A REVIEW ON PULSATILE DRUG DELIVERY SYSTEM

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***Abstract*: Pulsatile drug delivery systems are developed to deliver drug according to circadian behavior of diseases. The product follow a sigmoidal drug release profile characterized by a time period of no release (lag time) followed by a rapid and complete drug release. Thus drug can be delivered at right time, in right amount and at right site of action by use of such approach. A pulse must be planned so that a complete and rapid medication release is accomplished after the lag time. Pulsatile drug delivery system (PDDS) delivers the drug at specific time as per the patho-physiological need of the disease, resulting in improved therapeutic efficacy and patient compliance. Diseases wherein PDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children, and hypercholesterolemia. Various technologies such as time-controlled, pulsed, triggered and programmed drug delivery devices have been developed and extensively studied in recent years for chronopharmaceutical drug delivery. These systems are beneficial for diseases showing chronopharmacological behavior where night time dosing is required or for the drugs having high first pass effect or having site specific absorption in GIT, or for drugs with high risk of toxicity or tolerance. These systems also improve patient compliance by decreasing dosing frequency.**

***Keywords*: Pulsatile Drug Delivery System, chronopharmacotherapy Time-controlled Drug Delivery System, Circadian rhythm, Lag time.**

INTRODUCTION:

Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound within the body as required to safely achieve its desired therapeutic effect [1] . Drug delivery is of two types:

1. **Conventional**
   - Oral/Enteral
   - Rectal
   - Buccal
   - Parenteral
2. **Modified**
   - Sustained Drug Delivery
   - Delayed Release
   - Site specific targeting
   - Extended Release
   - Pulsatile [1]

PULSATILE DRUG DELIVERY SYSTEM

Pulsatile drug delivery is defined as the rapid and transient release of certain amount of active molecules within a short time period immediately after a predetermined off released period, i.e., lag time, or 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. Such a release pattern is known as pulsatile release [2]. 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 that 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 characterised by a time period. These systems are beneficial for drugs with chronopharmacological behavior, where nocturnal dosing is needed, and for drugs that show the first-pass effect [2].

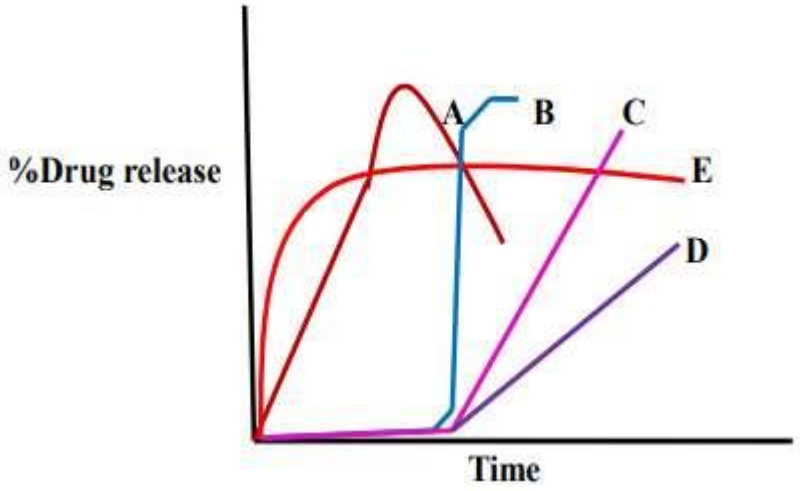


Fig.1: Drug release profiles from pulsatile drug delivery system.

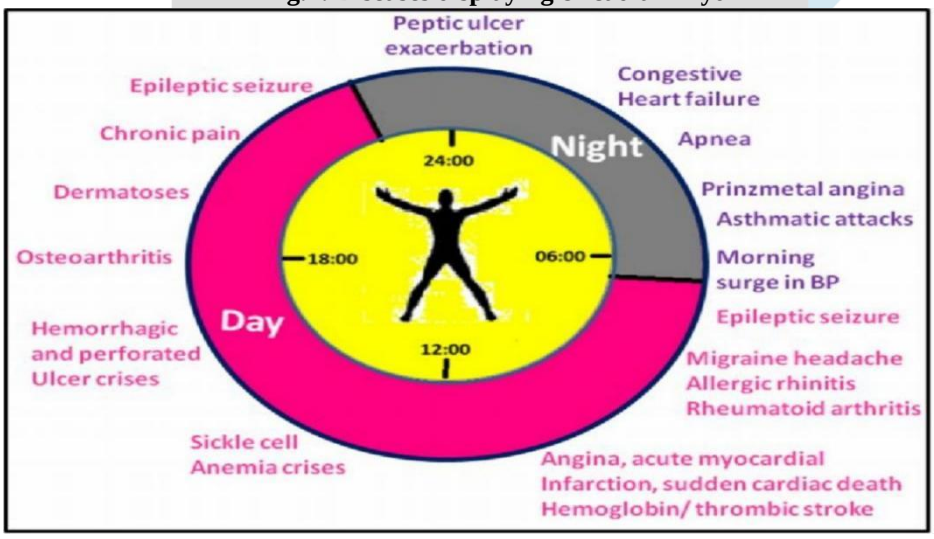
Where, **A:** Conventional release profile, **B:** Burst release of drug as a after a lag time, **C:** Delayed release profile after a lag time, **D:** Constant release profile in prolonged period after a lag time, **E:** Extended release profile without lag time.

Pharmaceuticals that show tolerance need that the drugs are not given at a constant rate, since the pharmacological impact diminishes with time at a constant drug concentration. The toxicity of the medication rises with time. The use of a dosage form that will only deliver the appropriate concentration of the medication at a certain time point is desirable in these situations. As a result, the concept of chronopharmaceutics has developed, which is study dedicated to the design and assessment of drug delivery systems that release a therapeutic agent at a rhythm that is optimally aligned with the biological need of a particular disease treatment regimen. The term "chronopharmaceutics" is made up of the terms chronobiology and pharmaceutics combined. Chronobiology is the study of biological rhythms and is a branch of biology. The mechanical rhythms that run through our bodies are classified into three categories.

Biological rhythm

A biological rhythm is a self-sustaining process inside the human body. It is defined as the process that occurs periodically in an organism in conjugation with and often in response to periodic changes in environmental condition. Our bodies' rhythm, also known as our biological clock, and the rhythm of the solar system that change night to day and lead one season into another. Our internal clocks are also dictated by our genetic makeup. [5]

Fig.2: Diseases displaying circadian rhythm



There are 4 types of rhythms in our body:

1. **Circadian:** This term is derived from the Latin words "circa" which means around, and "dies" which means day. Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 Hours and regulate many body functions like-metabolism, sleep pattern, hormone production etc. Several physiological processes in humans vary in a rhythmic manner, in synchrony with the internal biological clock [12] .
2. **Ultradian:** oscillation is a kind of oscillation with a shorter duration (more than one cycle per 24 h) E.g.90 minutes sleep cycle.

3. **Infradian:** Oscillations that last for more than 24 hours are considered to be periodic (less than one cycle per day). E.g. Monthly Menstruation
4. **Seasonal:** Seasonal affective disorder (SAD), which causes depression in susceptible people during the short days of winter.

NECESSITY OF PULSATILE DRUG DELIVERY SYSTEMS

There are many conditions and diseases where sustained release formulations don't show good efficiency. In such cases Pulsatile Drug Delivery System is applicable.

1. **First pass metabolism:** Some drugs, like beta blockers, and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturatemetabolizing enzymes in order to minimize pre-systemic metabolism. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability.
2. **Biological tolerance:** Continuous release drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitroglycerin.
3. **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.
4. **Local therapeutic need:** For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss.
5. **Gastric irritation or drug instability in gastric fluid:** For compounds with gastric irritation or chemical instability in gastric fluid, the use of a sustained release preparation may exacerbate gastric irritation and chemical instability in gastric fluid.
6. **Drug absorption differences in various gastro-intestinal segments:** In general, drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine. Compensation for changing absorption characteristics in the gastrointestinal tract may be important for some drugs.

Table 1: Circadian rhythm and the manifestation of clinical disease:

Disease	Chronological behavior	Drug used
Peptic ulcer disease	Acid secretion high in afternoon and at night	H2 blockers [4]
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 [6]
Asthma	Exacerbation more common during the sleep period & attacks after midnight or at early morning hours	β2 agonist, Antihistamines
Allergic rhinitis	Worse in the morning/upon rising	Antihistamines
Hormone secretion	Growth hormone and melatonin produced at night testosterone and cortisol in morning hr	Corticosteroids
Cancer	The blood flow to tumors is 3-fold greater during each daily activity phase of the circadian cycle than during the daily rest phase.	Vinca alkaloids, Taxanes [5]
Cardiovascular diseases	BP is at its most minimal during the sleep cycle and rises steeply during the early morning	Nitroglycerin, calcium channel blocker, ACE inhibitors [10]
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than day time.	HMG CoA reductase Inhibitors [8]
Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin [9]

MERITS:

1. Gastric residency time that is predictable, repeatable, and brief There is less diversity between and among individuals.
2. Increase the bioavailability of the drug
3. There is a low risk of local irritation.
4. Increased design flexibility leads to increased stability.
5. Improved Patient comfort and compliance
6. Reduced adverse effects.
7. Improved tolerability.
8. No risk of dose dumping and reduce dosage frequency.
9. Flexibility in design Achieve a unique release pattern
10. Extended daytime or nighttime activity
11. Drug targeting to specific site.
12. Drug loss is prevented by extensive first pass metabolism.
13. Less inter- and intra-subject variability.

DEMERITS:

1. Inadequate manufacturing repeatability and effectiveness A large number of process variables are involved.
2. Production costs are increasing.

3. Lack of manufacturing reproducibility and efficacy
4. Large number of process variables
5. Multiple formulation steps
6. Need of advanced technology
7. Trained/skilled personal needed for manufacturing

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEM

Various approaches of pulsatile drug:

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

1. Time controlled pulsatile drug delivery
2. Stimuli induced pulsatile drug delivery
3. Externally regulated pulsatile drug delivery

1. 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: s
   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.

I. Time controlled pulsatile drug delivery

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, that gets pushed away by swelling or erosion, and therefore the drug is released as a "Pulse" from the insoluble capsule body. [13] The lag time can be controlled by manipulating the dimension and therefore the position of the plug. [14,15]

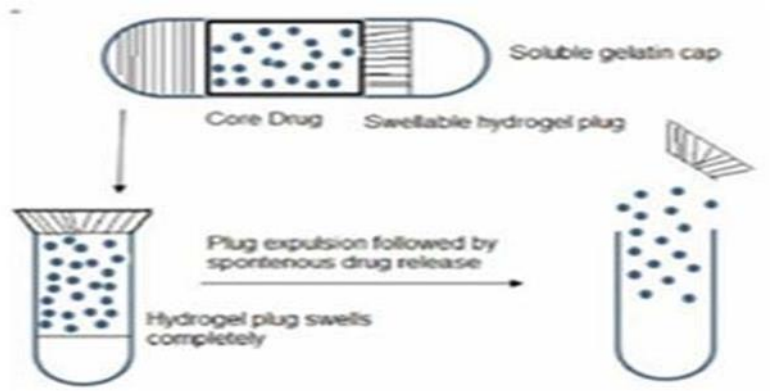


Fig.3: Design of Pulsincap system

Polymers used for designing of the hydrogel plug are as follows:

- Insoluble but permeable and swellable polymers (e.g., polymethacrylates)
- Erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, Polyethylene oxide)
- Congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate)
- Enzymatically controlled erodible polymer (e.g., pectin) The lag time can be controlled by manipulating the dimension and the position of the plug [16] .

2. Capsular system based on Osmosis

a. 'PORT' System [17]

The Port system 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 comprising of osmotically active agent and the drug formulation. [31] When this capsule interacted 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 utilized 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.

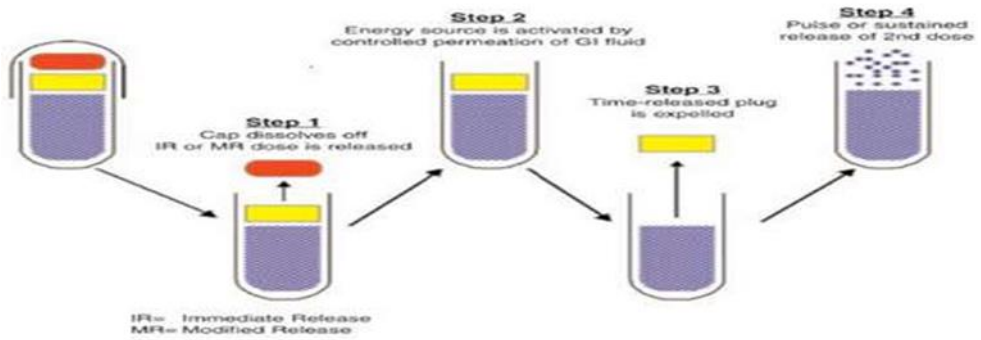


Figure. No. 04: Drug release mechanism from PORT system

b. System based on expandable orifice: To deliver the drug in liquid form, an osmotically driven capsular system was developed within which the liquid drug is absorbed into extremely porous particles, that release the drug through an orifice of a semipermeable capsule upheld by an expanding osmotic layer once the barrier layer is dissolved. [18]

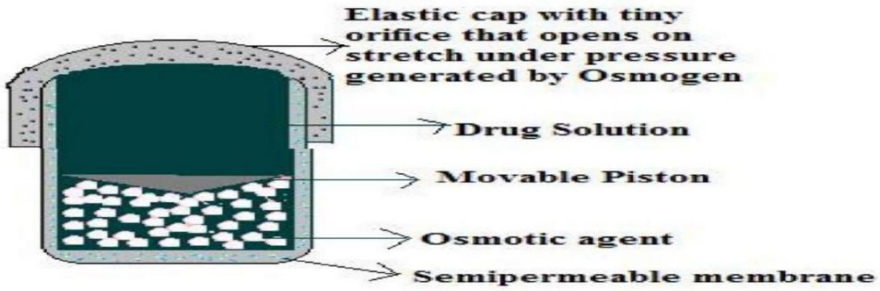


Figure. No. 05: System based on expandable orifice

The orifice is small enough in order that once the elastic wall relaxes, the flow of the drug through the orifice basically stops, however once the elastic wall is distended beyond threshold value, the orifice expands sufficiently to permit drug release at a required rate. E.g. Elastomers, such as styrenebutadiene copolymer are recommended. [19,20]

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 on the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession because the osmotic pressure rises above a threshold level. [21]

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. [22-24] The compositions contains the drug (salbutamol sulfate) 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, whereas NaCl has solubility of 321 mg/ml in water, and its saturation solubility is 320 mg/ml.

3. Pulsatile system with Erodible or soluble barrier coatings: Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released quickly from reservoir core. The lag time depends on the thickness of the coating layer.

a. The chronotropic system: The Chronotropic® system consists of a drugcontaining core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), that is responsible for a lag phase in the onset of release.[25- 27] Additionally, through the application of an outer gastricresistant 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.[28]

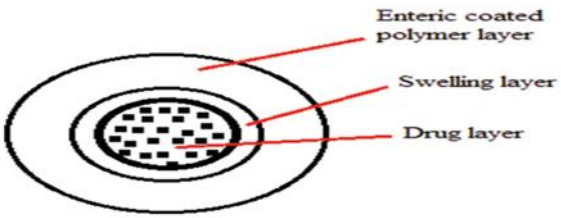


Fig. 6: The chronotropic system

The lag time is controlled by the thickness and the viscosity grades of HPMC.[29] 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.[30]

b. 'TIME CLOCK' System: [22-27]

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.[29-30]

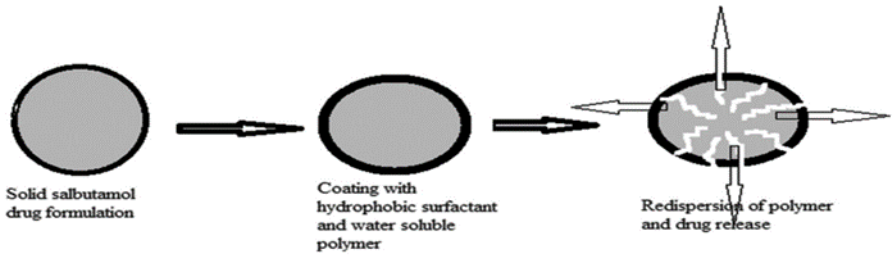


Fig.7: 'TIME CLOCK' System

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. [21] 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. [21]

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.

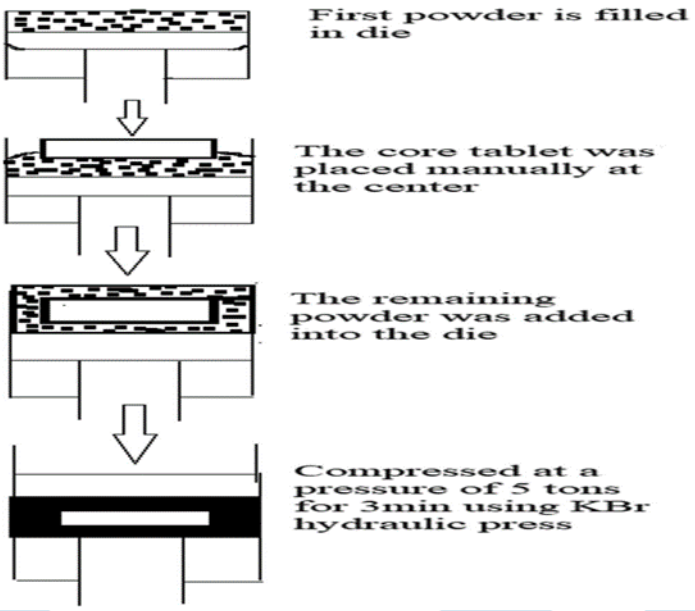


Figure. No. 08: press-coating technique

d. Multilayered Tablets: A delivery design with two pulses was gotten from a three-layered tablet containing two medication-containing layers separated by a medication-free gellable polymeric hindrance layer. [31] This three-layered tablet is coated on three sides with impermeable ethyl cellulose, and the top portion was left uncoated. Upon contact with dissolution medium, the initial dose incorporated into the top layer was released rapidly from the non coated surface. The second pulse is obtained from the bottom layer after HPMC layer gets eroded and dissolved. The rate of gelling or dissolution of the barrier layer control the appearance of the second pulse. The gelling polymers reported include cellulose derivatives like HPMC, methyl cellulose, or polyvinyl alcohols of various molecular weights and the coating materials include ethyl cellulose, cellulose-acetate propionate, methacrylic polymers, acrylic and mehtacrylic co-polymers, and polyalcohols.

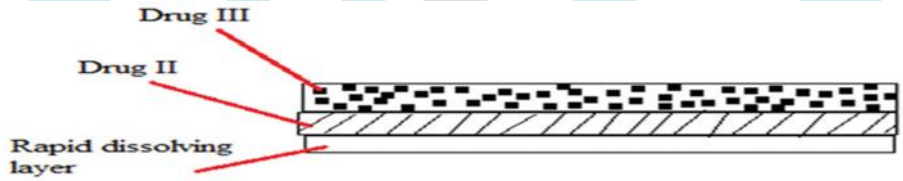


Figure. No. 09: Multilayered Tablet

4. **Pulsatile system with a rupturable coating**

This system depends on the disintegration of the coating for the release of the medication. The pressing factor essential for the rupture of the coating can be accomplished by the effervescent excipients, swelling agent, or osmotic pressing factor. An effervescent combination of citrus acid and sodium bicarbonate was fused in a tablet core coated with ethyl cellulose. The carbon dioxide created after penetration of water into the core resulted in a pulsatile release of medication after the rupture of the coating. The delivery may rely on the mechanical properties of the coating layer [32].

B. Multiparticulate / Multiple unit systems:

a) Pulsatile system based on rupturable coating: [25-28]

E.g. 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. [50-52] 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.

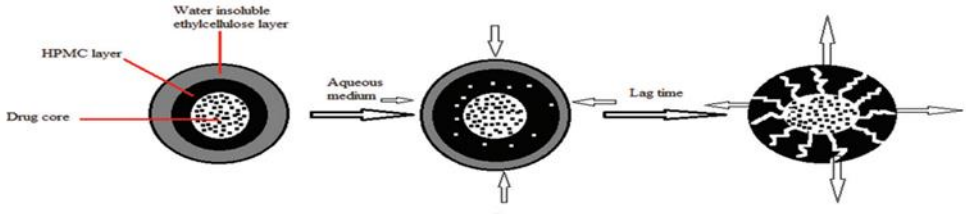


Figure. No. 10: Time –controlled Explosion system (TCES)

b. Osmotic based rupturable coating system:
This system depends on a combination of osmotic and swelling effects. The core containing the medication, a low mass density solid or potentially fluid lipid material (e.g., mineral oil), and a disintegrant were readied. This core was then covered with cellulose acetic acid derivation. Upon immersion in an aqueous medium, water penetrates the core displacing lipid material. After the exhaustion of lipid material, the inside pressure increments until basic pressure is reached, which brings about a break of coating [34].

c. Pulsatile delivery by a change in membrane permeability:
The permeability and water take-up of acrylic polymers with quaternary ammonium gatherings can be affected by the presence of various counter-particles in the medium. A few conveyance frameworks dependent on this particle trade have been created. Eudragit RS 30D is accounted for to be a polymer of decision for this reason. It commonly contains an emphatically spellbound quaternary ammonium bunch in the polymer side chain, which is constantly joined by regrettable hydrochloride counter-particles. The ammonium bunch being hydrophilic works with the collaboration of the polymer with water, consequently changing its permeability and permitting water to saturate the dynamic core in a controlled way. This property is fundamental to accomplish a decisively characterized lag time [34].

II. Stimuli induced pulsatile drug delivery

1. Temperature-induced pulsatile release
2. Chemical stimuli-induced pulsatile release:
   - Glucose-responsive insulin release devices
   - Inflammation-induced pulsatile release
   - Drug release from intelligent gels responding to antibody concentration.
   - Electric stimuli-responsive pulsatile release

1. Temperature-induced pulsatile release: Thermoresponsive hydrogels are investigated as possible drug delivery carriers for stimuli responsive drug delivery systems. [32-34] Poly (Nisopropylacrylamide) (PIPAAm) cross-linked gels have shown thermoresponsive, discontinuous swelling / deswelling phases: swelling, for example, at temperatures below 328○C, while shrinking above this temperature. Thermoresponsive polymeric micelle systems as Kataoka et al. [35] comprehensively reviewed, the properties and biological interests of polymeric micelles create 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 378 °C.

2. Chemical stimuli-induced pulsatile release
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. Many systems are 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 reduces the blood glucose level and after decreasing concentration of gluconic acid system goes to deswelling mode.

b) Inflammation-induced pulsatile release:
When any physical and chemical stress such as injury, broken bones etc occurs the various inflammatory reactions takes place at injury site. At inflammatory sites phagocytic cells like macrophages and polymorphonuclear cells, play role in healing process. During inflammation hydroxy radicals (OH) are generated from 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. [54]

c) Drug release from intelligent gels responding to antibody concentration:
There are numerous kinds of bioactive compounds that exist within the body. Novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/deswelling 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. [55]

d) Electric stimuli-responsive pulsatile release:
The combination of developments in several technologies, like microelectronics and micromachining, 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 [39] . Several approaches have also been presented in the literature describing the preparation of electric stimuli-responsive drug delivery systems using hydrogels. Kishi et al. [40] developed an electric stimuli induced drug release system using the electrically stimulated swelling /deswelling characteristics of polyelectrolyte hydrogels. They used a chemomechanical system, that contained a drug model within the polyelectrolyte gel structure. These gels exhibited reversible swelling / shrinking behavior in response to on–off switching of an electric stimulus. 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.[41]

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 systems contain magnetic beads within the implant. On application of the magnetic field, drug release occurs because of magnetic beads. Saslawski et al. [42] developed different formulation for in vitro magnetically triggered delivery of insulin based on alginate spheres. In case of ultrasonically modulated systems, ultrasonic waves cause the erosion of the polymeric matrix thereby modulating drug release. Miyazaki et al [43] evaluated the effect of ultrasound (1 MHz) on the discharge rates of bovine insulin from ethylenevinyl alcohol copolymer matrices and reservoir-type drug delivery systems during which they found sharp drop in blood glucose levels after application of ultrasonic waves. Additionally irradiation with light rays the desired drug release pattern. Mathiowitzet al [44] developed photochemically controlled delivery systems prepared by interfacial polymerization of polyamide microcapsules. For this purpose, azobisisobutyronitrile (AIBN), a substance that photochemically emanates nitrogen gas, was incorporated. Because of exposure of azobisisobutyronitrile to light, causing release of nitrogen and an increase in the pressure which ruptures the capsules thereby releasing the drug.

EVALUATION TEST OF PULSATILE DRUG DELIVERY SYSTEM:

Preformulation study:[47] Different physicochemical properties of drug and drug in excipient mass are evaluated in Preformulation study.

Drug excipients interaction study: [48] The Fourier transform infrared (FTIR) technique and Differential scanning calorimetry (DSC) can be used to study the physical and chemical interactions between the drug and excipients used.

Evaluation of granule: [47] Prepared granules are evaluated for Angle of Repose, Bulk Density, Tapped Density, Carrs index (or) % Compressibility, Hausner's Ratio.

Tablet Thickness:[47] Thickness of tablet is measured using vernier caliper. Five tablets are selected randomly from individual formulations and thickness is measured using vernier caliper scale. The test is carried out in triplicate.

Uniformity of weight: Twenty tablets are taken and their weight is determined individually and collectively on a digital weighing balance. The average weight of one tablet is determined from the collective weight. Not more than two tablets deviate from the percentage given below from the average weight and none deviate by more than twice the percentage shown. [47] The Pharmacopoieal Specification of weight variation is given in following table 03:

Table 3: Weight Uniformity Criteria for tablet

S.No.	Average weight of tablets(mg)	Percentage deviation
1.	80mg or less	± 10
2.	More than 80mg but less than 250mg	± 7.5
3.	250mg or more	± 5

Hardness/ Crushing strength: Hardness or tablet crushing strength (fc the force required to break a tablet in a diametric compression) is measured using Monsanto Hardness tester. It is expressed in Kg/cm2. Tablets require certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging, and shipping. [57]

Evaluation of polymeric film (only in film coating approach):

a) Visual evaluation: Casted films are visually evaluated for Physical properties of film like could be peeled off easily from the plate or not; Appearance of the film formed like smooth-rough surface, oily-non oily, Transparent-Opaque film.

b) Tensile strength: The casted films after drying are carefully cut into film strips (length 40 mm x width 20 mm) and investigated for tensile strength. The method used for evaluating the mechanical properties is based on guideline. Tensile strength =Breaking Force (F)/ Cross sectional area (A)

c) Folding endurance: The test is carried out to check the efficiency of the plasticizer and strength of the film prepared using varying concentration of the plasticizers. The folding endurance is measured manually. A strip of film (2 x 2 cm) is cut evenly and repeatedly folded at the same place until it breaks. The number of times counted until film could be folded at the same place without breaking, this is gave the value of folding endurance. The test is carried out in triplicate.

d) Mechanical properties: Polymer films (6.5 X 6.7 cm2) are fixed in a self-designed Teflon holder [59,60] with several holes (diameter 10 mm). Films are fixed using the holder and optionally immersed into 0.1 N HCl at 37 C for 2 h (wet films). The mechanical properties of the dry and wet films are measured with a puncture test using a Texture analyzer (n = 3). A metal probe with a hemispherical end (diameter 5 mm, length 15 cm) is driven at a speed of 5 mm/min until the film ruptured force– displacement curves are recorded and following parameters are calculated:

Puncture strength = Fmax/ ACS
Where, Fmax is the maximum applied force at film break, ACS is the cross-sectional area of the edge of the film located in the path of the cylindrical hole of the film holder, with ACS = 2rd where r is the radius of the hole in the holder and d is the thickness of the film.

***In vitro* dissolution study:** The in vitro dissolution study is performed using dissolution test given in monograph or in standard literature. In general case, dissolution media are 900 ml of 0.1 M HCl for 2 h (since average gastric emptying time is 2 h) and 900 ml of phosphate buffer pH 6.8 for 3 h (average small intestinal transit time). After 5 h, the dissolution medium is replacedwith pH 7.4 phosphate buffer (900 ml) and tested for the drug release up to specific hour dissolution study. At the predetermined time intervals, specific volume of dissolution media (1, 2, 5, 10 ml etc..) arewithdrawn, filtered through a 0.45 µm membrane filter, diluted, and assayed at wavelength maxima using a UV spectrophotometer. [51]

Comparison of dissolution profiles: The similarity factor (f2) given by SUPAC guidelines for a modified release dosage form is used as a basis to compare dissolution profiles. The dissolution profiles are considered to be similar when f2 is between 50 and 100. The dissolution profiles of products are compared using f2 which is calculated from the following formula: Where, n is the dissolution time and Rt and Tt are the reference) and test dissolution value at time t. [51]

Kinetic modeling of dissolution data: The dissolution profile of all batches are fitted to various models such as zero order, first order, Higuchi, Hixon Crowell, Korsmeyer and Peppas to ascertain the kinetic of drug release.[51]

***In vivo* study of prepared formulation:** The prepared formulation is tested for an in vivo study to check the passage of the dosage form throughout the GIT. The purpose of the in vivo study is to find the location of the capsule during its passage through the GI tract. In this study, drug granules are replaced with barium sulfate. The dosage form is prepared in the similar manner as optimized formulation. The volunteer with overnight fasting is taken for the study. The laxative is given to the volunteer before 12 h of the study to completely empty the GIT content. The X-ray study is performed at 2-h, 3-h, 5-h, and 8-h interval. [51]

Pharmacokinetic parameters comparision: Different pharmacokinetic parameters like Cmax (µg/ml), tmax (h), AUC (ng.h/ml), Kel (h-1) and t½ (h) are compare for optimized formulation and marketed tablet. [52]

Dissolution *ex-vivo* permeation study using everted rat intestine: Intestine is isolated from a male Wistar rat. A median incision is made into the abdomen, the small intestine is freed, and the lumen is carefully cleared with a Krebs-Ringer solution. The intestinal segment is everted and the distal 5 cm part is used. One end of the isolated everted intestinal segment is fixed to a straight cannula and at the other end tied using a thread to a 1 g weight. The system is filled with Krebs-Ringer solution and is completely immersed into the dissolution vessel of the dissolution test apparatus containing 900 mL of suitable dissolution fluid. During the study, assemblies are maintained at 37 ± 0.5°C, and aeration is ensured with a continuous supply of bubbled oxygen. Marketed samples of drug and prepared optimized batch is tested (n = 3). The drug diffused from the dissolution medium (mucosalside) into the serosal side (absorption compartment) and is analyzed by a validated analytical method at regular time intervals after filtration through a membrane filter of 0.45 µm pore size. [54-56]

RECENT ADVANCES IN THE PULSATILE DRUG DELIVERY [45-46]

At present, pulsatile drug delivery systems have great importance in various disease conditions specifically in diabetes where dose is suggested at different time intervals. The sub-systems, multi-particulate systems (e.g. pellets) offer various advantages over single unit that include no risk of dose dumping, flexibility of blending units with different release patterns, as well as short and reproducible gastric residence time. Multiparticulate systems consists pellets of various release profile which might be of any type like time dependent, pH dependent, micro flora activated system as discussed in the previous sections. Site and time specific oral drug delivery have recently been of great interest in pharmaceutical field to attain improved therapeutic efficacy. Gastroretentive drug delivery system is an approach to prolong gastric residence time, thereby targeting sitespecific drug release in upper gastrointestinal (GI) tract. Floating drug delivery system (FDDS) and bioadhesive drug delivery are widely used techniques for gastro retention. Low density porous multiparticulate systems are employed by researchers for formulation of FDDS. Various pulsatile technologies have been developed on the basis of methodologies as discussed previously. These includes OROS® technology, CODAS® technology, CEFORM® technology, DIFFUCAPS®
technology, Threedimensional printing®, timerx® etc.

Table 2: Marketed Products of Pulsatile Drug Delivery

Name	Active pharmaceutical ingredients	Disease	Mechanism
PULSYS®	Amoxicillin	Pharyngitis/tonsi llitis	Time controlled system
UNIPHYL®	Theophylline	Asthma	Externally regulated system
RITALIN β	Methyl phenidate	Attention deficit hyperactive disorder	Osmotically regulated system
CODAS®	Verapamil HCl	Hypertension	Multiparticular pH dependent system
ssDIFFUCAPS®	Verapamil HCl Propanolol HCl	Hypertension	Multiparticulate system

CURRENT SITUATION AND FUTURE SCOPE

Now a day's pulsatile drug delivery is gaining popularity. The prime advantage in this drug delivery is that drug is released when necessity comes. As a result chance of development of drug resistance which is seen in conventional and sustained release formulations is reduced. Furthermore, some anticancer drugs are very toxic. These drugs provide dangerous issues in conventional and sustained release therapies. Currently several Food and Drug Administration approved chronotherapeutic drugs are available in the market. This therapy is principally applicable whereever sustained action isn't needed and drugs are toxic. Key purpose of this formulation is to seek out circadian rhythm i.e. appropriate indicator which can trigger the discharge of drug from the device. Another point is absence of suitable rhythmic biomaterial which should be biodegradable, biocompatible and reversibly responsive to specific biomarkers in rhythmic manner. Regulatory is another big question. In preapproval phase it's typically difficult to show chronotherapeutic advantage in clinical settings. In post approval phase causal recreational drug abuse along with on a much larger scale, by the criminal diversion of these modified formulations for profit have arisen problems. The FDA has now heavily relied on the development and implementation of risk management programs as a strategy to allow an approval of a drug to go forward while exercising some restrictions. Many rsesearches are going on the pulsatile drug delivery to discover circadian rhythm with suitable device in the world. In future this delivery will be a leading way to deliver therapeutic agents due to its some unique characters like low chance of dose dumping, patient compliance and the above factors. [57]

CONCLUSION:

Pulsatile drug delivery system is most suitable for time specific and site specific delivery of drugs. Although sustained and controlled drug delivery systems have gained a lot of success and application in field of medication, these systems fail to deliver drug according to circadian behavior of diseases for which pulsatile systems are beneficial. The circadian rhythm of the body is an important concept for understanding the optimum need for the drug in the body. For successful development of chronotherapeutic dosage form, knowledge of circadian time structure, rhythm in disease pathophysiology or 24 hour pattern in symptom intensity of chronic medical conditions and chronopharmacology of medicationis needed. Significant progress has been made towards achieving pulsatile drug delivery system that can effectively treat diseases with non-constant dosing therapy. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place, and in right amounts, holds good promises of benefit to the patients suffering from chronic problems such as arthritis, ulcer, asthma, and hypertension. Thus, designing proper pulsatile drug delivery will enhance the patient compliance, optimum drug delivery to the target site, and minimizes the undesired effects.

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