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Research Article

Pulsatile drug delivery system - A review article

Roaa A. Nief*, Halah Talal Sulaiman, Saba Abdulhadi Jabir

ABSTRACT

Pulsatile drug delivery systems (PDDS) are developed to deliver drug according to circadian behavior of diseases. They deliver the drug at the right time, action and in the right amount, which provides more benefit than conventional dosages and increased patient compliance. The drug is released rapidly and completely as a pulse after a lag time. These systems are beneficial for drugs with chrono-pharmacological behavior, where nighttime dosing is required and for the drugs having a high first-pass effect and having specific site of absorption in the gastrointestinal tract. This article covers methods and marketed technologies that have been developed to achieve pulsatile delivery. Diseases wherein PDDS are promising include asthma, peptic ulcers, cardiovascular, arthritis and attention deficit syndrome in children and hypercholesterolemia.

KEY WORDS: Pulsatile drug delivery system, Capsular system, Rupturable coating

INTRODUCTION

Pulsatile drug delivery system (PDDS) is rapid and transient release of certain amount of drug molecules within a short time period immediately after a predetermined off-release period, i.e., lag time.[1] After the lag phase, pulsatile delivery systems may give rise to a prompt and quantitative, repeated or prolonged release pattern depending on their formulation characteristics which are shown in Figure 1.

NECESSITIES OF PDDS

These systems are beneficial for drugs having high first-pass effect; drugs administered for diseases that follow chrono-pharmacological behavior as shown in Table 1.[2,3]

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEMS

Single Unit Pulsatile Systems

Capsule based systems

Pulsincap system[4]

Pulsincap [Figure 2] was developed by R. P. Scherer International Corporation, Michigan, US, and is one such system that comprises a water-insoluble capsule enclosing the drug reservoir. When this capsule comes in contact with the dissolution fluid, it swells; and after a lag time, the plug pushes itself outside the capsule and the drug is released rapidly. The lag time can be controlled by manipulating the dimension and the position of the plug.

Polymers used for designing of the hydrogel plug are as follows:[5,6]

- Insoluble but permeable and swellable polymers (e.g., polymethacrylates)
- Erodible compressed polymers (e.g., hydroxypropylmethylcellulose, polyvinyl alcohol, and polyethylene oxide)
- Congealed melted polymers (e.g., saturated polyglycolated glycerides and glyceryl monooleate)
- Enzymatically controlled erodible polymer (e.g., pectin).

Capsular system based on osmosis

"PORT" system[7]

The port system (Figure 3) 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 formulation. 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.

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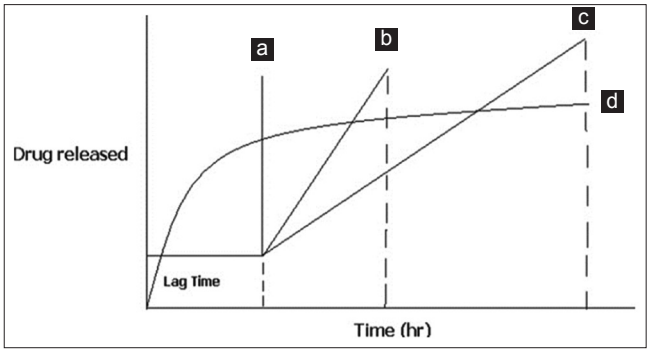

Figure 1: Drug release profiles: (a) Sigmoidal release after lag time, (b) delayed-release after lag time, (c) sustained release after lag time, and (d) extended-release without lag time

Table 1: Diseases required pulsatile drug delivery[2,3]

Disease	Chronological behavior	Drugs used
Peptic ulcer	Acid secretion is high in the afternoon and at night	H2 blockers
Asthma	Precipitation of attacks during the night or at early morning hour	β2agonist, antihistaminic
Cardiovascular disease	BP is at the lowest during sleep cycle and rises steeply during the early morning awakening days.	Nitroglycerin, calcium channel blocker, and ACE inhibitors
Diabetes mellitus	Increase in blood sugar level after meal	Sulfonylurea, insulin, and biguanid
Hypercholesterolemia	Cholesterol synthesis is generally higher during the night than during daytime	HMG CoA reductase inhibitors

BP: Blood pressure, ACE: Angiotensin-converting enzyme

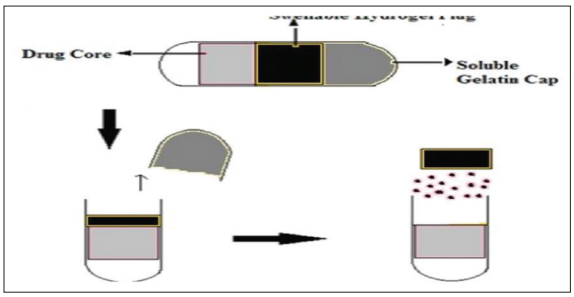

Figure 2: Design of pulsincap system

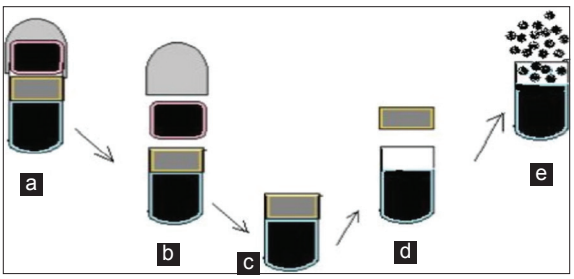

Figure 3: Drug release mechanism from PORT system. Where, a: Port system, b: Swelling of cap with the release of 1st dose, c: Permeation of more GI fluid with generation of internal pressure, d: Expulsion of time released plug, and e: Second released in pulsed or sustained form

System based on expandable orifice[8]

The capsular system delivers the drug by the capsule's osmotic infusion of moisture from the body (Figure 4). The capsule wall is made up of an elastic material and possesses an orifice. For example, elastomers, such as styrene-butadiene copolymer, have been suggested.

As the osmosis proceeds, the pressure within the capsule rises, causing the wall to stretch. The orifice is small enough so that when the elastic wall relaxes, the flow of the drug through the orifice essentially stops, but when the elastic wall is distended beyond a threshold value, the orifice expands sufficiently to allow drug release at a required rate.[9]

Delivery by series of stops

This system is for implantable capsules. The capsule contains a drug and water-absorptive osmotic engine that is placed in compartments separated by a movable slider that provides pulsatile release of the drug. Series of stops obstruct the movement of drug and provides lag time which is overcome as the osmotic pressure rises above a threshold level. This system was used to deliver porcine somatotropin.[10]

Pulsatile delivery by solubility modulation

The system was especially developed for delivery of salbutamol sulfate that contained sodium chloride as a modulating agent. Amount of NaCl was less than the amount needed to maintain saturation in a fluid that enters the osmotic device. The pulsed delivery is based on drug solubility. Salbutamol has solubility of

275 mg/ml in water and 16 mg/ml in saturated solution of NaCl, while NaCl has solubility of 321 mg/ml in water, and its saturation solubility is 320 mg/ml.[11]

These values show that the solubility of the drug is function of the modulator concentration, while the modulator's solubility is largely independent of drug concentration. The modulating agent can be a solid organic acid, inorganic salt, or organic salt. Ratio of drug/modulator may be varied to control zero-order release period and commence pulsed release.[12]

Pulsatile system with erodible or soluble barrier coatings

The chronotropic system

The chronotropic system (Figure 5) consists of a drug containing core coated by hydrophilic swellable hydroxypropyl methylcellulose (HPMC) that produces lag phase.[13]

"TIME CLOCK" system

The time clock system is a delivery device based on solid dosage form that is coated by an aqueous dispersion. The core is coated at 75°C with an aqueous dispersion of a hydrophobic surfactant layer (Beeswax, carnauba wax, and poly {oxyethylene}–sorbitan monooleate).[14]

A water-soluble coat is applied to improve adhesion to the core coat (Figure 6). Once in contact with the dissolution fluid, the dispersion rehydrates, and redisperses. The lag time could be controlled by varying the thickness of the film. After the lag time, i.e. the time required for rehydration, the core immediately releases the drug.[15]

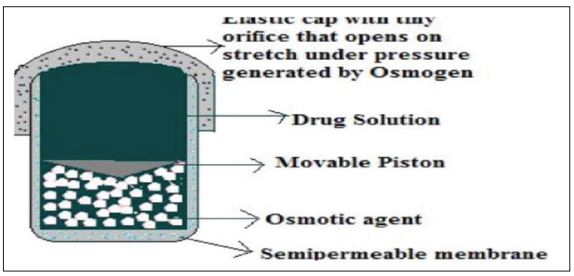

Figure 4: System based on expandable orifice

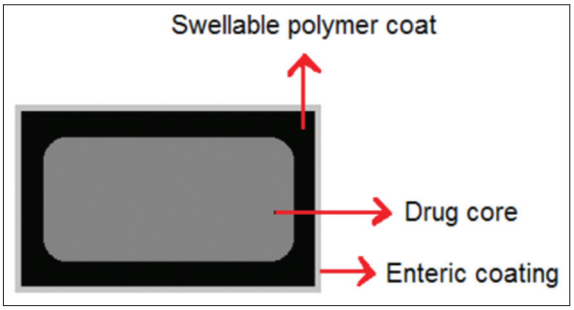

Figure 5: The chronotropic system

Compressed tablets

Compression coating involves direct compression of both the core and the coat, averting needs for the use of coating solutions. The outer tablet of the compression-coated tablet provides the initial dose, rapidly disintegrating in the stomach and the inner layer is formulated with components that are insoluble in gastric media but are released in the intestinal environment. Cellulose derivative may be used for this purpose. Compression is easy on laboratory scale.[16]

Multilayered tablets

Two pulses can be obtained from a three-layered tablet containing two drugs containing layers separated by a drug-free gellable polymeric barrier layer (Figure 7). This three-layered tablet is coated on three sides with impermeable ethyl cellulose, and the top portion was left uncoated. On contact with dissolution medium, the initial dose incorporated into the top layer was released rapidly from the non-coated surface. The second pulse is obtained from the bottom layer after HPMC layer gets eroded and dissolved.[17]

Pulsatile system with rupturable coating

These systems depend on disintegration of the coat for the release of the drug. The pressure needed for the rupture of the coating is achieved by effervescent excipients, swelling agents, or osmotic pressure. An effervescent mixture of citric acid and sodium bicarbonate incorporated in a tablet core coated with ethyl cellulose produced carbon dioxide after penetration of water into the core resulting in pulsatile release of drug after rupture of the coat.[18]

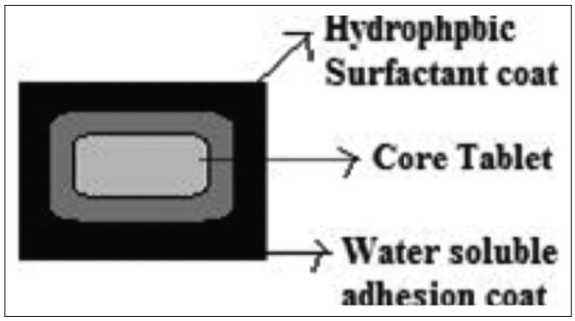

Figure 6: "TIME CLOCK" System

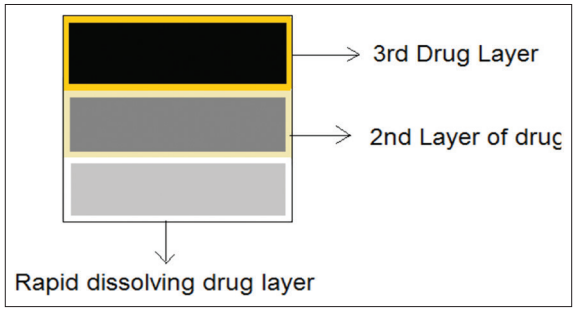

Figure 7: Multilayered tablet

The swelling of these materials resulted in a complete film rupture followed by rapid drug release. The lag time is function of the composition of the outer polymer layer. The presence of hydrophilic polymer like HPMC reduces lag time. The system can be used for delivery of both solid and liquid drug formulations.[18]

Multi-particulate/Multiple Unit Systems

Pulsatic system with rupturable coating

Time–controlled explosion system (TCES)

Multi-particulate system where drug is coated with nonpareil sugar seeds followed by a swellable layer and an insoluble top layer coating (Figure 8).[18] The swelling agents used include superdisintegrants such as sodium carboxymethyl cellulose, sodium starch glycolate, L-hydroxypropyl cellulose, and polymers such as polyvinyl acetate polyethylene glycol.

Alternatively, the effervescent system comprising a mixture of tartaric acid, citric acid, and sodium bicarbonate may also be used. On ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. This release is independent of environmental factors such as pH and drug solubility.

The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer. A rapid release after the lag phase can be achieved with increasing concentration of osmotic agent.[18]

Osmotic based rupturable coating system

This system is based on a combination of osmotic and swelling effects. The core contains drug, a low bulk density solid and/or liquid lipid material (Example mineral oil) and a disintegrant. The core is finally coated with cellulose acetate. On immersion in an aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of the coat.[19]

Pulsatile delivery by change in membrane permeability

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium.[20] Several delivery systems based on this ion exchange have been developed.

Eudragit is a polymer of choice for this purpose. It typically contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions. The ammonium group being hydrophilic facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner. The lag time increases with increasing thickness of the coat, but the release of the drug was found to be independent of this thickness and depended on the amount of salt present in the system.[21]

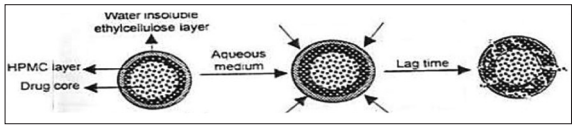

Figure 8: Time-controlled Explosion system

Sigmoidal release system

This consists of pellet containing drug and succinic acid coated with ammonio methacrylate copolymer. The water in the medium dissolves succinic acid. The drug inside and the acid solution increase the permeability of the polymer film. Instead of succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid is also used.[22]

Stimuli induced pulsatile systems

In these systems, there is the release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli. These systems are further classified into temperature induced systems and chemical stimuli induced system, on the basis of stimulus.

Temperature-induced systems

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 modulates drug release in the swollen state.[23]

Chemical stimuli induced pulsatile systems

Glucose-responsive insulin release devices

In case of 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. Examples of the pH-sensitive polymers include N,N dimethylaminoethyl methacrylate, chitosan, and polyol[24]

Inflammation-induced pulsatile release device

On receiving any physical or chemical stress, such as injury and fracture inflammation takes place at the injured sites. During inflammation, hydroxyl radicals

are produced from these inflammation-responsive cells. Yui *et al.* focused on the inflammatory-induced hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner. They used hyaluronic acid (HA) which is specifically degraded by the hyaluronidase or free radicals. Degradation of HA through the hyaluronidase is very low in a normal state of health. Degradation through hydroxyl radicals, however, is usually dominant and rapid when HA is injected at inflammatory sites. Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated HA gels as new implantable drug delivery systems.[24]

Drug release from intelligent gels responding to antibody concentration

Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/reselling characteristics. Special attention was given to antigen-antibody complex formation as the cross-linking units in the gel since such interactions are very specific.

Utilizing the difference in association constants between polymerized antibodies and naturally derived antibodies toward specific antigens, reversible gel swelling/deswelling, and drug permeation changes occur.[24]

pH-sensitive drug delivery system

By selecting the pH-dependent polymers drug release at specific location can be obtained. An example of pH-dependent polymers includes cellulose acetate phthalate, polyacrylates, and sodium carboxymethyl cellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine.[23]

Externally regulated pulsatile drug delivery

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 such as magnetism, ultrasound, electrical effect, and irradiation. Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads.[23,24]

Marketed Technologies of Pulsatile Drug Delivery

ACCU-T CR (controlled release) tri-layer tablets

The ACCU-T CR tablet contains CR medication at either end of the tablet separated by a drug-free break layer, allowing the CR dose to be divided into exact half doses without affecting the rate of drug release. In addition, an immediate release component can be added to CR tablets to add even more treatment options and potential product capabilities (Figure 9). [25]

Orbexa® technology

This technology consists of beads of a controlled size and density using granulation/extrusion and spheronization techniques. These beads provide higher drug concentration can be coated with functional polymer membranes for additional release rate control and can also be used for sensitive drugs such as proteins and enzymes. Orbexa beads can be filled into capsules or single-dose sachet (Figure 10).[26]

DIFFUCAPS® technology

Diffucaps is a multiparticulate bead system comprised multiple layers of drug, excipients, and release-controlling polymers are shown in Figure 11. The beads contain a layer of an organic acid or alkaline buffer to control the solubility of a drug by creating an optimal pH microenvironment for drugs that exhibit poor solubility in intestinal pH, in environments with pH >8.0. Alternatively, the beads can contain a solid solution of drug and crystallization inhibitor to enhance bioavailability by maintaining the drug in its

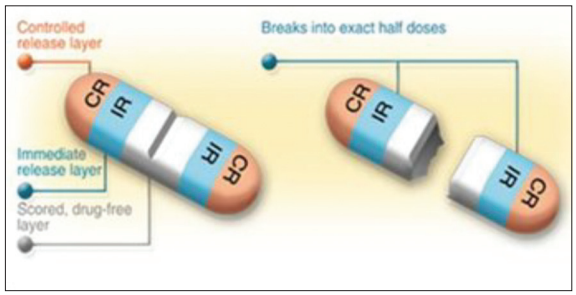

Figure 9: Spheroidal oral drug absorption system ® technology

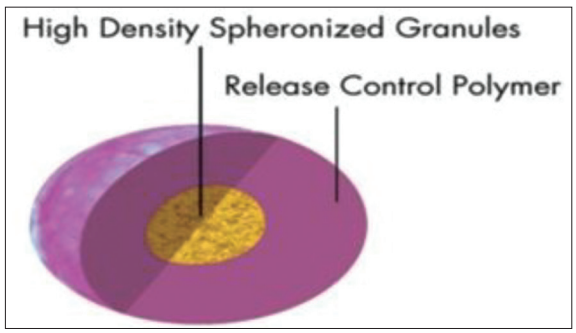

Figure 10: ORBEXA® technology

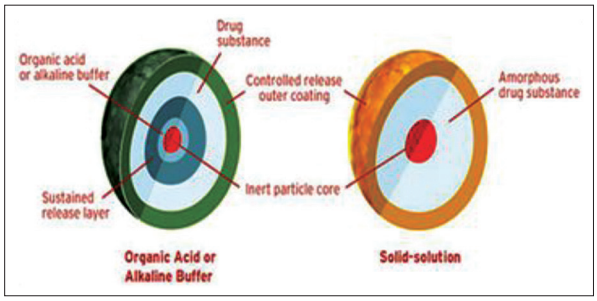

Figure 11: DIFFUCAPS® technology

amorphous state. Diffucaps technology is especially suitable for drugs that traditionally require multiple daily doses or drugs needing customized release formulations.[27]

DIFFUTAB® technology

Diffutab technology enables customized release profiles and region-specific delivery. Diffutab® technology uses a blend of hydrophilic and hydrophobic polymers to control drug release through diffusion through, and erosion of, a matrix tablet. Diffutab is particularly useful for high-dose

products and drugs that require sustained release and/or once-a-day dosing (Figure 12).[28]

Spheroidal oral drug absorption system (SODAS)® technology

SODAS can provide a number of tailored drug release profiles, including immediate release of drug followed by sustained release to give rise to a fast onset of action, which is maintained for 24 h. However, the opposite scenario can be achieved where drug release is delayed for a number of hours (Figure 13).[29]

CONCLUSION

Although sustained and controlled drug delivery systems have gained a lot of success and application in field of medication, these systems fail to deliver drug according to circadian behavior of diseases for which pulsatile systems are beneficial. For successful development of chronotherapeutic dosage form, knowledge of circadian time structure, rhythm in disease pathophysiology or 24 h pattern in symptom intensity of chronic medical conditions, and chrono-pharmacology of medication is needed. Significant progress has been made toward achieving PDDS that can effectively treat diseases with non-constant dosing therapy.

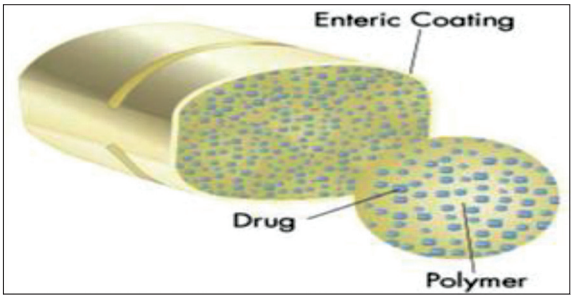

Figure 12: Diffutab® technology

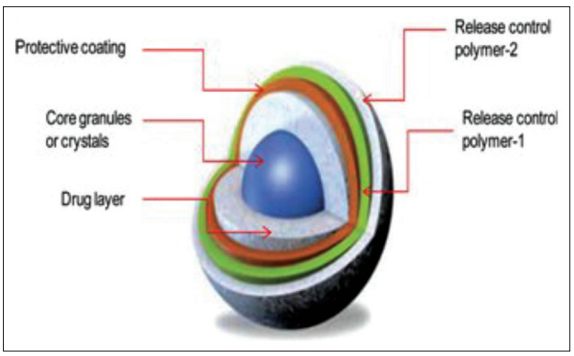

Figure 13: Spheroidal oral drug absorption system® technology

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