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Pulsatile Drug Delivery System: A Review

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ABSTRACT

To improve the patient compliance pulsatile drug delivery system is attaining a lot of attention day by day. Because this system delivers the drug at the right place at the right time and the right amount to the particular site of the body. This system is designed according to the circadian rhythm of the body. PDDS are beneficial for chronopharmacological related disease. Thus nocturnal dosing is required, so the drug should show the first-pass metabolism. This system is designed in such a way to increase the safety and efficacy of the drug by proliferating their peak plasma concentration during the 24hrs biological rhythm. To reduce the dose frequency this system is highly useful. Several classifications are available for the pulsatile drug delivery system, in that essential one is Time control release then it consists of a single unit system, multiple unit systems. Present review article discussed the reasons for the development of a pulsatile drug delivery system, classification, advantages, and limitations.

INTRODUCTION

The main aim of the pulsatile drug delivery system is to deliver the drug through the oral route, at a certain order of release and to maintain plasma concentration of drug for a prolonged duration of time. These systems are planned to attain time-specific and site-specific delivery of drugs according to the circadian rhythm of the body. PDDS are distinguishing by at least two individual drug release phases following a programmed lag time. Here the Drug release may be controlled by time, by site or arrangement of the two constraints. A delayed release delivery system would come across with the needs of chronopathologies with indications of mostly repetitive at night time or in the early morning.

This type of drug administration is coordinated with the biological rhythms to generate the best therapeutic effect and the least harmful effect on the patient. The pulsatile release is also suitable for the targeting release of the drug and it also increases the biological tolerance with a wide-range of the first-pass metabolism[1].

The oral pulsatile delivery system initiates with suitable formulation characteristics and releases performance. The plasma peak is procured at an optimum time by developing the pulsatile device, here multiple doses can be avoided; saturable first-pass metabolism and Tolerance development can also reduce, and it permits the discharge of active pharmaceutical material in single or successive pulses at exact and precise time periods, Drugs are frequently summarized in one way or another inside a barrier material, which is composed of an erodible or decomposable polymer, Depending on the barrier material structure and thickness, different release lag times can be attained. Later the barrier material is dissolved; eroded or degraded, drugs are quickly released from the internal reservoir core[2].

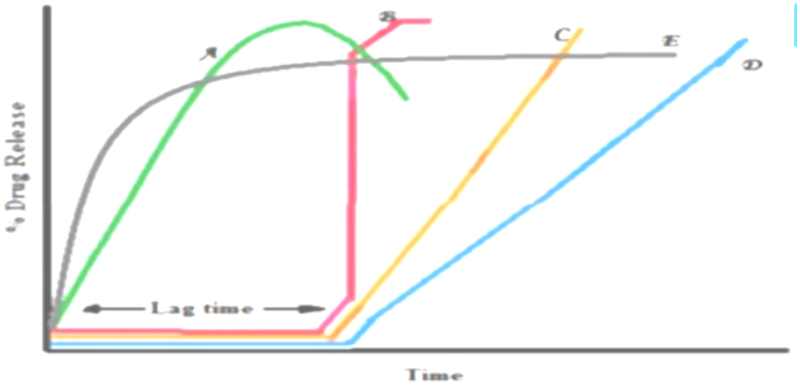


Figure No. 1: Drug release profiles from Pulsatile drug delivery system.

Where,

A= Conventional release Profile.

B= Burst release of drug after a lag time.

C=Delayed release profile after a lag time.

D= Constant discharge profile in the extended period after a lag time.

E= Extended-release profile without lag time.

Different modified release drug products[4,5].

1**. Prolonged Release**: It leads to double fold reductions in dosing incidence related to instantaneous release dosage forms.

2. **Controlled release**: This system shows slow drug discharge above the extended period but not at a fixed rate.

3. **Sustained-release**: The drug is delivered at a predetermined rate in this system over a long period.

4. **Delayed Release**: This dosage form discharges separate ratio of a drug at a period except for one portion, it may discharge quickly after administration.

5. **Targeted Release**: In this type of system drug releases close to the intentional site of action and shows prolonged-release features.

6. **Repeated Action**: Here the product is intended to release the first dose initially, followed by the second dose of the drug at a far ahead time.

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

Need for Pulsatile Drug Delivery Systems:

In many conditions sustain release formulation do not show proper efficacy. In such state pulsatile DDS is applicable.

1. First pass metabolism:

Extensive first-pass metabolism is seen in some of the drugs like beta-blockers blockers and salicylamide, to reduce the pre systemic metabolism, it requires fast drug input to saturate metabolizing enzymes, therefore sustained oral delivery would minimize oral bioavailability[6].

2. Biological tolerance:

A pharmacotherapeutic consequence of the drug is often accompanied to a decline in the plasma profile concentration.

3. Chronopharmaceutical need:

Here the Chronopharmaceutics is defined as the study of the biological rhythms and their mechanism,

Around 3 types of mechanical rhythms are there, among them are,

- **Ultradian Rhythms:** oscillations having a shorter duration are known as ultradian rhythms.

Eg: 90min sleep cycle.

- **Infradian Rhythms;** Longer duration oscillations are known as infradian rhythms.

Eg: Mensuration cycle.

- **Circadian rhythms;** Circadian rhythms are efficient, endogenous oscillations that ensue with a periodicity of 24 Hours.

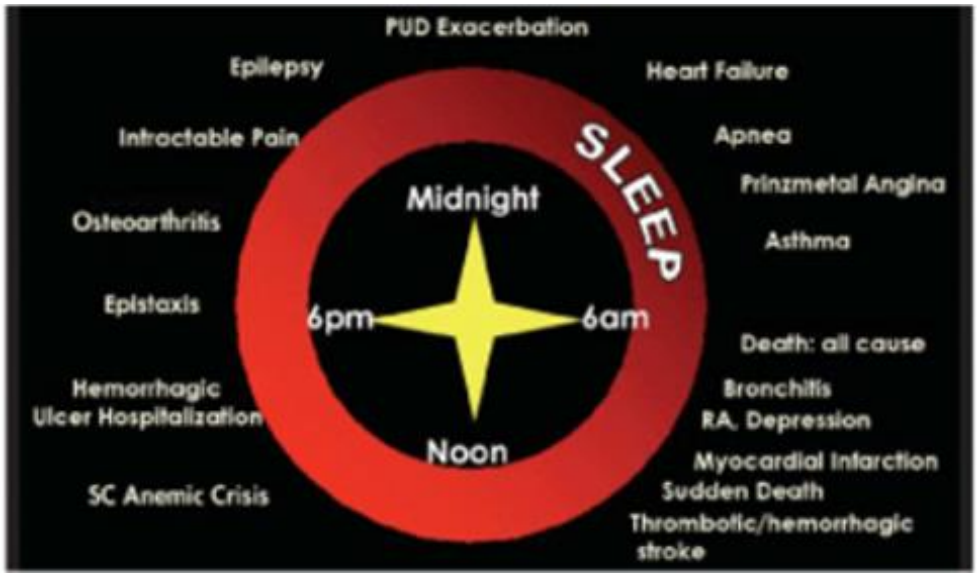


Figure No. 2: Circadian Rhythm Cycle.

The peak time of various biological Processes:

In the above figure, it displays the peak time of biological routes that shows the circadian performance of people who follows the daily day time routine activity i.e. 6 am to 10 pm. In the 24hr schedule, the disease exhibit a definite time of occurrence in the body.

Advantages of PDDS :[7, 8]

- Prolonged day time or night time action.
- Fewer side effects.
- Decrease dose size and dosing frequency.
- Better patient compliance.
- Daily fewer dosage units are required by patients in the treatment and hence cost is economical.
- Drug aiming to exact site like the colon.
- Defense to the mucosa from the nauseating drug.
- Drug loss is stopped by extensive first-pass metabolism e.g. proteins and peptide.

Disadvantages of PDDS [9]:

- Low drug filling capability and imperfect discharge of drug.
- Many manufacturing steps are seen in case of a drug delivery system.
- An instant removal of drug is impossible.
- Lack of manufacturing reproducibility and efficiency.
- It is a Batch manufacturing process.
- Huge quantity of process fluctuation is seen.

Classification

Pulsatile drug delivery system is classified into four classes.

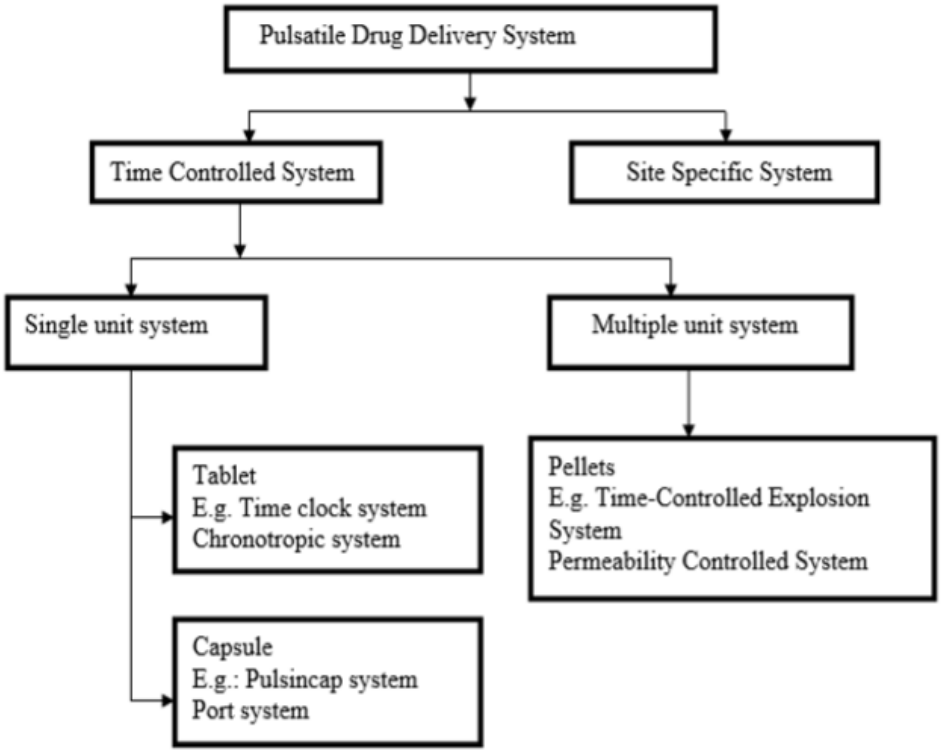
I. **Time controlled pulsatile release.**

II. **Stimuli induced**

III. **Chemical stimuli induced pulsatile system.**

IV. **External stimuli pulsatile release.**

I. Time controlled pulsatile release system.



This system is further classified into 2 units.

1. Single unit system[1].

a) Capsular system:

Here single unit capsular PDDS are achieved. In general, the design consists of an indecipherable capsule body and a plug. The plug is detached after a determined lag time. due to swelling, erosion, or dissolution.

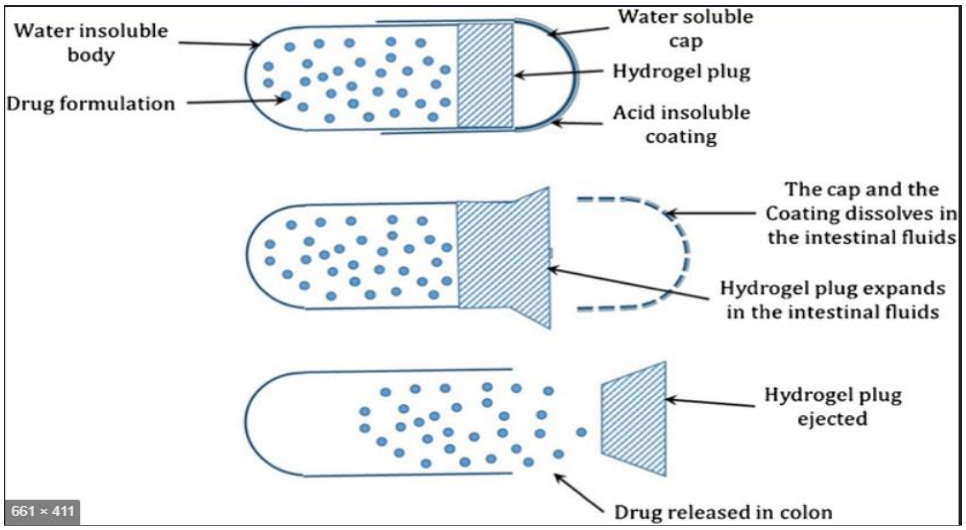


Figure No. 3: Capsular system

PDDS is the best example of a water-insoluble capsule and it is filled with the drug formulation. The body of the capsule is closed and opened at one end, that end is made up of Hydrogen swellable plug.

The plug is going to swell when it interacts with dissolution medium or gastrointestinal fluids.

The plug of the capsule should rupture only at a higher pH of the small intestine, to overcome from the gastric fluids the capsule should undergo for enteric coating for this system. (eg, for swellable polymer = polymethacrylates).

b) ERODIBLE MEMBRANE:

In this type of delivery system erosion of the outer coat will takes place, the drug release is controlled by the dissolution or by erosion from the core of the drug. Time reliant discharge of the active ingredient can be achieved by adjusting the thickness of the outer coat. HPMC is used as an enteric coating for chronotropic system.

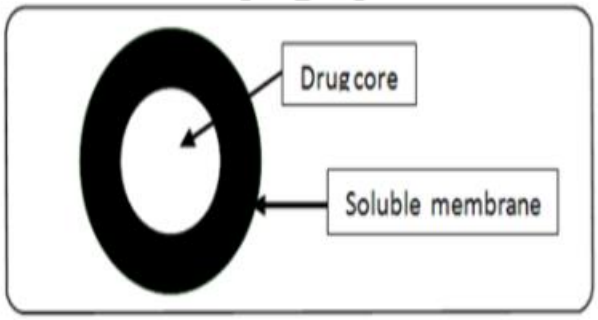


Figure No. 4: Erodible membrane delivery system.

The lag time of the drug is determined by the grade of HPMC used, while an increase in the thickness grade of HPMC leads to the extended lag period [13].

c) Reputable Coating:

Due to the pressure developed by the effervescent agents and swelling agent, coating of a drug is going to rupture, based upon a reservoir system and rupturable membrane. Citric acid & sodium bicarbonate is combined as an aerated mixture. When this system comes in contact with water it produces the carbon dioxide gas, which employs the pressure and ruptures the outer membrane.

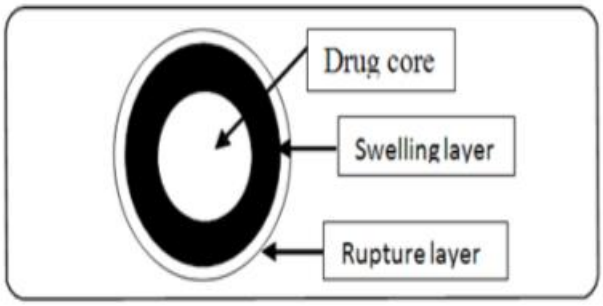


Figure No. 5: Reputable Coating

Crospovidone was used as the swellable substance and the lag time is controlled by the outer polymeric membrane [14][15].

(2) Multi-particulate system

a) A pulsatile system with rupturable coating:

It is a reservoir type of system with a coating in which neither breach nor change its permeability. The drug is layered over sugar seeds these pellets may then filled in a capsule or compressed with supplementary excipients to form a tablet. Sodium carboxymethyl cellulose, sodium starch are used as the swellable agent. When the swellable layer expands, resulting in breaking of the film with consequent rapid drug release. Though, drug loading in this system is difficult due to the greater requirement of excipients.

b) Pulsatile system by Change in Membrane Permeability:

As already stated that the discharge of the drug must be controlled regarding the therapeutical purpose and the pharmacological properties of the active ingredient. Insignificance, numerous pharmaceutical forms with the extended-release for oral administration are available.

To reduce the night-time symptoms or the symptoms upon emerging in the early morning chronic diseases like ischemic heart disease, asthma, and arthritis, the drugs should be managed in such a way that the anticipated therapeutical plasma level is reached only at the desired moment. For insistence, to escape any acclimatization and to minimize the side effects triggered by the active ingredient, it could be completely beneficial for the plasmatic rate to shadow the metabolic rhythm and the specific needs of the patient during early morning sleep.

Chen proposed that a large number of pellets made up of two or more populations of pellets or particles. Each pellet contains a drug-containing a core, and a water-soluble osmotic agent enclosed in water-permeable, water-insoluble polymer film which is Combined with the polymer film is a hydrophobic, water-insoluble agent which modifies the absorptivity of the polymer film. The film coating of each number of pellets varies from the coating of every new population of pellets, the dosage form in the amount at which water passes through the core and the rate at which drug scatters out of the core[16].

II. Stimuli Induced pulsatile system:

a) Temperature-induced system:

Thermo-reactive hydrogel systems have been established for pulsatile release. In these classifications, the polymer experiences swelling or deswelling phase in reaction to the temperature which moderate drug release in the swollen state. Y.H. Bae et al developed indomethacin pulsatile release pattern in the temperature ranges between 200C and 300C by using reversible swelling properties of copolymers of N-iso-propyl acrylamide and butyl acrylamide [17].

b) pH-Sensitive system:

In this pulsatile system it involves two components one is of immediate-release type and another one is pulsed release which discharges the drug in response to change in ph and Advantage has been taken on the fact that exists different pH environment at different parts of the gastrointestinal tract. By choosing the pH reliant polymers drug discharge at an exact site can be obtained.

III. Chemical induced pulsatile system:

a) Glucose-responsive Insulin Release Device:

Here there is a lot of attention in the development of stimuli-sensitive delivery systems that release a therapeutic agent in the presence of specific chemical moieties like enzyme or protein. One of the best examples is Glucose-responsive insulin release, in which insulin is released on increasing of blood glucose level. In diabetes mellitus, there is a rhythmic increase in the levels of glucose in the body requiring an injection of the insulin at the proper time. Many appliances have been developed for this purpose and all of them have a glucose

sensor built into the system. This enzyme is perhaps the most extensively used in glucose sensing and makes possible to apply different types of pH-sensitive hydrogels for modulated insulin delivery system.

IV. External stimuli Pulsatile release:

The peripheral stimuli like Magnetism, ultrasound, electrical effect, are automated to release the drug in a pulsatile manner.

A) ELECTRICALLY STIMULATED:

Poly Electrolytes prepares the electrically responsive delivery system, here the Polymers contain a high concentration of ionizable groups. Under the effect of the electric field, electroreceptive hydrogels usually bend, depend on the shape of the gel which is parallel to the electrodes whereas de swelling occurs when the hydrogel lies vertically to the electrodes (18).

B) MAGNETICALLY STIMULATED:

On the application of the magnetic field, drug release occurs due to magnetic beads and this system contains the implants. Essentially the automatic approach behind the policy is based on reducing the movement of oral drugs in the gastrointestinal system through magnetic attraction. The momentum of the drug travel through the stomach and the intestine can be delayed at a particular site by the help of external magnets (19).

CONCLUSION

Oral drug delivery system is the most convenient route of drug administration having Great patient compliance, easy in administration and easy in its formulations. This system delivers the drug at the right place at the right time to the body. Pulsatile drug delivery system is an important system to deliver the drugs according to chronopharmacological behavior. Sustain release drugs are not an effective treatment for the chronological disorder. PDDS is an advantage for the patients suffering from arthritis, asthma, hypertension, etc. because extended-release and immediate-release formulations are not efficient in treating the disease with chronological pathophysiology. Different pulsatile systems like Time, Stimuli, Externally regulated Multiparticulate regulated the designing of proper Pulsatile drug

delivery will improve the patient compliance from optimum drug delivery to the target site, and this system minimizes the undesired effect.

REFERENCES

1. Neha PS, Gangaraj G, Preeti K, A Review on Pulsatile Drug Delivery System; World Journal of Pharmacy and Pharmaceutical Sciences, 2016; 5(5): 479-491.
2. Gupta MK, Saraf S. Formulation and Evaluation of Pulsatile Drug Delivery System of Ramipril for Controlling Morning Spate of BP. Journal of Pharmaceutical Research. 2018 Jul 20; 17(1):2-12.
3. KUMAR YG, Pulla RP, Ganesh A, Naresh G, Saleem A. Formulation and In-Vitro Evaluation of Floating Pulsatile Drug Delivery System of Ivabradine. Journal of Drug Delivery and Therapeutics. 2019 May 15;9(3):188-93.
4. Modi MP, Prasanth VV, Mathew ST. PULSATILE: A TOOL FOR CIRCADIAN RHYTHM-A REVIEW. Journal of Drug Delivery and Therapeutics. 2012 Jan 19;2(1).
5. Sharma R, Singh A, Kumar S, Jamil F: Pulsatile drug delivery system. International Research Journal Of Pharmacy 2012; 3(7):103-107.
6. Rekha F, Review on Approaches to Pulsatile Drug Delivery System, International Journal for Pharmaceutical Research Scholars (IJPRS), V-4, I-2, 2015; 80-95.
7. Rompicharla B, Prabha KS. Tabassum, "A Comprehensive Review of Pulsatile Drug Delivery System". Int. Research J. of Pharmacy. 2012;3:106-8.
8. Modi MP, Prasanth VV, Mathew ST. PULSATILE: A TOOL FOR CIRCADIAN RHYTHM-A REVIEW. Journal of Drug Delivery and Therapeutics. 2012 Jan 19;2(1).
9. Gupta A. Review on Recent Advances in Pulsatile Drug Delivery System: A vision for a better future for the treatment of diseases. International Pharmaceutical Science. 2012; 2:71-6.
10. Wilding IR, Davis SS, Bakhshaee M, Stevens HN, Sparrow RA, Brennan J. Gastrointestinal transit and systemic absorption of captopril from a pulsed-release formulation. Pharmaceutical research. 1992 May 1;9(5):654-7.
11. Stevens HN, Wilson CG, Welling PG, Bakhshaee M, Binns JS, Perkins AC, Frier M, Blackshaw EP, Frame MW, Nichols DJ, Humphrey MJ. Evaluation of Pulsincap™ to provide regional delivery of dofetilide to the human GI tract. International journal of pharmaceutics. 2002 Apr 2;236(1-2):27-34.
12. Krögel I, Bodmeier R. Pulsatile drug release from an insoluble capsule body controlled by an erodible plug. Pharmaceutical research. 1998 Mar 1;15(3):474-81.
13. Krögel I, Bodmeier R. Floating or pulsatile drug delivery systems based on coated effervescent cores. International Journal of Pharmaceutics. 1999 Oct 5;187(2):175-84.
14. Bessemer T, Otto I, Bodmeier R. Pulsatile drug-delivery systems. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2001;18(5).
15. Lemmer B. Chronopharmacokinetics: implications for drug treatment. Journal of pharmacy and pharmacology. 1999 Aug;51(8):887-90.
16. Chen CM. Pulsatile particles drug delivery system. US5472708. 1995 Dec.
17. Bae YH, Kim SW, Valuev LI, inventors; University of Utah, assignee. Pulsatile drug delivery device using stimuli sensitive hydrogel. United States patent US 5,226,902. 1993 Jul 13.
18. Kulkarni RV., Biswanath SA., Electroresponsive polyacrylamide grafted- xanthan hydrogels for drug delivery, J. Bioactive Compatible Poly., 24: 368- 384, (2009).
19. AR Mullaicharam, A Review on Chronopharmaceutical Drug Delivery System; Research Journal of Pharmaceutical, Biological and Chemical Science., July - September 2013; 4(3): 200-208.
20. Rewar S, Bansal BK, Singh CJ, Sharma AK. Pulsatile drug delivery release technologies: An overview. Int. J. Res. Dev. Pharm. Life Sci. 2015;4:1386-93.
21. Arora S, Ali J, Ahuja A, Baboota S, Qureshi J. Pulsatile drug delivery systems: An approach for controlled drug delivery. Indian journal of pharmaceutical sciences. 2006;68(3).
22. Saini S. Chronotherapy: A Review. International Journal of Drug Delivery Technology. 2014;4(3):47-57.
23. Smolensky MH, Peppas N. Chronobiology, drug delivery, and chronotherapeutics. Adv Drug Deliv Rev

2007; 59: 828-51.
24. Survase S, Kumar N. Pulsatile drug delivery. Current Scenario Crips 2007; 8(2):27-33.
25. Manish KG, Swarnlata S. Formulation and Evaluation of Pulsatile Drug Delivery System of Ramipril for Controlling Morning Spate of B.P. J Pharm Res 2018:17 (1);1-12
26. Chiranjibi A, Gururaj S K, Shivakumar S. Formulation and evaluation of pulsatile drug delivery system of salbutamol sulfate for the chronotherapy of asthma. Asi J Pharm Clin Res. 2018:11(9); 305-311
27. Nizar A J, Nawal A R. Formulation and in vitro evaluation of azilsartan medoxomil nanosuspension. 2017:9(7); 110 119.
28. Abhijit S, Amrish C. Formulation and evaluation of pulsatile tablet in capsule device. Int J Pharm sci. 2013:5(2); 125-129
29. Brahmaiah B, Sarvani V, Sreekanth N, Donthiboina S, Suresh N. Formulation and evaluation of pulsatile drug delivery system of atenolol. Ameri J Bio-Pharm Res, 2014;1(1):28-33.
30. Patel JD, Aneja K, Majumdar SH. Pulsatile drug delivery system: a" user-friendly" dosage form. Asian Journal of Pharmaceutical Research and Health Care. 2010;2(2):204-15.

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