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PUSATILE DRUG DELIVERY SYSTEM- AN OVERVIEW

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ABSTRACT

Pulsatile drug delivery systems (PDDS) have attracted attraction because of their multiple benefits over conventional dosage forms. They deliver the drug at the right time, at the right site of action and in the right amount, which provides more benefit than conventional dosages and increased patient compliance. These systems are designed according to the circadian rhythm of the body, and the drug is released rapidly and completely as a pulse after a lag time. These products follow the sigmoid release profile characterized by a time period. These systems are beneficial for drugs with chronopharmacological behavior, where nocturnal dosing is required, and for drugs that show the first-pass effect. This review covers methods and marketed technologies that have been developed to achieve pulsatile delivery. Marketed technologies, such as Pulsincap™, Diffucaps®, CODAS®, OROS® and PULSYS™, follow the above mechanism to render a sigmoidal drug release profile. Diseases wherein PDDS are promising include asthma, peptic ulcers, cardiovascular ailments, arthritis and attention deficit syndrome in children and hypercholesterolemia. Pulsatile drug delivery systems have the potential to bring new developments in the therapy of many diseases.

KEYWORDS: capsular system, pulsatile drug delivery system, pulse, rupturable coating.

INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery system for the more obvious advantage of the oral routes of the administration. Such systems release the drug with constant or variable release rates. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance 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. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. The release of the drug as a pulse after a lag time (an interval of no drug release) has to be designed in such a way that a complete and rapid drug release follows the lag time. In chronopharmacotherapy (timed drug therapy) drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. By basing drug delivery on circadian patterns of Diseases, drug effect can be optimized and side effects can be reduced. If symptoms occur at daytime a conventional dosage form can be administered just prior the symptoms are worsening. If symptoms of a disease became worse during the night or in the early morning the timing of drug administration and nature of the drug delivery system need careful consideration. Pulsatile release is also useful for the targeting of the drug irritating the stomach or degradable therein, as well for drugs developing biological tolerance or with an extensive first-pass metabolism.[1]

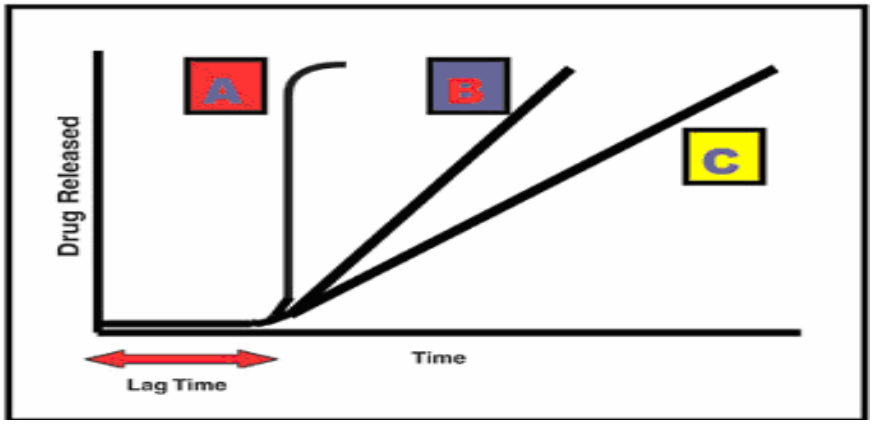

Figure 1: Drug release profile of pulsatile drug delivery system.[1,2]

A: Ideal sigmoidal release

B & C: Delayed release after initial lag time

The first pulsed delivery formulation that released the active substance at a precisely defined time point was developed in the early 1990s. In this context, the aim of the research was to achieve a so-called sigmoidal release pattern (pattern A in Figure). The characteristic feature of the formulation was a defined lag time followed by a drug pulse with the enclosed active quantity being released at once. Thus, the major challenge in the development of pulsatile

drug delivery system is to achieve a rapid drug release after the lag time. Often, the drug is released over an extended period of time (patterns B & C in Figure). This following reviews the various pulsatile drug delivery systems that are reported.

1.1 Necessity of Pulsatile Drug Delivery Systems

There are many conditions and diseases where sustained release formulations do not show good efficacy. In such cases Pulsatile Drug Delivery System is applicable.

- **First pass metabolism**

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

- **Biological tolerance**

Drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitroglycerin, salbutamol sulphate.

- **Special chronopharmacological needs**

Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24 hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours.

- **Local therapeutic need**

For the treatment of local disorders such as inflammatory bowel disease, inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

- **Gastric irritation or drug instability in gastric fluid**:

Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (e.g: peptide drugs), irritate the gastric mucosa (Non-Steroidal Anti Inflammatory Drugs) or induce nausea and vomiting.

1.2 Advantages of Pulsatile Delivery

- Reduced side effects

- Extended daytime or night time activity.
- Dosage frequency.
- Reduction in dose size.
- Improved patient compliance.
- Lower daily cost to patient due to fever dosage units are required by the patient in therapy.
- Drug adapts to suit circadian rhythms of body functions or diseases.
- Drug targeting to specific sites colon.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism.

1.3 Drawbacks of Pulsatile Delivery

- Lack of manufacturing reproducibility and efficacy.
- Large number of process variables.
- Multiple formulation steps.
- Higher cost of production.
- Need of advanced technology.

Table 1: Diseases required pulsatile delivery.[10]

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
Pain in the morning and more pain at night	NSAIDs, Glucocorticoids	Arthritis
Increase in the blood sugar level after meal	Sulfonylurea, Insulin	Diabetes mellitus
Cholesterol synthesis is generally higher during night than day time	HMG CoA reductase inhibitors	Hypercholesterolemia

Chronopharmacotherapy

Recent studies show that diseased have predictable cyclic rhythms and the timing of medication regimens can improve outcome in selected chronic conditions. "Chronopharmaceutics" consist of two words chronobiology and Pharmaceutics.[2] Chronobiology is the study of biological rhythms and their mechanisms. There are three types of mechanical rhythms in our body, they are:

- Ultradian
- Infradian
- Circadian

1. Ultradian Rhythms

Oscillations of shorter duration are termed Ultradian Rhythms (more than one cycle per 24 hours). E.g.90 minutes sleep cycle.[4]

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 that occur with a periodicity of about 24 Hours. 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.[4]

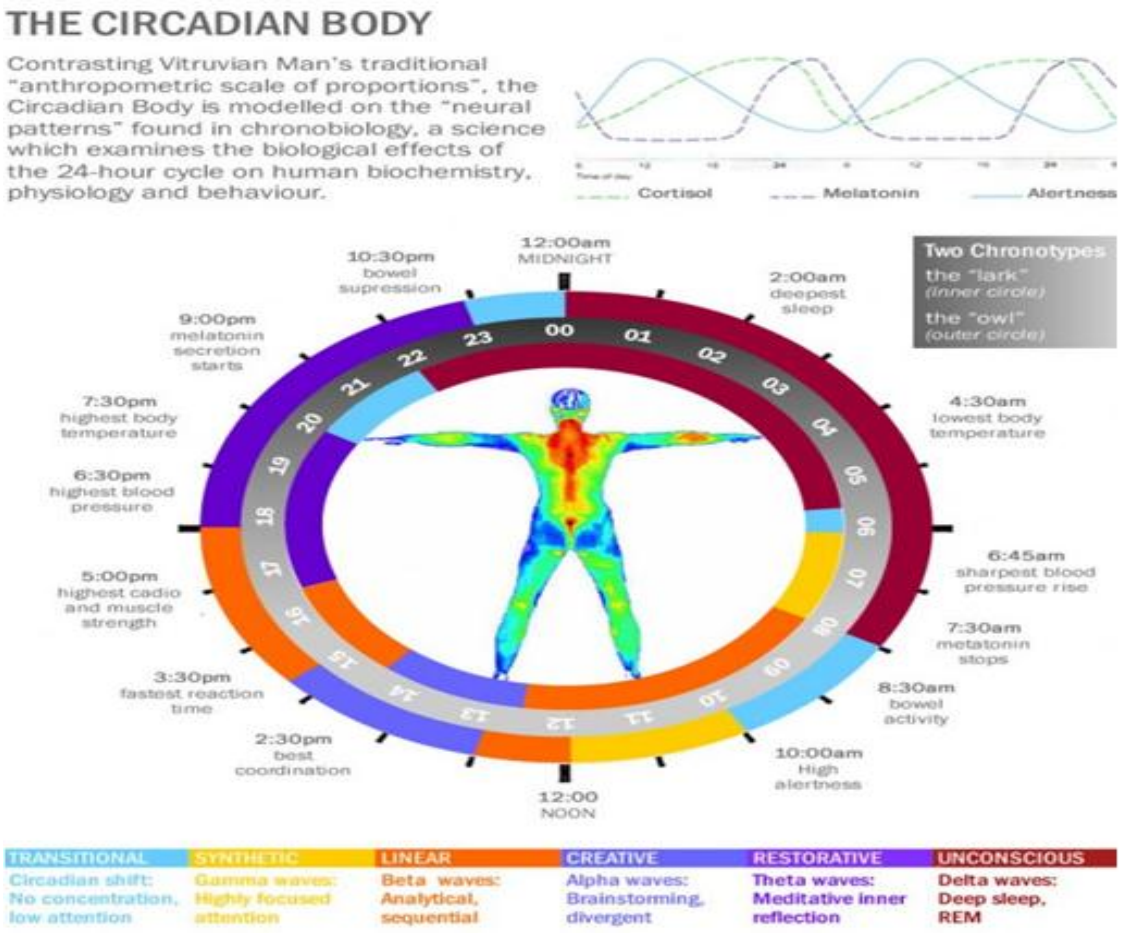

Figure 2: Diseases displaying circadian rhythm.[5]

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.[5]

Table 2: Disease Influenced by Chronotherapy.[5]

Disease	Influenced By Chronotherapy
Cardiovascular	Hypertension, angina, myocardial infarction
Inflammatory	Rheumatoid arthritis, related disorders
Neoplastic	Various forms of cancer
gastrointestinal	Peptic ulcer disease
Respiratory	Allergic rhinitis, asthma

Pulsatile system - To increase therapeutic efficacy of drug

In recent years considerable attention has been focused on the development of pulsatile drug delivery system. Delivery system with pulsatile release pattern has gained most popular form of controlled drug delivery system because conventional systems with a continuous release are not ideal. Oral controlled drug delivery systems are generally used due to convenient dosage form & it also releases drug in constant or variable rates. In these system drug release generally occurs within therapeutic window for prolong period of time. Hence these systems show sustained release of drug from dosage form.[6]

1.4 Classification of Pulsatile Drug Delivery systems

Various approaches of pulsatile drug

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

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. Multi particulate / Multiple unit systems:

1. Pulsatile system with rupturable coating

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

2. Osmotic based rupturable coating system

E.g. Permeability controlled system

3. Pulsatile delivery by change in membrane permeability.

E.g: Sigmoidal release system.

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.[7]

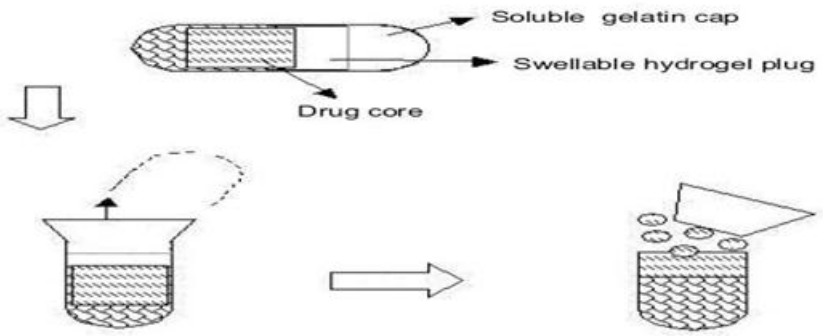

Figure 3: Design of Pulsincap system.

The lag time can be controlled by manipulating the dimension and the position of the plug.[8,9]

Polymers used for designing of the hydrogel plug

1) Insoluble but permeable and swellable polymers.

(e.g:polymethacrylates)

2) Erodible compressed polymers

(e.g., hydroxypropylmethylcellulose, polyvinyl alcohol, Polyethylene oxide).

3) Congealed melted polymers.

(e.g., saturated polyglycolated glycerides, glycerylmonooleate)

4) Enzymatically controlled erodible polymer (e.g., pectin).

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.[10]

2. Capsular system based on Osmosis

a. 'PORT' System

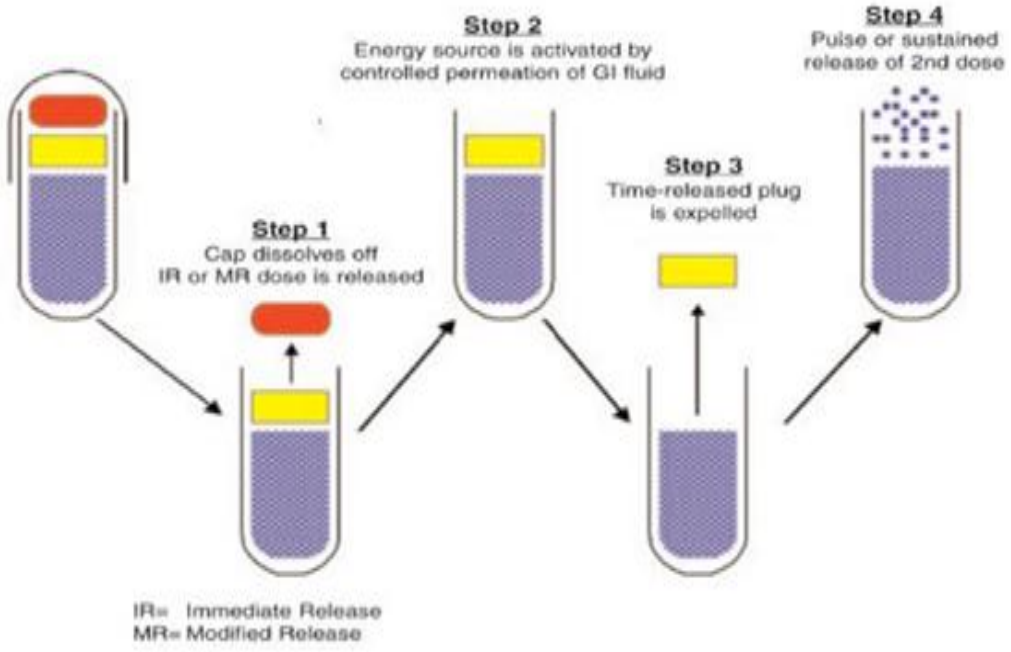

Figure 4: Drug release mechanism from PORT system.

The Port system fig. 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. 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[11]

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.

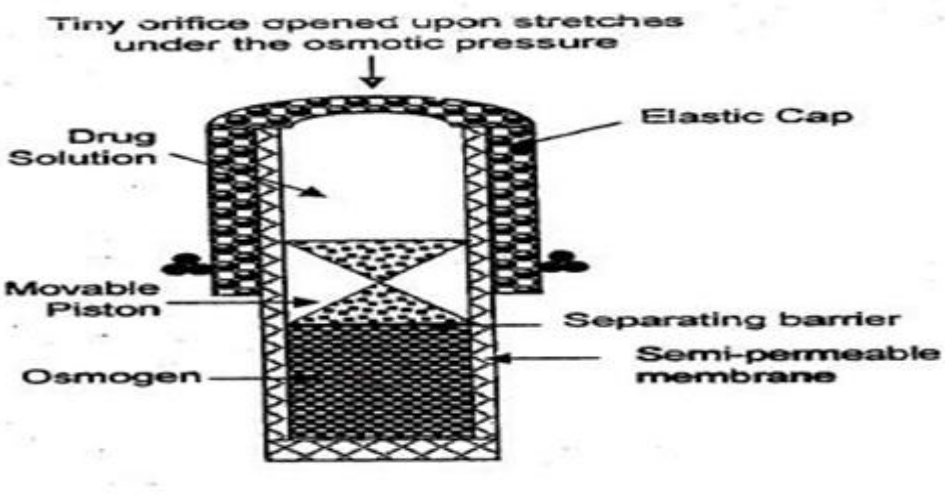

Figure 5: System based on expandable orifice.

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.

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.[12]

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.[13,14] The composition contains the drug (salbutamol sulphate) and a modulating agent (sodium chloride). The amount of Sodium Chloride (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 solutionof Sodium Chloride (NaCl), while Sodium Chloride (NaCl) has solubility of 321mg/ml in water, and its saturation solubility is 320 mg/ml.

2. 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

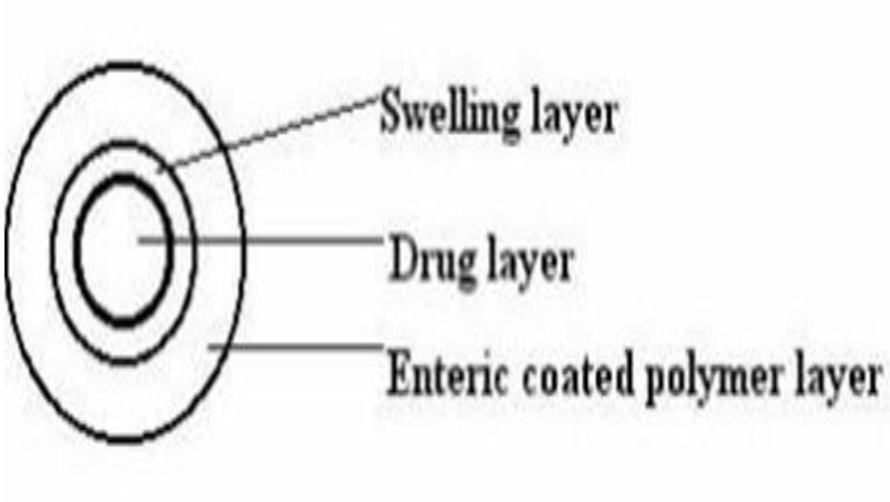

Figure 6: The chronotropic system.

The Chronotropic® system consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethylcellulose (HPMC), which is responsible for a lag phase in the onset of release.[15,16] 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 hydroxypropylmethylcellulose

(HPMC). Both in-vitro and in-vivo lag times correlate well with the applied amount of the hydrophilic retardin polymer. The system is suitable for both tablets and capsules.

b. 'TIME CLOCK' System

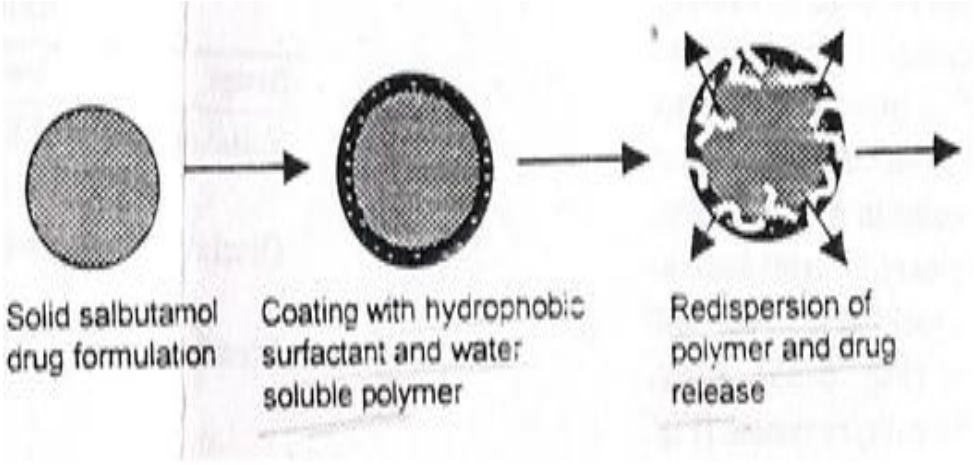

Figure 7: 'TIME CLOCK' System.

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. 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.[17]

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. These systems can involve direct compression of both the core and the coat
3. Materials Such as hydrophobic, hydrophilic can be used in press-coated pulsatile drug delivery system.
4. Press-coated pulsatile drug delivery systems involve compression which is easy on laboratory scale.
5. Press-coated pulsatile formulations release drug after "lag-time".
6. Press-coated pulsatile drug delivery formulations can be used to separate incompatible drugs from each other or to achieve sustained release.

d. Multilayered Tablets

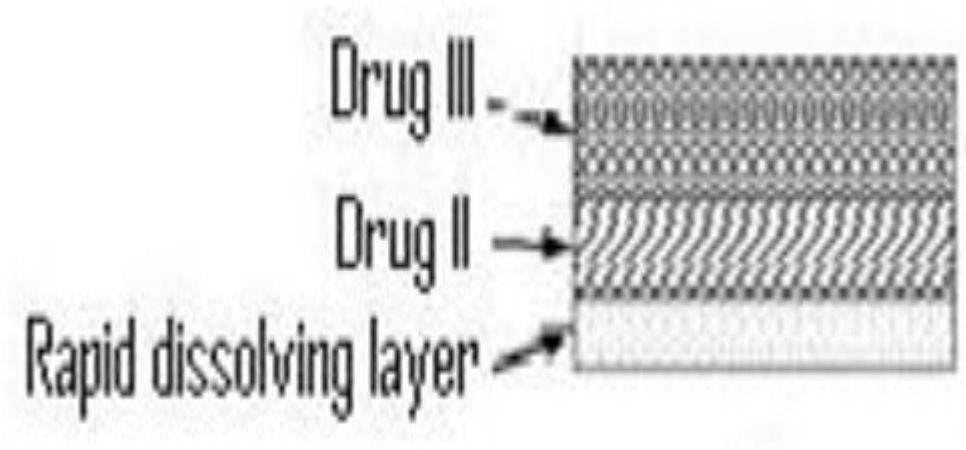

Figure 8: Multilayered Tablet.

A release pattern with two pulses was obtained from a threelayered tablet containing two drug containing layers separated by a drug-free gellable polymeric barrier layer.[18-20]

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. The release may depend on the mechanicalproperties of the coating layer.[21]

a) Pulsatile system based on rupturable coating

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

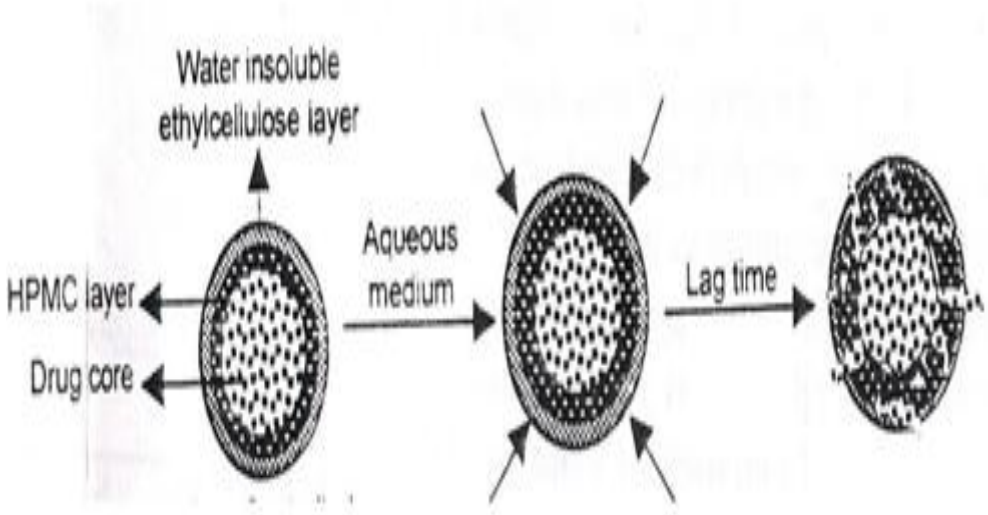

Figure 9: Time –controlled Explosion system (TCES).

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. 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.

b) 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 coating.

c) 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. 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.[22]

Advantages of multiparticulate systems over single unit systems

- Reproducible gastric residence time.
- No risk of dose dumping.
- Short gastric residence time.
- Flexible to blend pellets withdifferent composition or releasepattern.
- Lowest transit time variability.
- Unique profiles.
- Amenable to capsule & tablets.
- Capable of pulsatile release.

Disadvantages

- Low drug load.
- Incomplete release.
- High cost of production.
- Need of advanced technologies.
- Multiple manufacturing steps.

Stimuli-induced pulsatile release

1. Temperature-induced pulsatile release

Thermoresponsive hydrogels have been investigated as possible drug delivery carriers for stimuli responsive drug delivery systems.[23,25] PIPAAm cross-linked gels have shown thermoresponsive, discontinuous swelling/deswelling phases: swelling, for example, at temperatures below 328C, whileshrinking above this temperature. Thermoresponsive polymeric micelle systems As Kataoka et al.[26] comprehensively reviewed, the properties and biological interests of polymeric micelles make them a most noteworthy candidate as drug carrier for the treatment of cancer. The polymeric micelle is composed of amphiphilic block copolymers exhibiting a hydrophobic core with a hydrophilic corona. The application of a temperature gradient induced an on–off drug release regulation from PIPAAm PBMA micelles between 4 and 378C.

2. Chemical stimuli-induced pulsatile release

a) Glucose-responsive insulin release devices

Adecrease in or the absence of insulin secretion from pancreatic islets is the cause of diabetes mellitus. Diabetes mellitus patients suffer long term from a gradual decline in the efficiency of various organs, such as the occasional loss of eyesight. Several systems have already beendeveloped which are able to respond to glucose concentration changes. Glucose oxidase (GOD) catalyzes glucose oxidation. Utilizing this reaction, Ishihara et al. prepared two types of gel membrane systems to regulate insulin permeability. They prepared and nicotinamide-immobilized gel membranes, separately.

b) Drug release from intelligent gels responding to antibody concentration

There are numerous kinds of bioactive compounds which exist in the body. Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/deswelling characteristics. Miyata and co-workers focused on the introduction of stimuli-responsive cross-linking structures into hydrogels. Special attention was given to antigen antibody complex formation as the cross-linking units in the gel, because specific antigen recognition of an antibody can provide the basis for a new device fabrication.[27]

c) Electric stimuli-responsive pulsatile release

Thecombination of developments in several technologies, such as microelectronics and micromachineing, as well as the potential need for chronotherapy, have currently assisted the development of electronically assisted drug delivery technologies. These technologies include iontophoresis, infusion pumps, and sonophoresis. Several approaches have also been presented in the literature describing the preparation of electric stimuli-responsive drug delivery systems using hydrogels. Kishi et al.[28] developed an electric stimuli induced drug release system using the electrically stimulated swelling/deswelling characteristics of polyelectrolyte hydrogels. They utilized a chemomechanical system, which contained a drug model within the polyelectrolyte gel structure. Thus, drug molecules within the polyelectrolyte gels might be squeezed out from the electric stimuli-induced gel contraction along with the solvent flow. To realize this mechanism, poly (sodium acrylate) microparticulate gels containing pilocarpine as a model drug were prepared.

1.5 Advanced technology

Currently pharmaceutical company focused on developing and commercializing pulsatile drug products that fulfil unmet medical needs in the treatment of various diseases. For several diseases (e.g. bronchial asthma, hypertension, rheumatic disease and myocardial infarction) as well for control of body functions (blood pressure, levels of many hormones e.g. aldosterone, rennin, and Cortisol) influenced by circadian rhythms, delayed or pulsatile drug release could be an optimal approach. Recently develop various technologies are ACCU-BREAK™, AQUALON, CODAS®, PRODAS®, SODAS®, MINITABS®, DIFFUCAPS®, OROS® etc.

Table 3: Marketed technologies of pulsatile drug delivery.[29-33]

Technology	Mechanism	Proprietary name and dosage form	API	Disease
OROS*	Osmotic mechanism	Covera-H5*; XL tablet	Verapamil HCL	Hypertension
3 Dimensional Printing	Externally regulated system	Their Form*	Diclofenac sodium	Inflammation
DIFFUCAPS*	Multiparticulate system	Innopran*; XL tablets	Verapamil HCL, propranol HCL	Hypertension
PulsincapTM	Rupturable system	Pulsincap TM	Dofetilide	Hypertension

Diseases that require pulsatile drug delivery

Disease	Chronological behavior	Drugs used
Peptic ulcer	Acid secretion is high at afternoon and at night	H_2 Blockers
cancer	The blood flow to tumour is 3-fold greater during each dialy activity phase of the circadian cycle than during the dialy rest phase	Vinca alakaloids, Taxanes
Duodenal ulcer	Gastric acid secretion is highest at night while gastric and small bowel motility and gastric emptying are all slower at night	Proton pump inhibitors
Neurological disorders	The central pathway of epilepsy and the behavioural classification of convulsive events	MAO-B inhibitors
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than in day time	HMG Co A reductase inhibitors
Diabetes mellitus	Increase the blood sugar level after meal	Sulfonyl urea, Insulin
Arthritis	Level of pain increases at night	NSAIDs, Glucocorticoids
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning.	Nitroglycerin, calcium channel blockers, ACE inhibitors, Anti arrhythmic agents.
Asthma	Precipitation of attacks during night or at early morning	B_2 agonist, Anti histamines
Attention deficit syndrome	Increase in DOPA level in afternoon	Methylphenidate

REFERENCES

1. Gothoskar*et al.* 2004 & Shivakumar*et al.* 2003 & Nagar *et al.* 2010 & Tangri *et al.* 2011.
2. Shivakumar HG, Pramodkumar TM, Kashppa GD. Pulsatile drug deliverysystem, Indian J Pham Educ, 2003; 37(3): 125.
3. Ramesh D. Parmar, Rajesh K. Parikh, G. Vidyasagar, Dhaval V. Patel, Chirag J. Patel, Biraju D. Patel. Pulsatile Drug Delivery Systems: An Overview. Int J PharmaSci and Nanotechnology, 2009; 2(3): 605-614.
4. Botti B, Youan C: Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery, Jorn. Control. Rel, 2004; 98(3): 337-353.
5. http://thred.org/wp-content/uploads/2010/06/circadian-body-e128300967472... assessed on 1-2-2011.
6. Tangri *et al.* 2011 & Gennaro 2000 & Bussemer *et al.* 2001 & Das *et al.* 2003).
7. Neill MC, Rashid A, Stevens HN, GB Patent No. GB 2230442, 1993.
8. Sarasija S, Hota A, Colon-specific drug delivery systems, Ind. J. Pharm. Sci., 2002; 62(1): 1-8.
9. Kinget R, Kalala W, Vervoort L, Mooter GV, Colonic drug targeting, J. Drug Targeting, 1998; 6(2): 129-149.
10. Wu F, Zhang ZR, He WL, Zhang Y, Preparation and in vitro release of tetramethylpyrazine phosphate pulsincap capsule controlled by an erodible plug. Yao XueXueBao, 2002; 37(9): 733-738.
11. Pollock DC, Dong L, Wong P, A new system to deliver a delayed bolus of liquid drug formulation, Proceed Intern Symp, Control. Rel. Bioact. Mater, 2001; 28: 6033.
12. Balaban SM, Pike JB, Smith JP, Baile CA, Osmotically Driven Delivery Devices with Pulsatile Effect, US Patent No, 1993; 5209746.
13. Magruder PR, Barclay B, Wong PS, Theeuwes F, Composition Comprising Salbutamol, US Patent No. 4751071, 1988.
14. Magruder PR, Barclay B, Wong PS, Theeuwes F, Constant Release System with Pulsed Release, US Patent No. 4777049, 1988.
15. Gazzaniga A, Iamartino P, Maffione G, Sangalli ME, Oral delayed- release system for colonic specific delivery, Int. J. Pharm., 1994; 2(108): 77-83.
16. Gazzaniga A, Sangalli ME, Giordano F. Oral chronotopic drug delivery systems: achievement of time and/or site specifity, Eur. J. Biopharm., 1994; 40(4): 246-250.
17. Patel G: Specialized chronotherapeutic drug delivery systems, Pharmainfo.net.

18. Conte U, Colombo P, Manna A, Gazzaniga A: A new ibuprofen pulsed release oral dosage form. Drug Dev. Ind. Pharm., 1989; 15(14-16): 2583-2596.
19. Conte U, Manna A, Colombo P: Tablet for Pharmaceutical Use Able to Release Active Substances at Successive Times, US Patent No. 1989; 4: 865,849.
20. Conte U, Giunchedi P, Maggi L, Sangalli ME, Gazzaniga A, Colombo P, Manna A, Ibuprofen delayed release dosage forms: a proposal for the preparation of an in vitro/in vivo pulsatile system, Eur. J. Pharm., 1992; 38(6): 209-212.
21. Krögel I, Bodmeier R: Floating or pulsatile drug delivery systems based on coated effervescent cores. Int. J. Pharm., 1999; 187: 175-184.
22. Beckert TE, Pogarell K, Hack I, Petereit HU: Pulsed drug release with film coatings of Eudragit & Mac226; RS 30D, Proceed Int'l Symp Control. Rel. Bioact. Mater, 1999; 26: 533- 534.
23. T. Okano, N. Yui, M. Yokoyama, R. Yoshida: Advances in Polymeric Systems for Drug Delivery, Gordon and Breach, Yverdon, Switzerland, 1994.
24. Y.H. Bae, T. Okano, S.W. Kim: 'On–off' thermocontrol of solute transport. I. Temperature dependence of swelling of N-isopropylacrylamide networks modified with hydrophobic components in water, Pharm. Res., 1991; 8(4): 531–537.
25. Y.H. Bae, T. Okano, S.W. Kim: 'On–off' thermocontrol of solute transport. II. Solute release from thermosensitive hydrogels. Pharm. Res, 1991; 8(5): 624–628.
26. N. Yui, T. Okano, Y. Sakurai, Inflammation responsive degradation of crosslinked hyaluronic acid gels. J. Control. Release, 1992; 22: 105–116.
27. N. Yui, J. Nihira, T. Okano, and Y. Sakurai: Regulated release of drug microspheres from inflammation responsive degradable matrices of crosslinked hyaluronic acid. J. Control. Release, 1993; 25: 133–143.
28. R. Kishi, M. Hara, K. Sawahata, Y. Osada. Conversion of chemical into mechanical energy by synthetic polymer gels (chemomechanical system), in: D. DeRossi, K. Kajiwara, Y. Osada, A. Yamauchi (Eds.), Polymer Gels — Fundamentals and Biomedical Applications, Plenum Press, New York, 1991; 205–220.
29. Lemmer: Circadian rhythms and drug delivery. Jou. Control. Rel, 1991; 16: 63-74.
30. Jao F, Wong P, Huynh H, et al, 1992: 17.
31. Percel P, Vishnupad K and Venkatesh G, 2002; 13.
32. Katstra WE, Palazzolo RD, Rowe CW, et al. J. Control. Rel, 2000; 66: 1-9.
33. Stevens HNE, Wilson CG, Welling PG, et al. Int. J. pharm, 2002; 236: 27-34.