Pakistan Journal of Pharmaceutical Research
Faculty of Pharmacy, Bahuddin Zakaryia University Multan, Pakistan
ISSN: Applied January, 2015 Vol: 01 Issue: 01

Review Article

Chrono pharmacotherapy: A pulsatile Drug Delivery

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Received:05 Dec 2014
Revised: 25 Dec 2014
Accepted : 29 Dec 2014
Online: 1 Jan 2015

Abstract

Chronopharmacotherapy refers to a treatment in which controlled drug delivery is achieved according to circadian rhythms of disease by enhancing therapeutic outcomes and minimizing side effects. Colon targeting has gained great importance not only for the treatment of local diseases such as Crohn's disease, inflammatory bowel disease and ulcerative colitis but also very important in systemic delivery of proteins/peptides, anti-asthmatic drugs, anti-diabetic agents and anti hypertensive drugs, which mostly show their efficacy based on circadian rhythms of the body.Colon drug delivery is one of the difficult approaches to achieve the targeted and desired outcomes through pulsatile drug delivery by avoiding dose dumping. The main reason behind the use of pulsatile delivery is provision of constant drug release where a zero-order release is not preferred. Chronopharmacotherapy in colon targeting play its role by many systems such as capsular systems, pulsatile system and osmotic systems, which are based on use of rupturable membranes and biodegradable polymers. The objective of this review article is to provide latest knowledge about drugs with chrono-pharmacological behavior specially to the colon.

Keywords: Chronopharmacotherapy, colon targeting, pulsatile drug delivery, circadian rhythms, proteins and peptides

Introduction

Drug delivery systems are involved in transport of drugs to the to the target organs to alleviate disease states and restore them to normal state of health.

Mainly Drug Delivery Systems are of 3 types:

Controlled system: A parent drug delivery system of the continuing two systems i.e., time dependent and pulsatile, depends both on time and dose of therapy.

Time dependent system: It depends upon duration when mainly an action is desired by applied therapy.

Pulsatile system: It is mainly linked with circadian rhythms of the body that provides desired action by already determined natural or artificial stimuli (SaegerandVirley, 2004). It is totally different from sustained release formulation, it is actually controlled system which is designed according to need of the body i.e., actually chronophamacotherapy depends upon circadian rhythms of the body (Shigehiro, 2010).

Chronopharmacotherapy

"Chronopharmacotherapy" is combination of two words i.e., chronobiology and pharmacotherapy. Chronobiology is the study of biological rhythms and their mechanisms and pharmacotherapy is the application of drug to treat the ailment (Belanger, 2003). These rhythms are mainly of three types:

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They are:

Circadian: derived from Latin word "circa" means about and “dian” means day.

Ultrdian: ultra means short and dian means day (more than one cycle per day).

Infradian: Infra means longer and dian means day (one cycle cross a day).

In chronopharmacotherapy, circadian rhythms are of main concern (Chen, 2000). The main need of application of chrono-pharmaceuticals is to treat the disease by applying target drug delivery system (Daumesnil, 2004).

CVS (cardiovascular) disorders:

Cardiovascular functions like H.R (heart rate) and B.P (blood pressure)vary in whole day. Various components of the vascular systems are diurnally regulated such as endothelial cell activation, interaction of leukocyte and platelet and metabolism of lipoproteins (Ishino, 2003). All these changes like platelet aggregation, nonfatal M.I (myocardial infarction), and sudden death due to heart failure had noticeable circadian rhythms with a primary peak in the morning along with a secondary peak in the evening that requires a treatment based on circadian rhythms i.e. actually pulsatile system and for the delivery of protein and peptide based drug, colon targeting is required (Gurny, 2009).

Asthmic disorders:

Various studies statistically revealed that symptoms involved in asthma and broncho-spasmitic attacks are commonly seen at midnight to early morning i.e. from 2 a.m. and 6 a.m. every day (Ritschel, 2004). Chronopharmacotherapy

provides targeted and desired effect during the early morning hours. For example, a bronchodilator **UNIPHYL**, a long-acting theophylline, taken o.d. (once in a day) at evening provides desired maximum effective concentration of theophylline at early morning hours in order to relief severe asthmatic attacks mainly in case of nocturnal asthma (Smolensky, 2005).

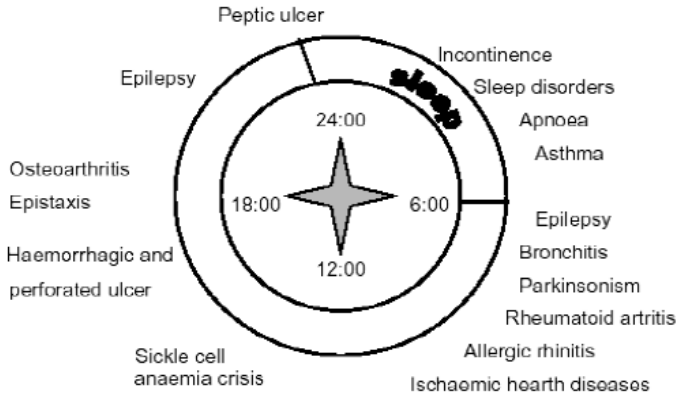
Diabetic problems:

It is found that protein that controls the biological clocks in mammals also responsible to maintain glucose production by liver and controlling this protein improves health of the diabetic patients and this protein is under the control of chronobiological behavior (Swapnaand Vinita, 2007). Eric Hang, a biologist worked on **cryptochrome**, a key protein involved in regulation of the genes in a rhythmic fashion and also in gluconeogenesis, according to the diurnal activity and alteration in cryptochrome levels would be proved as helper to decrease the diabetic effect in patients (Wilding, 1994).

Osteoarthritis:

Chronobiological based problems are also seen in case of arthritis linked pain which became worse in morning. To relieve such type of pain long acting pain killers are required at bedtime. In case of osteoarthritis, less pain was seen in the morning and more pain felt by patients at night (Takane, 2000). To relieve such type of pain long acting analgesics are required at noon or in the evening.

Figure 1 Circadian rhythms involved in disease state



Colon Cancer

Chronobiological patterns or cycles are different for a cancerous cell or a normal cell. Because of this reason, for the treatment of cancer, interest has

been taken in chronopharmacotherapy that provide desired drug at the desired organ within desired time. To get rid of such type of cancers, for morning time s-phase active cancer such as colon cancer chronopharmacotherapy at late nights was given and decrease in the tumour cell count with minor effect on normal cells was observed.

Colon targeting:

Various colonic diseases like inflammatory bowel diseases (IBW) that included Crohn's disease and ulcerative colitis and world's third most reported cancer such as colon cancer requires targeted drug delivery towards colon. By targeting colon site, many applications of interest such as chronopharmacotherapy, prophylaxis to colon cancer can be achieved (Gazzaniga*et al.,* 2004). The main challenge in colon drug delivery or targeting is to preserve the desired drug from harmful stomach environment that may lead to dose dumping, degradation or failure of therapy. To achieve such needs, focus is based on chronopharmacotherapy with the help of novel systems like pulsatile delivery by use of various biodegradable polymers that may not only provide sustained effect but also immediate effect can be provided, if desired along with the controlled and targeted effect (Bodmeier*et al.,* 2000).

Drugs like proteins and peptides are at the target of various body chemicals and enzymes specifically in upper gastrointestinal tract, that is main reason behind degradation of protein and peptidal drugs (Gazzaniga*et al.,*2003). Colon tageting also helps to overcome this probem in that it provides drug in its intact form to the target site to achieve maximum efficacy (Wilding, 1999). Examples of such drugs include insulin, vasopressin, cytokine inhibitors, calcitonin, and antibiotics such as nisin. A colon has large number of lymphoidal tissues and uptake of antigen by colonic mucosal mast cells cause rapid production of antibodies, it means efficient vaccine delivery can also be achieved by targetting the colon (Crison*et al.,* 2001). Absorption of drugs is desirable for chronopharmacotherapy by colon targeting, so that formulation must remain in colon for longer time period to overcome the diseases like asthma, cardiac arrhythmias, arthritis, hypertension, or inflammation, based on circadian rhthyms of the body, such type of problems either need night-time or early morning drug release that can only be achieved by chronopharmacotherapy. Inclusively, colon offers many advantages over other drug delivery systems (Koppisetti, 2010), which are mentioned as under

Advantages of colon targeting:

neutral pH,

longer transit time,

low proteolytic enzyme activity

absorption enhancement

prevent the release and degradation of the drugs in the upper GIT

Novel pharmaceutical approaches for targeting drugs to the colon:

Pulsatile

Pulsincap System

Port System

Pressure-controlled colon delivery capsules (PCCS-CTs)

CODES

Osmotically controlled colon targeted drug delivery (OROC-AT)

Azo hydrogels

Bioadhesion system

Nanoparticles

Pulsatile System:

Many diseased conditions demand drug release after a lag time; it means that drug is not released at initial phase of administration (Petereit, 2003). Such type of release arrangement is pulsatile release. Especially for that diseases that are based

Table 1: Diseases having chronological behavior

Chronological behavior	Drugs used	Diseases
Acid secretion is high in the Afternoon and at night	H2 blockers	Peptic ulcer
Precipitation of attacks during night or at early morning	β2 agonist, Antihistamines	Asthma
BP is at its lowest during the sleep cycle and rises steeply during the early morning	Nitroglycerin, calcium channel blocker, ACE inhibitors	Cardiovascular diseases
Pain in the morning and more pain at night	NSAIDs, Glucocorticoids	Arthritis
Increase in the blood sugar level after meal	Sulfonylurea, Insulin	Diabetes mellitus
Cholesterol synthesis is generally higher during night than day time	HMG CoA reductase inhibitors	Hypercholesterolemia

on circadian rhythms of the body and drugs like hormones such as renin, vasopressin, aldosterone, thyroxin and cortisol etc also needs chrono-pharmacotherapy administration (Krgel and Bodmeier, 2009). To develop focus should not only be the circadian rhythms of the body but also the internal environment of the body in which drug is going to be administed e.g., pH of the target organ, presence of proteolytic enzymes etc. For this purpose, colon is targeted to protect the drug from upper GIT portion and this is achieved by the latest introduced system i.e. PDDS, pulsatile drug delivery system (Lachman*et al.*, 2001).

Pulsatile colon targeted drug delivery:

Pulsincap DDS:

Pulsing cap system is based on a capsule form in which drug release is dependent on the plug inserted into the capsule and that plug is mostly hydrogel based that may become swell able on contact with the solvent present in colon (Lemmer, 2008). On swelling there may be creation of pores or removal of the plug that is responsible for the release of drug at the targeted site after a desired lag time. Such type of desired effect is achieved by using biodegradable polymers e.g. HPMC (hydroxy propyl methyl cellulose), PMMA (poly methyl methacrylate) and PVA (polyvinyl acetate). The lag time is measured by the length and point of intersection of the plug in the capsule body (Matsuo*et al.*, 2003).

Port system

Port system is also based on the capsule body that is further enclosed in a semipermeable membrane. Here plug is insoluble and is made up of osmotically active agent separately or by combination of osmotically active agent plus active ingredient (Nakagawa *et al.*, 2004). When the port system comes in contact with the dissolution fluid, surrounded membrane allows the fluid to get enter into the capsule, due to which pressure inside the capsule is developed that leads to release of drug due to removal of the plug. This system can also provide immediate release if desired along with the delayed release after passing the lag time with the help of inserted plug (Pozzi and Furlani, 2005).

Pressure-controlled capsules: colon targeting (PCCs-CT):

This a pressure based system in which drug release is totally dependent on colon pressure that was build due to peristaltic movments in the GIT and these movements only happens 3-4 times a day, in this way this system is also ciracadian rhythms based leads to introduction of chronopharmacotherapy. It is also a capsule system in which capsule is made up of gelatin material that is further coated EC, ethyl cellulose a water insoluble material. Active is first dissolved in a base that was added in the capsule shell (Mcneil, 2003). Release pattern is based on nature of the polymer and thickness of the coating material on the capsule shell and high amplitude propagated contractions i.e. peristaltic movements of colon (Ohdo, 2000).

Figure 2: Pulsin cap system

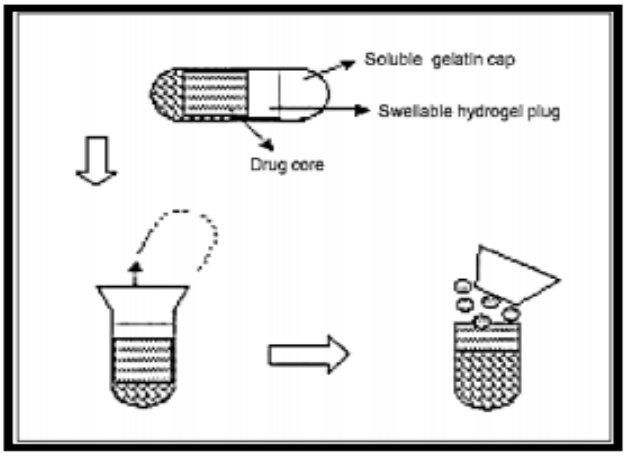
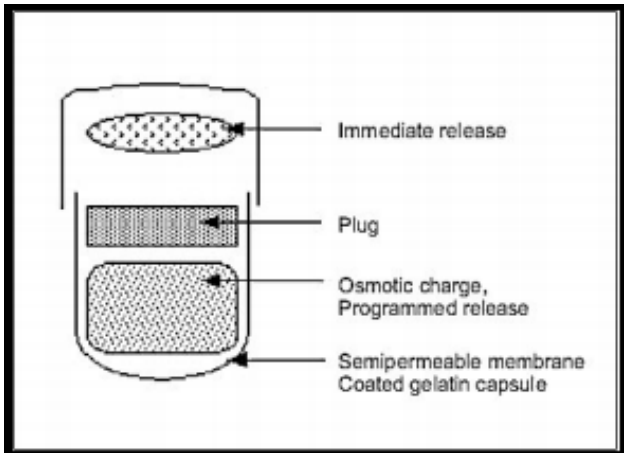


Figure 3: Port system



By increasing the thickness of the membrane, release is decreased and due to increase peristaltic pressure, drug release is also enhanced and vice versa. The system i.e. actually an ethyl cellulose (EC) balloon having drug solution in a suppository base that dissolves at body temperature (Yan, 2006).

CODES system:

CODES systemwas developed to avoid the problems linked with pH or time dependent systems by applying colon-specific drug delivery. The CODES system has many advantages on conventional systems due to use of certain polysaccharides that are only degraded by colonic bacteria, this system is further protected by pH-sensitive polymer coating that only allow release in colon. One distinctive conformation of CODES system consists of a core tablet that is further coated with three polymeric layers as shown in Fig 5.

The outermost coating contains enteric polymer like Eudragit® L which shows resistance to stomach portion, once system passes the stomach (pyloric region and enters in the small intestine) and first coating is degraded in duodenum, first portion of the small intestine and second coating layer appeared which is composed of Eudragit® E which is resistant to environment of the small or large intestine both (Mcneil, 2003). This environment only allows the desired release of active one for which purpose it is made. Here Eudragit E starts to dissolve only due to degradation of disaccharides used in formulation by colonic bacteria. And finally drug is released at the desired site to show its effect.

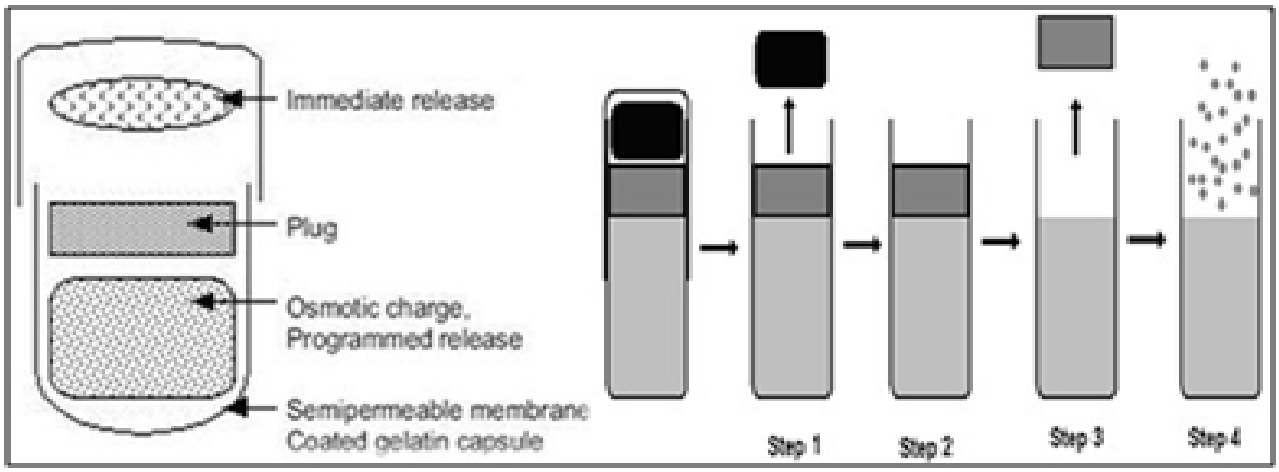
Osmotically controlled CT-DDS:

The Osmotically controlled CT-DDS (colon targeting drug delivery system) is used to target the drug to the colon for the treatment of colon specific diseases or to achieve systemic absorption of protein and peptides in case of circadian rhythms based diseases.

OROC-CT system:

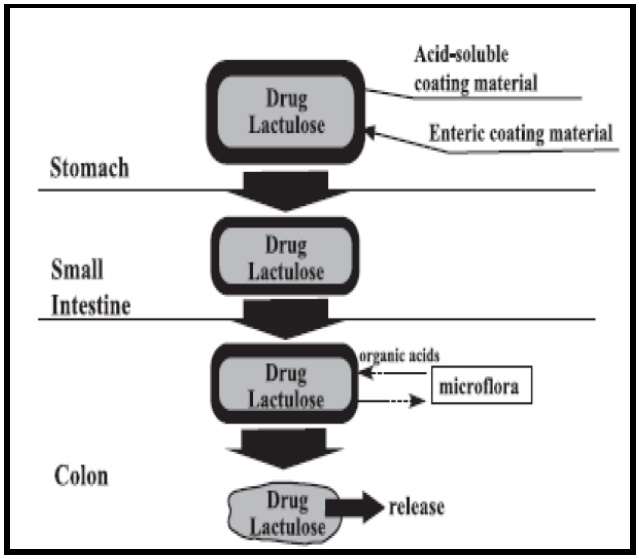
The OROC-CT system is also a capsule based system in which capsule is made up of gelatin along with 5-6 push pull units, having each 4mm pore in diameter as shown in Fig 6 in which every push pull unit is further surrounded by a semipermeable membrane that contains an osmotically active layer along with active drug (Matsuo *et al.*, 2003).

Figure 4: Mechanism of drug release through port system



Capsule is made up of gelatin that will rapidly dissolved after swallowing but system is enteric coated too from inside that will allow drug release at the target site, degradation of gelatin material is required for the contact of osomatically active agents with dissolution media.

Figure 5: CODES system



When these unit reached into small intestine, enteric coating of the unit get dissolve at pH > 7, water enters the unit leads to swelling of each unitthat allows the release of drug at desired site after passing each compartment one by one. Such type of system is developed for treating ulcerative colitis that can deliver persistent drug release for up to 24 h in the colon (Bussemer and Bodmeier, 2001).

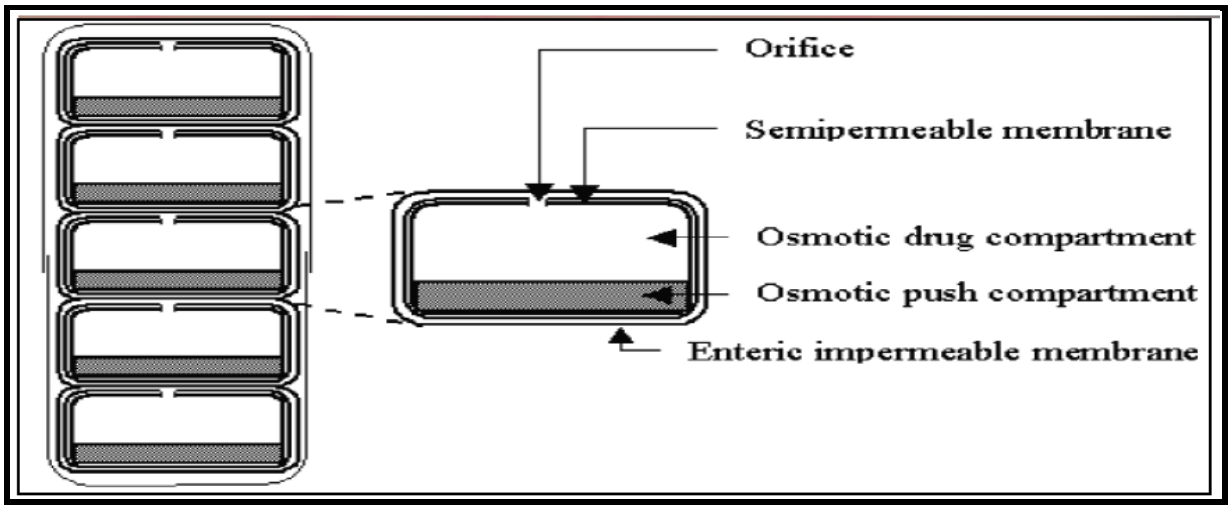
Hydrogel colon targeting system:

Hydrogels for targeting the colon is another novel approach in providing site specific drug delivery. Such type of hydrogel system is based on azo band that are degraded by colonic enzymes to provide the targeted release. On the other hand addition of acidic polymers make the system resistible towards stomach but after passing the stomach environment, system comes in contact with basic environment that leads to swelling of system and now system is available for the attack of azo-reductases enzymes in order to break the azo bond and permit the release of drug at targeted site.

Bioadhesive systems:

Novel techniques based on bio adhesion mechanism have high opportunity to design a desired targeted system for drug delivery to minimize the side effects and enhanced bioavailability. Bio adhesive system is a system in which a dosage form attached with specific organ for permitted period (Youan, 2004).

Figure 6: OROC system



Such type of attachment acts as absorption enhancer specifically in case of poorly absorbed drugs such as protein and peptides. To overcome these problems, colon is chose as targeted organ to achieve desired effect. Polymers like polycarbophils, polyethyleneand polyurethanes etc are commonly used in manufacturing of bioadhesive systems for colon targeting (Koppisetti, 2010).

Nanoparticles in colon targeting:

The nanoparticles are prepared mostly for the protection of proteins and peptides by polymeric materials using novel techniques like poly electrolyte complexation, polymerization, nano-precipitation, inverse phase microemulsion, coacervation and by combination of 2 or more above mentioned methods (Belanger, 2003). Heat is administered at various levels in this technique that is a major drawback of nanoparticles for heat labile drugs for that ionic gelation and poly electrolyte complexation method is more suitable (Pozzi and Furlani, 2005).

Conclusion:

The main concern of this article is to motivate the study and research based on chrono-pharmacotherapy as a real-world need by improving medical treatment with previously discovered active drugs. Mostly treatments are still given without any need of the disease condition because that disease is circadian rhythms based. Identification of a rhythmic marker by choosing chronopharmacotherapy helps in improving patient conditions with minimum input and maximum output. Further involvement of colon targeting along with chronopharmacotherapy offers more benefits for both local and systemic systems by reducing unwanted side effects. The main advantage of colon targeting combine with chrono-pharmacotherapy is that it not only protect the drug from acidic environment by reducing side effects but also make possible the availability of protein and peptides based drugs to the target site in their intact form and also provide desired release at targeted site by means of PDDS (pulsatile drug delivery system) specifically in circadian rhythms based diseases. Novel drug delivery systems are more site specific with maximum output with minimum side effects than conventional drug delivery systems.

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