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A review on: Pulsatile drug delivery system

Jyotsana K. Deshmukh* and Vidya Sable

Department of Pharmaceutics and Pharmaceutical Quality Assurance, Dadasaheb Balpande College of Pharmacy, Besa, Nagpur, MS, India

Abstract

In present time advancement are going on to develop modified dosage form i.e. sustain release, controlled release and extended release dosage form formulation to improve the therapeutic treatment, to improve patient convenience and compliance toward drug therapy. The recent studies, it was found that number of normal body function and disease condition show the chronobiological behavior. It was found that occurrence of diseases like asthma, peptic ulcers, cardiovascular diseases, diabetes mellitus, attention deficit syndrome in children, etc. Pulsatile drugs delivery systems are gaining lots of importance because it provides the delivery of drug at specific time, at specific amount and at specific site. Various systems like capsular, osmotic, and single and multiple unit systems that are modulated by soluble or erodible polymer coatings, Rupturable membranes are available in market. pulsatile drug delivery systems have the potential to bring new developments in the therapy of various diseases.

Keywords: Pulsatile, Lag Time, Chronobiology, Circadian Rhythm, Polymers, Technology, Classification.

***Correspondence Info:**
Jyotsana K. Deshmukh
Department of Pharmaceutics and Pharmaceutical Quality Assurance,
Dadasaheb Balpande College of Pharmacy,
Besa, Nagpur, MS, India

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1. Introduction

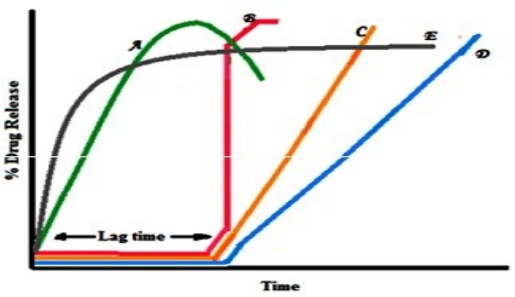
Pulsatile drug delivery system is gaining a lot of interest as the drug is released completely after defined lag time [1]. Pulsatile drug delivery is a lag of time and specific-site of action in drug delivery, thus providing spatial and temporal delivery and increase patient compliance [2]. This is defined as the rapid and burst manner within a very short time period immediately after a predetermined off-released period, i.e., lag time [3]. These systems are drugs which have long *in vivo* half lives showing an inherently prolong duration of action, drugs with very short in vivo half-life which require a proscriptive a large amount of active ingredients in dosage form, drugs which are required in large doses for therapeutic effect[4]. Additionally a delayed burst release can be utilized for enhancing absorption, reducing side effects, increasing and decreasing dose [5].

PDDS are suitable for diseases which are regulated by circadian rhythm of body and where drug dose is essential during sleep, drugs having greater first pass metabolism and absorption at precise location in digestive tract [6]. PDDS tries to correlate systemic availability of drug with the biological rhythm of disease for better therapeutic benefits [7].

Drug Release Profiles from Pulsatile Drug Delivery System [8]

Drug release profile from pulsatile drug delivery system is given fig 1.

Fig. 1: Drug release profiles of pulsatile drug delivery system



Where, A: Conventional release profile, B: Sigmoidal release after lag time, C: Delayed release after a lag time, D: Constant release in prolonged period after a lag time, E: Extended release without lag time.

2. Chronotherapeutic drug delivery system:

The term "chronopharmaceutics" consist of two wards chronobiology and pharmaceutics. In case of chronobiology, biological rhythms and their mechanisms that drive them. Chronobiologyis the science concerned with the biological mechanism of the diseases of the diseases according to a time structure. "chrono'' related to time and "biology" relates to the science of life.

There are four types of biological rhythms which control normal and disease related physiology of the body [9-13].

1) **Circadian:** This word comes from Latin word "circa" means about and "dies" means day. In case of circadian rhythm, the oscillation completed in 24 hrs. For e.g. sleeping and waking patterns.
2) **Ultradian:** In case of ultradian rhythm, the oscillations completed in a shorter duration i.e less than 24 hrs. For e.g. Milliseconds take in a neuron to fire or a 90 minute sleep cycle.
3) **Infradian:** In case of infradian rhythm, the oscillation completed in more than 24 hrs. (Less than one cycle per day). For e.g. 90 minutes sleep cycle.
4) **Seasonal:** In the short days of winter, seasonal affective disorder (SAD) causes depression for susceptible people.

Circadian rhythm is the main rhythm in the body which maintains all the physiological, chemical, biological, and behavioural processes [14].

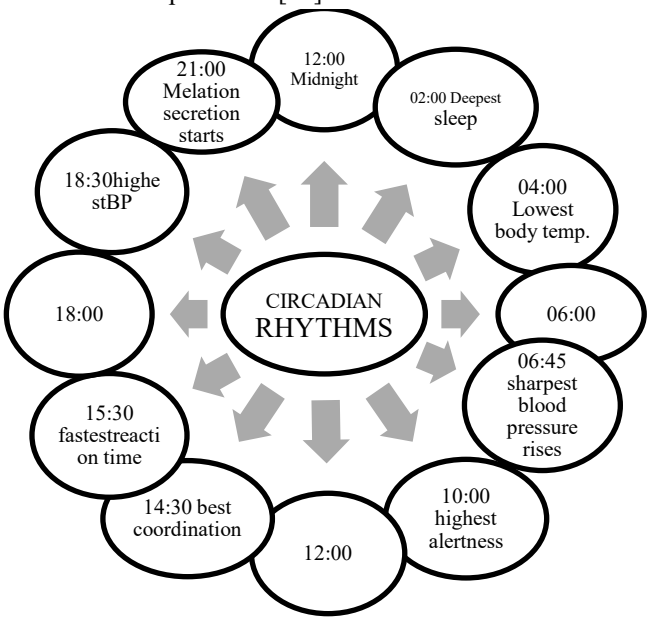


Fig.2: Cycle of Circadian Rhythms

2.1 Advantages of pulsatile drug delivery [15-18]

1) Extended daytime or night-time activity.
2) Reduced side effects.
3) Reduced dosage frequency.
4) Reduction in dose size.
5) Improved patient compliance.
6) Drug targeting to specific site like colon.
7) Protection of mucosa from irritating drugs.
8) Increases absorption and bioavailability than conventional immediate release or sustained release drug due to the ability to drug release in a burst manner, at target site of action.
9) Site targeting allows delivery of poorly bioavailable drugs that would get destroyed in higher GI tract environment e.g. (peptide and protein molecules).
10) Reduces dose of drug without decrease in therapeutic effects.
11) Decreases drug interaction due to lower cytochrome P450 is enzymes.
12) Decreases food effect (change occurring in bioavailability of drug when given with food).
13) Limited risk of local irritation.
14) No risk of dose dumping.
15) Flexibility in design.
16) Improve stability.

2.2 Disadvantages of PDDS [19]

1) Low drug loading.
2) Lack of manufacturing reproducibility and efficacy.
3) Large number of process variables.
4) Higher cost of production.
5) Need of advanced technology.
6) Trained/skilled personnel needed for manufacturing.
7) Proportionally higher need for excipients.
8) Difficult to manufacture and it is costly.

2.3 Needs of pulsatile drug delivery system[20-24]

1) **First Pass Metabolism:** Drugs, such as beta blockers and salicylamide, undergo substantial first pass metabolism and there will be reduction in the bioavailability of the drug require fast metabolizing enzymes in order to minimize pre-systemic metabolism. Thus a controlled/sustained oral method of drug delivery would result in reduced oral bioavailability.
2) **Biological Tolerance:** Drugs that produce biological tolerance demand for a system that will prevent their continuous exposure of a drug presence in the biophase as this tends to reduce their therapeutic effect.
3) **Special Chronopharmacological Needs:** Circadian rhythms are seen at specific time in 24 hrs for particular disease such as asthma and angina. This potentiates to the development & role of PDDS formulations in which work according to circadian rhythms.
4) **Local Therapeutic Need:** The treatment of local disorders such as an inflammatory bowel diseases, the drug of a compounds to the specific site for inflammation with no loss due to absorption for the small intestine is highly desirable to achieve the therapeutic effect.
5) **Gastric Irritation:** Protection from gastric irritation or chemical instability in gastric fluid, these are 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.

Diseases requiring pusatile drug delivery system [25-28]

Table 1: Diseases Requiring Pulsatile Drug Delivery System

Disease	Chronological behavior	Drugs used
Asthma	Precipitation of attacks after night or at early morning hours	B2 agonist, Antihistaminic
Peptic ulcer	Acid secretion high in afternoon and at night	H2 blockers
Cardiovascular diseases	BP is at its lowest during sleep cycle at higher in the morning awakening period	Calcium channel blokers, ACE inhibitors, nitroglycerin, etc.
Arthritis	Pain in the morning and more pain at night	$NSAID_S$, Glucocortioids
Diabetes mellitus	Increase in the blood level after meal	Sulfonylurea, insulin, Biguanide
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during night than during day time	HMG Co-A reductase enzyme
Angina pectoris	Chest pain and ECG changes more common in early morning	Anti anginal drugs
Stroke	Incidence higher in the morning	-
Myocardial infraction	Incidence higher in the early morning	Cardiovascular agents
Osteoarthritis	Symptoms worse in the middle /later portion of the day	$NSAID_S$
Allergic rhinitis	Worse in the morning /upon rising	Antihistamines
Hormone secretion	Growth hormone and melatonin produced at night testosterone and cortisol at morning hrs.	Corticosteroids
Sudden cardiac death	Incidence higher at the morning after awakening	-

3. Classification of PDDS [29]:

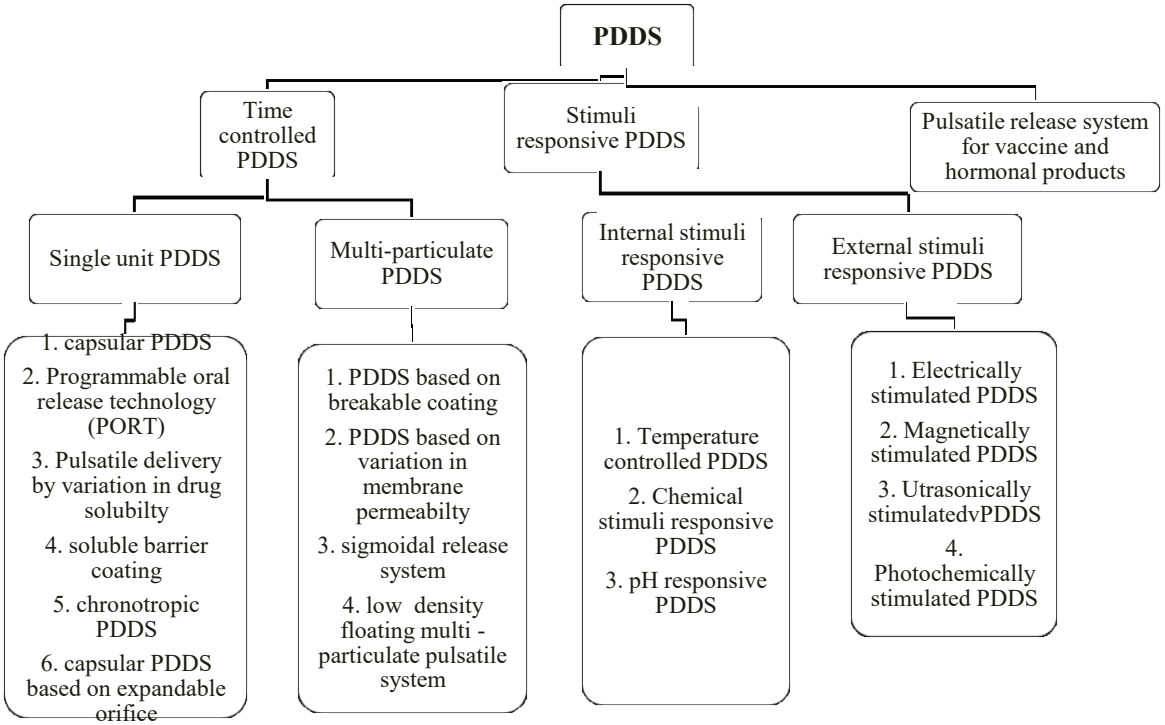


Fig.3: Classification of Pulsatile Drug Delivery System.

3.1 Time controlled PDDS:

In the development of time controlled PDDS, drug release is optimized after a definite time period, which mimics the circadian rhythm. This category of PDDS generally comprises the drug in two components; one is instant release type and second is a pulse release type. In time controlled PDDS, [30] release of drug is strictly controlled by the system. The drug release does not depend on the biological environment of the GIT. Delivery systems containing erodible coating layer. Bulk-eroding system. Bulk erosion that is the ingress of water is faster than the rate of degradation. In this case, degradation take places throughout the polymer sample and proceeded until a critical molecular weight is reached. At this point, degradation products become smaller enough to be solubilised and the structure starts to become significantly more porous and hydrated[31]. A number of research groups have investigated purposed formulation by using this system.Surface eroding system. In this type of system, the reservoir devices is coated with soluble or erodible layer, which dissolves with time and releases the drug after a specified lag periodof time[32].

3.1.1 Single Unit PDDS:

3.1.1.1 Capsular Systems:

Single-unit systems are mostly developed in capsule form. A general structure of such systems consists of an insoluble capsule bodyhousing a drug and a plug. The plug is removed after a predetermined lag time owing to swelling, erosion, or dissolution[33]. The lag time is controlled by a plug,which gets pushed away by swelling or erosion, releasing thedrug as a pulse from the insoluble body. Polymers used for designing and development of the hydrogel plug includes[34-36]:

1) Insoluble but permeable and swellable polymers e.g., polymethacrylates
2) Erodible compressed polymers e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, Polyethylene oxide
3) Congealed melted polymers e.g., saturated polyglycolated glycerides, glyceryl monooleate
4) Enzymatically controlled erodible polymer e.g., pectin.

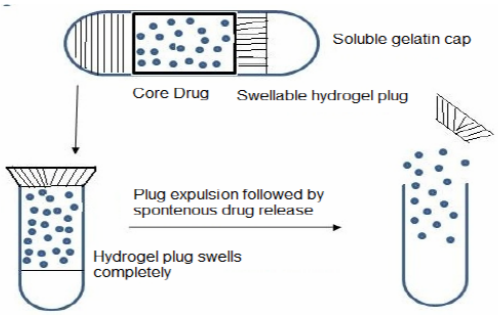


Fig. 4: Capsular System.

3.1.1.2 Port System (Programmable Oral Release Technology):

This system is a gelatin capsule coated with a semi permeable membrane (e.g., cellulose acetate) housing an insoluble plug consisting of osmotically active agent and the drug formulation [37]. (e.g. lipidic). Upon contact with the dissolution liquid, the semipermeable membrane of capsule allows the entry of water,which creates the pressure inside the capsule which led to discharge of the insoluble plug after a lag time[38].

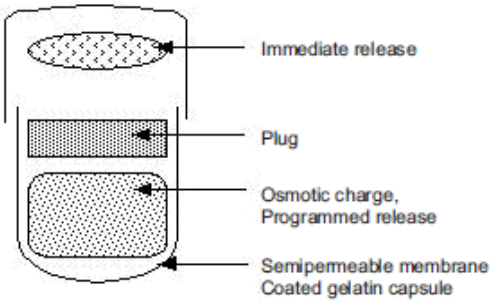


Fig. 5: Port System (Programmable Oral Release Technology)

3.1.1.3 Pulsatile Drug Delivery By Modulating Solubility

Magruder developed system consist of various solubility modulators. The system is used for anti-histaminic drug like salbutamol sulphate[39]. Composition contains salbutamol sulphate and modulating agent sodium chloride. The amount of sodium chloride required is less than the amount needed to maintain the saturation fluid enters in osmotic device. It gives pulse release[40].

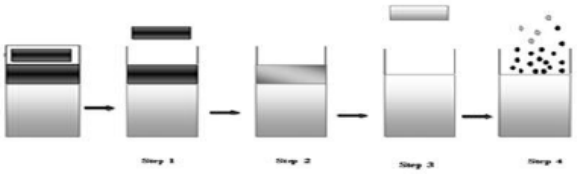


Fig. 6: Modulating Solubilty

3.1.2 Delivery By Reservoir Systems With Erodible Or Soluble Barrier Coatings

In this type of time controlled pulsatile release device the drug reservoir is coated with a barrier layer.After its dissolution or erosion of that barrier drug is released from the reservoir.this barrier corrodes or dissolves after a specific lag period, and the drug is afterward released rapidly from reservior core. The lag time depends on the thickness of coating layer[41].

i. Delivery Systems With Rupturable Coating Layer

These systems depend on the disintegration of the coating layer for the release of drug. The pressure necessary for the rupture of the coating can be achievd by the effervescent excipients, swelling agents or osmotic pressure [42]. The film rupture may be attained by including swelling, osmotic or effervescent additives in the reservoir. For the lag time, major factors are mechanical resistance of the outer membrane[43].

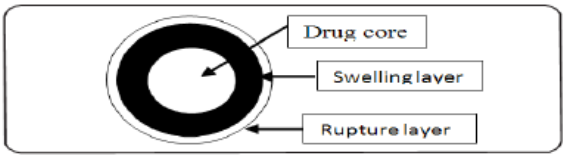


Fig. 7. Delivery Systems With Rupturable Coating Layer

ii. Delivery System With Erodible Coating Layer

Delivery systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing drug. The release of drug is depend upon the thickness of the outer coat so, time dependent releaseis obtained[44].

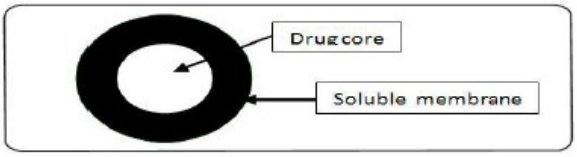


Fig. 6: Delivery Systems With Erodible Coating Layer

3.1.3 The Chronotropic System:

The Chronotropic system (Fig. 7) consists of a drug containing core coated by hydrophilic swellable HPMC that produces lag phase in the onset of release[45].

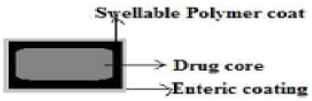


Fig.7: Chronotropic systems

3.1.4 System Based On Expandable Orifice:

The osmosis proceeds,the pressure within the capsule raises, causing the wall to stretch. The drug deliver in a form of liquid, 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 reinforced by an expanding osmotic layer after the barrier layer is dissolved (Figure 6)[46]. The orifice is small adequate so that when the elastic wall relaxes, the flow of the drug through the orifice essentially stops, but when the elastic wall is expanded further on threshold value, the orifice expands sufficiently to allow drug release at a required rate. e.g. Elastomers, such as styrenebutadiene copolymer have been suggested[47].

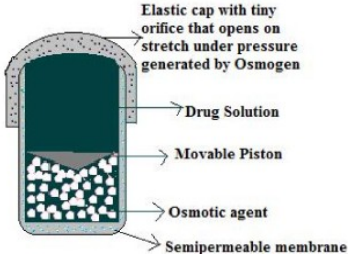


Fig. 8: System Based On Expandable Orifice

3.2 Multi-Particulate System:

This delivery systems are mainly oral dosage form are the multiplicity of small discrete units, each exhibiting some desired characteristics. the designing multiparticulate dosage form has a single unit dosage form. Its consisting of thousands spherical particles with diameter of 0.05-2.00mm [48]. Thus multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present in a number of small independent subunits. these are the system is less dependent on gastric empty ting, resulting in less inter and intra-subject variability in gastrointestinal transit time[49]. Their are also better distributed and less such as a local irritation. In the rupturable multiparticulate pulstile drug delivery system of drug containing inner core is layered by a swellable layer and water insoluble polymer membrane in a top layer. Upon water ingress, the swellable layer expanded resulting in film rupturing with subsequent rapid drug release. In case of hard/soft gelatin capsules the lag time and completeness of release was independent of capsules content and influenced remarkable by core composition in case of tablets [50].

The Properties of swelling layer as well as composition and thickness of the outer membrane are reported as major factors, affecting the rupturing and release parameters. These include no risk of dose dumping, flexibility of blending units with different release patterns, as well short and reproducible gastric residence time[51]. The rupturable multiparticulate pulsatile drug delivery system in a “time controlled explosion system". The drug is layered in a inner core, followed by a swellable layer and water insoluble polymer membrane as a top layer[52].

3.2.1 Reservoir Systems With Rupturable Polymeric Coating

The reservoir delivery systems are reservoir devices coated with a rupturable polymeric layer in depend upon water ingress, the drug is released from the core after rupturing is the surrounding polymer layer due to the pressure build-up within the system[53]. The pressure necessary to rupture the coating can be achieved by swelling agents, gas-producing effervescent excipients, or osmotic agent. Water permeation rate and mechanical resistance of the outer membrane are the key factors that decide the lag time period[54].

3.2.2 Time Controlled Expulsion System

These system based on the combination of osmotic and swelling effects. This core was then coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing lipid material. After the lag phase of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of coating [55].

3.2.3 Pulsatile Delivery By Change In Membrane Permeability

The delivery system change in membrane permeability and water uptake of acrylic polymers in quaternary ammonium groups can be influenced by in the different counter-ions in the medium. these are the several delivery systems depend on the ion exchange can be developed [56]. It contains positively polarized quaternary ammonium group with polymer side chain, In which is always accompanied by negative hydrochloride counter-ions. This property is essential to achieve a precisely defined as lag time. The cores were prepared by using theophylline as model drug and sodium acetate. These pellets were coated by using Eudragit RS30D (10% to 40% weight gain) in four different layer thicknesses[57].

3.2.4 Sigmoidal Release System

Sigmoidal release system is therapeutically effectivelly for timed release and colonic drug delivery, and observed in coated systems. The consist of pellets cores contaning drug and succinic acid coated with ammonio methacrylate copolymer was developed.the drug inside and the acid solution increase the permeabilty of the polymer film[58].

3.2.5 Low density floating multi-particulate pulsatile systems

Low density floating multiparticulate pulsatile dosage forms which are absorbed in stomach only and not affected by also pH, local environment or gastric emptying rate [59]. These are the dosage forms are specifically advantageous for drugs either absorbed in the stomach or requiring local delivery in stomach. In short time for multiparticulate pulsatile release dosage forms possessing gastric retention capabilities[60].

4. Stimuli responsive PDDS

4.1. Internal Stimuli Induced Pulsatile System

4.1.1 Temperature Induced System:

The temperature has important in pulsatile drug delivery. The temperature is rises above the physiological body temperature (37°C) in presence of pyrogens. Thermo responsive polymeric micelle systems[61]. The properties and biological interests of polymeric micelles makes them a mostlly use as drug carrier for the cancer treatment. This application is the temperature gradient induced an on-off drug release regulation from PIPAAm PBMA micelles between 4 and 378^0C[62].

4.1.2 Chemical Stimuli Induced System

4.1.2.1 Glucose-Responsive Insulin Release Devices

In a glucose that is the bloodstream after meal, the oxidation of glucose to gluconic acid catalysed by glucose oxidase can lower pH to approximately 5.8. Many systems are developed which are able to the respond to changes for glucose concentration. They prepared and nicotinamide-immobilized gel membranes[63].

4.1.2.2 Inflammation-Induced Pulsatile Release

When human beings receive as physical or chemical stress, such as injury, broken bones, etc., occurs the various inflammatory reactions takes place at injury site. At inflammatory sites phagocytic cells such as macrophages and polymorphonuclear cells, play role in healing process[64].

4.1.2.3 Drug Release From Intelligent Gels Responding To Antibody Concentration

There are bioactive compounds are present in body. if the concentration of these bioactive compounds change these are novel gels were developed which responded to the alter their swelling/deswelling characteristics[65].

4.1.3 PH Sensitive Drug Delivery System

The pH sensitive pulsatile drug delivery system are the approach to design chronotropic system to attain specified lag time period to the drug release by using pH dependent polymers[66]. This system advantage to exist in different pH environment at different parts of gastrointestinal tract. the pH dependent system is drug targeting at specific site of gastrointestinal tract. for e.g. polyacrylate and sodium carboxy methyl cellulose[67].

4.2 External Stimuli Induced System

Externally regulated system viz., magnetism, ultrasound, electrical effect and irradiation can be used as an alternative approach to release the drug in pulsatile drug delivery system. These types of open-loop systems are not self-regulated[68].

4.2.1 Electro Responsive Pulsatile Release

These technologies include iontophoresis, infusion pumps, and sonophoresis. Electric stimuli induced drug release system using the electrically stimulated swelling/ deswelling characteristic of polyelectrolyte hydrogels[69]. This depend upon the shape of gel which is lies parallel to the electrodes by using poly(acrylamide-grafted-xanthan gum) hydrogel for the transdermal drug delivery system[70].

4.2.2 Magnetically Stimulated Pulsatile System

In magnetically stimulated syetm, the magnetic field created by oscillating magnetic steel beads can be embedded in a polymer matrix with model drug. the alternatively creating compressive and tensile forces[71]. This in turn acts as a pump to push an increased amount of the drug molecule out the matrix. Magnetic carrier receive their magnetic response to a magnetic field from incorporated materials like that magnetite, iron, nickel, cobalt etc[72]. The use of an oscillating magnetic field to regulate the rates of drug release from polymer matrix was one of the first methodologies. the magnetic carriers must be water-based, biocompatible, non-toxic and non-immunogenic[73]. These are the possible by filling an additional magnetic component for the capsules or tablets are the speed traveling through the stomach and intestines can be slowed down at specific target site by an external magnet, thus changing the time and/ or extent of drug release into stomach or intestines[74].

4.2.3 Utrasound Induce Relese

Ultrasound is used as a enhancer for the improvement of drug permeation through biological barriers, such as skin. The interactions of ultrasound with biological tissues is divided into two broad caterories: thermal and non thermal effects.ultrasound waves on repeated exposure regulate the drug release by eroding the polymer matrix.pulsed drug delivery can be attained by the on-off application of ultrasound [75]. For e.g. Calcium alginate

4.2.4 Photochemically Stimulated PDDS

The pusatile drug deivery by light can be achieved the collaboration between light and material and that colabration is used as a marker for pulsatile drug delivery. Light sensitive hydrogels have apotential applications in developing optical switches, display units, and opthalmic drug delivery divices [76]. When hydrogel absorb the light and convert it to heat, raising the temperature of composite hydrogel above its LCST. Hydrogel collapses and result is an increased rate of release of soluble drug held within the matrix[77].

Figure 8: Mechanism of drug release from PDDS[78]

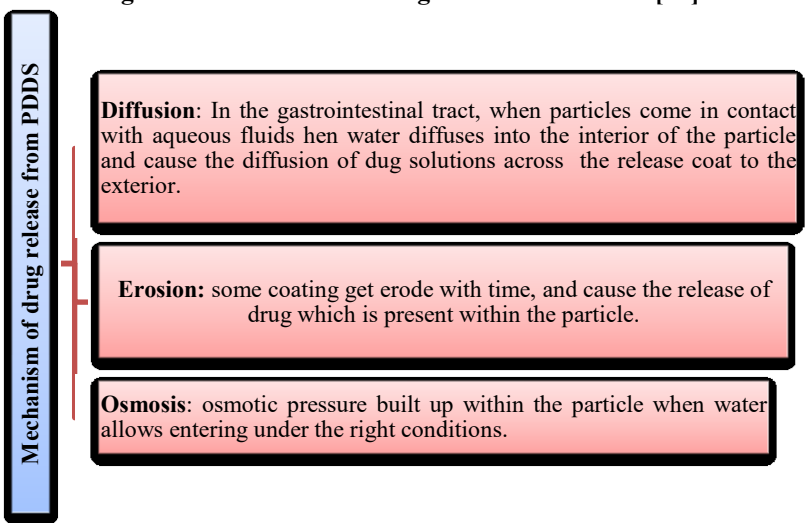


Table 3: Mechanism Of Drug Release From PDDS.

Advanced tecnologies of pdds and marketed product of pusatile drug delivery system[79-85]:

S. No	Technology	Description	API	Proprietary Name	Make	Diseases
1.	COER-24™	Controlled onset and extended release. It is osmotically controlled single unit system. It prevents that regulates absorption of water into the tablet by semipermeable membrane. And then second layer delay the passage of water into inner core. The third layer gives extended release. This system contains verapamil in which maintain blood pressure for 24 hrs.	Verapamil		Alza	
2.	Port® system	Programmable oral drug delivery system. Capsule coated with semi permeable membrane. Inside the plug consisting of osmotically active agents and the drug formulation. When it comes in contact with GI fluid then it allows water penetration and pressure to develop and the insoluble plug expelled after lag time, which controls coating thickness.	Methylphen Idate		Develops by TSRL, Michigan USA	
3.	Smartcoat™ Technology	It develops very high potency, controlled release tablets allowing for smaller size tablets while controlling the release over a 24 hrs period.	-		Biovail	
4.	Pulsincap™	Water insoluble capsule body filled with drug solution. Closed open end with swellable hydrogel plug. When it comes in contact with GI fluid polymer swells and pushing itself out of the capsule after lag time followed by rapid release.	Dofetilide	Pulsincap ™	Develops by R.P.Scherer International Corporation, Michigan, USA	Anti-arrhythmic
5.	Geoclock®	The press-coated tablets have an active drug inside and outer layer consisting of a mixture of hydrophobic wax in order to obtain a pH independent lag time prior to deliver the drug in predetermined release rate.	Prednisone	Lodotra ™	Skye Pharma	Rheumatoid arthritis
6.	Oros®	Osmotically controlled single unit system. First semipermeable membrane prevents absorption of water in to tablet and second layer delay the regulation of water into inner core and the third layer provide the extended release.	Verapamil	Covera-HS	Alza corporation, Mountain view, CA, USA	Hypertension
7.	Cefrom®	Biodegradable polymers/bio-actives are subjected to varying temperature, thermal	Diltiazem	Cardizem® LM	Fuisz Technologies,	Hypertension

		gradients and flow processes to produce microspheres of uniform size and shape.			Chantilly, VA, USA	
8.	Pulsystm	A novel pulsate delivery technology provides the prolonged release and absorption of a drug. Extended- release tablet consist of one immediate-release and two delayed release components with the use of soluble and insoluble coatings.	Amoxicillin	Moxatag™	Middlebrook Pharmaceuticals, Westlake, Texas, USA	Antibiotic therapy Middlebrook Pharmaceuticals, Westlake, Texas, USA
9.	Contin®	Release by pulse manner at the time of asthmatic attack in morning hrs.	Theophyline	Uniphyl® l		Asthma/increased bronchoconstriction in morning
10.	Diffucaps TM	Multiparticulate system that provides drug release profile from either single drug or combination of drugs. Customized drug release profile are created by first layering with active drug from solvent based drug solutions onto a neutral core and coating with one or more rate controlling membrane.	Propranolol	InnoPran ® XL	Reliant Pharmaceuticals	Hypertension

5. Conclusion and future prospective

It can be concluded that pulsatile drug delivery syetms is a solution for delivery of drugs exhibiting conditions like, chronopharmacological behavior, extensive first-pass metabolism, or absorption window in GIT. A variety of systems based on time or site controlled for pulsatile release of drug. A number of formulations with single and multiple unit systems have been designed in recent past but most lack the site specificity. This technological point of view, multiparticulate systems seem to be more efficient than single-unit dosage forms in achieving pulsatile drug delivery and it can become even more sophisticated when coating technologies are incorporated. There is a need to the comprehend the effects for the biological environment on release performance so that a successful design with expected *in-vivo* performance can be developed. Significant progress has been also made towards achieving pulsatile drug delivery technologies that can effectively treat diseases with non-constant dosing therapies, such as diabetes and for the delivery of active compounds for cancer treatment. Technologies or designs alone do not make a successful product. Technology needs to be implemented is an appropriate design for a successful product.

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