

Chronotherapeutically Design Colon Targeted Drug Delivery System: A Review.***S.V. Patil, A. D. Patil, K.S. Salunkhe, S. R. Chaudhari.**

Department of Pharmaceutics, Amrutvahini College of Pharmacy, Sangamner, Ahmednagar, Maharashtra, India.

Abstract

The colon is a site where both local and systemic delivery of drugs can take place. Colon is also site to deliver the drugs chronotherapeutically. A major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of diseases or symptoms. Various drugs which are unstable or do not get absorbed in stomach and required at specific time interval can be given chronotherapeutically in the colon. Medication and treatments provided according to the body's circadian rhythms will result in better outcomes. In present review information is given about chronotherapeutics, Different diseases which can be targeted chronotherapeutically, Different approaches to deliver the drug chronotherapeutically in the colon like Time dependent, pH dependent, Microbially triggered etc., In-vitro and In vivo-evaluation.

Key Words

Chronotherapeutics, Circadian rhythm, Colon, Approaches, Diseases.

Introduction

The term "chrono" basically refers to the study that every metabolic happening undergoes rhythmic changes in time.¹ Chronotherapeutics refers to a Therapy in which in vivo availability of drug is timed to match rhythms of disease or disorders in order to optimize therapeutic responses and minimize side effects, which makes it a profound and purposeful delivery of medications in unequal amounts over time. Assuming that physiological processes and biological functions display constancy over time, much effort had been devoted in the past in

developing the drug delivery systems that maintain a flatter plasma level for an extended period of time. However, chronobiological studies believe this concept. Along with many applications in local and systemic delivery of drugs, pulsatile release system would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythm, such as hypertension, nocturnal asthma, angina and rheumatoid arthritis². To maintain the effective plasma drug concentration, frequent administration is required. Due to poor drug efficacy, the

***Corresponding Author:**

swapnilpatil342@gmail.com

incidence of side effects, frequency of administration and patient compliance of these conventional drug preparations, many traditional drug dosage forms are undergoing replacement by second-generation, modified drug-release dosage forms.^{3,4} Treatments of numerous diseases using traditional drug products are often inconvenient and impractical if disease symptoms occur during the night or early morning. Recent studies also reveal that the body's biological rhythm may affect normal physiological function, including gastrointestinal motility, gastric acid secretion, gastrointestinal blood flow, renal blood flow, hepatic blood flow, urinary pH, cardiac output, drug-protein binding, and liver enzymatic activity, and biological functions such as heart rate, blood pressure, body temperature, blood-plasma concentration, intraocular pressure, stroke volume and platelet aggregation.⁵ Most organ functions vary with the time of the day, particularly when there are rhythmic and temporal patterns in the manifestation of a given disease state. The symptoms of many diseases, such as bronchial asthma, myocardial infarction, angina pectoris, hypertension, and rheumatic disease have followed the body's biological rhythm.⁶⁻⁷

Colon

In recent year colon targeted drug delivery of both conventional and labile molecule is developed. It is a drug delivery site for the treatment of local disease, associated with colon like crohn's disease,

ulcerative colitis, irritable bowel syndrome, also it is a potential site for systemic delivery of therapeutic drugs. Colon is also found to be a promising site when delay in absorption is desirable from therapeutic point of view. The colon specific drug delivery system should be capable of protecting the drug release before reaching to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon.

Chronotherapeutics

Chronopharmaceutics includes the fundamentals and research into various aspects of chronophysiology, chronopathology, chronogenetics, chronopharmacokinetics, chronopharmacodynamics, chronotherapeutics and chronotoxicology.

Broadly, chronopharmaceutics bring together chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and mechanisms in living systems. It assumes that the bioprocesses and functions of all living organisms exhibit predictable variability over time. "Pharmaceutics" is an area of biomedical and pharmaceutical sciences which deals with the design and evaluation of pharmaceutical dosage forms to assure its safety, efficacy, quality and reliability.⁸

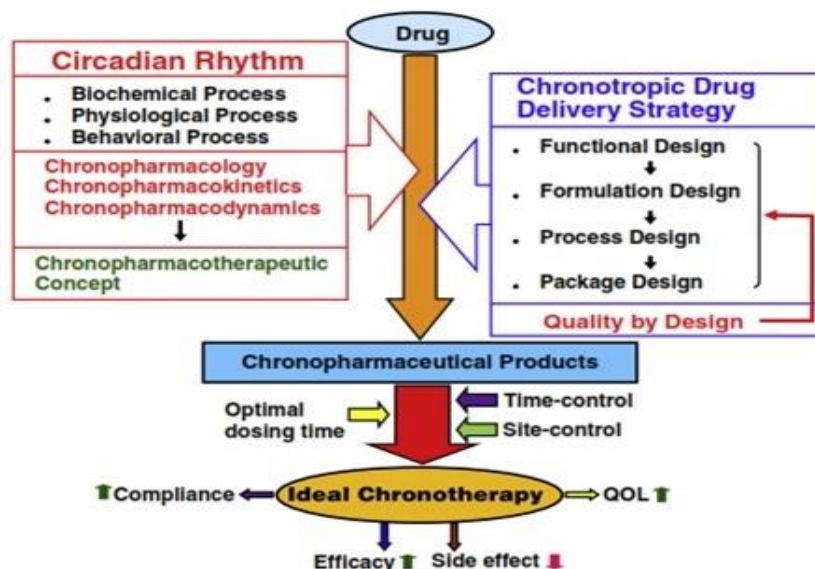


Fig. 1: Design and development of chronotherapeutic drug delivery according to circadian rhythm of body.

Chronopharmacology is the study of the manner and extent to which the kinetics and dynamics of medications are directly affected by endogenous biological rhythms, and also how the dosing time of medications affect biological punctuality and the features (period, level, amplitude, and phase) of biological rhythms.

Chronokinetics

This term includes both rhythmic changes in the drug bioavailability, pharmacokinetic and its excretion.

Chronodynamics

Chronodynamics refers to dosing time, i.e., rhythm-dependent, differences in the effects of medications⁹.

Rationale behind designing these chronotropic DDSs is to release the drug at desired time based on pathophysiological need of disease, which results in the improvement of

therapeutic efficacy and patient-compliance.

Circadian rhythm

It is derived from two words *circa*, meaning "about" and *dies*, meaning day which corresponds to approximately 24-hour cycles endogenously generated by an organism. Circadian rhythm is synchronized according to internal biological clocks that are related to the sleep-wake cycle. Circadian rhythms can change the sleep-wake cycles, hormone release, body temperature, and other important bodily functions driving the alteration of various physiological, biochemical, and behavioral processes.¹⁰ These are controlled by an inherited master clock network composed of the paired suprachiasmatic nuclei (SCN) that are situated in the hypothalamus and the pineal gland.

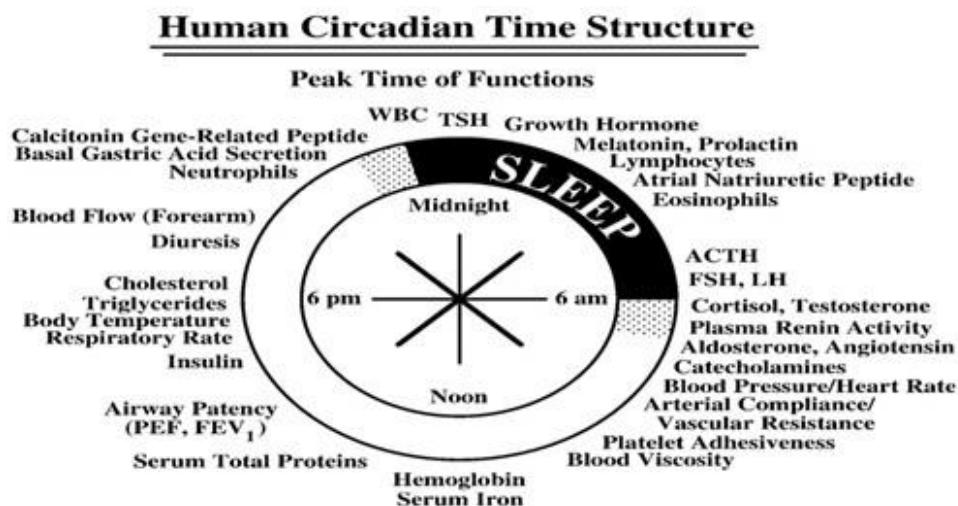


Fig. 2: Human circadian time structure.

A biological rhythm is a self-sustaining oscillation of endogenous origin. It is defined by the characteristics of period, phase, level and amplitude.¹¹

Period

Period is the duration of time required to complete a single cycle. There are three types of periods. Short period most common and give oscillation from few seconds to minutes (>0.5hrs). Intermediate period rhythms show oscillations as short as a few hours to as long as 6 days. Finally, long-period rhythms show oscillations of roughly a week, month, and year.

Phase

Phase refers to the clocking of specific features, such as the peak and trough values, of a rhythm relative to the corresponding time scale.

Level

Level is the baseline around which rhythmic variation occurs. The level of circadian rhythms oscillates in a predictable-in-time manner during the

month in young women and over the year in men and women, giving rise, respectively, to menstrual and annual biological rhythms.

Amplitude

It is a measure of the magnitude of the predictable in time variability due specifically to a biological rhythm. The amplitude of rhythms may change with aging.

Circadian rhythm regulates several body functions such as metabolism, physiology, behavior, sleep patterns, hormone production, and so on. The circadian rhythm not only affects most physiological functions but also influences the absorption, distribution, metabolism, and elimination (ADME) of drugs, leading to changes in drug availability and target cell responsiveness. Timing the administration of some medications in accordance with the body's circadian rhythm may significantly affect the drug's pharmacokinetics and pharmacodynamics (Fig. 3).¹²

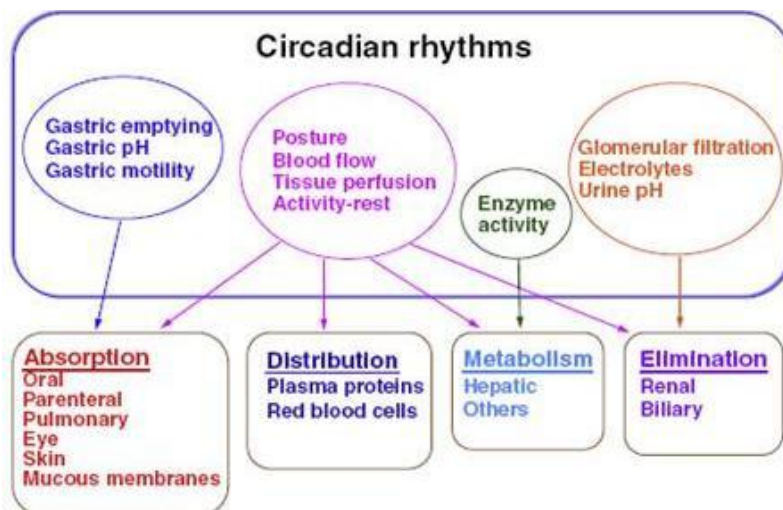


Fig. 3: Effect of circadian rhythm on ADME of drug.

Diseases with established circadian rhythms

Chronotherapy needs to be applied into those diseases and disorders which specifically follow circadian rhythms or in those diseases which are caused due to disrupted circadian rhythms. List of diseases, their behavior and drugs used are given in Table no. 1

Bronchial asthma

Symptoms of asthma occur 50 to 100 times more often at night than during the day. Airway resistance increases progressively at night in asthmatic patient. This asthma known as nocturnal asthma is an exacerbation of asthma with increase in symptoms, airway responsiveness and/or lung function. level of histamine which is a mediator of bronchoconstriction, peaked with the greatest degree of bronchoconstriction at 4:00 am in the morning.¹³

Pain

Pain control is one of the most important therapeutic priorities. Although numerous clinical practice

guidelines for pain management have been published, inadequate pain relief remains a significant health care issue. Pain threshold follows the different pattern in different tissues. The sensitivity threshold of the gingiva to a cold stimulus was maximal at 6:00 pm and reached a peak at 03:00 am. Tooth sensitivity was lowest between 03:00 pm and 6:00 pm, with a peak in pain intensity at 08:00 am.

Arthritis

In arthritis there is circadian rhythm in the plasma concentration of C-reactive protein and interleukin-6 of patient with rheumatoid arthritis. It was reported that levels of endogenous opioid peptides are higher at the starting point of the day and lower in the evening both in neonate and adult human volunteers. Patients with osteoarthritis tend to have less pain in the morning and more at night. While patients with rheumatoid arthritis have pain that usually peaks in the morning and decreases throughout day. The symptoms are swelling of finger and

pain at joint. Thus chronotherapy for all forms of arthritis using NSAID's should be timed to make sure that the highest blood levels of the drug coincide with peak pain.^{14,15}

Allergic rhinitis

Symptoms like sneezing, nasal rhinorrhea, red itchy eyes, nasal pruritus and nasal congestion are found in allergic rhinitis. There are two phases of occurrence of allergic rhinitis i.e. early phase (developing within minutes) and late phase (manifesting after 12–16 h). The early phase happens due to release of histamine, prostaglandins, cytokines, TNF- α , chemotactic factors etc resulting in sneezing, nasal itch, rhinorrhea. On the other hand late phase is shown due to elaboration, adhesion and infiltration of circulating leukocytes, T cells and eosinophils evoking nasal congestion, obstruction due to the exacerbation of inflammation of the nasal, sinus and other tissue of the upper airway.¹⁶

Cardiovascular diseases

In cardiovascular disease capillary resistance and vascular reactivity are higher in the morning and decreases latter in the day. Platelet agreeability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. Hence there is an increase in the incidence of early-morning myocardial infarction, sudden cardiac death, stroke, and episodes of ischemia. Ambulatory blood pressure measurements show a significant circadian variation to characterize blood pressure. This variation is affected by a variety of external

factors such as ethnicity, gender, autonomic nervous system tone, vasoactive hormones, hematologic and renal variables.⁽¹⁷⁾ Blood Pressure is at its lowest during the sleep cycle and rises steeply during the early morning awakening period. Myocardial ischemia, angina pectoris, acute myocardial infarction, and sudden cardiac death are also unevenly distributed during the 24 h with greater than expected events during the initial hours of the daily activity span, in the late afternoon or early evening. Both pharmacokinetics and pharmacodynamics of some oral nitrates, calcium channel blocker and β -adrenoceptor antagonist medications have been shown to be influenced by the circadian time of their administration.¹⁸

Diabetes

Generally insulin is released in pulsatile fashion but sometimes it is irregular. Insulin can show cyclic rhythmicity of 8–30 min which can conclude optimal action. The goal of insulin therapy is to mimic the normal physiological pattern of endogenous insulin secretion in healthy individuals, with continuous basal secretion as well as meal-stimulated secretion. The modulators of insulin release and action are secreted in a circadian fashion and secondarily impress the mode of insulin release. So, any difference between a daily maximum and minimum in plasma insulin concentration besides its short-term rhythmicity has to be considered as a complex secondary circadian rhythm. It is in particular due to variable secondary early-morning and late-afternoon insulin resistance.

Exogenous administration of mealtime doses promotes peripheral glucose as well as reducing hepatic glucose release.¹⁹

Hypercholesterolemia

It is generally higher during the night than during daylight, and diurnal synthesis may represent up to 30%–40% of daily cholesterol synthesis. Although cholesterol is synthesized during the night as well as daylight; the maximal production occurs early in the morning, i.e. 12 h after the last meal. Studies with 3-hydroxy-3-methylglutaryl-Coenzyme a (HMG-CoA) reductase inhibitors have suggested that evening dosing was more effective than morning dosing. The activity of rate limiting enzyme HMG-CoA is higher in the night time.²⁰ But the diurnal variations occur due to periodicity or degradation of this regulatory enzyme.

Renal diseases

Renal osteodystrophy is a condition due to chronic kidney disease and renal failure, with elevated serum phosphorus levels, low or normal serum calcium levels, and stimulation of parathyroid function, resulting in a variable admixture of bone disease. This condition can be managed with calcium supplements, vitamin-D metabolites or Calcitrio.²¹

Epilepsy

The influence of the biological clock on seizure of some partial seizures has been found in some experimental animal models. The methodology for measurement of the circadian rhythm in humans is also investigated. Behavioral chronobiology provides the detection of probable new regulation processes concerning the

central mechanisms of epilepsy. Because of this fact, the circadian psychophysiological patterns of epilepsy show dynamic biological systems which recommend some intermodulating endogenous processes between observation and seizure susceptibility. Furthermore, such chronobiologic studies applied to epileptic behavior suggest the development of new heuristic aspects in the field of comparative psychophysiology.²²

Neurological disorders

Alzheimer's disease and Parkinson's disease are neurological disorders associated with Change of circadian rhythm. Alzheimer's disease leads to pathological changes in the suprachiasmatic nucleus and thus it disrupts circadian rhythms of the brain's function. The core body temperature is also higher in patients with this disease. Alzheimer disease is characterized by sleep disruptions with awakenings and confusion.²³

Autonomic dysfunction seen in Parkinson's disease discloses many alterations in circadian rhythm of blood pressure, amplified diurnal blood pressure variability and postprandial hypotension. But existence of circadian rhythm in this disease has not been evaluated.²⁴

Infectious diseases

The elevation of body temperature, fever due to bacterial infections is higher in the evening while that due to viral infections is more likely in the morning. Influenza is epidemic in the winter season. It was reported that the morbidity and the mortality were greatest during the winter and least

during the summer. The central nervous system, the autonomous nervous system, the endocrine glands, peripheral endocrine tissues including the intestinal tract and adipose tissue, and the immune system show a complex time structure with rhythms and pulsatile variations in multiple frequencies.²⁵

Different Approaches for chronotherapeutical colonic delivery

Colon is the site to deliver the drug when a delay in absorption is needed. There are different techniques for delivering drug to the colon. Here there are some primary approaches and newly developed approaches.²⁶

[A]- Primary approaches for CDDS

- a - pH sensitive polymer coated drug delivery to colon
- b - Delayed (Time controlled release system) release drug delivery to colon
- c - Microbially triggered drug delivery to colon
- d- Prodrug approach for drug delivery to colon

[B]- Newly developed approaches for CDDS

- a) Pressure controlled drug delivery system (PCDCS)
- b) Osmotic controlled drug delivery to colon (OROS-CT)

A) Primary Approaches for CDDS

- a) pH Sensitive Polymer Coated Drug Delivery to the Colon

The pH dependent systems exploit the generally accepted view that pH of the human GIT increases progressively

from the stomach (pH 1-2 which increases to 4 during digestion) small intestine (pH 6-7) at the site of digestion and it increases to 7-8 in the distal ileum. The coating of pH sensitive polymers to the tablets, capsules or pellets provides delayed release and protects the active drug from gastric fluid. In the stomach, pH ranges between 1 and 2 during fasting but increases after eating.⁽²⁷⁾ The pH is about 6.5 in the proximal small intestine, and about 7.5 in the distal small intestine. From the ileum to the colon, pH declines significantly. It is about 6.4 in the cecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers.⁽²⁸⁾ The polymers described as pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises.²⁹ Although a pH dependent polymer can protect a formulation in the stomach, and proximal small intestine, it may start to dissolve in the lower small intestine, and the site-specificity of formulations can be poor.³⁰ The decline in pH from the end of the small intestine to the colon can also result in problems, lengthy lag times at the ileo-cecal junction or rapid transit through the ascending colon which can also result in poor site-specificity of enteric-coated single-unit formulations.²⁹ pH dependent polymers are given in Table no.2

- b) Time dependent delivery

It has also been proposed as a means of targeting the drug to colon. Time dependence systems release their drug load after a pre programmed time

delay. However, due to potentially large variations of gastric emptying time of dosage forms in humans, in these approaches, colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonic availability.³² Ideally, formulation was to be designed that are not affected by the individual difference in gastric emptying time, Ph of the stomach, small intestine or presence of anaerobic bacteria in the colon at the site of delivery. Various polymers used in time dependent delivery are given in Table no.3

Various methods used for time controlled release are,

Delivery with rupturable coating layer

These system consist of an outer release controlling water insoluble but permeable coating subject to mechanically induced rupture phenomenon.

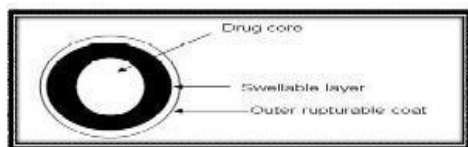


Fig. 4: delivery system with rupturable coating layer

The film rupture may be attained by including swelling, osmotic effervescent additives in the reservoir. By optimising the system, drug release can be obtained at specific time interval.³³

Delivery with erodible coating layers

In such systems the drug release is controlled by the dissolution or

erosion of the outer coat which is applied on core containing drug.³⁴

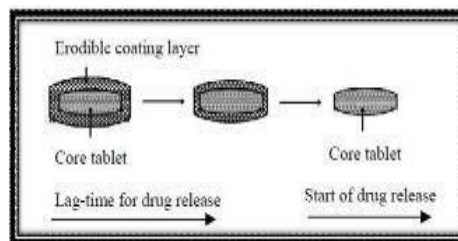


Fig. 5: Delivery system with erodible coating layer.

c. Microbially Triggered Drug Delivery to Colon

The microflora of the colon is in the range of 10^{11} - 10^{12} CFU/mL, consisting mainly of anaerobic bacteria, e.g. bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria and ruminococcus etc.³⁶ The basic principle involved in this method is degradation of polymers coated on the drug delivery system by microflora present in colon and there by release of drug load in colonic region because the bioenvironment inside the human GIT is characterized by presence of complex microflora, especially the colon is rich in microorganisms.³⁷

Polysaccharides offer an alternative substrate for the bacterial enzymes present in the colon. Many of these polymers are already used as excipients in drug formulations or are constituents of the human diet and are therefore generally regarded as safe. A large number of polysaccharides have already been studied for their potential as colon-specific drug carrier systems, such as chitosan, pectin, chondroitin sulphate, cyclodextrin, dextrans, guar gum, inulin, amylose, sodium alginate and locust bean gum. Polymers used

in microbially triggered drug delivery given in Table 4.

d) Prodrug Approach

A prodrug is pharmacologically inactive derivative of a parent drug molecule that requires spontaneous enzymatic transformation in vivo to release the active drug. In this method the prodrugs are designed to undergo minimum absorption and hydrolysis in the upper GIT and undergo enzymatic hydrolysis in the colon, thereby releasing the active drug moiety from the carrier. Different types of conjugates were used to prepare 5-ASA prodrugs, which are successful in releasing the 5-ASA in colonic region. They are biodegradable poly (ether-ester) azo polymers, azo-linked polymeric prodrugs³⁷, acrylic type polymeric prodrugs and cyclodextrin prodrugs.³⁹

(B) Newly developed approaches for CDDS

a) Pressure controlled drug delivery system

Peristaltic movements of intestines along with gastric contractile activity are responsible for the propulsion of intestinal contents. These peristaltic movements constitute elevated luminal pressure conditions in the colon. The design of pressure controlled drug delivery system is based upon above mechanism. Intensity and duration of this pressure varies with the muscular contractions in the visceral organs. It consists of a capsule shaped suppositories coated with the water insoluble polymer like ethyl cellulose (EC). Once taken orally, they behave like balloon of

ethyl cellulose because the base of the capsule was liquefy at the body temperature.⁴⁰ The thickness of the ethyl cellulose membrane play a very vital role in the disintegration of the capsule. The size and density of the capsule may also affect the system. The preferred thickness of the capsule wall is about 35- 60 μm . The viscosity of the luminal content is higher in the colon than the small intestine, because of re-absorption of water from the colon, so that drug dissolution in the colon could present a problem for colon-specific oral drug delivery system. When the pressure controlled capsule was administered to human volunteer, the lag time of three to five hours in relation of drug absorption were noted. And, found that disintegration of capsule achieved as the luminal pressure hikes.⁴¹

b) Osmotic Controlled Drug Delivery (OROS-CT)

A novel CDDS was introduced by Alza Corporation, to target the drug locally to the colon, which is known as OROS-CT. The OROS-CT system include either single osmotic unit or upto 6 push pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule. In this system a semi permeable membrane surrounds both osmotic push layer and drug layer.⁽⁴²⁾ Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. An orifice is drilled through the membrane next to the drug layer. Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves. Because of its

drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach, and hence no drug is delivered. As the unit enters the small intestine, the coating dissolves in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell, and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semipermeable membrane.⁴³

Evaluation of colon specific drug delivery system

In vitro dissolution testing

Dissolution testing has been an integral component in pharmaceutical research and development of solid dosage forms. It provides decisive information on formulation selection. Dissolution tests relating to CDDS may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behavior of formulations at different pH levels. The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine, and pH 7.4 to simulate the ileum segment. Another *in-vitro* method involves incubation of the drug delivery system in a fermentor with commonly found colonic bacteria.⁴⁴

In vivo evaluation

A number of animals such as dogs, guinea pigs, rats, and pigs are used to

evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the microflora of human GIT. Although animal models have obvious advantages in assessing colon-specific drug delivery systems, human subjects are increasingly utilized for evaluation of this type of delivery systems with visualization techniques such as gamma scintigraphy imaging.⁴⁵

Current situation and future scope

In today's world chronotherapeutic drug delivery is gaining importance as it delivers drug when required. As a result, the chance of development of drug resistance which is seen in conventional and sustained release formulations can be reduced. Many anticancer drugs are toxic and they cause toxicity when given in sustained release formulation hence drugs which are toxic and do not require sustainable action can be given by this way. Chronotherapeutic's goal is to provide optimal therapy by administering medication in the right amount, to the desired target organ, at the most appropriate time. Recently, many colon disorders and diseases, such as ulcerative colitis, diverticulitis, irritable bowel syndrome, Chron's disease, carcinomas, and other infections have been diagnosed. Future greatest challenge is the targeted delivery of drugs to the lower GI tract and colon. Now many FDA approved chronotherapeutic drugs are available in the market.

Conclusion

Chronotherapy aims at providing drug at the certain level of timing with regard to the diseased condition to be

treated. The performance achieved by designing a chronopharmaceutical modulated drug delivery always shows on upper hand in disease treatment compared to conventional therapy. It has been well established fact that human body follows the discipline during its normal functioning through circadian rhythm which works like a clock. Drugs which are unstable in stomach and absorbed in colon can be given chronotherapeutically in colon. Circadian rhythm is important concept for understanding optimum need of drug in the body. It should be pointed that these drug delivery system are still in the early developmental stage and much research will have to be conducted for such system in future. Advantages of chronotherapy are very vast and can be explored more in present and future for effective treatment of many more disease and disorders.

References

1. J Sajan, TA cinu ,AJ Chacko, J Litty and T Jaseeda, Chronotherapeutics and Chronotherapeutic Drug Delivery Systems, Tropical Journal of Pharmaceutical Research, October 2009; 8 (5): 467-475.
2. Traynor K, Newton DW, Hrushesky JM, Reiter RJ. A pharmacist's primer on chronotherapeutics. American Pharmacy, 32(2), 1992, 261-269.
3. L. Shargel, S. Wu-Pong, A. Yu, Applied Biopharmaceutics & Pharmacokinetics, 5th ed. McGraw-Hill, New York, 2005.
4. L.V. Allen, N.G. Popovich, H.C. Ansel, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 9th ed. Lippincott Williams & Wilkins, Philadelphia, 2010.
5. G. Labrecque, P.M. Belanger, Biological rhythms in the absorption, distribution, metabolism and excretion of drugs, Pharmacol. Ther. 52 (1991) 95–107.
6. Vidyavati S Koppiseti, Nikhil Chandra And M Bhagvan Raju, Vital Role of Chronopharmacology and Chronopharmacotherapy in Human Life, International Journal of Research in Pharmaceutical and Biomedical Sciences, Vol. 1 (2) Oct –Dec 2010, 36-40.
7. M.H. Smolensky, G.E. D'Alonzo, Medical chronobiology: concepts and applications, American Review of Respiratory Disease, 147 (6 Pt 2) (1993) S2–S19.
8. Bi-Botti C. Youan, Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery? J. Control. Release 98 (2004) 337–353.
9. Bélanger PM, Bruguerolle B, Labrecque G. Physiology and Pharmacology of Biological Rhythms, Handbook of Experimental Pharmacology. Vol. 125, Springer, Berlin, 1997, pp. 177 204.

10. Kalsbeek A, Palm IF, La Fleur SE, Scheer FA, Perreau-Lenz S, Ruiters M, Kreier F, Cailotto C, Buijs RM. SCN outputs and the hypothalamic balance of life. *J Biol Rhythms.*, 21, 2006, 458-469.
11. R.V. Trivedi K.J. Wadher, J.B. Taksande, J.G. Mahore, M.J. Umekar Chronotherapy: A Concept, Pauperism And Approches, *International journal of pharmaceutical development and technology*, 1(1)2011, 1-10.
12. B. Lemmer, The clinical relevance of chronopharmacology in therapeutics, *Pharmacol. Res.* 33 (1996) 107-115.
13. M.H. Smolensky, B. Lemmer, A.E. Reinberg, Chronobiology and chronotherapy of allergic rhinitis and bronchial asthma, *Adv. Drug Deliv. Rev.* 59 (2007) 852-882.
14. Z. Khan, V. Pillay, Y.E. Choonara, L.C. du Toit, Drug delivery technologies for chronotherapeutic applications, *Pharm. Dev. Technol.* 14 (2009) 602-612.
15. B. Bruguerolle, G. Labrecque, Rhythmic pattern in pain and their chronotherapy, *Adv. Drug Deliv. Rev.* 59 (2007) 883-895.
16. Asim Sattwa Mandal, Nikhil Biswas, Kazi Masud Karim, Arijit Guha, Sugata Chatterjee, Mamata Behera, Ketousetuo Kuotsu, Drug delivery system based on chronobiology-A review *Journal of Controlled Release*, 147(2010) 314-325.
17. F. Portaluppi, R.C. Hermida, Circadian rhythms in cardiac arrhythmias and opportunities for their chronotherapy, *Adv. Drug Deliv. Rev.* 59 (2007) 940-951.
18. F. Portaluppi, B. Lemmer, Chronobiology and chronotherapy of ischemic heart disease, *Adv. Drug Deliv. Rev.* 59 (2007) 952-965.
19. Hori K, Zhang QH, Li HC, Saito S, Sato Y. Timing of cancer chemotherapy based on circadian variations in tumor tissue blood flow. *Int J Cancer.*, 65, 1996, 360-364.
20. P.J.H. Jones, D.A. Schoeller, Evidence for diurnal periodicity in human cholesterol synthesis, *J. Lipid Res.* 31 (1990) 667-673.
21. Tsuruoka S, Wakaumi M, Sugimoto K, Saito T, Fujimura A. Chronotherapy of high-dose active vitamin D3 in haemodialysis patients with secondary hyperparathyroidism a repeated dosing study. *Br J Clin Pharmacol.*, 55, 2002, 531-537.
22. C. Poirel, M. Ennaji, Circadian aspects of epileptic behavior in comparative psychophysiology, *Psychol. Rep.* 68 (1991) 783-801.
23. Hering E, Epstein R, Elroy S, Iancu DR, Zelnik N. Sleep patterns in autistic children. *J Autism Dev Disord.*, 1999, 29, 143-7.

24. B. Bruguerolle, N. Simon, Biologic rhythms and Parkinson's disease: a chronopharmacologic approach to considering fluctuations in function, *Clin. Neuropharmacol.* 25 (2002)194–201.
25. E. Haus, Chronobiology in the endocrine system, *Adv. Drug Deliv. Rev.* 59 (2007) 985–1014.
26. McLeod AD, Friend DR, Thoma NT. Glucocorticoid-dextran conjugates as potential prodrugs for colon specific delivery- hydrolysis in rat gastrointestinal tract contents. *J Pharm Sci* 1994; 83(9):1284-1288.
27. Rubinstein A. Approaches and opportunities in colon-specific drug delivery. *Crit. Rev Ther. Drug carrier Syst* 1995; 12:101-149.
28. Bussemer T, Otto I, Bodmeier R. Pulsatile drug-delivery systems. *Crit Rev Ther Drug Carr Sys* 2001; 18:433-458.
29. Ashord M, Fell JT, Attwood D, Sharma H, Woodhead P. An evaluation of pectin as a carrier for drug targeting to the colon. *J Control Rel* 1993; 26:213-220.
30. Fukui E, Miyamura N, Kobayashi M. An in vitro investigation of the suitability of presscoated tablets with hydroxypropylmethylcellulose acetate succinate (HPMCAS) and hydrophobic additives in the outer shell for colon targeting. *J Control Rel* 2000; 70:97-107.
31. Semde, R., Amighi, K., Devleeschouwe, M.J., Moes, A.J., studies of pectin HM/Eudragit RL/Eudragit NE film coating formulations intended for colonic drug delivery, *Int. J. Pharm.*, 2000, 197, 181-192.
32. Gazzaniga A, Iamartino P, Maffino G, Sangalli ME. Oral delayed release system for colonic specific drug delivery. *Int J Pharm* 1994; 108:77-83.
33. Krogel I and Bodmeier R, Floating or pulsatile drug delivery systems based on coated effervescent cores. *Int. J. Pharm.*, 1999, 187; 175-184.
34. Sharma Ritika Singh Arjun, Kumar Sunil, Pulsatile Drug Delivery System: A Review, *International research Journal of Pharmacy*, 2012, 3(7), 103-107.
35. Gurmeet Singh, Dinesh Kumar, Mankaran Singh, Deepak Sharma and Sukhbir Kaur Emerging Techniques and Challenges in Colon Drug Delivery Systems *Journal of Applied Pharmaceutical Science* 02 (03); 2012: 139-147.
36. Vassallo M, Camilleri M, Phillip SF, Brow ML, Chapman NJ, Thomforde GM. Transit through the proximal colon influences stool weight in the a irritable bowel syndrome. *Gastroenterology* 1992; 102:102-108.

37. Sinha V R, Rachana Kumaria
Microbially triggered drug
delivery to the colon.
European Journal of
Pharmaceutical Sciences,
2003, 18: 3-18.
38. Samyn C, Kalala.W, Vanden
Mooter, Synthesis and in vitro
biodegradation of poly (ether-
ester) azo polymers designed
for colon targeting.
International Journal of
Pharmaceutics. 1995, 121:
211-216.
39. Etienne Schacht, An Gevaert,
El Refaie Kenawy, Polymers
for colon-specific drug
delivery,Journal of Controlled
Release, 1996, 39: 327-338.
40. Koteswara K.B., Naha A.,
Nampoothiri M. International
Journal of Research in
Ayurveda & Pharmacy. 2011;
2(1): 60-65.
41. Challa T., Vynala V., Allam
K.V. International Journal of
Pharmaceutical Sciences
Review and Research. 2011;
7(2): 171-181.
42. Rangasamy M. Colon
Targeted Drug Delivery
Systems: A Review.
International Journal of Drug
Formulation & Research.
2010; 1(2): 30-54.
43. Philip AK, Pathak K. Osmotic
flow through asymmetric
membrane: A means for
controlled delivery of drugs
with varying solubility. AAPS
PharmSciTech 2006; 7(3):1-
11.
44. Cole ET, Scott RA, Connor
AL, Wilding IR, Petereit HU,
Schminke C, Beckert T, Cadé
D. Enteric coated HPMC
capsules designed to achieve
intestinal targeting. Int J
Pharm 2002; 231(1):83-95.
45. Mooter VG, Kinget R. Oral
colon-specific drug delivery:
A review: Drug Delivery
1995; 2:881-931.

Table 1: Chronological behavior.

Disease	Chronological behavior	Drugs used
Peptic ulcer	Acid secretion is high in the afternoon and night	H ₂ Blockers
Asthma	Precipitation of attacks during night or early in the morning	B ² agonist, Antihistaminics
Cardiovascular diseases	BP is very low during sleep hours and rises during early morning awaking period.	Nitroglycerine, Calcium channel blockers, ACE inhibitors, B blockers
Arthritis	Pain early in the morning and night as compared to day time	NSAIDS, Glucocorticoids
Dibetis mellitus	Increase in blood sugar level after meals.	Sulfonylurea, Insulin
Hypercholesterolemia	Cholesterol synthesis is high during night compared to day	HMG COA reductase inhibitors

Table 2: Different pH dependent polymers used in colon targeted drug delivery system³¹

Polymer	pH
Eudragit E 100	5.0
Eudragit L 100	6.0
Eudragit S 100	7.0
Eudragit FS 30 D	6.8
Eudragit L 100-55	5.5
Polyvinyl acetate phthalate	4.5-4.8
Hydroxypropyl ethylcellulose phthalate	5.2

Table 3: Time dependent polymers used for various drugs³⁵

Sr. No.	Polymers Used	Drugs Used
1	Hydroxy propyl methyl cellulose	Pseudoephedrine HCL
2	Hydroxyethyl cellulose	Theophylline
3	Ethyl Cellulose, Microcrystallinecellulose Lactose/behinic acid	Indomethacin
4	Hydroxy propyl methyl cellulose	NS
5	Hydroxy propyl methyl celluloseacetate succinate	Diltiazem HCl
