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CHRONOPHARMACEUTICAL DRUG DELIVERY SYSTEM FOR HYPERTENSION: AN OVERVIEW

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ABSTRACT

Chronopharmaceutical Drug Delivery Systems is novel system which provides a pattern of real-time drug input at different release rates and it may be achieved by stimuli-sensitive and pulsatile drug delivery systems. Pulsatile Drug delivery systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. Pulsatile Drug Delivery systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, GIT motility, etc. These systems are designed for chronopharmacotherapy which is based on the circadian rhythm of the body. In chronopharmacotherapy (timed drug therapy) drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. Chronopharmaceutical drug delivery shows potential benefits for the diseases which show circadian rhythms like cardiovascular diseases. Several attributes of the cardiovascular system, including blood pressure (BP) and heart rate (HR), are characterized by predictable changes during the 24 h, for the most part, in synchrony with the rest–activity cycle. The predictable changes during the 24 h in environmental and biological variables give rise to the circadian pattern in BP and HR. Various latest and upcoming marketed technologies like OROS®,CODAS®,CEFORM®,DIFFUCAPS®,PULSINCAP®,PROCARDI XL.

Keywords: chronopharmacotherapy**,** chronobiology, circadian rhythm, cardiovascular diseases**,** pulsatile drug delivery system.

INTRODUCTION

Over the last 30 years the pharmaceutical market has been demonstrated increasing preferably for controlled and targeted drug delivery system. Such systems have been focused on constant, variable; sustain drug release and/or targeting the therapeutic agent to a specific site/tissue/ organ. However, recently there are certain conditions for which such release pattern is not suitable. Such conditions that lead to the requirements of a time programmed therapeutic system, which capable of releasing drug after predetermined time delay and maintain constant drug levels through the day. Traditionally, drug delivery has meant for getting a simple chemical absorbed predictably from the gut or from the site of injection. A second generation drug delivery goal has been the perfection of continuous, constant rate delivery of bioactive agents. However, living organisms are not ‘‘zero-order’’ in their requirement or response to drugs. They are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle which will maximize desired and minimize undesired drug effects.[1,2] To introduce the concept of chronotherapeutics, it is important to define the following concepts.

Chronobiology: Chronobiology is the science concerned with the biological mechanism of the diseases according to a time structure. "Chrono" pertains to time and "biology" pertains to the study, or science, of life. [3,4]

Chronopharmacology: Chronopharmacology is the science concerned with the variations in the pharmacological actions of various drugs over a period of time of the day. [5]

Chronopharmacokinetics: Chronopharmacokinetics involves study of temporal changes in drug absorption, distribution, metabolism and excretion. Pharmacokinetic parameters, which are conventionally considered to be constant in time, are influenced by different physiological functions displaying circadian rhythm. Circadian changes in gastric acid secretion, gastrointestinal motility, gastrointestinal blood flow, drug protein binding, liver enzyme activity, renal blood flow and urinary pH can play role in time dependent variation of drug plasma concentrations.[6]

Chronotherapy: Co-ordination of biological rhythms and medical treatment is called chronotherapy. [7]

Chronotherapeutics: Chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. It is becoming increasingly more evident that the specific time that patients take their medication may be even more significant than was recognized in the past. [7]

Biological Rhythms: A biological rhythm is a self-sustaining process inside the human body. It is defined as the process that occurs periodically in an organism in conjugation with and often in response to periodic changes in environmental condition. [8]

Ultradian Rhythms: Oscillations of shorter duration are termed Ultradian Rhythms (more than one cycle per 24 h). E.g.90 minutes sleep cycle. [9]

Infradian Rhythms: Oscillations that are longer than 24 hours are termed as Infradian Rhythms (less than one cycle per 24hours). E.g. Monthly Menstruation.

Circadian rhythms: Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 Hours. Interestingly, the term circadian is derived from the Latin circa which means "about" and dies which can be defined as "a day". Normally, circadian rhythms are synchronized according to internal biologic clocks related to the sleep-wake cycle. [6,10,11]

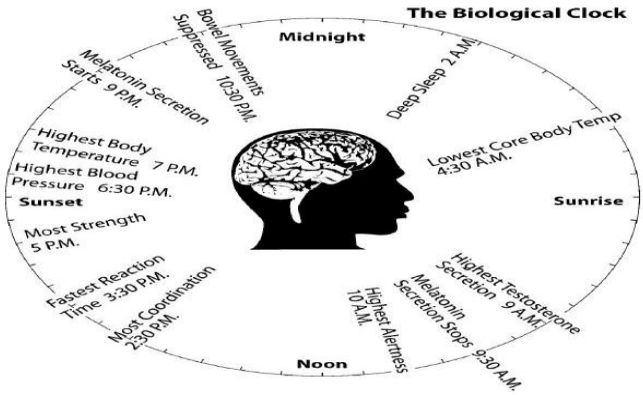

Fig.1: Diseases displaying circadian rhythm

Diseases & Chronotherapeutics

The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease. [12]

Cardiovascular Diseases: In cardiovascular disease capillary resistance and vascular reactivity are higher in the morning and decreases latter in the day. Cardiovascular diseases are one of the life threatening diseases of the world, Hypertension, Angina pectoris; Congestive heart failure and Myocardial infarction are the commonest diseases and require constant monitoring.[13-15]

Hypertension: Hypertension is defined conventionally as blood pressure ≥ 140/90. Elevated arterial pressure causes pathological changes in vasculature and hypertrophy of left ventricles; as a consequence hypertension is the principle cause of stroke, leads to disease of coronary arteries with myocardial infarction and is a major contributor to cardiac failure. Hypertension in adults is defined by World Health Organization (WHO) as a systolic pressure equal to or greater than160mmHg (21.3kPa) and a diastolic pressure (fifth phase) equal to or greater than 95 mmHg (12.7kPa).Hypertension results from increased peripheral resistance and reduced capacitance of the venous system. Although many of these individuals have no symptoms, chronic hypertension-either systolic or diastolic- can lead to CHF, MI, renal damage, and cerebrovascular accidents.[16,17] Heart rate and blood pressure are increased in the early morning hours (morning or A.M. surge). The blood pressure declines form mid afternoon and is minimum at midnight. In most hypertensive patients, there is a rather marked rise in blood pressure upon awakening that is called the morning or "a.m." Systolic blood pressure rises approximately 3mm Hg/hour for the first 4-6 hours post-awakening, while the rate of rise of diastolic blood pressure is approximately 2mm Hg/hour.[18,19]

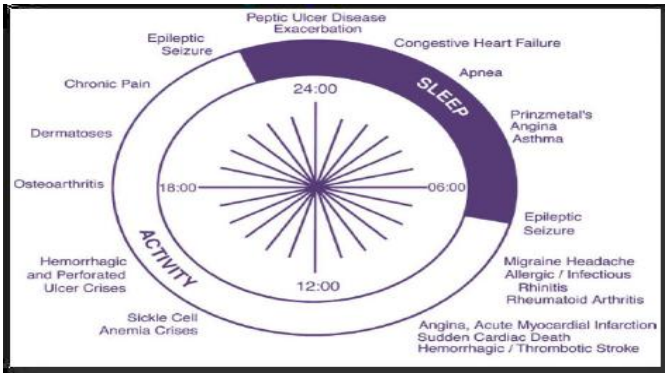

Fig.2: Diseases displaying circadian rhythm

Hypertension has been classified as "primary or essential hypertension" where definite cause for risk in blood pressure is not known and "secondary hypertension" which is secondary to renal, endocrine and vascular lesions. Hypertension, particularly essential or primary hypertension is wide spread and a major risk factor for stroke and to some extent ischemic heart diseases.

Antihypertensive drugs: Major drugs used in the treatment of hypertension are described as follows:

Table No. 1: Antihypertensive Drugs [16]

Direct Vasodilators	**Centrally Acting Sympatholytics**	**α -Blockers**	**Angiotensin II Antagonist**
Hydralazine, Minoxidil Sodium-nitroprusside Diazoxide	Clonidine, Guanabenz, Methyldopa, Guanfacine,	Doxazosin Prazosin Terazosin	Losartan potassium, Olmesartan, Candesartan
Diuretics	**ACE Inhibitors**	**β-Blockers**	**Calcium Channel Blockers**
Hydrochlorohtiazide Spironolactone Triamterene Bumetanide	Captopril Benazepril Enalapril, Fosinopril, Quinalpril, Ramipril	Atenolol Labetalol Metoprolol Propranolol Timolol	Amlodipine Diltiazem Felodipine Nicardipine, Nisoldipine Verapamil

Regulation of blood pressure: The main systems include the sympathetic nervous system, the rennin-angiotensin aldosterone system and tonically active endothelium-derived autacoids. Figure-6 summarizes physiological mechanisms that control arterial blood pressure and shows sites at which antihypertensive drugs act [16].

Symptoms of hypertension: Headache, Morning headache, Tinnitus, Dizziness, Confusion.

Congestive heart failure: Congestive heart failure occurs when cardiac output is insufficient to meet the demands of tissue perfusion. Heart failure may primarily be due to systolic or diastolic dysfunction [14].

Systolic dysfunction: The ventricles are dilated and unable to develop adequate wall tension to eject significant quantity of blood.

Diastolic dysfunction: The ventricular wall is thickened and unable to relax properly during diastole; ventricle filling is impaired due to which output is low. However most patients specially with long standing CHF have both systolic and diastolic dysfunction. The aim of drug therapy in CHF is to restore cardiac performance, restore congestive and low output symptoms and improve survival. Treatment includes the drug therapy with cardiac glycosides, ACE inhibitors, Ca2+ channel blockers, angiotensin II antagonists, diuretics etc.

Myocardial infarction: The term myocardial infarction refers to localized destruction of myocardial cells caused by interrupted blood supply. An acute thrombus at the site of atherosclerotic obstruction is the usual cause. Treatment includes the drug therapy with β-blockers, ACE inhibitors and other vasodilators, inotropic agents, anticoagulants etc [16].

CHRONOPHARMACOLOGY OF CARDIOVASCULAR DISEASES

Epidemiological studies document that the frequency of many cardiovascular diseases, including myocardial infarction and stroke, varies predictably in time over 24 hours (the circadian period). Advanced diagnostic technologies using ambulatory monitoring of the blood pressure and electrocardiogram have also demonstrated that there is marked variability in the level of pressure in hypertensive patients and the degree of myocardial ischemia in Patients with coronary disease. Consequently the cardiovascular system displays pronounced daily variations in its function as well as in its hormonal and biochemical regulatory mechanisms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregation increased and fibrinolytic activity is decreased in the morning, leading to state of relative hypercoagulability of the blood. In diurnally active patients, angina, acute myocardial infarction (AMI), sudden cardiac death, and ischemic and hemorrhagic stroke each is several fold more frequent in occurrence during the initial 3 to 5 hours of morning activity than at any other time of the day or night. In contrast, episodes of vasospasm in prinzmetal angina are most common during the sleep span. Table No.-2, gives the circadian variations frequencies of cardiovascular diseases [20].

Table-2: Circadian variations of the frequencies of cardiovascular disease

Disease		frequent time of onset
Arrhythmia	Atrial fibrillation	Night
	Ventricular tachycardia	Morning
	Ventricular fibrillation	Morning
Ischemic heart disease	Acute coronary syndrome (sudden death)	Morning
	Vasospastic angina	Early Morning
Hypertension	Morning surge	Morning
Stroke cerebral infarction		Morning
Subarachinoidal hemorrhage		Afternoon

Ischemic heart disease: Ischemic heart disease (IHD) is the generic designation for a group of closely related syndromes resulting from ischemia, an imbalance between the supply and demand of the heart for oxygenated blood. There are four overlapping ischemic syndrome, differing in rate of onset and severity of ischemia. They are myocardial infarction, angina pectoris, chronic IHD with heart failure and sudden cardiac death. There is an accumulation of ischemic cardiac events such as unstable angina and acute myocardial infarction within the first few hours after waking and assuming activity. The risk of these events is relatively lower during the rest of the day, especially during the sleep period. Most ischemic episodes occurred during the morning hours, beginning around 7-8 a.m., reach a plateau until 1 p.m., and gradually decreased therefore,

with possibly a second, smaller peak occurring around 6 p.m.; the fewest episodes occurred at night. The peak frequency of such events usually occurs between 10 a.m. and 12 p.m., and the trough value usually occurs at approximately 3 to 6 a.m. This timing is consistent with the timing of surge in a series of physiological parameters: heart rate, blood pressure, blood concentration of epinephrine and nor-epinephrine, angiotensin II level, and platelet agreeability. During this time, myocardial oxygen demand increases, while its supply may decrease. Also, coagulation activity is increased, and fibrinolytic activity is decreased. Together, these phenomena can account for the increased risk of ischemic events in the morning hours. In variant angina there appears to be a very early morning peak (between 5 and 6 a.m.) in both painful and silent episodes of ischemia. This is a time when ischemia occurs least frequently in patients who have a stable coronary artery disease. The 24-hour pattern in MI is also a result of the predictable timing of environmental triggers, change in posture and physical and mental loading occurring in the morning. These are largely responsible for the rapid increase in blood pressure, heart rate, and myocardial oxygen demand.[21,22]

Table.3: Diseases requiring pulsatile drug delivery [23]

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.	β_2 agonist, Antihistaminics
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning A wakening period.	Nitroglycerin,Calcium channel Blocker,ACE inhibitors etc.
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
Attention deficit Syndrome	Increase in DOPA level in Afternoon	Methylphenidate
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time.	HMG CoA reductase Inhibitors,

Chronopharmaceutical Drug Delivery system

Pulsatile system is amongst one of them and gaining a lot of interest as it is increasing patient compliance by means of providing time- and site specific drug delivery system, thus providing special and temporal delivery. Pulsed or pulsatile drug release is defined as the rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off-release period. Recent studies show that diseased have predictable cyclic rhythms and the timing of medication regimens can improve outcome in selected chronic conditions. Numerous studies conducted, suggest that pharmacokinetics, drug efficacy and side effects can be modified by following therapy matching the biological rhythm. Specificity in delivering higher amount of drug in a burst at circadian timings correlated with specific pathological disorder is a key factor to achieve maximum drug effect. Ideally, Chronopharmaceutical drug delivery systems (ChrDDS) should represent time- controlled and site-specific drug delivery systems. Evidence suggests that an ideal ChrDDS should: [9]

- Be non-toxic within approved limits of use,
- Have a real-time and specific triggering biomarker for a given disease state,
- Have a feed-back control system,
- Be biocompatible and biodegradable, especially for parenteral administration,
- Be easy to manufacture at economic cost, easy to administer to patients and enhances compliance to dosage regimen.

Necessities of Chronopharmaceutical DDS:

1. **First pass metabolism:** Some drugs, such as beta blockers and salicylamide undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize pre-systemic metabolism. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability. [24]
2. **Biological tolerance:** Drugs that produce biological tolerance demand a system that will prevent their continuous presence at the biophase, as this tends to reduce their therapeutic effect. The lag time is essential for drugs that undergo degradation in gastric acidic medium (e.g., peptide drug) and irritate the gastric mucosa or induce nausea and vomiting. Targeting a drug to a distal organ of gastrointestinal tract (GIT), like the colon, requires that the release is prevented in the two-third portion of the GIT. Drugs (β-blockers or β-estradiol) that undergo first-pass metabolism, resulting in reduced bioavailability, altered steady-state levels of drug and metabolite and potential food drug interaction, require delayed released to the extent possible. [28,29]
3. **Special Chronopharmacological needs:** Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24 hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours.[30]
4. **Local therapeutic need:** For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects. [26]
5. **Gastric irritation or drug instability in gastric fluid:** Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (eg, peptide drugs), irritate the gastric mucosa (NSAIDS) or induce nausea and vomiting.[27]
6. **Drug absorption differences in various gastro-intestinal segments:** In general, drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine. Compensation for changing absorption characteristics in the gastrointestinal tract may be important for some drugs. For example, it is rational for a delivery system to pump out the drug much faster when the system reaches the distal segment of the intestine, to avoid the entombment of the drug in the feces. [25]

MERITS [31-33]

1. Predictable, reproducible and short gastric residence time
2. Less inter- and intra-subject variability
3. Improve bioavailability
4. Limited risk of local irritation
5. No risk of dose dumping
6. Flexibility in design
7. Improve stability.

DEMERITS [34]

1. Lack of manufacturing reproducibility and efficacy
2. Large number of process variables
3. Batch manufacturing process
4. Higher cost of production

Dosage Forms

Types of dosage forms that can be designed:-

Compression coated/press coated tablets: These are timed release formulations, simple to manufacture, comprised of an inner core that contains an active pharmaceutical ingredient and excipients surrounded by an outer layer that dissolves or disintegrates slowly to produce the lag time. The core is placed between two layers of polymer and directly compressed by flat punches of tablet machine. Surrounding polymeric layers protect the drug from release before the desired lag time, hence effective delivery in chronotherapy as it

allows the drug release at the point in circadian cycle when clinical signs develop and increase. Drugs that treat cardiovascular disease (nifedipine, nitrendipine, amlodipine, diltiazem etc) and asthma (theophylline, budesonide) had been attempted to formulate such dosage forms. Swada et al. 2003 prepared timed release compression coated tablets of nifedipine for chronotherapy of angina and compared it in vitro-in vivo release profile with sustained release formulation.[35,36]

Core in cup tablets: It is a novel oral pulsatile release drug delivery system based on a core-in-cup dry coated tablet, where the core tablet surrounded on the bottom and circumference wall with inactive material. The system consists of three different parts, a core tablet, containing active ingredient, an impermeable outer shell and a top cover layer- barrier of a soluble polymer. The impermeable coating cup consisted of cellulose acetate propionate and the top cover layer of hydrophilic swellable materials such as polyethylene oxide, sodium alginate or sodium carboxy methyl cellulose. The system releases the drug after a certain lag time generally due to the erosion of top cover layer. The quantity of material, its characteristics (viscosity, swelling, gel layer thickness) and the drug solubility was found to modify lag time and drug release. The lag time increases when quantity of top layer increases, whereas drug release decreases. [37,38]

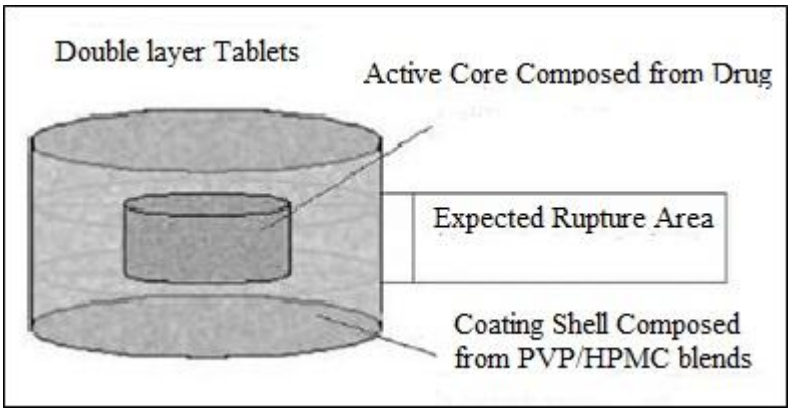

Fig. 3: Design of the press coated tablet

Pulsincap systems: As discussed previously that these are the well designed pulsatile release drug delivery systems capable of releasing drug at a pre determined time. Drug formulation is contained within the insoluble capsule body which is sealed by means of a hydrogel plug. On oral administration the water soluble capsule cap dissolves in the gastric juices and hydrogel plug swells. At a controlled and predetermined time point after the ingestion, the swollen plug is ejected from the pulsincap dosage form after which the encapsulated dosage formulation is then released. To simplify this technology, the hydrogel plug has been replaced by an erodible tablet, which has a tight fit in capsule to prevent the entry of fluid. During the release process it erodes away from the mouth of capsule. The effect of various parameters such as type and weight of swellable polymer, type of hydrophilic polymers used in erodible tablet formulation and erodible tablet weight was investigated in order to characterize the lag time and drug release profiles.[39-41,45]

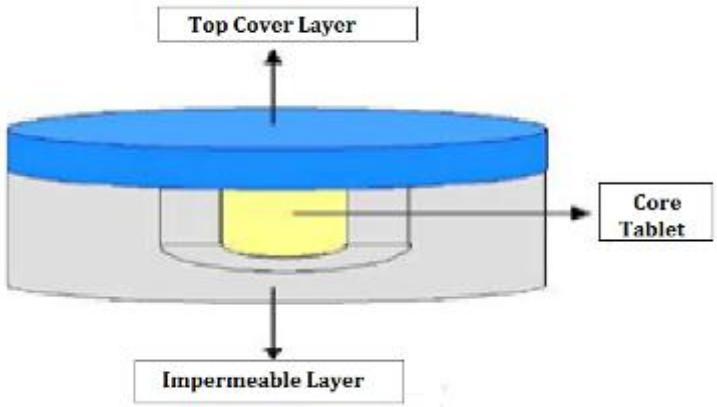

Fig. 4: "Core in cup tablet" as a pulsatile drug delivery system

The pulsatile capsule is designed for two drug doses. First is placed into the capsule cap while the second dose is released from an insoluble capsule body.lag time is determined by an osmotic system which presses an insoluble plug out of the capsule body.

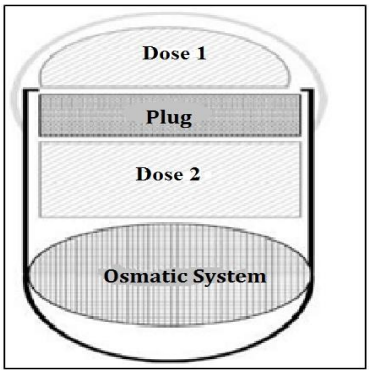

Fig. 5: Double coated hard gelatin capsules and tablets

These are time controlled rupturable pulsatile drug delivery systems either in form of hard gelatin capsules tablets. The capsules are filled with active pharmaceutical ingredient either for single pulse or multi-pulse release (in form of multiparticulates) and coated with a swelling layer followed by an external water insoluble semipermeable polymeric coating. Upon water ingress the swelling layer swells to attain a threshold hydrodynamic pressure required to rupture the outer coating and allowing the release of contents in surrounding medium. The time required by swelling layer to rupture outer coating surves the purpose of desired lag time required in chrono therapy of disease. The tablets are manufactured and coated on the same principle as that of double coated gelatin capsules.[42]

Pulsatile release muliparticulate systems: These systems have been developed on the basis of various approaches of designing pulsatile drug delivery system discussed later (like time controlled, stimuli induced or externally regulated pulsatile drug delivery systems).these can be developed in various types of dosage forms like: Pellets, Granules, Microspheres, Beads, Nanoparticles. In recent pharmaceutical applications involving pulsatile drug delivery, multiparticulate dosage forms are gaining much favour over single unit dosage forms. The potential benefits include increased bioavailability, predictable, reproducible, and generally short gastric residence time; no risk of dose dumping; reduced risk of local irritation; and flexibility to blend pellets with different compositions or release patterns. Because of their smaller particle size, these systems are capable of passing through gastrointestinal tract easily, leading to less inter- and intra-subject variability. A no. of multiparticulate pulsatile drug delivery systems has been developed for chronotherapy. For instance, colonic delivery of theophylline in form of microspheres and coated pellets for nocturnal asthma, formulation of indomethacin, ibuprofen, flurbiprofen, meloxicam, aceclofenac, diclophenac pellets and microspheres for chronotherapy of rheumatoid arthritis and floating beads of alginates encapsulating the active drug component in core, have been attempted to deliver many of the drugs which are absorbed in upper gastrointestinal tract. Numerous advanced technologies have been developed in designing of pulsatile release multiparticulate dosage forms and many of them are FDA approved and being marketed.[43,44]

Chronomodulating infusion pumps: Externally and internally controlled systems across a range of technologies including pre-programmed systems, as well as systems that are sensitive to modulated enzymatic or hydrolytic degradation, pH, magnetic fields, ultrasound, electric fields, temperature, light and mechanical stimulation. To our knowledge infusion pumps on the market that have been referred to as chronomodulating for drug delivery application include the Melodie, programmable Synchromed, Panomat V5 infusion, and the Rhythmic pumps. The portable pumps are usually characterized by a light weight (300-500 g) for easy portability and precision in drug delivery. For example portable programmable multi-channel pumps allowed demonstration of the clinical relevance of the chronotherapy principle in a sufficiently large patient population. Specifically, a clinical phase III trial involving several patients with metastatic gastrointestinal malignancies compared a flat versus the chronomodulated three-drug regimen, and demonstrated large,

simultaneous improvements in both tolerability and response rates in patients with metastatic colorectal cancer receiving chronotherapy. In case of insulin therapy, implantable infusion pumps containing a reservoir of insulin may be surgically placed within the subcutaneous tissue of the abdomen in the left upper or lower quadrant (above or below the belt). A catheter leads from the pump through the muscle layers into the peritoneal cavity, where it floats freely, and insulin delivery is by the intraperitoneal route. The insulin reservoir is refilled once a month or every 3 months at a physician's office by inserting a needle through the skin into the pump (a local anesthetic is first used). Doses adjustments are made by the patient (within ranges established by the physician) using radiotelemetry and an electronic device that is held over the pump. Their advantages include the fact that the peritoneum provides a large, well-vascularized surface area, and absorption is faster by this route than after subcutaneous injection (better insulin gradient), improved glycemic control and a reduction in the frequency of hypoglycemic episodes. Possible drawbacks of this approach include eventual formation of fibrous tissue pocket and local skin erosion. Catheter blockade which can reduce insulin delivery, are the most common problems with implantable pumps. However, these pumps have been effectively used in the chronotherapy of several diseases such as cancer and diabetes.[46,47]

Controlled-release microchip: An alternative method to achieve pulsatile or chronopharmaceutical drug release involves using microfabrication technology. Santini et al. reported a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand. The release mechanism was based on the electrochemical dissolution of thin anode membranes covering microreservoirs filled with chemicals in solid, liquid or gel form.[48]

Approaches for Chronopharmaceutical DDS:

Various approaches of pulsatile drug: Pulsatile drug delivery system can be broadly classified into three classes.

I. Time controlled pulsatile drug delivery
II. Stimuli induced pulsatile drug delivery
III. Externally regulated pulsatile drug delivery

I. Time controlled pulsatile release: These time-controlled systems can be classified as single unit (e.g., tablet or capsule) or multiple unit systems.

A. Single Unit Systems: 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 as a "Pulse" from the insoluble capsule body.

1. **Capsular 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 as a "Pulse" from the insoluble capsule body. The system that comprises of a water-insoluble capsule enclosing the drug reservoir. A Swellable hydrogel plug was used to seal the drug contents into the capsule body. When this capsule came in contact with the dissolution fluid, it swelled; and after a lag time, the plug pushed itself outside the capsule and rapidly released the drug. Polymers used for designing of the hydro gel plug were various viscosity grades of hydroxyl propyl methyl cellulose, poly methyl methacrylate, poly vinyl acetate and poly ethylene oxide. The length of the plug and its point of insertion into the capsule controlled the lag time.[49]
2. **Tablets system:** 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 consists of a solid dosage form coated with lipidic barriers containing carnauba wax and bees wax along with surf actants, 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. The Chronotropic® system consists of a drugcontaining core coated by Hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of release. [50,51]

B. Multiparticulate systems: Multiparticualte systems (e.g., pellets) 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 multiparticulate systems is lower due to presence of higher quantity of excipients. [50]

II. Stimuli induced:

1. **Temperature Induced System:** (Thermo-Responsive Pulsatile release) Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems the polymer undergoes swelling or de swelling phase in response to the temperature which modulate drug release in swollen state. Kataoka et al developed the thermo sensitive polymeric micelles as drug carrier to treat the cancer. [52,53]

2. **Chemically Induced System:** There has been much interest in the development of stimuli-sensitive delivery systems that release a therapeutic agent in presence of specific chemical moieties like enzyme or protein. One of the good examples is Glucose-responsive insulin release devices in which insulin is release on increasing of blood glucose Level. In diabetes mellitus there is rhythmic increase in the levels of glucose in the body requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the de swelling mode thereby decreasing the insulin release. [54]

III. External stimuli pulsatile release: For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation**.**

1. **Electrically Stimulated**: Electrically responsive delivery systems are prepared by poly electrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. Under the influence of electric field, electro responsive hydrogels generally bend, depending on the shape of the gel which lies parallel to the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes.[55]
2. **Magnetically Stimulated:** Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads. [57] Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials in beads such as magnetite, iron, nickel, cobalt etc**.**
3. **Pulsatile release systems 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.[56]

Recent Advances in Hypertension Chronopharmaceutical DDS

1. OROS Technology

Chronoset™ is proprietary OROS® (Osmotic-controlled Release Oral delivery System) developed by Alza Corporation (now part of Johnson and Johnson). The system is composed of two compartments-the drug vessel and the osmotic engine cap. When the system is exposed to an aqueous medium, water permeates into the osmotic engine cap via a ratecontrolling membrane. Hydration of the osmotic engine leads to its expansion, which exerts a driving force against the ridge of the drug vessel. The two compartments separate from each other by sliding apart. After disengaging, the open mouth of the drug vessel is exposed to the fluid environment. The Chronoset® can deliver essentially the entire dose and minimizes the drug residue in the drug vessel after the operation. The vessel is made of water impermeable ethylene-co-vinyl acetate copolymer (EVA), while the cap is made of proprietary water-permeable blends of polycaprolactone (TONE) and flux enhancers.[58,59]

2. CEFORM® technology

Ceform® allows the production of uniformly sized and shaped microspheres of pharmaceutical compounds. These microspheres are almost perfectly spherical, having a diameter that is typically 150 to 180 mm, and allow for high drug content. The microspheres can be used in a wide variety of dosage forms, including tablets, capsules, suspensions, effervescent tablets, and sachets. The microspheres can be coated for controlled release (Ceform CR), provided with an enteric coating (Ceform EC), or combined into a fast/slow release combination (Ceform EA/CR). [67,68]

3. **DIFFUCAPS® technology**

Diffucaps is a multiparticulate bead system comprised of multiple layers of drug, excipients, and release-controlling polymers. The beads contain a layer of organic acid or alkaline buffer to control the solubility of a drug by creating an optimal pH microenvironment for drugs that exhibit poor solubility in intestinal pH, in environments with pH greater than 8.0, or in physiological fluids. Alternatively, the beads can contain a solid-solution of drug and crystallization inhibitor to enhance bioavailability by maintaining the drug in its amorphous state. Each Diffucaps bead has an inert core surrounded by drug and coated with a functional polymer membrane to control the rate of drug release. Diffucaps beads are <1.5 mm in diameter and can be filled into capsules or compressed into orally disintegrating tablets.[63,64]

Advantages of Diffucaps:

- Ideal for drugs exhibiting poor solubility in lower intestinal pH, in environments with pH above 8.0, or in physiological fluids.
- Can combine multiple drugs and/or multiple release profiles in the same dosage form.
- Simple formulation of dose-proportional strengths.
- Can minimize food effect.

4. **CODAS® technology (Elan Drug Technologies, USA)**

CODAS (Chronotherapeutic Oral Drug Absorption System) are a multiparticle system designed for bedtime drug dosing, incorporating a 4–5-hour delay in drug delivery. This delay is introduced by the level of nonenteric release-controlling polymer applied to drug-loaded beads. The rate of release is essentially independent of pH, posture, and food. GeoClock® technology (Skye Pharma PLC, UK) Geoclock® tablets have an active drug inside an outer tablet layer consisting of a mixture of hydrophobic wax and brittle material in order to obtain a pH-independent lag time prior to core drug delivery at a predetermined release rate.[60-62]

Table.4: Marketed Technologies of Chronopharmacotherapy drug delivery

Technology	Mechanism	Proprietary name and Dosage form	API	Disease	Advantage
OROS® [58,59]	Osmotic mechanism	Covera-HS®; XL Tablet	Verapamil HCl	Hypertension	Prevent the dangerous surge of BP in the early morning
CODAS® [60-62]	Multiparticulate,pH dependent system	Verelan® PM; XL Release Capsule	Verapamil HCl	Hypertension	Early morning peaks plasma concentration after bed time dosing
DIFFUCAS® [63,64]	Multiparticulate System	Innopran®; XL tablets	Propranolol HCl, Verapamil HCl	Hypertension	Lag time is 4-5 hours. Release is pH independent
PULSINCAP® [65,66]	Rupturable system	Pulsincap®	Dofetilide	Hypertension	Lag time can be controlled by manipulating the dimension and the position of the plug

PROCARDIA XL® [9]	Sustained release	Procardia XL	Nifedipine	Hypertension	Increase ability to exercise and decrease the frequency of chest pain attacks
CEFORM® [67,68]	Extended Release tablet	Cardizem LA;	Diltiazem HCl, Verapamil HCl	Hypertension	Production of uniformly sized and shaped microspheres

DISCUSSION

Now a day's, in the field of drug delivery, more focused is done on the potential of systems that are able to release drugs after a programmable lag phase i.e. in a pulsatile mode. Beside these systems, multi particulate systems (e.g. pellets) offer several advantages over single unit .In addition to this, there are no risk of dose dumping, flexibility of blending units with different release patterns, as well as short and reproducible gastric residence time. The future of chronotherapeutics and delivering drugs in a pulsatile manner seems to be quite promising as in certain diseases states. It exhibit several advantages over the traditional zero or first order drug delivery mechanism. Time controlled or site specific single or multiple units are obtained by pulsatile drug delivery techniques.

Conclusions

Although sustained and controlled drug delivery systems have acquired a lot of success and application in field of Pharmacy. These systems are not able to deliver drug according to circadian behaviour of diseases but pulsatile systems have importance in this regard. Due to their high efficiency and lack of undesirable adverse effects to the whole body, the stimuli-responsive feature of these systems is useful for treatment of patients. But major drawbacks arise from the biological variations among individuals. The basic parameters in the design of polymer based pulsatile systems are the biocompatibility and the toxicity of the polymers used. It can be concluded that Pulsatile drug delivery system provide a unique way of delivering drugs possessing chronopharmacological behaviour, extensive first pass metabolism, necessity of night time dosing, or absorption window in GIT. Pulsatile drug delivery system shall be promising in future.

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