wjpmr, 2018,4(12), 130-142

SJIF Impact Factor: 4.639

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Review Article

ISSN 2455-3301

WJPMR

PULSATILE DRUG DELIVERY SYSTEM – A REVIEW

Sinchu Yesudanam[1*], Soumya SP[1], Anusree S[1], Dr. William Arputha Sundar AS[2] and Sam Jeeva Kumar E[3]

[1]Assistant professor, Sree Krishna College of Pharmacy and Research Centre, Trivandrum.
[2]Principal, Sree Krishna College of Pharmacy and Research Centre, Trivandrum.
[3]Head of the Department of Pharmacology, Sree Krishna College of Pharmacy and Research Centre, Trivandrum.

***Corresponding Author: Sinchu Yesudanam**

Assistant professor, Sree Krishna College of Pharmacy and Research Centre, Trivandrum.

Article Received on 24/09/2018 **Article Revised on 14/10/2018** **Article Accepted on 04/11/2018**

ABSTRACT

Controlled drug delivery systems have acquired a center stage in the arena of pharmaceutical R&D business. Such systems offer temporal or spatial control over the release of drug and grant a new lease on life to a drug molecule in terms of patentability. Controlled drug delivery systems release the drug with constant or variable rates. However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release. There are certain conditions which demands such systems they include; many body functions that follow circadian rhythm. A number of hormones like rennin etc shows daily fluctuations in the blood stream. Then the same is observed in certain diseases like the bronchial asthma, ulcer , etc display time dependence. This system is also preferable for the drug which produces biological tolerance and the drugs which undergo extensive first pass metabolism. All these conditions demand for a time programmed therapeutic scheme releasing the right amount of drug at the right time. This requirement is fulfilled by pulsatile drug delivery system only. Thus such systems is characterized by a lag time that is an interval of no drug release followed by rapid drug release.

KEYWORDS: spatial control, bronchial asthma, ulcer, metabolism.

INTRODUCTION

With the advancement of the technologies in the pharmaceutical field, drug delivery system have drawn an increasing interest over the last few decades. Nowadays, the emphasis of pharmaceutical galenic research is turned towards the development of more efficacious drug delivery systems with already existing molecules rather than going for new drug discovery because of the inherent hurdles posed in drug discovery and development process.

Traditionally, drug delivery means delivering a simple chemical substance which gets absorbed predictably from the gut or from the site of injection. A second generation drug delivery goal has been the perfection of continous, constant rate delivery of bioactive agents. However, living beings are not "ZERO ORDER" in their requirement or the response to drugs. They are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle which will maximize desired and minimize undesired effects. Till early nineties efforts have been made to design the drug delivery system which will release the drug at fairly constant rate.[1]

To introduce the concept of chronotherapeutics, it is important to define the following concepts

Chronobiology

Chronobiology is the science concerned with the biological mechanism of the diseases according to a time structure. "Chrono" pertains to time and "biology" pertains to the study, or science, of life.

Chronopharmacology

Chronopharmacology is the science concerned with the variations in thepharmacological actions of various drugs over a period of time of the day.

Chronopharmacokinetics

Chronopharmacokinetics involves study of temporal changes in drug absorption,distribution, metabolism and excretion. Pharmacokinetic parameters, which areconventionally considered to be constant in time physiological functions displaying circadian rhythm (CR). Circadian changes in gastric acid secretion gastrointestinal motility, gastrointestinal blood flow, drug protein binding, liver enzyme activity, renal blood flow and urinary pH can play role in time dependent variation of drug plasma concentrations.

Chronotherapy
Co-ordination of biological rhythms and medical treatment is called chronotherapy.

Chronotherapeutics
Chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. It is becoming increasingly more evident that the specific time that patients take their medication may be even more significant than was recognized in the past.[2]

Diseases where a constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of " PULSATILE DRUG DELIVERY SYSTEM"(PDDS) In these systems, there is rapid and transient release of certain amount of drug molecules within a short time period immediately after a predetermined off-release period.

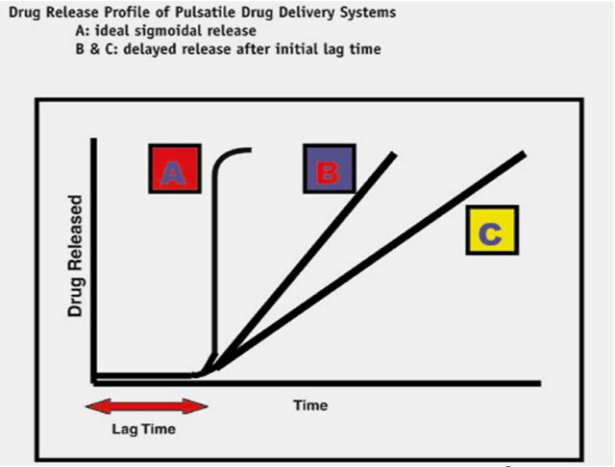

Fig.1: Drug release profile of PDDS[3]

Pulsatile drug delivery system are gaining a lot of interest as they deliver the drug at the right place at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. The principle rationale for the use of the pulsatile release of the drugs where a constant drug release is not desired a pulse has to be designed in such a way that a complete and rapid drug release is achieved after the lag time.[4]

Mechanism of Action

1.1 Generation of Circadian Rhythms

A circadian rhythm is any biological process that displays an endogeneous entrainable oscillation of about 24 hours. These rhythms are driven by a circadian clock. The term circadian comes from the Latin term where circa, meaning "around" (or "approximately"), and diem or dies, meaning "day. The Suprachiasmatic nucleus (SCN) or nuclei abbreviated SCN is a tiny region located in the hypothalamus, situated directly above optic chiasm. It is responsible for controlling circadian rhythms.[5]

The circadian rhythm is first coined by Halberg and Stephens in 1959. 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 24 hour period. It is easy to understand that some medical conditions present prevalence at certain periods of the day. It acts as biological clock and generate biological rhythm by control of clock genes. The rhythm cycle is generated by SCN and it calibrated by alternation of dark and brightness both through melatonin secretion through penal gland. Secretion of various hormones like aldosterone, rennin, and cortisol is fluctuated in blood levels. PDDS is mainly observed in pH, acid secretion, gastric emptying, cholesterol synthesis, and gastrointestinal blood transfusion.

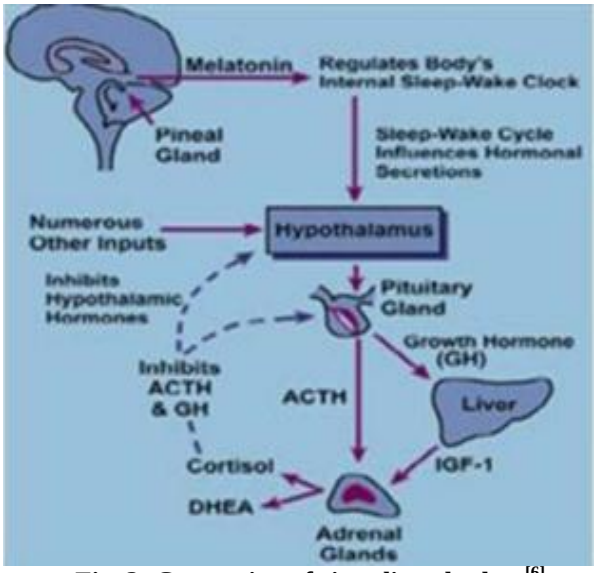

Fig. 2: Generation of circadian rhythm.[6]

To be called circadian, a biological rhythm must meet these four general criterias

1. **The rhythms must repeat once a day (they have a 24-hour period)**

In order to keep in track the time of day, a clock must be made at the same point at the same time of each day, i.e. it repeats every 24 hours.

2. **The rhythm persists in the absence of external cues (endogenous)**

The rhythm persists in constant conditions with a period of about 24 hours. The rationale for this criterion is to distinguish circadian rhythms from simple responses to daily external cues. A rhythm cannot be said to be endogenous unless it has been tested in conditions without external periodic input.

3. The rhythms can be adjusted to match the local time (entrainable)

The rhythm can be reset by exposure to external stimuli (such as light and heat), a process called entrainment. The rationale for this criterion is to distinguish circadian rhythms from other imaginable endogenous 24-hour rhythms that are immune to resetting by external cues, and hence do not serve the purpose of estimating the local time. Travel across time zones illustrates the ability of the human biological clock to adjust to the local time; a person will usually experience jet lag before entrainment of their circadian clock has brought it into synchrony with local time.

4. The rhythms maintain circadian periodicity over a range of physiological temperatures; i.e they exhibit temperature compensation

Some organisms live at a broad range of temperatures, and differences in thermal energy will affect the kinetics of all molecular processes in their cells. In order to keep track of time, the organism's circadian clock must maintain a roughly 24-hour periodicity despite the changing kinetics, a property known as temperature compensation.[7]

Chronopharmaceutics consist of two words chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. There are three types of mechanical rhythms in our body, they are: Circadian, Ultradian, Infradian.

1. Infradian Rhythms: Oscillations that are longer than 24 hours are termed as Infradian Rhythms (less than one cycle per 24hours) e.g. Monthly Menstruation.

2. Ultradian Rhythms: Oscillations of shorter duration are termed Ultradian Rhythms (more than one cycle per 24 h). E.g. 90 minutes sleep cycle.

3. Circadian Rhythms: Circadian rhythms are self sustaining, endogenous oscillations that occur with a periodicity of about 24 Hours.[8]

1.2. Effect of Circadian Rhythm on Pharmacokinetic of Drugs

1. **Circadian Rhythms in Absorption**

Absorption of drugs administered via the oral route have been shown to be affected by circadian rhythm, as gastric acid secretion and gastric pH, gastric motility, gastric emptying time, and gastrointestinal blood flow vary according to the time of the day. These changes may have impact on the time-dependent difference of drug absorption. For instance, circadian changes in pH may affect drug ionization according to its physicochemical properties. On the other hand, gastric emptying time is another important factor in the absorption of drugs.

2. Circadian Rhythms in Distribution

Circadian changes related to drug distribution are known to change according to time of the day. Blood flow depends on several regulatory factors, including the sympathetic and parasympathetic systems whose activities are known to be circadian time-dependent with a predominant diurnal effect of the sympathetic system. Thus, circadian variability in blood flow may explain a possible difference in drug distribution depending on dosing time. The liver activity varies due to circadian rhythm, and as a consequence, the levels of plasma proteins (albumin, globulins) changes over s 24-hour period. Most human plasma protein concentrations including albumin, and a1-glycoprotein fall down to their lowest during the night time, increase by day and reach to highest around noon. As a result, daily variations have been reported for drug protein binding. The effects of circadian rhythm on the plasma protein binding of drugs were first demonstrated for cortisol, which reaches to its highest level around noon. Furthermore, the synthetic analogs for cortisol have also been shown to be affected by circadian rhythm. Circadian rhythms in plasma protein binding have also been demonstrated for several mood stabilizers; valproic acid, 5-fluorouracil (5-FU), ketoprofen, carbamazepine, diazepam, lidocaine, prednisone, and cisplatin.

3. Circadian Rhythms in Metabolism

Hepatic drug metabolism seems to depend on liver xenobiotic-metabolizing enzyme activity and/or hepatic blood flow. Both factors show circadian time-dependent alterations. Circadian rhythm can affect blood flow in liver and thus, can affect the clearance of several drugs. In mammals, most of the xenobiotics are metabolized mainly in the liver; however there is also extrahepatic metabolism in brain, kidney, lung and other tissues. Xenobiotic metabolism is composed of three groups of proteins with distinct functions. The phase I group contains the microsomal cytochrome P450 (CYP450) enzymes. Phase II, or conjugating enzymes, comprises sulfotransferases (SULT), UDPglucuronotransferases (UGT), NAD (P) H: quinine oxidoreductases (NQO), epoxide hydrolases (EPH), glutathione-S-transferases (GST), and N acetyltransferases (NAT).

4. Circadian Rhythms in Excretion

The circadian timing system plays a key role in the toxicity profile of drugs by influencing their metabolisms in the liver and intestine in addition to their excretion via bile flow and urine. Rats with chronic biliary drainage under a rigid lighting schedule (light on at 6 am and off at 6 pm) were shown to exhibit a remarkable circadian rhythm of bile flow, biliary concentrations and excretory rates of bile salts, cholesterol and phospholipids . On the other hand, the excretion rates of these polyamines were found to be highest in the morning in healthy volunteer subjects.[9]

1.3. Importance of Pulsatile Drug Delivery System

Sustained delivery systems are not always able to fulfill all the needs of some diseases at that time dosage form that can release drugs after lag time or not releasing drugs in early phase of drug administration. In such case pulsatile delivery is the most effective way of treatment.

1. Many body functions follow circadian rhythm, i.e., their activity increases or decreases with time. A number of hormones like rennin, aldosterone, and cortisol show daily as well as fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid in these cases pulsatile delivery system is the preffered one.

2. Salbutamol sulphate is the drug which develop tolerance in the human body when given as sustained release dosage form. Many patients are required to upgrade their dosage regimen after one year under treatment using transdermal clonidine patches. Arterial pressure in patients exceeds the pretreatment value during the 3– 7 days following removal of their previous transdermal nitroglycerin patch. All these conditions can be treated effectively by pulsatile delivery systems.

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

4. 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 hr period day. E.g.: asthma and angina pectoris attacks occur generally in early morning.

5. Local treatment: In order to obtain effective drug treatment for local disorders such as inflammatory bowel disease 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.

6. Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (e.g., peptide drugs), irritate the gastric mucosa(NSAIDS) or induce nausea and vomiting. These conditions can be satisfactorily handled by enteric coating, and in this sense, enteric coating can be considered as a pulsatile drug delivery system.[10]

1.4. Advantages of Pulsatile Drug Delivery System

1. Extended daytime or nighttime activity.
2. Reduced side effects.
3. Reduced dosage frequency.
4. Reduction in dose size.
5. Improved patient compliance.
6. Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
7. Drug adapts to suit circadian rhythms of body functions or diseases.
8. Drug targeting to specific site like colon.
9. Protection of mucosa from irritating drugs.
10. Drug loss is prevented by extensive first pass metabolism.
11. Patient comfort and compliance.[11]

1.5. Limitations of Pulsatile Drug Delivery System

1. Lack of manufacturing reproducibility and efficacy
2. Large number of process variables
3. Multiple formulation steps
4. Higher cost of production
5. Need of advanced technology
6. Trained/skilled personal needed for manufacturing.[12]

1.6. Diseases Requiring Pulsatile Drug Delivery

Chronological behavior	Drugs used	Diseases
Acid secretion is high in the afternoon and at night	H2 blockers	Peptic ulcer
Precipitation of attacks during night or at early morning	β2 agonist, Antihistamines	Asthma
BP is at its lowest during the sleep cycle and rises steeply during the early morning	Nitroglycerin, calcium channel blocker, ACE inhibitors	Cardiovascular diseases
Pain in the morning and more pain at night	NSAIDs, Glucocorticoids	Arthritis
Increase in blood sugar level after meal	Sulfonylureas Insulin, pioglitazone	Diabetes mellitus
Cholesterol synthesis is generally higher during night than day time	HMG CoA reductase inhibitors Hypercholesterolemia	Hypercholesterolemia.[13]

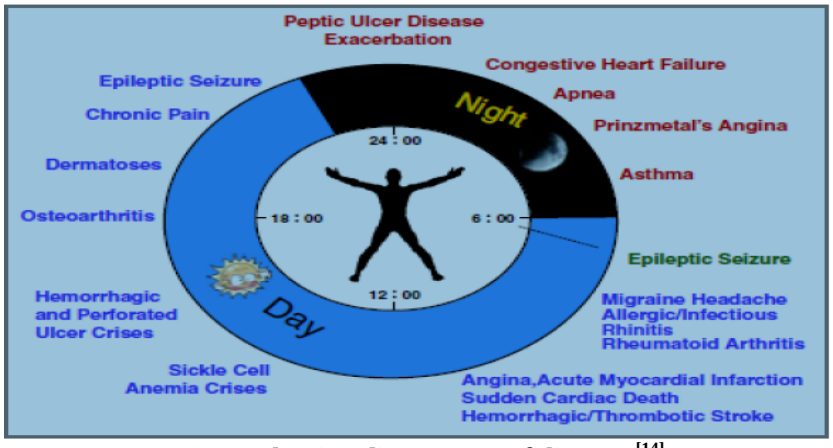

Fig. 3: The circadian pattern of diseases.[14]

2. Methodology of Pulsatile Drug Delivery System

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.[15]

It 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 which is depicted in figure no.4. 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. 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).[16]

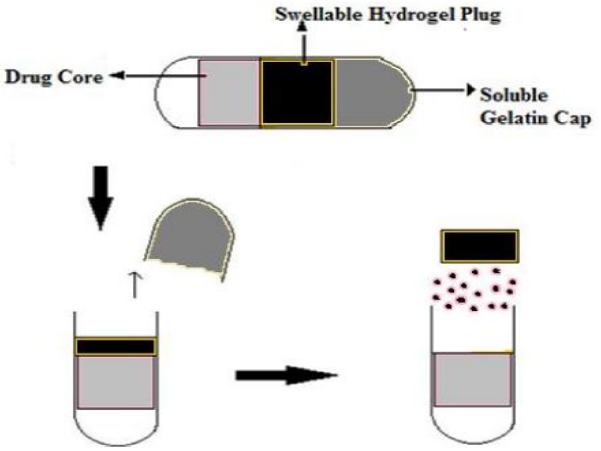

Fig. 4: The pulsincap system.

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.[17]

(2) Capsular system based on Osmosis

(a) 'PORT' System

It consists of a capsule coated with a semi permeable membrane mentioned in figure no.5. 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.[18]

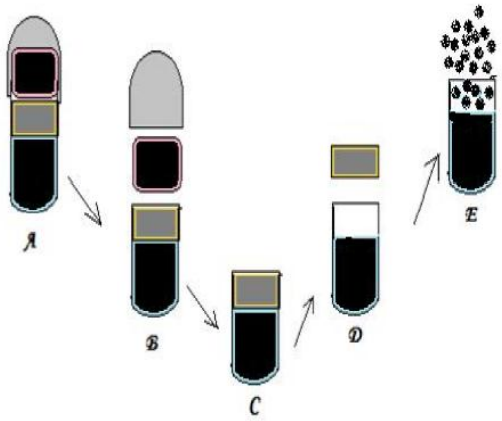

Fig. 5: Drug release mechanism from PORT system.

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.

(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.[19]

The capsular system delivers drug by the capsule's osmotic infusion of moisture from the body (fig 6). 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. 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.

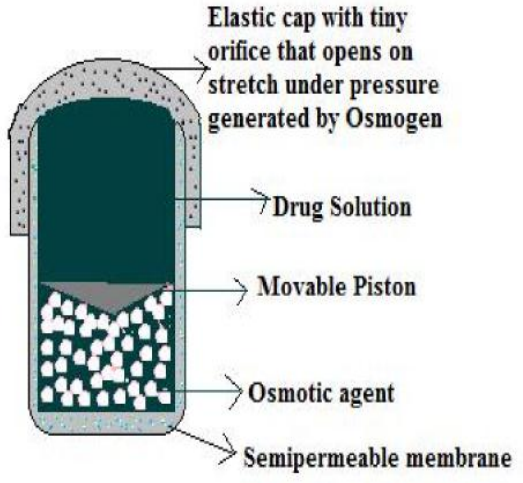

Fig. 6: System based on expandable orifice.[20]

(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.[21]

(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.[22,23]

(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 7) consists of a drug containing core coated by hydrophilic swellable HPMC that produces lag phase.[24]

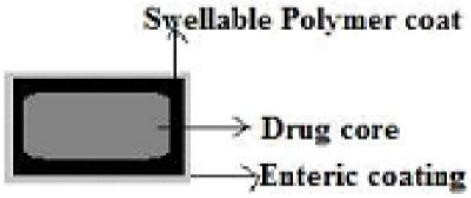

Fig. 7: The chronotropic system.

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[25]. 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.[26]

(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).[27] A water soluble coat is applied to improve adhesion to the core coat (fig 8). 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.[28]

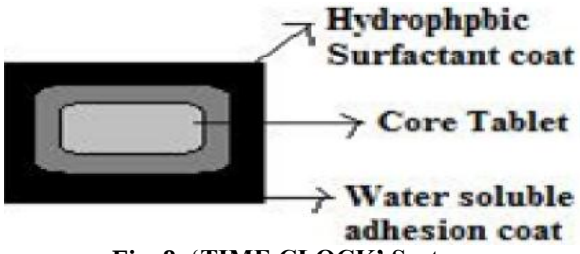

Fig. 8: 'TIME CLOCK' System.

(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.[29,30]

(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 9). 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.[31]

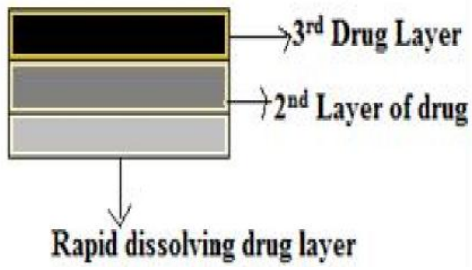

Fig. 9: Multilayered Tablet.

(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 super disintegrants (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.[32,33]

(B) Multiparticulate / Multiple unit systems

(1)Pulsatie system with rupturable coating

Time –controlled Explosion system (TCES)

Fig 10 Multiparticulate system where drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer coating[34]. The swelling agents used include Super disintegrants 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.[35]

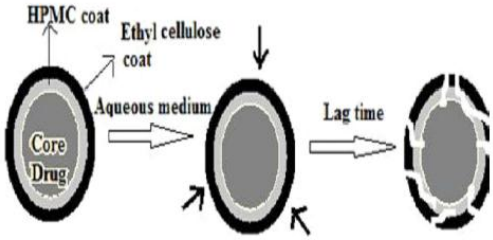

Fig. 10: Time –controlled Explosion system (TCES).

(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.[36]

Another system is based on a capsule or tablet composed of a large number of pellets with different release pattern.[37] 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.[38]

(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[39]. 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.[40]

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[41].

(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.

(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.[42]

©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.[41,42]

(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.[41]

III Externally regulated pulsatile drug delivery

These types of open-loop systems are not self-regulated. But for delivery of the drug in pulse manner another way in which drug release in programmed pattern can be the external regulated system. These systems are magnetically stimulated, ultrasonically modulated and photo stimulated.

i. Electro responsive pulsatile release

This system provides the drug release by action of applied electric field on rate limiting membrane and/ or directly on solute, thus controls it transport across the membrane. The polymer has two redox states, only one of which is suitable for ion binding. Drug ions are bound in redox state and release. The mechanism of drug transport of proteins and natural solutes across hydrogel membranes electrically induced swelling of membrane to alter effective pore size and permeability. Electrophoretic and electro osmotic agumentation of solute flux within a membrane. Electrostatics partitioning of charged solutes in charged membrane.

ii. Magnetically stimulated pulsatile system

In this system magnetic steel beads can be embedded in a polymer matrix with model drug. During exposure to the magnetic field, the beads oscillate within the matrix, alternatively creating compressive and tensile forces. This in turn acts as a pump to push an increased amount of the drug molecule out the matrix. Magnetic response comes from incorporated magnetic particle like magnetite, iron, nickel, cobalt and steel.

iii. Ultrasonically stimulated pulsatile system

Pulsed drug delivery can be achieved by the on–off application of ultrasound. During polymer degradation incorporated drug molecules are released by repeated ultrasonic exposure. It can be used for the augmentation of drug permeation through biological barriers such as skin, lungs, intestinal wall and blood vessels. Ultrasonic waves cause the erosion of the polymeric matrix thereby modulating drug release.[6]

iv. Photo chemically stimulated pulsatile system:

In this system the interaction between light and the material can be used for modulating the drug delivery. The study material should absorbs the light at desired wavelength and material uses energy from the absorb light. e.g Gold nanoshell (a thin layer of gold surrounding a core of active nano particle). Embedding the nanoshells in a NIPAAm-co-AAM hydrogel formed the required composite material. When exposed to near infrared light, nanoshells absorb the light and convert it to heat, raising the temperature of composite hydrogel above its LCST. That's result in the increase of release rate of the drug from the matrix system.[43]

3. Recently Available Various Chronopharmaceutical Technologies

- **OROS® technology**

Chronset™ is a proprietary OROS® delivery system that reproducibly delivers a bolus drug dose, in a time- or sitespecific manner, to the gastrointestinal tract. It is nothing but an osmosis-based system. The active pharmaceutical is kept in a reservoir surrounded by a semipermeable membrane laser, drilled with a delivery orifice, and formulated into a tablet. There are two layers in this tablet comprising of one drug layer, and the other, a cosmetically active agent. Upon contact with the GI fluid this osmotic agent changes its characteristic from a non dispensable to a dispensable viscosity. As a result the active pharmaceutical is pushed away through the channel due to the pump effect of the osmotic agent. It is generally used in the designing of an extended release tablet.

- **CEFORM® technology**

It produces uniformly sized and shaped microspheres of pharmaceutical compounds.This approach is based on 'melt-spinning,' which means subjecting solid feedstock (i.e., biodegradable polymer / bioactive agent combinations) to a combination of temperature, thermal gradients, mechanical forces, and flow and flow rates, during processing. The microspheres obtained are almost perfectly spherical, having a diameter that is typically of 150 – 180µm, and they 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 with an enteric coating or

may be combined into a fast / slow release combination. This technology has been actually used to develop CardizemR LA, a one-day diltiazem formulation like ChrDDS.

- **Continr technology**

In this technology, molecular coordination complexes are formed between a cellulose polymer and 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, as it has a uniform porosity (semipermeable matrixes), which may be varied. This technology has concretely enabled the development of tablet forms of sustained-release aminophylline, theophylline, morphine, and other drugs. The CONTINR technology provides for closer control over the amount of drug released to the bloodstream, and benefits patients in terms of reducing the number of doses they need to take every day, providing more effective control of their disease (particularly at night), and reducing unwanted side effects.

- **Diffucaps® technology**

A unit dosage form, such as a capsule is used for delivering drugs into the body in a circadian release fashion. DIFFUCAPS®, is a multiparticulate technology by Reliant Pharmaceuticals LLC, for a chronotherapeutic delivery of a combination of two drugs, Verapamil HCl and Propanolol HCl, as an extended release tablet (Innopran®). Pulsincap® system is one of the most used pulsatile systems based on capsules. It was developed by R. P. Scherer International Corporation, Michigan, US. Diffucaps®, and comprises 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 hours. The active core of the dosage form may comprise of 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., hydroxypropylmethylcellulose, polyvinylpyrrolidone) 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 the physiological need during the day, that is, mimicking the circadian rhythm and severity / manifestation 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 propranololcontaining ChrDDS (InnopranRXL) for the management of hypertension.

- **CHRONOTOPIC® technology**

It is also described in the system with an erodible, soluble or rupturable membrane system. It is basically a drug-containing core, coated with an outer release controlling layer. Both single and multiple unit dosage forms such as tablets and capsules or mini tablets and pellets have been employed as the inner drug formulation.

- **EGALET® technology**

It is a delayed release form consisting of an impermeable shell with two lag plugs, enclosing a plug of active drug in the middle of the unit. After erosion of the inert plugs the drug is released. Time taken to erode the inert plugs determines the lag time. The shells are made of slowly biodegradable polymers (e.g., ethylcellulose) and plasticizers (e.g., cetostearyl alcohol), while the matrix of the plugs is a mixture of pharmaceutical excipients, including polymers like polyethylene oxide (PEO).

- **CODAS® technology**

Chronotherapeutics Oral Drug Absorption System (CODAS) technology is a multi particulate system designed for bedtime dosing. Here a non enteric coating is applied on the drug-loaded beads to delay the release of the drug, up to five hours. Here release controlling contains a mixture of both water-soluble and water-insoluble polymers. When this dosage form comes in contact with the GI fluid, the water soluble polymer gets dissolved slowly and pores are formed on the coating layer. Drug diffuses through these resulting pores. The water-insoluble polymer, acting as a barrier, maintains the controlled, fashion-like release of Verapamil. The rate of release is independent of pH, posture, and food.

- **GeoClock® technology**

The concept is designed on the basis of Geomatrix technology. Initially a multilayer technology was recommended for constant drug release in this technology. The active core or hydrophilic matrix is coated partially on one or both bases. This partial coating adjusts the core hydration process and minimizes the surface area available for drug release. In the presence of the dissolution medium the barrier layer swells and becomes a gel. This gelling layer is not eroded, but acts as a modulating membrane to control the release process. The erodible surface is instead progressively removed by the dissolution medium. Upon erosion more of the planar surface(s) of the active core is exposed with increasing time to the outer environment, which helps drug release.

- **PORT® technology**

The Programmable Oral Release Technologies (PORT) system is a uniquely coated, encapsulated system that can provide multiple programmed release of the drug. It contains a polymeric core coated with a semipermeable, rate-controlling polymer. Poorly soluble drugs can be

coated with solubilizing agents, to ensure a uniform controlled release from the dosage form. In the capsule form, the gelatin capsule is coated with a semipermeable, rate-controlling polymer. Active medicament mixed with an osmotic agent is kept inside the capsule shell. A water-insoluble plug is used to seal the capsule shell. Immediate release compartment can be added according to need.

- **Three-dimensional printing® (3DP) technology**

Three-dimensional printing (3DP) is a novel technique used in the fabrication of complex oral dosage delivery pharmaceuticals, based on solid freeform fabrication methods. It is possible to engineer devices with complicated internal geometries, varying densities, diffusivities, and chemicals. Different types of complex oral drug delivery devices have been fabricated using the 3DP process: immediate-extended release tablets, pulse release, breakaway tablets, and dual pulsatory tablets. The enteric dual pulsatory tablets were constructed of one continuous enteric excipient phase into which diclofenac sodium was printed into two separated areas. These samples showed two pulses of release during in vitro with a lag time between the pulses of about four hours.This technology is the basis of the TheriForm technology.

- **TIMERx® technology**

It is a hydrogel-based, controlled release device. This technology can provide from zero order to chronotherapeutic release.It can provide a different release kinetic by manipulating molecular interactions. Basically, this technology primarily combines 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 TIMERx gum matrix, which expands to form a gel and subsequently releases the active drug substance.

- **Physicochemical modification of the API**

Physicochemical properties like solubility, drug lipophilicity, partition coefficient, crystalline form, membrane permeability, melting point, and so on, of the API (active pharmaceutical ingredient), can be modified by introducing new substitution to the original structure, to achieve a chronopharmaceutical effect.[92] The maximum plasma concentration of the drug (Tmax) varies upon the physiochemical modification of the parent compound.

- **Controlled-release microchip**

The solid-state silicon microchip is an alternative micro fabrication technique similar to micrometer scale pumps, valves, and flow channels, which delivers the active medicament in a pulsatile manner. It can provide controlled release of both single and multiple chemical substances according to the necessity. The release mechanism is based on the electrochemical dissolution of thin anode membranes covering the micro reservoir filled with chemicals in solid, liquid, or gel form.

- **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. To our knowledge infusion pumps in the market that have been referred to as Chronomodulating for drug delivery application include, Melodie®, programmable Synchromed®, Panomat® V5 infusion, and the Rhythmic® pumps. The portable pumps are usually characterized by a light weight (300 – 500 g) for easy portability and precision in drug delivery.[44]

CONCLUSION

It is known that sustained and controlled release products provide a desired therapeutic effect, but is a fall for diseases following biological rhythms. So there is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients by delivering drug at the right time, right place & in right amounts to coincide with circadian rhythm of body. Various methodologies are employed for developing pulsatile drug delivery like time controlled, stimuli induced, externally regulated system and multiparticulate drug delivery system. These considerations, along with the potential therapeutic benefits of pulsatile drug delivery systems, should ensure that the current high level of interest ensures the betterment of quality life.

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