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RECENT TRENDS IN PULSATILE DRUG DELIVERY SYSTEMS: A REVIEW

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Keywords:

Pulsatile Drug Delivery Systems, Chronopharmaceutics, Modified drug delivery systems, Time controlling, Stimuliinduced, Multiparticulate system

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ABSTRACT

Pulsatile Drug Delivery Systems are gaining a lot of interest as they deliver the drug at the right place at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. Diseases wherein PDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children, and hypercholesterolemia. The principle rationale for the use of pulsatile release of the drugs is where a constant drug release is not desired. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the lag time. Various systems like capsular systems, osmotic systems, single and multiple-unit systems based on the use of soluble or erodible polymer coating and use of rupturable membranes have been dealt with in the article.The current article focuses on the diseases requiring PDDS, methodologies involved for the existing systems, current situation and future scope, recent advances in PDDS and PDDS product currently available in the market.

INTRODUCTION

The oral route of drug delivery is typically considered the favored and the most having the highest degree of patient compliance because of user-friendly means of drug administration.[1]Traditionally, drug delivery systems have focused on constant/sustained drug output with the objective to optimize drug efficacy and to reduce adverse effects. A reduced dosing frequency and improved patient compliance.[2] Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. The release of the drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows the lag time. These systems are designed according to the circadian rhythm of the body. 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[3]. "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" meansday. ii)Ultradian:Oscillation of shorter duration are termed as ultradian (more than one cycle per 24 h).iii) Infradian:Oscillations that are longer than 24 h (lessthan one cycle per day)[4,5].

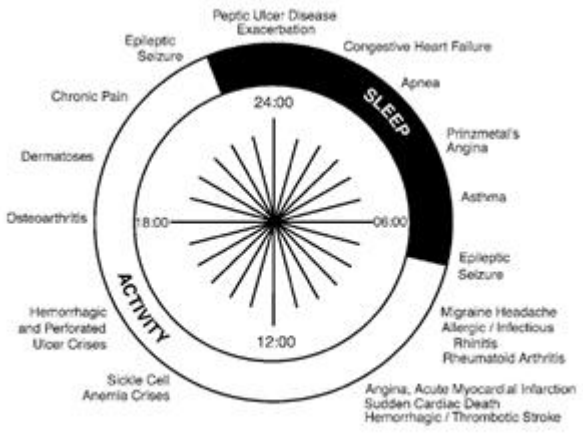

Fig 1: Schematic diagram of circadian rhythm showing diseases require PDDS.

Many systems in the human body such as cardiovascular, pulmonary, hepatic and renal systems how variation in their function throughout a typical day. They are naturally synchronized by the internal body clocks and are controlled by the sleep wake cycle.

Each bodily system exhibits a peak time of functionality that is in accordance with these rhythmical cycles. Similarly, disease states affect the Function of some of these systems in the body and therefore, they too exhibit a peak time of activity within a circadian rhythm[6]. A delivery system with a pulsatile release profile where the drug is released completely after a defined lag time is 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[7, 8].

Necessity of Pulsatile Drug Delivery Systems: There are many conditions and diseases where sustained release formulations do not show good efficacy so these conditions demand the releaseof drug after a lag time in, in other words it is required that the drug should not release at all during the initial phase of dosage form administration. In such cases Pulsatile DDS is applicable.

1. Many body functions follow circadian rhythm, i.e., their activity increases or decreases with time. A number of hormones like rennin, aldosterone, and cortisol show daily as well as timely fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion.
2. Severity of diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension is time dependent. Sharp increase in asthmatic attacks during early morning hours have been reported by Dethlefsan and Repges such a condition demands supplement of drug at particular time rather than maintaining constant plasma drug level. A drug delivery system administered at bedtime, but releasing drug as a burst after the time of administration (during morning hours), would be ideal in this case. Same is true for preventing heart attacks in the middle of the night and the morning stiffness typical of people suffering from arthritis.
3. Drugs like Salbutamol sulphate produce biological tolerance and hence demand for a system that will prevent their continuous presence at the site of action as this tends to reduce their therapeutic effect.

4. Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (e.g., peptide drugs), irritate the gastric mucosa (NSAIDS) or induce nausea and vomiting. These conditions can be satisfactorily handled by enteric coating, and in this sense, enteric coating can be considered as a pulsatile drug delivery system.
5. To achieve localized action at distal organs of GIT such as colon for drugs used in ulcerative colitis (e.g. Sulfasalazine) the drug release needs to be prevented in the upper two-third portion of the GIT.
6. The drugs that undergo extensive first-pass metabolism (ß-blockers) and those that are characterized by idiosyncratic pharmacokinetics or pharmacodynamics resulting in reduced bioavailability, altered drug/metabolite ratios, altered steady state levels of drug and metabolite,and potential food-drug interactions require delayed release of the drug to the extent possible[9].

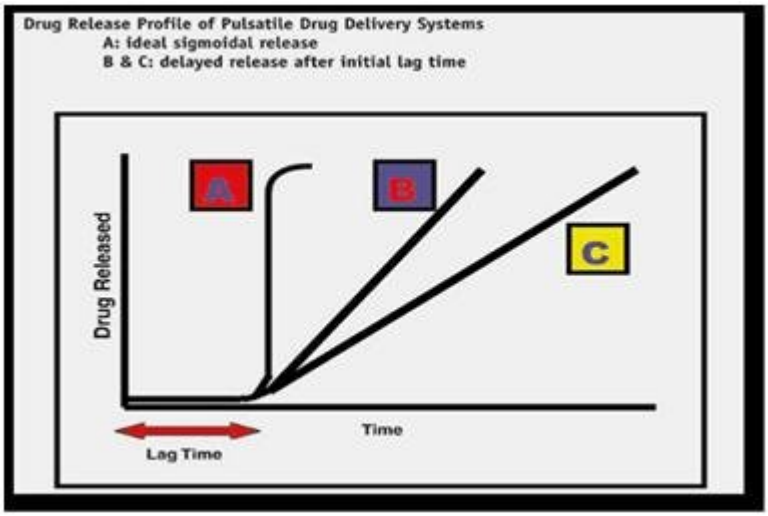

Fig 2: Drug release profile of pulsatile drug delivery systems

All of these conditions demand for an efficiently programmed drug delivery system releasing the right amount of drug at the right time. This can be achieved by Pulsatile Drug Delivery Systems. A pulsatile drug delivery system is characterized by a rapid drug release after a predetermined lag time that is an interval of no drug release[10].

DISEASES TARGETED FOR PULSATILE DRUG DELIVERY SYSTEM:

Diseases presently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify PDDS- compared to the conventional

drug administration approach[11]. They include: hypercholesterolemia, asthma, cancer, duodenal ulcer, arthritis, diabetes, neurological disorders, cardiovascular diseases (e.g., hypertension and acute myocardial infarction) and colonic delivery. The rationale for chronotherapy/pulsatile release of these diseases will be briefly reviewed below[12].

Asthma: The chronotherapy of asthma has been extensively studied. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients[13]. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. As broncho constriction and exacerbation of symptoms vary in a circadian fashion, asthma is well suited for chronotherapy. Chronotherapies have been studied for asthma with oral corticosteroids, theophylline, and β2-agonists[14].

Arthritis: The chronobiologies of pain have been extensively reviewed. For instance, there is a circadian rhythm in the plasma concentration of C - reactive protein and interleukin-6 in patients with rheumatoid arthritis. Increasingly, the arthritis have shown statistically quantifiable rhythmic parameters. Included in the latter group are joint pain and joint size. In addition, a number of drugs used to treat rheumatic diseases have varying therapeutic and toxic effects based on the time of day of administration Patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day. Chronotherapy for all forms of arthritis using NSAIDs such as ibuprofen should be timed to ensure that the highest blood levels of the drug coincide with peak pain. For osteoarthritis sufferers, the optimal time for a non steroidal anti-inflammatory drug such as ibuprofen would be around noon or mid-afternoon. The same drug would be more effective for people with rheumatoid arthritis when taken after the evening meal[15,16].

Duodenal ulcer: Many of the functions of the gastrointestinal tract are subject to circadian rhythms: gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are all slower at night. During night time, when gastric motility and emptying are slower, drug disintegration, dissolution, and absorption may be slower. In peptic ulcer patients, gastric acid secretion is highest during the night.

Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Therefore, for active duodenal ulcer, once daily at bedtime is the recommended dosage regimen for an H2 antagonist[17, 18].

Hypercholesterolemia: Diverse directions of circadian changes in lipid fractions in patients and normal subjects may contribute to alteration in the rhythm city of other metabolisms and in the blood coagulation system, thus leading to various complications. A circadian rhythm occurs during hepatic cholesterol synthesis. However, this rhythm varies according to individuals. Indeed, there is a large variation in plasma mevalonate concentrations between individuals. Therefore cholesterol synthesis is generally higher during the night than during daylight, and diurnal synthesis may represent up to 30%–40% of daily cholesterol synthesis. Many individuals display a paradoxical synthesis, with an inverted diurnal cholesterol synthesis. It seems therefore that cholesterol is synthesized during the night as well as during daylight; however the maximal production occurs early in the morning, i.e. 12 h after the last meal. Studies on HMG COA reductase inhibitors have suggested that evening dosing was effective than morning dosing[19].

Neurological disorders: As an integrative discipline in physiology and medical research, chronobiology renders the discovery of new regulation processes regarding the central mechanisms of epilepsy. Chronophysiology investigations considered at a rhythmometric level of resolution suggest several heuristic perspectives regarding (i), the central pathophysiology of epilepsy and (ii) the behavioural classification of convulsive events[20].

Cancer: Human and animal studies suggest that chemotherapy may be more effective and less toxic if cancer drugs are administered at carefully selected times that take advantage of tumour cell cycles while less toxic to normal tissue[21,22]. The blood flow to tumours was threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase[23]. The chronotherapy concept offers further promise for improving current cancer-treatment options, as well as for optimizing the development of new anticancer or supportive agents[24].

Hypercholesterolemia: Diverse directions of circadian changes in lipid fractions in patients and normal subjects may contribute to alteration in the rhythmicity of other metabolisms and in the blood coagulation system, thus leading to various

complications[25]. A circadian rhythm occurs during hepatic cholesterol synthesis. Therefore, cholesterol synthesis is generally higher during the night than during daylight, the maximal production occurs early in the morning, i.e., 12 h after the last meal[26, 27].

Cardiovascular diseases: Several functions such as, Blood pressure (BP), heart rate, stroke volume, cardiac output, blood flow of the cardiovascular system is subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood[28]. It was postulated that modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events. BP is at its lowest during the sleeping period and rises steeply during the early morning period. Most patients with essential hypertension have a similar circadian rhythm of BP as do normotensive persons, hypertensive patients have upward shift in profile[29].

Diabetes: The circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importances in case of insulin substitution in type I diabetes have been previously discussed. The goal of insulin therapy is to mimic the normal physiologic pattern of endogenous insulin secretion in healthy individuals, with continuous basal secretion as well as meal-stimulated secretion[30, 31].

Colonic delivery: The colon is also seen as the preferred absorption site for oral administration of protein and peptide drugs, because of the relatively low proteolytic enzyme activities in the colon. A colon-specific drug delivery system should prevent drug release in the stomach and small intestine, and affect an abrupt onset of drug release upon entry into the colon. Time dependent delivery has also been proposed as a means of targeting the colon. Time-dependent systems release their drug load after a pre-programmed time delay. To attain colonic release, the lag time should equate to the time taken for the system to reach the colon. The plug material consists of insoluble but permeable and swellable polymers (e.g. polymethacrylates), erodible compressed polymers (e.g. hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g. saturated polyglycolated glycerides, glycerylmonooleate), and enzymatically controlled erodible polymer (e.g., pectin). These

formulations were well tolerated in animals and healthy volunteers, and there were no reports of gastro-intestinal irritation. However, 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[32, 33].

Advantages of Pulsatile Drug Delivery Systems:

There is Predictable, reproducible and short gastric residence time. It has less inter- and intra-subject variability, reduced adverse effects and improved tolerability, bioavailability and stability. It has also Improve patient comfort and compliance. It has limited risk of local irritation and No risk of dose dumping. It contains Flexibility in design, achieve a unique release pattern, Extend patent protection,globalize product,overcome competition.

Drawbacks of Pulsatile Drug Delivery Systems:

Some of drawbacks of pulsatile drug delivery recognize like, Lack of manufacturing reproducibility and efficacy, Large number of process variables, Multiple formulation steps, Higher cost of production, Need of advanced technology, Trained/skilled personal needed for manufacturing[34].

METHODOLOGIES FOR THE PDDS CAN BE BROADLY CLASSIFIED INTO FOUR CLASSES;

I. Time controlled pulsatile release

A. Single unit system

- Capsular systems
- PORT systems
- Osmotic pressure based systems
- Based on solubility modification
- Reservoir systems

B. Multi-particulate system

- Rupturable coating systems
- Time controlled explosion systems
- Sigmoidal release systems
- Modified permeation systems
- Floating delivery based systems

II. Stimuli induced

A. Thermo-Responsive Pulsatile release

- Temperature controlled systems

B. Chemical stimuli induced Pulsatile systems

- Glucose sensitive systems
- Inflation induced systems

- Gel based systems
- Ph based systems

III. External stimuli pulsatile release

A. Electro responsive pulsatile release

B. Magnetically induced pulsatile release

IV. Pulsatile release systems for vaccine and Hormone products.

I. Time controlled pulsatile release

A. Single unit system

- **Capsular systems**

Single-unit systems are mostly developed in capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion, and the drug is released as a "Pulse" from the insoluble capsule body. Pulsincap® developed by R. P. Scherer International Corporation, Michigan, US, is one such system that comprises of a water-insoluble capsule enclosing the drug reservoir. A swellable hydrogel plug was used to seal the drug contents into the capsule body. When this capsule came in contact with the dissolution fluid, it swelled; and after a lag time, the plug pushed itself outside the capsule and rapidly released the drug. Polymers used for designing of the hydro gel plug were various viscosity grades of hydroxyl propyl methyl cellulose, poly methyl methacrylates, poly vinyl acetate and poly ethylene oxide. The length of the plug and its point of insertion into the capsule controlled the lag time[35].

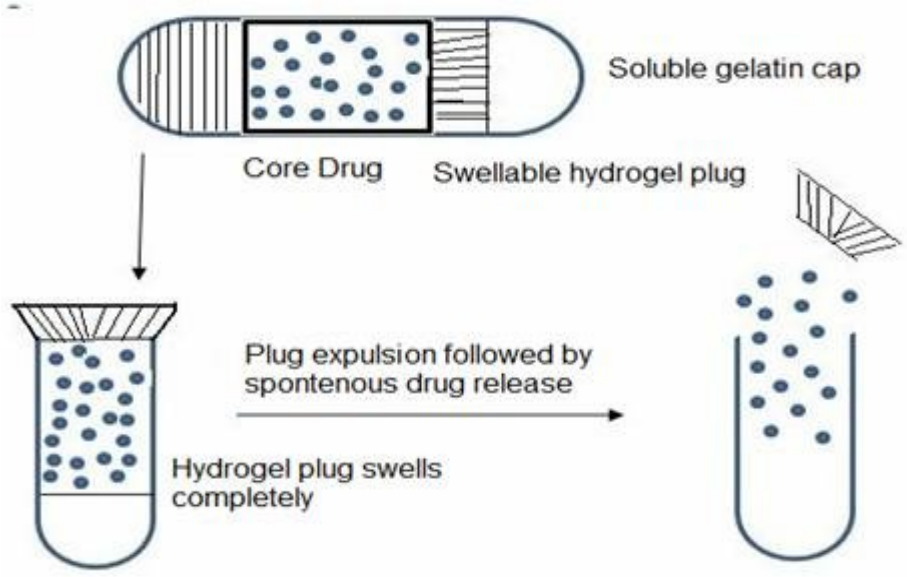

Figure 3: Design of Pulsincap system

- **PORT systems**

The Port System - consists of a gelatin capsule coated with a semi permeable membrane (e.g: cellulose acetate) housed in an insoluble plug lipophillic in nature and an osmotically active agent along with the drug[36]. When it comes in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a – time lag. The time lag is controlled by the thickness of semi permeable membrane. In order to deliver drug in liquid form, an osmotically driven capsular system was developed. In this system, liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi permeable capsule supported expanding osmotic layer after barrier layer is dissolved[37].

- **Osmotic pressure based systems having a series of stops**

This system contains a drug and a water-absorptive osmotic agent 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. This system was used to deliver porcine somatotropin[38-39].

- **Reservoir systems**

These systems are based up on a drug reservoir surrounded with a soluble or erodible barrier layer that dissolves with time and the drug releases at once after the lag time

These systems are of two types;

- Time clock systems
- Chronotropic systems

The Time Clock® system consists of a solid dosage form coated with lipid barriers containing carnauba wax and bees wax along with surfactants, such as polyoxyethylenesorbitan monooleate[40,41]. This coat erodes or emulsifies in the aqueous environment in a time proportional to film, and the core is then available for dispersion.

The Chronotropic® system consists of a drugcontaining core coated by hydrophilic swellablehydroxypropylmethyl 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 drug core.System is suitable for tablets, capsule formulations[42].

B. Multi-particulate system

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

- less inter and intra-subject variability in gastrointestinal transit time
- reduced adverse effects and improve tolerability
- no risk of dose dumping
- flexibility in design

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.

➢ **Rupturable coating systems**

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 glycollate, L-hydroxypropyl cellulose, etc. Upon absorption of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer[43].

➢ **Time controlled explosion systems**

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[44, 45].

➢ **Sigmoidal release systems**

This consists of pellet cores comprising drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type B. The time lag is controlled by the rate of water

influx through the polymer membrane. Drug delivery is caused by the presence of acid which increases the permeation[46].

- **Modified permeation systems**

This is based on the phenomenon of ion exchange drug delivery. The permeability and water uptake of acrylic polymers with quaternary ammonium groups is influenced by different counter-ions in the medium. Eudragit RS 30D is widely used for this method[47].

- **Floating delivery based systems**

The 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[48].

II. Stimuli induced

A. Thermo-Responsive Pulsatile release

- **Temperature controlled systems**

Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state. Y.H. Bae et al developed indomethacin pulsatile release pattern in the temperature ranges between 200C and 300C by using reversible swelling properties of copolymers of N-isopropylacrylamide and butyrylacrylamide. Kataoka et al developed the thermosensitive polymeric micelles as drug carrier to treat the cancer. They used endfunctionalizedpoly(*N*-isopropylacrylamide) (PIPAAm) to prepare corona of the micelle which showed hydration and dehydration behavior with changing temperature[49,50]**.**

B. Chemical stimuli induced Pulsatile systems

- **Glucose sensitive systems**

Glucose sensitive systems have been developed for the treatmenr of diabetes mellitus which follows a rythmic increase in the glucose levels. The system consists of a pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. It acts by the conversion of glucose into gluconic acid, by glucose oxidase, the acidic pH induces

swelling of the polymer (*N, N*-dimethylaminoethyl methacrylate, chitosan, polyol) which results in the release of insulin thereby reduction of glucose[51].

- **Inflammation induced systems**

During inflammation, hydroxyl radicals are produced from these inflammation responsive cells. Degradation via hydroxyl radicals occurs rapidly 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[52].

- **Gel based systems**

Recently, novel gels were developed which responded to the change in concentration ofbioactive compounds to alter their swelling characteristics. 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.

- **Ph based systems**

This type of PDDS contains two essential components. The first is rapid release type while the other is pulsed release which releases the drug in response to change in pH. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate,
polyacrylates, and sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine[53].

III. External stimuli pulsatile release

A.Electro responsive pulsatile release

Electrically responsive delivery systems are prepared from polyelectrolytes and are thus, pHresponsive as well as electro-responsive. Examples of such polymers are

1. Naturally occurring polymers – hyaluronic acid, chondroitin sulphate, agarose, carbomer, xanthan gum and calcium alginate.
2. Synthetic polymers are generally acrylate and methacrylate derivatives such as partially hydrolyzed polyacrylamide, polydimethylaminopropyl acrylamide[54].

B. Magnetically induced pulsatile release

The use of an oscillating magnetic field to modulate the rates of drug release from polymer matrix has been traditionally used. It involves the magnetic carriers which are water based, non-toxic, non-immunogenic. The drug release can be modified by an external magnet which alters the rate of absorption of the drug into the git. was one of the old methodologies. Magnetic carriers receive their magnetic response to a magnetic[55].

IV. Pulsatile release systems for vaccine and Hormone products

PDDS provide the possibility of single-shotvaccines if initial booster release of the antigen can be achieved from one system in which timing of booster release is controlled. Vizcarra et al. found 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 Hr[56].

RECENT ADVANCES IN THE PULSATILE DRUG DELIVERY SYSTEM

Nowadays pulsatile drug delivery systems are gaining importance in various disease conditions specifically in diabetes where dose is required at different time intervals. Among these systems, multi-particulate systems (e.g. pellets) offer various advantages over single unit which include no risk of dose dumping, flexibility of blending units with different release patterns, as well as short and reproducible gastric residence time[57]. Multiparticulate systems consists pellets of different release profile which can be of any type like time dependent, pH dependent, micro flora activated system as discussed in the previous sections. Site and time specific oral drug delivery have recently been of great interest in pharmaceutical field to achieve improved therapeutic efficacy. Gastroretentive drug delivery system is an approach to prolong gastric residence time, thereby targeting sitespecific drug release in upper gastrointestinal (GI) tract. Floating drug delivery system (FDDS) and bioadhesive drug delivery are widely used techniques for gastro retention. Low density porous multiparticulate systems have been used by researchers for formulation of FDDS. Sharma and Pawar developed multiparticulate floating pulsatile drug delivery system using porous calcium silicate and sodium alginate for time and site specific drug release of meloxicam[58]. Various pulsatile technologies have been developed on the basis of methodologies as discussed previously. These includes OROS® technology, CODAS® technology, CEFORM® technology, DIFFUCAPS® technology, Three-dimensional printing®, timerx® etc.

MARKETED TECHNOLOGIES OF PULSATILE DRUG DELIVERY[59,60,61]

Table 1: Marketed formulation of PDDS

Technology	Mechanism	Proprietary name and dosage form	API
OROS®	Osmotic Mechanism	Covera-HS®; XL	Verapamil HCL
CODAS®	Multiparticular pH dependent system	Verelan® PM; XL	Verapamil HCL
DIFFUCAPS®	Multiparticulate System	Innopran®; XL	Propranolol HCL
3D printing®	Externally regulated system	TheirForm®	Diclofenac Na
PulsincapTM	Rupturable system	PulsincapTM	Dofetilide
Pulsys®	Timed-controlled System	Pulsys®	Amoxicillin

CONCLUSION

Presently, oral delivery of drug is still by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in its formulations. Generally, sustained and controlled-release products provide a desired therapeutic effect, but fall short of diseases following biological rhythms. 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. Various methodologies are employed for developing pulsatile drug delivery like timecontrolled, stimuli induced, externallyregulated system and multiparticulate drugdelivery system. Thus designing of proper pulsatile drug delivery will enhances the patient compliance, optimum drug delivery to the target site and minimizes the undesired effects. One major challenge will be to obtain a better understanding of the influence of the biological environment on the release performance of pulsatile delivery systems in order to develop simple systems based on approved excipients with a good *in vitro in vivo* correlation.

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