Content available at: https://www.ipinnovative.com/open-access-journals

IP International Journal of Comprehensive and Advanced Pharmacology

Journal homepage: https://www.ijcap.in/

Review Article

# Present scenario of pulsatile drug delivery system

**Rajni Yadav**[1,*], **Megha Jha**[2], **Diksha Jat**[3], **Deepak Kumar Jain**[4]

[1]*Faculty of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh, India*
[2]*Pinnacle Biomedical Research Institute, Near, Bharat Scout and Guides Campus, Bhopal, Madhya Pradesh, India*
[3]*Oriental College of Pharmacy, Patel Nagar, Bhopal, Madhya Pradesh, India*
[4]*Medicinal Chemistry Research Laboratory, SLT Institute of Pharmaceutical Sciences, Guru Ghasidas Central University, Bilaspur, Chhattisgarh, India*

ARTICLE INFO

*Article history:*
Received 15-07-2022
Accepted 02-08-2022
Available online 13-01-2023

*Keywords:*
Lag time
Pulsatile drug release
Rupturable coating

ABSTRACT

In current years, pulsatile drug release systems (PDRS) are ahead raising attention as compared to conventional drugs. In this delivery system, the drug is liberate quickly after a well defined insulate-time, could be helpful for many medicines or treatments. It can be labeled in single and a couple of-pulse structures. Other structures consist of a drug-enclosed core, enclosed by means of a swelling layer and an outer layer is insoluble, however coating with semipermeable polymer. The lag time earlier to the rupture is specifically controlled via: the penetration and mechanical houses of the coated polymer and the behaviour of swelling depend on the swelling layer. As is within the residing frame frequently observed that, many fundamental capabilities are regulated with the aid of brief or pulsed launch of bioactive substances at a precise site and time. Therefore its miles grave to expand novel drug transport systems to attain pulsed launch of a sure amount of medicine a good way to imitate the feature of the dwelling systems, whilst reduce undesirable side results. Particular interest has been given to the thermally receptive poly (N-isopropylacrylamide) and its imitative hydrogels. Pulsatile drug transport is a machine that, by means of handing over drug at the right vicinity, right amounts and in proper time, grips suitable assures of benefit to the patients affected by continual problems like high blood pressure, allergies, arthritis.



## 1. Introduction

Conventional oral formulations are the top leading dosage form in global market. It is the preferential route for drug administration and management. The oral controlled-release systems show a distinctive model of drug targets to liberate in which the drug absorption is sustained in the curative window for an extended phase of time, thus safeguarding sustained therapeutic action. In certain situations this release pattern isn't always appropriate that insists discharge of a drug after an interval of time. The pulsatile system is in advance quite a few attention, as the drug is launched entirely after described insulates time (Figure 1). PDD is website online and time-specific drug shipping, as a consequence imparting spatial and chronological shipping and accumulative patient fulfillment. This drug transport gives the fast and fleeting delivery of certain amount of selected molecules within a small span of time immediately after a programmed duration, i.e., lag time, and these system have the process of handling the drug substance quickly and completely after an insulated time. Such a release model is called as pulsatile release.[1–4] Human's body show a particular circadian rhythms that are synchronized by the master circadian clock, the suprachiasmatic center. Chronopharmacotherapy of diseases (myocardial infarction,

* *Corresponding author*.
*E-mail address*: rajni.yadav@kalingauniversity.ac.in (R. Yadav).

https://doi.org/10.18231/j.ijcaap.2022.035

bronchial asthma, rheumatic disease, angina pectoris, ulcer and hypertension) that explain circadian rhythm in their etiology and management of such diseases entail PDDS, by which drug is released quickly and entirely as a pulse after insulate time.[4–6] There are several other conditions that require release of the drug in pulsatile manner, like many frame capabilities that trace circadian rhythms, consisting of secretion of hormones like luteinizing hormone, follicle stimulating hormone, progesterone and estrogen, acid secretion in the gastric emptying, stomach and GI blood transfusion. There are abundant benefits of the PDDS. These are:

1. Can be used extensively for day and night time action.
2. Low cost, side effects are low as dose frequency and dose size is less.
3. Adapts to body circadian rhythms.
4. Drug targeting is easy.
5. Defends the GI mucosa from irritating drugs.
6. First pass metabolism is lease.
7. Steady drug level is maintained in the blood plasma.[7–10]

### 1.1. Disadvantages

1. Loading capacity of drug is less.
2. Release of drug is less.
3. Formulation steps are complex.
4. Reproducibility and efficacy is poor.
5. Skilled/trained persons needed for manufacturing.

Present review focus on advanced methodologies for pulsatile manufacturing and up-gradation in the technologies for manufacturing.

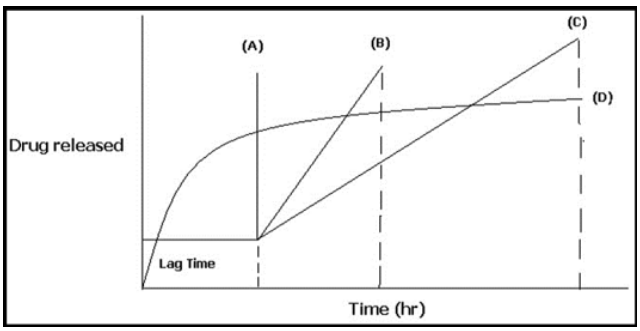



**Fig. 1:** Schematic representation of different drug delivery systems, with (A) sigmoidal release after lag time, (B) delayed release after lag time, (C) sustained release after lag time and (D) extended release without lag time. [Reproduced from: Jain D., Raturi R., Jain V., Bansal P., Singh R. Recent technologies in pulsatile drug delivery systems. Biomatter. 2011; 1: 57-65.]

### 1.2. Chronopharmacotherapy

The phrase chronopharmaceutics includes two words chronobiology and pharmaceutics. Chronobiology is the area which includes study of biological rhythms and their mechanisms in the body. Chronotherapeutic drug shipping machine is the drug delivery device that's based at the biological rhythms of frame. Chronomodulated machine is also recognized as pulsatile device or sigmoidal release system. There are 4 styles of mechanical rhythms in our body, which manage ordinary and disease associated body structure of the body (Figure 2).They are:

1. *Circadian:* The oscillation is completed in 24hrs.
2. *Ultradian:* The oscillation completed in shorter duration i.e. less than 24 hrs.
3. *Infradian:* The oscillations is longer than 24 hrs.
4. *Seasonal:* In the short days of winter, seasonal affected illness reasons melancholy in prone people. Out of four biological rhythms, circadian rhythm is the main rhythms in the body which maintains all the physiological, chemical, biological and behavioral processes.[11–13]

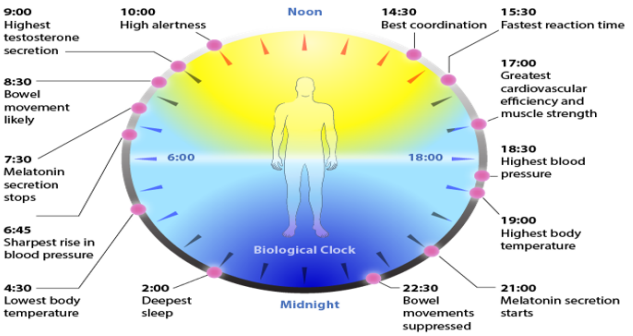



**Fig. 2:** Cycle of circadian rhythms [Reproduced from: https://cpapvictoria.com.au/blog.]

### 1.3. Necessitate of pulsatile drug delivery systems

1. Circadian rhythm follows many body functions which fluctuates according to the time.
2. Acid secretion, cholesterol synthesis, gastric emptying and GI blood transfusion might change with circadian rhythm.
3. Chronopharmacotherapy of illnesses which give an explanation for circadian rhythms of their path body structure.

### 1.4. Mechanism of drug release from pdds

The release happens from PDDS in different ways.[14]

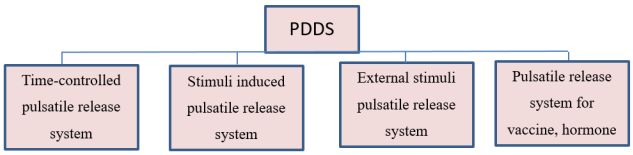
a) Diffusion $H_2O$ diffuses to the internal particle as soon as it comes in contact with aqueous fluids.

Erosion With time few particles erode slowly to release the drug.

Osmosis Osmotic pressure develops between the outside aqueous fluid and internal particle which can be one pathway of release of drug.

### *1.5. Classification of PDDS*

Pulsatile system are essentially time-controlled drug delivery system in which the system manages the lag time independent of environmental factors like enzyme, pH, GI motility etc. Pulsatile drug delivery systems can be generally categorized into four classes.[15]



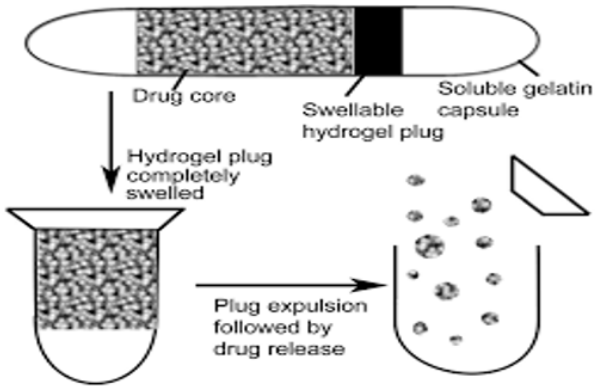




**Fig. 3:** Schematic design of pulsincap system. [Reproduced from: Shidhaye S.S., Lotlikar V.M., Ghule A.M., Phutane P.K., Kadam V.J. Pulsatile delivery systems: An approach for chronotherapeutic diseases. Sys. Rev. Pharm.2010; 1: 55-61.]

### *1.6. Time-controlled pulsatile release system*

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

#### *1.6.1. Single unit systems*

1.6.1.1. Capsular systems. Single-unit systems are mostly developed in capsule form. The insulate time is managed by way of a plug, which finds pushed away by erosion or swelling and the drug is launched as a Pulse from the insoluble pill frame. Polymers used for designing of the hydrogel plug are as following:[16]

1. Swellable materials coated with but permeable polymer (polymethacrylates).
2. Erodible compressed polymer (polyvinyl alcohol, HPMC).
3. Congealed melted polymer (glyceryl mono oleate).
4. Enzymatically controlled erodible polymer (pectin).[17]

These structures are made in a way that drug reservoir is covered with soluble or erodible layer that dissolves when in contact with fluid and drug is released after an insulated tiem.[18] For instance the biological clock of body.[19] It includes a strong dosage shape protected with lipid limitations containing surfactants.[20] The insulate time and movement of drug is managed by the thickness and grade of viscosity of polymer (Figure 5).

The system is coated with a rupturable membrane. The outer layer or membrane gets ruptured due to pressure by effervescent agents. In such a system sodium bicarbonate and citric acid are used as effervescent agents.[21] Ethyl cellulose coating is done in the core tablet when the system comes in contact with water it releases carbon dioxide which

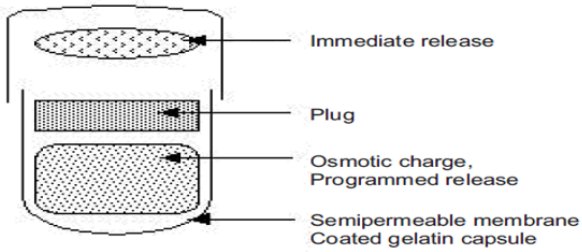



**Fig. 4:** Schematic design of osmotic system. [Reproduced from: Arora S., Ali J., Ahuja A., Baboota S., Qureshi J. Pulsatile drug delivery systems: An approach for controlled drug delivery. Indian J. Pharm. Sci. 2006; 68: 295-300] Pulsatile delivery by solubilisation (or) erosion of membrane

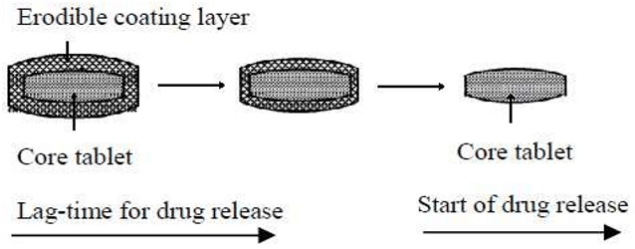



**Fig. 5:** Schematic diagram of delivery system with erodible coating layers [Reproduced from: Kotha R.K., Raghavapally S.G., Adavi S.L., Taranalli S., Pandey D. Current techniques in pulsatile drug delivery: a review. Int. Res. J. Pharm. 2013; 4:77-84.] Drug delivery system with rupturable layers/ membranes

creates pressure and after some time the membrane ruptures due to pressure (Figure 6). The lag time is controlled by way of the composition of the outer polymeric membrane.[22–25]

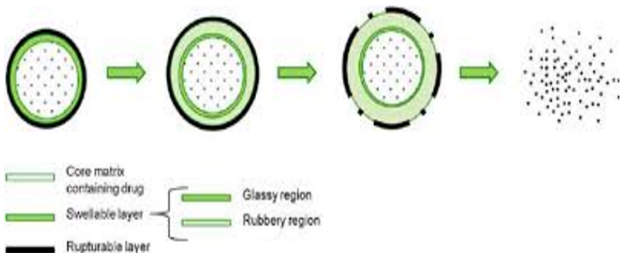



**Fig. 6:** Drug Release Mechanism from System with Rupturable coating Membrane [Reproduced from: Devi R., Kumar S. Pulsatile drug delivery system: new paradigms. Int. J. Innov. Pharm Sci. Res. 2017; 5: 34-49.]

### *1.7. Multiple unit pulsatile systems*

Gastric emptying pattern differs for multi-particulate formulations, such system are dispersed freely throughout the GITand is affected by transit time of food[26] (Figure 7). These systems are of two types.

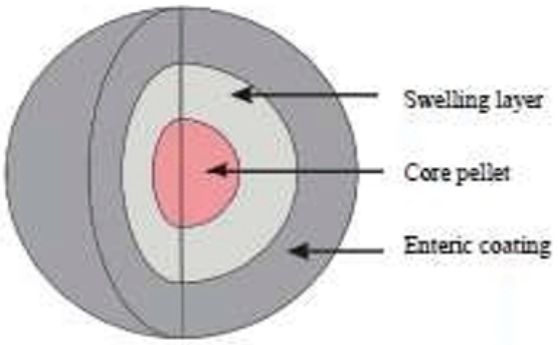



**Fig. 7:** Hypothetical designsof multiparticulate pulsatile systems [Reproduced from: Kotha R.K., Raghavapally S.G., Adavi S.L., Taranalli S., Pandey D. Current techniques in pulsatile drug delivery: a review. Int. Res. J. Pharm. 2013; 4:77-84.] Pulsatile system based on the change in membrane permeability

This system incorporates the interface of some acrylic polymers with quaternary ammonium corporations. The inside core is having drug and succinic acid coated with AMC USP/NF type

The water is responsible for liquefying the succinic acid. This scheme was used to design an acid-containing core and tested in beagle dogs. It shows a good in vitro/in vivo relationship of lag time.[27]

### *1.8. Stimuli-induced pulsatile release system*

This system release the drug in response to stimuli by the external surroundings.[28]

### *1.9. Thermoresponsive pulsatile release*

Hydrogel are the better example for thermo-sensitive drug delivery. The polymer is crosslinked and the transition in temperature is linked in the formation of hydrogel. Temperature-sensitive polymer used are ethyl, methyl, and propyl groups. Poly (N-isopropyl acrylamide) (PINPAm) are extensively used polymers.[29]

### *1.10. Chemical stimuli-induced pulsatile release*

The factor responsible for drug release is biological factors like pH, enzymes or any other chemical stimuli. Example is automatic release of insulin when glucose level rises in blood. Kazunori et. al., reported a gel that showed a remarkable change in swelling caused by glucose using phenylboronic acid.[30,31]

### *1.11. Externally regulated pulsatile release system*

Electro responsive pulsatile release

Application of electric field as an external stimulator. Electrically response delivery uses polyelectrolytes and are also sensitive to pH change. Poly (2-acrylamide-2-methyl propane sulfonic acid-co butyl methacrylate) hydrogels are example of such delivery system.[32,33]

### *1.12. Micro electro-mechanical systems*

The device made by this system have the ability to store and release many chemical moiety by moving mechanism. Better control over drug release is possible. Another advancement is microchip, which contains such reservoirs of impermeable substrate through an electrolyte.[34] Prototype microchip is made of silicon and contains drug reservoir which is covered at one end by gold that provides the electrochemical reaction and melts on application of electric potential.[35,36]

### *1.13. Pulsatile release systems for vaccine and hormone products*

The major mechanism involved in therapeutic benefit from vaccines is development of immunity.[37] Vaccine are administered to protect the bosy and hence co-administration is also needed to maintain the immunity.[38] PDDS can be used for delivery of vaccines.[38–42]

## 2. Marketed Technologies of Pulsatile Drug Delivery

Pharmaceutical companies worldwide are focusing on development of such PDDS which can help to treat major

**Table 1:** Example of FDA approved pulsatile drug delivery systems in market

| Proprietary name | Active pharmaceutical ingredient | Chronopharmaceutical technology | Drug release mechanism |
|---|---|---|---|
| Concerta® tablet | Methylphenidat HCl | Oros | Osmotic regulation |
| Cardizem LA | Diltiazem Hcl | Ceform microsphere technology | Diffusion/ erosion |
| Uniphyll$^R$ | Theophylline | Contin$^R$ | Controlled release |
| Innopran$^R$ XL | Propranolol Hcl & Verapamil | Diffucaps | Rapid/sustained release |
| Covera-HS$^R$ | Verapamil | Oros | Osmotic regulation |
| Verelan$^R$ PM | Verapamil | Codas | Delayed release |
| Pepcid | Famotidine | Physicochemical modification of API | Tablet |
| Lipovas$^{R,}$ | Simvastatin | Physicochemical modification of API | Tablet |
| Invega$^{TM}$ | Paliperidone | OROS | Osmotic regulation |
| Glucotrol | Glipizide | OROS | Osmotic regulation |
| Glizid-MR30 | Gliclizide | Hydrophilic matrix technology | Swelling/diffusion/erosion |
| Kapidex$^{TM}$ | Dexlansoprazole | DDR Technology | Dual drug release |
| Coruno® | Molsidomine | Geomatrix technology | Swelling/erosion |
| Theirform | Diclofenac sodium | 3DP | Immediate release/controlled release |
| PulsincapTM | Dofetilide | PulsincapTM | Rupturable system |
| Moxatag®: ER tablets | Amoxicillin | Pulsystm | Multiparticulate system |
| Their form | Diclofenac Na | Three dimensional printing | Externally regulated system |
| Opana® | Oxymorphone | Timerx® | Erodible/ soluble barrier coating ER Tablets |
| Cardiazem® LA | Diltiazem HCl,Verapamil HCl | Ceform® | Extended Release tablet |
| Procardia XL | Nifedipine | Procardia XL® | Sustained release |
| Hokunalin® tape | Tulobuterol | Transdermal chronodelivery System. | |

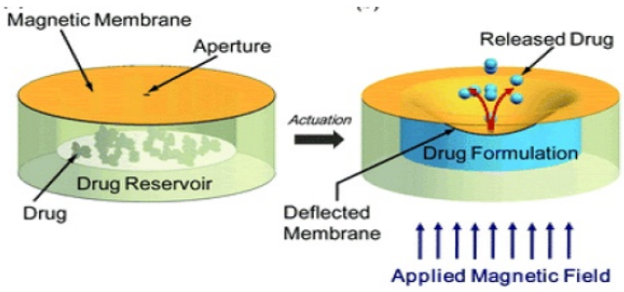



**Fig. 8:** Drug release from magnetically induced pulsatile systems [Reproduced from: Shanmugan P., Bandameedi R. Chronotherapeutic drug delivery systems. J. Drug Meta. Toxico. 2015; 6: 2-7.]

chronic disorders. Recently developed technologies used are listed in Table 1.

## 3. Recent Advances in the Pulsatile Drug Delivery System

There are many diseases that require pulsatile release like asthma, cancers, arthritis, ulcers, cardiovascular diseases, allergic problems.[27] The recent trend is multi particulate system that offers many advantages. The release pattern of drug is dependent upon pH, internal flora of GI, time release. For increasing therapeutic efficacy of oral delivery various technologies are developed.[42]

## 4. Accubreak Technology

Dose modification becomes easy by this technology. In this small dose of the tablet is taken and a controlled release medication is prepared. When it releases in the body the membrane ruptures and the drug is reduced to half prior to its release.[43]

## 5. TMDS Technology

In single tablet the release rate of multiple ingredients can be optimized.

## 6. Geoclock Technology

In this active drug is surrounded by an outer layer which contains a hydrophobic mixture and a brittle material. E.g. LODOTRA – for rheumatoid arthritis.

**Table 2:** Recent patent on pulsatile/controlled drug delivery systems/devices

| S. No. | Based on API/Device | Topic | Inventor | Status/Date | Patent No. |
|---|---|---|---|---|---|
| 1 | Device | Multi-dose drug delivery device and method | Robert Farra | Granted/ 2014-03-25 | US8679093B2 |
| 2 | Device | Medical device for controlled drug delivery and cardiac monitoring and/or stimulation | Barry M. Yomtov Stephen J. Herman | Granted/ 2011-03-29 | US7917208B2 |
| 3 | Device | Low-permeability, laser-activated drug delivery device | Jonathan Robert CoppetaKenneth N. HorneJohn T. Santini, Jr.John A. SchollGregory J. R. Spooner Cynthia L. Stevenson Naveed ShamsAndrew Poutiatine | Grant/ 2014-12-16, 2014-01-08 | US8911426B2, EP2533737B1 |
| 4 | Device | Portable drug delivery device including a detachable and replaceable administration or dosing element | Joseph Zhili Huang Guy DiPierro | Grant/2013-02-12, | US8372040B2 |
| 5 | Device& different APIs | Oral drug delivery system | Su Il YumGrant SchoenhardArthur J. TiptonJohn W. GibsonJohn C. Middleton | Grant/ 2012-03-13, 2015-09-23, 2012-02-01, 2013-06-12, 2013-09-17, 2010-11-11, 2016-01-11, 2011-01-26 | US8133507B2, EP2218448B1, JP4865330B2, CN101797221B, CA2810477C, DE60334401D1, DK2218448T3, ES2350689T3 |
| 6 | Delivery system | Drug delivery system | James M. Olsen | Granted/ 2010-08-03, 2007-11-14, 2008-09-11 | US7766885B2, EP1755703B1, DE602005003355T2 |
| 7 | Device | Cartridge insertion assembly for drug delivery system | Oz Cabiri | Granted/ 2012-04-17, 2014-08-13, 2014-07-02, 2014-05-07 | US8157769B2, EP2477679B1, JP5535321B2, CN102639169B |
| 8 | Ionizable pharmaceutical agent& lipophilic species | Transmucosal drug delivery system | John A. McCarty | Granted/ 2015-03-31, 2014-04-16, 2013-01-02, 2012-02-07, 2013-07-08, 2013-07-18, 2009-01-10 | US8992974B2, JP5475215B2, CN1777411B, CA2516816C, DK1599186T3, ES2414084T3, RU2342953C2 |
| 9 | Devices | Drug delivery devices, kits and methods there for | Gilbert H. KLIMAN | Granted/ 2013-08-27 | US8521273B2 |
| 10 | Devices | Gastric retention controlled drug delivery system | Kamlesh Mohanlal DudharaNitin Bhalachandra DharmadhikariVaishali Vijay Dhavse | Granted/ 2010-08-17, 2012-12-05, 2012-08-08, 2010-12-01, 2011-06-14, 2010-09-30, 2013-03-15, 2008-05-27 | US7776345B2, EP2238975B1, JP4994570B2, CN1520286B, CA2452738C, DE60237372D1, ES2398348T3, RU2325152C2 |
| 11 | Device | Transmucosal drug delivery device and method including chemical permeation enhancers | Scott UhlandEric PeetersHussain Fatakdawala | Granted/2014-11-11, 2014-11-19, 2015-05-07 | US8882748B2, EP2308465B8, JP5715368B2 |
| 12 | Delivery System | Controlled dose drug delivery system | Amir ShojaeiStephanie ReadRichard A. CouchPaul Hodgkins | Granted/ 2014-09-30 | US8846100B2 |

## 7. Duredas Technology (Dual release drug absorption system)

In this there are two layers in which one layer is responsible for immediate release of second layer and sustained action is produced.

### *7.1. Innoherb*

In this the herbal compound are converted into beads or pellets and coated within capsule. The coating is done by semi-permeable membrane which is also used to mask the bad tast. [44]

### *7.2. Orbexa technology*

Granulation is done for loading of drugs. Polymers are used for coating and this technology can be imparted in proteins. [19]

## 8. Conclusion

Oral delivery of drugs is the most suitable and cost-effective approach followed. The chrono pharmacology principles can be used and be a fairly promising delivery in many chronic illnesses. The new drug delivery system is need of the hour for better therapeutic efficacy and pulsatile release is one of them. While, controlled release delivery offer the desired therapeutic impact, however, drop brief of diseases following organic rhythms, circadian issues together with peptic ulcer, high blood pressure, osteoarthritis, and asthma which want chrono pharmacotherapy. Circadian rhythm of the body is a widespread concept for knowledge of the most reliable want of drug within the body. Pulsatile drug delivery helps patients to handle the drugs in proper manner in proper time in chronic problems also. Drug transport will help in achi ‘eving outcomes. We are sure that with an increase in technological development and higher design parameters those obstacles can be overcome inside the close to destiny and wider variety of patients will be significantly benefited from this system.

## 9. Source of Funding

None.

## 10. Conflict of Interest

None.

## References

1. Kikuchi A, Okano T. Pulsatile drug release control using hydrogels. *Adv Drug Deliv Rev*. 2019;54(1):53–60.
2. Santini JJ, Richards AC, Scheidt R, Cima MJ, Langer R. Microchips as controlled drug-delivery devices. *Angew Chem Int Ed Engl*. 2019;39(14):2396–407.
3. James HP, Sara L, Samuel B, Norman FJ, John MM, Jonathan C. Programmed polypeptide delivery from an implanted, multireservoir microchip device. *Nat Biotechnol*. 2006;24(4):437–8.
4. Santini J, Cima MJ, Langer R. A controlled-release microchip. *Nature*. 1999;28(397):335–43.
5. Shidhaye SS, Lotlikar VM, Ghule AM, Phutane PK, Kadam VJ. Pulsatile drug delivery systems: an approach for chronotherapeutic diseases. *Sys Rev Pharma*. 2019;1(1):55–61.
6. Amy C, Insung SC, Betty MT, Paul PW, Henry B, Michael JC. Multi-pulse drug delivery froma resorbable polymeric microchip device. *Nat Mater*. 2020;2(11):767–72.
7. Ritschel WA, Forusz H. Chronopharmacology: a review of drugs studies. *Methods Find Exp Clin Pharmacol*. 2018;16(1):57–75.
8. Reddy RK, Jyothsna MV, Mohamed TS, Chetty C. Review on: pulsatile drug delivery systems. *J Pharm Sci Res*. 2019;18(5):109–24.
9. Yang SY, Yang JA, Kim ES, Jeon G, Oh EJ, Choi KY. Single-file diffusion of protein drugs through cylindrical nanochannels. *ACS Nano*. 2019;4(7):3817–39.
10. Rathod S. Colon targeted pulsatile drug delivery: A review. *Pharma Rev*. 2020;5:5.
11. Harkness J, Richter MB, Panayi A, Pette K, Unger A, Pownall R. Circadian variation in disease activity in rheumatoid arthritis. *Br Med J*. 2020;284(6315):551–4.
12. Jha N, Bapat S. Chronobiology, drug delivery, and chronotherapeutics. *Kathmandu Univ Med J*. 2020;2(1):384–8.
13. Botti B, Youan C. Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery. *J Control Release*. 2020;98(3):337–53.
14. Patwekar SL, Baramade MK. Controlled release approach to novel multiparticulate drug delivery system. *Int J Pharm Pharm Sci*. 2019;4(3):756–63.
15. Bakhshaee M, Binns JS, Stevens H, Miller CJ. Pulsatile drug delivery to the colon monitored by gamma scintigraphy. *Pharm Res*. 2020;9:230.
16. Hebden JM, Wilson CG, Spiller RC, Gilchrist PJ, Blackshaw E, Frier M. Regional differences in quinine absoption from the undisturbed human colon assessed using a timed release delivery system. *Pharm Res*. 2020;16(7):1087–92.
17. Binns J, Stevens H, Mcewen J, Pritchard G, Brewer FM, Clarke A. The tolerability of multiple oral doses of pulsincap TM capsules in healthy volunteers. *J Control Release*. 2021;38(2-3):151–8.
18. Stevens HNE, Rashid A, Bakhshaee M. US Patent No., US5474784A; 2021. Available from: https://www.uspto.gov/patents.
19. Shidhaye S, Dhone A, Budhkar T, Surve C. Technologies in pulsatile drug delivery system. *Int J Adv Pharm Bio Chem*. 2019;1:438–45.
20. Crison JR, Siersma PR, Taylor D, Amidon GL. Programmable oral release technology, Port Systems & Mac226: a novel dosage form for time and site specific oral drug delivery. *Proceed Intern Symp Control Rel Bioact Mater*. 2020;22:278–9.
21. Gennaro AR. Remington: The Science and Practice of Pharmacy. Williams & Wilkins; 2019. p. 903–5.
22. Wildind IR, Davis SS, Bakhshaee M, Stevens HNE, Sparrow RA, Brennan J. Gastrointestinal transit and systemic absorption of captopril from a pulsed release formulation. *Pharm Res*. 2019;9:654–7.
23. Saeger H, Virley P. Pulsincap & Mac226: Pulsed release dosage form. Product information from Scherer DDS. Ltd; 2018.
24. Krögel I, Bodmeier R. Floating or pulsatile drug delivery systems based on coated effervescent cores”. *Int J Pharm*. 2019;187(2):175–84.
25. Amidon GL, Leesman GD. US Patent No. 5229131A; 2018. Available from: https://patents.google.com/patent/US5229131A/en.
26. Bechgaard H, Ladefoged K. Distribution of pellets in the gastrointestinal tract. The influence on transit time exerted by the density or diameter of pellets. *J Pharm Pharmacol*. 2017;30(11):690–2.
27. Yadav R, Tiwari SP, Galgano J. Recent challenges in COVID 19 vaccines and its future advancements. *IP Int J Comprehensive Adv Pharmacol*;7(1):1–7.

28. Ueda Y, Hata T, Yamaguchi H, Kotani M, Ueda S. Development of a novel drug release system, time-controlled explosion system (TES). Part 1: concept and design. *J Drug Target*. 2018;2:35–44.
29. Krezanoski JZ. Clear, water-miscible, liquid pharmaceutical vehicles and compositions which gel at body temperature for drug delivery to mucous membranes; 2018. Available from: https://patents.google.com/patent/US4188373A/en.
30. Ishihara K, Kobayashi M, Ishimura N, Shinohara I. Glucose induced permeation control of insulin through a complex membrane consisting of immobilized glucose oxidase and a poly(amine). *Polym J*. 2018;16:625–56.
31. Sershen S, West J. polymeric systems for modulated drug delivery. *Adv Drug Deliv Rev*. 2019;54:1225–60.
32. Burns JS, Stevens H, Mcewen J, Pritchard G, Brewer FM, Clarke A. Pulsatile drug delivery system. *J Control Release*. 2019;38:151–5.
33. Saeger H, Virley P. Pulsincap and Mac226: Pulsed- release dosage form. Scherer DDS, Ltd. 2019.
34. Yadav R, Jha M, Prasad S, Jat D, Jain D. Mayaro virus (MAYV) Disease: Past, present and future. *J Pharm Biol Sci*. 2022;10(1):1–10.
35. Yadav R, Dubey A, Tiwari SP, Shrivastava P, Mandal S. Nanotechnology and its Applications: A Scientific Boon for Future. *Int J Drug Deliv Technol*. 2022;12(1):1–8.
36. Santini JT, Richards AC, Schiedt R, Cima MJ, Langer R. Microchips as controlled-drug delivery devices. *Angew Chem Int Ed*. 2019;32(6):2396–407.
37. Ada G. Strategies for exploiting the immune system in the design of vaccines. *Mol Immunol*. 2019;28(3):225–30.
38. Kashyap P, Mishra SP, Dutta S, Yadav R, Mishra K, Sahu K. Traditional plant and herbs used in rural area for prevention of disease caused by water pollution. *IP Int J Comprehensive Adv Pharmacol*. 2021;6(4):152–7.
39. Rajput M, Sharma R, Kumar S, Jamil F, Sissodia N. Pulsatile drug delivery system: a review. *Int J Res Pharm Biom Sci*. 2019;3(1):118–22.
40. Patel PK, Patel CK. Pulsatile drug delivery system. *Asian J Pharm Clin Res*. 2019;1:44–51.
41. Kumar GA, Bhat A, Lakshmi AP, Reddy K. An Overview of Stimuli-induced pulsatile drug delivery system. *Int J Pharm Tech Res*. 2019;2(4):2375–3658.
42. Yadav R. An review on epidemiology, biochemical characteristics, treatment suggestions, and continued studies on diabetes and cardiovascular disease. *Int J Health Sci*. 2022;6(S3):5288–311.
43. Dey NS, Majumdar S, Rao M. Multiparticulate drug delivery systems for controlled release. *Trop J Pharm Res*. 2018;7(3):1067–75.
44. Sahu RK, Yadav R, Prasad P. Adverse drug reactions monitoring: prospects and impending challenges for pharmacovigilance. *SpringerPlus*. 2014;3:695.

## Author biography

**Rajni Yadav,** Assistant Professor https://orcid.org/0000-0002-6754-2862

**Megha Jha,** Assistant Professor

**Diksha Jat,** Assistant Professor

**Deepak Kumar Jain,** Assistant Professor

**Cite this article:** Yadav R, Jha M, Jat D, Jain DK. Present scenario of pulsatile drug delivery system. *IP Int J Comprehensive Adv Pharmacol* 2022;7(4):171-178.