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Review on Chronomodulated Drug Delivery Systems

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Abstract: *Chronomodulated drug delivery systems are gaining a lot of interest as they deliver the drug based on the circadian rhythm of disease. It releases drug at the right place at the right time and in the right amount, increasing patient compliance by reducing dosing frequency. Such systems are designed in such a way that complete and rapid drug release is followed by predetermined lag time they are also known as pulsatile drug delivery systems (PDDS), time-controlled systems, or sigmoidal release systems. Numerous systems like capsular systems, osmotic systems, single and multiple-unit systems based on the use of pH sensitive polymers, erodible polymer and swelling hydrophilic polymers have been discussed in the article. These systems are beneficial for the drugs having chronopharmacological behavior such as drug used in treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis like inflammatory disorders. This review article discuss various diseases targeted by pulsatile drug delivery system, types and classification of chronomodulaed delivery systems and patented technologies. A number of chronotherapeutic medications, aiming at synchronizing medications and the intrinsic biorhythms of disease have been developed by novel drug delivery technology.*

Keywords: Pulsatile drug delivery system, chronomodulated, circadian rhythm, chronobiology

I. INTRODUCTION

The phrase “circadian rhythm” was first described by Halberg and Stephens in 1959.[1] The biological clock was since found to be represented by the suprachiasmatic nucleus (SCN), which creates biological rhythms under the control of clock genes such as PER1,[2,3] PER2,[2] PER3,[4] CLOCK,[5] BMAL1,[6] TIM,[7] CRY,[1] CRY2,[8] tau[9] and coordinate peripheral oscillators, for functions including cell proliferation and cellular metabolism. The cycle duration generated at the SCN is calibrated by the alternation of light / darkness, both directly and through melatonin secretion by the pineal body [Figure1]. Period genes (PER) and the proteins produced by these genes generate circadian rhythms.[10] The transcription of PER is promoted by the CLOCK / BMAL1 complex, whose activation is inhibited by the PER1 / PER2 / PER3 / CRY1 / CRY2 / TIM complex. This giant complex acts as a negative auto-feedback system, which has an essential role in the generation of circadian oscillation. This biological clock generates signals of circadian rhythm, which are conducted to the supracervical sympathetic nucleus and the pineal body. The generated biological rhythms deal with the control of biological functions including those of the autonomic nerve system, endocrine system, and immune system, which are fundamental in homeostasis and in protection against various diseases [Figures 2 and 3].

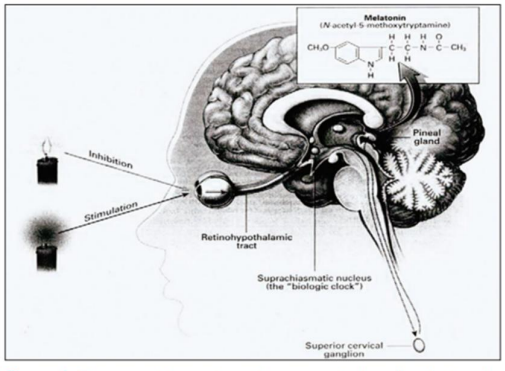

Figure 1: The suprachiasmatic nucleus controls circadian rhythms in response to hormonal variation in the body

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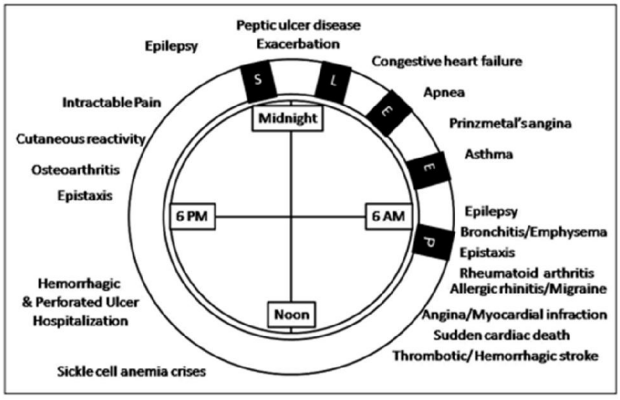

Figure 2: Time cycle when the diseases show their maximum effect

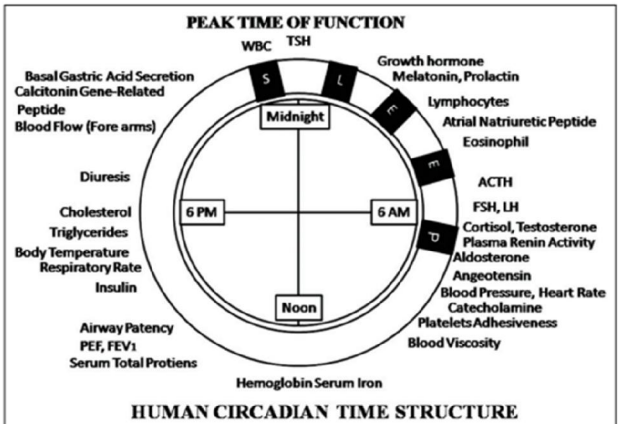

Figure 3: Human circadian time structure; shown is the approximate peak time of the circadian (24-hour) rhythms of selected biological variables in persons adhering to a normal routine of daytime activity (6 – 7 a.m. to 10 – 11 p.m.) alternating with night time sleep

Surprisingly not enough or very little consideration has yet to be given to a very important factor which may, by itself, represent a significant and often crucial determinant of therapeutic success: TIME. As all physiological functions oscillate rhythmically in time, the activity, toxicity, and kinetics of a medication may depend on its administration time, in relation to the staging of circadian and other biological rhythms. On the other hand, the temporal (biological rhythm) structure of the human body may be altered by disease, leading to significant changes in the response to therapy. Although sustained and constant release systems have been developed, the biological systems are not so responsive to these release systems. In addition, sustained and controlled release devices are not applicable in some cases like the timeprogrammed administration of hormones and many drugs. The pulsatile drug delivery system has fulfilled this requirement. Pulsatile drug release is a system where the drug is released suddenly after a well-defined lag time or time gap according to the circadian rhythm of disease states.[11] No drug is released from the device within this lag time. This delivery system is suitable in cases where drugs including proteins and peptides undergo great metabolic degradation. In case of chronic treatment, the drug resistance may grow and an adverse effect may be seen. Here chances are less because the desired concentration of the drug at a certain time point is available.[12,13] This method is good for drugs with extensive first pass metabolism and those targeted to specific sites in the intestinal tract. Therefore, by developing the pulsatile device for specific colonic delivery, the plasma peak is obtained at an optimal time, the number of doses per day can be reduced, it is with saturable first pass metabolism, and tolerance development can also be avoided.[14-19]

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Advantages and Disadvantages of the Pulsatile Drug Delivery System

Advantages

- Predictable, reproducible, and short gastric residence time
- Less inter- and intra-subject variability
- Improves bioavailability
- Reduced adverse effects and improved tolerability
- Limited risk of local irritation 6. No risk of dose dumping
- Flexibility in design
- Ease of combining pellets with different compositions or release patterns
- Improves stability
- Improves patient comfort and compliance
- Achieves a unique release pattern
- Extends patent protection, globalizes the product, and overcomes competition

Disadvantages

- Low drug loading
- Proportionally higher need for excipients
- Lack of manufacturing reproducibility and efficacy
- Large number of process variables
- Multiple formulation steps
- Higher cost of production
- Need of advanced technology
- Trained / skilled personnel needed for manufacturing

Circadian rhythms in gastrointestinal, liver, kidney, and other body processes and functions are of great importance for therapeutics, for example, in choosing when to administer medications, in relation to rhythm, influences their pharmacokinetics, effect-duration, efficacy, adverse effects, and beneficial outcomes.[19] Besides chronotherapeutic applications, oral pulsatile delivery systems may offer a number of different advantages. When designed to yield repeated release profiles, they could accomplish multiple daily dosing regimens for those drugs that fail to be candidates for prolonged-release formulations, on account of a strong first-pass effect or pharmacological tolerance. Of late, multi-pulse delivery of antibiotics has also been described as a means of limiting the development of resistant bacterial strains thus possibly improving the outcome of infectious disease therapy.[20] Moreover, delayed-release dosage forms have been proposed to prevent the occurrence of detrimental drug–drug interactions, without modifying the administration schedule of combined medications, which could negatively affect patient compliance.[21] Stevens et al., [22] have used extrusion / spheronization technology to produce a novel pellet formulation containing diltiazem that is coated with a mixed film coat comprising of ethylcellulose and Eudragit RS polymers. Although the ethylcellulose component acts as a diffusion barrier, retarding the release of diltiazem, the permeability of the Eudragit RS increases progressively. The overall effect is a sigmoidal release profile. The release profile of systems based on permeability changes depend strongly on the physicochemical properties of the drug and its interaction with the membrane. Therefore, with this system a pulsatile release profile may be obtained for some particular drug molecules in a specific formulation, but it cannot be generally applied to all drugs. This article reviews the current status and recent technologies available through a new sub-discipline chronopharmaceutics in a form of a chronomodulated drug delivery system.

Influence of Circadian Rhythms on Pharmacodynamics and Pharmacokinetics Chronopharmacodynamics

Biological rhythms at the cellular and subcellular levels can give rise to significant dosing-time differences in the pharmacodynamics of medications that are unrelated to their pharmacokinetics.[23-28] This phenomenon is termed ‘chronesthesy’.

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Drug Absorption

Circadian changes in drug absorption have been demonstrated for several orally administered drugs, in humans. Gastric acid secretion and pH, motility, gastric emptying time, and gastrointestinal blood flow vary according to the time of the day.[29,30] Such changes may contribute to the dosing time-dependent difference of drug absorption. For example, circadian changes of pH may induce circadian modifications of drug ionization according to its physicochemical properties. The dosing time-dependent difference of drug absorption is influenced by the physicochemical properties of a drug (lipophilicity or hydrophilicity).[31] The circadian changes in drug absorption are significant in lipophilic drugs, while such changes are not demonstrated for hydrophilic drugs.[32] Drug absorption by other than an oral route of administration is also influenced by biological rhythms.[33,34]

Drug Distribution

Circadian changes in biological fluids and tissues related to drug distribution are documented to vary according to the time of day.[35] Blood flow depends on several regulatory factors, including sympathetic and parasympathetic systems, in which activities are known to be circadian time-dependent with a predominant diurnal effect of the sympathetic system. [36] Thus, a diurnal increase and nocturnal decrease of blood flow and local tissular blood flows may explain a possible difference in drug distribution depending on the dosing time. Plasma proteins such as albumin or Alpha-1-glycoprotein acid have been documented to be circadian time-dependent.[37,38]

Drug Metabolism

Hepatic drug metabolism seems to depend on liver enzyme activity and / or hepatic blood flow. Both factors show a circadian time-dependent difference. Enzyme activities show a circadian time-dependent difference in many tissues such as brain, kidney, and liver.[39,40] Several chronopharmacological studies have indirectly investigated the temporal variations in hepatic drug metabolism by evaluating the chronopharmacokinetics of drugs and their metabolites. Thus, conjugation, hydrolysis, and oxidation show a circadian time-dependent difference. For example, circadian variations in the urinary 6β-hydrocortisol to cortisol ratio in man show these in the cytochrome CYP3A activity.[41]

Drug Elimination

Renal physiological functions such as glomerular filtration, renal blood flow, urinary pH, and tubular resorption show a circadian time-dependent difference with higher values during daytime.[42] These rhythmic variations in renal functions may contribute to a circadian-dependent change in drug urinary excretion. The rhythmicity in urinary pH modifies drug ionization and may explain that acidic drugs are excreted faster after an evening administration as demonstrated for sodium salicylate[43] and sulfasylazine.[44]

II. CIRCADIAN RHYTHMS IN OCCURRENCE AND SEVERITY OF DISEASE

The symptom intensity of many medical conditions and the occurrence of life-threatening medical emergencies exhibit rather precise timings. Gout,[45,46] gallbladder,[47] and peptic ulcer attacks[48] are most frequent at night. Acute pulmonary edema,[49] congestive heart failure,[50] and asthma[51,52] worsen nocturnally. Sudden infant death,[47] symptoms of allergic rhinitis,[53,54] and rheumatoid arthritis[55] are either most intense overnight or in the morning upon wakening. Migraine headache is typically triggered during rapid eyeball movement (REM) episodes during night time sleep or in the early morning hours after awakening.[56,57] Angina pectoris,[58,59] ventricular arrhythmia,[60,61] acute myocardial infarction,[62] sudden cardiac death,[63] stroke,[64,65] fatal pulmonary embolism, and hypertensive crises,[66] all are most frequent in the morning, as are other cardiovascular conditions.[67] Depression is most severe in the morning.[68] Symptoms of osteoarthritis worsen during the course of daily activity, being typically most intense in the late afternoon and evening.[69,70] Perforated and bleeding ulcer is reported to be most common in the afternoon.[71,72] Some seizure disorders are triggered during specific sleep stages and / or by transitions between sleep and wakefulness.[73,74]

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Recently Available Different Chronopharmaceutical Technologies

OROS® Technology

Chronset™ is a proprietary OROS®[75] delivery system that reproducibly delivers a bolus drug dose, in a time- or sitespecific manner, to the gastrointestinal tract.[76] It is nothing but an osmosis-based system. The active pharmaceutical is kept in a reservoir surrounded by a semipermeable membrane laser, drilled with a delivery orifice, and formulated into a tablet. There are two layers in this tablet comprising of one drug layer, and the other, a cosmetically active agent. Upon contact with the GI fluid this osmotic agent changes its characteristic from a nondispensable to a dispensable viscosity. As a result the active pharmaceutical is pushed away through the channel due to the pump effect of the osmotic agent. It is generally used in the designing of an extended release tablet.

CEFORM® Technology

It produces uniformly sized and shaped microspheres of pharmaceutical compounds.[77] This approach is based on 'melt-spinning,' which means subjecting solid feedstock (i.e., biodegradable polymer / bioactive agent combinations) to a combination of temperature, thermal gradients, mechanical forces, and flow and flow rates, during processing. The microspheres obtained are almost perfectly spherical, having a diameter that is typically of 150 – 180µm, and they 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 may be coated for controlled release with an enteric coating or may be combined into a fast / slow release combination. This technology has been actually used to develop CardizemR LA, a one-day diltiazem formulation like ChrDDS.[78]

CONTINR Technology

In this technology, molecular coordination complexes are formed between a cellulose polymer and non-polar solid aliphatic alcohol, optionally substituted with an aliphatic group, by solvating the polymer with a volatile polar solvent and reacting the solvated cellulose polymer directly with the aliphatic alcohol, preferably as a melt. This constitutes the complex having utility as a matrix in controlled release formulations, as it has a uniform porosity (semipermeable matrixes), which may be varied.[79] This technology has concretely enabled the development of tablet forms of sustained-release aminophylline, theophylline, morphine, and other drugs. The CONTINR technology provides for closer control over the amount of drug released to the bloodstream, and benefits patients in terms of reducing the number of doses they need to take every day, providing more effective control of their disease (particularly at night), and reducing unwanted side effects.[80,81]

DIFFUCAPS® Technology

In the DIFFUCAPS® technology,[82] a unit dosage form, such as a capsule is used for delivering drugs into the body in a circadian release fashion. DIFFUCAPS®, is a multiparticulate technology by Reliant Pharmaceuticals LLC, for a chronotherapeuticdelivery of a combination of two drugs, Verapamil HCl and PropanololHCl, as an extended release tablet (Innopran®). Pulsincap® system is one of the most used pulsatile systems based on capsules. It was developed by R. P. Scherer International Corporation, Michigan, US. Diffucaps®, and comprises of one or more populations of drug-containing particles (beads, pellets, granules, etc.). Each bead population exhibits a pre-designed rapid or sustained release profile, with or without a predetermined lag time of 3 – 5 hours. The active core of the dosage form may comprise of an inert particle or an acidic or alkaline buffer crystal (e.g., cellulose ethers), which is coated with an API-containing film-forming formulation and preferably a water-soluble film forming composition (e.g., hydroxypropylmethylcellulose, polyvinylpyrrolidone) to form a water-soluble / dispersible particle. The active core may be prepared by granulating and milling and / or by extrusion and spheronization of a polymer composition containing the API. Such a ChrDDS is designed to provide a plasma concentration time profile, which varies according to the physiological need during the day, that is, mimicking the circadian rhythm and severity / manifestation of a cardiovascular disease, predicted based on pharmacokinetic and pharmacodynamic considerations and In vitro / in vivo correlations. This technology has been used to formulate the first and recently FDA approved propranololcontaining ChrDDS (InnopranRXL) for the management of hypertension.[83]

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CHRONOTOPIC® Technology

It is also described in the system with an erodible, soluble or rupturable membrane system. It is basically a drug-containing core, coated with an outer release controlling layer. Both single and multiple unit dosage forms such as tablets and capsules or minitablets and pellets have been employed as the inner drug formulation.

EGALET® Technology

It is a delayed release form consisting of an impermeable shell with two lag plugs, enclosing a plug of active drug in the middle of the unit.[78] After erosion of the inert plugs the drug is released. Time taken to erode the inert plugs determines the lag time. The shells are made of slowly biodegradable polymers (e.g., ethylcellulose) and plasticizers (e.g., cetostearyl alcohol), while the matrix of the plugs is a mixture of pharmaceutical excipients, including polymers like polyethylene oxide (PEO).

CODAS® Technology

Chronotherapeutics Oral Drug Absorption System (CODAS) technology[84] is a multiparticulate system designed for bedtime dosing. Here a nonenteric coating is applied on the drug-loaded beads to delay the release of the drug, up to five hours. Here release controlling contains a mixture of both water-soluble and water-insoluble polymers. When this dosage form comes in contact with the GI fluid, the watersoluble polymer gets dissolved slowly and pores are formed on the coating layer. Drug diffuses through these resulting pores. The water-insoluble polymer, acting as a barrier, maintains the controlled, fashion-like release of Verapamil.[85] The rate of release is independent of pH, posture, and food.

GeoClock® Technology

The concept is designed on the basis of Geomatrix technology. [86] Initially a multilayer technology was recommended for constant drug release in this technology. The active core or hydrophilic matrix is coated partially on one or both bases. This partial coating adjusts the core hydration process and minimizes the surface area available for drug release. In the presence of the dissolution medium the barrier layer swells and becomes a gel. This gelling layer is not eroded, but acts as a modulating membrane to control the release process. The erodible surface is instead progressively removed by the dissolution medium. Upon erosion more of the planar surface(s) of the active core is exposed with increasing time to the outer environment, which helps drug release.

PORT® Technology

The Programmable Oral Release Technologies (PORT) system is a uniquely coated, encapsulated system that can provide multiple programmed release of the drug.[87] It contains a polymeric core coated with a semipermeable, rate-controlling polymer. Poorly soluble drugs can be coated with solubilizing agents, to ensure a uniform controlled release from the dosage form. In the capsule form, the gelatin capsule is coated with a semipermeable, rate-controlling polymer. Active medicament mixed with an osmotic agent is kept inside the capsule shell. A water-insoluble plug is used to seal the capsule shell. Immediate release compartment can be added according to need.

Three-Dimensional Printing® (3DP) Technology

Three-dimensional printing (3DP) is a novel technique used in the fabrication of complex oral dosage delivery pharmaceuticals, based on solid freeform fabrication methods. It is possible to engineer devices with complicated internal geometries, varying densities, diffusivities, and chemicals.[88] Different types of complex oral drug delivery devices have been fabricated using the 3DP process: immediate-extended release tablets, pulse release, breakaway tablets, and dual pulsatory tablets. The enteric dual pulsatory tablets were constructed of one continuous enteric excipient phase into which diclofenac sodium was printed into two separated areas. These samples showed two pulses of release during in vitro with a lag time between the pulses of about four hours.[89] This technology is the basis of the TheriForm technology.[90]

TIMERx® Technology

It is a hydrogel-based, controlled release device. This technology can provide from zero order to chronotherapeutic release.[91] It can provide a different release kinetic by manipulating molecular interactions. Basically, this technology

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primarily combines xanthan and locust bean gums mixed with dextrose. The physical interaction between these components works to form a strong, binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the TIMERx gum matrix, which expands to form a gel and subsequently releases the active drug substance.

Physicochemical Modification of the API

Physicochemical properties like solubility, drug lipophilicity, partition coefficient, crystalline form, membrane permeability, melting point, and so on, of the API (active pharmaceutical ingredient), can be modified by introducing new substitution to the original structure, to achieve a chronopharmaceutical effect.[92] The maximum plasma concentration of the drug (Tmax) varies upon the physiochemical modification of the parent compound.[93]

Controlled-Release Microchip

The solid-state silicon microchip is an alternative microfabrication technique similar to micrometer scale pumps, valves, and flow channels, which delivers the active medicament in a pulsatile manner.[94] It can provide controlled release of both single and multiple chemical substances according to the necessity. The release mechanism is based on the electrochemical dissolution of thin anode membranes covering the microreservoir filled with chemicals in solid, liquid, or gel form.

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, have been reviewed in detail elsewhere.[95] To our knowledgeinfusion pumps in the market that have been referred to as Chronomodulating for drug delivery application include, Melodie®, [96] programmable Synchromed®, [97] Panomat® V5 infusion,[98] and the Rhythmic®[99] pumps. The portable pumps are usually characterized by a light weight (300 – 500 g) for easy portability and precision in drug delivery.

Recent Advances in Pulsatile Drug Delivery Systems

S.No	Technology	Mechanism	name/ Marketed names/ Proprietor's name	Innovator'sCompany
1	OROS®	Osmotic Release Oral System. The system uses osmotic pressure as energy source for releasing drug	Concerta®Methylphenidate Procardia XL®: NifedipineInvega®: Paliperidone Ditropan XL	Corporation® Alza
2	ACCUBreak technology	Unique tablets that contain drug free layer which can be split into exact half for easy and precise dose adjustment.	ACCU-BTM bilayer tablet ACCU-TTM trilayer tablet	Accu-Break PharmaceuticalsInc, Plantation FL
3	SODAS®	technology Spheroidal Oral Drug Absorption System. Available in the form of oncedaily and extended-release formulation with a bi-modal release profile	Morphine- (Avinza®), Methylphenidate - (Ritalin® LA), Dexmethylphenidate hydrochloride- (Focalin® XR), fluvoxamine maleate (Luvox® CR)	Elan's Drug Technologies
4	MXDAS™	Technology Matrix Drug Absorption System. It contains drug in a blend of hydrophilic polymer matrix, which controls	. Afeditab®, a oncedaily nifedipine	Elan's Drug Technologies

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		release rate of drug through a process of diffusion and erosion in the gastrointestinal tract		
5	MXDAS™	Technology Matrix Drug Absorption System. It contains drug in a blend of hydrophilic polymer matrix, which controls release rate of drug through aprocess of diffusion and erosion in the gastrointestinal tract.	Afeditab®, a oncedaily nifedipine	Elan's Drug Technologies
6	CODAS®	Technology Chronotherapeutic Oral Drug Absorption System deliver drug to compliment a person's circadian pattern by showing lag time of 4-5 hrs after adminstrations	Verapamil is formulated as VERELAN	Elan's Drug Technologie
7	PRODAS®	Technology Programmable Oral Drug Absorption System. It consists of minitables filled in hard gelatin capsules	Minitablets with different release rates, or targeting to release drug at different sites can be developed. Technologies Possible to provide high drug loading in GI tract.	Elan's Drug
8	DUREDAS ™	Technology Dual Release Drug Absorption System bilayer tablet, Combines an immediaterelease granulate and a modified-release 9hydrophilic matrix complex as separate layers within the one tablet. which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form.	Drug release can be modified for achieving immediate and sustained release for different drugs or same drug.	Elan's Drug Technologies
9	GeoclockTM	Geoclock™ is a validated oral drug delivery technology that can be used to release the drug from the tablet after a pre-determined lag-time that is independent of food or pH.	released prednisone into the bloodstream in the early hours of the morning to suppress pro-inflammatory cytokine levels when they are at their peak LODOTRA® (RAY OS®	Skyepharma PLC UK
10	PulsysTM	This technology is used for once daily pulsatile dosing. Compressed tablet that contains pellets designed to release drug at different regions in the GI tract in a pulsatile manner.	Moxatag™Amoxicillin	MiddleBrookPharmaceuticals

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11	Eurand's MINITABS ®	It consists of cylindrical minitablets (2 mm diameter) for controlled release	Suitable for high drug loading	Aptalispharmaceutica l technologies,
12	Eurand's DIFFUCAP S®	Diffucaps is a multiparticulate bead system comprised of multiple layers of drug, excipients, and release controlling polymers Innopran	XL® propranolol and verapamil	Aptalispharmaceutica l technologies, US
13	Diffutab®	technology Hydrophilic and hydrophobic polymers are blended together to control the drug release by diffusion and erosion of a matrix tablet.	Particularly useful for high-dose products and drugs that require sustained release and/or once-a-day dosing	Aptalispharmaceutica l technologies, US
14	ORBEXA®	Consists of beads of a controlled size and density using granulation spheronization, and extrusion techniques	Well suited for sensitive molecules like proteins and suitable for high drug loading	Aptalispharmaceutica l technologies, US
15	BANNER'S VERSETR OL TM	Drug is uniformly dispersed in lipophillic or hydrophilic matrix and finally incorporated in soft gelatin capsule shell.	Provides time controlled release for wide range of drug	Banner's Pharmacaps Inc., US

CONCLUSION

Advances in chronobiology and chrono pharmocology has demonstrated the importance of biological rhythms in treatment of disease and this has led to a new approach to the development of novel drug delivery system-ChrDDS (Chronotherapeutical Drug Delivery System). As timing of drug administration in disease therapy has significant impact upon treatment success, ChrDDS in future is certainly going to gain popularity. Chronopharmaceutics will certainly improve patient outcome and optimize disease management in the future.

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