require fewer dosage units each day, lowering the daily cost.
- The ability to create combination dose forms and the simplicity with which pellets of different compositions or release patterns can be combined.

- Chronotherapy, or designed delayed release, is an effective way to cure disorders.
- Lower cytochrome P450 isoenzymes reduce medication interaction.
- Drugs that target a specific site, such as the colon.
- Mucosal protection from irritant medicines.
- There is less variation in gastro–intestinal transit time across and between subjects.
- There are fewer side effects and better tolerance.
- Design flexibility and stability are both present.

Limitation[3,12]

- Inadequate drug loading capacity and drug release.
- A higher production cost.
- Dosage form design necessitates the expertise of highly trained individuals.
- There are several manufacturing steps.
- The coated barrier must be homogeneous in order for the lag time to be predictable.
- The requirement for modern technologies.
- There are various sorts of multi-particulate systems.

Need Of Pulsatile Drug Delivery System[18,20,26,27]

4.1 First pass metabolism: Some medications, like beta blockers and salicylamide, go through a lot of first-pass metabolism and require a lot of drug to saturate the metabolizing enzymes. As a result, a constant/consistent oral delivery strategy would result in lower oral bioavailability.

4.2 Biological tolerance: Drug plasma profiles, such as biological tolerance of transdermal nitroglycerin and salbutamol sulphate, are frequently followed by a decrease in the drug's pharmacotherapeutic activity.

4.3 Special chrono pharmacological needs: Certain physiological functions have well-established circadian cycles. Many symptoms and disease onsets are observed during specific times of the 24 hour day; for example, asthma and angina pectoris attacks are most common in the morning hours.

4.4 Local therapeutic need: The delivery of chemicals to the site of inflammation with no loss owing to absorption in the small intestine is very desirable for the treatment of local illnesses such as inflammatory bowel disease.

4.5 Gastric irritation or drug instability in gastric fluid: Medicines that degrade in stomach acidic medium (e.g., peptide drugs), irritate the gastric mucosa (NSAIDS), or cause nausea and vomiting must be protected from the gastric environment.

Chronopharmacotherapy

"Chronopharmaceutics" consist of two words chronobiology and Pharmaceutics.[1] Co-ordination of biological rhythms and medical treatment is called chronotherapy. Chronotherapeutics is the discipline concerned with the delivery of drugs over a certain period of time.[2]

Table 1: Targets for pulsatile drug delivery.[1-3,8-10]

Disease	Chronological behaviour	Drugs Used
Asthma	Precipitation of attacks during night or at early morning	Antihistamines, B2 agonist
Attention deficit syndrome	Increase in DOPA level in afternoon.	Methylphenidate
Arthritis	Inflammatory cytokines, such as interleukin-6, are released in large amounts in the early morning, which causes pain to increase.	NSAIDs, Glucocorticoids
Cancer	During each daily activity phase of the circadian cycle, blood flow to the tumor is three times larger than during the daily rest phase.	Vinca alkaloids, Taxans
Duodenal ulcers	Gastric acid secretion is highest at night,bowel motility& gastric empting are slower at night	Proton pump inhibitors
Peptic ulcers	Acid secretion is high in afternoon & at night	H2 Blockers
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than day time	HMG CoA reductase inhibitor
Diabetes mellitus	Increase in blood sugar level after meal	Sulfonylurea, Insulin
Neurological disorder	Central pathophysiology of epilepsy and behavioural classification of convulsive events	MAO-B inhibitor
Cardiovascular disease	BP is at its lowest during sleep cycle.	Nitro-glycerine, CCBs, ACE inhibitors

Classification of Pulsatile Drug Delivery System[20,21,26,30-35]

I. Time controlled pulsatile release

A. Single unit system
B. Multi-particulate system

II. Stimuli induced

A. Inflammation-induced Pulsatile Release
B. Temperature induced systems
C. pH Sensitive Drug Delivery System

III. Chemical stimuli induced pulsatile systems

1. Glucose-responsive Insulin Release Devices
2. Drug release from intelligent gels responding to antibody concentration

IV. External stimuli pulsatile release

A. Micro Electro Mechanical Systems (MEMS)
B. Electro responsive pulsatile release
C. Magnetically induced pulsatile release

I] Time controlled Pulsatile release system

These time-controlled systems can be classified as single unit (e.g., tablet or capsule) ormultiple unit systems

A. Single Unit System Capsular Systems: There have been several single-unit capsular PDDS created. In general, such devices have an insoluble capsule body that houses a medication and a plug. Due to swelling, erosion, or dissolution, the plug is removed after a specific time period.[20,26]

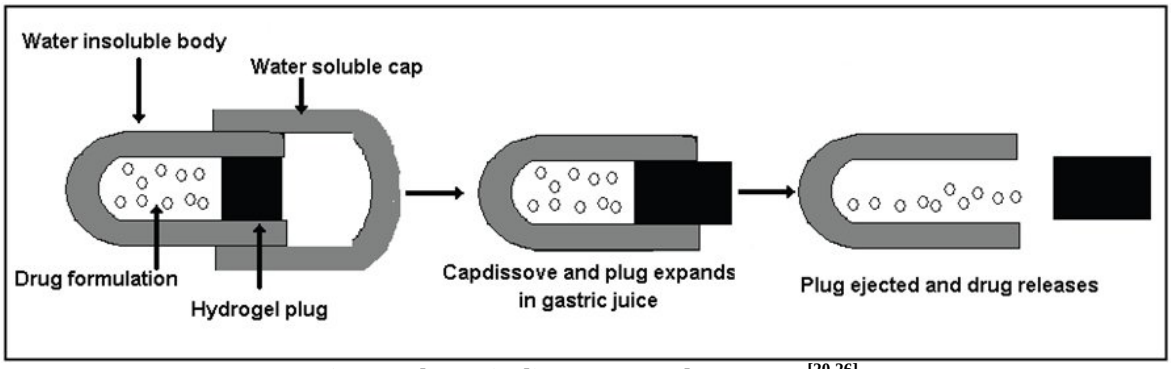


Fig. 1: Schematic diagram capsular system.[20,26]

The medicine is released as a "Pulse" from the insoluble capsule body after the lag time is controlled by a plug that is pushed away by swelling or erosion. Pulsincap® is a system that consists of a water-insoluble capsule containing the drug reservoir and was created by R. P. Scherer International Corporation in Michigan, United States.[26]

B. Multiparticulate Systems: Multiparticulate systems are reservoir-type devices that have a covering that ruptures or changes the device's permeability. The medication is coated on sugar seeds, then packaged into capsules or broken into tablets with additional excipients.[20] Swelling agents used include sodium carboxymethyl cellulose, sodium starch glycolate, and L-hydroxypropyl cellulose, which are all superdisintegrants. Polymers include things like polyvinyl acetate, polyacrylic acid, and polyethylene glycol.[31]

II] Stimuli Induced

A. Inflammation-induced Pulsatile Release- Inflammation takes place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells.[20] Yui and co-workersfocused on the inflammatory induced hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner.[21] Yui and co-workers used hyaluronic acid (HA), a linear mucopolysaccharide composed of repeating disaccharide subunits of N-acetyl-D-glucosamine and D-guluronic acid.[31]

B. Temperature induced systems - The polymer in these systems goes through a swelling or deswelling phase in response to temperature, modulating drug release in the swollen state. Using the reversible swelling capabilities of copolymers of N-isopropylacrylamide and butyrylacrylamide, Y.H. Bae et colleagues created an indomethacin pulsatile release pattern in the temperature ranges of 200C to 300C.[20] The properties and biological interests of thermoresponsive polymeric micelles make them a most noteworthy candidate as drug carrier for the treatment ofcancer.[33]

C. pH Sensitive Drug Delivery System -Such type of pulsatile drug delivery system contains two components one is of immediate release type and other one is pulsed release which releases the drug in response to change in Ph.[5] By selecting the pH dependent polymers drug release at specific location can be obtained.[10] Selecting pH dependent polymers like acetate phthalate, poly acrylates and sodium carboxy methyl cellulose.[12]

III] Chemical stimuli induced pulsatile systems

A. Glucose-responsive Insulin Release Devices-In case of diabetes mellitus there is rhythmic increase inthe levels of glucose in the body requiring injection of theinsulin at proper time.[11] Several systems that can respond to variations in glucose levels have been created. pH sensitive hydrogel incorporating glucose oxidase immobilized in the hydrogel is one such system.[5] When blood glucose levels rise, glucose oxidase converts glucose to gluconic acid, causing the pH of the system to shift. The polymer swells as a result of the pH change, resulting in insulin release.[10]

B. Drug release from intelligent gels responding to antibody concentration - In the body, there are many different types of bioactive chemicals. Novel gels have

recently been produced that respond to changes in bioactive compound concentrations by changing their swelling/reselling properties.[5] Antigen-antibody complex formation as cross-linking units in the gel was given special attention because such interactions are exceedingly specialized.[11] Reversible gel swelling/ deswelling and drug penetration alterations are caused by the differential in association constants between polymerized antibodies and naturally generated antibodies towards certain antigens.[12]

IV] External stimuli pulsatile release

A. Micro Electro Mechanical Systems (MEMS): A microfabricated device can store and release numerous chemical substances on demand using a method that does not require moving parts. When compared to traditional polymer-based devices, MEMS' digital capabilities may allow for better temporal control of medication release.[20] When compared to traditional polymer-based devices, MEMS' digital capabilities may allow for better temporal control of medication release. The microchip is advancement in MEMS technology. An array of reservoirs extends through an electrolyte-impermeable substrate on the microprocessor.[31]

B. Electro responsive pulsatile release: Poly electrolytes (polymers with a high concentration of ionisable groups along the backbone chain) are used to create electrically responsive delivery systems, which are both pH and electroresponsive.[2] The polymer has two redox states, only oneof which is suitable for ion binding. Drug ions are bound in redox state and release.[11] Complete on-off drug release was achieved, as no drug release was apparent without the application of electric current.[9] As a result of the electric stimuli-induced gel contraction and solvent flow, drug molecules in polyelectrolyte gels may be squeezed out. Poly (sodium acrylate) microparticulate gels containing pilocarpineas, a model drug, were developed to demonstrate this process.[20]

C. Magnetically induced pulsatile release: Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads.[2] Magnetite, Iron, Nickel, Cobalt, and other included materials provide magnetic carriers with their magnetic response to a magnetic field. The slowing down of oral medications in the gastrointestinal system is a mechanistic technique based on magnetic attraction that must be water-based, biocompatible, non-toxic, and non-immunogenic for biomedical applications.[10] Langer developed one system of polymeric matrix containing dispersed drug along with magnetic beads. Generally ethylene-vinyl acetate copolymer is used for this purpose.[11] When the beads are exposed to a magnetic field, they begin to oscillate within the matrix, causing compressive and tensile pressures. These pressures function as a pump, causing a greater amount of the drug molecule to be pushed out of the matrix. Because co-polymers with a greater Young's modulus were more resistant to steel bead generated motion, the magnetic field had a less effect on the rate of drug release from these materials.[12]

Evaluation of Pulsatile Drug Delivery System

Thickness and diameters:It is measured by using verniercalliper in mm.[18,36]

Hardness-The hardness of tablet was measured by using monsanto hardness tester. The unit of hardness is kg/cm2.[18]

Friability- The percentage of friability was calculated using a friability test device (percent). Each batch of 10 tablets was weighed independently (W initial) and placed in the friabilator, which was then turned 100 times at 25 rpm.[18,36]

The % friability was calculated by
F = (Wi-Wf)/ Wi×100 Where,
Wi = initial weight
Wf = final weight

Weight variation test- The USP weight variation test was performed by individually weighing 20 tablets, computing the average weight, and comparing the individual weight to the average weight.[18,24]

Determination of The Drug Content: The percentage drug content indicates how much of the drug was included in the formulation. It should not go beyond the bounds established by conventional monographs.[19,25]

Percentage Entrapment Efficiency: For quantifying the phase distribution of medication in produced formulations, percentage entrapment efficiency was shown to be reliable. Three methods were used to measure entrapment efficiency: microdialysis, ultra centrifugation, and pressure. Filtration at the ultra-high level.[19]

Swelling Studies

Each tablet was precisely weighed and stored in 50 mL of double distilled water. After 60 minutes, the pills were correctly removed, blotted with filter paper to remove any remaining water, and weighed accurately. SI = (Wet weight – Dry weight / Dry weight) X 100 was used to determine the percentage swelling index (SI).[18,19]

Lag time and Drug release

At body tem, lag time and drug release tests were conducted in stomach and intestinal fluids. This test was carried out in a USP dissolving equipment, in which the tablet was immersed in dissolution media and the sample was extracted at predetermined intervals before being evaluated using UV spectroscopy.[18]

Marketed technologies for pulsatile drug delivery system

Table 2: Marketed Technologies for Pulsatile Drug Delivery System.

Sr. No.	Technology	Mechanism	Proprietory Name And Dosage Form	API	Disease	References
1	CODAS®	Multiparticulate pH dependent System	Verelan® PM; XL release capsule	Verapamil HCl	Hypertension	[1-5,9,11,13]
2	OROS®	Osmotically regulated	Covera-HS®; XL tablet	Verapamil HCl	Hypertension	[1-5,8,9,13,18]
3	DIFFUCAPS®	Multiparticulate system	Innopran®; XL tablets	Verapamil HCl Propranolol HCl	Hypertension	[1-5,8-13,18]
4	Pulsincap™	Rupturable system	PulsincapTM	Dofetilide	Hypertension	[1,3,5,8,9,18]
5	PULSYS™	Multiparticulate system	Moxatag™ tablet	Amoxicillin	Infection	[1,3,5,918]
6	TIMERx®	erodible/soluble barrier coating	OPANA® ER tablet	oxymorphone	Pain managment	[1,2,5,13]
7	Covera-HS®	Osmotically regulated	Covera-HS® ER tablets	Verapamil HCl	Hypertension	[1,2]
8	Procardia XL®	Osmotically regulated	Procardia XL SR	Nifedipine	High blood pressure and Angina	[1,13]

Patents on puisatile drug delivery systems

Table 3: Patents on Pulsatile Drug Delivery Systems.

Sr. No.	Name	Active Agent	Date of Patent Filing
1	Puisatiledeug delivery system	Propranolol	20/07/1993
2	Puisatiledeug delivery system	Ivermectin	1/5/1987
3	Puisatile technology	Diltiazem	
4	Puisatile technology	Amphetamine	27/11/2001
5	Time controlled drug delivery system	Sotalol HCL	2003

Future Aspects

The development of chronotherapeutic, pulsatile-release products is most challenging as to get the right drug to the right place at the right time.[1] The new PDDS, on the other hand, places a greater emphasis on site and time-specificity. Novel PDDS are expected to be investigated in the near future for the treatment or management of various chronic and terminal illness conditions, such as diabetes, where doses are required at varied time intervals.[9] Multi-particulate systems (e.g. pellets) have a number of advantages over single-unit systems, including no possibility of dose dumping, the ability to blend units with variable release patterns, and a short and repeatable stomach residence period.[15] The gastroretentive drug delivery system is a method of extending gastric residence duration and thereby targeting site-specific medication release in the upper GI tract. Techniques for gastro retention include the Floating Drug Delivery System (FDDS) and bioadhesive drug delivery. Many studies are being conducted on pulsatile drug administration in order to discover a circadian rhythm with an appropriate device anywhere in the world. Due to several unique characteristics such as reduced risk of dose dumping, patient compliance, and the above criteria, this delivery will be a leading technique to deliver therapeutic medicines in the future.[33]

CONCLUSION

Oral medication administration is the most common, oldest, and preferred method of drug administration. In general, sustained and controlled-release products achieve the desired therapeutic impact, but they fall short in diseases characterized by biological rhythms, such as hypertension, osteoarthritis, peptic ulcer disease, asthma, and other conditions that necessitate chrono pharmacology. Today's drug delivery technologies allow drug molecules to be incorporated into innovative delivery methods, resulting in numerous therapeutic and commercial benefits. Pulsatile release systems should be promising in the future because the medicine is delivered when its true concentration is needed as per chronological demand.

REFERENCES

1. Shidhaye SS, Lotlikar VM, Ghule AM, Phutane PK, Kadam VJ. Pulsatile Delivery Systems: An Approach for Chronotherapeutic Diseases. Sys Rev Pharm, 2010; 1(1): 55-61.
2. Bansal RS, Singh BK, Sharma CJ, Pareek AK. Pulsatile Drug Delivery System: An Overview. JGTPS, 2014; 5(3): 1943 – 1955.
3. Shidhaye S, Dhone A, Budhkar T, Surve C. Technologies In Pulsatile Drug Delivery System. IJAPBC, 2012; 1(4): 438-445.

4. Paramr RD, Parikh RK , Vidyasagar G, Patel DV, Patel CJ, Patel BD. Pulsatile Drug Delivery System: An Overview, International Journal of Pharmaceutical Sciences And Nanotechnology, 2009; 2(3).
5. Patel VR, Patel VP. Pulsatile Drug Delivery System - A Review. IJPSR, 2015; 6(9): 3676-88.
6. Krishna GR, Neelima K, SrinivasaRao D, Ramu S. Formulation and Evaluation of Pulsatile Drug Delivery System of Flurbiprofen. IJPCBS, 2015; 5(4): 817-828.
7. Patel S, Modasiya MK, Patel VM, Patel AK. Design and Development of Floating Pulsatile Drug Delivery System Using Meloxicam. IJPRBS, 2012; 1(2): 215-235.
8. Reddy JR, Veera MJ, Jyothsna T, Saleem SM, Chetty CM. Review On: Pulsatile Drug Delivery Systems. J. Pharm. Sci. &Res, 2009; 1(4): 109-15.
9. Tajane SR, Kholwal BB, Suryawanshi SS, Tarkase KN. Current Trends In Pulsatile Drug Delivery Systems. IJPSR, 2012; 3(2): 358-66.
10. Sharma GS, Srikanth MV, Uhumwangho MU, Phani KS, Ramana Murthy KV. Recent Trends in Pulsatile Drug Delivery Systems - A Review. International Journal Of Drug Delivery, 2010; 200-12.
11. Patil ND, Bari MM, Barhate SD. A Review on Novel Approach Pulsatile Drug Delivery System. Int. J. Pharm. Sci. Rev. Res., 2013; 21(1): 209-22.
12. Sharma AR, Raina B, Bajwa PS, Bhargava A, VrindaGoel T. Pulsatile Drug Delivery System: A Review. Asian Pac. J. Health Sci., 2018; 5(3): 260-70.
13. Singh A, Dubey H, Shukla I, Sing DP. Pulsatile drug Delivery System: An Approach of Medication according To Circadian Rhythmh. Journal of Applied Pharmaceutical Science, 2012; 02(03): 166-76.
14. Sumathi P, Kaza R. Design and Development of Pulsatile Drug Delivery of Nateglinide Using Pulsincap Technology. International Journal of Innovative Pharmaceutical Research, 2014; 5(3): 425-30.
15. Patel JD, Aneja K, Majumdar SH. Pulsatile Drug Delivery System: A "User-Friendly" Dosage Form. JPRHC, 2010; 2(2): 204-15.
16. Singh S, Koland M. Formulation and Evaluation of Pulsatile Drug Delivery Systems of Glipizide for the Management of Type-Ii Diabetes Mellitus. Journal of Drug Delivery & Therapeutics, 2016; 6(1): 11-18.
17. Kamat AR, Shabaraya AR, Mohd A, Kamat KK. Formulation And Evaluation Of Pulsatile Drug Delivery System Containing Indomethacin Using Natural Polymer, IRJP, 2013; 4(2): 95-107.
18. Mali AD, Bathe RS. An Updated Review on Pulsatile Drug Delivery System. International Journal of Advances in Pharmaceutics, 2015; 4 (4).
19. Shelake1 S, Shinde A, Mujawar N, Jadhav P, Patil S, Patil S, A Review: Floating Pulsatile Drug Delivery System, EJPMR, 2017; 4(9): 203-12.
20. Singh NP, Ganarajan G, Kothiyal P. Pulsatile Drug Delivery System: A Review, World Journal Of Pharmacy And Pharmaceutical Sciences, 2016; 5(5): 479-91.
21. Ravichandiran V, Suba V, Senthilnathan B,Rajachandrika K, Padmapriya S, Saraswathy T, Masilamani K. Pulsatile Drug Delivery System, Biomedical & Pharmacology Journal, 2009; 2(2): 227-34.
22. Varun DS, Jadhav SB, Hambarde SK, Bharkad V. Development and Evaluation Of Pulsatile Drug Delivery System Of Diltiazem Hydrochloride. Int.J.Pharm Drug Anal, 3(7): 226-34.
23. Survase S, Kumar N. Pulsatile Drug Delivery: Current Scenario. Crips, 2007: 8(2): 27-33.
24. Rewar S. Design, Development and Evaluation of Pulsatile Drug Delivery System Of EprosartanMesylate For Chronopharmaco Theraphyasian. Journal of Research in Biological And Pharmaceutical Sciences, 2014; 2(4): 171 - 82.
25. P. Jitendra Kumara*,Y.Indira Muzibband Gitanjali Misrac, Formulation And Evaluation Of Pulsatile Drug Delivery Of Fluvastatin Sodium, Journal Of Chemical And Pharmaceutical Research, 2016; 8(2): 757-64.
26. Rewar S, Bansal BK, Singh CJ,Sharma AK, Pareek R. Pulsatile Drug Delivery System: An Overview, JGTPS, 2014; 5(3): 1943 – 55.
27. Devi R, Kumar S. Pulsatile Drug Delivery: Paradigms. International Journal of Innovative Pharmaceutical Sciences and Research, 2017; 5(12): 3928-35.
28. Sadaf M, Sayed AA, Hani U, Tauqeer MA. Formulation and Evaluation of Pulsatile Drug Delivery System Using Meloxicam. International Journal of Pharmacy Analytical Rrsearch, 2015; 4(1): 51-9.
29. Bilaskar VV, Patil IS, Patil OA, Mandke GR, Mohite SK. Design, Development And Optimization Of Pulsatile Drug Delivery Of Antihypertensive Drug. International Research Journal Of Pharmaceutical And Biosciences, 4(6).
30. Gajbhiye ND, Kadam VJ, Jadhav KR, Kyatanwar AU, Patel UJ. Pulsatile Drug Delivery System, Journal of Pharmacy Research, 2010; 3(1): 120-123.
31. Sarkhejiya NA, Bhardia PD. Newer Insights into Pulsatile Drug Delivery Systems. World J Pharm Sci., 2017; 5(2): 134-150.
32. Grover CI, Bhatt G, Kothiyal P. A Comprehensive Review Of Pulsatile Drug Delivery System, 2012; 1(7): 99-104.
33. Patel VP, Soniwala MM. Pulsatile Drug Delivery System For Treatment Of Various Inflammatory Disorders: A Review. Int. J. Drug Dev. & Res., 2012, 4(3): 67-87.
34. Patil V, Chandrasekhara S, Nagesh C, Praveen K, Rekha S. Pulsatile Drug Delivery System Of Terbutaline Sulphate; Using Ph Sensitive Polymer American Journal Of Advanced Drug Delivery, 2013; 1(4): 635-650.

35. Arora S, Ali J, Ahuja A, Baboota S , Qureshi J. Pulsatile Drug Delivery´An Approach Of Controlled Drug Delivery System, Indian Journal Of Pharmaceutical Sciences, 2006; 68 (3): 295-300.
36. Pastham R, Reddy S, Allenki V. Design And In-Vitro Evaluation Of Enteric Coated Pulsatile Drug Delivery System Of Zileuton Tablets. The Pharmaceutical And Chemical Journal, 2017; 4(4): 57-65.
37. Garg T, Chanana A, Gupta A, Khatri N , Sharma G. Pulsatile Drug Delivery Systems: Pulsincap System, IOSR Journal Of Pharmacy, 2012; 2(2): 338-39.