International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 1(2): September-October 2011

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Review Article……!!!**

Received: 22-09-2011; Accepted: 18-10-2011

A BIOLOGICAL RHYTHM-GUIDED APPROACH TO DRUG DELIVERY: CHRONOPHARMACEUTICS

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Keywords:

Chronotherapeutics; Circadian rhythm; Chronopharmaceutics; Drug delivery

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ABSTRACT

Chronotherapeutics refers to a treatment method in which *in-vivo* drug availability is timed to match rhythms of disease, in order to optimize therapeutic outcomes and minimize side effects. It is based on the observation that there is an interdependent relationship between peak-to-trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs. The specific time that patients take their medication is very important as it has significant impact on treatment success. Optimal clinical outcome cannot be achieved if drug plasma concentrations are constant. If symptoms of a disease display circadian variation, drug release should also vary over time. Chronopharmaceutical drug delivery system are gaining importance in the field of pharmaceutical technology as these systems deliver the right dose at specific time at a specific site. Some of the disease conditions wherein chronotherapeutics are promising include duodenal ulcer, cardiovascular diseases, arthritis, asthma, diabetes, neurological disorder, cancer, hypertension and hypercholesterolemia. Various technologies such as time-controlled, pulsed, triggered and programmed drug delivery devices have been developed and extensively studied in recent years for chronopharmaceutical drug delivery. The present article covers findings about the effects of biorhythms on various disorders, and their implications for drug therapy are discussed. Here we also reviewed the design of novel chronopharmaceutical drug delivery systems that might be able to release the therapeutic agents at predetermined intervals.

INTRODUCTION

The oral route of drug delivery is typically considered the favored and the most user-friendly means of drug administration having the highest degree of patient compliance, as a result of which much effort are aimed to identify orally active candidates that would provide reproducible and effective plasma concentrations in vivo [1]. Traditionally, drug delivery systems have focused on constant/sustained drug output with the objective of minimizing peaks and valleys of drug concentrations in the body to optimize drug efficacy and to reduce adverse effects. A reduced dosing frequency and improved patient compliance can also be expected for the controlled / sustained release drug delivery systems, compared to immediate release preparations [2].

However, in the field of modern drug therapy, growing attention has lately been focused on Chronopharmaceutical delivery of drugs for which conventional controlled drug-release systems with a continuous release are not ideal.

To introduce the concept of **Chronopharmaceutics**, it is important to define the concepts of Chronobiology and Pharmaceutics. **Chronobiology** is the study of biological rhythms and their mechanisms. Biological rhythms are defined by a number of characteristics [3]. **Pharmaceutics** is an area of biomedical and pharmaceutical sciences that deals with the design and evaluation of pharmaceutical dosage forms (or drug delivery systems) to assure their safety, effectiveness, quality and reliability.

Some of the rhythms that affect our body are:

Ultradian (cycles shorter than a day like firing of neurons take miliseconds),

Circadian (cycles lasting 24 h such as sleeping and waking pattern),

infradian (cycles longer than a day like menstrual cycles),

Seasonal rhythms (such as seasonal affective disorders causing more depression in susceptible individuals in winter) [4]

Many functions of the human body vary considerably in a day. These variations cause changes both in disease state and in plasma drug concentrations. Human circadian rhythm is based on sleep-activity cycle, is influenced by our genetic makeup and hence, affects the body's functions

day and night (24-hour period) [5]. The dependence of bodily functions in certain disease states on circadian rhythm is well known.

Diseases, such as hypertension, asthma, peptic ulcer, arthritis, etc, follow the body's circadian rhythm [6]. Many systems in the human body such as cardiovascular, pulmonary, hepatic and renal systems show variation in their function throughout a typical day. They are naturally synchronized by the internal body clocks and are controlled by the sleep wake cycle.

Each body system exhibits a peak time of functionality that is in accordance with these rhythmical cycles. Similarly, disease states affect the function of some of these systems in the body and therefore, they too exhibit a peak time of activity within a circadian rhythm [7].

Research in the chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy, and this has brought a new approach to the development of drug delivery systems. Optimal clinical outcomes cannot be achieved if drug plasma concentrations are constant. If symptoms of a disease display circadian variation, drug release should also vary with time. Another issue that has emerged from circadian variation of physiological function is that drug pharmacokinetics can be time-dependent (i.e., chronopharmacokinetics) [8].

Therefore, variation in disease state and drug plasma concentration need to be taken into consideration in the development of drug delivery systems intended for the treatment of diseases with adequate dose at the appropriate time. The term, 'Chronopharmaceutic Drug Delivery System', is used to describe a kind of drug formulation which can cause circadian variation in drug plasma levels [9-11]. It can be defined as a branch of pharmaceutics devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy.

The shift from conventional sustained release approach to modern Chronopharmaceutical delivery of drugs can be credited to the following reason(s):

1. **First pass metabolism:** Some drugs, such as beta blockers, and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize pre-systemic metabolism. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability.

2. **Biological tolerance:** Continuous release drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitroglycerin.
3. **Special chronopharmacological needs:** Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24 hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours.
4. **Local therapeutic need:** For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.
5. **Gastric irritation or drug instability in gastric fluid:** For compounds with gastric irritation or chemical instability in gastric fluid, the use of a sustained release preparation may exacerbate gastric irritation and chemical instability in gastric fluid.
6. **Drug absorption differences in various gastro-intestinal segments:** In general, drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine. Compensation for changing absorption characteristics in the gastrointestinal tract may be important for some drugs. For example, it is rational for a delivery system to pump out the drug much faster when the system reaches the distal segment of the intestine, to avoid the entombment of the drug in the feces [(12)].

CHRONOTHERAPEUTICS

The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. It is based on the observation that there is an interdependent relationship between the peak-to-trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs [(13)].

The tradition 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 changing as researchers' report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms [14].

The chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules, and a special drug delivery system to synchronize drug concentrations to rhythms in disease activity. The concept of chronotherapeutics is not new; the roots of clinical chronobiology date back to 1814, when Joseph Virey empirically recommended that opium should be dosed late in the evening, rather than in the morning. In the last few years recognition of the importance of the circadian rhythm to the health sciences has increased significantly [15].

Circadian Time Structure

The term circadian rhythm was first given by Halberg and Stephens in 1959. Circadian rhythm governs every process of our body [16-17]. In fact the human circadian time structure presents peaks of actions directly related to the daily routine of most human beings. As human physiology and biochemistry predictably vary during a 24 hour period it is easy to understand that some medical conditions present prevalence at certain periods of the day.

One means of illustrating the human circadian time structure is to depict the peak time of 24-h rhythms on a clock--like diagram like that shown in Fig. 1 & 2 [4, 18]. This figure shows the peak time of a select number of human circadian rhythms in relation to the typical synchronizer routine of most human beings — Sleep in darkness from 10:30 p.m. to 6:30 a.m. and activity during the light of the day between 6:30 a.m. and 10:30 p.m [18].

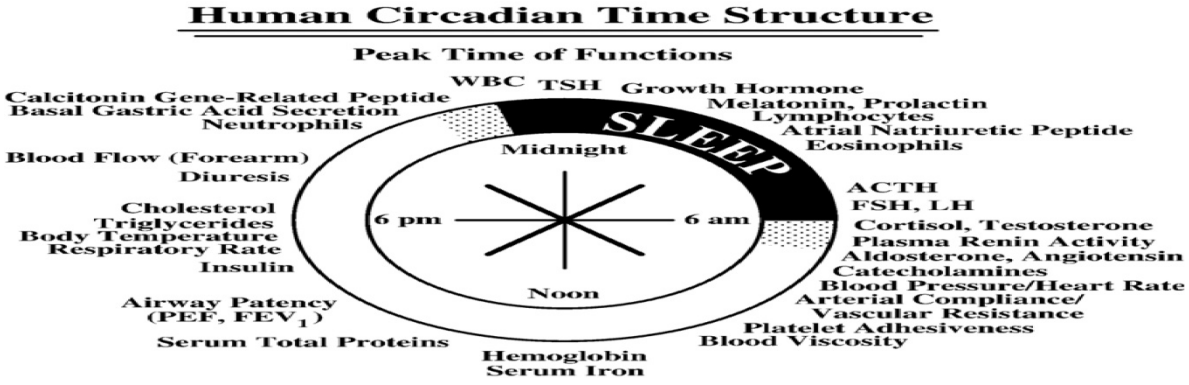


Fig. 1…. Human Circadian time structure

The circadian rhythms of white blood count (WBC), thyroid stimulating hormone (TSH), growth hormone, melatonin, prolactin, atrial natriuretic peptide, and esosinophil and lymphocyte cell numbers in blood peak between bedtime and early hours of sleep.

Circadian rhythms in the blood level of adrenocortical tropic hormone (ACTH), follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, cortisol, catecholamines, renin activity, aldosterone, and angiotensin peak near the end of nighttime sleep or start of daytime activity.

The morning peak of the rhythm in vaso-active entities contributes to the morning peak time of the circadian rhythms in heart rate, blood pressure, arterial compliance, and vascular resistance in normotensive and uncomplicated essential hypertension persons, and the morning peak of the circadian rhythm in blood catecholamines gives rise to the morning peak of the circadian rhythm in platelet aggregation.

Circadian rhythms of hemoglobin and serum iron peak around mid-day and total serum proteins and airway caliber — PEF (peak expiratory flow rate) and FEV1 (forced expiratory volume in 1 s)—peak in the afternoon [18].

Circadian rhythms of body temperature and respiratory rate and blood insulin, cholesterol, and triglycerides peak late in the afternoon, while those of urine production (diuresis), forearm blood flow, neutrophils, basal gastric acid production, and calcitonin-generelated peptide (a vascular dilator) peak late in the activity span.

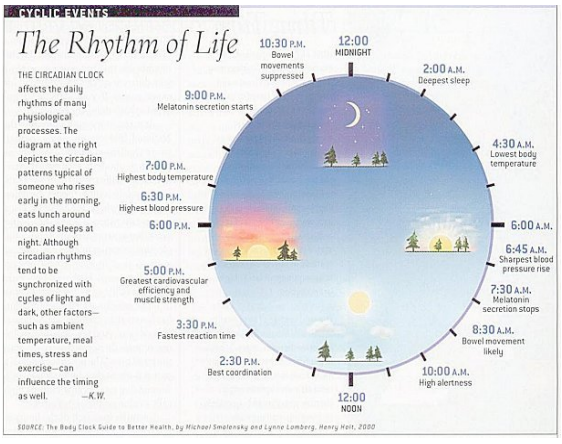


Fig. 2(a)… Various Rhythm of life

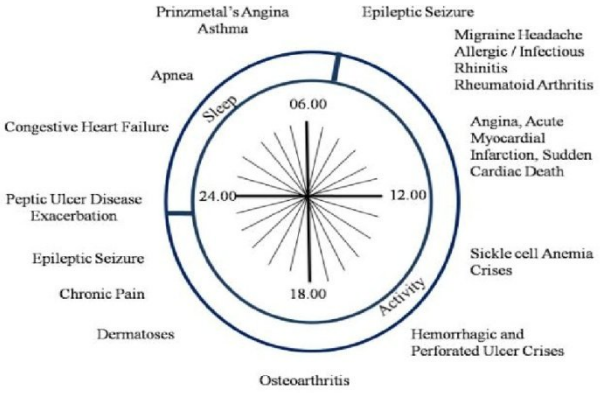


Fig. 2(b)…Circadian pattern of diseases

The onset of migraine headache is most frequent in the morning around the time of awakening from nighttime. The sneezing and runny nose in allergic and infectious rhinitis is worst in the morning upon arising from nighttime [19].

The symptoms of rheumatoid arthritis are worst when awaking from nighttime, while those of osteoarthritis are worst later in the day. The morbid and mortal events of myocardial infarction are greatest during the initial hours of daytime.

The incidence of thrombotic and hemorrhagic stroke is greatest in the morning around the time of commencing diurnal activity. Ischemic events, chest pain, and ST-segment depression of angina are strongest during the initial three to four hours of daytime.

Pain and gastric distress at the onset and acute exacerbation of peptic ulcer disease are most likely in the late evening and early morning. Epilepsy seizures are common around sleep, onset at night and offset in the morning.

The symptoms of congestive heart failure are worse nocturnally. The manifestation of ST-segment elevation in Prinzmetal's angina is most frequent during the middle to latter half of the nighttime.

CHRONOTHERAPY OF DISEASES

Cardiovascular Diseases

The differences in patterns of illness between day and night for cardiovascular disorders such as hypertension, angina, heart attack, sudden cardiac death and stroke have been documented [5]. Chronotherapeutic approach gives more accurate determination of the time when patients are at highest risk and in greatest need of therapy. For example, it has often been found that the blood pressure of a hypertensive patient increases rapidly in the morning after awakening, typically peaks in the middle to late time of the day, decreases in the evening, and is lowest while the patient sleeps at night [5]. It may also be important to recognize that the risk of heart attack appears to be greatest during the early morning hours after awakening.

For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hyper coagulability of the blood. BP is at its lowest during

the sleeping period and rises steeply during the early morning period [20-22]. Many antihypertensive drugs do not control the early morning blood pressure, when given once daily early in the morning [23].

Hermida et al, studied the impact of antihypertensive treatment and the time of therapy on the circadian pattern of blood pressure in 585 hypertensive patients with diabetes mellitus. Blood pressure was measured at 20 min intervals from 07:00 to 23:00 h and at 30 min intervals at night for 48 consecutive h. Blood pressure was reduced during diurnally active h, but not during nocturnal sleep, as compared to untreated patients ($P<0.001$). Results from this study indicate the need to establish a proper chronotherapeutic scheme that could reduce BP and modify the altered circadian profile into a dipper BP pattern, associated to a lower cardiovascular risk [24-25].

Koga et al, conducted a chronotherapeutic test for β – blockers to prevent the morning surge of hypertension by evening administration of carvedilol. In their study, they treated 12 male and 5 female patients with hypertension for 4 weeks at controlled blood pressure. The patients exceeding blood pressure 140/90 mmHg were treated with 10 mg/day carvediol as single dose in the evening. Results showed that the morning surge was suppressed with carvedilol and the 24 h mean systolic pressure was also reduced [26].

Diabetes

The most widespread application of chronotherapy is insulin pump, which is used to administer insulin for the treatment of diabetes mellitus. With the insulin pump, patients can customize insulin delivery to meet their particular requirements.

Several systems were developed to respond the change in glucose concentration like pH sensitive hydrogel containing glucose-oxidase enzyme immobilized in hydrogel. As the blood concentration of glucose rises, glucose oxidase converts glucose into gluconic acid, which changes the pH of system. Due to change in pH, swelling of polymer takes place and this result into insulin release. Insulin decreases the blood glucose level and consequently the gluconic acid level also declines and system turns to de-swelling and hence decreasing the insulin release [27].

Cancer

An important issue in the treatment of cancer is its tolerability by patients. Drugs having good therapeutic effect by killing tumour cells are always limited in their use by their toxicity on healthy tissues. So it is the greatest importance to find differences in the behaviours of healthy and cancer cells towards aggression by antitumour treatments [(28)]. The blood flow to tumors was threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase [(29)].

Hrushesky et al, conducted research on chronotherapy for gynecological and genitourinary cancers including advanced renal cell carcinoma. These studies demonstrated the superiority of chronotherapy with respect to response and side effects when compared to conventional chemotherapy [(30-31)].

Adler et al, conducted phase I clinical trial for chronotherapy of colorectal cancer in eight patients with 5-fluorouracil (initial dose of 500 mg/m^2/day) and folinic acid (20 mg/m^2/day] as a continuous intravenous infusion over five consecutive days. Compared with conventional Phase I/II trials using a five days infusion regimen, the maximal tolerated dose of 5 - fluorouracil and folinic acid was slightly higher. The results suggest that the circadian timing of 5-fluorouracil and folinic acid may not always allow the safe application of high dose levels [(32)]. In a study, the chronotherapeutic schedules were used for safe activity of the combination of oxaliplatin, 5-fluorouracil, and leucovorin against metastatic colorectal carcinoma. The results offer that the chronotherapy concepts improve current cancer treatment [(33)].

Renal Diseases

A repeated dosing study of high-dose active vitamin D3 in haemodialysis patients with secondary hyperparathyroidsm was conducted. A higher dose (3 mg) was given orally to 13 haemodialysis patients at 08.00 h or 20.00 h for 12 months by a randomized, cross-over design with an 8-week washout period. Serum concentrations of calcium and inorganic phosphate were determined by orthocresolphtalein complex method, and ammonium molybdate method with an autoanalyser, respectively. The results indicate that a higher dose of oral D3 is more effective and safe after dosing at evening in patients with renal osteodystrophy [(34)].

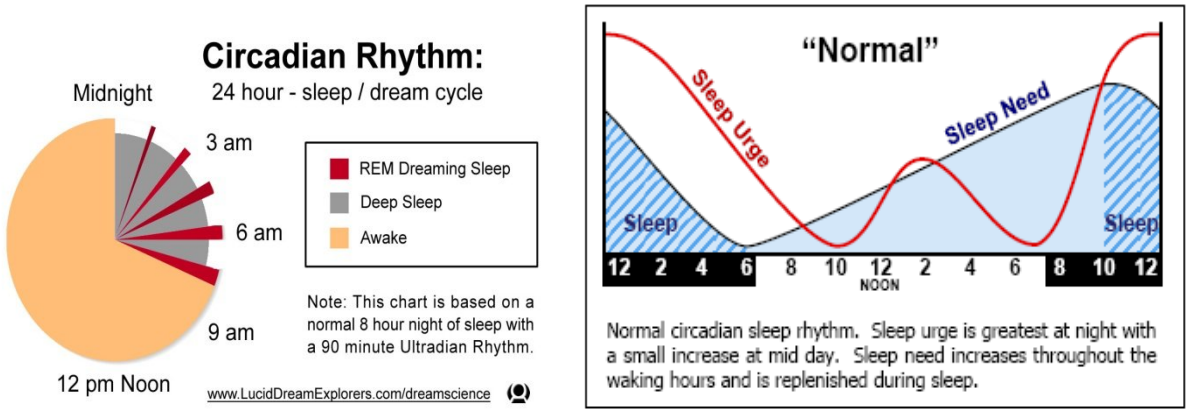
Asthma

It has been estimated that symptoms of asthma occur 50 to 100 times more often at night than during the day [35]. Many circadian-dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms. For example, cortisol (an anti-inflammatory substance) levels were highest at the time of awakening and lowest in the middle of the night, and histamine (a mediator of bronchoconstriction) concentrations peaked at a level that coincided with the greatest degree of bronchoconstriction at 4:00 am [6].

Asthma is well suited for chronotherapy, with beta 2- agonists and oral corticosteroids [36]. Once-daily evening theophylline chronotherapy meets these goals, providing rising blood levels at night and in the early morning, when most needed. Theophylline chronotherapy is as well tolerated as more frequently administered methylxanthine preparations despite the relatively large single doses required by the prolonged dosing interval. Theophylline chronotherapy does not provide constant blood levels over the 24 h [37].

Sleep Disorders

The circadian rhythm is not an immutable rhythm; it can be controlled by certain factors such as light and darkness, social interaction, sleep-wake schedule, timing for taking meals, etc. The rhythms of sleep is shown in figure 3(a & b).



(a) **(b)**

Fig. 3(a & b)….. Rhythm of sleep cycle

In the international classification published in 1990, sleep rhythm disorders such as non 24 h sleep-wake syndrome and delayed sleep phase syndrome are grouped together as circadian rhythm sleep disorder and treated as dyssomnias (Table 1).[38]

Table 1 Classification of sleep disorders

Dyssomnias	1) Intrinsic Sleep disorders 2) Extrinsic sleep Disorders 3) Circadian Rhythm Sleep Disorders
Parasomnias	1) Arousal Disorders 2) Sleep – wake transition Disorders 3) Parasomnias associated with REM
Sleep disorders associated with medical / psychiatric disorders	1) Associated with mental disorders 2) Associated with neurological disorders 3) Associated with other medical disorders

Arthritis

The cardinal signs of rheumatoid arthritis are stiffness, swelling and pain of joints of the body characteristically most severe in the morning. Patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day. Taking long-acting NSAIDs like flubiprofen, ketoprofen and indomethacin once-a-day forms optimizes their therapeutic effect and minimizes or averts their side effects [39-40].

Ulcers

It is well established that patients with peptic ulcer disease often experience the greatest degree of pain near the time that they go to bed, as the rate of stomach acid secretion is highest at night[5]. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Therefore, for active duodenal ulcer, once daily at bedtime is the recommended dosage regimen for an H2 antagonist.

Approaches for Chrono-pharmaceutical drug delivery system

Several techniques have been developed and applied to design chronopharmaceutic delivery systems for desired drug release. Different chronopharmaceutical technologies and marketed products are given in Table 2[41], and various US patents in the field of chronotherapy are given in Table 3[42]. These techniques are broadly classified into following three major categories:

I. TIME CONTROLLED PULSATILE RELEASE

(a) Single unit system

(i) Capsular Systems

(ii) Port systems

(iii) Delivery by solubility modulation

(iv) Delivery by reservoir systems with erodible or soluble barrier coatings

(b) Multi-particulate system

(i) Pulsatile System Based on Rupturable Coating

(ii) Time controlled expulsion system

(iii) Pulsatile Delivery by Change in Membrane Permeability

(iv) Sigmoidal Release System

II. STIMULI INDUCED PULSATILE RELEASE

(a) Chemical stimuli induced Pulsatile systems

(i) Glucose-responsive insulin release devices

(ii) Inflammation-induced pulsatile release

(iii) Drug release from intelligent gels responding to antibody concentration

(b) pH sensitive drug delivery system

III. EXTERNAL STIMULI INDUCED RELEASE

(a) Electro responsive pulsatile release

(b) Micro electro mechanical systems (MEMS)

(c) Magnetically induced pulsatile release

I. TIME CONTROLLED PULSATILE RELEASE

The drug is released as a burst within a short period of time immediately after a predetermined off release period. These time-controlled systems can be classified as single unit (e.g., tablet or capsule) or multiple unit systems.

(A) Single unit systems

(i) Capsular Systems

A general -design of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined time lag due to swelling, erosion, or dissolution. The Pulsincap® system is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation [(59)]. The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a time lag. This is followed by a spontaneous release of the drug (Fig 4).[(60)] The time lag can be controlled by manipulating the dimension and the position of the plug. The plug material consists of insoluble but permeable and swellable polymers (e.g.:polymethacrylates) [(61-62)], erodible compressed polymers (e.g: HPMC, PVP, PVA, PEO), congealed melted polymers (e.g: saturated polyglycolated glycerides, glycerylmonoole and enzymatically controlled erodible polymer e.g: pectin).

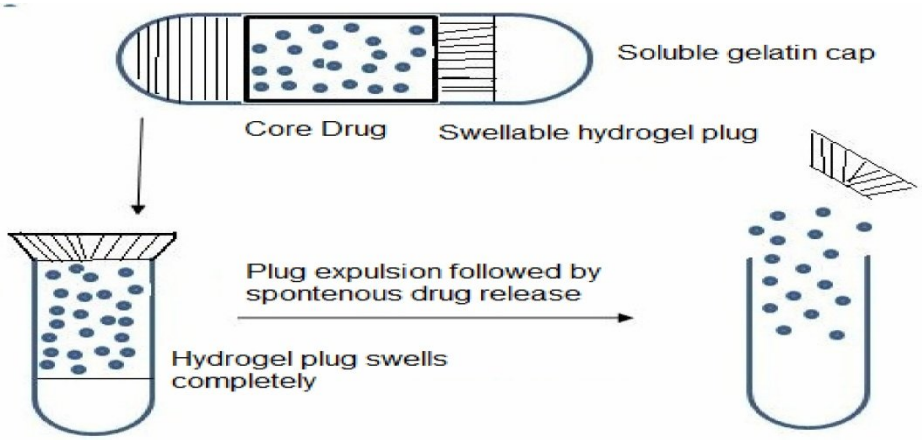


Fig. 4…….Schematic diagram of capsular system

(ii) Port systems

The Port System - consists of a gelatin capsule coated with a semi permeable membrane (e.g: cellulose acetate) housing an insoluble plug (e.g: lipidic) and an osmotically active agent along with the drug formulation [(63)]. When it comes in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a – time lag. The time lag is controlled by the thickness of semi permeable membrane. In order to deliver drug in liquid form, an osmotically driven capsular system was developed. In this system, liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved [(64)]. The capsular system delivers drug by the capsule's osmotic infusion of moisture from the body. The capsule wall is made up of an elastic material and possesses an orifice. As the osmosis proceeds, the pressure within the capsule rises, causing the wall to stretch. The orifice is small enough so that when the elastic wall relaxes, the flow of the drug through the orifice essentially stops, but when the elastic wall is distended beyond threshold value, the orifice expands sufficiently to allow drug release at a required rate. Elastomers, such as styrene-butadiene copolymer have been suggested [(65-66)].

(iii) Delivery by solubility modulation

These systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate [(67)]. The compositions contain the drug (salbutamol sulphate) and a modulating agent, sodium chloride (NaCl). The amount of NaCl was such that it was less than the amount needed to maintain saturation in a fluid that enters the osmotic device. The pulsed delivery is based on drug solubility. Salbutamol has solubility of 275 mg/ml in water and 16 mg/ml in saturated solution of NaCl, while NaCl has solubility of 321 mg/ml in water, and its saturation solubility is 320 mg/ml. These values show that the solubility of the drug is a function of the modulator concentration, while the modulators solubility is largely independent of drug concentration. The modulating agent can be a solid organic acid, inorganic salt, or organic salt.

(iv) Delivery by reservoir systems with erodible or soluble barrier coatings

Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly. The time lag depends on the thickness of the coating layer [(68)].

The Time Clock® system consists of a solid dosage form coated with lipid barriers containing carnauba wax and bees wax along with surfactants, such as polyoxyethylene sorbitan mono-oleate[(69-70)]. This coat erodes or emulsifies in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion. The major advantage of this system is its ease of manufacture without any need of special equipment. The disadvantage of this system is a premature drug release when the penetrating water dissolves the drug.

The Chronotropic® system consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of drug release [(71)]. Time lag is controlled by the thickness and the viscosity grades of HPMC used in coating the drug core. The system is suitable for both tablets and capsule formulations [(72)].

(B) Multiparticulate Systems

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, in which the active substance is present as a number of small independent subunits. They provide many advantages over single-unit systems because of their small size, less inter and intra-subject variability in gastrointestinal transit time, reduced adverse effects and improved tolerability, no risk of dose dumping, flexibility in design and finally Improve stability However, there are some draw backs in this system, which include lack of manufacturing reproducibility, high cost of production, multiple formulation steps and also the need of advanceed technologies.

There are different types of multi-particulate systems and these are enumerated and explained below:

(i) Pulsatile System Based on Rupturable Coating

This is a multiparticulate system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer [(73-74)]. The swelling agents used include

superdisintegrants like sodium CMC, sodium starch glycollate, L-hydroxypropyl cellulose, etc. Upon ingress of water, the swellable layer expands resulting in rupture of film with subsequent rapid drug release. The release is independent of environmental factors like pH and drug solubility. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer.

(ii) Time controlled expulsion system

This system is based on a combination of osmotic and swelling effects. The core contains the drug, a low bulk density solid and/or liquid lipid material (e.g., mineral oil) and a disintegrant. The core is further coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing the lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of the coating material [(75)]. Another system is based on a capsule or tablet composed of a large number of pellets consisting of two or more pellets or part [(76)].

(iii) Pulsatile Delivery by Change in Membrane Permeability

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium [(77)]. Several delivery systems based on this ion exchange have been developed. Eudragit RS 30D is reported to be a polymer of choice for this purpose [(78)]. It typically contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions. The ammonium group being hydrophilic it facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner.

(iv) Sigmoidal Release System

This consists of pellet cores comprising drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type B. The time lag is controlled by the rate of water influx through the polymer membrane. The water dissolves acid and the drug in the core. The acid solution in turn increases permeability of the hydrated polymer film. The different types of acids

that can be used include succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid [79-80].

Table 2 Various developed chronopharmaceutic systems[41]

Proprietary name	Chronopharm. Technology used	API	Disease
Cardizem® LA	CEFORM® technology	Diltiazem HCl	Hypertension
InnoPran® XL	DIFFUCAPS® technolog	Propranolol HCl	Hypertension
Covera-HS®	OROS® technology	Verapamil HCl	Hypertension
InnoPran® XL	DIFFUCAPS® technology	Verapamil HCl	Hypertension
Verelan® PM	CODAS® technology	Verapamil HCl	Hypertension
Pepcid®	Physico-chemical modification of the API	Famotidine	Ulcer
Lipovas®	Physico-chemical modification of the API	Simvastatin	Hyperlipidemia
Uniphyl®	CONTIN® technology	Theophylline	Asthama

Table 3 List of patents on chronopharmaceutic systems

S. No.	US Patent no.	Technology used	API	Reference
(1)	**US 7048945**	Time controlled or position controlled drug delivery system	Sotalol Hcl.	42 – 45
(2)	**US 5914134**	Pulsatile technology	Dilitazem Hcl.	46
(3)	**US 6217904**	Pulsatile technology	Methylphenidate	47
(4)	**US 5439689**	Pulsatile technology	Dilitazem Hcl.	48
(5)	**US 5834023**	Pulsatile technology	Dilitazem Hcl.	49
(6)	**US 6635277**	Pulsatile technology	Dilitazem Hcl.	50
(7)	**US 6605300, 6322819**	Pulsatile technology	Amphetamine	51
(8)	**US 6555136**	Pulsatile technology	Methylphenidate	47, 52
(9)	**US 4003379**	Implantable electro-mechanically driven device		53
(10)	**US 5490962**	Three dimensional printing technology		54

(11)	**US 3692027**	Self powered medication system		55
(12)	**US 4003379**	Implantable infusion device		56
(13)	**US 4146029**	Self powered medication system		57
(14)	**US 5797898**	Microchip drug delivery devices		58

II. STIMULI INDUCED PULSATILE RELEASE

The drug release from these systems is based on the physicochemical processes of body. These systems are meant for site specific targeted drug delivery by the induction of various physicochemical stimuli at target site. Biological stimuli like release of enzymes, hormones, antibodies, pH of target site, temperature of the site, concentration of biomolecules (glucose, neurotransmitters, inflammatory mediators) etc acts as stimuli to trigger the release of drug from these types of drug delivery systems [(4)]. The mechanisms of drug release include ejection of the drug from the gel as the fluid phase synerges out, drug diffusion along a concentration gradient, electrophoresis of charged drugs towards an oppositely charged electrode and liberation of the entrapped drug as the gel or micelle complex erodes [(81)].

(A) Chemical stimuli induced pulsatile systems

(i) Glucose-responsive insulin release devices

In case of Diabetes mellitus there is rhythmic increase in the levels of glucose in the body, requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release. Examples of the pH sensitive polymers include N, N-dimethylaminoethyl methacrylate, chitosan, polyol etc [(82-83)].

(ii) Inflammation-induced pulsatile release

On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. Degradation via hydroxyl radicals however, is usually dominant and rapid when Hyaluronic Acid gel is injected at inflammatory sites. Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated HA gels as new implantable drug delivery systems [(84)].

(iii) Drug release from intelligent gels responding to antibody concentration

There are numerous kinds of bioactive compounds which exist in the body. Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/deswelling characteristics. Special attention was given to antigen-antibody complex formation as the cross-linking units in the gel, since such interaction is very specific. Utilizing the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/deswelling and drug permeation changes occurs.

(B) pH sensitive drug delivery system

This type of PDDS contains two components. The first is fast release type while the other is pulsed release which releases the drug in response to change in pH. In case of pH dependent system, advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine [(85)].

III. EXTERNAL STIMULI PULSATILE RELEASE

External stimuli like ultrasound, magnetic field, electrical effect and irradiation are required to control the drug release from these systems. When these external factors are applied on the delivery system, conductors present in the delivery system get sensitized to trigger the release of drug from the delivery system. This system was divided into three subparts and is discussed below:

(A) Electro responsive pulsatile release

Electrically responsive delivery systems are prepared from polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. Examples of naturally occurring polymers include hyaluronic acid, chondroitin sulphate, agarose, carbomer, xanthan gum and calcium alginate. The synthetic polymers are generally acrylate and methacrylate derivatives such as partially hydrolyzed polyacrylamide, polydimethylaminopropyl acrylamide [(86)].

(B) Micro electro mechanical systems (MEMS)

A micro fabricated device has the ability to store and release multiple chemical substances on demand by a mechanism devoid of moving its parts [(86-87)]. The digital capabilities of MEMS may allow greater temporal control over drug release compared to traditional polymer-based systems. Another development in MEMS technology is the microchip. The microchip consists of an array of reservoirs that extend through an electrolyte-impermeable substrate. The prototype microchip is made of silicon and contains a number of drug reservoirs, each reservoir is sealed at one end by a thin gold membrane of material that serves as an anode in an electrochemical reaction and dissolves when an electric potential is applied to it in an electrolyte solution. The reservoirs are filled with any combination of drug or drug mixtures in any form (i.e. solid, liquid or gel). When release is desired, an electric potential is applied between an anode membrane and a cathode, the gold membrane anode dissolves within 10-20 seconds and allows the drug in the reservoir to be released. This electric potential causes oxidation of the anode material to form a soluble complex with the electrolytes which then dissolves allowing release of the drug. Complex release patterns (such as simultaneous constant and pulsatile release) can be achieved from the microchips. Microchip has the ability to control both release time and release rate.

(C) Magnetically induced pulsatile release

The use of an oscillating magnetic field to modulate the rates of drug release from polymer matrix was one of the old methodologies. Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials such as Magnetite, Iron, Nickel, Cobalt etc. For biomedical applications, magnetic carriers must be water-based, biocompatible, non-toxic and non-immunogenic mechanistic approach based on magnetic attraction is the slowing down of

oral drugs in the gastrointestinal system. This is possible by filling an additional magnetic component into capsules or tablets. The speed of travel through the stomach and intestines can then be slowed down at specific positions by an external magnet, thus changing the timing and/ or extent of drug absorption into stomach or intestines [88].

RECENT TECHNIQUES OF TIME CONTROLLED PULATILE TECHNOLOGY

Currently, pharmaceutical companies have been focused on developing and commercializing PDDS that fulfil unmet medical needs in the treatment of various diseases. Recently developed technologies are SODAS® Technology, IPDAS® Technology, CODAS™ Technology, GEOCLOCK® Technology, PULSYS™ Technology, CONTINR, OROSR, CEFORMR, DIFFUCAPSR, chronomodulating infusion pumps, EURANDs pulsatile and chrono release System, TIMERxR, Magnetic Nanocomposite Hydrogel.

Spheroidal Oral Drug Absorption System (SODAS)

This technology is based on the production of controlled release beads and it is characterized by its inherent flexibility, enabling the production of customized dosage forms that respond directly to individual drug candidate needs. SODAS can provide a number of tailored drug release profiles, including immediate release of drug followed by sustained release to give rise to a fast onset of action, which is maintained for 24 hours. An additional option is pulsatile release, where a once daily dosage form can resemble multiple daily doses by releasing drug in discrete bursts throughout the day [89].

The Intestinal Protective Drug Absorption System (IPDAS)

This Technology is a high density multiparticulate tablet technology, intended for gastrointestinal irritant compounds. The IPDAS® technology is composed of numerous high density controlled release beads, which are compressed into a tablet form. Once an IPDAS® tablet is ingested, it rapidly disintegrates and disperses beads containing a drug in the stomach, which subsequently pass into the duodenum and along the gastrointestinal tract in a controlled and gradual manner, independent of the feeding state. Release of active ingredient from the multiparticulates occurs through a process of diffusion either through the polymeric membrane and or the micro matrix of polymer/active ingredient formed in the extruded/spheronized multiparticulates.

Chronotherapeutic Oral Drug Absorption System (CODAS)

This technology was designed to release its drug component after a prolonged period of time when administered. A good example is Verelan® PM, which was designed to release Verapamil approximately four to five hours after ingestion. This delay is introduced by the level of release-controlling polymer applied to the drug-loaded beads .The release-controlling polymer is a combination of water-soluble and water-insoluble polymers. When fluid from the gastrointestinal tract contacts the polymer coat beads, the water-soluble polymer slowly dissolves, and the drug diffuses through the resulting pores in the coating. The water- insoluble polymer continues to act as a barrier, maintaining the controlled-release of the drug. When taken at bedtime, this controlled onset extended release delivery system enables a maximum plasma concentration of Verapamil in the morning hours, when blood pressure normally is high [(90)].

GEOCLOCK® Technology

Geoclock® tablets have an active drug inside an outer tablet layer consisting of a mixture of hydrophobic wax and brittle material in order to obtain a pH-independent lag time prior to core drug delivery at a predetermined release rate. This dry coating approach is designed to allow the timed release of both slow release and fast release active cores by releasing the inner tablet first after which the surrounding outer shell gradually disintegrates. Skye Pharma has used this novel technology to develop Lodotra™, a rheumatoid arthritis drug, which delivers the active pharmaceutical ingredient at the most suitable time of day to treat the disease condition [(91)].

CONTINR technology:

In this technology, molecular coordination complexes are formed between a cellulose polymer and a 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 since it has a uniform porosity (semi permeable matrixes) which may be varied [(92)]. This technology has concretely enabled the development of tablet forms of sustained-release aminophylline, theophylline, morphine, and other drugs. Research suggested that evening administration of UniphylR (anhydrous theophylline) tablets represented a rational dosing schedule for patients with asthma who often exhibit increased

broncho constriction in the morning. Patients demonstrated improved pulmonary function in the morning compared with use of twice-daily theophylline when once-daily UniphylR was administered in the evening. Thus, evening administration of once-daily theophylline may block the morning dip in lung function commonly seen [93].

OROSR technology

OROSR technology [94] uses an osmotic mechanism to provide pre-programmed, controlled drug delivery to the gastrointestinal tract. The dosage form comprises a wall that defines a compartment. The active drug is housed in a reservoir, surrounded by a semi-permeable membrane/wall (e.g. cellulose esters, cellulose ethers and cellulose ester–ethers) and formulated into a tablet. The tablet is divided into two layers, an active drug layer and a layer of osmotically active agents [e.g. poly (ethylene oxide)] comprising means for changing from a non-dispensable viscosity to a dispensable viscosity when contacted by fluid that enters the dosage form. For example, water from the gastrointestinal tract diffuses through the membrane at a controlled rate into the tablet core, causing the drug to be released in solution or suspension at a predetermined rate. This creates a 'pump' effect that pushes the active drug through a hole in the tablet. This technology, especially the OROSR Delayed Push– Pull k System, also known as controlled onset extended release (COER) was used to design Covera-HSR, a novel anti-hypertensive product. It actually enabled delayed, overnight release of verapamil to help prevent the potentially dangerous surge in BP that can occur in the early morning [95].

CEFORMR technology

The CEFORMR technology [96] allows the production of uniformly sized and shaped microspheres of pharmaceutical compounds. This ChrDDS approach is based on ''melt-spinning'', which means subjecting solid feedstock i.e. biodegradable polymer/bioactive agents combinations to the combination of temperature, thermal gradients, mechanical forces, flow, and flow rates during processing. The microspheres obtained are almost perfectly spherical, having a diameter that is typically 150–180 Am, and allow for high drug content. The microspheres can be used in a wide variety of dosage forms, including tablets, capsules, suspensions, effervescent tablets, and sachets. The microspheres may be coated for controlled release either with an enteric coating or combined into a fast/ slow release combination. This technology has been actually used to develop CardizemR LA, 1-day diltiazem formulation as ChrDDS [97].

DIFFUCAPSR technology

In the DIFFUCAPSR technology [98], a unit dosage form, such as a capsule for delivering drugs into the body in a circadian release fashion, is comprising 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 h. The active core of the dosage form may comprise 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. HPMC, PVP) 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 physiological need during the day, i.e. mimicking the circadian rhythm and severity / manif-estation 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 propranolol-containing ChrDDS (InnopranR XL) for the management of hypertension

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 [99]. To our knowledge infusion pumps on the market that have been referred to as chrono modulating for drug delivery application include the Melodie R programmable Synchromed R , Panomat R V5 infusion pumps.[100] The portable pumps are usually characterized by a light weigh (300–500 g) for easy portability and precision in drug delivery. For example portable programmable multi-channel pumps allowed demonstration of the clinical relevance of the chronotherapy principle in a sufficiently large patient population. Specifically, a clinical phase III trial involving several patients with metastatic gastrointestinal malignancies compared a flat versus the chrono modulated three-drug regimen, and demonstrated large, simultaneous improvements in both tolerability and response rates in patients with metastatic colorectal cancer receiving chronotherapy.

TIMERxR technology

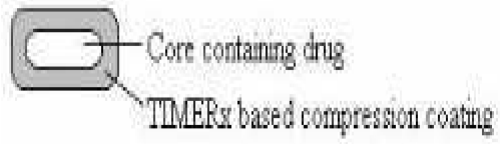


Fig. 5: Schematic diagram of tablet based on TIMERx technology

The TIMERxR technology (hydrophilic system) [101] combines primarily 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 TIMERxR gum matrix, which expands to form a gel and subsequently releases the active drug substance. This system can precisely control the release of the active drug substance in a tablet by varying the proportion of the gums, together with the third component, the tablet coating and the tablet manufacturing process. A chronotherapeutic version of this technology platform is being tested in clinical trial with a bioactive agent known as AD 121 against rheumatoid arthritis. Potential application ofthis technology is the development of an oral, CR opioid analgesic oxymorphone [102].

PULSYS™ Technology

This is an oral drug delivery technology that enables once daily pulsatile dosing. The PULSYS™ dosage form is a compressed tablet that contains pellets designed to release drug at different regions in the gastro-intestinal tract in a pulsatile manner. The dosage form is made up of multiple pellet types of varying release profiles that are combined in a proportion so as to produce a constant escalation in plasma drug levels in the early portion of the dosing interval. The transit properties of pellets enhance the overall absorption-time window and offer improved bioavailability compared to tablet matrix forms.

EURANDs pulsatile and chrono release System

This system is capable of providing one or more rapid release pulses at predetermined times lag. They can help to optimize efficacy and/or minimize side -effects of a drug substance. For example, Eurand has created a circadian rhythm release (CRR) dosage form for a cardiovascular

drug, Propranolol hydrochloride, with a four -hour delay in release after oral administration. When administered at bedtime, Propranolol is released after the initial delay such that maximum plasma level occurs in the early morning hours, when the patient is mostly at risk [103].

Magnetic Nano-composite Hydrogel

Magnetic nano-composite was synthesized by incorporation of super paramagnetic Ferric oxide particles in temperature sensitive poly (N-isopropylacrylamide) hydrogels. High frequency alternating magnetic field was applied to produce pulsatile drug release from nano-composite hydrogel. Nano-composites hydrogel are one type of On--Off device where drug release can be turn on by application of alternative magnetic field [104].

CONCLUSION

The effectiveness and toxicity of certain drugs depends on dosing time associated with 24 h rhythms under control of the circadian clock. The application of biological rhythm to pharmacotherapy may be correlated by the appropriate timing of dosing of these drug delivery systems to synchronize drug concentrations to rhythms in disease state. Chronopharmaceutics will certainly improve patient outcome and optimize disease management in the future. Research in chronopharmacology has demonstrated the importance of biological rhythms in drug therapy and this has led to a new approach to the development of drug delivery systems. Applications of chronotherapeutic drug delivery systems are now better understood for selected disease such as cancer, peptic ulcer, sleep disorder, hypertension etc. One goal of this article is to educate biologists, clinicians, and pharmaceutical scientists of the importance of biological clocks and chronobiology to health and disease. A second goal is to stimulate further experimental and clinical research in the field of chronopharmacology. However, the most important goal of the issue is to motivate the development and applications of chronotherapeutics as a practical means of improving the outcomes and safety of medical treatment.

ACKNOWLEDGEMENT

The authors are thankful to PDM College of Pharmacy for providing the necessary facilities, enthusiasm, moral & economical support and congenial atmosphere for carrying out the work.

REFERENCES

1. Charman S, Charman W. Oral modified-release delivery systems; In: Modified release drug delivery technology. New York, Marcel Dekker 2003; 1-11.
2. Burnside, B.A., Guo, X., Fiske, K., Couch, R.A., Treacy, D.J., Chang, R.K., McGuinness, C.M., Rudnic, E.M.: US20036605300 (2003).
3. M.H. Smolensky, G.E. D'Alonzo, Biologic rhythms and medicine, Am. J. Med. 1988; 85:34– 46
4. Awasthi Rajendra, Kumar Pravin, Chronotherapy: Science and technology of drug scheduling on basis of biological rhythm, Journal of Chronotherapy and Drug Delivery,2010, 1(1) :9 -18.
5. Evans RM, Marain C. Taking Your Medication: A Question of Timing. American Medical Association: 1996:3-8.
6. Ura J, Shirachi D, Ferrill M. The chronotherapeutic approach to pharmaceutical treatment. California Pharmacist. 1992; 23(9): 46-53.
7. Jason T. Recent trends in oral drug delivery.DrugDelivReportAutumn/Winter2005;24-27.
8. Bruguolle B, Lemmer B. Recent advances in chronopharmacokinetics: methodological problems. Life Sci 1993; 52: 1809-1824.
9. Halsas M, Hietala J, Veski P, Jürjenson H, Marvola M. Morning vs. evening dosing of ibuprofen using conventional and time-controlled release formulations. Int J Pharm 1999; 189: 179-185.
10. Halsas M, Ervasti P, Veski P, Jürjenson H, Marvola M. Biopharmaceutical evaluation of time-controlled press-coated tablets containing polymers to adjust drug release. Eur J Drug Metabol Pharmacokinet 1998; 23: 190-196.
11. Halsas M, Simelius R, Kiviniemi A, Veski P, Jürjenson H, Marvola M. Effect of different combinations of HPMC on bioavailability of ibuprofen from press-coated time-controlled tablets. STP Pharma Sci. 1998; 8: 155-161.
12. Burnside, B.A., Guo, X., Fiske, K., Couch, R.A., Treacy, D.J., Chang, R.K., McGuinness, C.M., Rudnic, E.M.: US20036605300 (2003).
13. Traynor K, Newton DW, Hrushesky JM, Reiter RJ. A pharmacist's primer on chronotherapeutics. American Pharmacy. 1992; NS32 (3): 261-269.
14. Evans RM, Marain C. Taking Your Medication: A Question of Timing. American Medical Association: 1996:13-18.
15. Wal Pranay , Wal Ankita, Rai K Awani, Saxena Ashutosh, Chronopharmaceutics as a novel approach for drug delivery, Journal of pharmaceutical science and technology, 2009, 1(2), 59-62
16. Youan BIBC. Chronopharmaceutics: Gimmick or clinically relevant approach to drug delivery. J Controlled Release. 2004; 98: 337 - 53.
17. A time to Heal: Chronotherapy tunes in to body's rhythms. Available: http://www.medicinenet.com/script/main/art.asp?articlekey=551(cited 2009, June 9).

18. Devdhawala Mehul G , Seth Avinash K. Current status of chronotherapeutic drug delivery system: An overview, J. Chem. Pharm. Res., 2010, 2(3):312-328.
19. J Sajan, TA Cinu, AJ Chacko, J Litty and T Jaseeda, Chronotherapeutics and Chronotherapeutic Drug Delivery Systems, Tropical Journal of Pharmaceutical Research, 2009; 8 (5): 467-475.
20. Lemmer B. Cardiovascular chronobiology and chronopharmacology. Biological Rhythms in Clinical and Laboratory Medicine 1992; 418– 427.
21. Tofler GH, Brezinski D, Schafer AI, Czeisler CA, Rutherford JD, Willich SN, Gleason RE, Williams GH, Muller JE. Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. J Med 1987; 316: 1514–1518.
22. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Circulation 1989; 79:733– 743.
23. White WB. Relating cardiovascular risk to out-of-office blood pressure and the importance of controlling blood pressure 24 hours a day. Am J Med 2008; 121: S2 - S7.
24. Hermida RC, Ayala DE, Fernande´z JR. Chronotherapy improves blood pressure control and reverts the nondipper pattern in patients with resistant hypertension. Hypertension 2008; 69-76.
25. Hermida RC, Calvo C, Ayala DE, Covelo M, Rodriguez M, Mojon A, Fernandez JR, Fontao MJ, Soler R, Lopez JE. P-66: Effects of the circadian time of antihypertensive treatment on the ambulatory blood pressure pattern of hypertensive patients with type 2 diabetes. Am J Hypertens. 2005; 18: 32A - 32A.
26. Konga H, Hayashi J, Yamamoto M, Kitamoto K. Prevention of morning surge of hypertension by the evening administration of carvedilol. JMAJ. 2005; 48 (8): 398 – 403.
27. Peppas N, William L. Stimuli-sensitive hydrogels: ideal carriers for chronobiology and chronotherapy. J. Biomater. Sci. Polymer Edn. 2004; 15 (2): 125 - 144.
28. Halberg F, Haus E, Cardoso SS, Scheving LE, Kuhl JFW, Shiotsuka R. Toward a chronotherapy of neoplasia: tolerance of treatment depends upon host rhythms. Experientia. 1973; 29: 909 - 1044.
29. 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 1996; 65:360–364.
30. Hrushesky WJM, Von Roemeling R, Lanning RM, Rabatin JT. Circadian-shaped infusion of floxuridine for progressive metastatic renal cell carcinoma. J Clin Oncol. 1990; 8: 1504 - 1513.
31. Kobayashi M, Wood PA, Hrushesky WJM. Circadian chemotherapy for gynecological and genitourinary cancers. Chronobiol Int. 2002; 19: 237- 251.
32. Adler S, Lung S, Langenmayer L, Eibesfeldt BE, Rump W, Emmerich B, Hallek M. Chronotherapy with 5- Fluorouracil and Folinic Acid in Advanced Colorectal Carcinoma. Cancer. 1994; 73 (12): 2905 - 2912.
33. Mormont MC, Levi F. Cancer Chronotherapy, Cancer. 2003; 97 (1): 155 - 169.

34. Tsuruoka S, Wakaumi M, Sugimoto K, Saito T, Fujimura A. Chronotherapy of high-dose active vitamin D3 in haemodialysis patients with secondary hyperparathyroidsm: a repeated dosing study. Br J Clin Pharmacol. 2002; 55: 531 – 537.
35. Washington N, Wilson CG. Can oral controlled drug delivery meet the challenges posed by chronotherapeutics,Available from:http://www.egalet.com/multimedia/Chronotherapy.
36. Martin RJ, Shlegel SB. Chronobiology of asthma. Am. J. Respir. Crit. Care Med. 1998; 158: 1002 - 1007.
37. Chronotherapy of reversible airways disease with once-daily evening doses of a controlled-release theophylline preparation, Ann N Y Acad Sci. 1991; 618: 490 - 503.
38. Ohta T. Circadian rhythm sleeps disorders: A brief with sleep reference to long-term follow-up. Nagoya J. Med. Sci. 1995; 58: 83 – 93.
39. Kowanko IC, Pownall R, Knapp MS. Circadian variations in the signs and symptoms of rheumatoid arthritis and in the therapeutic effectiveness of flurbiprofen at different times of the day. British Journal of Clinical Pharmacology. 1981; 11: 477 - 484.
40. Huskisson EC. Chronopharmacology of ant-rheumatic drugs with special reference to indomethacin. In: Inflammatory Arthropathies. EC Huskisson and GP Velo Editors. Amsterdam, Excepta Medica. 1976; 99 - 105.
41. Shigehiro OHDO. Chronopharmaceutics: Pharmaceutics Focused on Biological Rhythm. Biol. Pharm. Bull. 2010; 33(2): 159 - 167.
42. Gohel MC, Sumitra M : US20010046964 (2001).
43. Gohel MC, Sumitra M, Modulation of active pharmaceutical ingredient release from a novel tablet in capsule system containing an effervescent blend, J control release, 2002; 79:157-164.
44. Percel P, Vishnupad KS, Venkatesh GM : US20016627223
45. Percel P, Vishnupad KS, Venkatesh GM, Lee DY : US20037048945 (2003).
46. Sharma VK: US5914134 (1999)
47. Midha KK, Teicher MH : US20016217904 (2001).
48. Hendrickson D.L, Dimmitt D.C, Williams M.S, Baltezor M.J : US5439869 (1995)
49. Chen C.M : US5834023 (1998)
50. Sharma V.K: US20036635277 (2003).
51. Burnside B.A,Guo X.,Fiske K.,Couch R.A,Chang R.K,Rudnic E.M : US6322819 (1998).
52. Midha K.K : US20036555136 (2003)
53. Ellinwood, Jr.; Everett H. : US4003379 (1977)
54. Linda G., Michael J. : US5490962 (1996)
55. Ellinwood Jr., Everett H. : US3692027(1972)
56. Ellinwood Jr., Everett H.: US4003379 (1977)
57. Ellinwood Jr., Everett H.: US4146029 (1979)
58. Santini Jr., John T., Cima, Michael J., Langer, Robert S. : US5797898 (1998)
59. Saeger H, Virley P. Pulsincap& Mac226: Pulsed-Release Dosage Form. Product

information from Scherer DDS, Ltd; 2004.
60. Sharma GS, Srikanth MV, Uhumwangho MU, Phani Kumar KS and Ramana Murthy KV, Recent trends in pulsatile drug delivery systems - A review, International Journal of Drug Delivery 2 (2010) 200-212.
61. Bodmeier R. Pulsatile drug release from an insoluble capsule body controlled by an erodible plug. Pharm Res 1998; 15(3): 474-481.
62. Krgel I, Bodmeier R. Evaluation of an enzyme-containing capsular shaped pulsatile drug delivery system. Pharm Res 1999; 16(9): 1424-1429.
63. Crison JR, Siersma PR, Taylor MD, Amidon GL. Programmable oral release technology, Port Systems & Mac226: a novel dosage form for time and site specific oral drug delivery. Proceed Intern Symp Control Rel Bioact Mater 1995; 22: 278-279.
64. Pollock Dove C, Dong L, Wong P. A new system to deliver a delayed bolus of liquid drug formulation. Proceed Intern Symp Control Rel Bioact Mater 2001; 28: 6033.
65. Linkwitz A, Magruder JA, Merrill S. Osmotically Driven Delivery Device with Expandable Orifice for Pulsatile Delivery Effect. US Patent No. 5,318,558; 1994.
66. Linkwitz A, Magruder JA, Merrill S. Osmotically Driven Delivery Device with Expandable Orifice for Pulsatile Delivery Effect. US Patent No. 5,221,278; 1993.
67. Magruder PR, Barclay B, Wong PSL, Theeuwes F. Composiition comprising salbutamol. US Patent No.4751071;1988.
68. Pozzi F, Furlani P. Orale Feste Pharmazeutische Darreichungsform Mit Programmierter Freisetzung. DE Patent No. 4122039; 1992.
69. Wilding IR, Davis SS, Pozzi F, Furlani P, Gazzaniga A. Enteric coated timed release systems for colonic targeting. Int J Pharm 1994; 111: 99-102.
70. Gazzaniga A, Iamartino P, Maffione G, Sangalli ME. Oral delayed-release system for colonic specific delivery. Int J Pharm 1994; 2(108): 77-83.
71. Maroni A, Sangalli ME, Cerea M, Busetti C, Giordano F, Gazzaniga A. Low viscosity HPMC coating of soft and hard gelatin capsules for delayed and colonic release: preliminary investigations on process parameters and in vitro release performances. Proceed Int Control Rel Bioact Mater 1999; 26: 887-888.
72. Ueda Y, Hata T, Yamaguchi H, Ueda S, Kotani M, Time Controlled Explosion System and Process for Preparation for the Same. US Patent No. 4,871,549; 1989.
73. Ueda Y, Hata T, Yamaguchi H, Kotani M, Ueda S, Development of a novel drug release system, time-controlled explosion system (TES). Part 1: concept and design. J Drug Targeting 1994; 2: 35-44.
74. AmidonGL,LeesmanGD.,Pulsatile Drug Delivery System.US Patent No.5,229,131; 1993.
75. Chen CM.Multiparticulate Pulsatile Drug Delivery System.USPatentNo.5,508,040; 1996.
76. Bodmeier R, Guo X, Sarabia RE, Skultety P. The influence of buffer species and strength on diltiazem HCl release from beads coated with aqueous cationic polymer dispersions, Eudragit RS, RL 30D. Pharm Res 1996; 13(1): 52-56.

77. Beckert TE, Pogarell K, Hack I, Petereit HU. Pulsed drug release with film coatings of Eudragit & Mac226; RS 30D. Proceed Int'l Symp Control Rel Bioact
78. Narisawa S, Nagata M, Danyoshi C, Yoshino H, Murata K, Hirakawa Y, Noda K. An organic acid-induced sigmoidal release system for oral controlled-release preparations. Pharm Res 1994; 11(1):111-116.
79. Narisawa S, Nagata M, Hirakawa Y, Kobayashi M, Yoshino H. An organic acid-induced sigmoidal release system for oral controlled-release preparations. Part II: permeability enhancement of Eudragit RS coating led by the physicochemical interactions with organic acid. J Pharm Sci 1996; 85(2):184-188.
80. Roy, Shahiwala A. Multiparticulate formulation approach to pulsatile drug delivery: Current perspectives. J Control Rele 2009; 134:74–80.
81. Dinaravand RD, Emanele A. Use of thermoresponsive hydrogels for on-off release of molecules. J Control Rel 1995; 221-227.
82. Gutowska A, Bark JS, Kwon IC, Bae YH, Kim SW. Squeezing hydrogels for controlled oral drug delivery. J Control Rel 1997; 48: 141-148.
83. Yui N, Okano T, Sakurai Y. Inflammation Responsive Degradation of Cross-Linked Hyaluronic-Acid Gels. J Control Rel 1992; 22:105-116.
84. Miyata T, Asami N, Uragami T. A reversibly antigen-responsive hydrogel. Nature 1999; 399:766-769.
85. Sachin sanvase, Neeraj kumar. Pulsatile drug delivery: Current scenario.CRIPS 2007; 8:27-33.
86. Santini JT, Cima MJ, Langer R. A controlled-release microchip. Nature 1999; 335-338.
87. Santini JT, Richards AC, Schiedt R, Cima MJ, Langer R. Microchips as controlled-drug delivery devices. Angew Chem Int Ed 2000; 2396-2407.
88. Chen H, Langer R. Magnetically-responsive polymerizedliposomes as potential oral delivery vehicles. Pharm Res 1997; 537-540.
89. Dvane, John G, Stark, Paul, Fanning, Niall MM. Multiparticulate modified release composition. US Patent No.4863742 2009.
90. White WB, Mehrotra DV, Black HR, Fakouhi TD. Effects of controlled onset extended release Verapamil on nocturnal blood pressure (dippers versus nondipprs)-verapamil study group; Am J Cardiol 1997;80:469-474.
91. Gopi Venketesh. New tools for timed, pulsatile drug delivery. Pharma Formu & Qual 2005.
92. S. Leslie, in: Euroceltique, SA, United States, 1982, p. 20.
93. S. Leslie, J. Allergy Clin. Immunol. 1986; 78:768–773.
94. F. Jao, P. Wong, H. Huynh, K. McChesney, P. Wat, Alza Corporation, United States, 1992, p. 17.
95. W.B. White, D.V. Mehrotra, H.R. Black, T.D. Fakouhi, Am. J. Cardiol. 1997; 80: 469– 474.

96. R. Fuisz, Fuisz Technologies Ltd, United States, 1996, p. 34.
97. R. Verma, G. Sanjay, Pharm. Technol. 2001;25 :1– 14.
98. P. Percel, K. Vishnupad, G. Venkatesh, in: Eurand Pharmaceuticals Ltd., United States, 2002, p. 13.
99. S. Sershen, J. West, Adv. Drug Deliv. Rev. 2002; 54: 1225–1235.
100. S.T. Tzannis, W.J. Hrushesky, P.A. Wood, T.M. Przybycien, Proc. Natl. Acad. Sci. USA 1996;93:5460– 5465.
101. A. Baichwal, J. Staniforth, Penwest Pharmaceuticals Co., United States, 2002, p. 19.
102. Oxymorphone-Endo/Penwest: EN 3202, EN 3203, Drugs R.D. 2003; 204– 206.
103. Parcel P, Vishnupad KS, Venkatesh GM. Timed pulsatile drug delivery systems. US Patent 6, 627, 2231.
104. Nitin S, Satarkar, Zach Hilt S. Magnetic hydrogel nanocomposite for remote controlled pulsatile drug release. J Cont Relea 2008; 130: 246-251.