



A Comprehensive Review on Drug Delivery Systems and Technology Based on Chronotherapeutics

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ABSTRACT

All functions in human being are well controlled in time as biological rhythms of varied periods, both in health and disease. The circadian rhythm has been most explored and shown the great importance to the practice of medicine and chronotherapy. The application of circadian rhythm to chronotherapy may be accomplished by the pertinent timing of dosage forms to synchronize drug concentrations to rhythms in disease activity. The particular time that patients take their medicine is significant as it has significant impact on treatment success. Chronotherapeutic drug delivery system is valuable in the cure of disease, in which availability of drug is timed to match rhythms of disease, in order to optimize therapeutic effect and minimize side effects. In last few years various drug delivery systems and technologies based on chronotherapeutics have been developed and extensively studied.

Keywords: Chronotherapy, Circadian rhythm, Drug delivery systems, Lag time.

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INTRODUCTION

The term chrono basically refers to the observation that each metabolic event undergoes rhythmic changes in time.¹ Chronopharmaceutics consist of two words chronobiology and pharmaceutics.² Chronobiology is the study of biological rhythms and their mechanism³, whereas pharmaceutics is the science of dosage form design.⁴ Chronopharmacology is the science concerned with variations in the pharmacological actions of various drugs in a day.⁵ Physiological and biological conditions of the human body vary considerably during a day; results in changes in both disease state and plasma drug concentrations. Human circadian rhythm is based on sleep-activity cycle, is influenced by genetic makeup and hence, affects the body's functions day and night period. The dependence of bodily functions in certain disease states on biological time is well documented. A number of hormones are released in the morning, while others are released during sleep. Accordingly, diseases such as hypertension, asthma, allergic rhinitis, peptic ulcer and arthritis follow the body's circadian rhythm.^{1,6}

Chronotherapeutics is that the discipline concerned with delivery of medicines *in vivo* to match rhythms of disease symptoms so as to optimize therapeutic outcomes and minimize side effects. As more is learned about

chronotherapeutics, it's becoming increasingly more evident that the medication intake time could also be even more considerable than was recognized in the past.^{1,6} The practice of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hour period, may be altering as researchers report that some medications may work better if their administration is synchronized with day-night patterns and biological rhythms.⁷ From these points of view, development of dosage forms, in which drug is released only at a required time and effective drug levels are maintained, has been desired for chronotherapy. Chronomodulated drug delivery system is mainly concerned with delivery of the drug to synchronize the plasma drug concentrations to biological rhythm in diseased condition. When constant drug plasma levels need to be avoided, as in chronotherapy, time-controlled or pulsed-release formulations are preferable, especially in the treatment of early morning symptoms.¹ By timing drug administration, plasma peak is obtained at an optimal time and the number of doses per day can be reduced. Saturable first-pass metabolism and tolerance development can also be avoided.⁷

The chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated dosage form, and the special drug delivery system to synchronize drug concentrations to rhythms in disease state activity.⁸ Now a days chronotherapy is widely used in clinical medicine; these include special evening theophylline systems for chronic obstructive pulmonary disease⁹, conventional evening H₂-receptor antagonists for peptic ulcer disease^{7, 10}, conventional evening cholesterol medications for hyperlipidemia^{7,11}, and special



bedtime tablet and capsule blood pressure-lowering medication systems.¹²

Chronopharmacology and chronotherapeutics:

Chronopharmacology is the study of the manner and the extent to which the kinetics and dynamics of medications are directly affected by endogenous biological rhythms.^{7,13} In recent days because of scientific advancement, new insights in the functioning of the body were gained by 24 h monitoring of heart beat, hormone levels, temperature etc. Many diseases are identified to be based on body rhythm such as cardiovascular diseases, arthritis, duodenal ulcers, asthma, cancers, diabetes, hypercholesteremia, some neurological conditions, psychiatric disorders and sleep disorders as discussed earlier.^{12,13} Severe episodes of asthma occur mainly during the night and early mornings. The peak in serum cortisol, aldosterone, testosterone, adrenaline, platelet adhesiveness and blood viscosity was observed during the initial hours of diurnal activity. Whereas the peak, in the rhythms of basal gastric acid secretion, white blood cells, lymphocytes, prolactin, melatonin, eosinophils, ACTH, follicle stimulating hormone (FSH) and leutinizing hormone (LH) is manifested during specific times of sleep span. Insulin, cholesterol, triglycerides, platelet numbers and uric acid peak occur during the day and evening.^{14,15}

The administration of drugs as per circadian rhythms of diseases has to be taken into consideration while treating any disease. Chronotherapeutics may be achieved by optimizing the dosing schedules of 12 h medication systems, better timing of conventional once-a-day medication/delivery systems, or application of special tablet and capsule formulations dosed at designated times to proportion medications over the 24 h in synchrony with rhythm-determined requirements.^{12,13}

Chronotherapeutics is a branch of therapy that involves synchronizing the drug application in a manner that coincides with circadian rhythms in order to achieve an optimal therapeutic success.^{16,17} The knowledge of 24 h rhythm in the risk of disease plus evidence of rhythm dependencies of drug pharmacokinetics, effects, and safety constitutes the rationale for chronotherapy.⁸ Chronotherapeutics takes into account rhythm determinants in chronopathology, chronokinetics, chronodynamics and chronotoxicology of medications, and circadian time structure to determine the drug-delivery pattern and administration time to optimize desired benefits and minimize adverse effects. Chronotherapeutics need not involve only new medicines but also the better application of established ones in a different and more biologically efficient manner.^{12,13}

Drug delivery systems for chronotherapeutics

Using the concept of circadian rhythms, chronotherapeutic disorders can be treated via specialized drug delivery systems.¹⁸ In recent years, extensive emphasis has been placed on drug delivery systems that provide pulsatile drug release for the treatment of chronotherapeutic disorders.

When treating chronotherapeutic disorders where pulsatile drug delivery is necessary, drug may be released after a lag-phase at a predetermined time intervals when they are most needed. Pulsatile drug delivery offers advantages such as extended day-time or night-time activity, reduced side-effects, reduced dosing frequency and dose size, improved patient compliance and lower treatment costs.^{16,19} Pulsatile release formulations include time controlled release and site-specific dosage forms. When constant drug plasma levels need to be avoided, as in chronotherapy, time-controlled or pulsed-release formulations are preferable, especially in the treatment of early morning symptoms. By timing drug administration, plasma peak is obtained at an optimal time, and the number of doses per day can be reduced.^{1,20}

Various technologies to develop chronotherapeutic drug delivery systems have been extensively studied in recent decades. Chronotherapeutic delivery systems may be a single unit or multiple unit systems, mainly include tablet, capsule, advanced osmotic devices and multiparticulate delivery system. These units have the capability of delivering therapeutic agents into the body in a time or position controlled pulsatile release fashion.

System with rupturable polymeric coating

These types of devices are consisting with a core surrounded by rupturable polymeric layer. As the water/media ingress through the polymeric coating membrane, a positive pressure builds up inside the system which results in rupture of outer polymeric layer. The core having active component contains swelling polymer/agents, osmogens or gas-producing effervescent excipients. The major factors that affect the lag time are the rate of water permeation through outer membrane and mechanical resistance of the surrounding layer. Ueda et al., (1994) reported a time controlled explosion system (TES), where drug was released neither by diffusion control nor by dissolution control but a quite novel mechanism i.e. explosion of the outer membrane.²²⁻²⁴ Ranjan OP et al. (2014) developed a chronomodulated drug delivery system of montelukast sodium coated with a blend of ethyl cellulose and eudragit L100 for management of asthma. It consists of fast-swelling tablet core containing montelukast sodium coated with a blend of different ratios of ethyl cellulose (gastrointestinal tract (GIT)-insoluble polymer) and eudragit L100 (enteric polymer). With increasing percentage of eudragit L100 in coating composition, the lag time decreased and release rates significantly increased.²⁵

System with soluble or eroding polymeric coating

These are a class of reservoir type pulsatile drug delivery system (PDDS) based on soluble/erodible polymeric layers surrounding the drug containing core. It may be of a single unit or multiparticulate. The surrounding outer layer dissolves or erodes after a definite period of time followed by burst release of active pharmaceuticals from the reservoir core. The onset of release and lag time can be



controlled by the thickness of the outer barrier membrane.²³

System with change in membrane permeability

A change in membrane permeability depends mainly on the physicochemical characteristics of the drug and its interaction with the surrounding rate controlling layer. A minute quantity of sodium acetate, citric acid, succinic acid etc. in the core has also momentous effect on the drug permeability of the eudragit film. As these acids in the core solubilizes, the permeability of the polymeric membrane increases. That leads to the release of complete dose within a few hours after initial lag time.²⁶

Compression coated tablet

These are composed of an inner drug containing core surrounded by an outer layer that gradually erodes/dissolves to make a lag time of drug release. This compression coating technique eliminates the complicated and time-consuming coating processes and also protects the drug from moisture to make it stable. Factors affecting the drug release are mainly percentage weight ratio of the coating polymers, type of polymer coatings and component of excipients in the core tablets. The polymers in the coat of the tablet formulation to control drug release could include non-saccharidic swelling polymers viz., hydrophilic cellulose derivatives, alginic acid, carrageenans, guar gum (Gug), xanthan gum (XG) and locust bean gums, polyvinyl alcohol (PVA) and polyethylene oxide (PEO); hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC) and calcium or sodium carboxymethylcellulose (CMC), as well as hydrophobic polymers, ethylcellulose.²⁷

Capsule type delivery system

Several systems have been designed based on capsular drug delivery for pulsatile release. These systems mainly consist of an insoluble capsule body, filled with drug and then sealed with a swellable hydrogel plug. The lag time is controlled by a plug which either erodes or pushes itself outside the insoluble capsule body allowing the drug to release rapidly. Polymers used for developing these hydrogel plugs are various viscosity grades of different swellable polymer like hydroxypropyl methylcellulose (HPMC), polymethylmethacrylates, PVA, PEO, sodium alginate, guar gum, xanthan gum etc. Gohel and Sumitra developed a system wherein weighed quantity of dicalcium phosphate (DCP) was filled into the capsule body followed by the drug (diltiazem HCl). Weighed amount of the hydrophilic swellable polymers such as HPMC/guar gum was placed on top and compressed lightly using a rod to form a compact plug.²⁸ Nayak et al. (2009) designed a capsule-based drug delivery system for delayed delivery of valsartan for early morning surge of blood pressure. The hydrogel plug has been replaced by an erodible tablet, which has a tight fit in the capsule to prevent entry of fluid. Assembly of the pulsed release capsule device consisted of (i) swellable polymer weighed into the precoated capsule

body; (ii) a drug tablet placed onto the compacted swellable polymer layer; (iii) an erodible tablet made up of hydrophilic polymers inserted into the mouth of the capsule. During the release process, it erodes away from the mouth of the capsule. The erosion rate of tablet plug controls the lag time of release. The capsule body is closed with water soluble cap.²⁹

Osmotic drug delivery system

Osmotic based delivery systems are most promising strategy-based devices for controlled drug delivery. Osmosis can be defined as the net transport of water across a semi-permeable membrane driven by difference in osmotic pressure due to solute concentrations across the membrane. Osmosis is exploited for development of ideal controlled drug delivery system. Osmotic pressure created by osmogen is used as driving force for these systems to release the drug in controlled manner. These osmotic based systems suitable for oral administration usually consist of a core containing drug, osmotic agent and a water swellable polymer which is further coated with a semipermeable polymeric membrane having one or more delivery ports/orifice. As the core absorbs water, it expands in volume, which delivers the drug solution or suspension out through delivery orifice. The rate of absorption of water by core mainly depends on the difference in osmotic pressure cross the semi-permeable membrane. The major advantages of osmotic based systems are that they are applicable to drugs with wide range of aqueous solubility and release the drug at a rate that is independent of the pH and hydrodynamics of the external dissolution medium.³⁰ Ranjan OP et al. (2013) designed an osmotically controlled pulsatile release capsule of montelukast sodium for chronotherapy of asthma. Assembly of the capsular systems consisted of push, active and plug tablet arranged from bottom to top in hard gelatin capsule. The capsule system was coated with a semi-permeable membrane of cellulose acetate and drilled towards plug side in cap.³¹

Multiparticulate delivery system

Various techniques are available for the pulsatile delivery, broadly classified as, Single-unit and Multiple-unit systems. In recent pharmaceutical applications involving pulsatile delivery, multiparticulate dosage forms are gaining much favor 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 the flexibility to blend pellets with different compositions or release patterns. Because of their smaller particle size these systems are capable of passing through the GI tract easily, leading to less inter- and intra-subject variability. The major mechanism by which the drug is released from pellets depends on the type of coating; insoluble coating under all physiological conditions, pH-dependent coating whose solubility changes dramatically at some point in GI tract and slowly erodible coating.^{23, 24}



Ueda et al. (1994) developed a time-controlled explosion system (TES), where drug is released by a quite innovative mechanism i.e. by sudden explosion of the outer membrane. It is especially useful with low solubility drugs in which drug release is delayed due to slow diffusion of the drug through a permeable coating. Pulsatile release pellets containing diclofenac sodium were prepared by extrusion-spheronization technology further coated with two layers, inner swelling layer and outer controlled layer. The lag time and rate of drug release were influenced by the swelling material, the coating level of the inner swelling layer and the outer controlled layer.²²⁻²⁴

Narisawa et al. (1993 and 1996) have developed a delivery system capable of pulse release depending on the change in diffusion properties of eudragit RS. They found significant increase in release pattern from a core of theophylline coated with eudragit RS in presence of organic acid solution containing succinic, acetic, glutaric, tartaric, malic, or citric acid. When succinic acid was incorporated into the core of eudragit RS-coated theophylline beads, the drug release profile showed a typical sigmoidal pattern. This was due to the interaction of quaternary ammonium groups present in eudragit RS with acids which leads to greater hydration of film.^{32, 33}

Tekade and Gattani, (2010) prepared dual cross-linked pulsatile release beads containing theophylline (TPH) as a model drug and employing a simple technique (ionotropic gelation) using sodium alginate and delonix regia gum (DRG).³⁴ The purpose of combining sodium alginate and DRG for formulation of dual cross-linked bead is to get the advantage of increased swelling of both these natural polymers in higher pH followed by burst release after a pre-determined lag time. The prepared beads were further coated with eudragit polymers having pH-dependent solubility in order to increase the lag time prior to rapid and complete drug release. It has been reported that eudragit L 100 and S 100 in a ratio of 1:2 w/w showed maximum solubility in pH 6.8 buffer solution. Thus, this combination of these two polymers was selected for coating of dual cross-linked beads. Khan et al., (2010) has developed pH dependent micro beads of alginate and chitosan beads exploiting pH sensitive property for colon targeted delivery of theophylline. Alginate and chitosan beads were prepared by ionotropic gelation method followed by enteric coating with Eudragit S100. The formulated beads can be used effectively for the delivery of drug to colon.¹⁶

Low density floating multiparticulate PDDS reside specifically in the stomach and are not affected by variability of pH, local environment, or the gastric emptying rate. A blend of floating and pulsatile principles of drug delivery system would have the advantage that a drug can be released in the upper GI tract after a definite time period of no drug release. Sharma and Pawar, (2006) developed a low density floating beads of sodium alginate containing porous calcium silicate (Florite RE), for time and site specific drug release of meloxicam for chronotherapy

of rheumatoid arthritis. The floating time for this system was controlled by density of beads and hydrophobic character of drug.³⁵ Badve et al., (2007) developed hollow calcium pectinate beads for floating-pulsatile release of diclofenac sodium intended for chronopharmacotherapy of rheumatoid arthritis.³⁶

Marketed chronopharmaceutical technologies

Various systems have been developed and marketed taking chronopharmaceutics in consideration. One of the first commercially available oral products to employ the use of chronotherapy is the long acting bronchodilator Uniphyll[®] (Purdue Frederick Co., Norwalk, Connecticut, USA). Chronopharmaceutical technologies currently available include: OROS[®] (DURECT Corporation, Cupertino, California, USA), CODAS[®] (Elan Corporation, Gainesville, Florida, USA), CEFORM[®] (Biovail Corporation, Mississauga, Ontario, Canada), CONTIN[®] (Purdue Pharma, Pickering, Ontario, Canada), TIMERx[®] (Penwest Pharmaceutical Company, Danbury, Connecticut, USA), Diffucaps[®] (Eurand Pharmaceuticals, Yardley, Pennsylvania, USA) and Pulsincaps[®] (CatalentPharma Solutions, Somerset, New Jersey, USA).

OROS[®]

OROS[®] delivery system patented by the DURECT Corporation (Cupertino, California, USA) utilizes an osmotic mechanism to provide pre-programmed, controlled drug delivery in a time or site specific manner to the gastrointestinal tract. The drug delivery technology comprises a drug-loaded compartment, a push compartment and a semi permeable membrane laser drilled to link the drug layer with exterior of the drug delivery system. Drug release occurs due to the influx of fluid across the semi-permeable membrane into the push compartment. The increase in osmotic pressure forces drug to diffuse through the microscopic orifice.¹⁶ Covera-HS[®] (verapamil), an antihypertensive was formulated using L-OROS[®] technology by Alza Corporation for delayed overnight drug release to prevent the surge in blood pressure that occurs in patients during the early morning.

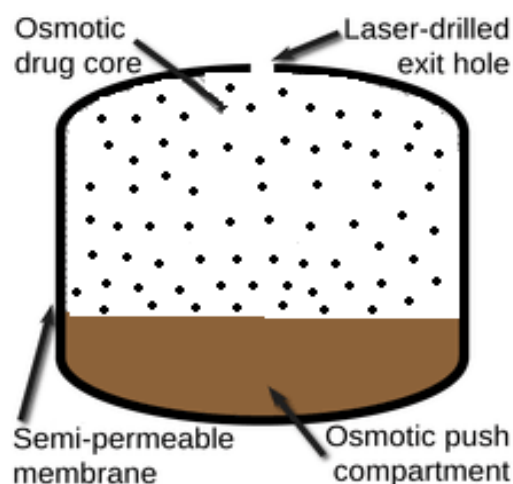


Figure 1. OROS Technology

CODAS[®]

Chronotherapeutic Oral Drug Absorption System (CODAS[®]) manufactured by Elan Corporation (Florida, USA) is a multiparticulate system designed for bedtime dosing that provides a delayed onset of drug release. The technology comprises a drug loaded core and a release controlling membrane surrounding the core. Here, release controlling layer contains a mixture of both water-soluble and water-insoluble polymers. When these dosage forms are exposed to GI fluid or water, the water-soluble polymer dissolves and drug diffuses through the pores present in the coating. The water-insoluble polymer acts as a barrier and maintains the release of the drug.¹⁶ The CODAS[®] technology has been applied to the chronopharmaceutical, Verelan[®] PM (verapamil) and introduced into the US market (Schwarz Pharma, USA). This formulation is designed to release verapamil, 4-5 h after ingestion. Bedtime administration of this formulation, the maximum plasma concentration is achieved in the early hours of the morning.³⁷

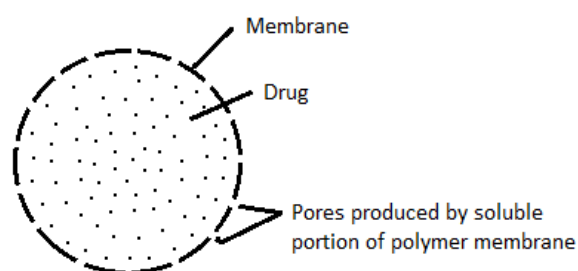


Figure 2. CODAS Technology

CEFORM[®]

The CEFORM[®] technology (Biovail Corporation, Mississauga, Ontario, Canada) allows the production of uniformly shaped and sized microspheres, having a diameter of 150-180 μm . The microspheres can be used in a wide variety of dosage forms including tablets, capsules, suspensions, effervescent tablets and sachets.^{16, 38} The microspheres can be coated for controlled release either with an enteric coating or combined into a fast/slow release combination.²⁶ The technology was developed for chronotherapeutic drug delivery of Cardizem[®] LA which is a once-daily diltiazem formulation.¹⁶ Graded-release diltiazem HCl extended release formulation (GRD) administered once daily at bedtime significantly reduces blood pressure and heart rate over the 24 h interval. Greater reduction is obtained between 6 a.m. and 12 p.m., when circadian BP is highest, compared to morning administration of the same dose.^{29, 38}

CONTIN[®]

CONTIN[®] technology developed by Purdue Pharma (Ontario, Canada), involves combining a drug and hydrophilic polymer followed by selective hydration with a polar solvent and fixation through a higher aliphatic alcohol.^{16, 40} Here, cellulose polymer and a nonpolar solid aliphatic alcohol constitute molecular coordination complexes between them having utility as a matrix in

controlled release formulations since it has a uniform porosity which may be varied. This technology is employed in the long-acting bronchodilator Uniphyll[®].⁴¹

TIMERx[®]

TIMERx[®] technology was developed by Penwest Pharmaceuticals (Danbury, Connecticut, USA). This technology enables the drug to be delivered after a predetermined lag-phase that coincides with the circadian rhythm or allows the drug to be delivered to various sites within the gastrointestinal tract. This system is based on a hydrophilic matrix combining a hetero-dispersed mixture composed primarily of two polysaccharides, xanthan gum and locust bean gum, in the presence of dextrose. The drug release is controlled by the rate of water penetration into the TIMERx[®] gum matrix, which expands to form a gel and subsequently releases the active drug substance. The rate of water permeation can be controlled precisely by varying the proportion of the gums, together with the tablet coating.⁴²

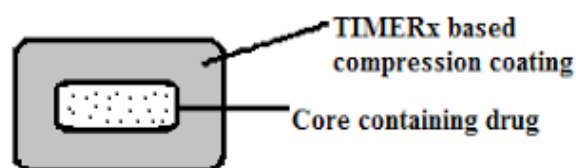


Figure 3. TIMERx Technology

Diffucaps[®]

Diffucaps[®] technology developed by Eurand Pharmaceuticals (Pennsylvania, USA) capable of delivering drug to the body according to circadian rhythms.¹⁶ It is a capsule based system containing one or more drug-containing particles (e.g. beads, pellets, granules etc.). Each bead shows pre-programmed rapid or sustained release profile with or without lag time.⁴³ The drug is layered onto an inert particle such as sugar spheres. The drug loaded core is then coated with a plasticized enteric coating and thereafter with a mixture of water insoluble and enteric polymers. The technology provides the versatility of combining two or more drugs in order to increase patient compliance and has been used to produce a chronopharmaceutical product known as InnoPran[®] XL.⁴⁴

Pulsincaps[®]

Pulsincap[®] system was developed by Catalent Pharma Solutions (Somerset, New Jersey, USA).¹⁶ It consists of an insoluble capsule body enclosing the drug reservoir sealed with swellable hydrogel plugs and closed with soluble cap. Hydrogel plugs are made up of polymers like hydroxypropyl methyl cellulose, poly methyl methacrylates, poly vinyl acetate, polyvinyl alcohol, poly ethylene oxide, saturated polyglycolate d-glycerides, glyceryl monooleate, pectin etc.^{26, 27} On oral administration the water soluble capsule cap dissolves in the gastric juices and the 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 released into the small intestinal fluid.²⁸ The variation in dimensions of the plug and its point/depth of insertion into the capsule determines the lag time produced prior to drug release.^{26, 27} Pulsincaps[®] technology has the versatility of allowing one or more mini-tablets, coated tablets, multiparticulates or granules to be loaded within the capsule for delivery of drug in a chronotherapeutic manner.²⁶

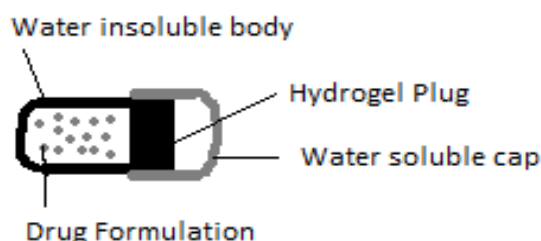


Figure 4. Pulsincap Technology

EGALET[®] technology

Egalet[®] technologies offer controlled release profiles ranging from zero order release to delayed release.³⁹ The delayed release form consists of impermeable shell with two lag plugs, enclosing a plug of active drug in the middle of the unit. The impermeable shells are made of ethylcellulose and plasticizers (such as cetostearyl alcohol) while the matrix of the plug is a blend of pharmaceutical excipients including polymers like polyethylene oxide (PEO). Time taken to erode the inert plug determines the lag time as drug releases after erosion of inert plug.^{26, 39}

CONCLUSION

Conventional delivery systems that are existing now do not efficiently treat disease conditions with chronobiological pathophysiology. Chronotherapeutic drug delivery system (CDDS) developed to solve this problem because these systems can release the drug according to the circadian rhythm. These systems useful for various diseases like asthma, cardiovascular disease, hypertension, diabetes etc. which follow circadian variation. Different technologies have been applied to develop time controlled, pulsed, triggered and programmed drug delivery systems in recent years. Since it appears that timing medicine intake in disease management has significant impact upon treatment success, chronotherapeutics remains an imperative area for abiding research.

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