



METHODS AND TECHNOLOGIES OF PULSATILE DRUG DELIVERY SYSTEMS: AN OVERVIEW

Suresh Rewar*, Bansal BK, Singh CJ, Sharma AK

Department of pharmaceutics, Rajasthan University of Health Sciences, Jaipur, Rajasthan



SURESH REWAR

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ABSTRACT

Pulsatile Drug delivery systems are gaining a lot of interest as they deliver the drug at the right site of action, at the right time and in the right amount, as per the pathophysiological needs of the diseases, resulting in increasing patient compliance. Pulsatile Drug Delivery systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, GIT motility, etc. Various techniques are available for the pulsatile delivery like pH dependent systems, time dependent systems, etc. These systems are designed for chronopharmacotherapy which is based on the circadian rhythm of the body. The major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time. A pulse has to be generated in such a way that a complete and rapid drug release is achieved after the lag time so as to match body's circadian rhythms with the release of drugs. Many of circadian dependent diseases display acute symptoms in early morning hours or in the morning at awakening. In case of cardiovascular diseases, BP is at its lowest during the sleep cycle and rises steeply during the early morning period. 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. Advantages of the pulsatile drug delivery system are reduced dose frequency; reduce side effects, drug targeting to specific site like colon and many more. Now in market varies technologies of pulsatile drug delivery system like Pulsincap, Diffucaps etc. are launched by pharmaceutical companies.

KEY WORDS: PDDS, pulsatile release technique, Chronopharmacotherapy, Chronobiology

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. 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.[1,2]

Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions such as asthma where the crisis are mostly

happening late at night, osteoarthritis where the pain is more intense again during night, rheumatoid arthritis where the pain peaks at the morning, duodenal ulcer where the highest gastric secretion is happening in the nighttimes, neurological disorders such as epilepsy where the oscillations are following melatonin secretion, hypercholesterolemia where the cholesterol synthesis is higher during the night and several cardiovascular diseases such as cardiac and/or platelet aggregation. Diseases with time structures other than circadian rhythm are also possible, for example, diabetes is following the secretion of insulin stimulated by meal, or tumour growth in cancer states that follows body changes in blood flow. Menstrual cycle and the corresponding hormonal flux are also following cyclic patterns.

Pulsatile system gaining a lot of interest as it is increasing patient compliance by means of providing time- and site-specific drug delivery system, thus providing special and temporal delivery. Pulsed or pulsatile drug release is defined as the rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off-release period. Recent studies show that diseased have predictable cyclic rhythms and the timing of medication regimens can improve outcome in selected chronic conditions [3, 4].

Drugs which exhibit tolerance should not be delivered at a constant rate, since the drug effect decreases with time at constant drug level. In addition drug toxicity increases with time when drug levels are held constant. In such cases it is preferable to opt for dosage form which will provide desired concentration of drug at particular time point only. Now, concept of chronopharmaceutics has emerged, wherein, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy. "Chronopharmaceutics" consist of two words chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms.

MERITS:

1. Predictable, reproducible and short gastric residence time
2. Less inter- and intra-subject variability
3. Improve bioavailability
4. Limited risk of local irritation
5. No risk of dose dumping
6. Flexibility in design
7. Improve stability

DEMERITS:

1. Lack of manufacturing reproducibility and efficacy
2. Large number of process variables
3. Batch manufacturing process
4. Higher cost of production
5. Trained/skilled personal needed for Manufacturing [5]

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. There are number of diseases which required to be formulated as PDDS as like: hypercholesterolemia, asthma, cancer, duodenal ulcer, arthritis, diabetes, neurological disorders, cardiovascular diseases and colonic delivery. A circadian rhythm occurs during hepatic cholesterol synthesis. Therefore, cholesterol synthesis is generally higher during the night than during daylight. The maximal production occurs early in the morning, i.e. 12 h after the last meal. Studies with HMG CoA reductase inhibitors have suggested that evening dosing was more effective than morning dosing [6, 7].

Circadian rhythm regulates many body functions in humans, viz., metabolism, behaviour, Physiology, sleep patterns, hormone production, etc. In case of cardiovascular diseases, BP is at its lowest during the sleep cycle and rises steeply during the early morning period. Platelet agreeability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. Circadian increase in

the blood sugar level after meal has been observed in Diabetes mellitus. Circadian variations seen in DOPA level in afternoon in case of Attention deficit syndrome.[32,33,34]

Table.1: Diseases Requiring Pulsatile Delivery:

Disease	Chronological behaviour(category of drugs used)
Asthma	Precipitation of attacks during night or at early morning hour
Arthritis	Pain in the morning and more pain at night (NSAID, Glucocorticoids)
Cardiovascular disease	BP is at its lowest during the sleep cycle and rise steeply during the early morning awakening period (Nitroglycerine, calcium channels blockers)
Diabetes mellitus	Increase in the blood sugar level after meal(sulfonylurea,Biguanide, insulin)
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time (Statins)
Peptic ulcer	Acid secretion is high(H^2 blockers)

Human and animal studies suggest that chemotherapy may be more effective and less toxic if cancer drugs are administered at carefully selected times that take advantage of tumour cell cycles while less toxic to normal tissue. In GI ulcer, many of the functions of the gastrointestinal tract are subject to circadian rhythms: gastric acid secretion is highest at night while gastric and small bowel motility and gastric emptying are all slower at night. During night time, when gastric motility and emptying are slower, drug disintegration, dissolution, and absorption may be slower, pulse release is curative[8.9].

Asthma is one such disease where pulsatile drug delivery system can be useful. Circadian changes are seen in normal lung function, airway resistance increases progressively at night in asthmatic patients. Chronotherapies have been studied for asthma with oral corticosteroids, theophylline, and B2- agonists [10].

The colon is also seen as the preferred absorption site for oral administration of protein and peptide drugs, because of the relatively low proteolytic enzyme activities in the colon. A colon-specific drug delivery system should prevent drug release in the stomach and small intestine, and affect an abrupt onset of drug release upon entry into the colon. Time dependent delivery has also been proposed as a means of targeting the colon[11].

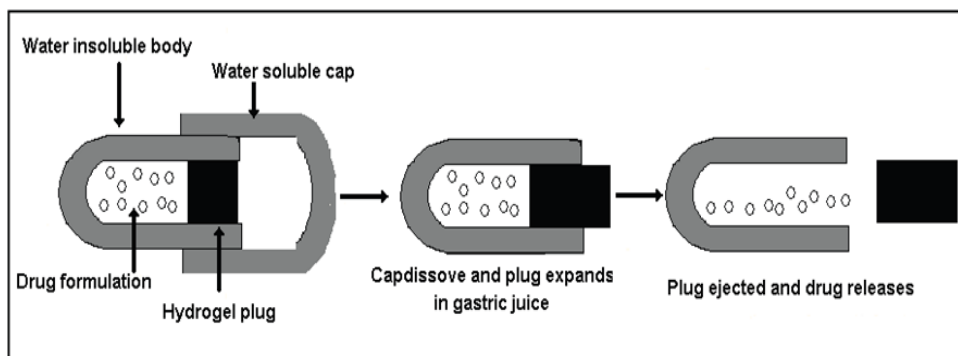


Fig 1: CAPSULE-BASED SYSTEM

CLASSIFICATION OF PDDS (TECHNOLOGY USED)

From technological point of view pulsatile drug release system are further divided to single and multiple units system.

SYSTEM UNIT SYSTEM

These are subdivided as capsule-based system, osmotic system, delivery system with soluble or erodible membranes, and delivery system with reparable coating.

CAPSULE-BASED SYSTEM

Capsule based system consists of pulsincap system, which consists of an insoluble capsule body and swellable and degradable plugs made of approved substances such as hydrophilic polymers or lipids. The lag time is controlled by plug, which pushed away by swelling or erosion and drug is released as a pulse from the insoluble capsule i.e. Pulsincap®.

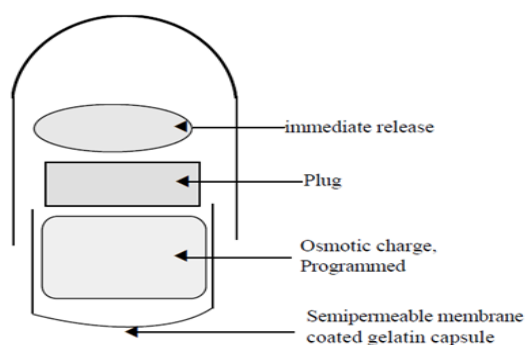


Fig 2: OSMOTIC SYSTEM

A swellable hydrogel plug seals the drug contents in to capsule body. When this capsule body came in to contact with dissolution medium, the hydrogel plug swells, and after the lag time the plug pushed itself outside the capsule and rapidly released the drug [12]. Various types of material used for formulation of swellable plug which include hydroxyl propyl methyl cellulose, poly vinyl acetate and poly ethylene oxide. The length of plug decides lag time. Plug material is generally made up of HPMC, polyvinyl alcohol, glyceryl mono oleate, pectin, polymethacrylates.

OSMOTIC SYSTEM

Osmotic system consists of capsule coated with the semipermeable membrane. Inside the capsule there is an insoluble plug consisting of osmotically active agent and the drug formulation [13].

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.

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 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 [14].

DELIVERY SYSTEM WITH SOLUBLE OR ERODIBLE MEMBRANES

In such systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing drug. Time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer coat. e.g chronotropic system which consists of a drug containing core layered with HPMC optionally coated with an outer enteric coating.

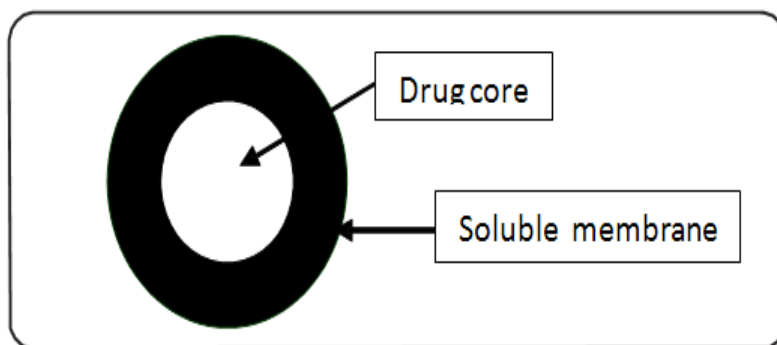


Fig 3 Delivery System with Soluble or Erodible Membranes

The lag time prior to drug release is controlled by the thickness and the viscosity grade of HPMC layer. 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 [15].

DELIVERY SYSTEM WITH REPTURABLE COATING

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. 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. 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.

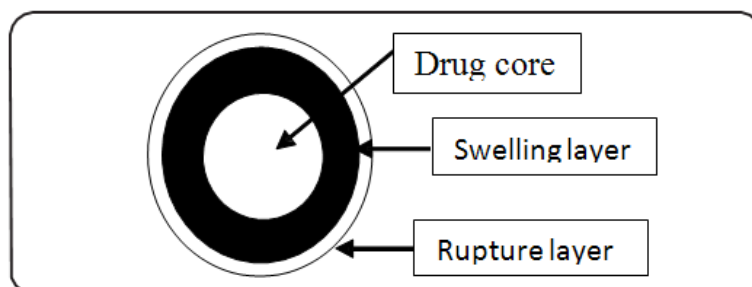


Fig 4: Delivery System with Repturable Coating

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 [1, 2]. Sunthongjeen et al developed a tablet system consisting of core coated with two layers of swelling and rupturable coatings wherein they used spray dried lactose and microcrystalline cellulose in drug core and then core was coated with swelling polymer croscarmellose sodium and an outer rupturable layer of ethylcellulose[16].

II. Multiple Units

Systems Based on Change in Membrane Permeability

Numerous pharmaceutical forms with delayed release for oral administration are available. As already mentioned the release of the drug must be controlled according to therapeutic purpose and the pharmacological properties of the active ingredient. In consequence, it is not always desirable the blood levels to be constant. On the contrary, in order to avoid any habituation and in order to limit the side effects provoked by the active ingredient, it would be absolutely advantageous for the plasmatic rate to follow the metabolic rhythm and the specific needs of the patient during certain periods. For instance, in order to

diminish the nocturnal symptoms or the symptoms upon awakening in the case of certain chronic diseases such as ischemic heart disease, asthma and arthritis, the drugs should be administered in such a way that the desired therapeutical plasmatic level is reached only at the desired moment, i.e. during sleep or at the moment of awakening.

Chen described a system composed of a large number of pellets made up of two or more populations of pellets or particles. Each pellet contains a drug containing core, and a water soluble osmotic agent enclosed in a water permeable, water-insoluble polymer film. Incorporated into the polymer film is a hydrophobic, water insoluble agent which alters the permeability of the polymer film. The film coating of each population of pellets differs from the coating of every other population of pellets in the dosage form in the rate at which water passes through to the core and the rate at which drug diffuses out of the core. The osmotic agent dissolves in the water, causing the pellet to swell and regulating the rate of diffusion of drug into the environment of use. As each population of pellets releases drug into the environment sequentially, a series of pulsatile administrations of the drug from a single dosage form is achieved [17].

CLASSIFICATION OF PDDS BASED ON STIMULI INDUCED

1. Temperature induced system
2. Chemically induced system
3. Externally induced system

1. TEMPERATURE INDUCED SYSTEM

Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state [16]. Y.H. Bae et al developed indomethacin pulsatile release pattern in the temperature ranges between 20°C and 30°C by using reversible swelling properties of copolymers of N-isopropylacrylamide and butyrylacrylamide. Kataoka et al developed the thermosensitive polymeric micelles as drug carrier to treat the cancer. They used endfunctionalized poly (N isopropylacrylamide) (PIPAAm) to prepare corona of the micelle which showed hydration and dehydration behavior with changing temperature[18,19].

2. CHEMICALLY INDUCED SYSTEM

There has been much interest in the development of stimuli-sensitive delivery systems that release a therapeutic agent in presence of specific chemical moieties like enzyme or protein. One of the good example is Glucose-responsive insulin release devices in which insulin is release on increasing of blood glucose Level. In diabetes mellitus there is rhythmic increase in the levels of glucose in the body requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release [20].

Yui et al. designed drug delivery systems based on the polymers which responded to the hydroxyl radicals and degraded in a limited manner. Yui and co-workers used hyaluronic acid (HA), in the body, HA is mainly degraded either by hydroxyl radicals or a specific enzyme, hyaluronidase. Degradation through hydroxyl radicals however, is usually dominant and rapid when HA is injected at inflammatory sites. Thus, they designed crosslinked HA with ethylene glycol diglycidylether or polyglycerol polyglycidylether Thus, a surface erosion type of degradation was achieved. Patients with inflammatory diseases, such as rheumatoid arthritis, can be treated using this type of system [21, 22].

In Enzymatically- Activated liposomes, drug loaded liposomes was incorporated into microcapsules of alginate hydrogels. Liposomes inside the microcapsules were coated with phospholipase A2 to achieve a pulsatile release of drug molecules. Phospholipase A2 was shown to accumulate at the water/liposome interfaces and remove anacyl group from the phospholipids in the liposome. Destabilised liposomes

release their drug molecules, thus allowing drug release to be regulated by the rate determining microcapsule membrane [23].

Miyata et al. focused on the development of stimuli responsive crosslinking structures into hydrogels. Special care was given to antigen-antibody complex formation as the cross-linking units in the gel, since specific antigen recognition of an antibody can provide the foundation for a new device fabrication. Using the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/deswelling and drug permeation changes could occur. Thus, biological stimuli responsive hydrogel were created [24].

3. EXTERNALLY INDUCED SYSTEM

For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation.

ELECTRICALLY STIMULATED

Electrically responsive delivery systems are prepared by polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. Under the influence of electric field, electro responsive hydrogels generally bend, depending on the shape of the gel which lies parallel to the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes. An electroresponsive drug delivery system was developed by R. V. Kulkarni, et al., using poly (acrylamide-grafted-xanthan gum) (PAAm-g- XG) hydrogel for transdermal delivery of ketoprofen [25].

MAGNETICALLY STIMULATED

Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads [26]. Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials in beads such as magnetite, iron, nickel, cobalt etc. Tingyu Liu, et al developed the magnetic hydrogels which was successfully fabricated by chemically crosslinking of gelatin hydrogels and Fe₃O₄ nanoparticles (ca. 40–60 nm) through genipin (GP) as cross-linking agent. Saslawski et al.[19] developed different formulations for in vitro magnetically triggered delivery of insulin based on alginate spheres. In an experiment, ferrite microparticles (1 μ m) and insulin powder were dispersed in sodium alginate aqueous solution. The ferrite-insulin alginate suspension was later dropped in aqueous calcium chloride solution which causes the formation of cross linked alginate spheres, which were further cross linked with aqueous solution of poly(L-lysine) or poly(ethylene imine). They described that the magnetic held characteristics due to the ferrite microparticles and the mechanical properties of the polymer matrices could play role in controlling the release rates of insulin from the system [27].

ULTRASONICALLY STIMULATED

Ultrasound is mostly used as an enhancer for the improvement of drug permeation through biological barriers, such as skin. The interactions of ultrasound with biological tissues are divided into two broad categories: thermal and nonthermal effects. Thermal effects are associated with the absorption of acoustic energy by the fluids or tissues. Non-thermal bio-effects are generally associated with oscillating or cavitating bubbles, but also include noncavitation effects such as radiation pressure, radiation torque, and acoustic streaming [28]. Kost et al. described an ultrasound-enhanced polymer degradation system. During polymer degradation incorporated drug molecules were released by repeated ultrasonic exposure. As degradation of biodegradable matrix was enhanced by ultrasonic exposure, the rate of drug release also increased. Thus, pulsed drug delivery was achieved by the on-off application of ultrasound [29].

PHOTO STIMULATED

The interaction between light and material can be used to modulate drug delivery. This can be accomplished by combining a material that absorbs light at a desired wavelength and a material that uses energy from the absorbed light to modulate drug delivery. Embedding the nanoshells in a NIPAAm-co-AAM hydrogel formed the required composite material. When exposed to near-infrared light, nanoshells absorb the light and convert it to heat, raising the temperature of composite hydrogel above its LCST. That's result in the increase rate

release of the drug from matrix system[30].Light-sensitive hydrogels have potential applications in developing optical switches, display units, and ophthalmic drug delivery devices[31].

Table.2: Marketed Technologies of Pulsatile System:

Pulsincap® Scherer DDS, Ltd	A water impermeable capsule body with hydro gel plug. Plug length and insertion depth controls lag time. Patent No. US5631022
PULSYS™ MiddleBrook Pharmaceuticals™	The typical PULSYS drug delivery format is a tablet containing multiple pellets with different release profiles
Diffucaps® Eurand	The active drug is layered onto a neutral core (such as cellulose spheres) and then one or more rate-controlling, functional membranes are applied. Patent No. US7387793B
Orbexa® Eurand	This technology produces beads that are of controlled size and density using granulation, spheronization and extrusion techniques.
OROS® Push Pull™ Alza	A bilayer / trilayer tablet core consisting of one or more drug layers, surrounded by a semipermeable membrane with a drilled orifice.

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. Various methodologies are employed for developing pulsatile drug delivery like time Controlled, stimuli induced externally regulated system and multiparticulate drug delivery system. These considerations, along with the potential therapeutic benefits of pulsatile drug delivery systems, should ensure that the current high level of interest in this area would stretch well into future and ensures the betterment of quality life.

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