Review Article

Pulsatile Drug Delivery Systems: An Overview

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ABSTRACT: Pulsatile Drug Delivery Systems are gaining a lot of interest as they deliver the drug at the right place at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. The principle rationale for the use of pulsatile release of the drugs is where a constant drug release is not desired. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the lag time. Various systems like capsular systems, osmotic systems, single- and multiple-unit systems based on the use of soluble or erodible polymer coating and use of rupturable membranes have been dealt with in the article. It summarizes the latest technological developments, formulation parameters, and release profiles of these systems. These systems are beneficial for the drugs having chronopharmacological behavior where night time dosing is required, such as anti-arythmic and anti-asthmatic.

KEYWORDS: Pulsatile; Rupturable; Erodible; Osmotic

Introduction

Modified release dosage forms have acquired a great importance in the current pharmaceutical R&D business. Such systems offer control over the release pattern of drug and provide better control over drug regimen. Oral Modified release dosage forms represent the most popular form of controlled drug delivery systems due to the obvious advantages of oral route of drug administration. Such systems release the drug with predetermined release rates, either constant or variable. These dosage forms offer numerous advantages, such as nearly stable plasma drug level without much fluctuations, reduction in dose of drug, reduced dosage frequency, least side effects, and improved patient compliance.

Modified release dosage forms show different release profiles depending on their type. Sustain release dosage forms may maintain nearly constant plasma drug concentration in therapeutic window for prolonged time as shown in the Figure 1(A). Pulsatile release dosage forms release drug in pulsatile manner and maintain plasma drug level within therapeutic range as shown in figure 1(B).

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Pulsatile Drug Delivery Systems

Pulsatile drug delivery systems, which release the drug rapidly and completely after a lag time, thus provide spatial and temporal delivery and increasing patient compliance, have generated increasing interest during recent years for a number of diseases and therapies. Different types of Pulsatile systems have been developed, including eroding and reputable systems.

Necessity of Pulsatile Drug Delivery Systems

There are many conditions and diseases where sustained release formulations do not show good efficacy. In such cases Pulsatile DDS is applicable.

- Many body functions follow circadian rhythm, i.e., their activity increases or decreases with time. A number of hormones like rennin, aldosterone, and cortisol show daily as well as timely fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion. (Goo et al., 1987)
- Severity of diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension is time dependent (Lemmer et al., 1999). Sharp increase in asthmatic attacks during early
morning hours have been reported (Dethlefsen et al., 1985) Such a condition demands supplement of drug at particular time rather than maintaining constant plasma drug level. A drug delivery system administered at bedtime, but releasing drug as a burst after the time of administration (during morning hours), would be ideal in this case. Same is true for preventing heart attacks in the middle of the night and the morning stiffness typical of people suffering from arthritis.

- Some drugs (e.g. Salbutamol sulphate) produce biological tolerance and hence demand for a system that will prevent their continuous presence at the site of action as this tends to reduce their therapeutic effect (Chang et al., 1999).

- Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (e.g. peptide drugs), irritate the gastric mucosa (NSAIDS) or induce nausea and vomiting. These conditions can be satisfactorily handled by enteric coating, and in this sense, enteric coating can be considered as a pulsatile drug delivery system.

- To achieve localized action at distal organs of GIT such as colon for drugs used in ulcerative colitis (e.g. Sulfasalazine) the drug release needs to be prevented in the upper two-third portion of the GIT (Gazzaniga et al., 1994)

- The drugs that undergo extensive first-pass metabolism (ß-blockers) and those that are characterized by idiosyncratic pharmacokinetics or pharmacodynamics resulting in reduced bioavailability, altered drug/metabolite ratios, altered steady state levels of drug and metabolite, and potential food-drug interactions require delayed release of the drug to the extent possible (Gothoskar et al., 2004).

All of these conditions demand for a efficiently programmed drug delivery system releasing the right amount of drug at the right time. This can be achieved by Pulsatile Drug Delivery Systems. A pulsatile drug delivery system is characterized by a rapid drug release after a predetermined lag time that is an interval of no drug release. The ideal drug-release profile of pulsatile drug delivery systems is depicted in Figure 2.
The first pulsatile drug delivery formulation that released the active substance at a precisely defined time point was developed in the early 1990s. In this context, the aim of the research was to achieve a so-called sigmoidal release pattern (pattern A in Figure 2). The characteristic feature of the formulation was a defined lag time followed by a drug pulse with the enclosed active quantity being released at once (Petereit et al., 2003).

Thus, the major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time. Often, the drug is released over an extended period of time (patterns B & C in Figure 2).

Currently Available Systems

Pulsatile systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastro-intestinal motility, etc. These time-controlled systems can be classified as single unit (e.g., tablet or capsule) or multiple unit (e.g., pellets) systems.

Single-Unit Systems

Capsular Systems

Different single-unit capsular pulsatile drug delivery systems have been developed. A general structure of such systems consists of an insoluble capsule body containing a drug and a plug. The plug may be erodible, swelling or soluble which is removed after a predetermined lag time. The Pulsincap® system (Scherer DDS, Ltd) is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation (McNeil et al., 1990, Wilding et al., 1992 and Saeger et al., 2004). The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastro-intestinal fluids, the plug swells and after a lag time, pushes itself out of the capsule. This leads to drug release as a pulse. The lag time can be controlled by manipulating the dimension and the position of the plug. For water-insoluble drugs, a rapid release can be ensured by incorporation of disintegrants or effervescent agents. The plug material consists of insoluble but permeable and swellable polymers (eg, polymethacrylates), erodible compressed polymers (eg, hydroxypropyl/methyl cellulose, polyvinyl alcohol, polyethylene oxide) (Krögel et al., 1998), congealed melted polymers (eg, saturated polyglycolated glycerides, glyceryl monoleate), and enzymatically controlled erodible polymer (eg, pectin, agar) (Krögel et al., 1999). These formulations were well tolerated in animals and healthy volunteers, and there were no reports of gastro-intestinal irritation (Saeger et al., 2004). However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine (Binns et al., 1996).

Osmosis Based Capsular System

The Port® System (Port Systems, LLC) consists of a gelatin capsule coated with a semipermeable membrane (eg, cellulose acetate). Inside the capsule was an insoluble plug and an osmotically active agent along with the drug formulation (Figure 4). (Crison et al., 1995). When this capsule came in contact with the dissolution medium, water diffuses across the semipermeable membrane, resulting in increased pressure inside that ejects the plug after a predetermined lag time. The lag time is controlled by coating thickness. The system showed good correlation in lag times of in-vitro and in-vivo experiments in humans (Crison et al., 1996). Such a system was utilized to deliver methylphenidate used in the treatment of attention deficit hyperactivity disorder (ADHD) in school-age children. This system avoided second time dosing, which was beneficial for school children during daytime (Crison et al., 2001).
A System Based on Expandable delivery Orifice: To deliver the drug in liquid form, a capsular system based on osmotic pressure was developed in which the liquid drug is absorbed into highly porous particles housed in a semipermeable capsule supported by an expanding osmotic layer and having a delivery orifice covered by barrier layer, which release the drug through the delivery orifice after the barrier layer is dissolved. (Pollock-Dove et al., 2001). The delivery of the drug was driven by the osmotic infusion of the moisture by the capsule from a physiological environment. The capsule wall is made up of an elastic material and possesses an orifice. As the osmosis proceeds, the pressure within the capsule rises which causes 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 threshold value, the orifice expands sufficiently to allow drug release at a required rate. Use of elastomers, such as styrene-butadiene copolymer have been reported (Linkwitz et al., 1993 and 1994). Lag times can be modified by changing the thickness of the barrier layer and that of semipermeable membrane (Pollock-Dove et al., 2001). After this lag time the drug is released in Pulsatile manner. A capsule designed for implantation can deliver drug intermittently at intervals of 6 hours for 2 days.

Delivery by a Series of Stops: This system is designed for implantable capsules. The capsule containing a drug and a water-absorbent osmotic engine placed in compartments separated by a movable partition. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level. The number and frequency of the pulses is controlled by the number of stops and the longitudinal placements of the stops along the length of the capsule, and the pulse intensity is controlled by configuration of the partition. This system was used to deliver porcine somatotropin (Balaban et al., 1993)

Pulsatile Delivery by Modulating Solubility: Such systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of antiasthmatic drug, salbutamol sulphate (Magruder et al., 1988 and 1989). The compositions contain the drug (salbutamol sulphate) and a modulating agent (sodium chloride). The amount of sodium chloride was such that it 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 sodium chloride, while sodium chloride has solubility of 321 mg/ml in water, and its saturation solubility is 320 mg/ml. These values show that the solubility of the drug is dependent on the modulator concentration, while the modulator’s solubility is largely independent of drug concentration. The modulating agent can be a solid either organic acid or inorganic/organic salt. By changing the ratio of drug/modulator, zero-order release period and commencement of pulsed release can be controlled. After the period of zero-order release, the drug is delivered as one large pulse. A similar system is described for delivery of terbutaline and oxprenolol (Magruder et al., 1988). However, the large-scale manufacturing of these
systems is complicated and require special equipments and several manufacturing steps.

**System with Erodible or Soluble Barrier Coatings**

Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag time, after that the drug is released rapidly. The lag time depends on the thickness of the coating layer.

The Time Clock® system (West Pharmaceutical Services Drug Delivery & Clinical Research Centre) consists of a solid dosage form coated with lipidic barriers containing carnauba wax and bees’ wax along with surfactants, such as span 80 (Pozzi et al., 1992 and Wilding et al., 1994). After a lag time proportional to the thickness of the film, this coat erodes or emulsifies in the aqueous environment, and the core is then available for dispersion. A study with human volunteers has shown that the lag time was independent of gastric residence time, and the hydrophobic film redispersion did not appear to be influenced by mechanical action of stomach or gastrointestinal pH or the presence of intestinal enzymes (Gazzania et al., 1994). The lag time increased with increasing coating thickness. Such systems are better applied in a fluidized bed coater. The applied amount of the hydrophilic coating materials include ethyl cellulose, cellulose-acetate-propionate, methacrylic polymers, acrylic and methacrylic co-polymers, and polyalcohols (Conte et al., 1989). A marketed product of this class is SyncroDose™.

**System with Rupturable Coatings**

In place of swelling or eroding, these systems are dependent on the disintegration of the coating for the release of drug. The pressure necessary for the rupture of the coating can be achieved by the swelling disintegrants, effervescent excipients, or osmotic pressure.

An effervescent mixture of citric acid and sodium bicarbonate was incorporated in a tablet core coated with ethyl cellulose. The carbon dioxide gas generated after penetration of dissolution fluid into the core resulted in a pulsatile release of drug after rupture of the coating (Krögel et al., 1999). The lag time is controlled by the mechanical properties of the coating layer. It is reported that the weak and non-flexible ethyl cellulose film ruptured efficiently as compared to more flexible films. The lag time increases with increasing coating thickness and increasing hardness of the core tablet.

Superdisintegrants based on principle of swelling were used to design a capsule-based system comprising a drug, swelling agent, and rupturable polymer layer (Bussem et al., 1999) Examples of superdisintegrants include cross carmelllose sodium (CCS), sodium starch glycollate (SSG), and low substituted hydroxypropyl...
cellulose (L-HPC). These materials swell upon contact with dissolution fluid resulting in a complete film rupture followed by rapid drug release. The lag time is dependent on the composition of the outer polymer layer. The presence of hydrophilic polymer like HPMC reduced the lag time. The system can be used for delivery of both solid and liquid drug formulations. Literature shows reservoir system with a semipermeable coating for delivery of drugs that exhibit extensive first-pass metabolism. The release pattern was similar to that obtained after administration of several immediate-release doses (Amidon et al., 1993)

**Multiparticulate Systems**

Multiparticulate systems (eg, pellets, beads) offer various advantages over single-unit systems (Daumesnil et al., 1994). These systems have no risk of dose dumping, they provide flexibility of blending units with different release patterns, and provide reproducible and short gastric residence time. But the drug-carrying capacity of multiparticulate systems is lower due to presence of higher quantity of excipients. Such systems are a reservoir type with either rupturable or altered permeability coating and generally housed in capsular body.

**System Based on Rupturable Coating**

*Time-Controlled Explosion System: This type of system is multiparticulate system in which drug is loaded through coating on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer (Udea et al., 1989 and 1994). Superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycolate, L-hydroxypropyl cellulose are used as swelling agents. Coating polymers used are like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc are used. Alternatively, an effervescent system comprising a mixture of tartaric acid and sodium bicarbonate may also be used. Upon coming in contact with water, the swellable layer expands, resulting in rupture of film coat with subsequent rapid drug release. The release is independent of environmental factors like pH and drug solubility. The lag time depends on coating thickness and amounts and type of plasticizer incorporated in the outermost layer. A rapid release after the lag phase was achieved with increased concentration of osmotic agent. In-vitro studies of time-controlled explosion system (TCES) with an in-vitro lag time of three hours showed appearance of drug in blood after 3 hours, and maximum blood levels after 5 hours (Hata et al., 1994)*

**Osmotic-Based Rupturable Coating Systems**

*Permeability Controlled System: This system is based on a combination of osmotic and swelling effects. This system contains a core of the drug, a low bulk density solid and/or liquid lipid material (eg, mineral oil) and a disintegrants. This core is then coated with cellulose acetate. Upon immersion in 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 coating (Amidon et al., 1993).*

Another system is based on a capsule or tablet composed of a large number of pellets of different release pattern (Chen, 1996). Each pellet has a core that contains the therapeutic drug and a water-soluble osmotic agent coated with water-permeable, water-insoluble polymer film. A hydrophobic, water-insoluble agent that alters permeability (eg, a fatty acid, wax, or a salt of fatty acid) is incorporated into the polymer film. The film coating of each formulation differs from any other pellet coating in the dosage form in terms of rate of water influx and drug efflux. The osmotic agents dissolve in the water causing the pellets to swell, thereby regulating the rate of drug diffusion. The effect of each pellet population releasing its drug content sequentially provides a series of pulses of drug from a single dosage form. The coating thickness can be varied amongst the pellets. This system was used for the delivery of antihypertensive drug, diltiazem.

The use of osmotically active agents that do not undergo swelling is reported (Schultz et al., 1997). The pellet cores consist of drug and sodium chloride. These were coated with a semipermeable cellulose acetate polymer. This polymer is selectively permeable to water and is impermeable to the drug. The lag time increased with increase in the coating thickness and with higher amounts of talc or lipophilic plasticizer in the coating. The sodium chloride facilitated the desired fast release of drug. In absence of sodium chloride, a sustained release was obtained after the lag time due to a lower degree of core swelling that resulted in generation of small fissures.

A system containing a core of drug and osmotically active agent (sodium chloride) coated with an insoluble permeable membrane has also been proposed (Chen, 1993). The coating materials reported include different types of poly (acrylate-methacrylate) co-polymers and magnesium stearate, which reduces water permeability of the membrane, thus allowing for use of thinner films. Thicker films are to be avoided as they do not rupture completely. With use of ethyl cellulose as a
coating material, it was possible to affect lag time of enteric polymer to achieve rupturing after a predetermined time (Chen, 1993 and Fan et al., 2001).

**Delivery by Change in Membrane Permeability**

The permeability and water uptake of acrylic polymers with quaternary ammonium groups (e.g. Eudragit RS 30D) can be influenced by the presence of different counter-ions in the medium (Bodmeier et al., 1996). This ion exchange has been used to develop several delivery systems. Eudragit RS 30D is reported to be 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, and hence changes its permeability and allows water to permeate the active core in a controlled manner. This property is essential to achieve a precisely defined lag time. Theophylline as a model drug and sodium acetate were used to prepare the cores. These pellets were coated using Eudragit RS30D (10% to 40% weight gain) in four different layer thicknesses. A correlation between film thickness and lag time was observed. The result showed dramatic change in the drug permeability of the Eudragit film when even a small amount of sodium acetate was incorporated in the pellet core. After the lag time, interaction between the acetate and polymer increases the permeability of the coating so significantly that the entire active dose is liberated within a few minutes (Beckert et al., 1999).

The lag time depended on the 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.

**Sigmoidal Release System:** This consists of pellet cores containing drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type B (Guo et al., 1996). The lag time is controlled by the rate of water influx through the polymer membrane. The water dissolves succinic acid, and the drug in the core and the acid solution in turn increases permeability of the hydrated polymer film. In addition to succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid can be used. The increased permeability can be explained by improved hydration of film, which increases free volume. These findings were used to design a coated delivery system with an acid-containing core (Narisawa et al., 1994 and 1996). The in-vitro lag time correlated well with in-vivo data when tested in beagle dogs (Narisawa et al., 1995).

**Marketed Products**

A lot of work is being carried out to achieve pulsatile release so that the drug can be delivered according to circadian rhythms of our body. Advancis Pharmaceutical Corp., German town, Maryland, USA has developed once-a-day pulsatile delivery system called Pulsys®, this system enables the delivery of antibiotic amoxicillin in regular concomitant pulses. The rationale behind designing such a system is that it has been reported that antibiotics are more effective against fast-growing bacteria. When an immediate release antibiotic is administered, bacteria respond to it by going into a dormant stage, while the administration of a pulsatile system in such a case is more effective because the regular release of increased pulses of antibiotic does not allow defense system of the bacteria to go into a dormant stage. The preclinical studies have shown that pulsatile approach of delivering antibiotic is more effective. Another example is of a bronchodilator “Uniphyl” (theophylline) (Urwitz et al., 1987), which was developed by Purdue Pharmaceuticals Products L. P., Stamford, USA, and approved by FDA in 1989. It is a once-a-day formulation. When administered in the evening, it reaches to peak blood levels in the morning hours, resulting in improved lung functioning and relief to the patient.

There are examples where varying plasma levels are required during the day time. Elan applied this technology to a product of Novartis, Ritalin®, containing methylphenidate to get a pulsatile once-daily dosage form that replaces the twice-a-day regimen.

**Conclusion**

It can be concluded that pulsatile drug delivery systems offer a solution for delivery of drugs exhibiting chronopharmacological behavior, extensive first-pass metabolism, necessity of night-time dosing, or absorption window in GIT. A variety of systems based on single or multiple units are developed for pulsatile release of drug. One major challenge will be to obtain a better understanding of the influence of the biological environment on the release performance of pulsatile delivery systems in order to develop simple systems based on approved excipients with a good in vitro-in vivo correlation.

**References**


