ISSN:0975-1459

Ravikumar Reddy J. et al /J. Pharm. Sci. & Res. Vol.1(4), 2009, 109-115..

Journal of Pharmaceutical Sciences and Research

www.jpsr.pharmainfo.in

REVIEW ON: PULSATILE DRUG DELIVERY SYSTEMS

J. Ravi Kumar Reddy*[1], M.Veera Jyothsna,T. S.Mohamed Saleem[2], C.Madhu Sudhana Chetty[1].

[1]Department of Pharmaceutics, Annamacharya College of Pharmacy, New boyanapalli, Rajampeta – 516126, Kadapa, Andhra Pradesh, India.

[2]Department of Pharmacology, Annamacharya College of Pharmacy, New boyanapalli, Rajampeta – 516126, Kadapa, Andhra Pradesh, India.

Abstract

Traditionally, drugs are released in an immediate or extended fashion. However, in recent years, pulsatile drug release systems are gaining growing interest. 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 semipermeable 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. Special attention has been given to the thermally responsive poly (*N*-isopropylacrylamide) and its derivative hydrogels. Thermal stimuli-regulated pulsed drug release is established through the design of drug delivery devices, hydrogels, and micelles. Therefore Pulsatile drug delivery is one such systems 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

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

Introduction

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 systems release 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 (sustained release), thereby ensuring 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. 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 biophase 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.

All of these conditions demand for a time-controlled therapeutic scheme releasing the right amount of drug at the right time. This requirement is fulfilled by Pulsatile Drug Delivery Systems. The fallowing figures (Fig 1 and Fig 2) are showing the release profiles of drug from pulsatile drug delivery systems.

Diseases Requiring Pulsatile Delivery

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

Methods For Pulsatile Drug Delivery

Single unit systems

Capsular system

Single unit systems are mostly developed in capsule form. The lag time is continued by a plug, which gets pushed away by swelling or erosion, and the drug is released as a pulse from the insoluble capsule body [5].

e.g.: Pulsincap® system

In this system a water insoluble body containing the drug formulation, system is closed with a swellable hydrogel. Plugged (insoluble but permeable & swellable) at open end. Upon contact with, gastro-intestinal fluid or dissolution medium the plug swells pushing itself out of the capsule after lag-time. Position & dimensions of plug, control lag-time. For rapid release of water insoluble drug effervescent or disintegrating agents are added [6]. 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 (glyceryl mono oleate).
- Enzymatically controlled erodible polymer (pectin).

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 *invivo* 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

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].

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 3).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 thicknes [9, 10].

Pulsatile Delivery by Solubilisation (or) Erosion of Membrane

These systems are based up on a drug reservoir surrounded with a soluble or erodible barrier layer that dissolves with time and the drug releases at once after the lag time.e.g. Time Clock® system.The Time Clock system consists of solid dosage form coated with lipid barriers such as carnauba wax & beeswax along with surfactants like polyoxyethylene sorbitan monooleate. When this system comes in contact with the aqueous medium the coat emulsifies or erodes after the lag-time depending on the thickness of coat. The lag time of system is

Table 1. Diseases required pulsatile delivery

Chronological behavior	Drugs used	Diseases
Acid secretion is high in the Aternoon 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

Table 2. Marketed technologies of pulsatile drug delivery [31]

Technology	Mechanism	Proprietary name and dosage form	API	Disease
OROS*	Osmotic mechanism	Covera-H5*; XL tablet	Verapamil HCL	Hypertension
Three dimentional 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

independent of the gastrointestinal motility, PH, enzyme & gastric residence [11-15].

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

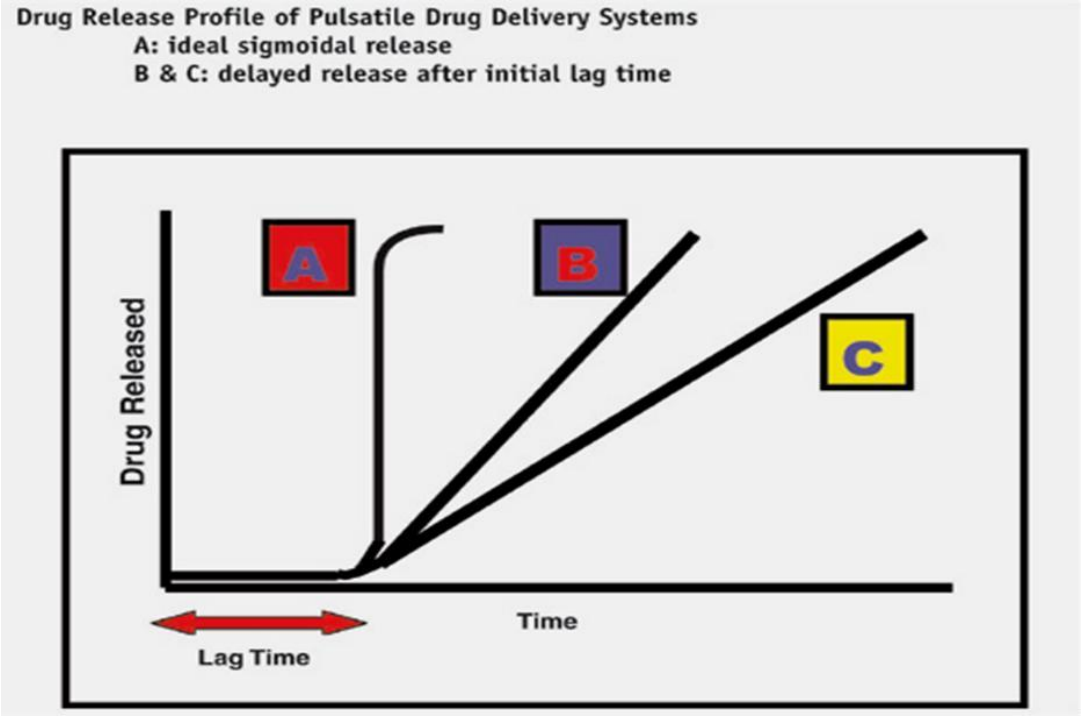


Fig 1: Drug release profile of pulsatile drug delivery systems

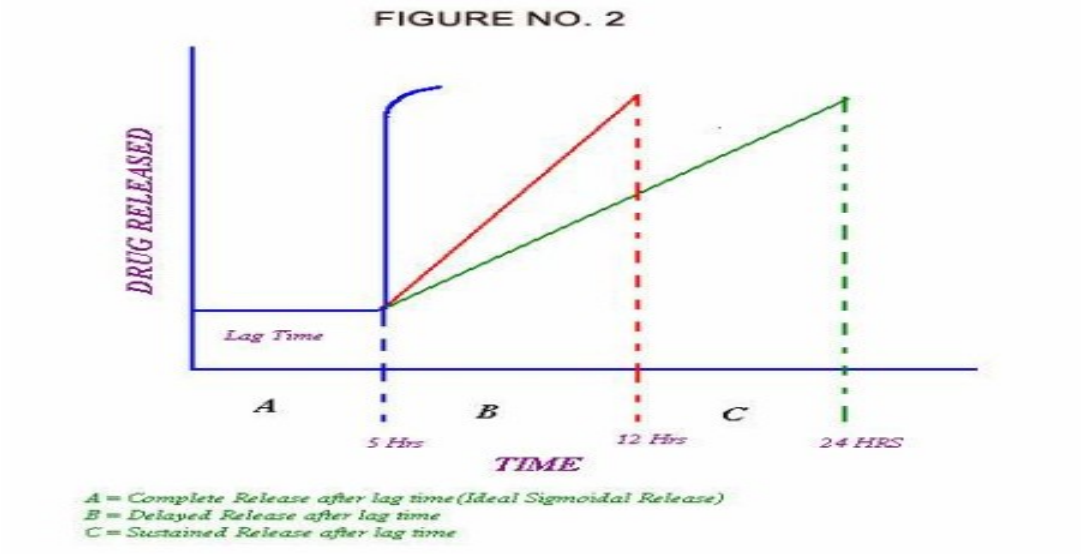


Fig 2: Drug release profile of pulsatile drug delivery systems

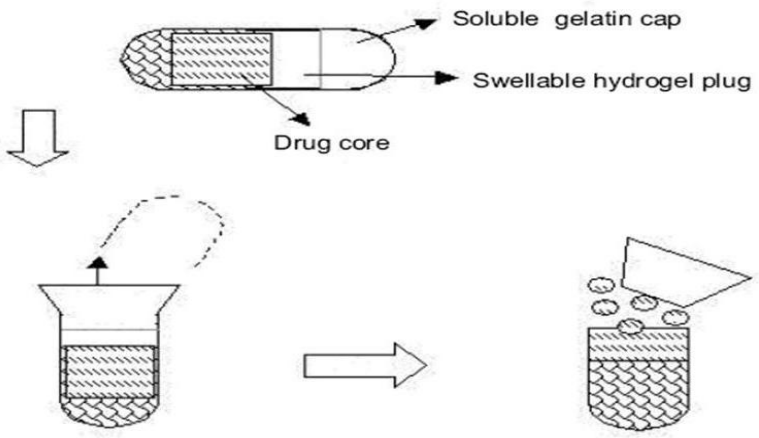
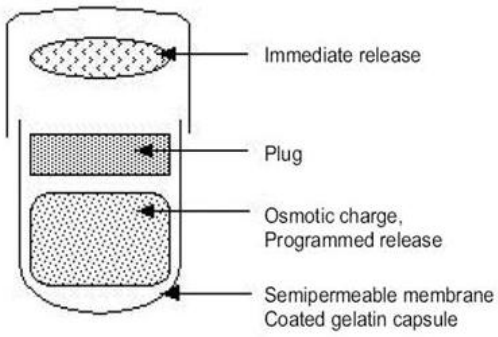


Fig 3: Design of Pulsincap® system

Fig 4: Plan of Port® System



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, 25].

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 [26-28]. The timing of release was controlled by the thickness of coating and the amount of water soluble polymer to achieve the pulsed release [29]. 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 [30]. The commercial products of pulsatile drug delivary system are present in table 2 [31].

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

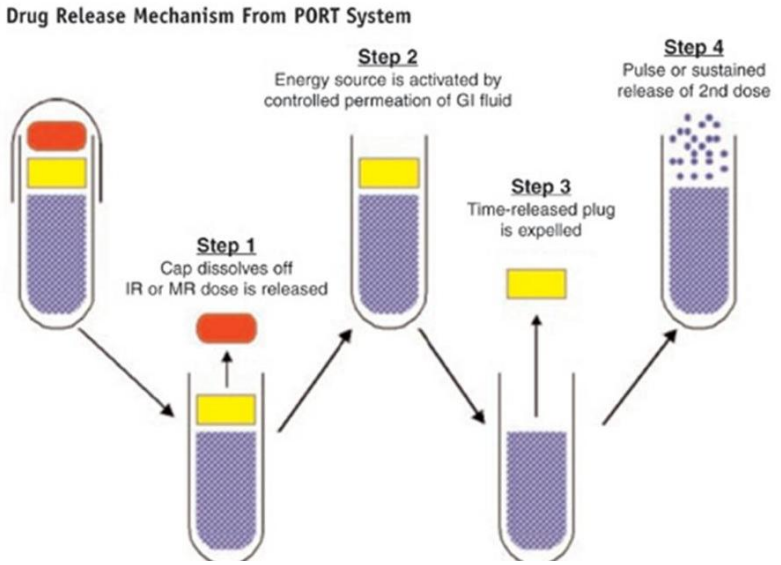


Fig 5: Drug release mechanism from PORT system

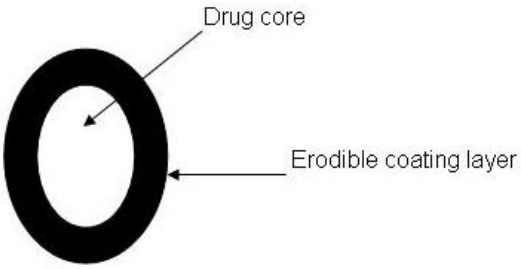


Fig 6: Schematic diagram of Delivery systems with erodible coating layer.

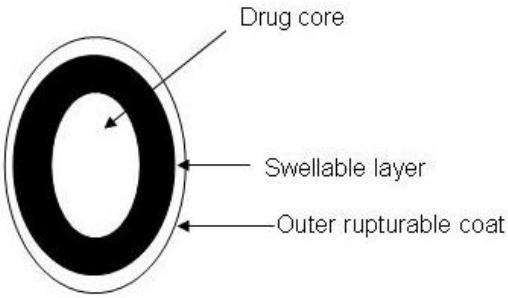


Fig. 7: Schematic diagram of Delivery systems with rupturable coating layer.

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 Syst. 18 (5) (2001) 433-458.

[2] Lemmer, B., Chronopharmacokinetics: implications for drug treatment, J. Pharm. Pharmacology, 51 (1999) 887-890.

[3] Ritschel.,W.A., Forusz, H., Chronopharmacology: a review of drugs studies, Methods Find. Exp. Clin. Pharmacol. 16 (1) (1994) 57-75.

[4] Peppas, N.A., Fundamentals on pH- and temperature-sensitive delivery systems, Pulsatile Drug Delivery, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1993, 41–56.

[5] Baker, R.W., Controlled release delivery system by an osmotic bursting mechanism. US Patent 3,952,741, 1976.
[6] Ueda, T., Hata, Yamaguchi, H., Kotani, M., Ueda, Y., Development of a novel drug release system, time-controlled explosion system (TES). I. Concept and design, J. Drug Target. 2 (1994) 35-44.
[7] Schultz, P.A. Kleinebudde. P., New multiparticulate delayed release system. Part I: dissolution properties and release mechanism, J. Control. Release 47 (1997) 181–189.
[8] 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 63 (2000) 279-304.
[9] Caramella, P., Colombo,G. Bettinetti, F. Giordano, U. Conte, A.L. Manna, Swelling properties of disintegrants, Acta Pharm. Technol. 30 (2) (1984) 132-139.
[10] Wan, L.S.C., Prasad, K.P.P., Comparison of the swelling character- istics of tablet disintegrations at the microscopic level, Acta Pharm. Technol. 36 (1990) 20-23.
[11] Gennaro AR, ed. Remington: The Science and Practice of Pharmacy. 20th ed. USA: Lippincott, Williams & Wilkins; 2000; 20:903-905.
[12] Das NG, Das SK. Controlled release of oral dosage forms, formulation, finish, and fill. 2003; 10-16.
[13] Ashford M, Fell JT, Attwood D, Sharma H, Wood head PJ. Int J Pharm 1993a, 95: 193-199.
[14] Evans., D.F, Pye G, Bramley R, Hardcastle JD. G.ut 1988, 29:1035-1041.
[15] Gurny, R., Junginger, H.E. and 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. Int J Pharm 2001, 227: 157-165.
[18] Takaya T, Ikada C, Imagawa N, Niwa K, Takada K. 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. Review.
[20] 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. 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.
[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] 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 Targeting. 1994; 2:35-44.
[27] Schultz P, Tho I, Kleinebudde P. A new multiparticulate delayed release system. Part II: coating formulation and properties of free films. J Contr Rel. 1997; 47:191-199.
[28] Chen C-M. Multiparticulate Pulsatile Drug Delivery System. US Patent No. 5,508,040; 1996.
[29] Schultz P, Kleinebudde P. A new multiparticulate delayed release system. Part I: dissolution properties and release mechanism. J Contr Rel. 1997; 47:181-189.
[30] Schultz P, Tho I, Kleinebudde P. A new multiparticulate delayed release system. Part II: coating formulation and properties of free films. J Contr Rel. 1997; 47:191-199.
[31] Survase S, Kumar N. Pulsatile Drug Delivery: Current Scenario. CRIPS. 2007; 8(2): 27-33.