A REVIEW ON PULSATILE DRUG DELIVERY SYSTEM AND VARIOUS APPROACHES USED TO DESIGN

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Abstract: Pulsatile drug delivery is an interesting area which is gaining attention as it offers more sophisticated and better approach over the traditional sustained release and conventional drug delivery systems. The main advantages are improved dosage regimen, reduced first pass metabolism, reduced dose dumping and side effects and, better bioavailability of medicine. A well structured pulsatile system would control the fluctuations in plasma drug level by facilitating the preprogrammed drug release with a definite predetermined lag time to mimic the circadian rhythm of the disease.

A pulse is designed in such a way so as to achieve a complete and rapid drug release after the lag time which matches the circadian rhythm of body that increases the efficacy and safety of drugs by adjusting their peak plasma concentrations in synchronization with biological rhythm. This review gives an overview of various approaches employed to develop pulsatile drug delivery system.

***Keywords*: Pulsatile, polymers, circadian rhythm, bioavailability, preprogrammed, lag time.**

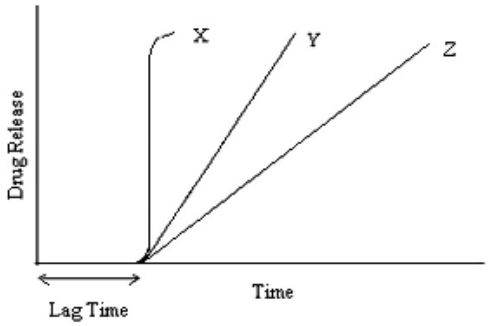
INTRODUCTION

Conventional oral controlled drug delivery system is the most preferred delivery system. This is because of the patient's compliance with oral route of drug administration. These systems release the drug in either constant or variable rate depending upon the need. The controlled release shows a specific pattern in which the drug concentration is achieved in therapeutic window for a prolonged time period (sustained release), thus ensuring continuous therapeutic effect [1]. However, there are some conditions which demand the release of drug after a lag time, which is known as chronopharmacotherapy of disease, showing the circadian rhythm in their pathophysiology. Many Studies have shown that the disease have certain cyclic rhythm which is predictable and with that the timing of medication can improve the outcome in the selected chronic conditions [2]

Recent studies have revealed that in diseases having predictable cyclic rhythms, the timing of medication can improve the outcome[3]. Drugs displaying tolerance should not be delivered at a constant rate, since the effects of drug decrease with time at a constant drug level. In addition drug toxicity increases with time, when drug levels are kept constant. Such conditions can be tackled by opting dosage forms which provide desired concentration of drug at particular time. In recent years, the concept of chronopharmaceutics has emerged. It deals with 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.

Chronopharmaceutics consist of two words chronobiology and pharmaceutics. Chronobiology is the study of biological rhythm and its mechanism [4]. Pharmaceutics is discipline of pharmacy that deals with all aspects of process turning a new chemical entity into safe and effective medication. It is the science of dosage form design which deals with formulation of pure drug substance into a dosage form.

Pulsatile drug delivery system has fulfilled this requirement. This kind of delivery is often defined as rapid and transient release of definite amount of molecules within a brief period of time immediately after a predetermined off-released period, i.e., lag time,(fig 1) 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 acknowledged as pulsatile release [5]. Chronopharmacotherapy of diseases such as bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer and hypertension show circadian rhythms in their pathophysiology and treatment of such diseases require pulsatile drug delivery systems, by which drug is released rapidly and completely as a pulse after a lag time [6].



X= complete drug release after lag time
Y = delayed drug release after lag time
Z= sustained drug release after lag time

Figure No.1: Pulsatile drug release pattern

Diseases which are required to be formulated as per Pulsatile drug delivery system are: hypercholesterolemia

- Asthma
- Cancer
- Duodenal ulcer
- Arthritis
- Diabetes
- Neurological disorders
- Cardiovascular diseases and
- Colonic delivery.

A circadian rhythm is followed by hepatic cholesterol synthesis. Therefore, cholesterol synthesis is usually higher during night time in comparison to daylight. The maximum production occurs early in the morning, i.e. 12 hrs after last meal [7].

Need of Pulsatile drug delivery [8, 9].

- When circadian rhythm is altered by the hormone such as rennin, aldosterone and cortisol etc level in blood.
- When rhythmic variation seen in acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion.
- Disease like bronchial asthma, myocardial infraction, angina pectoris, rheumatic disease, ulcer, and hypertension display time dependence.
- The lag time is essential for the drugs that undergo degradation in gastric acidic medium.
- It is possible to deliver the drugs to the distal part of GIT like colon targeting with pulsatile drug delivery
- Drugs that undergo extensive first-pass metabolism are administered successfully as pulsatile drug delivery systems.

Advantage of pulsatile drug delivery system [10, 11]

- Due to its ability to release drug in a burst manner, it increases absorption and bioavailability at target site of absorption.
- Limit risk of mucosal irritation.
- Loss of drug by extensive first pass metabolism is prevented.
- Chronotherapy, programmed delayed release provides optimal treatment of diseases.
- Decreases drug interaction due to lower cytochrome P450 isoenzymes.
- Avoidance of undesirable side effects.
- Improved patient compliance.
- Flexibility in design.

Disadvantage of pulsatile drug delivery system [12]

- Low drug loading capacity and incomplete release of drug
- Lack of manufacturing reproducibility and efficacy
- Large number of process variables.
- Higher cost of production.
- Batch manufacturing process
- Unpredictable
- Body function that follow circadian rhythms IVIVC.
- Need of advanced technology

APPROACHES FOR PULSATILE DRUG DELIVERY [13]

Different approaches of pulsatile system are generally divided as follows:

- Osmotic pressure based systems
- Reservoir systems with rupturable coating
- Reservoir systems with swellable/ erodible/soluble coatings
- Reservoir systems with diffusive polymeric coating
- Capsular systems with polymeric plugs
- Stimuli induced pulsatile release system

1. Osmotic pressure based pulsatile drug delivery systems

The various types of osmotic pulsatile delivery systems are discussed below

1.1 The PORT system

The Port system is based on a semipermeable capsule body divided into compartments by a slidable separator (Fig.2). It consists of a hydrophilic, swellable container, such as a hard gelatin or hydroxypropyl methylcellulose capsule body that has been coated with a semi permeable film. Inside the capsule body are two compartments formed by a non swelling, slidable separator. One or both of the compartments can contain drug while the lower compartment below the separator contains water-soluble excipients.

The mechanism of action for drug release begins as water diffuses through the semipermeable membrane into the capsule body. The water-soluble formulation components contained in the capsule body are solubilized by the influx of water creating an osmotic pressure gradient between the inside of the capsule and the outside gastrointestinal environment. The hydrostatic pressure inside the capsule body pushes the slidable separator out as more water enters the capsule through the membrane. At a predesigned time, the separator slides completely out of the capsule body and the contents are released. [14, 15, 16, 17, 18]

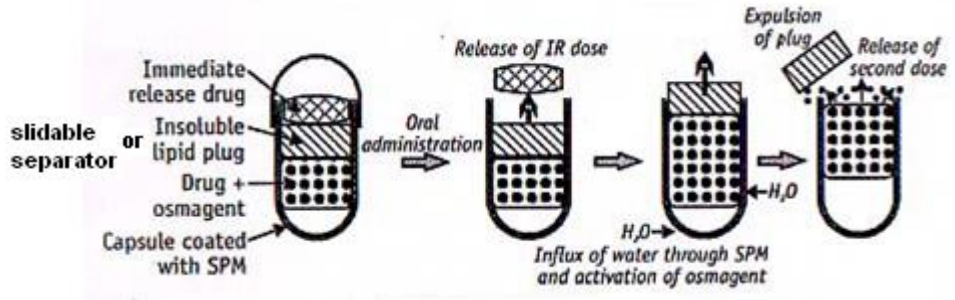


Figure No. 2: PORT system for pulsatile release

1.2 Capsule or tablet composed of large number of pellets

Each pellet has therapeutic drugin the centre with water soluble osmotic agent. This is enclosed by a water permeable but insoluble polymer film. On exposure to water and its subsequent penetration into the pellets, the osmotic agent dissolves which causes the pellet to swell and there by regulate the rate of diffusion of drug from the dosage form (Fig 3). The pellets may be designed for the single pulse or may be differently coated to give multiple pulses. [19]

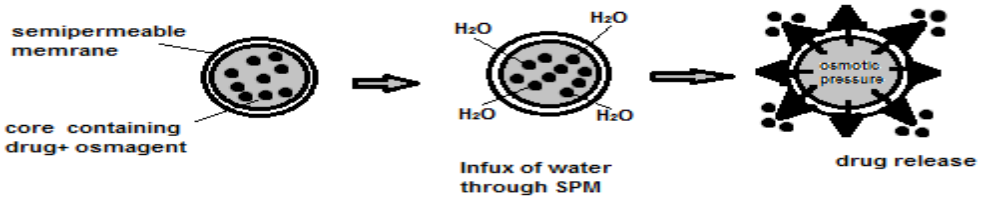


Figure No. 3: Pellet type pulsatile drug delivery system.

1.3 Chronset system

The underline mechanism in release of this drug is osmotically active layer in the semi permeable vessel. This layer pushes the cap out off the impermeable vessel after a predetermined interval [20]. The full release of the drug, which is generally problematic in capsular-shaped dosage forms, is achieved by an expanding layer at the bottom of the capsule body.

2. Reservoir systems with rupturable coatings

This system consists of a drug in the core, covered by a pressure generated layer and an outer insoluble, semi permeable polymer coating(Fig 3).The pressure generating layer comprises of effervescent excipients(mixture of citric/ tartaric acid and sodium bicarbonate), swelling agents or omagents such as cellulose ethers, polysaccharides, ion exchange resins, or superdisintegrants. In contact with gastrointestinal fluid, water penetrates through the outer polymer coating and generates the pressure due to effervescence, hydration of swelling polymer or osmosis. This in turn ruptures the external polymer coating leading to rapid drug release[21, 22] .The lag time prior to the rupture is mainly controlled by two factors

- ✓ The permeation and mechanical properties of the polymer coating, and
- ✓ The degree of pressure generated by the effervescent agents, swelling agents or osmagents.[23, 24]

Figure No. 3: Typical designs of rupturing pulsatile drug delivery system.
D--drug containing core; DS - drug containing core with swelling capacity;
S - swelling layer; M - water permeable insoluble membrane.

Rupturable coated pulsatile systems can be designed as monolithic system or as multiparticulates. Some of the examples of rupturable systems are discussed below.

2.1 Time controlled explosion system

It has a four layered spherical pellet structure, consisting of an inert core surrounded by a layer of drug, swelling agent and a water insoluble polymer membrane made up of ethyl cellulose. It is characterized by rapid drug release with a programmed lag time. When water penetrates through the polymer membrane, the swelling agent expands, leading to destruction of the membrane with subsequent drug release. [25, 26, 27, 28, 29]

2.2 Compression coated/ press coated pulsatile release tablets

It comprises of core tablet containing a large amount of disintegrant together with active ingredient which is press coated with an outer shell of ethyl cellulose that controls water penetration. When pulsatile release tablet is administered orally, water penetrates through the outer shell slowly depending upon the thickness and composition of coating. Once the water reaches the core of pulsatile release tablet, the disintegrant swells and collapses the outer shell due to the high swelling pressure to release the contents as a pulse. Press coated tablet can be designed for time release by modulating the coat instead of drug core by making the former swellable, soluble, erodible or disintegratable which detaches itself from the drug core after a certain lag time. [30, 31, 32, 33]

3. Reservoir systems with swellable/erodible/soluble coatings

In this drug delivery system, drug release occurs through barrier or polymer coatings, which dissolves, swells or erode after a specific lag period, following which the drug is released rapidly from the reservoir core (Fig 4) [34]

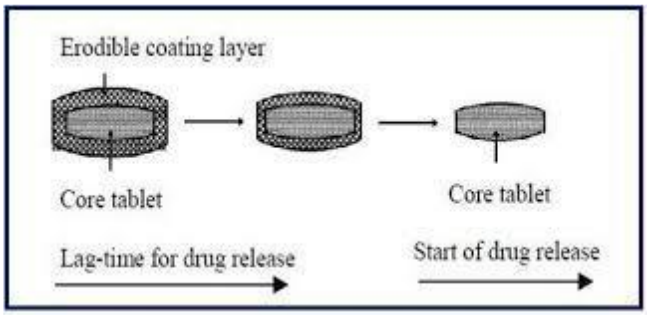


Fig No. 4: Schematic diagram of drug delivery with erodible coating layer.

Some examples of reservoir systems with swellable/erodible/soluble coatings are discussed below.

3.1 Time clock system

The Time Clock system is proposed for oral dosage form, which enables fast and complete release of drug after a predetermined lag time. A tablet containing the drug molecule and bulking agents (lactose, polyvinylpirrolydone, corn starch and magnesium stearate) is prepared. This drug core is coated with a hydrophobic dispersion of carnauba wax, beeswax, polyoxyethylene sorbitan monooleate and HPMC in water. By changing the thickness of coating the lag time can be modulated. In vitro results indicated rapid release after certain lag time for the Time Clock system with a hydrophobic coating. This approach may also be used to control the release onset time. Since the drug core is contains soluble ingredients so dissolution/ disintegration of coating becomes the key factor in controlling the lag time. Moreover, normal physiological conditions such as pH, digestive state and anatomical position at the time of release do not affect the drug release. [35, 36]

3.2 Hydrophilic Sandwich (Hs) Capsule

It is a manually assembled delivery system based on a capsule-within a capsule, in which the inter capsular space was filled with a layer of hydrophilic polymer (HPMC). This effectively created a "hydrophilic sandwich" between the two gelatin capsules. When the outer capsule dissolved, the sandwich of HPMC formed a gel barrier layer that provided a time delay before fluid could enter the inner capsule and cause drug release [37]. The time delay was controlled by the molecular weight of the polymer and could be further manipulated by the inclusion of a soluble filler e.g., lactose, in the hydrophilic layer (Fig.5).

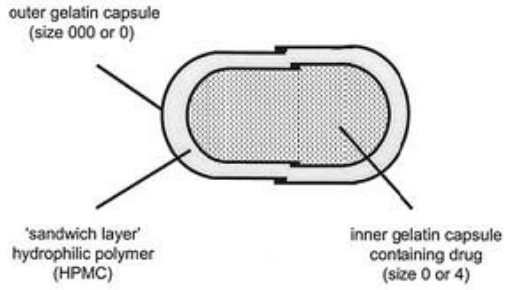


Figure No. 5: Hydrophilic Sandwich (Hs) Capsule

3.3 Chronotropic system

Chronotropic system consists of a drug containing core and an HPMC layer, optionally coated with an outer enteric coating. The lag time prior to drug release was controlled by the thickness and viscosity grade of the HPMC layer. With the degradation of the HPMC layer, a distinct pulse was observed. To avoid the retarding effects in the drug release phase, the thickness as well as the viscosity grade of the HPMC layer should be limited. The system works best for poorly water soluble drugs, because highly water-soluble drugs may diffuse through the swollen HPMC layer prior to complete erosion. This system is not particularly well suited for the applications to multiparticulate systems, because relatively thick barrier layers were needed and the resulting drug loading of the system, often more critical in multi dose systems, could be further decreased. [38, 39, 40, 41]

4 Reservoir systems with diffusive polymeric coating

A typical example of this system is sigmoidal release system (SRS), multiparticulate drug delivery system comprising of drug/succinic acid mixture loaded on nonpareil seeds and an outermost Eudragit RS film applied by spray coating. The lag time is controlled by the rate of water influx through the polymer membrane. The water dissolves succinic acid, and the drug in the core and the acidic solution in turn increases the permeability of the hydrated polymer film by interaction with quaternary ammonium groups contained in acrylic polymer there by permitting the dissolved drugs to diffuse out. [42, 43, 44]

5. Capsular systems with polymeric plugs

Several single unit pulsatile dosage forms with a capsular design have been developed. Most of them consist of an insoluble capsule body, which contains the drug, and a plug, which prevents drug release during the lag phase. Mechanisms of plug removal include dissolution, erosion, or induced pushing out of the plug by swelling or osmotic pressure.

5.1 The Pulsincap system

It consists of a capsule with water soluble cap, an insoluble body (hard gelatin capsule coated with ethyl cellulose), filled with the drug formulation and sealed with a hydrogel plug. On administration, the soluble cap dissolves there by allowing the hydrogel plug to swell and expand. The plug swells and pushes itself out of the capsule after a lag time, followed by a rapid release of the drug content (Fig.6). The lag time is controlled by the dimension and the position of the hydrogel plug. In order to ensure rapid release of the drug content, effervescent agents or disintegrants can be added in the drug formulation, with water insoluble drugs [45, 46, 47].

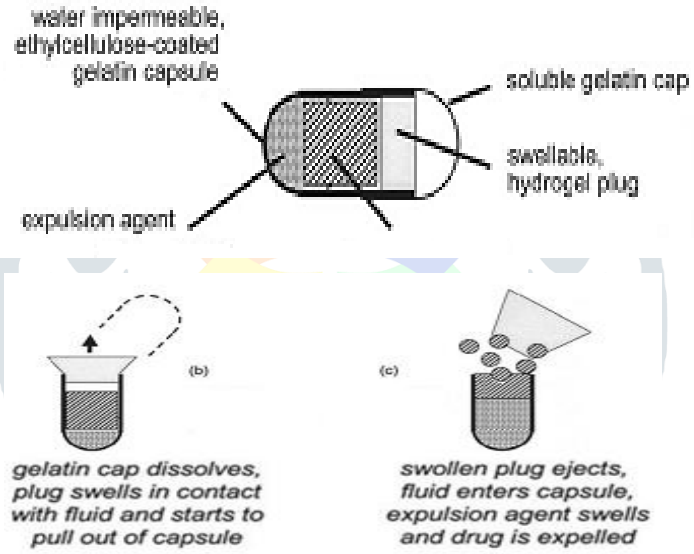


Figure No. 6: Pulsincap delivery system

5.2 Pulsatile capsule device with erodible tablet plug

This system is similar to that of Pulsincap system but only difference is that they employed a simple erodible compressed tablet in place of the swelling hydrogel plug (Fig.7). Since the tablet eroded in place, it did not move relative to the capsule body and this factor overcame the need for the precise dimensional tolerances between plug and capsule required by the sliding mechanism of the plug in the earlier Pulsincap formulations. [48, 49]

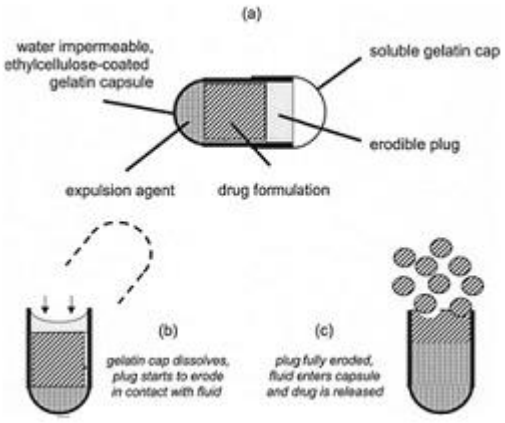


Figure No. 7: Erodible plug time delayed capsule

6. Stimuli induced pulsatile release system

6.1 pH sensitive drug delivery system

This type of Pulsatile drug delivery system contains two components rapid release type and pulsed release type. The release of the drug in this system is dependent on the fluctuation in pH. The principle of this system is the difference in the pH environment in different parts of the gastrointestinal tract. By selecting the pH dependent polymers optimum drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose [50, 51].

CONCLUSION

Pulsatile drug delivery system is intended to release the drug according to the circadian cycle of the disease as per the physiological need of the patient. The sudden release of the drug can be achieved by altering the mechanism of PDDS formulation. Circadian rhythm dependent disease demand different lag times depending upon the type of disease, and lag time can be modified by adopting these approaches. Various research works are focusing on the pulsatile drug delivery to discover circadian rhythm with suitable device. In future this way of drug delivery will be a leading way to deliver therapeutic agents due to its unique characters like low probability of dose dumping and higher patient compliance.

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