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CHRONOTHERAPEUTICS IN DEVELOPMENT OF PULSATILE DELIVERY SYSTEMS

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ABSTRACT

Many therapeutic agents are most effective when made available at constant rates, near the absorption sites or at the correct time of administration. Pulsatile drug delivery system is the most interesting time-specific and site-specific system. This system is designed for chronopharmacotherapy which is based on circadian rhythm. Recently a greater effort has been taken in designing delivery systems which synchronize drug delivery with circadian rhythms in order to optimize efficacy and /or minimize side effects. Pulsatile systems deliver the drug at right site of action at the right time and in the right amount. Chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. Chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease. This review gives an outline as to how pulsatile drug delivery systems based on circadian rhythms are developed.

INTRODUCTION: Oral route of drug delivery is considered the favoured and most user friendly means of drug administration having the highest degree of patient compliance, as a result of which much efforts are aimed to identify orally active candidates that would provide reproducible and effective plasma concentrations *in vivo* [1]. Oral drug delivery can be classified into three categories:

A. Immediate release-which is designed for immediate release of drug for rapid absorption.

B. Sustained release designed on the basis of spansule technology for extended absorption.

C. Controlled and targeted drug delivery system-which offer more pharmaceutical and clinical superiority over conventional immediate release pharmaceutical products [2].

Traditionally, drug delivery systems have focused on constant/sustained drug output with the objective of minimizing peaks and valleys of drug concentrations in the body, to optimize drug efficacy and to reduce adverse effects.

Modified release dosage forms offer control over the release pattern of drug and provide better control over drug with predetermined release rates. These dosage forms offer numerous advantages, such as nearly stable plasma drug level without much fluctuation, reduction in dose of drug, reduced dosage frequency, least side effects, and improved patient compliance.

Pulsatile system is amongst one of them and gaining a lot of interest as it is increasing patient compliance by means of providing time-specific and site-specific drug delivery system, thus providing special and temporal delivery [3].

Pulsed or pulsatile drug release is defined as the rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off-release period [4]. Recent studies show that diseases have predictable cyclic rhythms and the timing of medication regimens can improve outcome in selected chronic conditions [5].

Modified release dosage forms show different release profiles depending on their type. Sustained release dosage forms may maintain nearly constant plasma drug concentration in therapeutic window for prolonged time as shown in figure 1. But there are certain conditions which demand release of drug after a period of no drug release which is known as lag time [6]. Diseases wherein constant drug levels are not preferred, but need a pulse of therapeutic concentration in a periodic manner, act as stimuli for the development of "Pulsatile Drug Delivery Systems"[7].

Pulsatile release dosage forms release drug in pulsatile manner and maintain plasma drug level within therapeutic range as shown in figure 1. Specificity in delivering higher amount of drug in a burst at circadian timings correlated with specific pathological disorder is a key factor to achieve maximum drug effect [8-10] (**figure 1**).

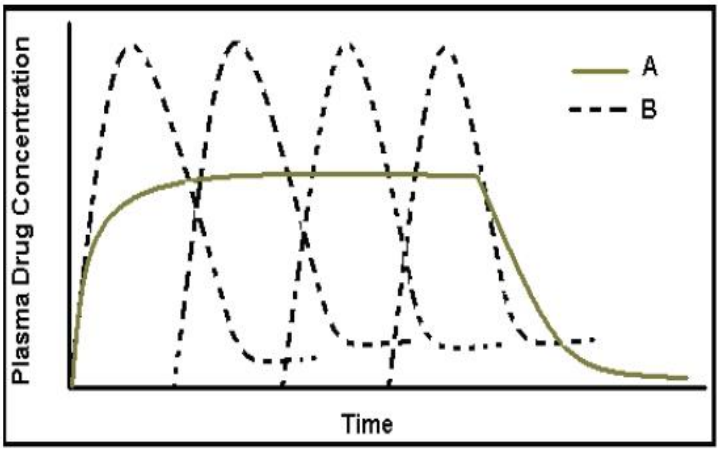


FIGURE 1: RELEASE PATTERN OF SUSTAINED (A) AND PULSATILE RELEASE (B).

A delivery system with a release profile that is characterized by a time period of no drug release (lag time) followed by a rapid and complete drug release (pulse release) can be called as an ideal pulsatile drug delivery system. In other words, it is required that a drug should not be released at all during the initial phase of dosage form administration.

Lag time is defined as the time between when a dosage form is placed into an aqueous environment and the time at which the active ingredient begins to get released from the dosage form; precisely lag time is an interval of no drug release followed by rapid drug release [1] (**Figure 2**).

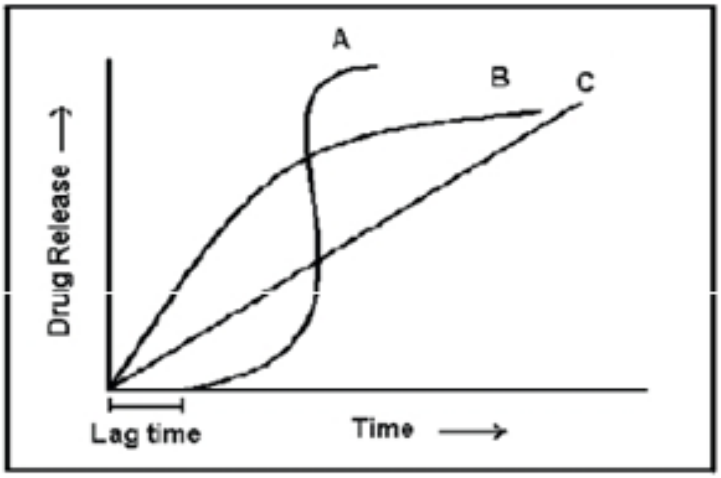


FIGURE 2: DRUG RELEASE PROFILES (A) PULSATILE, (B) CONVENTIONAL AND (C) EXTENDED RELEASE[9]

"Chronopharmaceutics" consists of two words chronobiology and pharmaceutics.

The study of biological rhythms and their mechanisms is known as chronobiology. They are regulated by sunlight.

There are three types of mechanical rhythms in our body [12, 11, 13];

1. Ultradian
2. Infradian
3. Circadian

1. **Ultradian rhythms**: They are the rhythms that have a period of shorter than 24 hours.

2. **Infradian rhythms:** They are the rhythms which have a frequency ranging from 28 hours to 6 days [12].

3. **Circadian rhythms:** The term "circadian", coined by Franz Halberg, comes from the Latin circa, "around", and Diem of dies, "day", meaning literally "approximately one day". Our body appears to be genetically programmed to function on roughly a 24-hour cycle.

These rhythms allow organisms to anticipate and prepare for precise and regular environmental changes. They are important in determining the sleeping and feeding patterns of animals, including human beings. There are clear patterns of core body temperature, brainwave activity, hormone production, and other biological activities linked to this cycle (**Figure 3**).

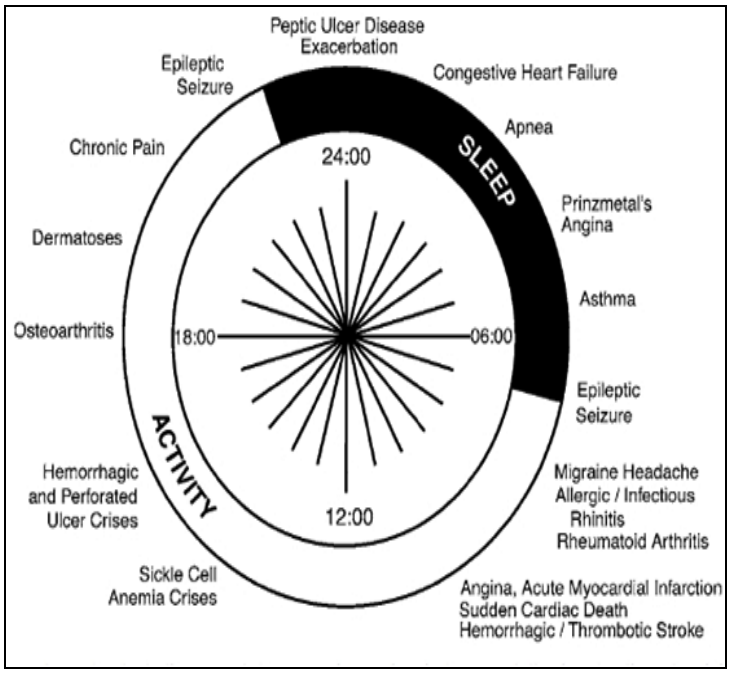


FIGURE 3: SCHEMATIC DIAGRAM OF CIRCADIAN RHYTHM SHOWING DISEASES REQUIRE PDDS

Chronotherapeutics: It is the purposeful delivery of medications in unequal amounts over time during 24 hours. Chronotherapeutics takes into account rhythm determinants in disease pathophysiology, chrono-pharmacology of medications, dose and administration time to optimise desired/ minimise adverse effects.

Chronopharmaceutics has emerged, wherein, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy.

Chronotherapeutics does not involve only new medicines but also the improved applications of established once in a different and more biologically efficient manner. In certain instances, chrono-therapeutics may be achieved by unequal morning and evening dosing schedules of sustained release 12 hours medication systems, better timing of conventional once a day medication/delivery systems, or application of special tablet and capsule formulations dosed at designated times to proportion medications over 24 hours in synchrony with rhythm determined requirements.

Goal of chronotherapeutics: It is the management or reversal of existing acute or chronic medical conditions and delivery of drugs to the body to the right site, at the right time, and at the optimal dose.

- **Pulsatile drug delivery is used under below circumstances:**

  a) Chronopharmacotherapy of diseases which shows circadian rhythm in their patho-physiology.

  b) Avoiding the first pass metabolism e.g. protein and peptides [13].

  c) Drugs for which the tolerance is rapidly established.

  d) For targeting specific site in intestine e.g. colon.

  e) For time programmed administration of hormone and drugs.

  f) For drugs having short half life.

Need for of Pulsatile Drug Delivery Systems: There are many conditions and diseases where sustained release formulations do not show good efficacy. The shift from conventional sustained release approach to modern pulsatile delivery of drugs can be credited to the following reasons:

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 24 hour day, e.g., asthma and angina pectoris attacks are most frequent in the morning hours.

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.

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 nitro-glycerine.

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 due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

Drug absorption differences in various Gastrointestinal Segment: 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. For example, it is rational for a delivery system to pump out the drug much faster when the system reaches the distal segment of the intestine, to avoid the entombment of the drug in the faeces.

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.

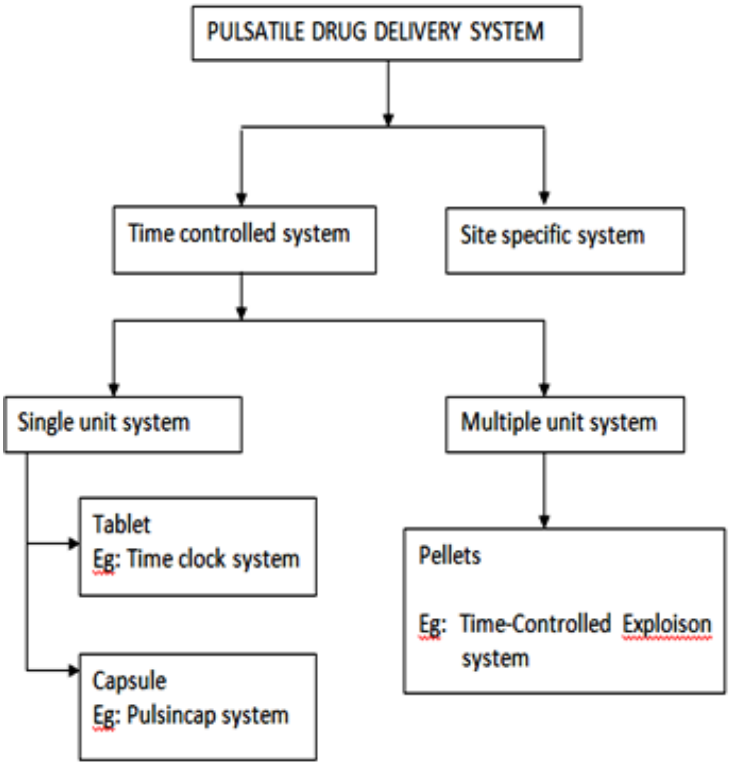
Merits:

- Predictable, reproducible and short gastric residence time
- Less inter- and intra-subject variability
- Improve bioavailability
- Limited risk of local irritation
- No risk of dose dumping
- Flexibility in design
- Improve stability

Demerits:

- Lack of manufacturing reproducibility and efficacy
- Large number of process variables
- Batch manufacturing process
- Higher cost of production
- Trained/skilled personal needed for manufacturing

Classification of Pulsatile Drug Delivery Systems:



Methodologies for the PDDS can be broadly classified into four classes;

1. **Time Controlled Pulsatile Release:**
   A. Single unit system
   B. Multi-particulate system
2. **Stimuli induced:**
   A. Thermo-Responsive Pulsatile release
   B. Chemical stimuli induced pulsatile systems
3. **External stimuli Pulsatile Release:**
   A. Electro responsive pulsatile release
   B. Magnetically induced pulsatile release
4. **Pulsatile release systems for Vaccine and Hormone Products:**

1. **Time Controlled Pulsatile Release System:** In time controlled drug delivery system, drug is released in pulsatile manner after specific time interval in order to deliver the drug at the proper site, thus mimicking the circadian rhythm [14]. These time-controlled systems can be classified as single unit (e.g., tablet or capsule) or multiple unit systems.

A. Single unit systems

B. Multiparticulate systems

A. SINGLE UNIT SYSTEM:

i. **Pulsatile System Based On Capsule:** Different single-unit capsular pulsatile drug delivery systems have been developed. A general architecture of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined lag time owing to swelling, erosion, or dissolution. The Pulsincap system is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation. The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a lag time. This is followed by a rapid drug release. Manipulating the dimension and the position of the plug can control the lag time.

For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymers (e.g., polymethacrylates), erodible compressed polymers(e.g., hydroxypropylmethylcellulose, polyvinyl-alcohol, polyethyleneoxide), congealed melted poly mers (e.g., saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (e.g., pectin).

There was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine [15-19] (**Figure 4**).

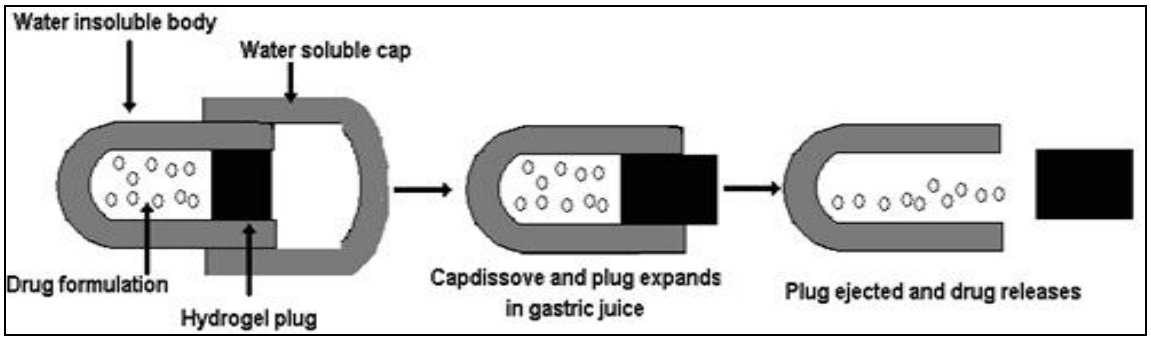


FIGURE 4: SCHEMATIC DIAGRAM OF RELEASE OF DRUG FROM CAPSULE

ii. **Port System:** The Port® System consists of a gelatin capsule coated with a semipermeable membrane (eg, cellulose acetate) housing an insoluble plug (eg, lipidic) and an osmotically active agent along with the drug formulation. When in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. Coating thickness controls the lag time. The system showed good correlation in lag times of in-vitro and *in-vivo* experiments in humans. The system was proposed to deliver methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in school-age children. Such a system avoids a second daily dose that otherwise would have been administered by a nurse during school hours (**Figure 5**).

iii. **Delivery by a series of stops:** This system is described for implantable capsules. The capsule contains a drug and a water-absorptive osmotic engine that are placed in compartments separated by a movable partition. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level.

The number of stops and the longitudinal placements of the stops along the length of the capsule dictate the number and frequency of the pulses, and the configuration of the partition controls the pulse intensity. This system was used to deliver porcine Somatotropin.

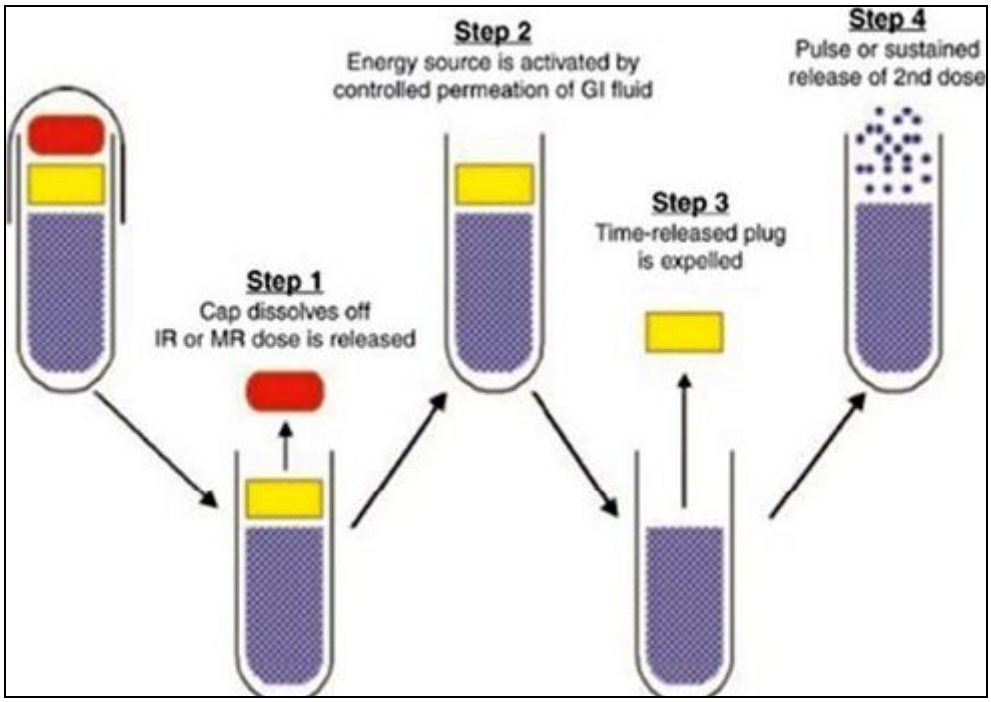


FIGURE 5: DRUG RELEASE MECHANISM FROM PORT SYSTEM

iv. **Delivery by Solubility Modulation:** These systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate. The compositions contain the drug (salbutamol sulphate) 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 enters the osmotic device. The pulsed delivery is based on drug solubility. The modulating agent can be a solid organic acid, inorganic salt, or organic salt.

v. **Delivery by Reservoir Systems with Erodible or Soluble Barrier Coatings:** Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. Barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly. The time lag depends on the thickness of the coating layer.

1. **The Time Clock System:** It consists of a solid dosage form coated with lipid barriers containing carnauba wax and bees wax along with surfactants, such as polyoxyethylene sorbitan monooleate. This coat erodes or emulsifies in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion. The major advantage of this system is its ease of manufacture without any need of special equipment. The disadvantage of this system is a premature drug release when the penetrating water dissolves the drug (**Figure 6**)

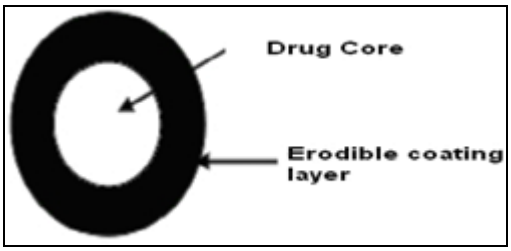


FIGURE 6: TIME LOCK SYSTEM

2. **The Chronotropic system:** It consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of drug release. Time lag is controlled by the thickness and the viscosity grades of HPMC used in coating the drug core. The system is suitable for both tablets and capsule formulations (**Figure 7**).

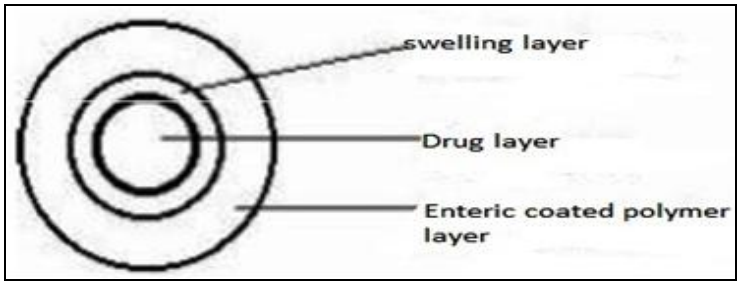


FIGURE 7: THE CHRONOTROPIC SYSTEM

3. **Multiparticulate systems:** Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, in which the active substance is present as a number of small independent subunits. They provide many advantages over single-unit systems because of their small size, less inter and intra-subject variability in gastrointestinal transit time, reduced adverse effects and improved tolerability, no risk of dose dumping, flexibility in design and finally Improve stability However, there are some draw backs in this system, which include lack of manufacturing reproducibility, high cost of production, multiple formulation steps and also the need of advanced technologies. There are different types of multiparticulate systems and these are enumerated and explained below:

a. **Pulsatile System Based on Rupturable Coating:** 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 glycolate, L-hydroxypropyl cellulose, etc. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The release is independent of environmental factors like pH and drug solubility. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer (**Figure 8**).

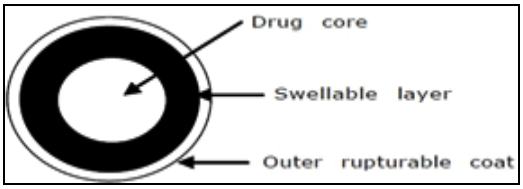


FIGURE 8: SCHEMATIC DIAGRAM OF DRUG DELIVERY WITH RUPTURABLE COATING LAYER

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

c. **Sigmoidal Release System:** This consists of pellet cores comprising drug and succinic acid coated with ammonia- methacrylate copolymer USP/NF type B. The time lag is controlled by the rate of water influx through the polymer membrane. The water dissolves acid and the drug in the core. The acid solution in turn increases permeability of the hydrated polymer film. The different types of acids that can be used include succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid.

d. **Low Density Floating Multiparticulate Pulsatile Systems:** Low density floating multiparticulate pulsatile dosage forms reside only in stomach and not affected by variability of pH, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach [20].

Stimuli induced Pulsatile Release System: The mechanisms of drug release include ejection of the drug from the gel as the fluid phase synerges out, drug diffusion along a concentration gradient, electro-phoresis of charged drugs towards an oppositely charged electrode and liberation of the entrapped drug as the gel or micellecomplex erodes.

Chemical Stimuli induced Pulsatile Systems: In these systems, there is release of the drug after stimulation by any biological factor like enzyme, pH or any other chemical stimuli. In these systems, the polymer undergoes swelling or deswelling phase in response to chemical reaction with membrane, alteration of pH

and Inflammation induce, release of drug from polymer by swelling the polymer.

1. **Glucose-responsive Insulin Release Devices:** In case of Diabetes mellitus there is rhythmic increase in the levels of glucose in the body, requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release. Examples of the pH sensitive polymers include N,N-dimethylaminoethyl methacrylate, chitosan, polyol etc.

2. **Inflammation-induced Pulsatile Release:** On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. Degradation via hydroxyl radicals however, is usually dominant and rapid when hyaluronic acid gel 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.

3. **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. Special attention was given to antigen-antibody complex formation as the cross-linking units in the gel, since such interaction is 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.

4. **pH sensitive Drug Delivery System:** pH-sensitive polymers are polyelectrolytes that bear in their structure weak acidic or basic groups that either accept or release protons in response to changes in environmental pH. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, sodium carboxymethyl-cellulose.

Thermoresponsive Pulsatile Release: The temperature variation sometimes can act as a stimulus that triggers the release of therapeutic agents from several temperature-responsive drug delivery systems for diseases accompanying fever. The temperature induced pulsatile/triggered drug delivery systems utilize various polymer properties, including the thermally reversible coil/globule transition of polymer molecules, swelling change of networks, glass transition and crystalline melting.

This type of release is classified into two classes, namely

A. Thermoresponsive polymeric micelle systems

B. Thermoresponsive hydrogel systems

A. Thermoresponsive Polymeric Micelle Systems: In this type, the gel system tightly stores targeted drug in the micelles and rapidly releases controlled amount of the drug by switching on-off of external stimuli such as temperature or infrared laser beam.

Jianxiang Zhang *et al*., synthesized thermally responsive amphiphilic poly(N-isopropylacryl-amide) (PNIPAm)- grafted-poly-phosphazene (PNIPAm-g- PPP) by stepwise cosubstitution of chlorine atoms on polymer backbones with amino-terminated NIPA oligomers and ethyl glycinate (GlyEt) [21].

Diflunisal (DIF)- loaded micelles were prepared by dialysis method. *In vitro* release test at various temperatures was also performed to study the effect of temperature on the drug release profiles.

B. Thermoresponsive Hydrogel Systems: Thermo-responsive hydrogel systems employ hydrogels which undergo reversible volume changes in response to changes in temperature. These gels shrink at a transition temperature that is referred to the lower critical solution temperature (LCST) of thelinear polymer. Thermo-sensitive hydro-sensitive hydrogels have a certain chemical attraction for water, and therefore they absorb water and swell at temperatures below the transition temperature whereas they shrink or deswell at temperatures above the transition temperature by expelling water. Thermally responsive hydrogels and membranes have been extensively exploited as platforms for the pulsatile drug delivery [22].

External Stimuli Pulsatile Release: This system is not self operated, but requires externally generated environmental changes to initiate drug delivery. This includes magnetic fields, ultrasound and electric field.

1. **Electro responsive Pulsatile Release:** Electrically responsive delivery systems are prepared from polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. Examples of naturally occurring polymers include hyaluronic acid, chondroitin sulphate, agarose, carbomer, xanthan gum and calcium alginate. The synthetic polymers are generally acrylate and methacrylate derivatives such as partially hydrolyzed olyacryl-amide, polydimethylaminopropyl acrylamide.

2. **Magnetically induced Pulsatile Release:** 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 based on magnetic attraction is the slowing down of oral drugs in the gastrointestinal system. This is possible by filling an additional magnetic component into capsules or tablets. The speed of travel through the stomach and intestines can then be slowed down at specific positions by an external magnet, thus changing the timing and/or extent of drug absorption into stomach or intestines [23-25, 26].

3. **Ultrasound induces Release:** Ultrasound is mostly used as an enhancer for the improvement of drug permeation through biological barriers, such as skin. The interactions of ultrasound with biological tissues are divided into two broad categories: thermal and nonthermal effects. Thermal effects are associated with the absorption of acoustic energy by the fluids or tissues [27]. Non-thermal bio-effects are generally associated with oscillating or cavitating bubbles, but also include non-cavitation effects such as radiation pressure, radiation torque, and acoustic streaming.

4. **Pulsatile Release Systems for Vaccine and Hormone Products:** PDDS offer the possibility of single-shot vaccines if initial booster release of the antigen can be achieved from one system in which timing of booster release is controlled. It was found that in nutritionally anoestrous cows, GnRH administered in pulses of 2 mg over 5 min every hour for 13 days produced a higher frequency of luteal activity by 13th day than cows given continuous infusions or pulses every 4 hrs [28].

Drugs which requires Pulsatile Drug Delivery:

Diseases	Chronological behavior	Drugs used
Peptic ulcer	Acid secretion is high in the noon and at night	H_2 blockers
Asthma	Precipitation of attacks during night or at early morning hours	B_2 agonist, Antihistaminics
Cardiovascular diseases	BP is at its lowest during sleep cycle and rises in early morning	Nitroglycerin, Calcium channel blocker, ACE inhibitors etc
Arthritis	Pain in the morning & more pain in the night	NSAIDs, Glucocorticoids
Diabetes mellitus	Increase in blood sugar level after meal	Sulfonylurea,Insulin, Biguanide
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than day	HMG CoA reductase inhibitors

CONCLUSION: Chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. Chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease. There is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients.

Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place & in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension, etc .Thus, designing of proper pulsatile drug delivery will enhance the patient compliance, optimum drug delivery to the target side & minimizing the undesired effects.

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