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REVIEW ARTICLE

Approaches to Pulsatile Drug Delivery System

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ABSTRACT

Pulsatile drug delivery system (PDDS) is a popular drug delivery system, intended to deliver a rapid, transient and able to provide the release of two subsequent drugs which quantify the medication release after a predetermined off-release period (lag time). PDDS has number of advantages over the other oral doses form, it avoids the degradation of drugs in the stomach & its first-pass metabolism, capability to simultaneous administration of two different drugs, allows their release at different sites within the GIT and provides a release burst of drug at one or more predetermined time intervals as per patient requirements. The PDDS having a unique mechanism of drug delivery, in which the drug release rapidly after the lag time, there are numbers of PDDSs formulations available in the markets which replaced the modified-release dosage forms.

KEYWORDS

Pulsatile, Chronotherapeutic, Drug delivery system, Lag time

INTRODUCTION

Pulsatile drug delivery system (PDDS) is a popular drug delivery system, intended to deliver a rapid, transient and able to provide the release of two subsequent drugs which quantify the medication release after a predetermined off-release period (lag time).[1,2,3,4] PDDS has number of advantages over the other oral doses form, it avoids the degradation of drugs in the stomach & its first-pass metabolism, capability to simultaneous administration of two different drugs, allows their release at different sites within the GIT and provide a release burst of drug at one or more predetermined time intervals as per patient requirements. Other advantages of PDDS extend to drugs with chronopharmacological behaviors, where night time dosing is required and for various diseases that are influenced by circadian rhythms[5].

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The PDDS having a unique mechanism of drug delivery, in which the drug release rapidly after the lag time, there are numbers of PDDSs formulations available in the markets which replaced the modified-release dosage forms. The release patterns of some PDDS are illustrate in following figure[6,7].

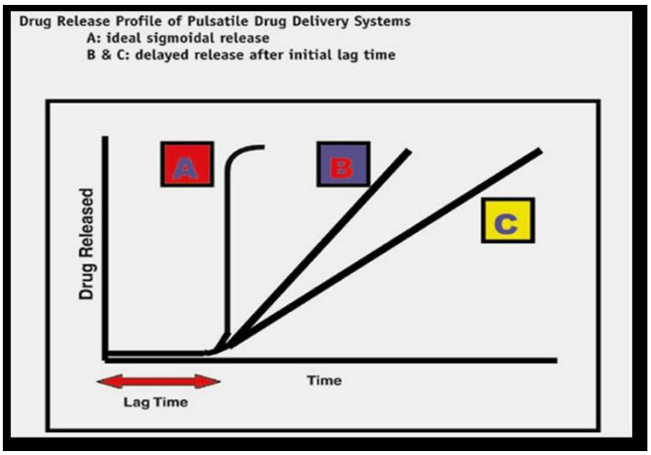

Figure 1: Drug release profile of pulsatile drug delivery systems[8]

The prime prerequisites of Pulsatile drug release formulations releases the independently from GI environment factors like gastric pH, enzymes activity, intestinal mortality, these factors determined by the formulation's design[9]. In many chronic drugs or therapies like arthritis, asthma, hypertension the pulsatile drug release becomes advantageous, specially where the controlled drug delivery system is not suitable. The pulsatile drug release may define as doses form releases 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[10].

Pulsatile drug delivery system may consider as controlled drug delivery system where the drug released after a preprogrammed lag time, which characterized by two release phase, first phase consists of little or no drug release, followed by a second phase consisting the release of drug completely within a short period of time after the lag time[11]. Pulsatile drug delivery system is a controlled drug delivery system where drug is released after a preprogrammed lag time.

Various approaches have been used to design a pulsatile release formulation, erodible devices provided with hydrophilic polymer coating are widely used and such a system when exposed to dissolution medium undergo swelling, dissolution and/or erosion. Lag time in such a system can be controlled by using various hydrophilic polymers such as HPMC, polyethylene oxide, sodium alginate, sodium CMC. The concentration and viscosity of these polymers play a significant role in controlling the lag time and release pattern[12].

A pulsatile release profile after a defined lag time is advantageous for the drugs targeted to a specific site in the intestinal tract i.e., to the colon. Such site-specific drug delivery systems are expected to provide majority of their drug load to colon without being released in stomach and small intestine. 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." 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. 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[13.]

Advantages of Pulsatile Drug Delivery System:[14,15]

- Extended daytime or nighttime activity.
- Reduced side effects.
- Reduced dosage frequency.
- Reduction in dose size.
- Improved patient compliance.
- Lower daily cost of drug therapy.
- Drug targeting to specific site like colon.
- Protection of mucosa from irritating drugs.
- No risk of dose dumping.
- Improved bioavailability, tolerability and reduces side effects.
- Avoidance of undesirable side effects.
- Flexibility in design.
- Improved stability.
- Drug loss is prevented by extensive first pass metabolism.
- Metabolism e.g. proteins and peptide.

Disadvantage of Pulsatile Drug Delivery System:[16,17]

- Difficult to manufacture and it is costly.
- Low drug loading capacity and incomplete release of drug.
- Large number of process variables.
- Lack of manufacturing reproducibility and efficacy.
- Batch manufacturing process.
- Unpredictable IVIVC.

- Multiple manufacturing steps in case of Multiparticulate pulsatile drug delivery system.
- *In-vivo* variability in single unit pulsatile drug delivery system.
- Need of advanced technology.
- Trained/ skilled personal needed for manufacturing.

Need of Pulsatile Drug Delivery:[18]

- Chronic disease like bronchial asthma, myocardial infraction, angina pectoris, rheumatic disease, ulcer, and hypertension need the drug after a suitable lag time.
- Lag time essential for the drugs that undergo degradation in gastric acidic medium.
- It is possible to targeted deliver the drugs to specific sites of GIT like colon targeting with pulsatile drug delivery.
- PDDS needs when rhythmic variation seen in acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion.
- This dosages form is suitable for drug undergo extensive first-pass metabolism are administered successfully as pulsatile drug delivery systems.
- To prolong therapeutic effect by continuously releasing the medication over as extended period of time after administration of single dose.
- To delay the releases of drug hence control the onset of drug action.

Chronopharmaceutics:

It is evident that drug delivery and therapy should be modified to achieve an efficient drug level at an optimum time, rather than merely maintaining constant drug concentrations. Thus, the time-controlled function of third-generation DDSs currently under development is finding application in new and improved disease therapeutics. Biological rhythms may be applied to pharmacotherapy by adopting a dosage form that synchronizes drug concentrations to rhythms in disease activity[19]. During the past two decades, diseases that follow rhythmic patterns have given rise to the creation of new drug delivery dosage forms, called chronopharmaceuticals[20]. Chronopharmaceutics includes the fundamentals and research into various aspects of chronophysiology, chronopathology, chronogenetics, chronopharmacology, chronopharmacokinetics, chronopharma-codynamics, chronotherapeutics, and chronotoxicology. Broadly, chronopharmaceutics bring together chronobiology and pharmaceutics[21]. Chronobiology is the study of biological rhythms and mechanisms in living systems. It assumes that the bioprocesses and functions of all living organisms exhibit predictable variability over time.

Mechanism of Drug Release from Pulsatile Drug Delivery System:[22]

The mechanism of drug release from PDDS can be occurring in the following ways

Diffusion: Water diffuses into the interior of the particle when particle come in contact with aqueous fluids in the gastrointestinal tract and resultant drug solutions diffuse across the release coat to the exterior.

Erosion: Some coatings designed to erode gradually with time, result in the release of drug contained within the particle.

Osmosis: An osmotic pressure can be built up within the interior of the particle when water allows entering under the right circumstances. The drug is forced out of the particle into the exterior through the coating

Classification of Pulsatile Drug Delivery Systems:

A. 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

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.[23]

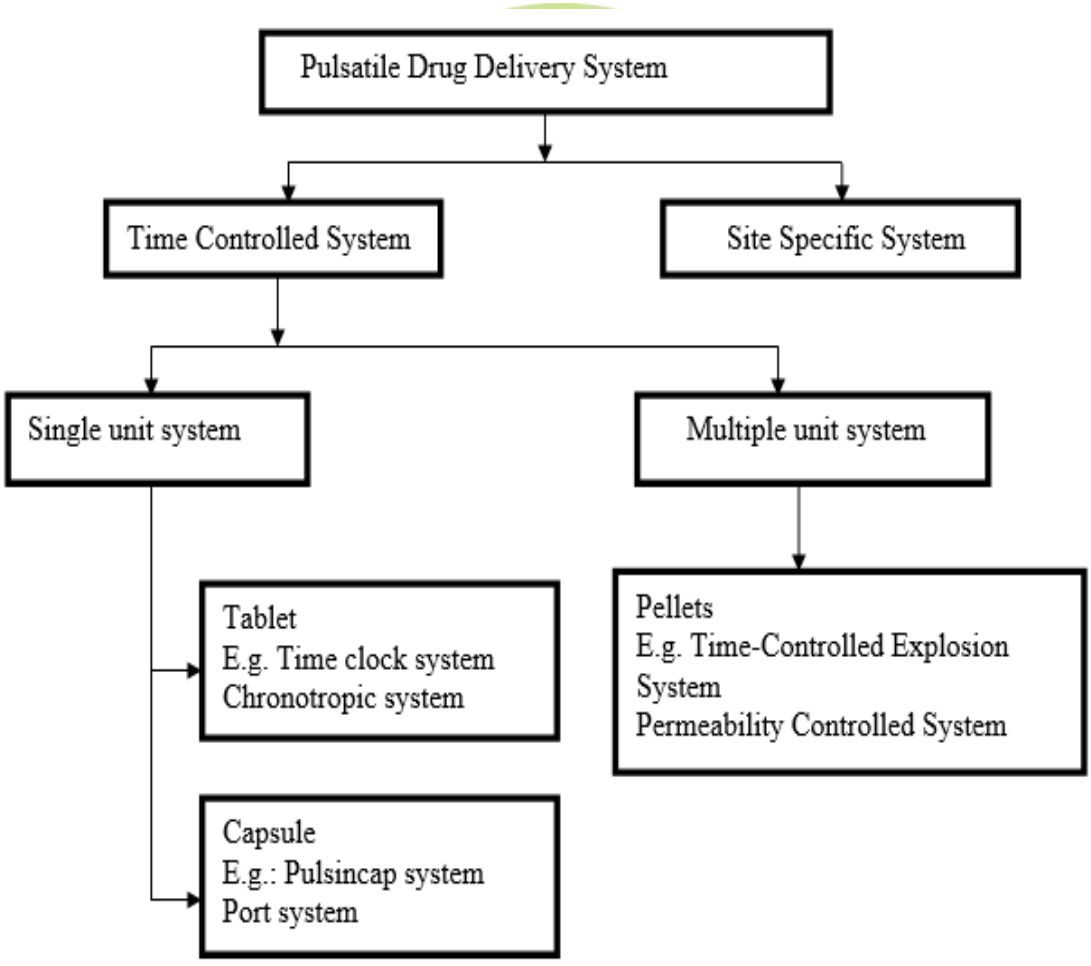

Figure 2: Classification of pulsatile drug delivery system[24]

A. Single Unit Pulsatile Systems:

1. Capsule based System:

Single –unit system are mostly formulated in the form of capsule. The lag time is restrained by a plug, and when this plug pushed away by swelling or erosion, the drug is released as a "Pulse" from the insoluble capsule body[25]. The drug contents sealed into the capsule body by using a swellable hydrogel plug. As the capsule came in contact with the dissolution fluid, it get swelled; and after a lag time, the plug forced itself outside the capsule and immediately release the drug. The length of the plug and its point of infusion into the capsule controlled the lag time[26]. By manipulating the dimension and the position of the plug, we can control the lag time. This formulation does not cause GI irritation and some time it is overcome by enteric coating[27,28].

For water-insoluble drugs, inclusion with effervescent agents or disintegrants assures a rapid release.

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)[29,30].

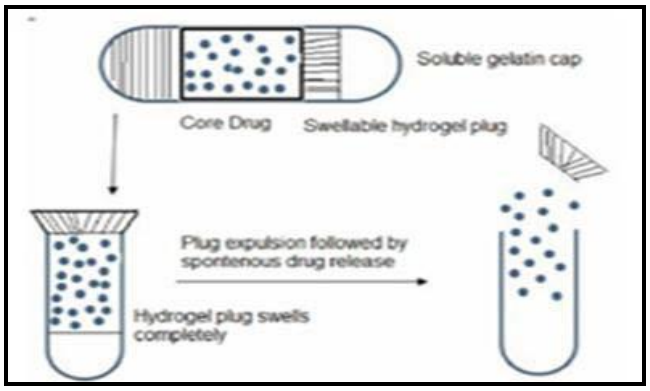

Figure 3: Schematic diagram capsular system

2. Capsular System based on Osmosis

A. 'PORT' System

The PORT system consists of a capsule coated with a semi permeable membrane (e.g. cellulose acetate).An insoluble plug (e.g., lipidic) was present inside the capsule which consist an osmotically active agent and the drug formulation[31]. As the capsule came in contact with the dissolution fluid, the semi permeable membrane permit the entry of water, which led to pressure development and the insoluble plug dislodge after a lag time. The coating thickness control the lag time. The system exhibit good relationship in lag time of in-vitro and in-vivo experiments in humans. Such a system was appropriate to deliver methylphenidate used in the treatment of attention deficit hyperactivity disorder as the pulsatile port system. This system averted second time dosing, which was favorable for school children during daytime.

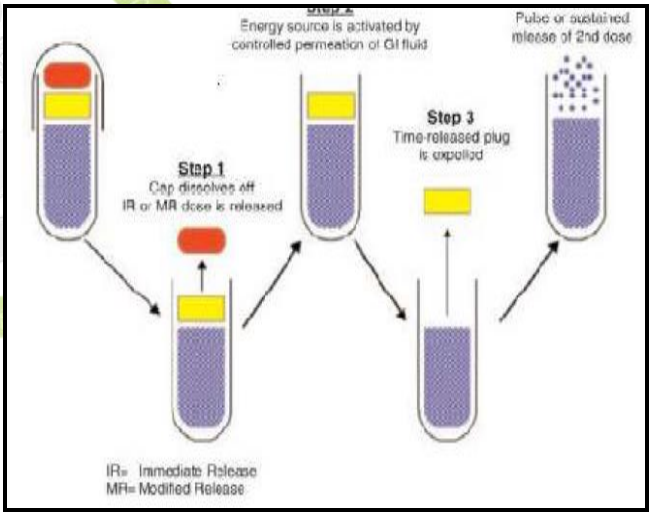

Figure 4: Drug release mechanism from PORT system[32]

B. System based on Expandable Orifice

An osmotically driven capsular system was developed to deliver drug in liquid form. In this system, liquid drug is captivated into highly porous particles, and as the barrier layer diffuses the drug released through an orifice of a semi permeable capsule supported by an expanding osmotic layer. The capsule wall is made up of an elastic material and have an orifice. The orifice is small enough so that when the elastic wall relaxes, the movement of the drug through the

orifice necessarily stops, but when the elastic wall is inflated beyond threshold value, the orifice expands sufficiently to allow drug release at a required rate expected. E.g. elastomers, such as styrene-butadiene copolymer have been suggested. The system was schemed to deliver drug as liquid formulation and associate the benefit of extended release with high bioavailability. The liquid formulation is well suitable for the delivery of insoluble drugs. As the system came in contact with the aqueous environment, water penetrate across the rate controlling membrane which activates the osmotic layer. The liquid OROS hard cap TM was enclosed to hold more viscous suspension with higher drug –loading capacity. The lag time can be deferred from 1 to 10 hrs, depending on the permeability of the rate-controlling membrane and thickness of the barrier layer[33,34].

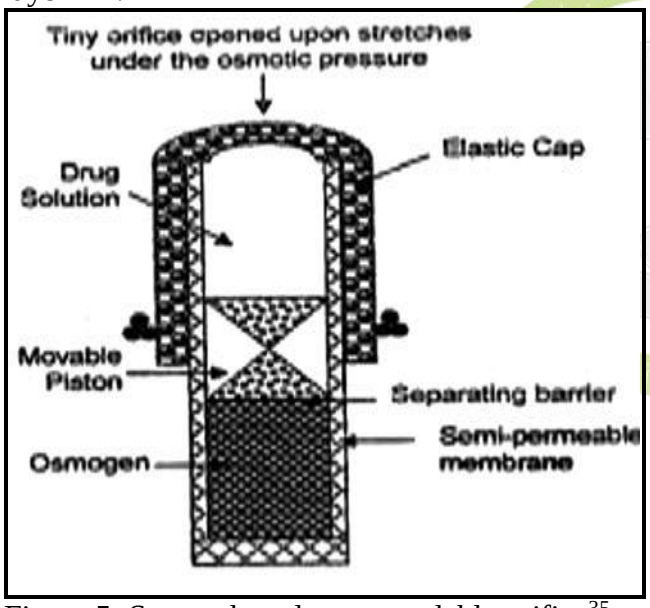

Figure 5: System based on expandable orifice[35]

C. Delivery by Series of Stops:

The system specifically described for implantable capsules. The capsule consist a drug and a water absorptive osmotic engine that are implanted in compartments divided by a movable partition. The pulsatile delivery is attained by a series of stops along the inner wall of the capsule. These stops hamper the movement of the partition but are overwhelm in succession as the osmotic pressure increases above a threshold level[36]

D. Pulsatile Delivery by Solubility Modulation:

These systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was particularly developed for delivery of antiasthematic drugs like salbutamol sulphate[37]. The compositions include the drug and a modulating agent, sodium chloride (NaCl). The amount of NaCl was such that it was less than the amount needed to maintain saturation in a fluid that invade the osmotic device. The pulsed delivery is based on drug solubility. Salbutamol has solubility of 275 mg/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 a function of the modulator concentration, while the modulators solubility is largely independent of drug concentration. By changing the ratio of drug modulator, zero order release period and initiation of pulse release can be controlled. After the period of zero order release, the drug is delivered as one large pulse.

3. Pulsatile System with Erodible or Soluble Barrier Coatings:

In these systems the dissolution or erosion of the outer coat controls drug release. This outer coat was applied on the core containing drug. Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. After a specific lag period, this barrier erodes or dissolves and finally the drug is released rapidly from reservoir core. The lag time depends on the thickness of the coating layer.

A. The Chronotropic System:

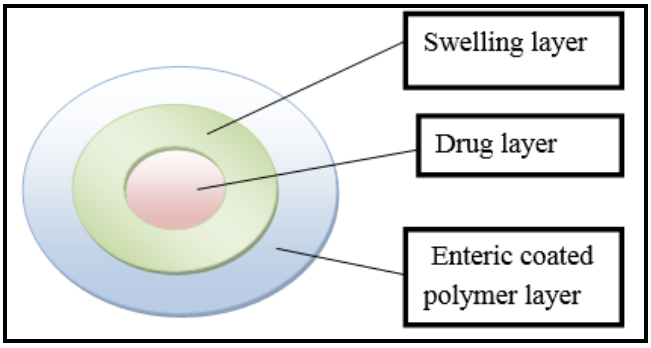

Figure 6: The chronotropic system[38]

The Chronotropic system have drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of release[39,40]. In addition, the variability in gastric emptying time can be overcome through the application of an outer gastric resistant enteric film and a colon-specific release can be obtained, relying on the relative reproducibility of small intestinal transit time[41]. The lag time is regulated by the thickness and the viscosity grades of HPMC[42]. 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[43].

B. 'TIME CLOCK' System:

The Time Clock system contain solid dosage form coated with lipid barriers such as carnuba wax & beeswax along with surfactants like polyoxyethylene sorbitan monooleate. 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 coat erodes or emulsifies in the aqueous environment. The thickness of coat is directly proportional to the time required to release the drug. The lag time is increase with increase in thickness of the coating[44].

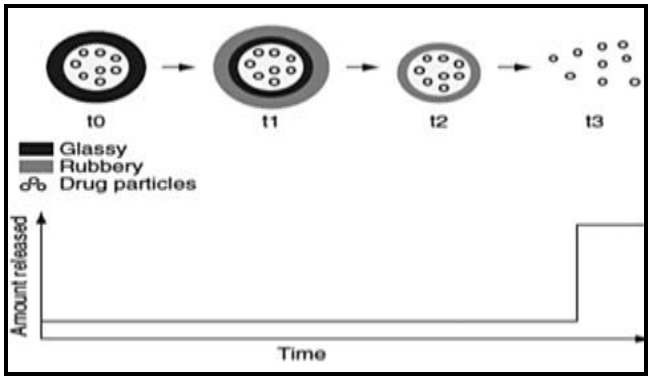

Figure 7: The Chronotropic system

This type of system is suitable for water soluble drugs. The main advantage of this system is to formulate without any special equipment. The premature drug release occurs and it will dissolve with dissolution medium and release with sustained manner without complete erosion thereby it retard the release in pulsatile manner. The mean lag time of drug release was 345 and 333 min respectively.

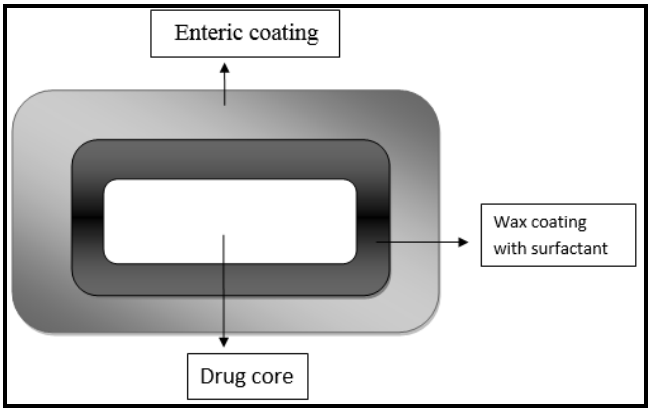

Figure 8: 'TIME CLOCK' System

C. Compressed Tablets:

Compression coating can associate direct compression of both the core and the coat, obviating needs for isolated 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 derivatives 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[45].

Press-coated pulsatile drug delivery systems:

1. Press-coated pulsatile drug delivery systems can be used to assure hygroscopic, light-sensitive, oxygenlabile or acid-labile drugs.
2. Press-coated pulsatile drug delivery systems are comparably simple and cheap.
3. These systems can associate direct compression of both the core and the coat.
4. In press-coated pulsatile drug delivery system materials such as hydrophobic, hydrophilic can be used.
5. Press-coated pulsatile drug delivery systems having compression which is easy on laboratory scale.

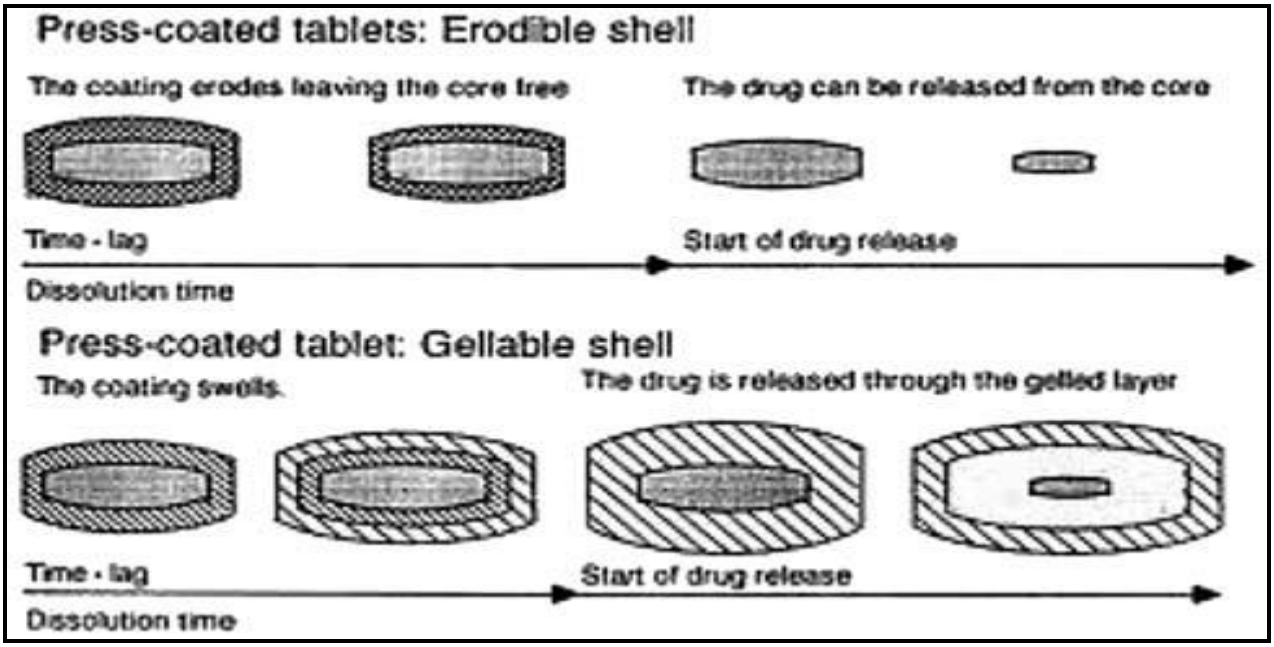

Figure 9: Press-coated tablet

6. Press-coated pulsatile formulations release drug after "lag-time".
7. Press-coated pulsatile drug delivery formulations can be used to separate unsuitable drugs from each other or to achieve sustained release.

D. Multilayered Tablets:

With the three layered tablet release design with two pulses was achieve, two drug layers are separated by a drug free gellable polymeric barrier layer. This three-layered tablet was coated on three sides with in impermeable ethyl-

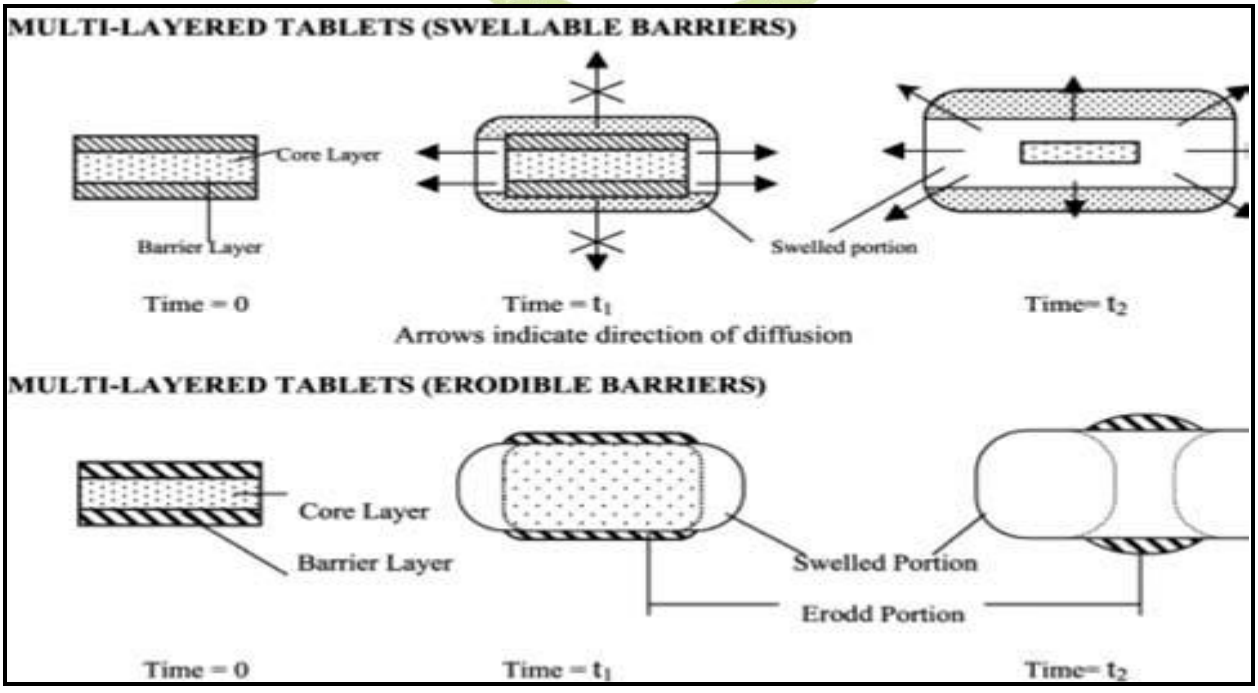

Figure 10: Multi layered Tablet

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 polymer reported contain cellulose derivative like HPMC, methyl cellulose or polyvinyl propionate, methacrylic polymers, acrylic and methacrylic copolymer, and polyalcohol's[45,46].

4. Pulsatile System with Rupturable Coating:

These systems depend on the disintegration of the coating for the release of drug. The pressure essential 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 mechanical properties of the coating layer[47].

B. Multiparticulate /Multiple Unit System:

1. Pulsatile System based on Rupturable Coating:

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[48,49]. 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. An effervescent system comprising a mixture of tartaric acid and sodium bicarbonate may also be used. The release is independent of environment factors like pH and drug solubility. The lag time can be varied by varying coating thickness or adding high amount of lipophilic plasticizer in the outermost layer.

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 coating[50].

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[51]. 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[52].

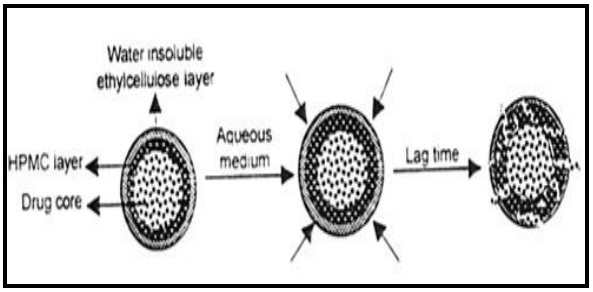

Figure 11: Time –controlled Explosion system (TCES)

II. Stimuli-Induced Pulsatile Release:

1. Temperature-Induced Pulsatile Release:

The temperature is important for pulsatile drug

delivery. The temperature is rises above the physiological body temperature (37°c) in presence of pyrogens. This deviation is important in various temperature responsive drug deliveries to release drug from temperature sensitive polymer in the disease occupying fever. The thermal stimuli induced pulsatile drug delivery systems like hydrogels and micelles were developed. This deviation from normal range acts as a stimulus that triggers the release of therapeutic agents from several temperature-responsive drug delivery systems. Various polymer properties, including the thermally reversible coil/globule transition of polymer molecules, swelling change of networks, glass transition and crystalline melting utilized by temperature induced triggered drug delivery systems[53,54].

2. Chemical Stimuli Induced Pulsatile Systems:[55]

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 designed 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. Swelling of the polymer observed due to pH change which results in insulin release. Examples of the pH sensitive polymers include N, N-dimethylaminoethylmethacrylate, chitosan, polyol etc.

B. Inflammation-Induced Pulsatile Release:

On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. Hydroxyl radicals are produced due to inflammation from these inflammation-responsive cells. Degradation via hydroxyl radicals however, is usually dominant and rapid when Hyaluronic Acid gel is injected at inflammatory sites. These gels are used for delivery of drugs to particular inflamed sites.

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/deswelling characteristics. Antigen-antibody complex formation as the cross-linking units in the gel gained special attention, since such interaction is very specific.

D. pH Sensitive Drug Delivery System:

This type of PDDS contains two components. The first is fast release type and the 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. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, and sodiumcarboxymethyl-cellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine.

III. External Stimuli Pulsatile Release:[56,57]

This system was divided into three subparts and is discussed below.

A. Electro Responsive Pulsatile Release:

Polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) are used for preparing electrically responsive delivery systems and are thus, pH-responsive as well as electro-responsive. Examples of naturally occurring polymers include hyaluronic acid, chondroitin sulphate etc.

B. Micro Electro Mechanical Systems (MEMS):

A micro fabricated device has the ability to store and release multiple chemical substances on demand by a mechanism devoid of moving its parts. The digital capabilities of MEMS may

allow greater temporal control over drug release compared to traditional polymer-based systems. The micro chip is the other development in the MEMS. The microchip consists of an array of reservoirs that extend through an electrolyte-impermeable substrate.

C. Magnetically Induced Pulsatile Release:

The use of an oscillating magnetic field to modulate the rates of drug release from polymer matrix was one of the old methodologies. Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials such as Magnetite, Iron, Nickel, Cobalt etc. For biomedical applications, magnetic carriers must be water based biocompatible, non-toxic and non-immunogenic mechanistic approach.

Table 2: Polymers employed in PDDS[59]

Synthetic	**Natural**
HPMC K4 M	Sodium alginate
HPMC K15 M	Pectin
HPMC K100 M	Karaya gum
Eudragit	Gelatin
Ethyl cellulose	Xanthan gum
Cellulose acetate pethalate	Chitosan
Polymethacylic acid	Guar gum

Table 1: List of drugs formulated as single and multiple unit forms of PDDS[58]

Capsules	Metoprolol tartrate, Propranolol HCl, Diclofenac sodium, Actaminophen, Ibuprofen, Metoprolol tartrate, Mesalazine, Diltiazem Hydrochloride, Nifedipine, Valsartan, Dofetilide
Pellets	Aceclofenac, Diltiazem HCl, Indomathacin, 5- aminosalicylic acid, Propranolol Hcl, Isosorbide-5-mononitrate, Diclofenac sodium
Microspheres	Salbutamol sulfate (pH-sensitive ion exchange resins), Theophylline, 5-aminosalicylic acid, Diltiazem hydrochloride
Films	Insulin, Diclofenac sodium
Tablets	Verapamil HCl, Propranolol HCl, Chlorpheniramine maleate, Felodipine, Salbutamol sulphate, Ranitidine HCl, Acetaminophen, Theophylline, Buflomedil hydrochloride, Isoniazid, Ketoprofen, Nifedipine, Antipyrine, Pseudoephedrine hydrochloride, Diclofenac sodium,
Beads	Meloxicam, Diclofenac sodium, Theophylline, Aceclofenac,
Micelles	Diflunisal, Doxorubicin
Thermoresponsive Hydrogel	Gentamicin, Indomethacin, Sulfonamide, Diltiazem hydrochloride

Evaluation of Pulsatile Drug Delivery System:

Thickness and Diameters:

It is measured by using vernier calliperin mm.

Hardness:

The hardness of tablet was measured by using monsanto hardness tester. The unit of hardness is kg/cm^2.

Friability:

Friability of tablet was found to be USP friabilator. First of all tablet batch was weighed and placed in friabilator for 100 revolution in 4 minutes. The % friability was calculated by

$$F = (Wi-Wf)/ Wi \times 100$$

Where, Wi = initial weight Wf = final weight

Weight Variation Test:

The USP weight variation test was done by weighing 20 tablets individually calculating average weight and comparing the individual weight to the average.

Table 3: Weight variation limit

S. No.	Average weight of tablet (mg)	Maximum difference
1	80mg or less	10%
2	More than 80 mg but less than 250mg	7.5
3	250 mg or more	5%

Lag Time and Drug Release:

The lag time and drug release studies was carried out in gastric and intestinal fluids at body tem. This test is performed in USP dissolution apparatus, in this test the tablet was placed in dissolution media and the sample was withdrawn at specific time interval and after that analyzed in UV spectroscopy.

Rupture Test:

The rupture test on coated tablets was carried out using USP paddle apparatus. Here all other Parameters were same as *In-Vitro* Dissolution Method. The time at which the outer coating layer starts to rupture is called as lag time. This was determined by Rupture test.

Drug Content:

In this test accurately weight amount of powder was dissolved in water and filtered. After that the absorbance was measured at fixed wave length by UV spectrophotometer.

Water Uptake Study:

The % water uptake of pulsatile release tablets was determined in medium filled container placed in a horizontal shaker (100 ml of 0.1 N HCl, 37 0.50C, 74 rpm n=3) at predetermined time points, the tablets were removed from the dissolution medium. They were then carefully blotted with the tissue paper to remove surface water, then weighed and then placed back in the medium up to the time when the coating of the tablet ruptured. The % water uptake update was calculated as follow:

$$\%\text{Water uptake} = [(Wt-W_O/W_O)]\ 100$$

where, Wt- weight of tablet at time t and W_O - is weight of dry tablet

Swelling Index:

The individual tablets were weighed accurately and kept in 50 ml of double distilled water. Then tablets were taken out properly after 60 min., then blotted with filter paper so as to remove the water present on the surface and weighed accurately. Percentage swelling index (SI) was calculated by using the formula

SI = (Wet weight – Dry weight / Dry weight) X 100.

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