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PULSATILE DRUG DELIVERY SYSTEM; NEW PARADIGMS

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Abstract

Pulsatile drug delivery systems (PDDS) are gaining lots of importance because it provides the delivery of drug at specific time, at specific amount and at specific site. Patient compliance and therapeutic efficacy are better improved by such type of drug delivery systems. Many diseases like hypertension, asthma, peptic ulcer, arthritis, and hypercholesterolemia and attention deficit syndrome in children may be better controlled and treated by pulsatile drug delivery system, because in such type of system drug is released in a programmed manner. Pulsatile drug delivery system offers maximum benefits with fewer side effects. Pulsatile drug delivery systems shows maximum benefits over conventional dosage form. In this system, drug is released rapidly after predetermined lag time, which is very useful for disease treatment. Pulsatile drug delivery system low the risk of dose dumping, provide flexibility in design and desirable release patterns with less inter and intra subject variability. PDDS classified into five systems; time controlled system, internal stimuli induced system, externally regulated system, multiparticulate system and system for vaccine and hormone products. In this article, focuses on the various advantages of pulsatile drug delivery system, mechanism of drug release from pulsatile drug delivery system, classification of pulsatile drug delivery system, marketed technologies, current situation and future scope.

Keywords: Pulsatile release, lag time, programmed pattern, classification, disease, pulsatile drug delivery system.

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INTRODUCTION

Due to the advancement of the technologies in the pharmaceutical field, pulsatile drug delivery systems have got lots of interest over the last few decades. There are many worldwide researches going on for the development of new delivery system. For e.g. in case of the conventional therapy, drug is released very rapidly after medication. So, in case of conventional therapy, the plasma concentrations of the drug are raised and sometimes cause the toxic effect. The main objective of drug discovery is to get maximum drug efficacy and minimum side effect of the drug. The sustained and controlled drug release systems are not applicable in the time- programmed administration and release of many drugs. For the time programmed system, pulsatile drug delivery system is the best choice. Pulsatile drug delivery system is a type of intelligent drug delivery system, because it is capable of adjusting drug release rates in response to a physiological need. Pulsatile drug delivery system also known as Chronotherapeutic drug delivery system [1-3]. Pulsatile drug delivery system is defined as the rapid and transient release of drug molecules within a very short time period immediately after a predetermined lag time. Pulsatile drug delivery aims to release drug on programmed pattern i.e at appropriate time and at appropriate site of action [4-5].

CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEM:

The term Chronopharmaceutics is a combination of two words i.e chronobiology and pharmaceutics. In case of chronobiology, biological rhythms and their mechanisms are involved. Chronotherapeutic drug delivery system is the drug delivery system which is based on the biological rhythms of the body. Chronomodulated system is also known as pulsatile system or sigmoidal release system. There are four types of biological rhythms which control normal and disease related physiology of the body: [6-7]

1. **CIRCADIAN:** In case of circadian rhythm, the oscillation completed in 24 hrs. For e.g. waking and sleeping patterns.
2. **ULTRADIAN: In** case of ultradian rhythm, the oscillations completed in a shorter duration i.e less than 24 hrs.
3. **INFRADIAN:** In case of infradian rhythm, the oscillations completed in more than 24 hrs.
4. **SEASONAL:** In the short days of winter, seasonal affective disorder (SAD) causes depression in susceptible people.

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Out of four biological rhythms, circadian rhythm is the main rhythm in the body which maintains all the physiological, chemical, biological and behavioural processes.

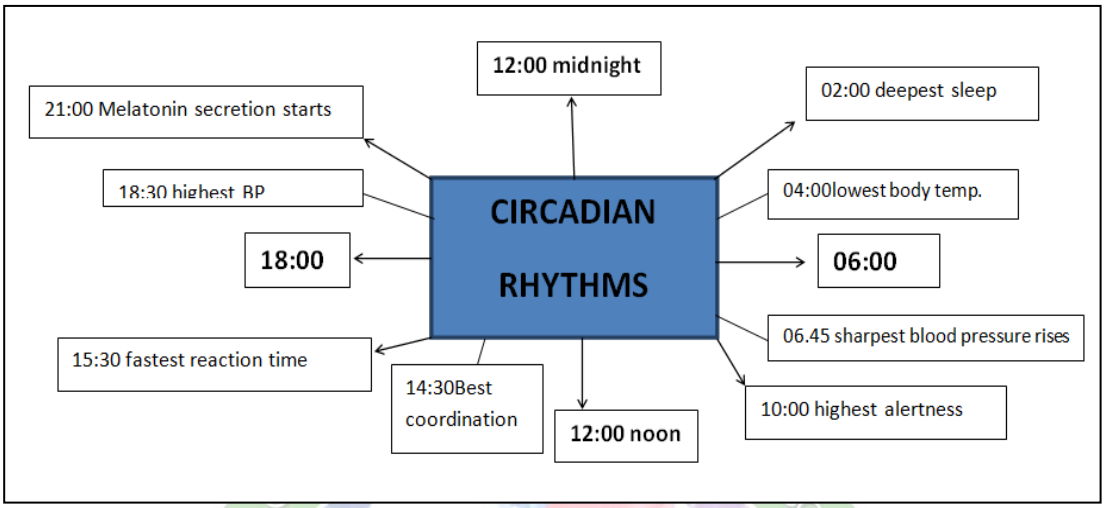

Fig. 1: Cycle of circadian rhythms

ADVANTAGES OF PULSATILE DRUG RELEASE: [8, 14, 17, 32, 33]

- Pulsatile drug delivery system extended daytime or night time activity.
- Pulsatile drug delivery system reduced dosage frequency and side effects.
- Pulsatile drug delivery system gives site specific drug targeting like colon.
- Pulsatile drug delivery system prevent the drug loss by extensive first pass metabolism e.g. proteins and peptide.
- Pulsatile drug delivery system improved patient compliance and patient comfort.
- Pulsatile drug delivery system provides protection of mucosa from irritating drugs.
- There is no risk of dose dumping and flexibility in design.

NEED OF PULSATILE DRUG DELIVERY SYSTEM [21, 42, 46, 50]

- Protection from gastric environment.
- To achieve localized action.
- First pass metabolism can be overcome.
- Follow circadian rhythm.

TYPES OF PULSATILE DRUG DELIVERY SYSTEM [39, 43, 45, 48]

OPEN LOOP CONTROL SYSTEMS: They are also known as pulsed or externally regulated systems. The externally controlled devices apply external triggers for pulsed delivery of drugs such as magnetism, ultrasound and electrical effect.

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It includes the following:

- Magnetically modulated pulsatile systems.
- Ultrasonically modulated pulsatile systems.
- Electrically modulated pulsatile systems.
- Thermo sensitive drug delivery systems.

CLOSED LOOP CONTROL SYSTEM: They are also known as self- regulated systems in which release rate of drug is controlled by feedback information, without any external intervention.

It includes the following:

- pH responsive drug delivery
- glucose-responsive insulin delivery
- inflammation-induced pulsatile release

DISEASES REQUIRING PULSATILE DRUG DELIVERY: [9-10]

Table 1: Chronological behaviour of diseases

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	Beta2agonist, Antihistaminic
Cardiovascular diseases	BP is at its lowest during sleep cycle and rises steeply during the early morning awakening period	Nitroglycerin, calcium channel blockers, ACE inhibitors
Arthritis	Pain in the morning and more pain at night	NSAIDs, glucocorticoids
Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonylurea, insulin, biguanide
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time	HMG CoA reductase inhibitors
Attention	Increase in DOPA level in afternoon deficit syndrome	Methylphenidate

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MECHANISM OF DRUG RELEASE FROM PDDS: [24]

Table 2: Mechanism of drug release from PDDS

DIFFUSION:	EROSION:	OSMOSIS:
In the gastrointestinal tract, when particles come in contact with aqueous fluids then water diffuses into the interior of the particle and cause the diffusion of drug solutions across the release coat to the exterior.	Some coating get erode with time, and cause the release of drug which is present within the particle.	Osmotic pressure built up within the particle when water allows entering under the right conditions.

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEMS:[25]

It is divided into two parts;

- TIME CONTROLLED SYSTEM
- SITE SPECIFIC SYSTEM

TIME CONTROLLED SYSTEM: It is not dependent of the biological environment condition like pH, enzymes and pressure in GIT. It includes single unit system i.e Tablet and Capsule.

SITE SPECIFIC SYSTEM: In case of site specific system, drug release is depend on the environment in the gastro intestinal track. It includes multiunit system i.e Pellets.

APPROACHES OF PDDS [25, 44, 47, 49, 52]

Different approaches of pulsatile drug delivery system are divided as follows;

TIME CONTROLLED SYSTEM

a) Capsule based system
b) System based on osmosis
c) Solubilisation or erosion
d) Rupturable coating layer

INTERNAL STIMULI INDUCED

a) Temperature induced
b) Chemical stimuli induced

EXTERNALLY REGULATED

a) Magnetically induced

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b) Ultrasonic induced

c) Electrically induced

d) Light induced

- MULTIPARTICULATE SYSTEMS.
- SYSTEM FOR VACCINE AND HORMONE PRODUCTS.

TIME CONTROLLED SYSTEMS: [11-13]

CAPSULE SHAPED BASED PULSATILE DRUG RELEASE: Mostly, the single unit systems are developed in the capsule form, and the lag time is controlled by a plug, which gets pushed away by swelling or erosion. From the insoluble capsule body, drug is released as a Pulse. The insoluble capsule body is filled with drug and swellable and degradable plugs. The plugs are made up of hydrophilic polymers or lipids. The dimension and position of the plug is responsible for the lag time. There are various polymers used for the hydrogel plug i.e:

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

SYSTEM BASED ON OSMOSIS: In this system, the capsule is coated with the semipermeable membrane, and inside the capsule is an insoluble plug which contains the osmotically active agent and drug formulation. When the capsule comes in contact with fluid, the semipermeable membrane allows water to enter inside, and develop the pressure which causes the expellation of plug after a lag time. E.g. Port system. This system is utilized to deliver methylphenidate for the treatment of attention deficit hyperactivity disorder.

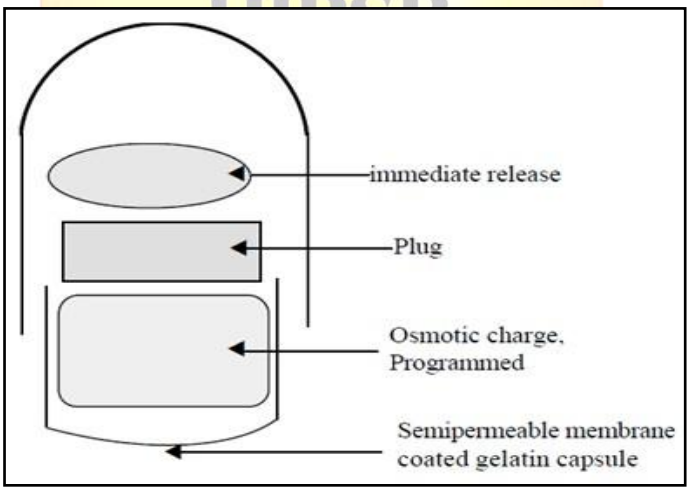

Fig. 2: Osmotic system

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SOLUBILISATION OR EROSION SYSTEMS

In this system, the core drug is coated with the soluble or erodible polymer as the outer coat. The release of the drug is controlled by the solubilisation or erosion of the outer coat. The release of drug is also depending upon the thickness of the outer coat so, time dependent release is obtained. E.g. The Chronotropic system and The Time Clock system.

SYSTEM WITH RUPTURABLE COATING MEMBRANE

In this system, the pressure is necessary for the rupture of the coating layer and it can be achieved by the swelling, disintegrant, effervescent or osmotic pressure In place of swelling or eroding, this system is dependent on the disintegration of the coating for the release of drug. For the lag time, major factors are mechanical resistance of the outer membrane. E.g. Buflomedil HCl is used for treatment of peripheral arterial disease.

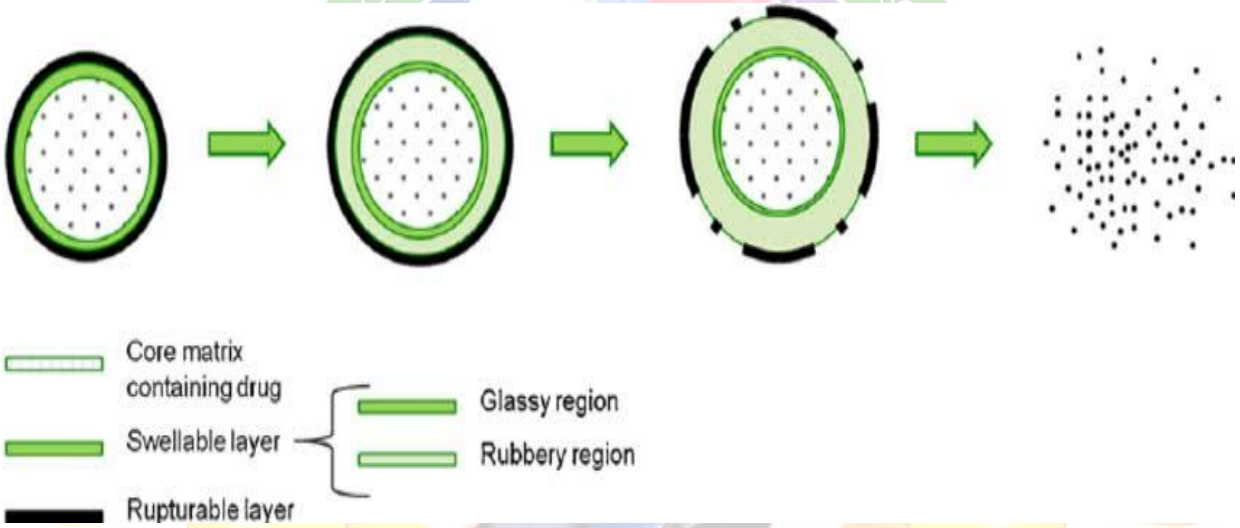

Fig. 3: Drug Release Mechanism from System with Rupturable Coating Membrane.

INTERNAL STIMULI INDUCED SYSTEMS [18, 20, 22, 23, 25, 31]

TEMPERATURE INDUCED SYSTEMS

The temperature induced pulsatile/triggered drug delivery systems utilize various polymer properties, including the thermally reversible coil/globule transition of polymer molecules swelling change of networks, glass transition and crystalline melting.

THERMO RESPONSIVE HYDROGEL SYSTEMS

In this system, the hydrogels undergo reversible volume changes in response to changes in temperature. These gels shrink at a transition temperature i.e. lower critical solution temperature (LCST) of the linear polymer. Thermo sensitive hydro sensitive hydrogels have a certain

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chemical attraction for water, so they absorb water and swell at temperature below the transition temperature. For the pulsatile drug delivery, the thermally responsive hydrogels and membranes is extensively exploited platform.

THERMO RESPONSIVE POLYMERIC MICELLE SYSTEMS

In this type, the gel system tightly stores targeted drug in the micelles and rapidly releases controlled amount of the drug by switching on- off of external stimuli such as temperature or infrared laser beam. E.g. Y.H. Bae et al developed indomethacin pulsatile release pattern in the temperature ranges between 20^{o}C and 30^{o}C by using reversible swelling properties of copolymers of N- isopropylacrylamide and butyrylacylamide.

CHEMICAL STIMULI INDUCED SYSTEMS

In this system, because of stimulation of any biological factor like enzyme, pH or any other chemical stimuli, drug release occurs.

pH SENSITIVE DRUG DELIVERY SYSTEMS

This system contains two components. The first one is fast release type and second one is pulsed release which release the drug in response to change in pH. There is different pH environment at different parts of the gastrointestinal tract so it is advantage for the pH dependent system. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine. E.g. Eudragit in colon targeted systems.

GLUCOSE RESPONSIVE INSULIN RELEASE DEVICES

In a glucose rich environment, such as the bloodstream after a meal, the oxidation of glucose to gluconic acid catalysed by glucose oxidase can lower the pH to approximately 5.8. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release. Examples of the pH sensitive polymers include N, N-dimethylaminoethyl methacrylate, chitosan, polyol etc.

INFLAMMATION INDUCED PULSATILE RELEASE

Any injury, stress and fracture cause inflammation at the injured sites. Hydroxyl radicals are produce by the inflamed cells. Scientist Yui and his co- workers focused on the hydroxyl radicals and drug delivery systems, which shows respond on the hydroxyl radicals and hydroxyl radicals degraded in a limited manner. Hyaluronic acid is used because it degraded by the free radicals or

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hyaluronidase. The process of degradation is very low. But in case we use hydroxyl radicals, the degradation process is rapid when hyaluronic acid is injected at inflammatory sites. Thus, the patients suffering from inflammatory diseases like rheumatoid arthritis are treated by using anti-inflammatory drug incorporated hyaluronic acid gels.

DRUG RELEASE FROM INTELLIGENT GELS RESPONDING TO ANTIBODY CONCENTRATION

There are various bioactive compounds are present in human body. If concentration of these bioactive compounds changes then these changes are detected by the novel gels to alter their swelling/deswelling characteristics. Due to specific interaction, cross linking units in the gel form the antigen-antibody complex. Some changes like swelling/deswelling and drug permeation is occur due to the difference in association constants between antibodies (polymerized) and naturally derived antibodies towards specific antigens.

EXTERNALLY REGULATED SYSTEM [14, 15, 16, 26, 27, 31]

MAGNETICALLY INDUCED SYSTEMS

For modulate the rates of drug release from polymer matrix by the use of an oscillating magnetic field is very old methodology. From the magnetic field, magnetic carriers receive their magnetic response, by incorporated materials such as magnetite, iron, nickel, cobalt etc. The magnetic carriers used to be non- toxic, water based, biocompatible and non- immunogenic. This magnetically induced system contains magnetic beads were engrafted in an ethylene and vinyl acetate copolymer matrix and loaded with bovine serum albumin. The tensile and compressive forces are developing when beads oscillate in matrix on exposure to the magnetic field. It acts as a pump and push active solute out of the matrix.

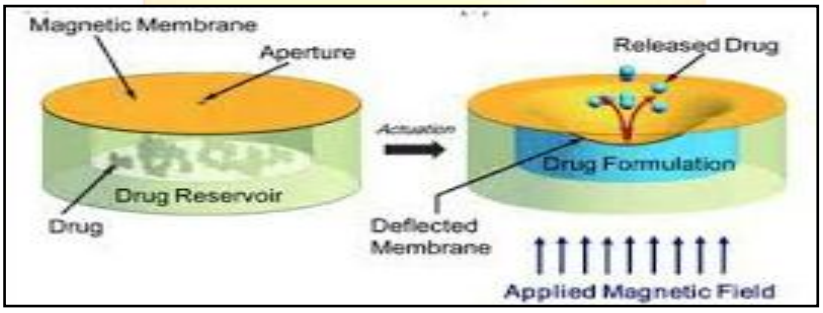

Fig. 4: Drug release from magnetically induced pulsatile systems

ULTRASOUND INDUCED RELEASE SYSTEMS

Ultrasound is mostly used as an enhancer for the improvement of drug permeation through biological barriers, such as lungs, skin. Ultrasound devices are used to achieve up to a 27- fold

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increase in the release of 5- fluorouracil from an ethylene and vinyl acetate matrix. The rate of drug release and ultrasonic exposure enhanced by degradation of biodegradable matrix. The amount of 5- fluorouracil release increased by increasing the strength of the ultrasound.

ELECTRIC FIELD INDUCED SYSTEM

Polyelectrolytes are used for the preparation of electrically responsive delivery systems. Polyelectrolytes are the polymer which contains high concentration of ionisable groups along backbone chain. So polyelectrolytes are both pH responsive as well as electro responsive. These technologies also involve infusion pumps and iontophoresis. Because of the electric field, electro responsive hydrogels bend, and depending on the shape of the gel which lies parallel to electrodes. Deswelling occurs when the hydrogel lies perpendicular to the electrodes. E.g. poly (acrylamide- grafted xanthan gum) hydrogel for transdermal delivery of ketoprofen

LIGHT INDUCED RELEASE SYSTEMS

Light sensitive hydrogels have potential applications in developing optical switches, display units, and ophthalmic drug delivery devices. The interaction between light and material can be used to modulate drug delivery. When hydrogel absorb the light and convert it to heat, raising the temperature of composite hydrogel above its LCST, hydrogel collapses and result in an increased rate of release of soluble drug held within the matrix.

MULTIPARTICULATE SYSTEMS

The main aim of designing multiparticulate dosage form is to form a reliable formulation that has all the plus points of single unit formulation and yet devoid of the danger of alteration in drug release profile. Multiparticulate system includes reservoir systems with rupturable polymeric coatings, reservoir systems with soluble or eroding polymer coatings, floating multiparticulate pulsatile systems.

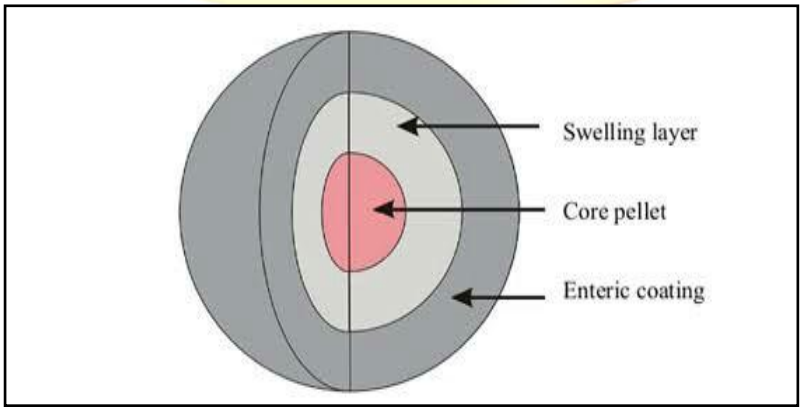

Fig. 5: Multiparticulate pulsatile system.

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SYSTEM FOR VACCINE AND HORMONE PRODUCTS

Vaccines are traditionally administered as an initial shot of an antigen followed by repeated booster shots to produce protective immunity. PDDS offer the possibility of single shot vaccines if initial booster release of the antigen can be achieved from one system in which timing of booster release is controlled. GnRH for synthesis and secretion of luteinizing hormone and follicle stimulating hormone in cows.

ADVANCED TECHNOLOGIES OF PULSATILE DRUG DELIVERY SYSTEM: [30]

Table 3: ADVANCED TECHNOLOGIES OF PDDS

S.NO.	TECHNOLOGY	DESCRIPTION
1	KV/24	Release of drug is express by one or more drug compounds which remain encapsulated. Coating is done by one or more polymers neutral core is coated with drug to obtain once a day release profile. The drug is combined with the neutral core or drug is incorporated into the coating process.
2	CONTIN technology	Release by pulse manner at the time of asthmatic attack in morning hrs.
3	CEFORM technology	This technology used for treatment of hypertension and gives pulse release.
4	API modification	Physico- chemical modification of the API.
5	INNOHERB	Pellets are coated inside of the capsule. Herbal compound converted into small beads or micro pellets. For improving stability and mask taste the coating of these carried out by semi permeable membrane.
6	COER-24TM	It is osmotically controlled single unit system. It shows both controlled onset and extended release. It prevents absorption of water into the tablet by semipermeable membrane. And then 2nd layer delay the passage of water. Last 3rd layer gives extended release.
7	CODASTM	In this, after administration it gives 5 hrs delays in drug delivery by an extended drug release and peak plasma concentration occurring approximately 11 hr. Capsule contains various pellets having inner core, which is surrounded by drug and water soluble and insoluble polymers. Release of the drug occurs through pores of polymer coating.
8	DiffucapsTM	This system is multiparticulate in which drug release profile occur either single drug or combination of drugs. Drug release is occur by first layering with active drug from solvent based drug solutions onto a neutral core and coating is done by one or more rate controlling membrane.
9	pulsincapTM	Water insoluble capsule body filled drug solution. The capsule body closed at 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.
10	Ticking capsule	Controlling pulsatile drug release couple with electronic timing.

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MARKETED PRODUCTS OF PULSATILE DRUG DELIVERY SYSTEM [14-19]

Table 4: Marketed products of PDDS

S.NO.	TECHNOLOGY	API	DISEASE
1	DIFFUCAPS®	Propranolol HCl, Verapamil HCl	Hypertension
2	CEFORM®	Diltiazem HCl, Verapamil HCl	Hypertension
3	Physico- chemical modification of API	Simvastatin	Hypercholesterolemia
4	OROS®	Methylphenidate HCl	Anti –psychotic
5	PROCARDIA XL®	Nifedipine	Hypertension
6	PULSYSTM	Amoxicillin	Infection
7	CODAS®	Verapamil HCl	Hypertension
8	TIMERx®	Oxymorphone	Pain management
9	OROS®	Paliperidone	Schizophrenia
10	CONTIN®	Theophylline	Asthma
11	PULSYSTM	Dofetilide	Antiarrhythmic
12	OROS®	Verapamil HCl	Hypertension

FUTURE SCOPE AND CURRENT SCENARIO OF PDDS

The future of drug delivery system as pulsatile manner seems to be very promising for certain diseases. It shows maximum advantages over the zero or first order drug delivery mechanism. Various systems like site specific, time controlled, single or multiple units are obtained by pulsatile drug delivery techniques. Release of drug in pulsatile system is achieved by using different polymers in coating layer or by changing the thickness of coat. Beside this, multiparticulate systems shows more advantages over single unit.

PATENTS ON PULSATILE DRUG DELIVERY SYSTEM [34-40]

Table 5: Patents

S.NO	NAME	ACTIVE AGENT	DATE OF PATENT FILLING
1	Pulsatile drug delivery system	Propranolol	20-07-1993
2	Pulsatile drug delivery system	Ivermectin	01-05-1987
3	Pulsatile technology	Diltiazem	
4	Pulsatile technology	Amphetamine	27-11-2001
5	Time controlled drug delivery system	Sotalol HCl	2003

CONCLUSION

It is known that sustained and controlled release products provide a desired therapeutic effect, but fall for diseases following biological rhythms. It can be concluded that pulsatile drug delivery systems offer a solution for delivery of drugs exhibiting chronopharmacological behaviour, extensive first –pass metabolism, necessity of night-time dosing, or absorption window in GIT. One major challenge will be to obtain a better understanding of the influence of the biological

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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. Pulsatile drug delivery system shall be promising in future because drug is delivering in this system when its actual concentration is needed as per chronological need.

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