AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Time Controlled Pulsatile Drug Delivery System – A Review

Nirav P. Chauhan[1*], Jayant Despande[1], Pratik H Upadhyay[1], Shreeraj R Shah[1], Jatin Trivedi[1]

1. L.J Institute of Pharmacy, Sarkhej, Ahmedabad, Gujarat, India

ABSTRACT

Traditionally, drugs are released in an immediate or extended fashion. A pulsatile drug release, where the drug is released rapidly after a well defined lag-time, could be advantageous for many drugs or therapies. Pulsatile release systems can be classified in multiple-pulse and single-pulse systems. A popular class of single-pulse systems is that of rupturable dosage forms. Other systems consist of a drug-containing core, covered by a swelling layer and an outer insoluble, but semi-permeable polymer coating or membrane. 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. As is frequently found in the living body, many vital functions are regulated by pulsed or transient release of bioactive substances at a specific site and time. Thus it is important to develop new drug delivery systems to achieve pulsed delivery of a certain amount of drugs in order to mimic the function of the living systems, while minimizing undesired side effects. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance.

Key words: Lag time, pulsatile drug release, Rupturable coating

*Corresponding Author Email: chauhannirav73@gmail.com

Received 4 March 2012, Accepted 5 April 2012

Please cite this article in press as: Chauhan NP. *et al.*, Time Controlled Pulsatile Drug Delivery System – A Review. American Journal of PharmTech Research 2012.

INTRODUCTION:

Nowadays Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such this type of systems releases the drug with constant or variable release rates. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time, thereby require sustained therapeutic action[1.] But there are certain conditions which demand release of drug after a lag time. i.e., Chronopharmacotherapy of diseases which shows Circadian rhythms in their pathophysiology. In recent years, pulsatile release systems have gained increasing interest. Ideally, with a pulsatile system, the drug is released rapidly and completely after a defined lag time of no drug release. Alternative terms used to describe pulsatile release are delayed or sigmoidal release. Besides one-pulse systems, multipulse systems release the drug in subsequent pulses[30.] The application of pulsatile release systems can be advantageous to adapt a drug therapy to chronopharmacological needs or to target a drug to a specific site in the gastrointestinal tract (GIT), e.g., to the colon.Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions[2]. There are many conditions that demand pulsatile release like[3] **a)** many body functions that follow circadian rhythm. e.g: Secretion of hormones, acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion. **b)** Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension. **c)** Drugs that produce biological tolerance demand for a system that will prevent their continuous presence at the bio-phase as this tends to reduce their therapeutic effect. **d)** The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g: peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting. **e)** Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon requires that the drug release is prevented in the upper two-third portion of the GIT. **f)** The drugs that undergo first-pass metabolism resulting in reduced bioavailability, altered steady state levels of drug and metabolite, and potential food drug interactions require delayed release of the drug to the extent possible. So time controlled therapeutic scheme releasing the right amount of drug at the right time. This requirement is fulfilled by Pulsatile Drug Delivery Systems. The following figures (Figure 1 & 2) are showing the release profiles of drug from pulsatile drug delivery systems.

Disease requiring in pulsatile delivery system[4]

Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication can improve outcome in selected chronic conditions[4]. The list of diseases which are required pulsatile release given in Table 1.

Table1. Diseases required pulsatile delivery

Chronological behavior	Drugs used	Diseases
Acid secretion is high in the 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	Nitroglycerin, calcium channel blocker, ACE inhibitors	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 higher during night than day time	HMG CoA reductase inhibitors	Hypercholesterolemia

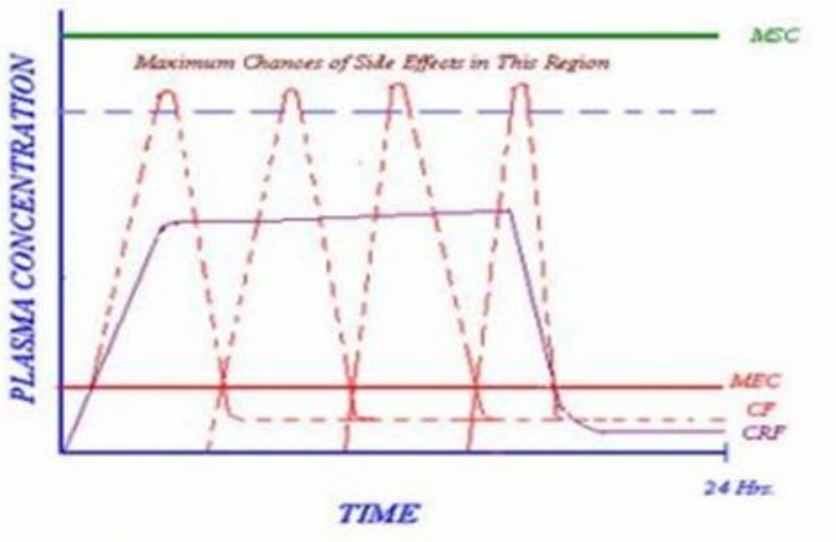

Figure 1: Drug release profile of pulsatile drug delivery systems

METHODS FOR PULSATILE DRUG DELIVERY

SINGLE UNIT SYSTEMS

Capsular system

Single unit systems are mostly developed in capsule form. A general -design of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined time lag due to swelling, erosion, or dissolution[5].

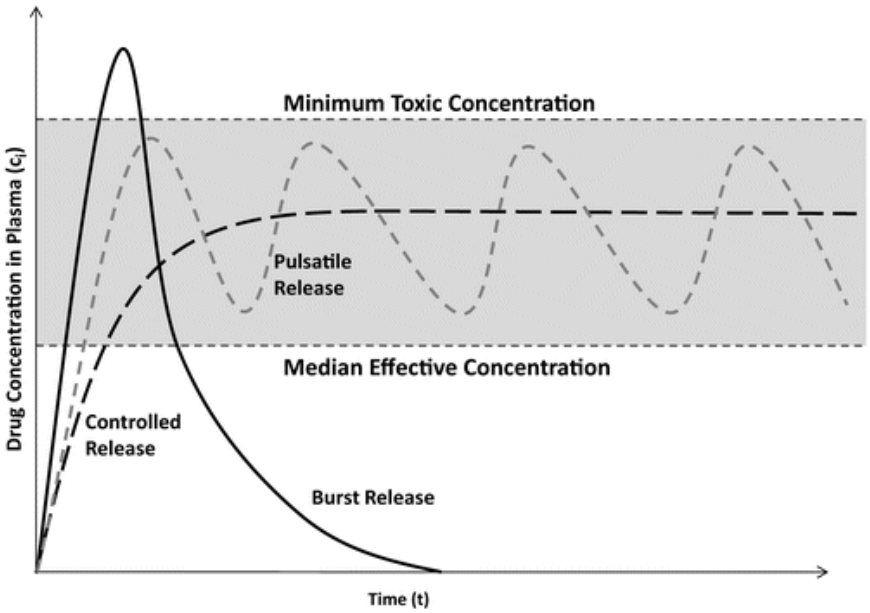

Figure 2: Drug release profile of pulsatile drug delivery systems

Pulsincap system

The Pulsincap system consisted of a water-insoluble body (hard gelatin capsule coated with polyvinyl chloride), filled with the drug formulation.[36, 37] the capsule half was closed at the open end with a swellable hydrogel plug. Upon contact with dissolution media or gastrointestinal fluids, the plug swelled and pushed itself out of the capsule after a lag time, followed by a rapid release of the capsule content. The lag time prior to the drug release was controlled by the dimension and the position of the plug.

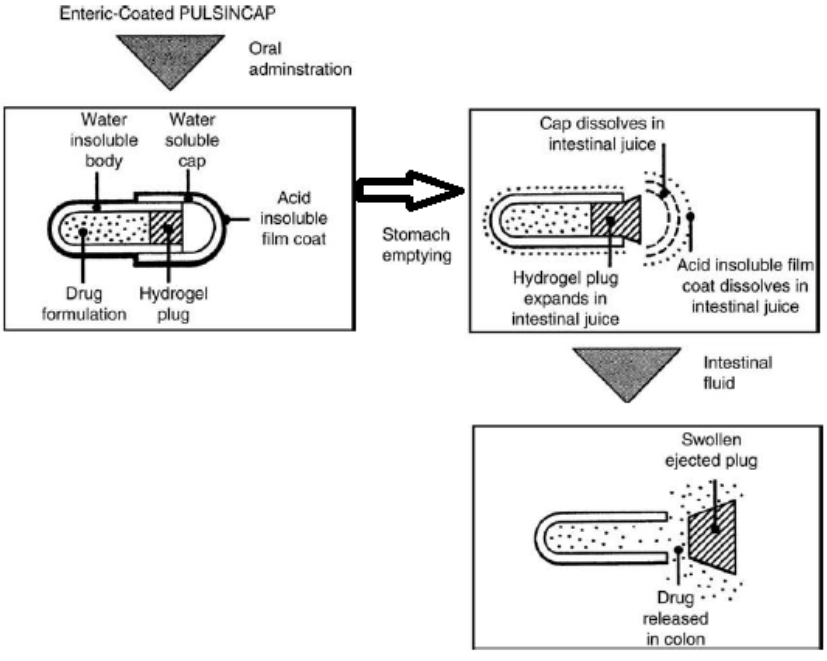

Figure 3: Pulsincap

- Plug material is generally made up of following:
- Swellable materials coated with but permeable polymer (polymethacrylates).
- Erodible compressed polymer (HPMC, polyvinyl alcohol).
- Congealed melted polymer (glycerylmono oleate).
- Enzymatically controlled erodible polymer (pectin).

Egalet system

This technology comprises an impermeable shell containing a drug core and two erodible outer layers at each open end. On erosion of the outer layer the drug in the core dissolve on exposure of GI tract contents. Another drug in erodible outer layer for sustained release follows by pulsed release of a different drug from the inner core.[39]

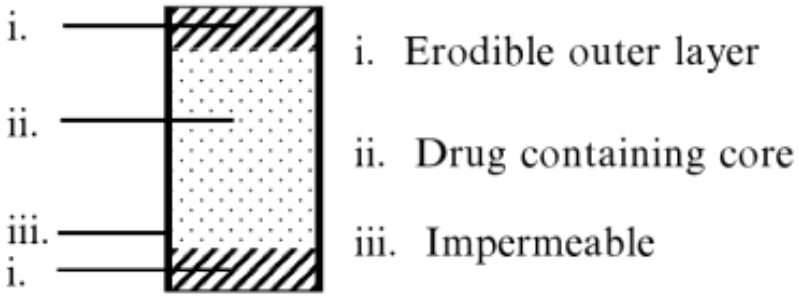

Figure 4: The Egalet device

Hydrophillic sandwich capsule

The hydrophilic sandwich capsule:

1. Two different-sized capsules, one contained within the other [i]
2. The void space contain various concentrations of a hydrophilic polymer such as HPMC, creating a hydrophilic sandwich[iv]
3. A drug containing core [iii] is housed within the inner capsule [ii].

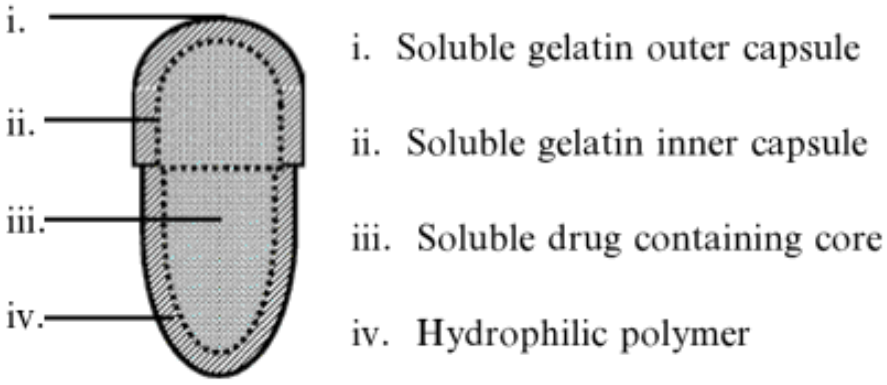

Figure 5: The HS capsule

The outer capsule rapidly dissolves on exposure to an aqueous environment. The hydrophilic "sandwich" then forms a gel barrier, protecting the inner drug layer for a predetermined lag time depending on gel layer thickness and concentration/type of hydrophilic polymer [40]

Pulsatile Delivery by Osmosis

This system consists of a capsule coated with a semi permeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation [7]. This system shows good in-vivo and invitro correlation in humans and used to deliver methylphenidate to school age children for the treatment of Attention Deficit Hyper activity Disorder (ADHD),

e.g.: Port® System, Chronset system

Another system is also based on expendable orifice that contain capsular system in which liquid drug is absorbed on highly porous particles. Drug releases through orifice of a semi permeable capsule supported by an expending osmotic layer after the barrier layer is dissolved [8].

Port® System

The Port® System (Port Systems, LLC) consists of a gelatin capsule coated with a semi permeable membrane (e.g., cellulose acetate) housing an insoluble plug (e.g., lipidic) and an osmotically active agent along with the drug formulation (Figure 6&7).When in contact with the aqueous medium, water diffuses across the semipermeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. The lag time is controlled by coating thickness[9,10].

Chronset system

In the Chronset_ system, the driving force for the drug release was an osmotically active layer in the semi permeable vessel, which pushed the cap out off the impermeable vessel after a predetermined time interval.[35] The complete release of the drug, often problematic in capsular-shaped dosage forms, was ensured by an expanding layer at the bottom of the capsule body. Even more sophisticated were insoluble high frequency (HF) capsules, which released the drug in a pulsed fashion after a high-frequency signal was applied externally to the human body.[36,37] These HF capsules were used to evaluate the absorption of drugs from distinct regions within the digestive tract. A similar capsule activated by an oscillating magnetic field has been published recently, which ejected an active compound or a radioactive marker to localize the position of the dosage form in the gastrointestinal tract.[38]

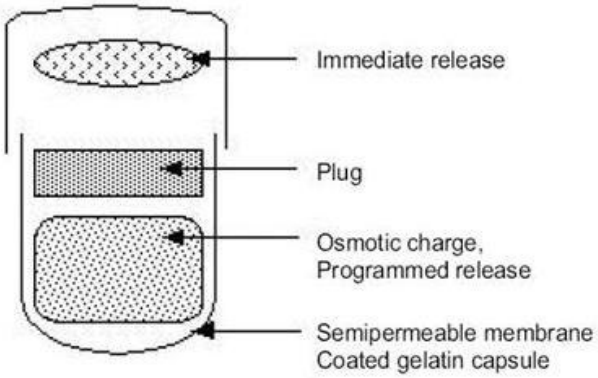

Figure 6: Port system

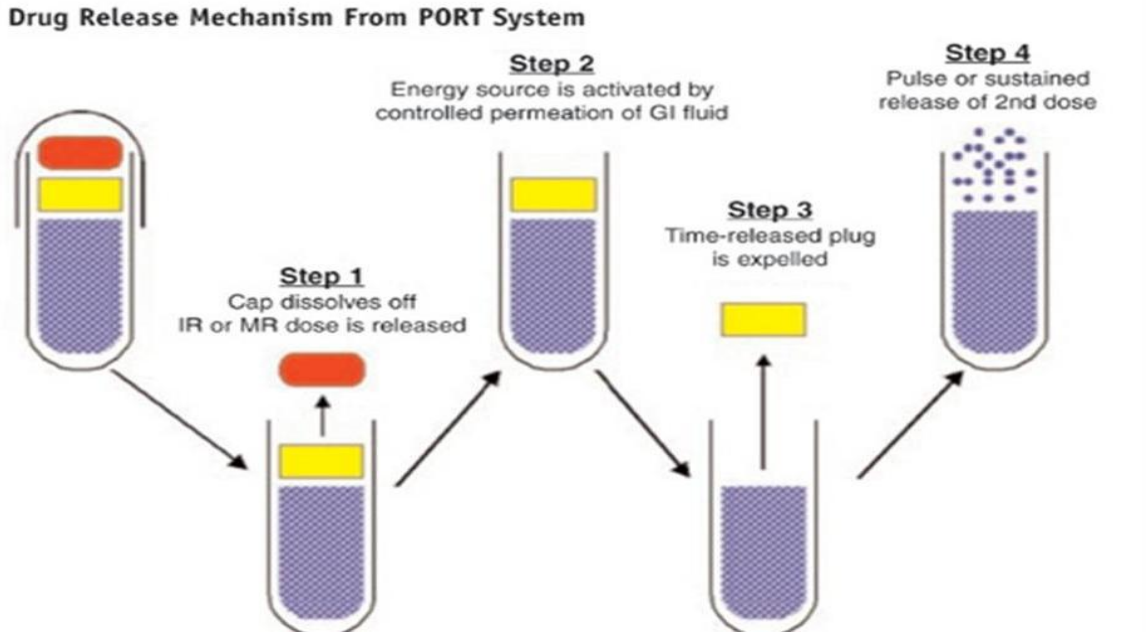

Figure 7: Port system

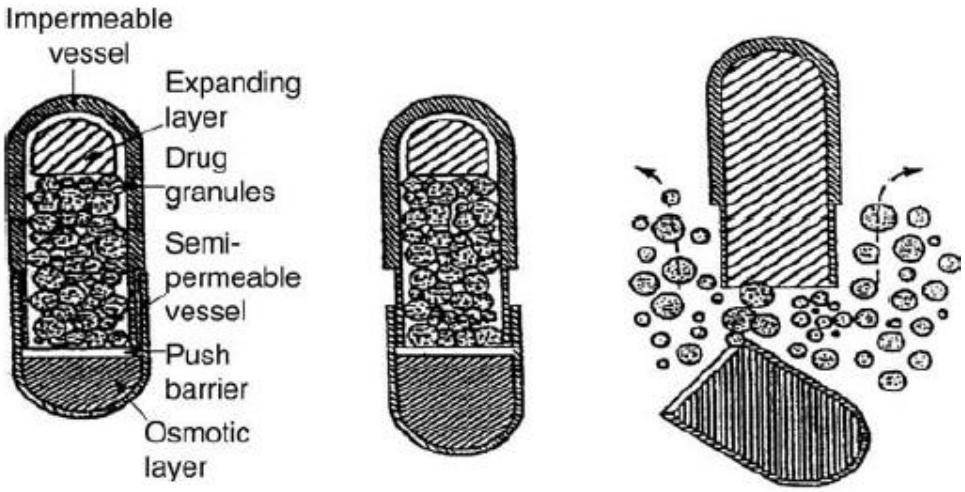

Figure 8: The Chronset system

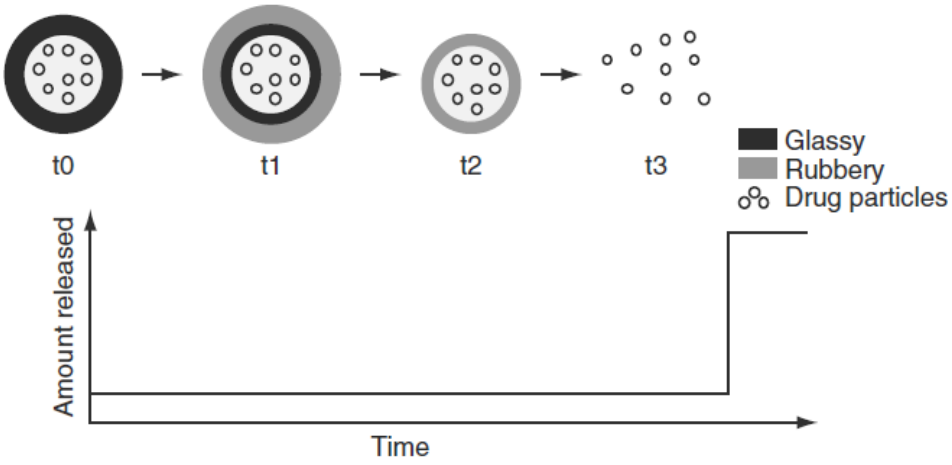

Figure 9: The Chrnotropic system

Pulsatile Delivery by eroding or soluble coating

Most pulsatile delivery systems are reservoir devices coated with a barrier layer. The barrier dissolves or erodes after a specified lag time, after which the drug is released rapidly from the reservoir core. In general, the lag time prior to drug release can be controlled by the thickness of the coating layer. Various lag times have been achieved with press coated tablets, where the press-coated barrier layer consisted of a mixture of a soluble polymer, hydroxypropylmethyl cellulose (HPMC), and different water insoluble polymers, such as ethylcellulose, Eudragit_ RS, or polylactic acid in different ratios.[29] The release medium permeates through the coating and then results in disintegration of the tablet, whereby the lag time prior to disintegration decreases with increasing proportion of the water-soluble polymer. The Chronotopic system consisted of a core tablet containing the drug and a HPMC layer, optionally coated with an outer enteric coating.[30-33] The lag time prior to drug release was controlled bythe thickness and the viscosity grade of the HPMC layer. After erosion or dissolution of the rubbery HPMC layer, a distinct pulse was observed. To avoid retarding effects in the drug release phase, the thickness as well as the viscosity grade of the HPMC layer should be limited.[34] The system probably works best for poorly water-soluble drugs. Highly water soluble drugs could possibly diffuse through the swollen HPMC layer prior to complete erosion.

Another dosage form with an erosion-controlled lag time had a drug-containing core, which was incorporated into a compressed, hollow cylinder consisting of hydroxypropyl cellulose (HPC).[34] The flat surfaces of the tablet were coated with an impermeable polymer, poly(ethylene vinyl acetate). The delivery system was prepared by hand: a hole was drilled into a tablet to obtain the hollow matrix, the inner drug core was placed into this hole, and the system was coated by hand

on the two flat base surfaces. This preparation would be quite complicated for large-scale manufacturing and the use of a non-approved polymer and benzene as a coating solvent would limit the application of this system. Lag times between 6 and 11 hr were achieved with either a fast drug release after the lag time (using microcrystalline cellulose or lactose in the core) or sustained release (with HPC in the core).

The lag time increased with increasing thickness of the matrix cylinder. Lactose-containing cores developed an internal osmotic pressure, leading to a fast separation of the coating from the core. Thus drug was delivered before complete erosion of the outer HPC matrix. On the other hand, microcrystalline cellulose-cores had no osmotic effect, coating separation did not occur, and the lag time was longer. The complete erosion of the matrix was necessary to release the drug. The lipid barrier of the Time Clock_ system, containing carnauba wax and beeswax, eroded or was emulsified into aqueous media because of incorporated surfactants (polyoxyethylene sorbitan monooleate).[33] The lag time increased with increasing coating thickness and was independent of the environmental pH. In vivo assessment with gamma-scintigraphy of an enterically coated Time Clock_ system was in good agreement with the in vitro predicted data with regard to the lag time.[34] When the viscosity of the dissolution medium of the in vitro test was raised to 120 cps, the lag time was prolonged to the same value as obtained with in vivo data. The advantage of this system was its ease of manufacturing without the need of special equipment. However, controlled release delivery systems based on lipids may have a high in vivo variability (e.g., food effects).

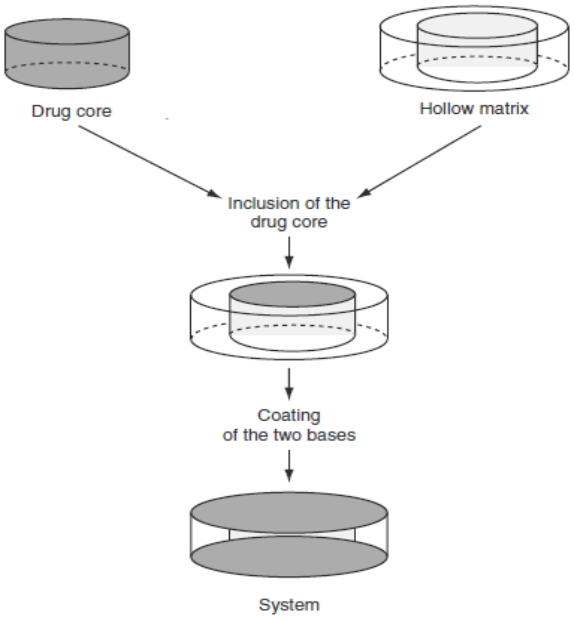

Figure: 10 eroding system with hollow cylinder and coated surface

Pulsatile Delivery by Rupture of Membrane

These systems are based up on a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents (or) swelling agent [16-18] Citric acid & sodium bicarbonate is incorporated as effervescent mixture in tablet core coated with ethyl cellulose, when system comes in contact with water it produces carbon dioxide gas which exerts pressure & after lag time rupture the membrane & rapid release of drug occurs [19]. A reservoir system with a semi permeable coating is proposed especially with drugs with high first pass effect in order to obtain in-vivo drug pattern similar to the administration of several immediate release doses croscarmellose sodium starch glycollate or low substituted hydroxy propyl cellulose were used as swelling substances, which resulted in complete film rupture followed by rapid drug release. The lag time is controlled by composition of outer polymeric membrane [20-23].

MULTIPLE UNIT SYSTEMS

Multiparticulate systems are reservoir type of devices with a coating, which either ruptures or changes its permeability. Drug is coated over sugar seeds these granules may then be packaged in a capsule or compressed with additional excipients to form a tablet.

The active pharmaceutical ingredient may also be blended or granulated with polymers before coating to provide an additional level of control. However, drug loading in this type of system is low due to higher need of excipients [24].

Table2. Marketed technologies of pulsatile drug delivery [6]

Technology	Mechanism	Proprietary name and dosage form	API	Disease
OROS*	Osmotic mechanism	Covera-H5*; XL tablet	Verapamil HCL	Hypertension
Three dimensional printing*	Externally regulated system	Their Form*	Diclofenac sodium	Inflammation
DIFFUCAPS*	Multiparticulate system	Innopran*; XL tablets	Verapamil HCL, propranolol HCL	Hypertension
PulsincapTM	Rupturable system	PulsincapTM	Dofetilide	Hypertension

Pulsatile Delivery by Rupturable Coating

Similar to single unit system, the rupturing effect is achieved by coating the individual units with effervescent (or) swelling agents. Drug deliver was controlled by the rupture of the membrane [27, 28]. The timing of release was controlled by the thickness of coating and the amount of water soluble polymer to achieve the pulsed release [27]. The swelling agent includes superdisintegrents like carboxy methylcellulose, sodium starch glycollate, and L-hydroxy propyl cellulose.

Polymers like polyacrylic acid, polyethylene glycol etc. alternatively comprising of a mixture of tartaric acid & sodium bicarbonate that used as effervescent agent. The commercial products of pulsatile drug delivery system are present in table 2.

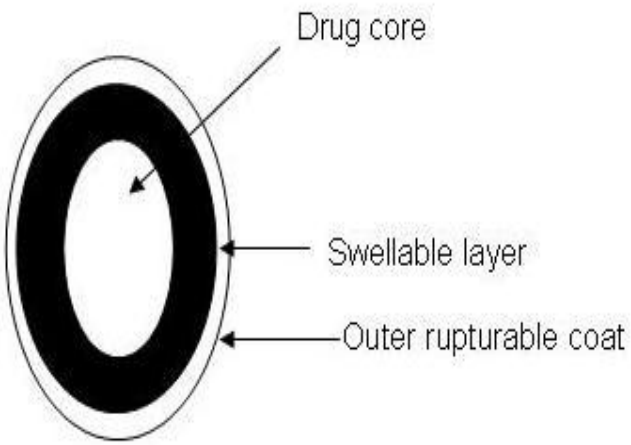

Figure 7: **Schematic diagram of Delivery systems with rupturable coating layer.**

CONCLUSION

Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. There is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension etc. Thus designing of proper pulsatile drug delivery will enhances the patient compliance, optimum drug delivery to the target site and minimizes the undesired effects. The approaches in this article represent attempts conducted over the past decade to achieve pulsatile release. It should be pointed that these drug delivery systems are still in the early developmental stage and much research will have to be conducted for such systems become practical clinical alternatives.

REFERENCES

1. Bussemer T, Otto I, Bodmeier R. Pulsatile drug-delivery systems. Crit Rev Ther Drug Carrier Sys 2001; 18 (5):433-458.
2. Lemmer B. Chronopharmacokinetics: implications for drug treatment. J Pharm Pharmacology 1999; 51:887-890.
3. Ritschel WA, Forusz H. Chronopharmacology: a review of drugs studies, Methods Find. Exp Clin Pharmacol 1994; 16 (1):57-75.

4. Ananthas Nayaki Ravula, Bairi Agalah Goud. Recent Advances in oral pulsatile drug delivery. J Advance Pharma Sci 2011; 1(1):57-63.
5. Peppas NA. Fundamentals on pH- and temperature-sensitive delivery systems. Pulsatile Drug Delivery 1993: 41–56.
6. SS Shidhaye, VM Lotlikar, AM Ghule. Pulsatile delivery systems: An approach for chronotherapeutic diseases. Systemic review in pharmacy 2010; 1(1):55-61.
7. Baker RW. Controlled release delivery system by an osmotic bursting mechanism 1976, US Patent 3, 952, 741, www.uspto.gov.
8. Ueda T, Hata Yamaguchi H, Kotani M, Ueda Y. Development of a novel drug release system, time-controlled explosion system (TES). J Drug Target 1994; 2:35-44.
9. Schultz PA, Kleinebudde P. New multiparticulate delayed release system. Part I: dissolution properties and release mechanism. J Control Release 1997; 47:181–189.
10. Morita R, Honda Y, Takahashi R. Development of oral controlled release preparations, a PVA swelling controlled release system (SCRS). I. Design of SCRS and its release controlling factor. J Control Release 2000; 63: 279-304.
11. Caramella P, Colombo G, Bettinetti F, Giordano U, Conte AL. Manna. Swelling properties of disintegrant. Acta Pharm Technol 1984; 30(2):132-139.
12. Wan LSC, Prasad KPP.Comparison of the swelling character of tablet disintegrations at the microscopic level. Acta Pharm Technol 1990; 36:20-23.
13. Gennaro AR, ed. Remington: The Science and Practice of Pharmacy. 20th ed. USA: Lippincott, Williams & Wilkins; 2000; 20:903-905.
14. Das NG, Das SK. Controlled release of oral dosage forms, formulation, finish, and fill. 2003; 10-16.
15. Gurny R, Junginger HE, Peppas N. Eds. In; Pulsatile Drug Delivery: Current Application and Future Trends. Wissenschefliche Verlagsgesellschaft, Stuttgart, Germany, 1993.
16. Valentine CI, Richard AK & Abdul WB. Drug delivery to colon. The drug delivery componies report summer 2004.
17. Basit AW, Lacey LF. Colonic metabolism of ranitidine: Implications for its delivery and absorption. Int J Pharm 2001; 227:157-165.
18. Takaya T, Ikada C, Imagawa N, Niwa K Takada K. Development of a Colon Delivery Capsule and the Pharmacological Activity of Recombinant Human Granulocyte Colony-stimulating Factor (rhG-CSF) in Beagle Dogs. J Pharm Pharmacol 1995, 47:474- 478.

19. Bussemer T, Otto I, Bodmeier R. Pulsatile drug delivery sysyems. Crit Rev The Drug Carrier System. 2001; 18(5):433-58.
20. Wildind IR, Davis SS, Bakhshaee M, Steven HNE, Sparrow RA, Brennan J. Gastrointestinal transit and systemic absorption of captopril from a pulsed release formulation. Pharm Res 1992; 9:654-657.
21. Saeger H, Virley P. Pulsincap & Mac226: Pulsed Release Dosage Form. Product information from Scherer DDS. Ltd; 2004.
22. Krögel I, Bodmeier R. Floating or pulsatile drug delivery systems based on coated effervescent cores. Int J Pharm. 1999; 187:175-184.
23. Amidon GL, Leesman GD. Pulsatile Drug Delivery System. US Patent No. 5,229,131; 1993, www.uspto.org.
24. Daumesnil R. Marketing Considerations for multiparticulate drug delivery systems. In: Ghebre-Sellassie I, ed. Multiparticulate Oral Drug Delivery. New York, NY: Marcel Dekker, Inc.; 1994:457-474.
25. Ueda Y, Hata T, Yamaguchi H, Ueda S, Kotani M. Time Controlled Explosion System and Process for Preparation for the Same. US Patent No. 4,871,549; 1989.
26. Schultz P, Tho I, Kleinebudde P. A new multiparticulate delayed release system. Part II: coating formulation and properties of free films. J Control Rel. 1997; 47:191-199.
27. Chen C-M. Multiparticulate Pulsatile Drug Delivery System. US Patent No. 5,508,040; 1996.
28. Korsatko-Wabnegg B, Korsatko W, Wegleitner K. Delayed-Release Pharmaceutical Preparation. US Patent 5,151,273, September 29, 1992.
29. Gazzaniga A, Busetti C, Moro L, Crimella T, Sangalli ME, Giordano F. Evaluation of low viscosity HPMC as retarding coating material in the preparation of a time based oral colon specific delivery system Proceed. Int. Symp. Control. Rel. Bioact. Mater. Controlled Release Society: Minneapolis, MN, 1995; 242.
30. Gazzaniga A, Iamartino P, Maffione G, Sangalli ME. Oral delayed-release system for colonic specific delivery. Int J Pharm 1994; 108:77–83.
31. Gazzaniga A, Sangalli ME, Giordano F. Oral chronotopic drug delivery systems: achievement of time and/or site specificity. Eur J Pharm Biopharm 1994; 40 (4):246–250.
32. Poli S, Busetti C, Moro L. Oral Pharmaceutical Composition for Specific Colon Delivery. EP Patent 0, 572, 942, December 8, 1993.

33. Vandelli MA, Forni L, Bernabei MT. In vitro evaluation of a potential colonic delivery system that releases drug after a controllable lag-time. Eur J Pharm 1996; 43 (2):148–151.
34. Wilding IR, Davis SS, Pozzi F, Furlani P, Gazzaniga A. Enteric coated timed released systems for colonic targeting. Int J Pharm. 1994, 111, 99–102.
35. Pozzi F, Furlani P, Gazzaniga A, Davis SS, Wilding IR. The time clock system: a new oral dosage form for fast and complete release of drug after a predetermined lag time. J Control Release 1994, 31, 99–108.
36. Wong PSL, Theeuwes F, Larsen SD, Song LC. Osmotic Device for Delayed Delivery of Agent. US Patent 5,443,459, August 22, 1995.
37. Clear NJ, Milton A, Humphrey M, Henry BT, Wulff M, Nichols DJ, Anziano RJ, Wilding I. Evaluation of the intelisite capsule to deliver theophylline and frusemide tablets to small intestine and colon". Eur. J. Pharm. Sci. 2001, 13, 375–384.
38. Graul EH, Loew D, Schuster O. Voraussetzung fur die Entwicklung einer sinnvollen Retard- und Diuretikakombination. Therapiewoche 1985; 35:4277–4291.
39. Wilding IR, Hirst PH, Connor AL. The enterion capsule: a novel technology for the assessment of drug absorption in man. Proceed. Int. Symp. Control. Rel. Bioact. Mater. Boston, MA, 2001; Controlled Release Society:Minneapolis, MN, 1999; 6068.
40. Crison JR, Siersma PR, Amidon GL. A novel Programmable oral release technology for delivering drugs: human feasibility testing using gamma scintigraphy. Proceed. Int. Symp Control Rel Bioact 1996; Controlled Release Society: Minneapolis, MN, 1996; 51.
41. Krogel I, Bodmerer R. Development of a multifunctional matrix drug delivery system surrounded by impermeable cylinder. J Control Release 61:43-50.
42. Stevens HNE. Pulsincap and hydrophilic sandwich (HS) capsules: innovative time delayed oral drug delivery technologies. Drug Pharm Sci 126:257-262.