WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 10, 370-390. Review Article ISSN 2277– 7105

CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEM: A NOVEL APPROACH

Sachin Laxman Munde* and Dr. Bindiya Chauhan

School of Pharmacy, Parul University, Vadodara, Gujarat, India.

Article Received on
26 May 2022,

Revised on 15 June 2022,
Accepted on 06 July 2022

DOI: 10. 20959/wjpr202210-24872

***Corresponding Author**
Sachin Laxman Munde
School of Pharmacy, Parul University, Vadodara, Gujarat, India.

ABSTRACT

Coordination of biological rhythms with medical treatment is called chronotherapy. Chronotherapy considers a person's biological rhythms in determining the timing and amount of medication to optimize a drug's desired effects and minimize the undesired ones. Study of influence of biological rhythm on the effects of medication is known as chronopharmacology while the science of study of biological rhythms is known as chronobiology. With the understanding of biological time keeping it since that these rhythms must affect how the body responds to drugs administered over the course of the day. Appropriate timing of administration can improve efficacy and diminish toxicity. Chronotherapy is relevant when the risk or intensity of the symptoms of disease vary with time as in the case of allergic rhinitis, arthritis, asthma, myocardial infarction, congestive heart failure, stroke and peptic ulcer disease.

1. INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience, and cost effective manufacturing process. For many drug substances conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamics profiles with acceptable level of safety to the patient.[1] The oral controlled release system shows the typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby sustain therapeutic action.[2] **(Fig. No. 1)**

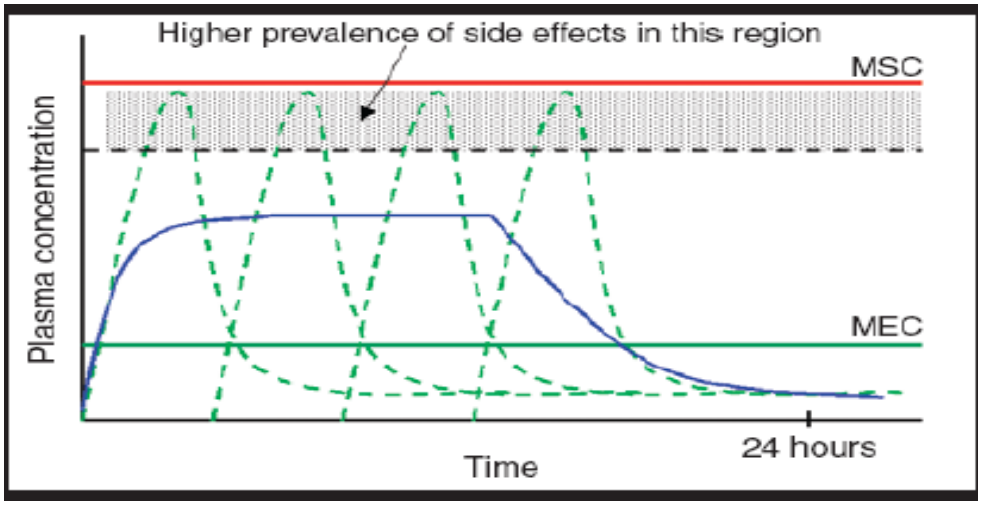


Fig. No. 1: Plasma drug concentration profiles for conventional.

formulation (- - -) and a zero order controlled release formulation (———)[3]

MEC = Minimum Effective Concentration; MSC = Maximum Safe Concentration.

Multiple unit dosage forms such as microspheres or micro beads have gained in popularity as oral drug delivery systems because of more uniform distribution of the drug in the gastrointestinal tract, optimum uniform drug absorption or required drug absorption necessary for eliciting desired therapeutic effect, reduced local irritation and elimination of unwanted intestinal retention of polymeric material, when compared to non-disintegrating single unit dosage form. Micro beads are small, solid and free flowing particulate carriers containing dispersed drug particles either in solution or crystalline form that allow a sustained release or multiple release profiles of treatment with various active agents without major side effects.[1]

The term microbead is defined as spherical particle with a size varying from 15 nm to 2 mm containing a core substance. Beads have several advantages over single unit dosage forms. They are capable of passing through the GI tract easily, leading to low inter and intra subject variability. Moreover, beads improves bioavailability of embedded drug, increases the surface area of exposure, ensures more uniform drug absorption and provide greater product safety.[4]

In chronotherapeutics multiparticulate systems are gaining a lot of interests because of predictable gastric empting, flexible release patterns and increased bioavailability with inter and intra subject variability. Here the core with drug is covered by polymeric layer. These

formulations can be utilised in time-controlled drug administration when a lag time is needed.[5]

Advantages of microbeads over other conventional dosage forms of oral drug delivery

1. Uniform distribution of the drug in the gastrointestinal tract.
2. Increases the surface area of exposure.
3. More uniform drug absorption.
4. Beads improve bioavailability of embedded drug.
5. Reduced local irritation.
6. Elimination of unwanted intestinal retention of polymeric material.
7. They are capable of passing through the GI tract easily.
8. Leading to low inter and intra subject variability.

CHRONOTHERAPEUTICS

Chronotherapeutics is the purposeful delivery of medications in unequal amounts over time. Chronotherapeutics takes into account rhythm determinants in (i) disease pathophysiology (chronopathology), (ii) chronopharmacology (chronokinetics, chronodynamics, chronesthesy, and chronotoxicology) of medications, and (iii) attributes (period, phase, amplitude, and level) of the human circadian time structure to determine the drug-delivery pattern, dose, and administration time to optimize desired and/or minimize adverse effects. Chronotherapeutics need not involve only new medicines but the improved application of established ones in a different and more biologically efficient manner.[67]

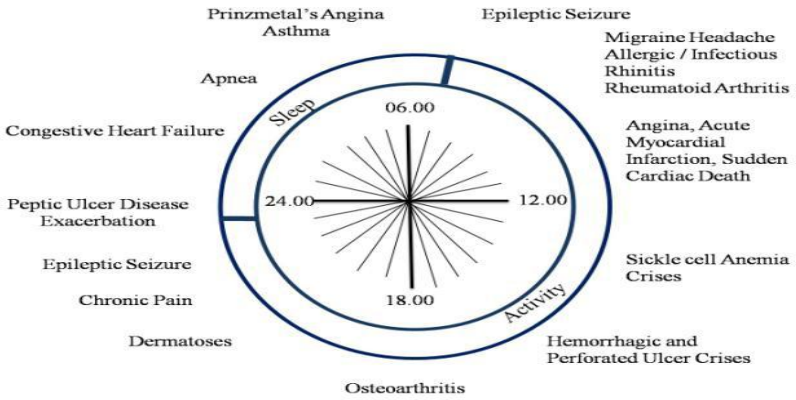


Fig. No. 2: The circadian pattern of diseases.

CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEM (CDDS)

Controlled release formulations can be divided into subgroups of rate-controlled release, delayed-release and pulsed-release formulations. Delayed-release formulations include time-

controlled release and site specific dosage forms. When constant drug plasma levels need to be avoided, as in chronotherapy, time-controlled or pulsed-release formulations are preferable, especially in the treatment of early morning symptoms. By timing drug administration, plasma peak is obtained at an optimal time and the number of doses per day can be reduced. Saturable first-pass metabolism and tolerance development can also be avoided. Various technologies to develop time controlled peroral drug delivery systems have been extensively studied in recent decades.[8]

APPROACHES FOR CDDS[8]

I. ENTERIC-COATED SYSTEMS

II. LAYERED SYSTEMS

III. TIME-CONTROLLED EXPLOSION SYSTEMS

IV. SIGMOIDAL RELEASE SYSTEM

V. PRESS-COATED SYSTEMS

I. ENTERIC-COATED SYSTEMS

Enteric coatings have traditionally been used to prevent the release of a drug in the stomach (**Fig. No. 3**). Enteric coatings are pH sensitive and drug is released when pH is raised above 5 in the intestinal fluid. These formulations can be utilized in time-controlled drug administration when a lag time is needed. Because of the unpredictability of gastric residence, such systems cannot be the first choice when a time-controlled release is required. In the treatment of nocturnal asthma, a salbutamol formulation containing a barrier coating which is dissolved in intestinal pH level above about 6, has been successfully used. The system contains a core which is film coated with two polymers, first with HPMC and then with a gastro-resistant polymer (Eudragit® L30D). In this system the duration of the lag phase in absorption can be controlled by the thickness of the HPMC layer.

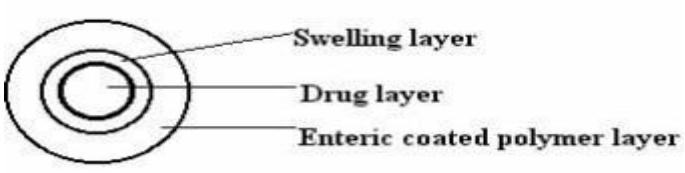


Fig. No. 3: Schematic representation of enteric coated system.

II. LAYERED SYSTEMS

These are one or two impermeable or semipermeable polymeric coatings (films or compressed) applied on both sides of the core. To allow biphasic drug release, a three-layer tablet system was developed. The two layers both contain a drug dose. The outer drug layer contains the immediately available dose of drug. An intermediate layer, made of swellable polymers, separates the drug layers. A film of an impermeable polymer coats the layer containing the other dose of drug. The first layer may also incorporate a drug-free hydrophilic polymer barrier providing delayed (5 h) drug absorption. It consists of a hydrophilic matrix core containing the drug dose. This kind of three layer device has been used in the treatment of Parkinsonian patients using L-dopa/benserazide. Night-time problems and early-morning symptoms of Parkinsonism can be avoided by using a dual-release Geomatrix@ formulation, which allows daily doses of drug to be reduced and leads to extent of bioavailability 40 % greater than when a traditional controlled release formulation is employed.

III. TIME-CONTROLLED EXPLOSION SYSTEMS

These have been developed for both single and multiple unit dosage forms. In both cases, the core contains the drug, an inert osmotic agent and suitable disintegrants. Individual units can be coated with a protective layer and then with a semipermeable layer, which is the rate controlling membrane for the influx of water into the osmotic core. As water reaches the core, osmotic pressure is built up. The core ultimately explodes, with immediate release of the drug. The explosion of the formulation can also be achieved through the use of swelling agents. Lag time is controllable by varying the thickness of the outer polymer coating.

IV. SIGMOIDAL RELEASE SYSTEM

For the pellet-type multiple unit preparations, sigmoidal release system containing an osmotically active organic acid have been coated with insoluble polymer to achieve different lag-times. By applying different coating thicknesses, lag times *in vivo* of up to 5 hours can be achieved. Release rates from SRS, beyond the lag time, has been found to be independent of coating thickness.

V. PRESS-COATED SYSTEMS

Delayed release and intermittent release formulations can be achieved by press--coating. Press-coating, also known as compression coating, is relatively simple and cheap, and may involve direct compression of both the core and the coat, obviating the need for a separate coating process and the use of coating solutions. Materials such as hydrophilic cellulose

derivatives can be used and compression is easy on a laboratory scale. On the other hand, for large-scale manufacture, special equipment is needed. The major drawbacks of the technique are that relatively large amounts of coating materials are needed and it is difficult to position the cores correctly for the coating process.

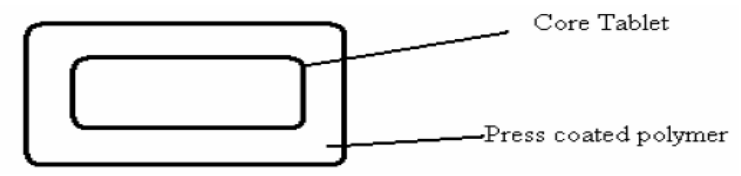


Fig. No. 4: Schematic representation of a press coated system.

In recent years, various controlled release, especially time-controlled release, drug delivery systems based on compression coating technology have been studied. Most of such formulations release drug after a lag phase, followed by a rapid dissolution of the core. **Conte *et* al**[8]; have developed a press coated device in which the inner core contains the drug and the outer coat is made of different types of polymers. The outer barrier, which controls drug release, can be either swellable or erodible. Lag times can be varied by changing the barrier formulation or the coating thickness. **Matsuo *et al***[8]; have developed a diltiazem hydrochloride formulation intended for use in the treatment of time-related symptoms of ischaemic heart disease and hypertension .The tablet consists of a core, which contains the drug, and a coat formed by compressing hydroxyl ethyl cellulose. Diltiazem is rapidly released after a delay of several hours. **Marvola *et al***[8]; have developed a press-coated tablet formulation in which most of the total amount of drug is in the tablet core .Hydrophilic polymers such as hydroxyl propyl methylcellulose and sodium alginate have been used in the coat to control drug release as illustrated in **Fig. No. 4**. The extent of bioavailability of furosemide, ibuprofen and salbutamol sulphate from the system developed has been found to be satisfactory**.**

DESIGNING OF CHRONOTHERAPEUTIC SYSTEM[10]

There are two systems are involved in the designing of chronotherapeutic system i.e. pulsatile drug delivery system and time dependent chronotherapeutic system.

1.1 PULSATILE DRUG DELIVERY SYSTEM[10,11]

Chronomodulated system is also known as pulsatile system or sigmoidal release system. The word chronomodulated is related with chronopharmaceutics and comes from chronobiologic

system. Chronobiology is the study of biological rhythms and their mechanism. There are three types of mechanical rhythms in our body.[10]

a) Circadian Rhythm:-The oscillations in our body that are completed in 24 hours are termed as Circadian rhythm.
b) Ultradian Rhythm: - The oscillations that are completed in a shorter duration of less than 24 hours are termed as ultradian rhythm.
c) Infradian Rhythm: - The oscillations that are completed in more than 24 hours are termed as Infradian rhythm.

The Circadian rhythm is the main rhythm in the body which maintains all the physiological, chemical, biological and behavioral processes. Thus Circadian rhythms causes the changes in the pathophysiology of certain disease states which may worsen the disease condition **(Fig. No. 5)**. Treatments of such type of disease require a time controlled, pre-programmed drug delivery which exactly matches the circadian changes in the body. Thus Chronomodulated or Pulsatile drug delivery system is a novel system which can be used for treatment of such disease.[12]

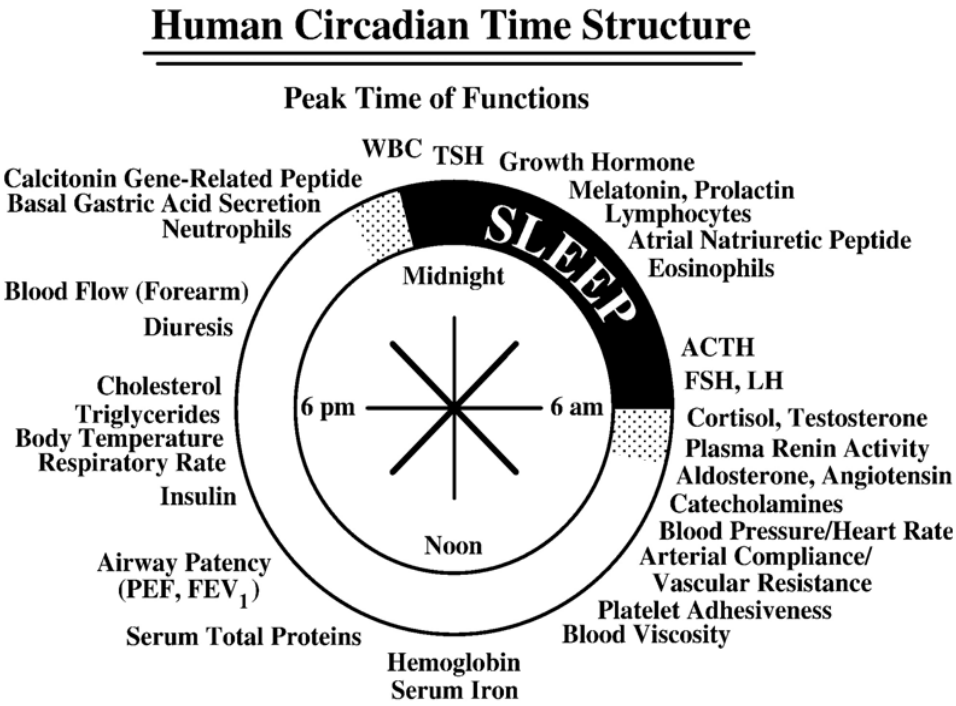


Fig. No. 5: A 24-hr Clock Diagram of the Peak Time of Selected Human Circadian Rhythm with Reference to the Day-Night Cycle.[12]

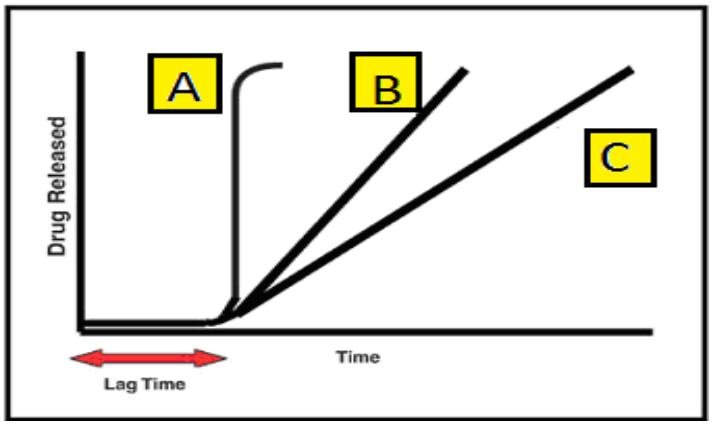


Fig. No. 6: Drug Release Profile of Pulsatile Drug Delivery System.[13, 14, 15]

A: Ideal Sigmoidal Release

B & C: Delayed Release after Initial Lag Time

A pulsatile drug delivery system is characterized by a lag time that is an interval of no drug release followed by rapid drug release. The principle rational behind designing this drug delivery system is to release the drug at desired time as per the pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. These system are developed when zero order drug release in not desired. Pulsatile drug delivery systems are designed to release certain amount of drug at specific site within a short period of time, immediately after a predetermined lag time[16]. This system shows typical release pattern as shown in **Fig. No. 6**.

The following table gives various pulsatile drug delivery systems that are reported.

The diseases which are affected by circadian changes in body and need the treatment of pulsatile drug delivery system are as shown in **Table No. 1**.

Table No. 1: Target Disease in Chronotherapy.[16]

Sr. No.	Diseases	Chronopharmacological Behaviour	Drugs Used
1.	Peptic ulcer	Acid secretion is high in afternoon and in night	H_2 blockers
2.	Asthma	Precipitation of attacks during night or at early morning hour	B_2 agonist, Antihistaminic
3.	Cardiovascular diseases	Blood pressure is at its lowest during the sleep and rises steeply during the early morning awakening period	Nitroglycerin, Calcium channel blockers, ACE inhibitors, β- Blockers
4.	Rheumatoid Arthritis	Symptoms are most intense on	NSAIDs,

		awakening	Glucocorticoids
5.	Diabetes mellitus	Increase in blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
6.	Attention deficit syndrome	Increase in DOPA level in afternoon	Methyl phenidate
7.	Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time	HMG COA reductase inhibitors.
8.	Osteoarthritis	Symptoms worse in the middle/latter portion of the day	NSAIDs, Glucocorticoids

1.1.1 Advantages of Pulsatile Drug Delivery System[12, 15, 17]

- Many body functions that follow circadian rhythm. A number of hormones like rennin, aldosterone, and cortisol show daily fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid secretion in stomach, gastric emptying and gastro-intestinal blood transfusion.
- Diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension display time dependence. Sharp increase in asthmatic attacks during early morning hours, a condition demands considerations of diurnal progress of the disease rather than maintaining constant plasma drug level. A drug delivery system administered at bedtime, but releasing drug well after the time of administration (during morning hours), would be ideal in this case. It is true for preventing heart attacks in the middle of the night and the morning stiffness typical of people suffering from arthritis.
- Drugs that produce biological tolerance demand for a system that will prevent their continuous presence at the biophase, as this tends to reduce their therapeutic effect.
- The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g. peptide drugs) irritate the gastric mucosa 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.
- Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon requires that the drug release be prevented in the upper two-third portion of the GIT.
- The drugs that undergo extensive first-pass metabolism (β-blockers) and those that are characterized by idiosyncratic pharmacokinetics or pharmacodynamics resulting in reduced bioavailability, altered drug/metabolite ratios, altered steady state levels of drug and metabolite, and potential food-drug interactions require delayed release of the drug to the extent possible.

1.1.2 Classification of Pulsatile Drug Delivery Systems.[18, 19]

Pulsatile drug delivery systems (PDDS) can be classified as site-specific and time-controlled systems. Drug release from site-specific systems depends on the environment in the gastro intestinal tract, e.g. on pH, presence of enzymes and the pressure in the gastro intestinal tract. In contrast, time-controlled DDS are independent of the biological environment. The drug release is controlled only by the system. Time-controlled pulsatile delivery has been achieved mainly with drug-containing cores, which are covered with release-controlling polymeric layer. **(Fig. No. 7)**

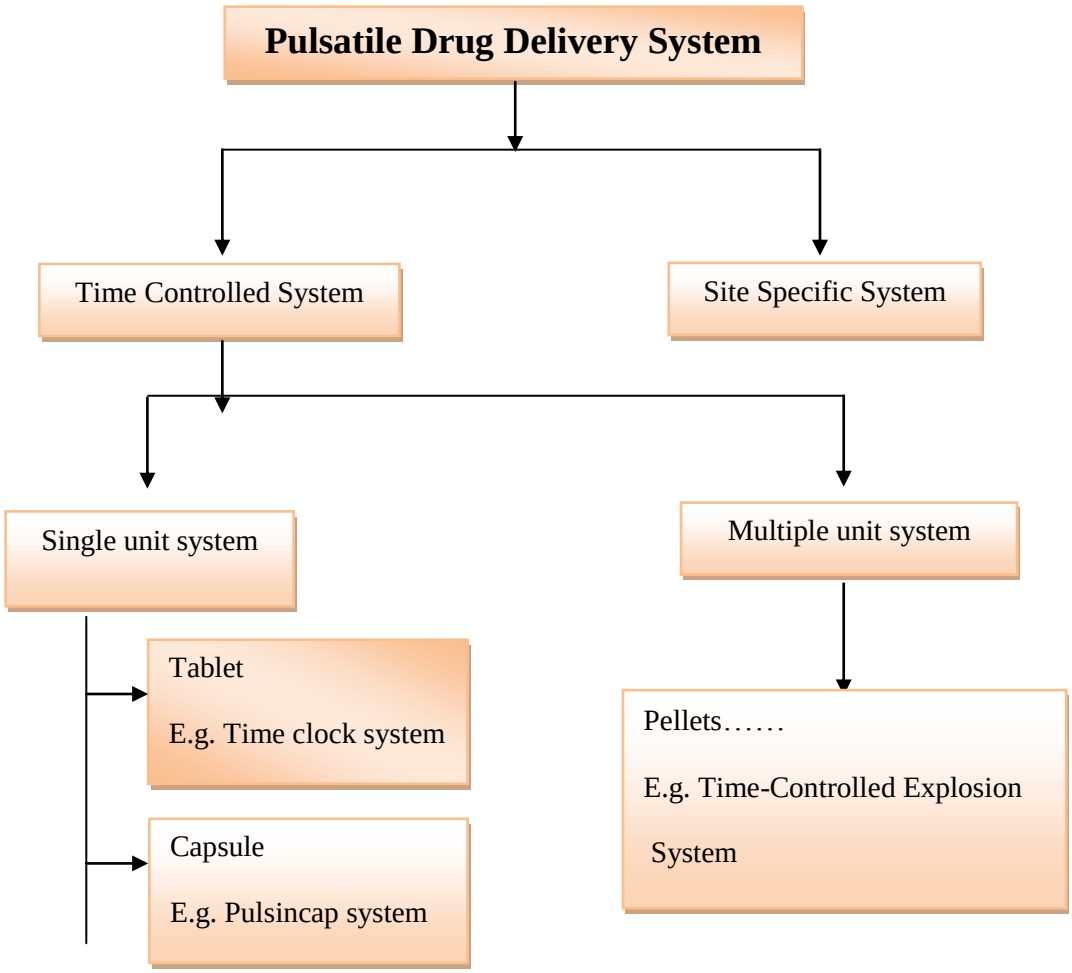


Fig. No. 7: Classification of Pulsatile Drug Delivery System.[18, 19]

1.1.2.1 Single Unit System

A. Tablets System[18, 19]

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

a. Tablet System with Erodible or Soluble Barrier Coating.[18, 19]

Eg.1. The Time Clock®[14] system consists of a solid dosage form coated with lipidic barriers containing carnuba wax and bees wax along with surfactants, such as polyoxyethylene sorbitan mono oleate. This coat erodes or emulsifies in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion. The lag time increases with increasing coating thickness. Such systems are better suited for water-soluble drugs. The major advantage of this system is its ease of manufacturing without any need of special equipment. However, such lipid-based systems may have high *in-vivo* variability (e.g. food effects). The possible problems of erosion-controlled systems include a premature drug release when the penetrating water dissolves the drug, which diffuses out through the barrier layers, and sustained release after the lag phase when the barrier layer is not eroded or dissolved completely, thereby retarding the drug release.**(Fig. No. 8)**

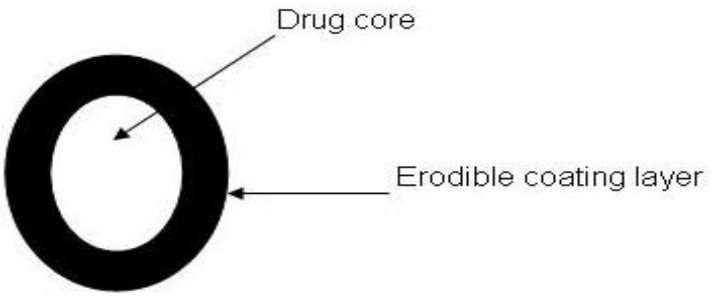


Fig. No. 8: Schematic Diagram of Delivery Systems with Erodible Coating Layer.[18]

b. Tablet System with Erodible or Soluble Barrier Coating

Eg.2. The Chronotropic®[18,19] system consists of a drug-containing core coated by hydrophilic swellable hydroxyl propyl methyl cellulose (HPMC), which is responsible for a lag phase in the onset of release. In addition, through the application of an outer gastric-resistant enteric film, the variability in gastric emptying time can be overcome, and a colon-specific release can be obtained, relying on the relative reproducibility of small intestinal transit time. The lag time is controlled by the thickness and the viscosity grades of HPMC. The cores containing antipyrine as the model drug were prepared by tableting and retarding, and enteric coats were applied in a fluidized bed coater. The *in-vitro* release curves displayed a lag phase preceding drug release, and the *in-vivo* pharmacokinetic data showed a lag time prior to presence of detectable amounts of drug in saliva. Both *in-vitro* and *in-vivo* lag times correlate

well with the applied amount of the hydrophilic retarding polymer. The system is suitable for both tablets and capsules. **(Fig. No. 9)**

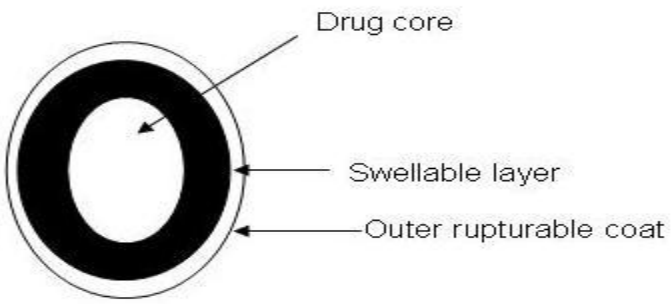


Fig. No. 9: Schematic Diagram of Delivery Systems with Rupturable Coating Layer.[14]

c. Osmotic Pulsatile Systems.[18,19]

Permeability controlled System is based on a combination of osmotic and swelling effects. The core containing the drug, a low bulk density solid and/or liquid lipid material (e.g. mineral oil) and a disintegrant were prepared. This core was then 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 coating.[18]

Another system is based on a capsule or tablet composed of a large number of pellets consisting of two or more pellets or parts (i.e. populations). 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. 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.

B. Capsular system

a. Capsular System Based on Osmosis.[14,20]

The Port® System[14,19] consists of a gelatin capsule coated with a semipermeable membrane (e.g. cellulose acetate) housing an insoluble plug (e.g. lipidic) and an osmotically active agent

along with the drug formulation. When in contact with the aqueous medium, water diffuses across the semipermeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. Coating thickness controls the lag time. This system showed good correlation in lag times of *in-vitro* and *in-vivo* experiments in humans. **(Fig. No. 10)**

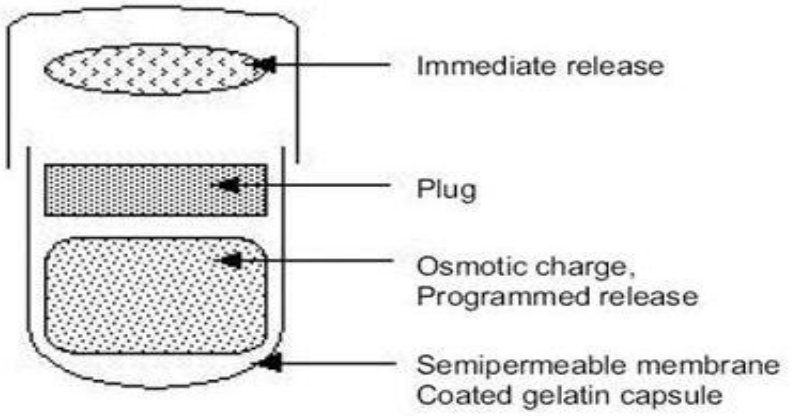


Fig. No. 10: Plan of Port® System.[14, 19]

b. Capsular System with Swellable Plug[14]

Different single-unit capsular pulsatile drug delivery systems have been developed. A general architecture of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined lag time owing to swelling, erosion, or dissolution.

Eg. The Pulsincap® System[14] is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation. The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a lag time. This is followed by a rapid drug release. Manipulating the dimension and the position of the plug can control the lag time. For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymers (e.g. polymethacrylates), erodible compressed polymers (e.g. hydroxypropyl methyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g. saturated polyglycolated glycerides, glycerylmonooleate), and enzymatically controlled erodible polymer (e.g. pectin). These formulations were well tolerated in animals and healthy volunteers and there were no reports of gastro-intestinal irritation. However, there was a

potential problem of variable gastric residence time, which was overcome by enteric coating. **(Fig. No. 11)**

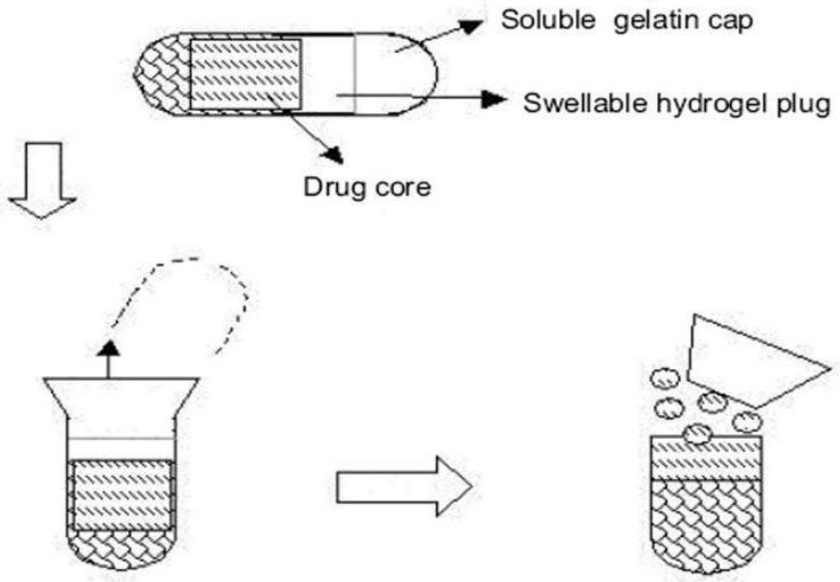
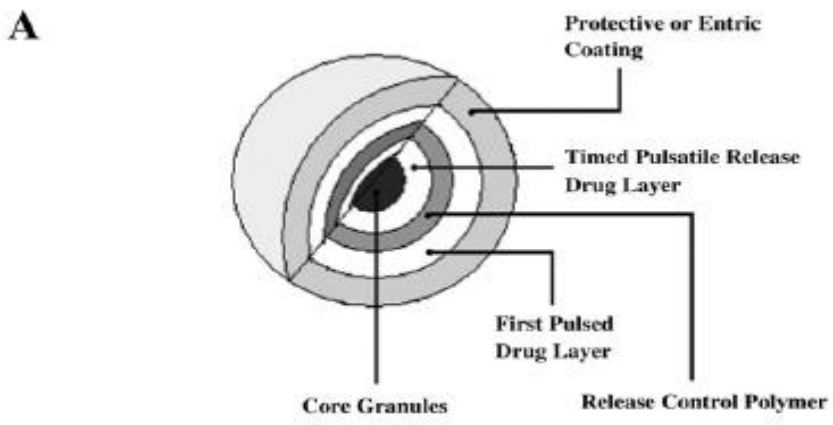


Fig. No. 11: Design of Pulsincap® System.[14, 19]

1.1.2.2 Multiparticulate Systems[2,16]

Multiparticualte systems (e.g. pellets) offer various advantages over single-unit systems. These include no risk of dose dumping, flexibility of blending units with different release patterns, and reproducible and hasshort gastric residence time. But the drug-carrying capacity of multiparticulate systems is lower due to presence of higher quantity of excipients. Such systems are invariably a reservoir type with either rupturable or altered permeability coating**.** **(Fig. No. 12)**



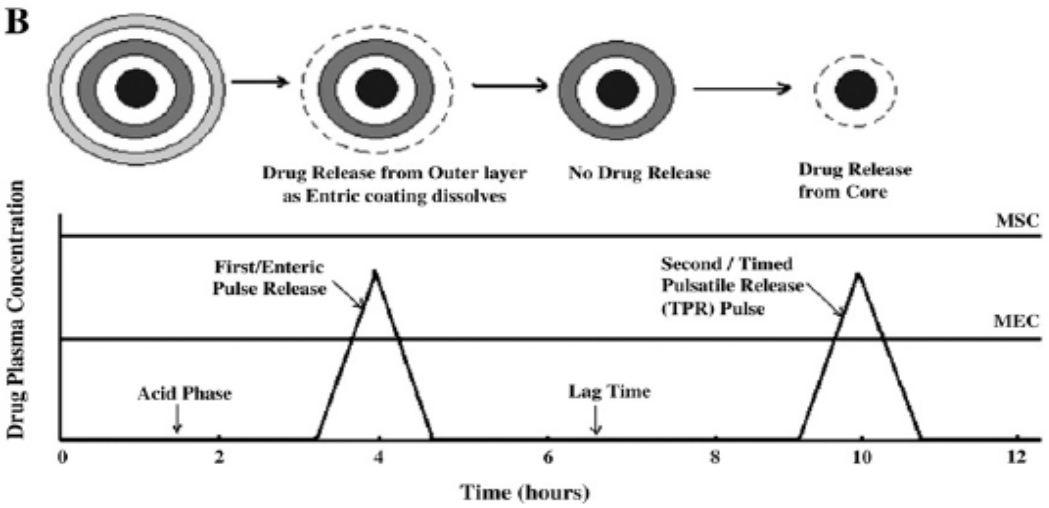


Fig. No. 12: Hypothetical Design and Plasma Drug Profile of a Multiparticulate.

Pulsatile System. (A) Design of a Pellet with Multiple Coatings,

(B) Predicted Bi-Modal Plasma Concentration Profile[14, 21]

a) Pulsatile System Based on Rupturable Coating.[17, 21]

These systems are based on a reservoir system coated with a rupturable membrane. Upon water access the drug is released from the core after rupturing of adjoining of the polymer layer, due to pressure build-up inside the system. The pressure required to rupture the coating can be achieved with swelling agents, gas- producing effervescent excipients or amplified osmotic pressure. Water soluble drugs are mainly released by diffusion while for water insoluble drug; the release is dependent on dissolution of the drug.

The release is independent of environmental factors like pH and drug solubility. Varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer can vary the lag time**.**

b) Pulsatile Delivery by Change in Membrane Permeability[10, 21]

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. Several delivery systems based on this ion exchange have been developed. Eudragit RS 30D is reported to be a polymer of choice for this purpose. 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.[9]

c) Time Controlled Expulsion System.[10, 21]

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

d) Low Density Floating Multiparticulate Pulsatile Systems[10, 21]

Conventional multiparticulate pulsatile release dosage forms mentioned above are having longer residence time in the gastrointestinal tract and due to highly variable nature of gastric emptying process may result in *in vivo* variability and bioavailability problems. In contrary, low density floating multiparticulate pulsatile dosage forms reside only in stomach and not affected by variability of pH, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery.

1.1.2.3 Stimuli Induced Pulsatile System[22]

a. Temperature Induced System

Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems the polymer undergoes swelling or de-swelling phase in response to the temperature which modulate drug release in swollen state**.**

b. Chemically Induced System[18]

There has been much interest in the development of stimuli-sensitive delivery systems that release a therapeutic agent in presence of specific enzyme or protein. One prominent application of this technology has been development of a system that can autonomously release insulin in response to elevated blood glucose levels. Several existing strategies that may be feasible for glucose-responsive drug delivery are discussed below: pH-dependent systems for glucose stimulated drug delivery are based on the reaction that glucose oxidase catalyses oxidation of glucose to gluconic acid. This reaction can be used to drive the swelling of pH-dependent membrane. A dual membrane system was formed. In the first membrane, glucose oxidase was immobilized on cross linked polyacrylamide and this was referred to as glucose sensing.

In pH sensitive system there are 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. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethyl cellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine.

1.1.2.4 Externally Induced System[22]

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.

a. Magnetically Stimulated.[22]

In an experiment, ferrite microparticles (1μm) and insulin powder were dispersed in sodium alginate aqueous solution. The ferrite-insulin alginate suspension was later dropped in aqueous calcium chloride solution which causes the formation of cross linked alginate spheres, which were further cross linked with aqueous solution of poly(L-lysine) or poly(ethylene imine). They described that the magnetic held characteristics due to the ferrite microparticles and the mechanical properties of the polymer matrices could play role in controlling the release rates of insulin from the system**.**

b. Ultrasonically Stimulated.[22]

Ultrasound is mostly used as an enhancer for the improvement of drug permeation through biological barriers, such as skin, lungs, intestinal wall and blood vessels. There are several reports describing the effect of ultrasound on controlled drug delivery. During polymer degradation incorporated drug molecules were released by repeated ultrasonic exposure. As degradation of biodegradable matrix was enhanced by ultrasonic exposure, the rate of drug release also increased. Thus, pulsed drug delivery was achieved by the on-off application of ultrasound.

c. Photo Stimulated.[22]

The interaction between light and material can be used to modulate drug delivery. This can be accomplished by combining a material that absorbs light at a desired wavelength and a

material that uses energy from the absorbed light to modulate drug delivery. When exposed to near-infrared light, nanoshells absorb the light and convert it to heat, raising the temperature of composite hydrogel. That's result in the increase release rate of the drug from matrix system.

d. Electrically Stimulated.[22]

An electric field as an external stimulus has advantages such as availability of equipment, which allows precise control with regards to the magnitude of the current, duration of electric pulses, interval between pulses etc. Electrically responsive delivery systems are prepared from polyelectrolytes and are thus pH- responsive as well as electro responsive. Under the influence of electric field, electro responsive hydrogel generally de-swell, swell or erode. This rapid drug release was attributed to the electrostatic force, squeezing effect, and electro-osmosis of the gel.

1.2 NEED FOR THE STUDY.[10, 19]

Conventional controlled release drug delivery system are based on single or multiple-unit reservoir or matrix system, which are designed to provide constant or nearly constant drug levels over an extended period of time. However, there are certain conditions for which such a release pattern is not suitable due to some following reason which force to think about the shift from conventional sustained release approach to the modern chronotherapeutic delivery of drugs.

1. **First Pass Effect**: When drug is subjected to large metabolic degradation due to first pass effect there will be reduction in the bioavailability of the drug because, gradual release can result in greater degradation.
2. **Short Half Life:** Drug with short half life need to be administered repeatedly which result in patient noncompliance.
3. **Chronic Treatment:** In case of chronic treatment, where drug is given in sustained release dosage form, continues exposure of the drug to the body may lead to adverse effect. For example, diabetes mellitus require chronic treatment with sustained release formulation of drug like sulfonylurea which will damage the pancreas earlier than the corresponding immediate release dosage form.
4. **Tolerance:** Drug which exhibit tolerance should not be delivered at a constant rate, since the drug effect decreases with time at constant drug level.
5. **Drug Toxicity:** Drug toxicity increases with time when drug level held constant.

6. **Chronopharmacological Needs**: According to circadian rhythms, it has been observed that many symptoms and onset of disease occur during specific time periods of the 24 hour.
7. **Local Therapeutic Need**: For the treatment of local disorders such as inflammatory bowel disease (IBD), inflammatory bowel syndrome (IBS), Crohn's disease and ulcerative colitis. The absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

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 can be achieved by modulating the chronobiologic system and is known as chronomodulated drug delivery system.

The principle rational behind designing this drug delivery system is to release the drug at desired time as per the pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance.

Table No. 2: Marketed Technologies of Chonotherapeutic Drug Delivery.[14, 16, 23, 25]

Technology	Propritory Name: Dosage form	API	Disease
CONTIN	Uniphyl, ER Tablet	Theophylline	Asthma / IncreasedBroncho constriction
OROS	Covera, ER Tablet	Verapamil HCL	Hypertension/Increased BP in early morning
CODAS	Verelan, E R Tablet	Verapamil HCl	Hypertension
CEFORM	Cardizem, ER tablet	DiltiazemHCl,Verapamil HCl	Hypertension
DIFFUCAPS	Innopran –XL	Propranolol,Verapamil HCl	Hypertension
Physico-chemicalModification of API	Pepcid, Tablet	Famotidine	Ulcer / Increased gastric acid secretion in evening.
Physico-chemicalModification of API	Zocor, Tablet	Simvastatin	Hypercolesterolemia
Pulsys®	Moxatag,Tablet	Amoxicillin	Pharyngitis/ Tonsillitis
TIME^{Rx}	Opana®, ER tablet	Oxymorphone	Pain medicine
Covera HS	Covera HS, ER tablet	Verapamil HCl	Hypertension
Pulsincap	Pulsincap	Dofetilide	Hypertension

API: - Active Pharmaceutical Ingredients ER: - Extended Release

REFERENCES

1. Sherina V.M., Santhi K., Sajeeth C.I. Formulation and Evaluation of sodium alginate microbeads as a carrier for the controlled release of nifedipine. IJPCS. 2012; 1(2): 699-710.
2. Sharma GS, Srikanth MV, Uhumwangho MU, Phani Kumar KS., Recent trends in pulsatile drug delivery systems - a review. Int. J. Drug Delivery. 2010; 2**:** 200-212.
3. Brahmankar DM, Jaiswal SB. Biopharmaceutics & Pharmacokinetics a Treatise. 1st Edition. Vallabh Prakashan: New Delhi; 1995. p.335-336.
4. Atyabi F., Majzoob S., Iman M., Salehi M., Dorkoosh F. In-vitro evaluation and modification of pectinate gel beads containing trimethyl chitosan, as a multiparticulate system for delivery of water soluble macromolecules to colon. Carbohyr. Polym, 2005; 61-39.
5. Mandal AS., Biswas N., Kazi MK., Guha A., Chatterjee S., Behera M., Kuotsu K. Drug delivery system based on chronobiology - A review. J. Cont. Rls., 2010; 147: 314-325.
6. Smolnesky HM. & Peppas AN. Chronobiology drug delivery and chronotherapeutics. Advanced Drug Delivery Reviews, 2007; 59: 828-851.
7. Awasthi R., Kumar P., Pawar V. Chronotherapy: Science and technology of drug scheduling on the basis of biological rhythm. J. Chr. DD. 2010: 09-18.
8. Sajan J., Sinu T.A., Chacko A.J., Litty J., Jaseeda T. Chronotherapeutics and Chronotherapeutic Drug Delivery Systems. Trop J. Pharm. Res. 2009; 8(5): 467-475.
9. Parmar RD, Parikh RK, Vidyasagar G, Patel DV, Patel CJ, Patel BD. Pulsatile drug delivery: an overview. Int. J. Pharm. Sci. Nanotech, 2009; 03: 605-614.
10. Singhai SK, Chopra VS, Nagar M, Gautam N,. Chronotherapy: a novel concept in drug delivery. Scholars Res. Lib. 2010; 2: 136-153.
11. Shan-Yang L, Kawashima Y. Current status and approaches to developing press-coated chronodelivery drug systems. J. Cont. Rel. 2011.
12. Smolensky MH, Peppas NA. Chronobiology, drug delivery and chronotherapeutics. Adv. Drug Delivery Rev. 2007; 59: 828-851.
13. Reddy JR, Jyothsna MV, Saleem TSM, Chetty CMS. Review on: pulsatile drug delivery system. J. Pharm. Sci. Res. 2009; 04: 109-115.
14. Sidhaye SS, Lottikar VM, Ghule AM, Phutane PK, Kadam VJ. Pulsatile drug delivery systems: an approach for chronotherapeutic diseases. Sys. Rev. Pharm. 2010; 01: 55-61.
15. Modasiya MK, Patel VM. Pulsatile drug delivery system for colon-a review. Int. J. Res. Pharm. Biomed. Sci., 2011; 3: 934-941.

16. Nagar M, Singhai S, Chopra V.S, Gautam N, Trivedi P. Chronotropic systems; an emerging trend in drug delivery for pulsed release in chronopharmacotherapy. Int. J. Pharm. Clin. Res., 2010; 2(1): 10-19.
17. Shaji J, Shinde AM. Oral multiparticulate pulsatile drug delivery systems: a review. Int. Res. J. Pharm., 2011; 02: 22-27.
18. Navneet S, Verma S, Mathur P, Saroha K, Handa V. Pulsatile drug delivery system an innovative approach for controlled drug delivery. Int. Res. J. Pharm. Sci. 2010; 01(01): 0001.
19. Arora S, Ali J, Ahuja A, Baboota S, Qureshi J. Pulsatile drug delivery system: an approach for controlled drug delivery. Ind. J. Pharm. Sci., 2006; 68(3): 295-300.
20. Moroni A, Zema L, Curto MDD, Loreti G, Gazzaniga A. Oral pulsatile delivery: rational and chronopharmaceutical formulations. Int. J. Pharm, 2010; 398: 1-8.
21. Roy P, Shahiwala A. Multiparticulate formulation approach to pulsatile drug delivery: current perspectives. J. Cont. Rel., 2009; 134: 74-80.
22. Patel JD, Aneja KS, Majumdar SH. Pulsatile drug delivery systems: an ‘’user friendly’’ dosage form, J. Pharm. Res. Health, 2010; 2: 204-215.
23. Ghosh T, Ghosh A. Drug delivery through osmotic systems – an overview. J. of applied pharm. Sci., 2011; 01: 38-49.
24. Venkatesh G, Lai J, Vyas NH, Stevens PJ, Gosselin M, et al. QD diffucaps® drug delivery systems for weakly basic pharmaceuticals actives. Eurand Icn Vandalia, OH 45377 (USA).
25. Survase S, Kumar N. Pulsatile drug delivery: current scenario. Curr. Res. Inf. Pharm. Sci., 2007; 02: 27-33.