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Pulsatile Drug Delivery System: an Approach of Medication according to Circadian Rhythm

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ABSTRACT

Pulsatile drug delivery systems are developed to deliver drug according to circadian behavior of diseases. This means that these systems will deliver drug at time when disease display it's most morbid and mortal state within a circadian cycle (24 hrs.). The product follow a sigmoidal drug release profile characterized by a time period of no release (lag time) followed by a rapid and complete drug release. Thus drug can be delivered at right time, in right amount and at right site of action by use of such approach. The potential benefits of chronotherapeutics have been investigated and established for number of diseases like asthma, arthritis, cancer, diabetes, epilepsy, hypertension, ulcer, hypercholesterolemia etc. Various capsular, osmotic, single and multiple unit systems that are modulated by soluble or erodible polymer coatings, rupturable membranes are available in market. These systems are beneficial for diseases showing chronopharmacological behavior where night time dosing is required or for the drugs having high first pass effect or having site specific absorption in GIT, or for drugs with high risk of toxicity or tolerance. These systems also improve patient compliance by decreasing dosing frequency.

Keywords: Pulsatile, circadian cycle, chronotherapeutics, hypercholesterolemia, chronopharmacological

INTRODUCTION

Today, a vast amount of literature reports that biological processes are not constant but vary according to time. Although much of drug delivery research has focused on constant drug release rate due to limitations of delivering drug according to disease rhythmicity, clinical studies show that magnitude of rhythmic differences can be to a great extent and a strong determinant of when during 24 hour most morbid and mortal event will occur. For many drugs constant release system is not suitable. Drugs not suitable for constant release are used in disease condition that exhibit rhythmic variation within a circadian cycle. For, drugs with decrease bioavailability due to first pass metabolism, gradual release of drug from constant release systems can result in greater degradation. Drugs with more toxic effects, continuous exposure may lead to increased adverse effects. For, drugs which exhibit tolerance, constant exposure decreases drug effect**.** Modified release dosage forms have acquired a great importance in the current pharmaceutical research and development field. These dosage forms show different release profiles depending on their type. This dosage form is used to describe products that alter the timing and rate of release of drug substance (Survase *et al.*, 2007).

Various modified release drug products

Extended Release: It leads to two fold reductions in dosing frequency compared to immediate release dosage forms. *(i)*

Controlled release: This system allows slow drug release over extended period of time but not at predetermined rate. *(ii)*

Sustained release: This system delivers drug at predetermined rate over a long period.

Delayed Release: This dosage form releases discrete portion of drug at a time other than readily after administration, although one portion may be released promptly after administration.

Targeted Release: These delivery systems deliver drug at or near the intended site of action and may have extended release characteristics.

Repeated Action: This product is designed to release first dose initially, followed by second dose of drug at a later time.

Prolonged Action: This dosage form releases drug slowly and provide continuous supply of drug over an extended period (Mamidala *et al.,* 2009).

PULSATILE DRUG DELIVERY SYSTEMS

A Pulsatile drug delivery system delivers drug in rapid and burst manner within a short time period immediately after a programmable lag phase (Geest *et al.,* 2006). There are many situations where drug is needed to be released immediately (after bursting the delaying film coat) at specific site. These situations, therefore, compel designing a delayed fast release systems. These systems are mainly appropriate for drugs that are metabolized to pharmacological active compounds, drugs which have long in vivo half lives showing an inherently prolonged duration of action, drugs with very short in vivo half life which require a prohibitively large amount of active ingredients in dosage form, drugs which are required in large doses for therapeutic effect and drugs which are required in very low dose. Additionally a delayed burst release can also be utilized for enhancing absorption, reducing side effects, increasing and decreasing dose (Adel *et al.,* 2006).

Advantage of pulsatile drug delivery system

There are many advantages of pulsatile dosage form over conventional dosage form.

- Increases absorption and bioavailability than conventional immediate release or sustained release drug due to its ability to release drug in a burst manner, at target site of absorption.
- Site targeting allows delivery of poorly bioavailable drugs that would get destroyed in higher GI tract environment e.g. (peptide and protein molecules)
- Reduces dose of drug without decrease in therapeutic effects.
- Decreases side effects.
- Decreases drug interaction due to lower cytochrome P450 isoenzymes.
- Decreases food effect (change occurring in bioavailability of drug when given with food).
- Improved compliance.
- Chronotherapy, programmed delayed release provides optimal treatment of diseases.
- Pulse release allows multiple dosing in a single dosage form.
- Allows site specific release for local treatment of diseases. Drug release is not affected by change in pH of the gastrointestinal tract, viscosity of lumen contents, and agitation rate of GI tract.
- The system can be utilized for many solid dosage forms like granules, microspheres, microparticles, tablets, capsules, and pellets (Adel *et al.,* 2006).

Drug release profiles from pulsatile drug delivery system

Drug release profile from pulsatile drug delivery system is given fig 1.

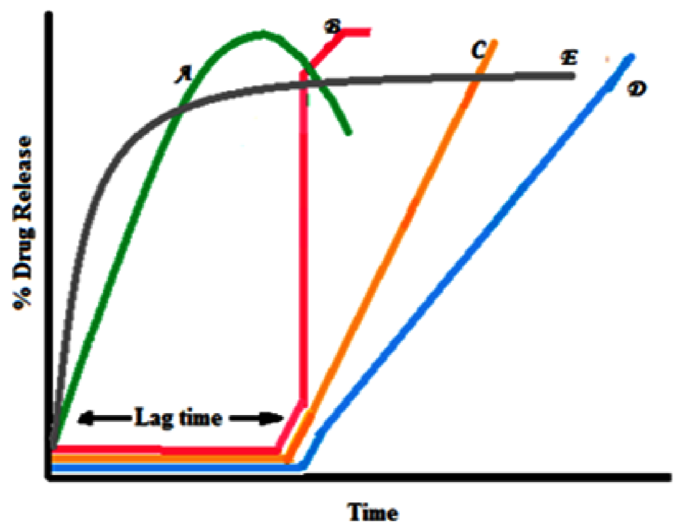

Fig. 1: Drug release profiles from pulsatile drug delivery system.
Where, A: Conventional release profile, B: Burst release of drug as a after a lag time, C: Delayed release profile after a lag time, D: Constant release profile in prolonged period after a lag time, E: Extended release profile without lag time.

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEMS

I. Time controlled pulsatile drug delivery

(A) Single unit pulsatile systems

(1) Capsule based systems

Pulisincap system

Single-unit systems are mostly developed in capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion, and the drug is released (Arora *et al.,* 2006). Pulsincap (fig 2) was developed by R. P. Scherer International Corporation, Michigan, US, and is one such system that comprises of a water-insoluble capsule enclosing the drug reservoir. When this capsule comes in contact with the dissolution fluid, it swells; and after a lag time, the plug pushes itself outside the capsule and the drug is released rapidly. The lag time can be controlled by manipulating the dimension and the position of the plug. Polymers used for designing of the hydrogel plug are as follows.

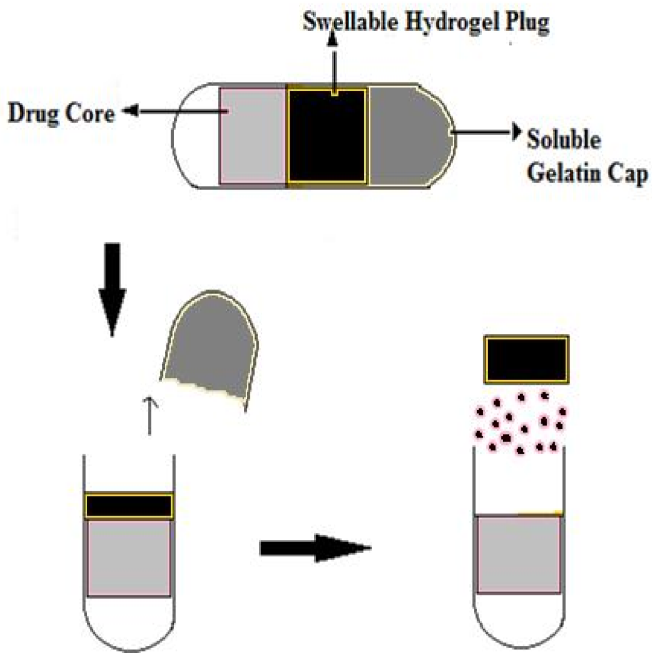

Fig.2: Design of Pulsincap system.

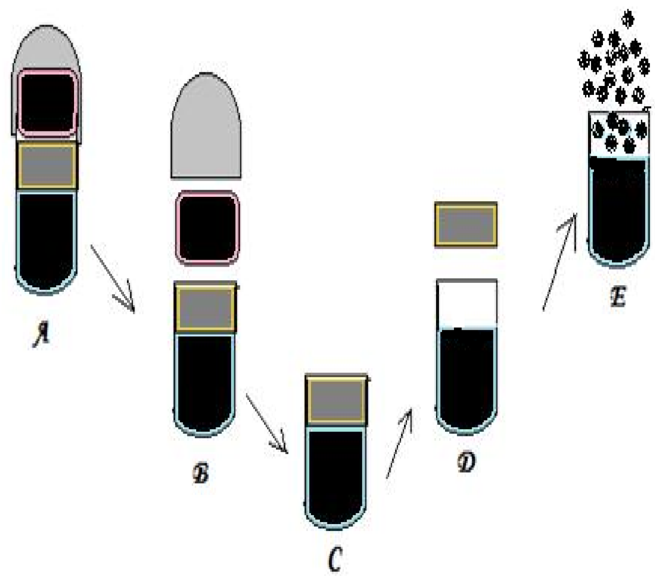

Fig.3: Drug release mechanism from PORT system.
Where, A: Port System, B: Swelling of cap with release of 1st dose, C: Permeation of more GI fluid with generation of Internal pressure, D: Expulsion of Time Released Plug, E: 2nd released in Pulsed or sustained form.

- Insoluble but permeable and swellable polymers (e.g., polymethacrylates)
- Erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, Polyethylene oxide)
- Congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate)
- Enzymatically controlled erodible polymer (e.g., pectin).
- The Pulsincap™ device consists of impermeable capsule body containing drug sealed in the capsule with a plug made of hydrogel.This plug swells in GI fluid and exits away releasing drug after a defined lag time that is controlled by thickness of hydrogel plug. Alternative to Pulsincap plug is erodible tablet (Howard *et al.,* 2002; Patel *et al.,* 2009].

(2) Capsular system based on Osmosis

(a) 'PORT' System

The Port system (fig.3) was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA, and consists of a capsule coated with a semi permeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug Formulation. When this capsule came in contact with the dissolution fluid, the semipermeable membrane allowed the entry of water, which caused the pressure to develop and the insoluble plug expelled after a lag time. Such a system was utilized to deliver methylphenidate used in the treatment of attention deficit hyperactivity disorder as the pulsatile port system. This system avoided second time dosing, which was beneficial for school children during daytime (Crison *et al.,* 2001).

(b) System based on expandable orifice

To deliver the drug in liquid form, an osmotically driven capsular system was developed in which the liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semipermeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved. This system has combined benefit of extended release with high bioavailability. Delivering drug in liquid form is suitable for insoluble drugs, Polypeptides and Polysaccharides (Patrick *et al.,* 2003). The capsular system delivers drug by the capsule's osmotic infusion of moisture from the body (fig 4). The capsule wall is made up of an elastic material and possesses an orifice.

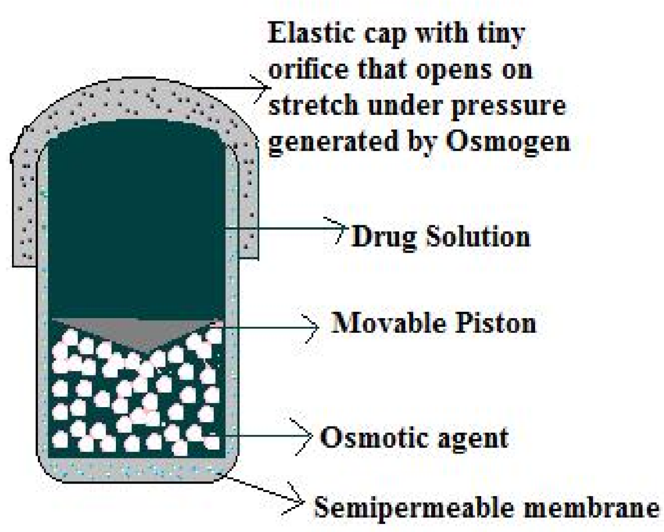

Fig. 4: System based on expandable orifice.

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. For example, elastomers, such as styrene-butadiene copolymer have been suggested. Pulsatile release was achieved after lag times of 1 to 10 hrs, depending on the thickness of the barrier layer and that of semipermeable membrane. A capsule designed for implantation can deliver drug intermittently at intervals of 6 hours for 2 days (Sharma, 2008).

(c) Delivery by series of stops

This system is for implantable capsules. The capsule contains a drug and water-absorptive osmotic engine that are placed in compartments separated by a movable slider that provides pulsatile release of drug. Series of stops obstruct the movement of drug and provides lag time which is overcome as the osmotic pressure rises above a threshold level. The number of stops and the longitudinal placements of the stops along the length of the capsule dictate the number and frequency of the pulses, and the configuration of the partition controls the pulse intensity. This system was used to deliver porcine somatotropin (Balaban *et al.*, 1993).

(d) Pulsatile delivery by solubility modulation

Solubility modulator of system provides pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate that contained sodium chloride as modulating agent. Amount of NaCl 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 275mg/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 function of the modulator concentration, while the modulator's solubility is largely independent of drug concentration. The modulating agent can be a solid organic acid, inorganic salt, or organic salt. Ratio of drug/ modulator may be varied to control zero order release period and commence pulsed release. After the period of zero-order release, the drug is delivered as one large pulse (Magruder *et al.*, 1988; Magruder *et al.*, 1989).

(3) Pulsatile system 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 from reservoir core. The lag time depends on the thickness of the coating layer.

(a) *The chronotropic system*

The Chronotropic system (fig 5) consists of a drug-containing core coated by hydrophilic swellable HPMC that produces lag phase (Gazzaniga *et al.*, 1994).

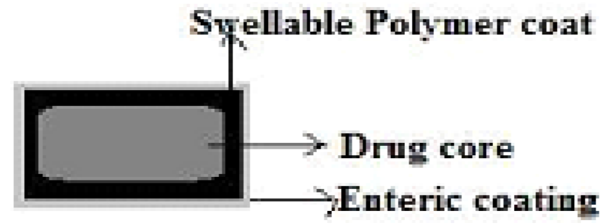

Fig. 5: The chronotropic system.

The variability in gastric emptying time can be overcome by application of an outer enteric film, and a colon-specific release can be obtained, assuming that small intestinal transit time is not changed (Poli *et al.*, 1993). The lag time is controlled by the thickness and the viscosity grades of HPMC. Both *in-vitro* and *in-vivo* lag times correlate well with the applied amount of the hydrophilic retarding polymer (Sangalli *et al.*, 2001).

(b) 'TIME CLOCK' System

The time clock system is a delivery device based on solid dosage form that is coated by an aqueous dispersion. The core is coated at 75°C with aqueous dispersion of a hydrophobic surfactant layer (Beeswax, carnubawax, poly {oxyethylene} - sorbiton monooleate) (Wilding *et al.*, 1994). A water soluble coat is applied to improve adhesion to the core coat (fig 6). Once in contact with the dissolution fluid, the dispersion rehydrates and redisperses. The lag time could be controlled by varying the thickness of the film. After the lag time, i.e., the time required for rehydration, the core immediately releases the drug. This system has shown reproducible results *in vitro* and *in vivo* (Sandrine *et al.*, 2005).

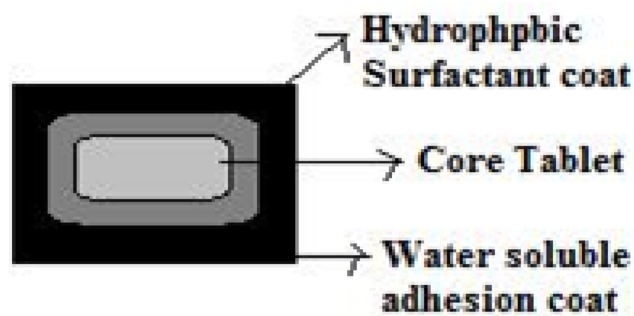

Fig. 6: 'TIME CLOCK' System.

(c) Compressed tablets

Compression coating involves direct compression of both the core and the coat, averting needs for use of coating solutions. The outer tablet of the compression-coated tablet provides the initial dose, rapidly disintegrating in the stomach and the inner layer is formulated with components that are insoluble in gastric media but are released in the intestinal environment. Cellulose derivative may be used for this purpose. Compression is easy on laboratory scale. The major drawbacks of this technique are that relatively large amounts of coating materials are needed and it is difficult to position the cores correctly. Advantages of Press-coated pulsatile drug delivery systems can protect hygroscopic, light sensitive, acid labile drug, they are simple and cheap in making (Conte *et al.*, 1993; Ozeki *et al.*, 2003).

(d) Multilayered Tablets

Two pulses can be obtained from a three layered tablet containing two drugs containing layers separated by a drug-free gellable polymeric barrier layer (fig 7). This three-layered tablet is coated on three sides with impermeable ethyl cellulose, and the top portion was left uncoated. Upon contact with dissolution medium, the initial dose incorporated into the top layer was released rapidly from the non coated surface. The second pulse is obtained from the bottom layer after HPMC layer gets eroded and dissolved. The rate of gelling or dissolution of the barrier layer control the appearance of the second pulse. The gelling polymers reported include cellulose derivatives like HPMC, methyl cellulose, or polyvinyl alcohols of various molecular weights and the coating materials include ethyl cellulose, cellulose-acetate propionate, methacrylic polymers, acrylic and mehtacrylic co-polymers, and polyalcohols (Abdul *et al.,* 2004).

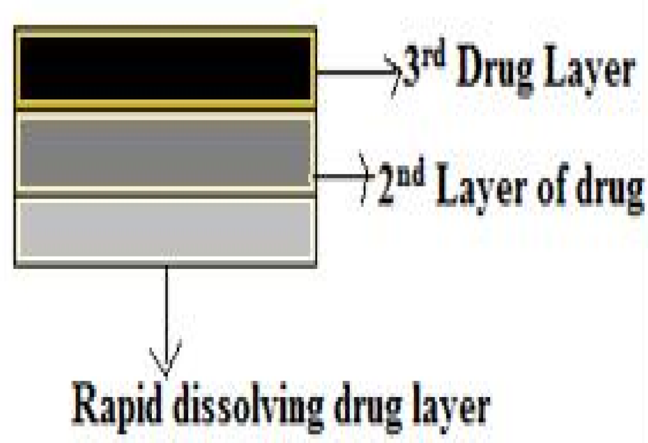

Fig. 7: Multilayered Tablet.

(4) Pulsatile system with rupturable coating

These systems depend on disintegration of the coat for the release of drug. The pressure needed for the rupture of the coating is achieved by effervescent excipients, swelling agents, or osmotic pressure. An effervescent mixture of citric acid and sodium bicarbonate incorporated in a tablet core coated with ethyl cellulose produced carbon dioxide after penetration of water into the core resulting in pulsatile release of drug after rupture of the coat. The release may depend on the mechanical properties of the coating layer. It is reported that the weak and non-flexible ethyl cellulose film ruptured sufficiently as compared to more flexible films. The lag time increases with increasing coating thickness and increasing hardness of the core tablet. Highly swellable agents, also called superdisintegrants (cross carmellose, sodium starch glycollate, and low substituted hydroxypropyl cellulose) were also used to design a capsule-based system comprising a drug, swelling agent, and rupturable polymer layer. The swelling of these materials resulted in a complete film rupture followed by rapid drug release. The lag time is function of the composition of the outer polymer layer. The presence of hydrophilic polymer like HPMC reduces lag time. The system can be used for delivery of both solid and liquid drug formulations. A reservoir system with a semi permeable coating was designed for delivery of drugs that exhibit extensive first-pass metabolism. The release pattern was similar to that obtained after administration of several immediate-release doses (Krogel *et al*., 1999; Bussemer *et al.,* 2003).

(B) Multiparticulate / Multiple unit systems

(1) Pulsatic system with rupturable coating

Time –controlled Explosion system (TCES)

Fig 8 Multiparticulate system where drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer coating (Ueda *et al.,* 1994). The swelling agents used include Superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose and Polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc. Alternatively, effervescent system comprising a mixture of tartaric acid, citric acid and sodium bicarbonate may also be used. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. This 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. A rapid release after the lag phase can be achieved with increasing concentration of osmotic agent. *In-vivo* studies of time-controlled explosion system (TCES) with an *in-vitro* lag time of three hours showed appearance of drug in blood after 3 hours, and maximum blood levels after 5 hours (Hata *et al.,* 1994).

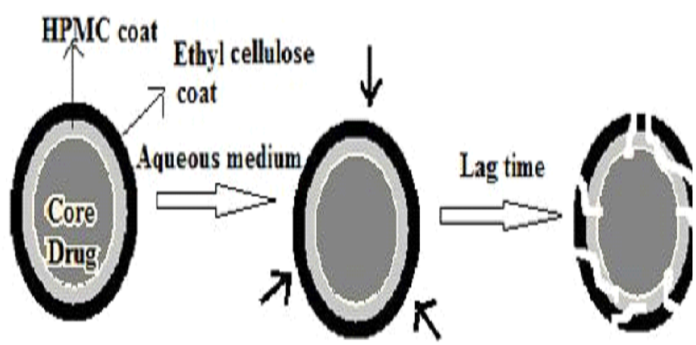

Fig. 8: Time –controlled Explosion system (TCES).

(2) Osmotic based rupturable coating system

This system is based on a combination of osmotic and swelling effects. The core contains drug, a low bulk density solid and/or liquid lipid material (eg, mineral oil) and a disintegrant. The core is finally coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of coat (Amidon *et al.,* 1993). Another system is based on a capsule or tablet composed of a large number of pellets with different release pattern (Chen *et al.,* 1996). Each pellet has a core that contains the therapeutic drug and a water-soluble osmotic agent. Water-permeable, water-insoluble polymer film encloses each core. A hydrophobic, water-insoluble agent that alters permeability (e.g. a fatty acid, wax, or a salt of fatty acid) is incorporated into the polymer film. The rate of water influx and drug efflux causes the film coating of each population to differ from any other pellet coating in the dosage form. The osmotic agents dissolve in the water causing the pellets to swell, thereby regulating the rate of drug diffusion. The effect of each pellet population releasing its drug content sequentially provides a series of pulses of drug from a single dosage form. The coating thickness can be varied amongst the pellets. This system was used for the delivery of antihypertensive drug, Diltiazem.

The use of osmotically active agents that do not undergo swelling is also reported. These pellet cores contain drug and sodium chloride coated with semipermeable cellulose acetate polymer. This coat is selectively permeable to water and is impermeable to the drug. Sodium chloride facilitated the desired fast release of drug. In absence of sodium chloride, a sustained release of drug was achieved after lag time due to lower degree of core swelling that generated small fissures (Schultz *et al.,* 1997).

(3) 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 (Bodmeier *et al.,* 1996). Several delivery systems based on this ion exchange have been developed. Eudragit is a polymer of choice for this purpose. 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 facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner. This property is essential to achieve a precisely defined lag time. The cores were prepared using theophylline as model drug and sodium acetate. These pellets were coated using Eudragit (10% to 40% weight gain) in four different layer thicknesses. A correlation between film thickness and lag time was observed. It was found that even a small amount of sodium acetate in the pellet core had a dramatic effect on the drug permeability of the Eudragit film. After the lag time, interaction between the acetate and polymer increases the permeability of the coating so significantly that the entire active dose is liberated within a few minutes (Beckert *et al.,* 1993). The lag time increases with increasing thickness of the coat, but the release of the drug was found to be independent of this thickness and depended on the amount of salt present in the system.

Sigmoidal Release System

This consists of pellet containing drug and succinic acid coated with ammonio-methacrylate copolymer (Guo, 1996). The water in the medium dissolves succinic acid. The drug inside and the acid solution increase the permeability of the polymer film. Instead of succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid is also used. This system was used to design an acid containing core (Narisawa *et al.,* 1994; Narisawa *et al.,* 1996). Good *in vitro/in vivo* correlation of lag time was observed (Narisawa *et al*., 1995).

II. Stimuli induced pulsatile systems

In these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli .These systems are further classified into temperature induced systems and chemical stimuli induced system, on the basis of stimulus.

(1) Temperature induced systems

Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state (Survase *et al.,* 2007).

(2) Chemical stimuli induced pulsatile systems

(a) 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, Ndimethylaminoethyl methacrylate, chitosan, polyol etc (Kikuchi *et al.,* 2002).

(b) Inflammation induced pulsatile release device

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. Yui and co-workers focused on the inflammatory-induced hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner. They used hyaluronic acid (HA) which is specifically degraded by the hyaluronidase or free radicals. Degradation of HA via the hyaluronidase is very low in a normal state of health. Degradation via hydroxyl radicals however, is usually dominant and rapid when HA 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 (Kikuchi *et al.,* 2002).

(c) 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/reselling characteristics.

Special attention was given to antigen-antibody Complex formation as the cross-linking units in the gel, since such interactions are 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 (Survase *et al.,* 2007; Kikuchi *et al.,* 2002).

(d) pH sensitive drug delivery system

Such type of pulsatile drug delivery system contains two components one is of immediate release type and other one 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. An example of pH dependent polymers includes cellulose acetate phthalate, polyacrylates, and sodium carboxy methyl cellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine (Survase *et al.,* 2007).

III. Externally regulated pulsatile drug delivery

For releasing the drug in a pulsatile manner, another way can be the externally regulated Systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads (Survase *et al.,* 2007; Kikuchi *et al.,* 2002).

Need for pulsatile drug delivery system

All endogenous biological processes and functions are programmed in time during the 24 hour for the conduct of specific activities at discrete times. A number of diseases show their pathognomonic following a biological rhythm.

Asthma

Circadian changes are seen in normal lung function, which drops in the early morning hours. The decreased lung function is more pronounced in people with asthma (Janugade *et al.,* 2009)**.** It is usually highest at 4 pm and lowest at 4 am. It is the 4 am when asthma is more prevalent (Qureshi *et al.,* 2008).

Arthritis

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. Proinflammatory cytokines exhibit a peculiar rhthmicity, in particular serum TNF and serum IL-6, and together with other relevant immunological parameters display an elevation in early morning hours in patients with rheumatoid arthritis. Hence such patients experience joint pain, morning stiffness and functional disability in early morning hours. Chronotherapy for all forms of arthritis using NSAIDS should be timed to ensure that highest blood level of drug coincide with the peak pain (Cutolo *et al.,* 2008).

Duodenal Ulcer

Gastric acid secretions are highest at night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing, once daily bed time dosage regimen is recommended for H_2 antagonists (Roy *et al.,* 2009)

Cancer

Chemotherapy may be more effective and less toxic if anticancer agents are administered keeping in mind the tumor cell cycles. This way it will be less toxic to normal tissue. Blood flow to tumors and tumor growth rate are each up to three fold greater during each daily activity phase of circadian cycle than during daily rest phase. Chronotherapy concept offers promise for improving current cancer treatment options. However chronotherapy is still uncommon, limited to only 50 cancer centers throughout world. For chronotherapy to be widely accepted additional randomized clinical trials is needed to be conducted (Ross *et al.,* 2006; Levi *et al.,* 2007; Ishida, 2007; Atilla *et al.,* 2009).

Diabetes

Circadian behavior in glucose and insulin secretion in diabetes was revealed and studied. Increase in blood sugar level is found after meal (Zvonic *et al.,* 2006; Aaron *et al.,* 2008; Haus, 2007).

Hypercholesterolemia

Hepatic cholesterol synthesis is also found to follow circadian rhythm. But the rhythmicity varies according to individuals. There is a large difference in plasma mevalonate concentration between individuals. However cholesterol synthesis is generally higher during the night than during daylight. Diurnal synthesis is only 30-40% of daily cholesterol synthesis. Maximum production occurs early in the morning i.e. 12 hours after the last meal. The evening dose of HMG CoA reductase inhibitors is more effective than morning dose (Ishida, 2007).

Neurological Disorder

Investigation on epilepsy and convulsion demonstrate chronological rhythm. It is mentioned that brain area with highest concentration in noradrenergic nerve terminals and noradrenalin have a circadian rhythm in their content of noradrenalin (Hofstra *et al*., 2008; Fred *et al.,* 2001).

Cardiovascular Diseases

Angina pectoris, ventricular arrhythmia, acute myocardial infarction, sudden cardiac death, stroke, fatal pulmonary embolism, and hypertensive crisis's all are most frequent in morning as are other cardiovascular conditions. Cardiovascular events in a diurnally active person achieves peak in between 6 am to noon (Francesco *et al.,* 2007; Izzedine *et al.,* 2006; Lemmer, 2006; Smolensky, 1996; Piccione *et al.,* 2005; Pasic *et al.,* 1998).

Peak time of various biological processes

The figure below shows the peak time of biological processes that follow circadian behavior in persons adhered to daily day time routine activity i.e. 6 am to 10 pm. The intensity of symptom of many medical conditions follow in time during 24 hour schedule and severity of diseases exhibit a definite time of occurrence in 24 hour (Smolensky *et al.,* 2007). Peak time of human diseases exhibiting circadian rhythm, this is explained with the help of diagram given in fig 9.

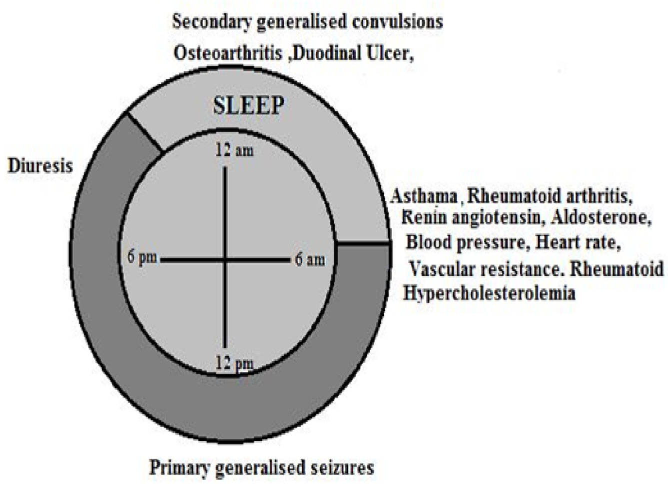

Fig. 9: Cycle of circadian Rhythm.

Technologies used in chronopharmaceutics

Major objective of chronopharmaceutics is to deliver the drug in higher concentrations during the time of greatest need and in lesser concentrations when need is less to minimize unnecessary side effects. Various technologies used in development of chronopharmaceutical drug delivery system are discussed below.

CONTIN Technology

In this technology cellulosic polymer is solvated with volatile polar solvent. The resulting solvated cellulose polymer is reacted with aliphatic alcohol to form molecular coordination complexes. The complex is used as a matrix in controlled release formulations since it has a uniform porosity that can be varied .This technique has been used in development of sustained release tablet of aminophylline, theophylline, morphine, and other drugs.

Physico-chemical modification of API

In this, a proprietary method is used to modify the physicochemical properties like solubility, permeability, partition coefficient of drug. The method is useful when it is approved that bioavailability of drug is affected by solubility and permeability. Physicochemical property can be altered by altering chemical structure, melting point, molecular weight. Chronotherapeutic system by this technique has been formulated for antihyperlipidemic statins and ant ulcerative agents.

OROS Technology

This technology uses osmotic agents to provide pre-programmed, controlled drug delivery to the gastrointestinal tract. This technology , especially the OROS® delayed push pull™ system, also known as controlled onset extended release (COER) was used to design covera- HS® , a novel antihypertensive product. This enables delay, overnight release of verapamil to prevent surge in BP in morning.

CODAS Technology

Chronotherapeutic oral drug absorption system (CODAS®) is multiparticular system, dosed at bed time that delays drug release for 4-5 h. The delay is provided by non enteric coating of the drug loaded beads. The technique has been used in formulation of Verapamil extended release capsules Verelan® PM.

CEFORM® Technology

This technique helps in development of microspheres of uniform size and shape. It is based on "melt spinning" in which biodegradable polymer or bioactive agents combination is subjected to combination of temperature, thermal gradients, mechanical forces, flow, and flow rates during processing. The microspheres can be used in tablet capsule, suspension, sachet form. It can also be coated for controlled release. The technique has been actually used to develop cardiazem®LA, 1 day diltiazem chronotherapeutic drug delivery system.

DIFFUCAPS® Technology

By this technique, unit dosage form like capsule is prepared. It consists of one or more population of drug containing particles (beads pellets, granules etc.).The drug core may consist of an inert particle or alkaline buffer crystal (e.g. cellulose ethers) which is coated with hydrophilic API-containing film forming agents like HPMC, PVP etc. The drug core may also be prepared by granulating and milling or by extrusion and spheronization of polymer composition containing the API. Such a chronomodulated drug delivery system is discovered to provide plasma concentration- time profile, which mimic the circadian rhythm and cardiovascular disease severity. This technique has been used in formulating Innopran® XL containing Propranol for hypertension.

Chronomodulated infusion pumps

Infusion pumps available in market for chronomodulated drug application are Melodie®, Programmable synchromed®, Panomat®, V5 infusion and Rhythmic® pumps. The portable pumps are usually light weight (300-500 g) for easy portability and precision in drug delivery. In case of Insulin therapy, Implantable infusion pump containing insulin reservoir is placed surgically in subcutaneous tissue of abdomen in the left upper or lower quadrant. A catheter leads from the pump through the muscle layers into the peritoneal cavity, where it floats freely, and insulin delivery is by intraperitoneal route. This insulin containing reservoir is refilled once a month or every 3 months at physician's office by inserting needle through the skin into the pump.

Doses adjustments are made by the patient in range established by Physician using radiotelemetry and an electronic device that is held over the pump. The advantages are that absorption is faster by peritoneum route because of large surface area that is well vascularized than subcutaneous injection. Glycemic control is improved. Drawback of it is catheter blockade which can reduce insulin delivery. Pumps are used in diseases like cancer and diabetes.

TIMERx® Technology

This technology uses combination of xanthan gum and locust bean gum mixed with dextrose. The physical interaction between these component works to form a strong binding gel in presence of water. Release of drug is controlled by rate of water penetration from GIT to the above mentioned gum matrix, which expands to form a gel and releases active drug substance. Release of drug from tablet can be controlled by varying the proportion of gums, together with third component, the tablet coating and tablet manufacturing process. Potential application of this technology is development of oral, CR opioid analgesic oxymorphone.

THREE DIMENSIONAL PRINTING®

By this technique it is possible to engineer devices with complicated internal geometries, varying densities, diffusivities and chemicals. Different type of complex oral drug delivery devices that have been fabricated using this technique are: immediate extended release tablets, pulse release, breakaway tablets, and dual pulsatory tablets. The same technique is basis of theriform® Technology. In this products may be designed on a computer screen as three dimensional models before actual implementation of their preparation process. This versatile technique may find chronotherapeutic application in future.

Other CR erodible polymers

Erodible polymers are widely used in chonomodulated drug delivery system. Drug was sealed inside insoluble capsule body by an erodible tablet made of an insoluble dibasic calcium phosphate and gel forming HPMC excipient. In brief, by careful selection and combination of polymeric drug carrier of different erosion/degradation kinetic , or by manipulating the interaction energy between the drug and the polymer, it is possible to control drug release according to requirement of biological rhythm of given disease state (Youan, 2004).

Controlled-release microchip

This microfabrication Technology has the potential to be used in design of chronomodulated drug delivery system. With a better control over drug release kinetic to match biological requirement.

PULSYS™

This technology was used to develop chronotherepeutic system for amoxicillin. The rationale for designing this system was that antibiotics are more effective against fast growing bacteria. On administering immediate release system, bacteria respond to it by going into dormant stage, while pulsatile system is more effective because pulses of drug release after a regular time interval do not allow bacteria to go into dormant stage. Preclinical studies have shown that approach of using Pulsatile systems is more effective (Parmar *et al*., 2009).

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. However, the opposite scenario can be achieved where drug release is delayed for a number of 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 (Dvane *et al.,* 2009).

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 or spheronized multiparticulates. The intestinal protection of IPDAS® technology is by virtue of the multiparticulate nature of the formulation, which ensures wide dispersion of irritant drug throughout the gastrointestinal tract. Naprelan®, which is marketed in the United States and Canada, employs the IPDAS® technology. This innovative formulation of naproxen sodium is a novel controlled release formulation indicated for the treatment of acute and chronic pain (White *et al.,* 1997).

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. SkyePharma 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 (Venketesh, 2005).

Table. 1: Marketed products of pulsatile drug delivery system.

Proprietary chronopharmaceutical Technology	Proprietary name	API	Mechanism and dosage form	Indication
CODAS®	Verelan® PM	Verapamil HCl	Extended release capsule	Hypertension (Youan,2004; Mandal *et al.*, 2010)
CONTIN®	Uniphyl®	Theophylline	Extended release tablet	Asthma (Youan,2004; Mandal *et al.*, 2010)
OROS®	Covera- HS®	Verapamil HCl	Extended release tablet	Hypertension (Youan,2004; Mandal *et al.*, 2010)
DIFFUCAPS®	Innopran®XL	Propranolol HCl, Verapamil HCl	Extended release capsule	Hypertension (Youan,2004; Mandal *et al.*, 2010)
OROS®	Invega™	Paliperidone	Tablet	Schizophrenia (Mandal *et al.*, 2010)
PULSYS™	Pulsincap™	Dofetilide	Rupturable system	Antiarrhythmic (Shidhaye *et al*., 2010)
OROS®	Concerta®	Methylphenidate HCl	Tablet	Anti-psychotic (Mandal *et al.*, 2010)
PULSYS™	Moxatag™ Tablet	Amoxicillin	Multiparticulate system	Infection (Shidhaye *et al*., 2010)
TIMERx®	OPANA®	Oxymorphone	Erodible/ soluble barrier coating ER Tablets	Pain management (Shidhaye *et al*., 2010)
CEFORM®	Cardiazem® LA	Diltiazem HCl, Verapamil HCl	Extended Release tablet	Hypertension (Youan,2004; Mandal *et al.*, 2010)
Physico-chemical modification of API	Pepcid®,	Famotidine	tablet	Ulcer (Youan,2004; Mandal *et al.*, 2010)
Physico-chemical modification of API	Zocor®	Simvastatin	Tablet	Hypercholesterolemia (Youan,2004; Mandal *et al.*, 2010)
PROCARDIA XL®	Procardia XL	Nifedipine	Sustained release	Hypertension (Youan,2004)

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 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 (Parcel *et al.*, 2003).

History and initial application of chronotherapeutics

The first chronotherapy clinically applied was introduced in 1960s that consisted of alternate day morning schedule of conventional tablet corticosteroid medication. Since than other chronotherapies have been used in clinical medicine in US, Europe and Asia this include evening theophylline systems for chronic obstructive pulmonary disease. Conventional evening H_2 receptor antagonist for peptic ulcer and conventional evening cholesterol medications for hyperlipidemia. In Past 10-15 years, bedtime tablet and capsule for blood pressure lowering were introduced that released drug in synchrony with circadian behavior of SBP and DBP in primary hypertension (Smolensky *et al*., 2007). Different chronomodulated systems are marketed for treatment of Hypertension (Table 1).

CONCLUSIONS

Although sustained and controlled drug delivery systems have gained a lot of success and application in field of medication, these systems fail to deliver drug according to circadian behavior of diseases for which pulsatile systems are beneficial. For successful development of chronotherapeutic dosage form, knowledge of circadian time structure, rhythm in disease pathophysiology or 24 hour pattern in symptom intensity of chronic medical conditions and chronopharmacology of medication is needed. Significant progress has been made towards achieving pulsatile drug delivery system that can effectively treat diseases with non-constant dosing therapy.

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