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Review Article

Pulsatile Drug Delivery System (PDDS): An Overview

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ABSTRACT

Pulsatile Drug Delivery systems (PDDS) 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. System has to be developed to deliver drug according to circadian behavior of diseases. . A pulsatile drug release, where the drug is released rapidly after a well-defined lag-time, could be advantageous for many drugs or therapies. The potential benefits of chronotherapeutics have been investigated and established for number of diseases like asthma, arthritis, cancer, diabetes, epilepsy, hypertension, ulcer, and hypercholesterolemia. This drug delivery system is programmed drug delivery system in harmonization with body clock. The pulse has to be designed in such a way that a complete and rapid dug release is achieved after the lag time. Various capsular, osmotic, single and multiple unit systems that are modulated by soluble or erodible polymer coatings, rupturable membranes are available in market. 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. These systems are beneficial for diseases showing chronopharmacological behavior. These systems also improve patient compliance by decreasing dosing frequency.

INTRODUCTION

With the advancement of the technologies in the pharmaceutical field, drug delivery systems have drawn an increasing interest over the last few decades. Nowadays, the emphasis of pharmaceutical research is turned towards the development of more efficacious drug delivery systems with already existing molecule rather going for new drug discovery because of the inherent hurdles posed in drug discovery and development process [1]. The oral controlled release system shows a typical pattern of drug release (Fig. 1) in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action.

Various Modified Release Drug Products [2]:

Extended Release*:* It leads to two fold reductions in dosing frequency compared to immediate release dosage forms.

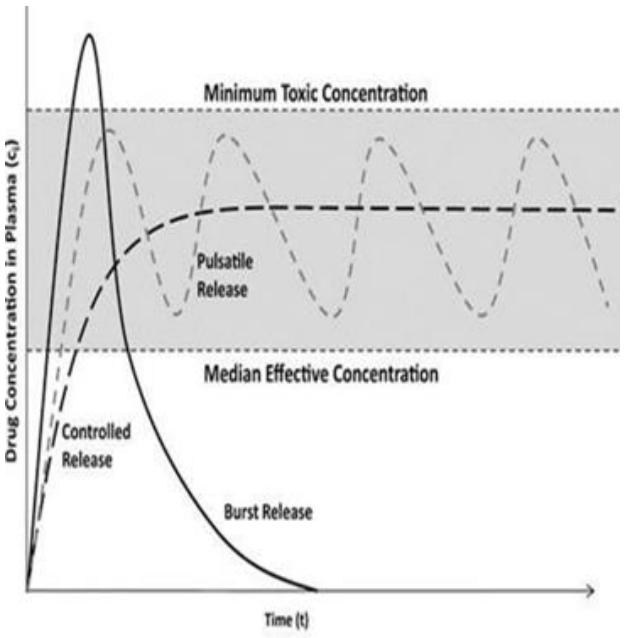

Figure 1: Plasma Concentration Drug Release Profile

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Controlled Release: This system allows slow drug release over extended period of time but not at predetermined rate.

Sustained Release: This system delivers drug at predetermined rate over a long period.

Delayed Release*:* This dosage form releases discrete portion of drug at a time other than readily after administration, although one portion may be released promptly after administration.

Targeted Release*:* These delivery systems deliver drug at or near the intended site of action and may have extended release characteristics.

Repeated Action*:* This product is designed to release first dose initially, followed by second dose of drug at a later time.

Prolonged Action*:* This dosage form releases drug slowly and provide continuous supply of drug over an extended period.

For many of the drugs, use of such systems is not suitable because of a number of reasons. This is particularly true in cases where the drug is subjected to large metabolic degradation. Due to 'first pass effect' there will be reduction in the bioavailability of the drug because; gradual release can result in greater degradation. Secondly drugs with short half-life need to be administered.

Pulsatile Drug Delivery Systems

A Pulsatile drug delivery system delivers drug in rapid and burst manner within a short time period immediately after a programmable lag phase. There are many situations where drug is needed to be released immediately (after bursting the delaying film coat) at specific site. These situations, therefore, compel designing a delayed fast release systems. These systems are mainly appropriate for drugs that are metabolized to pharmacological active compounds, drugs which have long *in vivo* half-lives showing an inherently prolonged duration of action, drugs with very short *in vivo* half-life which require a prohibitively large amount of active ingredients in dosage form, drugs which are required in large doses for therapeutic effect and drugs which are required in very low dose. Additionally a delayed burst release can also be utilized for enhancing absorption, reducing side effects, increasing and decreasing dose.

Diseases where a constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of "Pulsatile Drug Delivery Systems" [3]. In these systems, there is rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off release period (Fig. 2)**.** Various techniques are available for the pulsatile delivery like pH dependent systems, time dependent systems, micro-flora activated systems, etc. which can be designed as per the physiology of disease and properties of the drug molecule. The focus of the present review is primarily on the pulsatile drug delivery methodologies and the upcoming technologies, which are being exploited on an industrial scale.

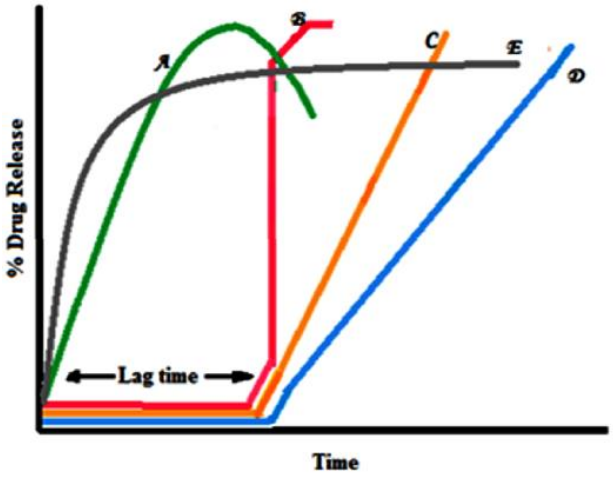

Figure 2: Drug Release Profiles from Pulsatile Drug Delivery System.
Where, A: Conventional release profile, B: Burst release of drug as a after a lag time, C: Delayed release profile after a lag time, D: Constant release profile in prolonged period after a lag time, E: Extended release profile without lag time.

Advantage of Pulsatile Drug Delivery System [4, 5]:

There are many advantages of pulsatile dosage form over conventional dosage form.

- Increases absorption and bioavailability than conventional immediate release or sustained release drug due to its ability to release drug in a burst manner, at target site of absorption.
- Site targeting allows delivery of poorly bioavailable drugs that would get destroyed in higher GI tract environment. e.g. (peptide and protein molecules)
- Reduces dose of drug without decrease in therapeutic effects.

- Decreases side effects.
- Decreases drug interaction due to lower cytochrome P450 isoenzymes.
- Decreases food effect (change occurring in bioavailability of drug when given with food).
- Improved compliance.
- Chronotherapy, programmed delayed release provides optimal treatment of diseases.
- Pulse release allows multiple dosing in a single dosage form.
- Allows site specific release for local treatment of diseases. Drug release is not affected by change in pH of the gastrointestinal tract, viscosity of lumen contents, and agitation rate of GI tract.

The system can be utilized for many solid dosage forms like granules, microspheres, microparticles, tablets, capsules, and pellets.

Drawbacks:

- Lack of manufacturing reproducibility and efficacy.
- Large number of process variables.
- Multiple formulation steps.
- Higher cost of production.
- Need of advanced technology.
- Trained/skilled personal needed for manufacturing

Diseases Requiring Pulsatile Drug Delivery:

Thorough understanding of the disease physiology is required before designing the pulsatile drug delivery system. A disease where rhythmic circadian organization (Fig. 3) of the body plays an important role, pharmacokinetics and/or pharmacodynamics of the drugs is not constant within 24 h [6]. Table 1 enumerates various diseases showing such a chronological behavior. Asthma is one such disease where pulsatile drug delivery system can be useful. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. In case of cardiovascular diseases, several functions (e.g. BP, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms.

For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood [7]. Circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance in case of insulin substitution in type 1 diabetes has been well exploited.

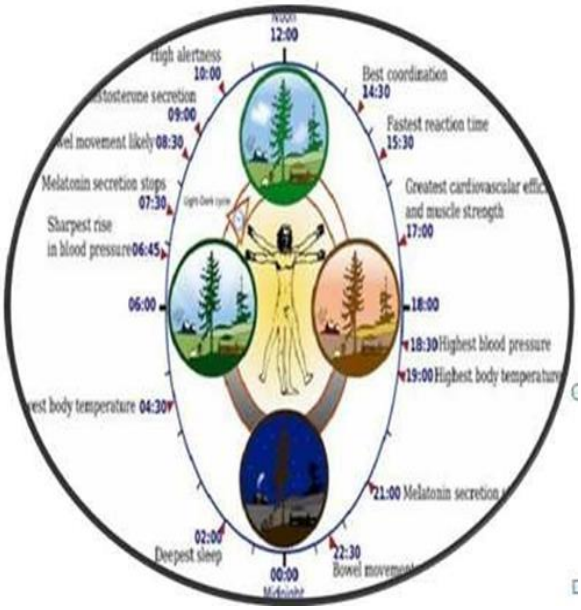

Figure 3: Cycle of Circardian Rhythm

Table 1: Diseases requiring Pulsatile Drug Delivery

DISEASE	CHRONOLOGICAL BEHAVIOR	DRUGS USED
Peptic Ulcer	Acid secretion is high in the afternoon and at night	H2 blockers
Asthma	Precipitation of attacks during night or at early morning hour	β2agonist, Antihistaminic
Cardiovascular Diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period	Nitroglycerin, Calcium channel blockers, ACE inhibitors etc.
Arthritis	Pain in the morning and more pain at night	NSAIDs,
Diabetes Mellitus	Increase in the blood sugar level after meal	Glucocorticoids, Sulfonylurea, Insulin, Biguanide
Attention Deficit Syndrome	Increase in DOPA level in afternoon	Methylphenidate
Hyper Cholesterolemia	Cholesterol synthesis is generally higher during night than during day time	HMG-CoA reductase inhibitors

Furthermore diverse directions of circadian changes in lipid fractions in patients and normal subjects may contribute to alteration in the rhythmicity of other metabolisms and in the blood coagulation system, thus leading to various complications. A circadian rhythm occurs during hepatic cholesterol synthesis. In case of arthritis there is a circadian rhythm in the plasma concentration of C- reactive protein and interleukin-6 of patients with rheumatoid arthritis [8].

Polymers Used In Pulsatile Drug Delivery System

Pulsatile drug delivery systems are required for applications in which the continuous release of a drug would be detrimental and repeated dosing would be difficult, painful or otherwise problematic. A key example is insulin delivery for the treatment of diabetes. For effective management, insulin release levels need to be generally very low but significantly elevated after meals. Additional examples of the desirability of pulsatile drug delivery include the delivery of blood pressure medications and immunization boosters, and many hormone treatments. Pumps have been successfully used for pulsatile drug delivery and are now used for many diabetic patients. However, these suffer from a number of limitations, most notably the need to run tubing across the skin, which produces pathways for infection. Completely implantable systems would reduce this risk.

The system proposed by Langer and co-workers exploits the wide tailor ability of biodegradation of the poly (lactic-*co*-glycolic acid) (PLGA) family of biocompatible polyesters. By varying the relative amounts of lactic acid and glycolic acid in the copolymer and also the molecular weight of the copolymer, one can controllably and widely vary the degradation rate of the material. To release bursts of drug at different times, several PLGA copolymers with different degradation rates were used as 'gatekeepers'. Each copolymer was designed to hold back a burst of drug until that particular membrane had degraded sufficiently to allow the drug to escape. With this system, Langer and colleagues were able to achieve pulsatile release of several types of 'model drugs' with different properties. The drug-delivery system is based on a microchip formed from poly lactic acid, the most slowly degrading of this polyester family.

Classification of Pulsatile Drug Delivery 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, beads) systems.

Single-Unit Systems:

- ❖ Capsular systems
- ❖ Capsular system based on osmosis
- ❖ Pulsatile system with erodible or soluble barrier coating
- ❖ Pulsatile system with rupturable coating

Multiple-Unit Systems:

- ❖ Pulsatile system based on rupturable coating
- ❖ Osmotic-based rupturable coating systems
- ❖ Pulsatile delivery system by change in membrane permeability

Single Unit System:

Capsular Systems:

Pulisincap System

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 [9]. Pulsincap (Fig. 4) 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. 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.

- Insoluble but permeable and swellable polymers (e.g., polymethacrylates)
- Erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, Polyethylene oxide)
- Congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate)
- Enzymatically controlled erodible polymer (e.g., pectin).
- The Pulsincap™ device consists of impermeable capsule body containing drug sealed in the capsule with a plug made of

hydrogel. This plug swells in GI fluid and exits away releasing drug after a defined lag time that is controlled by thickness of hydrogel plug. Alternative to Pulsincap plug is erodible tablet [10].

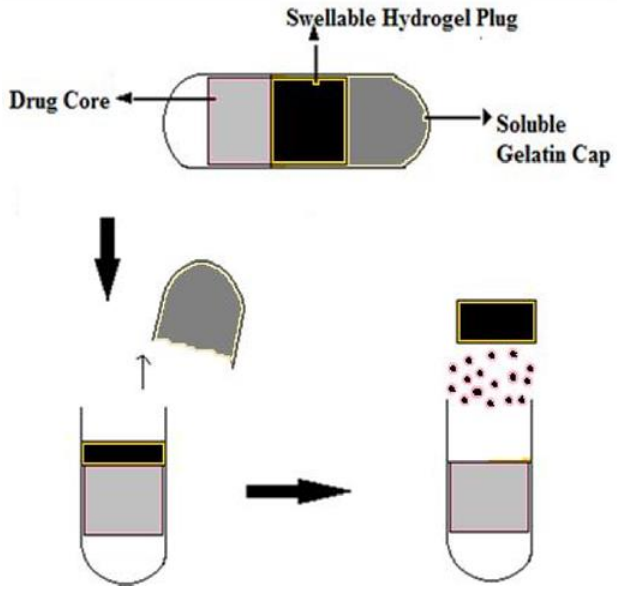

Figure 4: Design of a Pulsincap System

Capsular System Based on Osmosis:

'PORT' System

The Port system (Fig.5) was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA, and consists of a capsule coated with a semi permeable membrane.

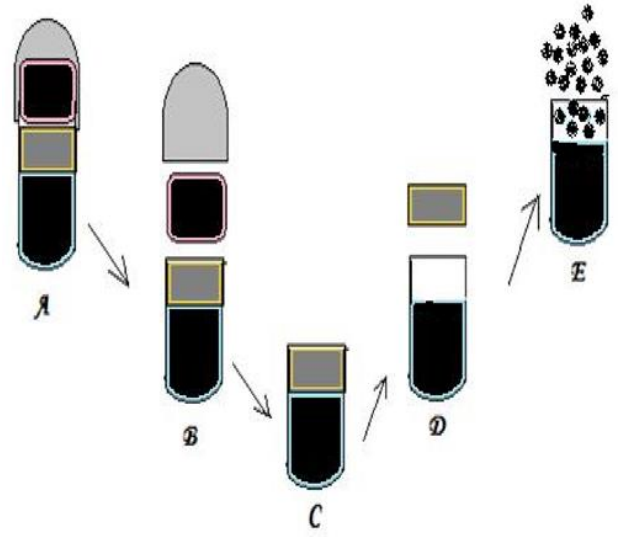

Figure 5: Drug Release Mechanism from Port System

Where, A: Port System, B: Swelling of cap with release of 1st dose, C: Permeation of more GI fluid with generation of Internal pressure, D: Expulsion of Time Released Plug, E: 2nd released in Pulsed or sustained form.

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. 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 [11].

System Based on Expandable Orifice

To deliver the drug in liquid form, an osmotically driven capsular system was developed in which the liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semipermeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved. This system has combined benefit of extended release with high bioavailability. Delivering drug in liquid form is suitable for insoluble drugs, polypeptides and polysaccharides [12]. The capsular system delivers drug by the capsule's osmotic infusion of moisture from the body (Fig 6). The capsule wall is made up of an elastic material and possesses an orifice.

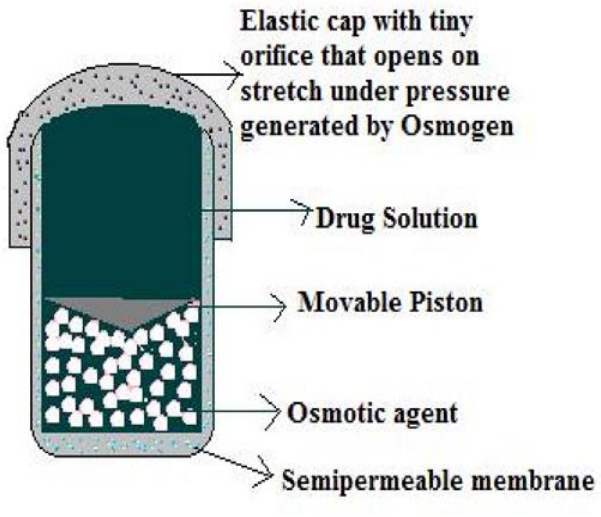

Figure 6: System Based on Expandable Orifice

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 threshold value, the orifice expands sufficiently to allow drug release at a

required rate. For example, elastomers, such as styrene-butadiene copolymer have been suggested. Pulsatile release was achieved after lag times of 1 to 10 hrs, depending on the thickness of the barrier layer and that of semipermeable membrane. A capsule designed for implantation can deliver drug intermittently at intervals of 6 hours for 2 days [13].

Delivery by Series of Stops

This system is for implantable capsules. The capsule contains a drug and water-absorptive osmotic engine that are placed in compartments separated by a movable slider that provides pulsatile release of 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. The number of stops and the longitudinal placements of the stops along the length of the capsule dictate the number and frequency of the pulses, and the configuration of the partition controls the pulse intensity. This system was used to deliver porcine somatotropin [14].

Pulsatile Delivery by Solubility Modulation

Solubility modulator of system provides pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate that contained sodium chloride as 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 275mg/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. 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. After the period of zero-order release, the drug is delivered as one large pulse [15].

Pulsatile System with Erodible or Soluble Barrier Coating:

Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly. The lag time depends on the thickness of the coating layer. The Time Clock® system shown in (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 polyoxyethylene sorbitan monooleate. This coat erodes or emulsifies in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion. In a study with human volunteers, it was shown that the lag time was independent of gastric residence time, and the hydrophobic film redispersion did not appear to be influenced by the presence of intestinal enzymes or mechanical action of stomach or gastro-intestinal pH. The lag time increased with increasing coating thickness. Such systems are better suited for water- soluble drugs. The major advantage of this system is its ease of manufacturing without any need of special equipment. However, such lipid-based systems may have high *in-vivo* variability (e.g., food effects) [16, 17]. The possible problems of erosion controlled systems include a premature drug release when the penetrating water dissolves the drug, which diffuses out through the barrier layers, and sustained release after the lag phase when the barrier layer is not eroded or dissolved completely, thereby retarding the drug release.

Multilayered Tablet

A release pattern with two pulses was obtained from a three-layered tablet containing two drug containing layers separated by a drug-free gellable polymeric barrier layer. This three-layered tablet was coated on three sides with in impermeable ethyl cellulose, and the top portion was left uncoated. Upon contact with dissolution medium, the initial dose incorporated into the top layer was released rapidly from the noncoated surface. The second pulse was obtained from the bottom layer after the gelling barrier layer of HPMC was eroded and dissolved. The rate of gelling and/or dissolution of the barrier layer control the appearance of the second pulse. The gelling polymers reported include cellulose derivatives like HPMC, methyl cellulose, or polyvinyl alcohols of various molecular weights and the coating materials include ethyl cellulose, cellulose-acetatepropionate, methacrylic polymers, acrylic and methacrylic co polymers, and polyalcohols [18, 19].

***Pulsatile System with Rupturable Coating*:**
In contrast to the swellable or erodible coating systems, these systems depend 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 effervescent excipients, swelling agents, 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 developed after penetration of water into the core resulted in a pulsatile release of drug after rupture of the coating. The release may depend on the mechanical properties of the coating layer. It is reported that the weak and non-flexible ethyl cellulose film ruptured sufficiently as compared to more flexible films. The lag time increases with increasing coating thickness and increasing hardness of the core tablet. The highly swellable agents, also called super disintegrants, were used to design a capsule-based system comprising a drug, swelling agent, and rupturable polymer layer. Examples of superdisintegrants include cross carmellose, sodium starch glycollate, and low substituted hydroxypropyl cellulose. 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 reduced the lag time. The system can be used for delivery of both solid and liquid drug formulations. A reservoir system with a semipermeable coating was designed 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 [20, 21].

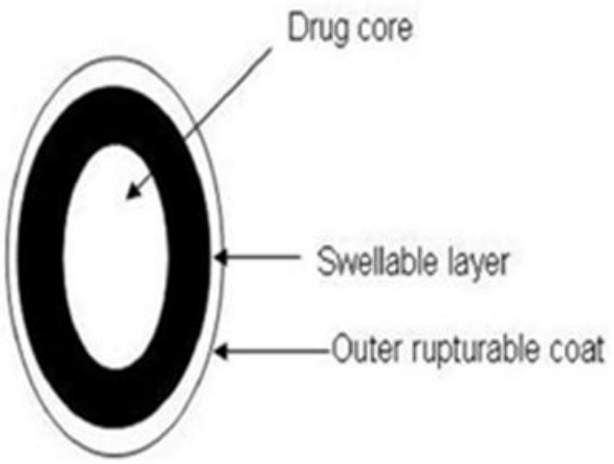

Figure 7: Schematic Diagram of Delivery Systems with Rupturable Coating Layer

Multiple - Unit Systems:
Multiple systems (e.g., pellets, beads) offer various advantages over single unit systems. These include no risk of dose dumping, flexibility of blending units with different release patterns, and reproducible and short gastric residence time. But the drug carrying capacity of multiple systems is lower due to presence of higher quantity of excipients. Such systems are invariably a reservoir type with either rupturable or altered permeability coating.

Pulsatile System Based on Rupturable Coating:
Time-Controlled Explosion System
This is a multiple system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer. The swelling agents used include superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L- hydroxypropyl cellulose, polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc. Alternatively, an effervescent system comprising a mixture of tartaric acid and sodium bicarbonate may also be used. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The release is independent of environmental factors like 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 was achieved with increased concentration of osmotic agent. *In vivo* 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 [22, 23].

Osmotic-Based Rupturable Coating Systems:
Permeability Controlled System:
This system is based on a combination of osmotic and swelling effects. The core containing the drug, a low bulk density solid and/or liquid lipid material (e.g., mineral oil) and a disintegrant was prepared. This core was 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. Another system is based on a capsule or tablet composed of a large number of pellets consisting of two or more pellets or parts (e.g., populations). Each pellet has a core that contains the therapeutic drug and a water-soluble osmotic

agent. Water-permeable, water-insoluble polymer film encloses each core. A hydrophobic, water-insoluble agent that alters permeability (e.g., a fatty acid, wax, or a salt of fatty acid) is incorporated into the polymer film. The rate of water influx and drug efflux causes the film coating of each population to differ from any other pellet coating in the dosage form.

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 was reported by Schultz and Kleinebudde. The pellet cores consisted of drug and sodium chloride. These were coated with a semi-permeable 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 [24].

Pulsatile Delivery System 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. Several delivery systems based on this ion exchange have been developed. 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, thereby changing its permeability and allowing water to permeate the active core in a controlled manner. This property is essential to achieve a precisely defined lag time. The cores were prepared using theophylline as model drug and sodium acetate. 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. It was found that even a small amount of sodium acetate in the pellet core had a dramatic effect on the drug permeability of the Eudragit film. 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. 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 [25].

Sigmoidal Release System

This consists of pellet cores comprising drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type B. 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. The *in- vitro* lag time correlated well with *in-vivo* data when tested in beagle dogs [26, 27].

Table 2: Marketed Technologies of Pulsatile Drug Delivery

Technology	Mechanism	Proprietary name and Dosage form	API	Diseases
OROS®	Osmatic mechanism	Covera-HS ®: XL Tablet	Verapamil HCL	Hypertension
Three Dimensional printing®	Externally regulated system	Theirform®	Diclofenac sodium	Inflammation
CODAS®	Multi-particular pH dependent system	Verelan® PM : XL release capsule	Verapamil HCL	Hypertension
PULSINCAP®	Rupturable system	Pulsincap®	Dofetilide	Hypertension

CONCLUSION

Oral drug delivery is the largest, oldest, and most preferred route of drug delivery. Universally sustained and controlled-release products provide a desired therapeutic effect, but fall for diseases following biological rhythms. Circadian disorders such as asthma, osteoarthritis, RA, cholesterol synthesis, etc., require chronopharmacotherapy. Pulsatile drug delivery can effectively crack this problem as it is modulated according to body's circadian clock giving release of drug after a specified lag time. During the last two decades, technologies to ensure time controlled pulsatile release of bioactive compounds have been developed. A significant progress has been made toward achieving pulsatile drug delivery system that can effectively treat diseases with nonconstant dosing therapies. Various pulsatile technologies are researched and brought in the market, which surely assure a bright and promising future.

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