

Review on Pulsatile Drug Delivery System

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ABSTRACT

Now a day's pulsatile system gaining interest as this system gives drug delivery at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. This system design as per the circadian rhythm of the body. The principle behind the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. Pulsatile drug delivery systems are generally classified into time-controlled and site-specific delivery systems. 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. Products available as once-a-daily formulation based on Pulsatile release like Pulsincap[®], Ritalin[®], and Pulsys[®] are also covered in the review. These systems are beneficial for the drugs having chronopharmacological behaviour where night time dosing is required and for the drugs having high first-pass effect and having specific site of absorption in GIT. 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

Keywords: Lag time, Pulsatile drug release, Rupturable coating.

1. 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 action¹. 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 conditions².

1.1 There are many conditions that demand pulsatile release like³

a) Chronopharmacotherapy of diseases which shows circadian rhythms in their

pathophysiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension.

- b) 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.
- c) 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.
- d) 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.

- e) Many body functions that follow circadian rhythm. e. g: Secretion of hormones, acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion.
- f) 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.

CLASSIFICATION OF PULSATILE SYSTEMS

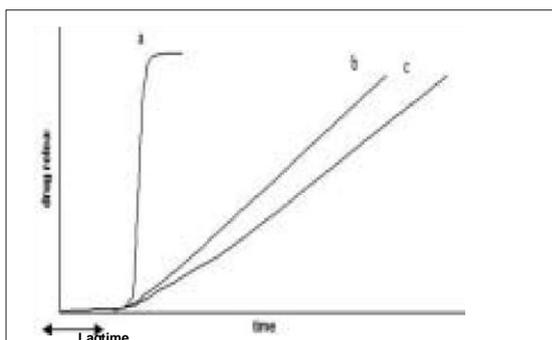


Fig. 1: Drug release profiles from pulsatile drug delivery system a = release of drug as a “pulse” after a lag time, b = delivering

Pulsatile systems can be classified into single- and multiple-unit systems. Single-unit systems are formulated either as capsule-based or osmosis-based systems. Single unit systems are designed by coating the system either with eroding/soluble or rupturable coating. In multiple unit systems, however, the pulsatile release is induced by changing membrane permeability or by coating with a rupturable membrane.

2.1 Single unit pulsatile systems

These are sub-classified as capsule-based systems, osmotic systems, delivery systems with soluble or erodible membranes, and delivery systems with rupturable coating.

2.2 Capsule based systems

Single-unit systems are mostly developed in capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion, and the drug is released as a “Pulse” from the insoluble capsule body. Pulsincap[®] was developed by R. P. Scherer International Corporation, Michigan, US, and is one such system that comprises of a water-insoluble capsule enclosing the drug reservoir. A

swellable hydrogel plug was used to seal the drug contents into the capsule body⁴. When this capsule came in contact with the dissolution fluid, it swelled; and after a lag time, the plug pushed itself outside the capsule and rapidly released the drug. Polymers used for designing of the hydro gel plug were various viscosity grades of hydroxyl propyl methyl cellulose, poly methyl methacrylates, poly vinyl acetate and poly ethylene oxide. The length of the plug and its point of insertion into the capsule controlled the lag time. Pulsincap[®] was studied in human volunteers and was reported to be well tolerated⁵⁻⁷. A low-volume diagnostic test kit was marketed in 1997 under the trade name of ‘Sprintsalmoneilla’ by Oxoid Ltd., Basingstoke, U.K. Steven *et al.* developed a Pulsincap[®] system with erodible compressed tablet⁸. As the swelling hydrogel polymer plug replaced the erodible tablet, the dependence of the dimensional accuracy between the plug and the capsule for the pulling mechanism of the plug from the capsule was also overcome (fig. 2). Ross *et al.* used low substituted hydroxypropylcellulose for the expulsion system for the release of propranolol over a time period of 2-10 h. This could be controlled using compressed erodible tablets made of lactose and HPMC⁹. Krogel and Bodmeier¹⁰ studied the release of chlorpheniramine utilizing the erodible plugs fitted in the capsules. Altering the composition and the weight of the erodible plug could control release of drug. Stevens *et al.* designed a hydrophilic sandwich capsule that was based on a system where a capsule was enclosed within a capsule and the space in between was a gel barrier layer composed of HPMC. When the outer capsule dissolved, the delay in the second pulse was provided by the barrier gel layer¹¹. Soutar *et al.* studied the delivery of 500 mg paracetamol with a gastroresistant hydrophilic sandwich capsule targeted to ileocaecal junction / proximal colon. Analysis of salivary samples gave a mean T_{max} of 7.9 h (SD±0.96)¹².

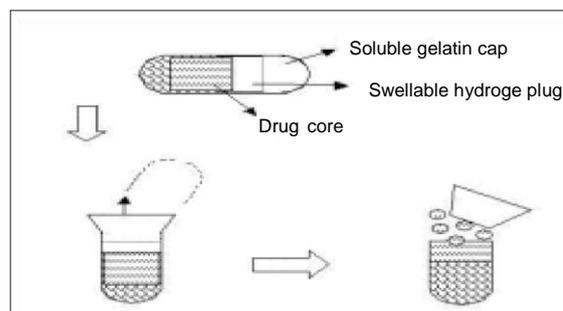


Fig. 2: Design of Pulsincap

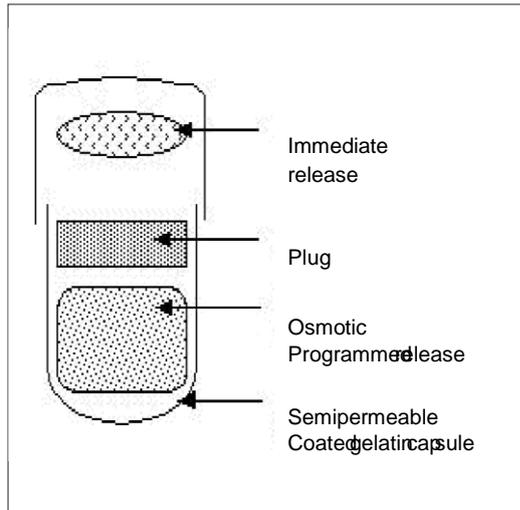


Fig. 3: Plan of Port system

2.3 Systems based on osmosis

The Port[®] system was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA, and consists of a capsule coated with a semipermeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation¹³. When this capsule came in contact with the dissolution fluid, the semipermeable membrane allowed the entry of water, which caused the pressure to develop and the insoluble plug expelled after a lag time (fig. 3).

Such a system was utilized to deliver methylphenidate used in the treatment of attention deficit hyperactivity disorder as the pulsatile port system. This system avoided second time dosing, which was beneficial for school children during daytime.

Linkwitz *et al.* invented an osmotic drug (single-unit) delivery capsule from which the

delivery of the drug was driven by the osmotic infusion of the moisture by the capsule from a physiological environment. It was provided with a delivery orifice that opened intermittently to achieve a pulsatile delivery effect¹⁴. The technology involves a movable position that divides the capsule interior into two compartments – one for the beneficial agent and the other for the osmotically active agent. The orifice is located on the capsule wall surrounding the beneficial agent side.

The whole capsule is surrounded by an elastic wall in the osmotically active compartment due to inward diffusion of water, which is transmitted through the partition. When the pressure in the drug compartment exceeds the threshold, it results in opening of the orifice and as a result, an amount of beneficial agent is released and it relieves the pressure in the drug compartment. This release in pressure causes the elastic material to relax and results in closure of the orifice. There are various factors affecting the degree and manner in which the pulsatile effect can be controlled, viz., the choice of elastic material, the thickness of the wall section, the configuration and location of the orifice and the viscosity and surface tension of the beneficial agent formulation. The choice of elastic material is done on the ability to stretch at least twice their original length and to retract very rapidly when released. Examples include styrene butadiene copolymer polychlorophene, nobile rubbers, butyl rubber and polycrylatis. The thickness of the elastic material may vary, but best results are generally obtained with thickness of at least 0.06 cm.

The pulsatile delivery provided by the aforementioned devices in this invention may be for therapeutic purpose, nutritional purpose, preventive purpose, and a wide variety of situations in general.

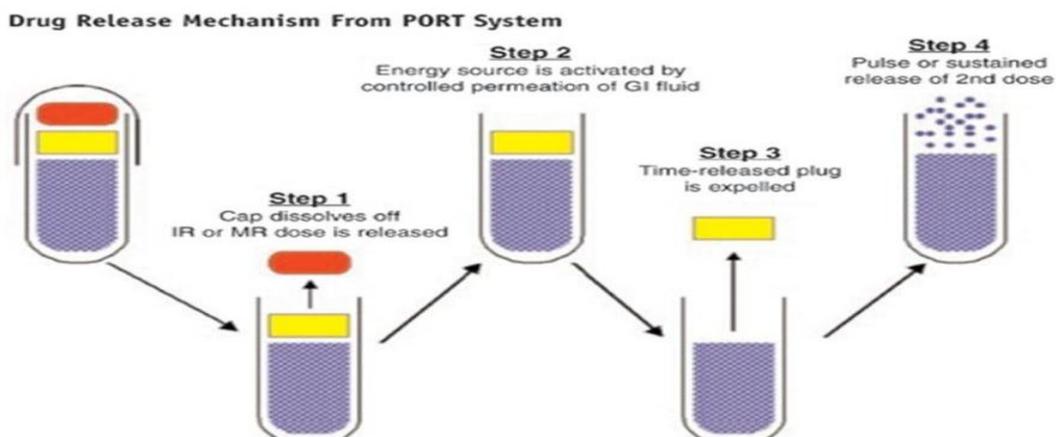


Fig. 4: Drug release mechanism from PORT system

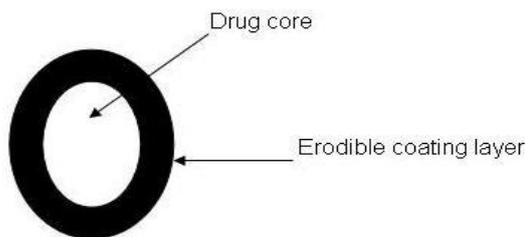


Fig. 5: Schematic diagram of Delivery systems with erodible coating layer

2.4 Drug delivery system with rupturable layers/ membranes

These systems are based upon a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents or swelling agents. Sungthongjeen *et al.* designed a pulsatile drug delivery system where the tablets of bufloxedil HCl prepared by direct compression with varying amounts of spray-dried lactose and microcrystalline cellulose were coated with an inner swelling layer using croscarmellose sodium and an outer rupturable layer using ethyl cellulose. It was observed that by increasing the amount of ethyl cellulose coating, the lag time could be prolonged. Ethyl cellulose, being water insoluble, retarded the water uptake. Similar results were obtained with croscarmellose sodium. Increasing the amount of microcrystalline cellulose decreased the lag time substantially¹⁴.

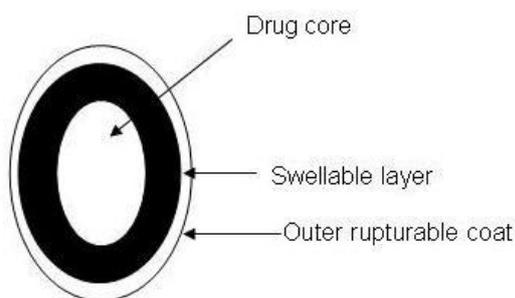


Fig. 6: Schematic diagram of Delivery systems with rupturable coating layer.

Bussemer *et al.* worked on a pulsatile system with rupturable coating on drug present in hard gelatin capsules. These capsules were first coated with a swelling layer and then with an insoluble but waterpermeable outer coating. These coated capsules when immersed in the release media could take up the media at a constant rate up to a point when the outer coating would rupture because of the pressure

caused by the swelling layer. It could be concluded that by increasing the swelling layer, the lag time could be shortened. However, by increasing the outer coating, the lag time could be prolonged. It was also observed that addition of HPMC to the outer coating shortens the lag time¹⁵.

In another similar work, Bussemer *et al.* studied the effect of various swelling agents and the outer polymeric coating on the lag time and the drug release. They developed a pulsatile system based on soft gelatin capsules with an inner swelling and outer polymeric coating. It could be concluded from this study that croscarmellose sodium was a better swelling agent as compared to HPMC (E5 and K100 M). Also, cellulose acetate propionate and ethyl cellulose gave better rupturing by virtue of their brittle nature when compared to Eudragit RS, which gave a flexible polymer coating. Cellulose acetate propionate coated capsules gave better drug release as compared to those coated with ethyl cellulose¹⁶.

2.5 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 independent of gastrointestinal motility, Ph, enzyme and gastric residence.¹⁷⁻²¹

2.6 Multiple unit pulsatile systems

More reliable gastric emptying patterns are observed for multiparticulate formulations as compared to single-unit formulations, which suffer from 'all or none' concept. As the units of multiparticulate systems are distributed freely throughout the gastrointestinal tract, their transport is affected to a lesser extent than single-unit formulations by the transit time of food²². Multiparticulate systems are further classified as systems based upon change in membrane permeability and systems based upon rupturable coating.

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 enhance the patient compliance, optimum drug delivery to the target site and minimize 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.

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