Review Article

Pulsatile drug delivery system for chronopharmacological disorders: an overview

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Received on:18-08-2008; Accepted on :08-12-2008

ABSTRACT

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery thus increasing patient compliance. These systems are designed according to the circadian rhythm of the body. 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. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hour period, may be changing as researcher's report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms. The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease.

Key words: Pulsatile drug delivery, Chronotherapeutics, Circadian rhythm, Asthma, Chronobiology

INTRODUCTION

Over the last 30 years the pharmaceutical market has been demonstrated increasing preferably for controlled and targeted drug delivery system. Such systems have been focused onconstant, variable; sustain drug release and/or targeting the therapeutic agent to a specific site/tissue/ organ.However, recently there are certain conditions for which such release pattern is not suitable. Such conditions that lead to the requirements of a time programmed therapeutic system, which capable of releasing drug after predetermined time delay and maintain constant drug levels throught the day.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 the pharmacological actions of various drugs over a period of time of the day.[1]

Chronopharmacokinetics

Chronopharmacokinetics involves study of temporal changes in drug absorption, distribution, metabolism and excretion. Pharmacokinetic parameters, which are conventionally considered to be constant in time, are influenced by different physiological functions displaying circadian rhythm. 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.[2]

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. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hour period, may be changing as researcher's report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms.[3]

Biological rhythms:

1. Ultradian Rhythms:

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

2. Infradian Rhythms:

Oscillations that are longer than 24 hours are termed as Infradian Rhythms (less than one cycle per 24hours). E.g. Monthly Menstruation.[4]

3. Circadian rhythms:

Circadian rhythms are self-sustaining, endogenous oscillations

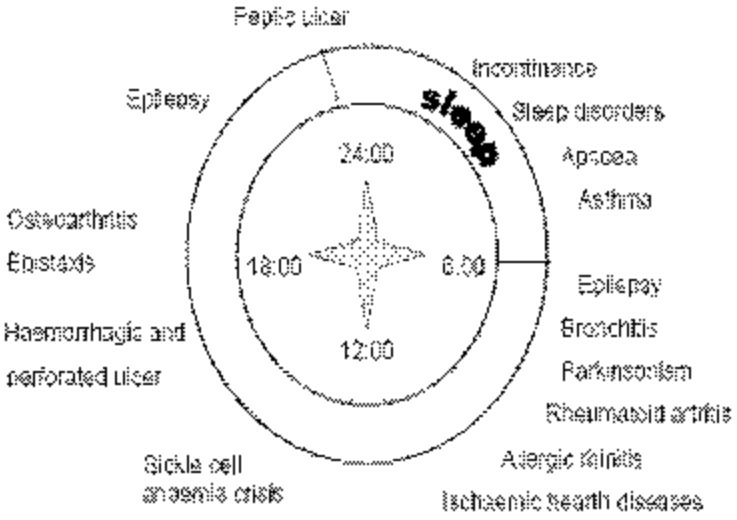


Figure 1: Diseases displaying circadian rhythm

that occur with a periodicity of about 24 Hours.[1] Interestingly, the term circadian is derived from the Latin circa which means "about" and dies which can be defined as "a day". Normally, circadian rhythms are synchronized according to internal biologic clocks related to the sleep-wake cycle. Our circadian rhythm is based on sleep-activity cycle and is influenced by our genetic makeup and thereby affects our bodies' function throughout day and night (24-hour period). Circadian rhythm regulates many body functions in humans like metabolism, physiology, behavior, sleep pattern, hormone production.[5] There are number of conditions which show circadian pattern and advantage could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease. Diseases, such as cardiovascular, asthma, peptic ulcer, arthritis etc follow the body's circadian rhythm.

Diseases and Chronotherapeutics:

The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease.[3]

Table: 1 Disease Influenced by Chronotherapy.

Sl.no	Selected Diseases	Influenced by Chronotherapy
1	Cardiovascular	Hypertension,angina , myocardial infarction
2	Inflammatory	Rheumatoid arthritis, related disorders
3	Neoplastic	Various forms of cancer
4	Gastrointestinal	Peptic ulcer disease
5	Respiratory	Allergic rhinitis, asthma

Cardiovascular Diseases:

Cardiovascular diseases such as hypertension and angina, or chest pain, also follow a definite circadian rhythm.

Hypertension:

Heart rate and blood pressure are increased in the early morning hours (morning or A.M. surge). The blood pressure declines form mid afternoon and is minimum at midnight. In most hypertensive patients, there is a rather marked rise in blood pressure upon awakening that is called the morning or "a.m." Systolic blood pressure rises approximately 3mm Hg/hour for the first 4-6 hours post-awakening, while the rate of rise of diastolic blood pressure is approximately 2mm Hg/hour.

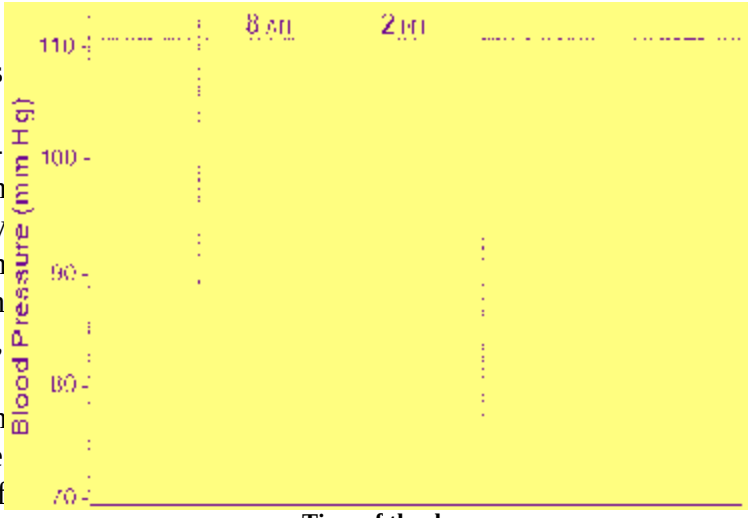


Fig.2: circadian variations in Blood Pressure

Myocardial Infarction:

Onset of myocardial infarction has been shown to be more frequent in the morning with 34% events occurring between 6 A.M. and noon. Acute cardiac arrest and transient myocardial ischemia shows an increased frequency in morning. The causes for these findings have been suggested to be release of catecholamine, cortisol increase in the platelet aggregation and vascular tone.

The major objective of chronotherapy is to deliver the drug in higher concentration during time of greatest need (i.e. early in the morning) and lesser when the need is less (i.e. lower amount at night).[1]

ACE inhibitors are more effective when administered during night. Atenolol, Nifedipine and amolodipine are more effective when administered at night.

Arthritis:

Patients suffering from osteoarthritis are reported to have less pain in morning hours than night, while patients suffering from rheumatoid arthritis feel more pain in the morning hours.[4]

In this case taking medication at night is an obvious solution. NSAIDs such as ibuprofen need to be administered 4 to 6 hours before achieving their maximum benefit, as a result peak will occur at patients waking and the effect will be decline as patient start to wake up.

The new cyclooxygenase-2 inhibitors effectively relieve osteoarthritis symptoms when taken in the morning, better results are obtained in the rheumatoid arthritis when part of the dose is taken in the evening.

Neoplastics:

Antineoplastic drugs cause cytotoxic effects on healthy and diseased tissues. As would be expected, the biological rhythms of both healthy and tumor cells may influence the susceptibility of normal and malignant cells to these agents. It has been demonstrated that "susceptibility rhythms" to drugs may differ between healthy tissue and cancerous tissue. Therefore, the"correct" timing of drug treatment may reduce host toxicity, increase the maximum drug tolerance, and ultimately result in better tumor management. In addition to considering the pharmacologic and pharmacokinetic properties of the drug, clinicians may also recognize how rhythmic changes in DNA and RNA synthesis, RNA translational activity and mitotic activity may influence tumor cell susceptibility. It appears that the timing of drug administration in the treatment of cancer can have a significant impact upon treatment success, including the patient's ultimate survival.[4]

Peptic ulcer disease:

Because of maximal acid secretion, peptic ulcer disease pain, and perforation of gastric and duodenal ulcers are more common at night, administration of drugs at bedtime is more effective. Nocturnal administration not only reduces acid secretion more effectively but also promotes ulcer healing and reduces ulcer recurrence. Bedtime H_2-receptor blockade is one such regimen.

Bronchial asthma:

Asthma is a chronic inflammatory disease of the airways, characterized by hyper responsiveness to a variety of stimuli. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours.[6]

The worsening of asthma at night, commonly referred to as nocturnal asthma (NA).A drug delivery system administered at bedtime but releasing drug during morning hours would be ideal in this case.[7]

Chronobiology of Nocturnal Asthma:

Nocturnal asthma is a variable exacerbation of the underlying asthma condition associated with increases in symptoms, need for medication, airway responsiveness, and/or worsening of lung function. Generally, a reduction in peak flow or forced expiratory volume in one second (FEV1) of at least 20% is implicit in this definition. Approximately two-thirds of asthmatics suffer from nighttime symptoms. In a large study involving 8,000 asthmatics it is observed that, 75% awakened one night per week, 64% awakened 3 nights per week and 39% had their sleep disturbed on a nightly basis. The patients who self-characterized their asthma as mild, 26% had nightly awakenings and 53% of asthma deaths occurred during the nighttime hours.[8]

General Principles:

1. Circadian Rhythms:

The function of circadian regulation is to impose a temporal organization on physiologic processes and behavior. In addition to the sleep–wake cycle, other examples of circadian regulation occur in body temperature, multiple hormones, and the autonomic nervous system. Disorders of circadian regulation are typically expressed as sleep disorders. It is necessary to understand circadian regulation in order to understand the pathophysiology and treatment of diseases.

2. Sleep:

In asthma, the resistance increases progressively across the night, whether subjects sleep or not, although the increase is much greater during sleep. These results are supported by the observations that the onset of asthmatic attacks is less common in the first part of the night.

First, it seems likely that both circadian and sleep factors play a role in asthma. Although sleep seems to play a role in the

pathogenesis of asthma, asthmatic individuals also have evidence of problems with sleep. Studies reveal that asthmatic individuals or those with obstructive lung disease complain frequently of difficulty in maintaining sleep poor sleep quality and excessive daytime sleepiness.[8]

3. Nocturnal Asthma and Chronobiology:

The principles of chronobiology provide a framework for understanding nocturnal asthma.Chronobiology is the study of biological rhythms and their mechanisms. Every biological rhythm has a periodicity. Circadian rhythms have a periodicity of about 24 hours. It is well known that circadian rhythms influence disease processes and physiological events. For example, most myocardial infarctions occur in the early hours of the morning. Lung function (e.g., peak expiratory flow rate or FEV1) is usually highest at 4 PM and lowest at 4 AM the latter time is generally when asthma symptoms are most prevalent.

Dethlefsen and Repges studied a population of more than 3,000 patients (mainly asthmatics) and demonstrated that more than 90% of their dyspneic episodes occurred during the nighttime hours.

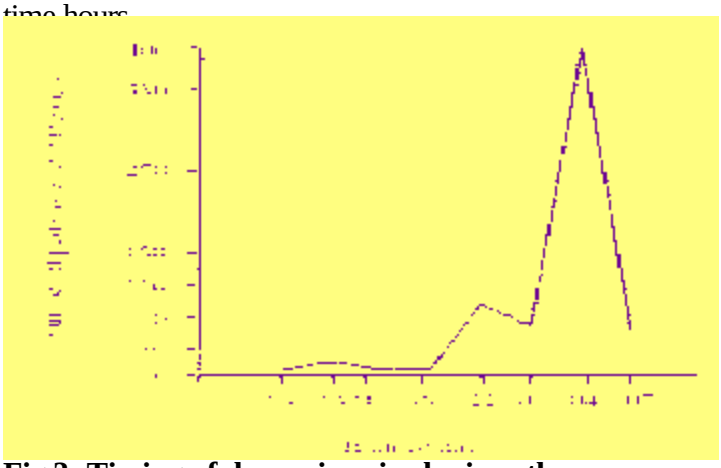


Fig.3: Timing of dyspneic episodes in asthma

Asthma symptoms occurred most often between 10.00 pm and 07.00 am hours, with a peak occurrence at 4am. Clark and Hetzel showed that diurnal variation in lung function exists in both healthy and asthmatic subjects (Fig.4).

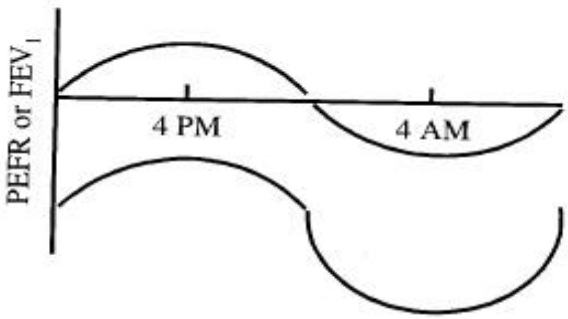


Fig. 4: Diurnal variation in lung function in healthy (top curve) and asthmatic (bottom curve) subjects. PEFR =peak expiratory flow rate; FEV1 = forced expiratory volume in one second.

However, the amplitude of variation is much greater in asthmatics, due to the greater dip in their peak expiratory flow rate at 4 in the morning. These investigators found that, on average, the diurnal variation was 8% in healthy subjects and **51% in asthmatics.**[7]

Chronotherapy of nocturnal asthma:

Bodily functions have been incorrectly assumed to be relatively constant throughout the 24 h of the day and other periods of time. The kinetics and dynamics of pharmacotherapies vary significantly according to the biologic time of administration during the 24 h-cycle. Chronotherapeutics is the synchronization of medication levels in time with reference to need, taking into account biologic rhythms in the pathophysiology of medical conditions, and/or rhythm-dependencies in patient tolerance for given chemical interventions.

ß2-Agonists, Theophylline, and Anticholinergic Therapy:

Certain SR formulations of theophylline can be administered so that a rising blood level of the drug occurs when airway obstruction is increasing, while adverse effects are reduced. For this purpose, SR theophylline is administered once daily, in the evening, for the management of nocturnal asthma. Various tablet formulations for the sustained-release of ß-agonists have been used in a chronotherapeutic fashion for the management of asthma. As with theophylline, very little information exists about comparing the effects of or adding a long-acting $ß_2$ -agonist oral preparation to an inhaled corticosteroid using chronotherapeutic techniques. The long-acting inhaled $ß_2$-agonists salmeterol and formoterol have been studied for the treatment of nocturnal asthma. These agents have a lower adverse-effect profile than do long-acting oral agents. Salmeterol has been shown to control symptoms of nocturnal asthma to a substantial degree, and to improve sleep quality and daytime cognitive performance in patients with chronic asthma. Drugs that antagonize the vagal nervous system should be useful in the management of nocturnal asthma. Inhaled cholinergic antagonists such as ipratropium bromide and oxitroprium bromide have reduced the morning decline in airflow in asthmatic individuals.

Corticosteroids and Leukotriene –active drugs:

Corticosteroids have been used in a chronotherapeutic manner, with the finding that their long-term oral administration at 8:00A M. and 3:00PM. was more effective in controlling nocturnal asthma than the same doses given at 3:00P.M. and 8:00P.M.. Other studies have shown that a single 3:00P.M. dose of prednisone improved lung function and reduced airway inflammation more effectively than the same single dose given at 8:00A.M. and 8:00P.M.

Although the leukotriene-active drugs, including zileuton, zafirlukast and montelukast, are new in the treatment of asthma, they have been shown to alleviate the symptoms and the decrement in lung function seen in nocturnal asthma. It has been shown that zileuton in particular decreased nighttime increases in leukotriene B4 (LTB_4) and (LTE_4) while improving lung function. Zafirlukast has also been shown to decrease nighttime awakenings and improve morning PEF rates. Although these agents have only been studied at set doses and times regardless of the presence or absence of nocturnal asthma, the improvements observed were significant, and it is likely that these agents will prove very useful in the treatment of nocturnal asthma when used chronotherapeutically.[8]

Leukotrine Antagonists:

It was realized that cystennyl leukotrines ($LT\text{-}D_4$) are important mediators of bronchial asthma, efforts wear made to develop their antagonists and synthesis inhibitors. Two $cysLT_1$ receptor antagonists montelukast and zafirlukast are available.

Montelukast and zafirlukast:

Both have similar actions and clinical utility .They competitively antagonize $cysLT_1$ receptor mediators bromchoconstriction, increased vascular permeability and recruitment of eosinophils. Bronchodilation, reduced sputum eosinophil count, supression of bronchial inflammation and hyperreactivity are noted in asthma patients. Parameters of lung function show variable but definite improvement.

Montelukast and zafirlukast are indicated for prophylactic thearapy of mild-to-moderate asthma as alternatives to inhaled glucocorticoids. In severe asthma,they may permit reduction in steroid dose and need for rescue $ß_2$ agonist inhalations.

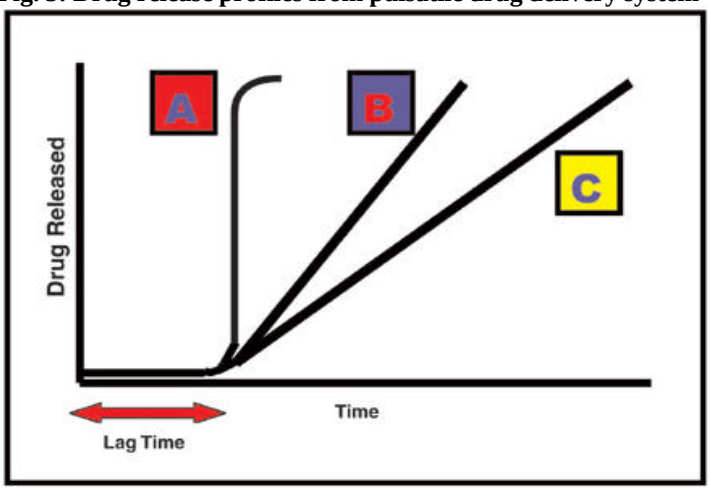
Both Montelukast and zafirlukast are very safe drugs, produce side effects like headache and rashes. Eosinophiliass and neuropathy are infrequent.[9]

Pulsatile drug delivery systems:

It is the one type of drug delivery system, where the delivery device is capable of releasing drug after predetermined time-delay (i.e. lag time) known as pulsatile drug delivery system.[10] Pulsatile drug delivery systems are gaining lot of interest and attention these days. These systems have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release."

Though most delivery systems are designed for constant drug release over a prolonged period of time, pulsatile delivery systems are characterized by a programmed drug release, as constant blood levels of a drug may not always be desirable.[5] (fig.5)

Fig. 5: Drug release profiles from pulsatile drug delivery system



A = Release of drug as a "pulse" after a lag time, B = Delivering the drug rapidly and completely after a "lag time" and C = Constant drug release over a prolonged period of time after a "lag time".

Classification of pulsatile drug delivery systems:

Pulsatile drug delivery system can be broadly classified into three classes;

I. Time controlled pulsatile drug delivery
II. Stimuli induced pulsatile drug delivery
III. Externally regulated pulsatile drug delivery

I. Time controlled pulsatile drug delivery

A. Single unit pulsatile systems

1. Capsule based systems
   E.g. Pulisincap system
2. Capsular system based on Osmosis
   a. 'PORT' System
   b. System based on expandable orifice
   c. Delivery by series of stops.
   d. Pulsatile delivery by solubility modulation
3. Pulsatile system with Erodible or soluble barrier coatings.
   a. The chronotropic system
   b. 'TIME CLOCK' System.
   c. Compressed tablets
   d. Multilayered Tablets
4. Pulsatile system with rupturable coating

B. Multiparticulate / Multiple unit systems:

1. Pulsatic system with rupturable coating
   E.g. Time –controlled Explosion system (TCES)
2. Osmotic based rupturable coating system
   E.g. Permeability controlled system
3. Pulsatilc delivery by change in membrane permeability
   E.g.Sigmoidal release system.

A. Single unit pulsatile systems

1. Capsule based systems:

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 as a "Pulse" from the insoluble capsule body. [11]

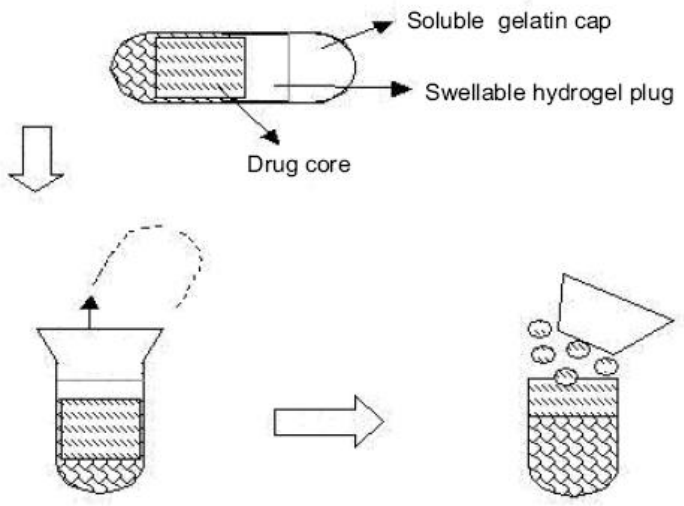


Fig 6: Design of Pulsincap system

Pulsincap (Fig.6) was developed by R. P. Scherer International Corporation, Michigan, US, and is one such system that comprises of a water-insoluble capsule enclosing the drug reservoir. When this capsule came in contact with the dissolution fluid, it swelled; and after a lag time, the plug pushed itself outside the capsule and rapidly released the drug. The lag time can be controlled by manipulating the dimension and the position of the plug. [12, 13]

Polymers used for designing of the hydrogel plug

1) Insoluble but permeable and swellable polymers (e.g., polymethacrylates)
2) Erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, Polyethylene oxide)
3) Congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate)
4) Enzymatically controlled erodible polymer (e.g., pectin). [14,15]

Steven *et al*. developed a Pulsincap® system with erodible compressed tablet. [16] As the swelling hydrogel polymer plug replaced the erodible tablet, the dependence of the dimensional accuracy between the plug and the capsule for the pulling mechanism of the plug from the capsule was also lactose and HPMC. [17] The preparation and invitro release of tetramethylpyrazine phosphate pulsincap capsule has been reported. It was prepared by sealing the drug tablet and fillers inside an impermeable capsule body with erodible plug. To meet the chronotherapeutic requirements, a suitable lag time can be achieved by adjusting the content of gel-forming polymer (HPMC) and the erodible plug weight. [18]

2. Capsular system based on Osmosis

a. 'PORT' System

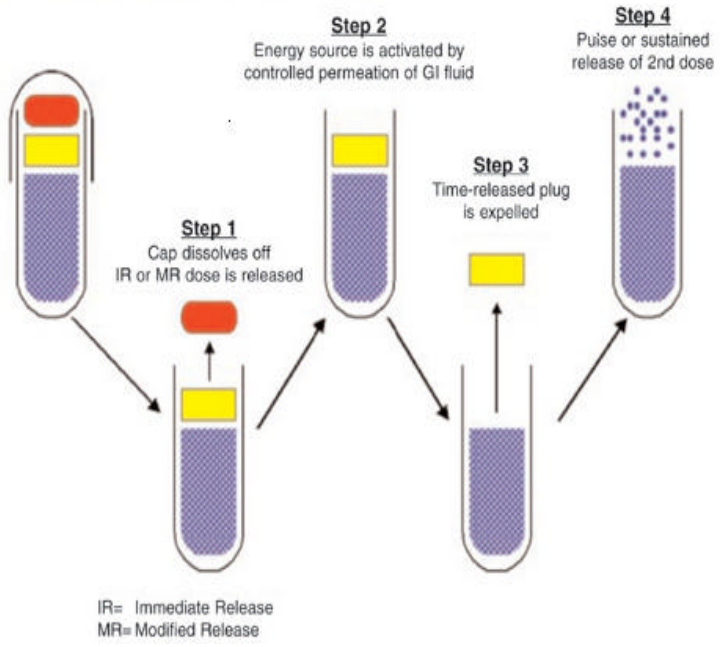


Fig 7: Drug release mechanism from PORT system

The Port system fig. (7) was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA, and consists of a capsule coated with a semipermeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation. [19] 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.

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. [20]

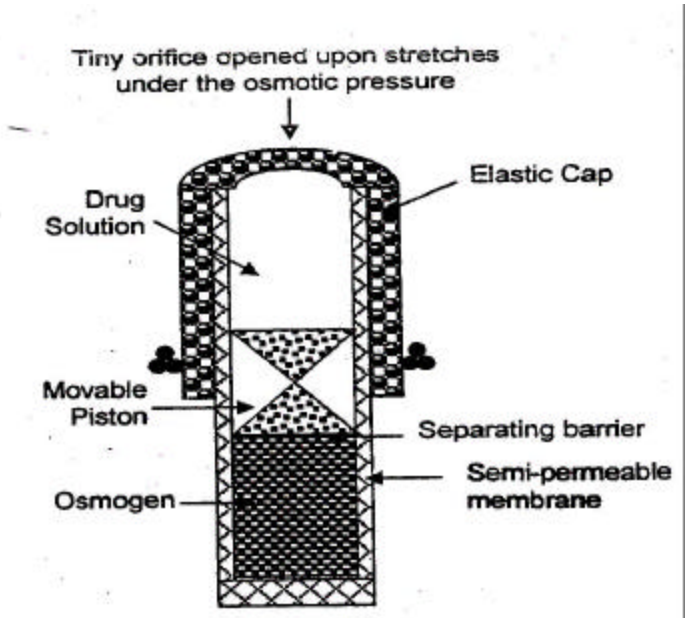


Fig. 8: System based on expandable orifice

The capsular system delivers drug by the capsule's osmotic infusion of moisture from the body. The capsule wall is made up of an elastic material and possesses an orifice. As the osmosis proceeds, the pressure within the capsule rises, causing the wall to stretch. The orifice is small enough so that when the elastic wall relaxes, the flow of the drug through the orifice essentially stops, but when the elastic wall is distended beyond threshold value, the orifice expands sufficiently to allow drug release at a required rate. E.g. Elastomers, such as styrene-butadiene copolymer have been suggested.[21,22]

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.

c. Delivery by series of stops:

This system is described for implantable capsules. The capsule contains a drug and a water-absorptive osmotic engine that are placed in compartments separated by a movable partition. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession 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.[23]

d. Pulsatile delivery by solubility modulation:

Such systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate.[24-26] The compositions contains the drug (salbutamol sulphate) and a modulating agent (sodium chloride). The amount of NaCl was such that it was less than the amount needed to maintain saturation in a fluid that enters the osmotic device.

The pulsed delivery is based on drug solubility. Salbutamol has solubility of 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. In order to control zero-order release period and commencement of pulsed release, ratio of drug/modulator can be varied. After the period of zero-order release, the drug is delivered as one large pulse.

3. Pulsatile system with Erodble 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:

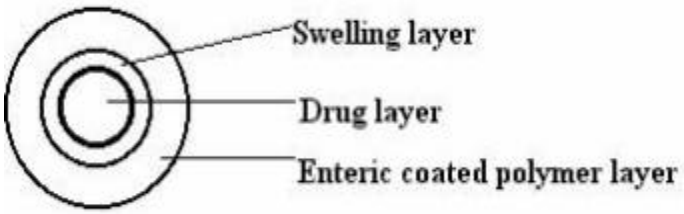


Fig. 9: The chronotropic system

The Chronotropic® system consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of release.[27-29]

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.[30] The lag time is controlled by the thickness and the viscosity grades of HPMC.[31] 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.[32]

b. 'TIME CLOCK' System:

Fig.10: 'TIME CLOCK' System

The time clock system is a delivery device based on solid dosage form that is coated by an aqueous dispersion.[33] This coating is a hydrophobic-surfactant layer to which a water-soluble polymer is added to improve adhesion to the core. 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*.

The effect of low calorie and high calorie meal on the lag time was studied using gamma scintigraphy. The mean lag time of drug release was 345 and 333 min respectively.

c. Compressed Tablets:

Compression coating can involve direct compression of both the core and the coat, obviating needs for separate coating process and 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.[34] Materials such as hydrophilic cellulose derivates can be used. Compression is easy on laboratory scale. 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.

Press-coated pulsatile drug delivery systems:

1. Press-coated pulsatile drug delivery systems can be used to protect hygroscopic, light-sensitive, oxygenlabile or acid-labile drugs.
2. Press-coated pulsatile drug delivery systems are relatively simple and cheap.
3. These systems can involve direct compression of both the core and the coat.
4. Materials Such as hydrophobic, hydrophilic can be used in press-coated pulsatile drug delivery system.
5. Press-coated pulsatile drug delivery systems involve compression which is easy on laboratory scale.
6. Press-coated pulsatile formulations relese drug after "lag-time".
7. Press-coated pulsatile drug delivery formulations can be used to separate incompatible drugs from each other or to achieve sustained release.

d. Multilayered Tablets:

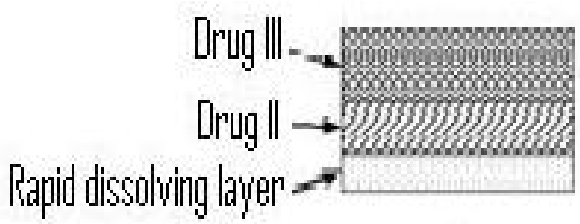


Fig.11: Multilayered Tablet

A release pattern with two pulses was obtained from a three-layered tablet containing two drug containing layers separated by a drug-free gellable polymeric barrier layer.[35-37] This three-layered tablet was 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 was obtained from the bottom layer after the gelling barrier layer of HPMC was

eroded and dissolved. The rate of gelling and/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.

4. Pulsatile system with rupturable coating:

These systems depend on the disintegration of the coating for the release of drug. The pressure necessary for the rupture of the coating can be achieved by the effervescent excipients, swelling agents, or osmotic pressure. An effervescent mixture of citric acid and sodium bicarbonate was incorporated in a tablet core coated with ethyl cellulose. The carbon dioxide developed after penetration of water into the core resulted in a pulsatile release of drug after rupture of the coating.[38] 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. The highly swellable agents, also called superdisintegrants, were used to design a capsule-based system comprising a drug, swelling agent, and rupturable polymer layer[39] Examples of superdisintegrants include cross carmellose, sodium starch glycollate, and low substituted hydroxypropyl cellulose. 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 reduced the lag time. The system can be used for delivery of both solid and liquid drug formulations. A reservoir system with a semipermeable 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.[40]

B. Multiparticulate / Multiple unit systems:

Multiparticualte systems (e.g., pellets) offer various advantages over single-unit systems.[41] These include,

1.No risk of dose dumping

2.Flexibility of blending units with different release patterns

3.Reproducible and short gastric residence time.

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.

1. Pulsatile system based on rupturable coating:

E.g. **Time –controlled Explosion system (TCES):**

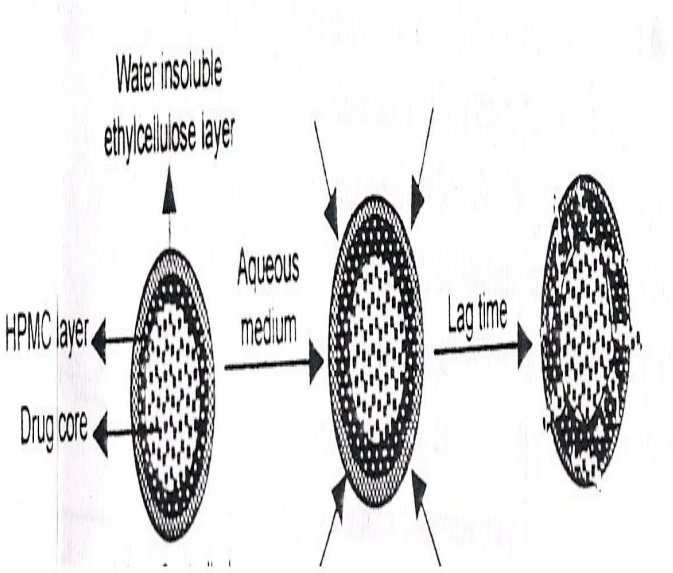


Fig.12: Time –controlled Explosion system (TCES)

This is a multiparticulate system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer.[42-45]

The swelling agents used include

Superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose.

Polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc.

Alternatively, an effervescent system comprising a mixture of tartaric 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.

The release is independent of environmental factors like pH and drug solubility. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer. A rapid release after the lag phase was achieved with increased 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.[46]

2. Osmotic based rupturable coating system:

This 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 (eg, mineral oil) and a disintegrant was 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 coat-

ing.[40] 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).[47] 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 (eg, 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.

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.[48]

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. 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 RS30D (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.[49] The lag time increases with increasing thickness of the coat, but the release of the drug was found to be independent of this thickness and depended on the amount of salt present in the system.

Sigmoidal Release System:

A Sigmoidal release system (SRS) is reported which is based upon the interaction of acrylic polymers with quaternary ammonium groups in the presence of different counter ions. SRS system consists of pellet cores having drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type (B). The water in the medium dissolves succinic acid. The drug inside and the acid solution increase the permeability of the polymer film. This system was used to design an acid-containing core. Good *in vitro/in vivo* correlation of lag time was observed.[50]

II. Stimuli induced pulsatile drug delivery:

In these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli (Fig.13).

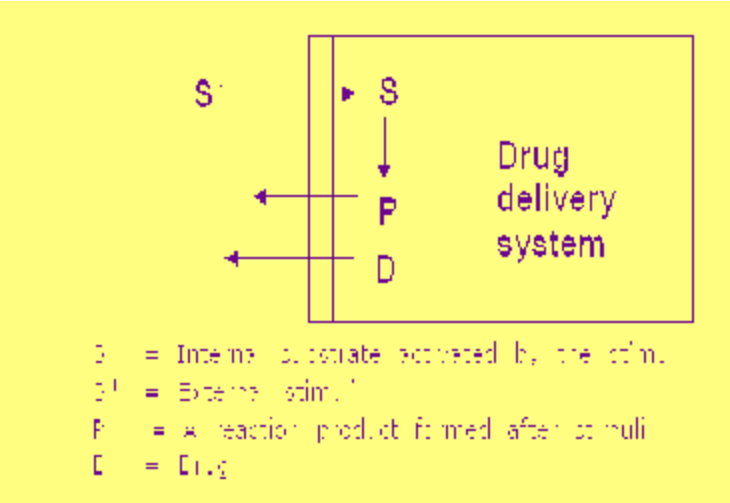


Fig.13: General scheme for stimuli sensitive pulsatile drug delivery system

These systems are further classified in to temperature induced systems and chemical stimuli induced system, on the basis of stimulus.

1. Temperature induced systems
2. Chemical stimuli induced Pulsatile systems
   a. Glucose-responsive insulin release devices
   b. Inflammation-induced pulsatile release
   c. Drug release from intelligent gels responding to antibody concentration
   d. pH sensitive drug delivery system[51,52]

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.[51,52]

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 includes N, Ndimethylaminoethyl methacrylate, chitosan, polyol etc.[52]

b. Inflammation-induced pulsatile release:

On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. 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.[53,54]

c. Drug release from intelligent gels responding to antibody concentration:

There are numerous kinds of bioactive compounds which exist in the body. Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/reselling characteristics. Special attention was given to antigen-antibody complex formation as the cross-linking units in the gel, since such interactions are very specific. Utilizing the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/ deswelling and drug permeation changes occurs.[52]

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 carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine.

III. Externally regulated pulsatile drug delivery:

For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads.[51, 52]

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Source of support: Nil, Conflict of interest: None Declared