International Journal for Pharmaceutical Research Scholars (IJPRS)

V-4, I-2, 2015 ISSN No: 2277 - 7873

REVIEW ARTICLE

Review on Pulsatile Drug Delivery System

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Manuscript No: IJPRS/V4/I2/00456, Received On: 24/04/2015, Accepted On: 01/05/2015

ABSTRACT

The recent research on modified release drug delivery systems gives special attention to pulsatile drug delivery systems because of its unique release pattern. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the lag time so as to match body's circadian rhythms with the release of drug which increases the efficacy and safety of drugs by proportioning their peak plasma concentrations during the 24 hours in synchrony with biological rhythm. The aim of this review is to describe several types of drug delivery systems. The data include rational behind the use of chronotherapeutic release of drug and application in various diseases and prerequisites of drug for pulsatile drug delivery system. Advantages, disadvantages and commercial marketed technologies of pulsatile drug delivery system launched by pharmaceutical companies is also included in data.

KEYWORDS

Pulsatile release, Chronopharmaceutics, Modified drug delivery systems, Time controlling, Stimuli induced, Externally regulated, Multiparticulate system

INTRODUCTION

Modified release dosage forms have acquired a great importance in the current pharmaceutical R&D business. Such systems offer control over the release pattern of drug and provide better control over drug regimen. Such systems release the drug with predetermined release rates, either constant or variable. These dosage forms offer numerous advantages, such as nearly stable plasma drug level without much fluctuations, reduction in dose of drug, reduced dosage frequency, least side effects, and improved patient compliance. Modified release dosage forms show different release profiles depending on their type. Sustain release dosage forms may maintain nearly constant plasma drug concentration in therapeutic window for prolonged time as shown in the Figure 1(A).

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Pulsatile release dosage forms release drug in pulsatile manner and maintain plasma drug level within therapeutic range as shown in figure 1[1].

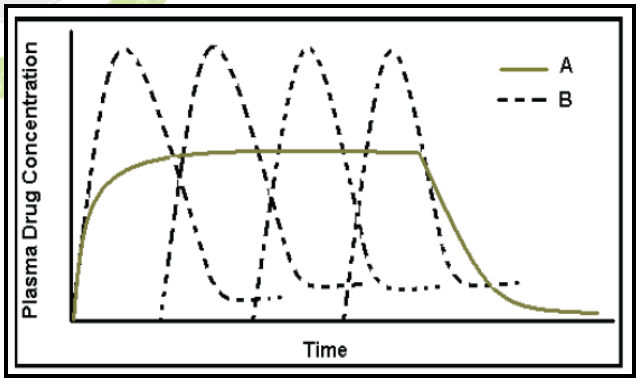

Figure 1: Release pattern of Sustained (A) and Pulsatile Release (B)

Pulsatile system is amongst one of them and gaining a lot of interest as it is increasing patient compliance by means of providing time- and site-specific drug delivery system, thus providing special and temporal delivery[2]. 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[3]. Recent studies show that diseased have predictable cyclic rhythms and the timing of medication regimens can improve outcome in selected chronic conditions[4]. Numerous studies conducted, suggest that pharmacokinetics, drug efficacy and side effects can be modified by following therapy matching the biological rhythm. 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 [5-7].

"Chronopharmaceutics" consists of two words chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. There are three types of mechanical rhythms in our body. They are:

i. Circadian: "Circa" means about and "dies" means day

ii. Ultradian: Oscillation of shorter duration are termed as ultradian (more than one cycle per 24 h)

iii. Infradian: Oscillations those are longer than 24 h (less than one cycle per day)

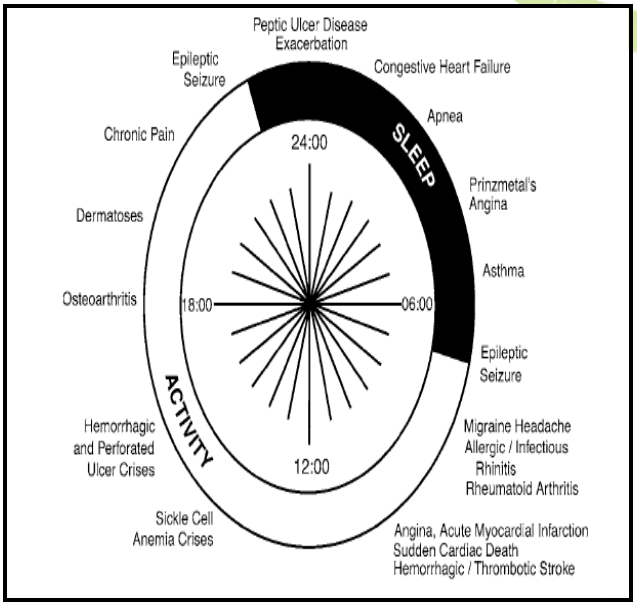

Figure 2: Schematic diagram of circadian rhythm showing diseases require PDDS

Necessities of Pulsatile DDS

1. 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.

2. Biological Tolerance

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

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

5. Gastric Irritation or Drug Instability in Gastric Fluid

Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (eg, peptide drugs), irritate the gastric mucosa (NSAIDS) or induce nausea and vomiting[1,8].

Merits[8]

- 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[8]

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

Formulation Consideration

Different approaches of pulsatile system are broadly divided as follows:

1. Time controlled,
2. Internal stimuli induced,
3. Externally regulated,
4. Multiparticulate.

1. Time Controlled System

In time controlled drug delivery system, drug is released in pulsatile manner after specific time interval in order to coincide the drug with proper site, thus mimic the circadian rhythm[10].

A. Pulsatile Delivery by Solubilisation or Erosion of layer

In such systems, the core containing drug is coated with the soluble or erodible polymer as outer coat and drug release is controlled by the dissolution or erosion of the outer coat[2]. Time dependent release of the drug can be obtained by optimizing the thickness of the outer coat as shown in Figure 3. e.g. The Time Clock® system[11,12] and the Chronotropic® system[13].

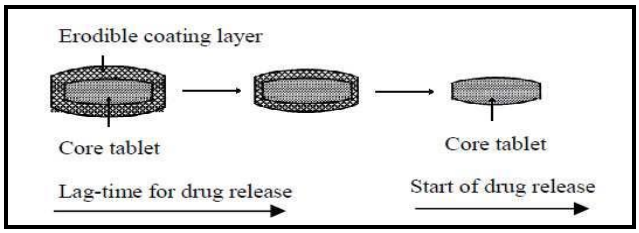

Figure 3: Schematic diagram of drug delivery with erodible coating layer

B. Pulsatile Delivery by Rupture of Membrane

In place of swelling or eroding, these systems are dependent on the disintegration of the coating for the release of drug. The pressure necessary for the rupture of the coating can be achieved by the swelling, disintegrants, effervescent excipients, or osmotic pressure. Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time.

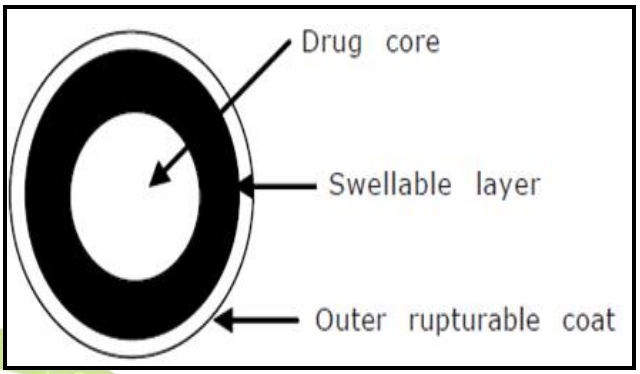

Figure 4: Schematic diagram of drug delivery with rupturable coating layer

C. Capsule Shaped Pulsatile Drug Delivery System

This dosage form consists of an insoluble capsule body containing a drug and swellable and degradable plugs made of approved substances such as hydrophilic polymers or lipids and release controlling plug between immediate release compartment and pulsed release compartment. On contact with aqueous fluids, the cap rapidly dissolves thereby releasing the immediate release component followed by pulsed release component. The length of plug decides lag time[14,15].

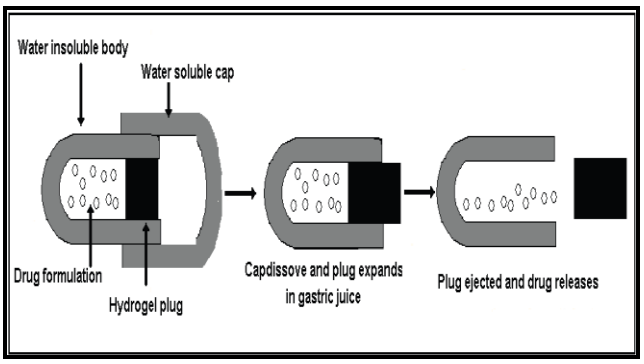

Figure 5: Schematic diagram of release of drug from capsule

D. Pulsatile System Based On Osmosis

Osmotic system consists of capsule coated with the semipermeable membrane. Inside the capsule there is an insoluble plug consisting of osmotically active agent and the drug formulation[16].

e.g. The Port® System[17]

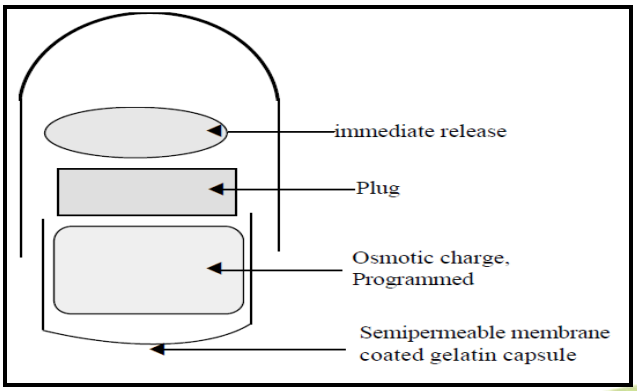

Figure 6: Schematic diagram of osmosis system

Internal Stimuli Induced System

In these systems, the release of the drug takes place after stimulation by any biological factor like temperature, or any other chemical stimuli[18]. Many of the polymeric delivery systems experience phase transitions and demonstrate marked swelling-deswelling changes in response to environmental changes including solvent composition ionic strength, temperature, electric fields, and light[19].

A. Temperature–Induced Pulsatile Release

This deviation 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 [19-24].

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 the linear polymer. Thermo-sensitive hydrosensitive 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 [25].

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 isopropylacrylamide) (PNIPAm)-grafted polyphosphazene (PNIPAm-g- PPP) by stepwise cosubstitution of chlorine atoms on polymer backbones with amino-terminated NIPAm oligomers and ethyl glycinate (GlyEt)[25]. 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. 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.

C. Glucose-Responsive Insulin Release Devices

In a glucose-rich environment, such as the bloodstream after a meal, the oxidation of glucose to gluconic acid catalysed by glucose oxidase can lower the pH to approximately 5.8. This enzyme is probably the most widely used in glucose sensing, and makes possible to apply different types of pH sensitive hydrogels for modulated insulin delivery[26]. 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. Kazunori Kataoka, et al reported remarkable change in the swelling induced by glucose demonstrated for the gel composed of PNIPAAm with phenylboronic acid moieties. On-off regulation of insulin release from the gel achieved through a drastic change in the solute transport property as a result of the formation and disruption of the surface barrier layer of the Gel[27].

D. 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 carboxy methyl cellulose.

E. Inflammation-Induced Pulsatile Release

Physical or chemical stress, such as injury, broken bones, etc., initiates inflammation reactions, because of which hydroxyl radicals ('OH) are produced from these inflammation-responsive cells. Yui et al. designed drug delivery systems based on the polymers which responded to the hydroxyl radicals and degraded in a limited manner. Yui and co-workers used hyaluronic acid (HA), in the body, HA is mainly degraded either by hydroxyl radicals or a specific enzyme, hyaluronidase. Degradation through hydroxyl radicals however, is usually dominant and rapid when HA is injected at inflammatory sites. Thus, they designed crosslinked HA with ethylene glycol diglycidylether or polyglycerol polyglycidylether Thus, a surface erosion type of degradation was achieved. Patients with inflammatory diseases, such as rheumatoid arthritis, can be treated using this type of system[28,29].

F. Drug Release from Intelligent Gels Responding to Antibody Concentration

Miyata et al. focused on the development of stimuli responsive crosslinking structures into hydrogels. Special care was given to antigen-antibody complex formation as the cross-linking units in the gel, since specific antigen recognition of an antibody can provide the foundation for a new device fabrication. Using the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/deswelling and drug permeation changes could occur. Thus, biological stimuli responsive hydrogels were created[30,31].

G. Enzymatically-activated Liposome

Drug loaded liposomes was incorporated into microcapsules of alginate hydrogels. Liposomes inside the microcapsules were coated with phospholipase A2 to achieve a Pulsatile release of drug molecules. Phospholipase A2 was shown to accumulate at the water/liposome interfaces and remove an acyl group from the phospholipids in the liposome. Destabilised liposomes release their drug molecules, thus allowing drug release to be regulated by the rate determining microcapsule membrane[32,33].

Externally Regulated Pulsatile Release System

This system is not self-operated, but instead requires externally generated environmental changes to initiate drug delivery. These can include magnetic fields, ultrasound, electric field, light, and mechanical force.

A. Magnetic Induces Release

Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials such as magnetite, iron, nickel, cobalt etc. Magnetic-sensitive behaviour of intelligent ferrogels for controlled release of drug was studied by Tingyu Liu, et al. An intelligent magnetic hydrogel (ferrogel) was fabricated by mixing poly (vinyl alcohol) (PVA) hydrogels and Fe_3O_4 magnetic particles through freezing-thawing Cycles[34]. Although the external direct current magnetic field was applied to the ferrogel, the drug got accumulated around the ferrogel, but the accumulated drug spurt to the environment instantly when the magnetic fields instantly switched “off”. Furthermore, rapid slow drug release can be tunable while the magnetic

field was switched from "off" to "on" mode. The drug release behaviour from the ferrogel is strongly dominated by the particle size of Fe_3O_4 under a given magnetic field[35]. Tingyu Liu, et al developed the magnetic hydrogels which was successfully fabricated by chemically crosslinking of gelatin hydrogels and Fe_3O_4 nanoparticles (ca. 40–60 nm) through genipin (GP) as cross-linking agent[36].

B. 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 is divided into two broad categories: thermal and nonthermal effects. Thermal effects are associated with the absorption of acoustic energy by the fluids or tissues[38]. Non-thermal bio-effects are generally associated with oscillating or cavitating bubbles, but also include noncavitation effects such as radiation pressure, radiation torque, and acoustic streaming.

C. Electric Field Induces Release

Electrically responsive delivery systems are prepared by polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. Under the influence of electric field, electro-responsive hydrogels generally bend, depending on the shape of the gel which lies parallel to the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes. An electroresponsive drug delivery system was developed by R. V. Kulkarni, et al., using poly(acrylamide-grafted-xanthan gum) (PAAm-g- XG) hydrogel for transdermal delivery of ketoprofen[38].

D. Light Induces Release

Light-sensitive hydrogels have potential applications in developing optical switches, display units, and opthalmic drug delivery devices[39]. The interaction between light and material can be used to modulate drug delivery. When hydrogel absorb the light and convert it to heat, raising the temperature of composite hydrogel above its LCST[40], hydrogel collapses and result in an increased rate of release of soluble drug held within the matrix.

Multipaticulate System

Recent trends indicate that multiparticulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. Such systems are reservoir type with either rupturable or altered permeability coating and generally housed in capsular body. The purpose of designing multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulation and yet devoid of the danger of alteration in drug release profile and formulation behaviour due to unit to unit variation[41].

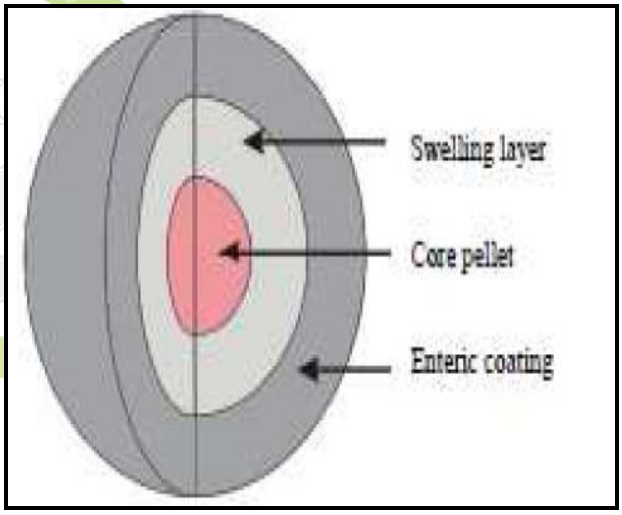

Figure 7: Hypothetical design of a multiparticulate pulsatile system

Andrei Dashevsky, et al. developed a pulsatile multiparticulate drug delivery system (DDS), coated with aqueous dispersion of Aquacoat® ECD. A rupturable pulsatile drug delivery system consists of (i) a drug core; (ii) a swelling layer, comprising a superdisintegrant and a binder; and (iii) an insoluble, water-permeable polymeric coating[42]. Upon water ingress, the swellable layer expands, resulting in the rupturing of outer membrane with subsequent rapid drug release. Regarding the cores, the lag time was shorter; theophylline was layered on sugar cores

compared with cores consisting of theophylline. Regarding swelling layer, the release after lag time was fast and complete. Drug release was achieved after the lag time, when low-substituted hydroxypropyl cellulose (L-HPC) and sodium starch glycolate (Explotab®) were used as swelling agents. Outer membrane, formed using aqueous dispersion Aquacoat® ECD was brittle and ruptured sufficiently to ensure fast drug release, compared to ethylcellulose membrane formed using organic solution. The addition of talc led to increase brittleness of membrane and was very advantageous. Drug release starts only after rupturing of outer membrane.

C. Sun, et al. developed novel pH sensitive copolymer microspheres containing methylacrylic acid and styrene cross-linking with divinylbenzene were synthesized by free radical polymerization. The copolymer microspheres showed pulsatile swelling behavior when the pH of the media changed. The pH sensitive microspheres were loaded with diltiazem hydrochloride (DH)[43]. The release characteristics of the free drug and the drug-loaded microspheres were studied under both simulated gastric conditions and intestinal pH conditions. The in vivo evaluation of the pulsatile preparation was subsequently carried out using beagle dogs.

Sigmoidal Release System: This consists of pellet cores containing drug and succinic acid coated with ammoniomethacrylate copolymer USP/NF type B[44]. 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 acid solution in turn increases permeability of the hydrated polymer film.

In addition to succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid can be used. The increased permeability can be explained by improved hydration of film, which increases free volume. These findings were used to design a coated delivery system with an acid containing core[45,46]. The in-vitro lag time correlated well with in-vivo data when tested in beagle dogs[47].

Marketed Technologies of Pulsatile System

Technology	Mechanism	API	Ref.
Pulsys®	Timed-controlled System	Amoxicillin	48
Uniphyl®	Externally regulated System	Theophylline	48
Ritalina®	Osmotically regulated	Methyl Phenidate	48
CODAS®	Multiparticular pH dependent system	Verapamil HCl	49
DIFFUCAPS®	Multiparticulate system	Verapamil HCl, Propranolol HCL	50

CONCLUSION

It is known that sustained and controlled release products provide a desired therapeutic effect, but fall for diseases following biological rhythms. So there is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients by delivering drug at the right time, right place & in right amounts to coincide with circadian rhythm of body. Various methodologies are employed for developing pulsatile drug delivery like time controlled, stimuli induced, externally regulated system and multiparticulate drug delivery system. These considerations, along with the potential therapeutic benefits of pulsatile drug delivery systems, should ensure that the current high level

of interest in this area would stretch well into future and ensures the betterment of quality life.

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