A NOVEL APPROCH: PULSATILE DRUG DELIVERY SYSTEM

Asija Rajesh*, Patel Jaimin, Asija Sangeeta
Department of pharmaceutics, Maharishi Arvind Institute of Pharmacy, Jaipur, India

ABSTRACT
Pulsatile drug delivery system (PDDS) is useful in the treatment of disease, in which drug availability is timed to match rhythms of disease, in order to optimize therapeutic effect and minimize side effects. PDDS have attracted attraction because of their multiple benefits over conventional dosage forms. The specific time that patients take their medication is very important as it has significant impact on success of treatment. If symptoms of a disease display circadian variation, drug release should also vary over time. Diseases wherein pulsatile drug delivery systems are promising include cardiovascular diseases, arthritis, asthma, cancer, hypercholesterolemia, duodenal ulcer, neurological disorders and diabetes. In pursuit of pulsatile release, various design strategies have been proposed, mainly including time controlling, stimuli induced, externally regulated and multiparticulate formulations. This review will cover methods that have been developed to control drug delivery profile with different polymeric systems like time controlling, internal stimuli induced (temperature induced and chemical stimuli-induced), and external induced (magnetic fields, ultrasound, electric fields and light stimulation) and multiparticulate system. Pulsatile drug delivery systems have the potential to bring new developments in the therapy of many diseases.
KEY WORDS: PDDS, Circadian rhythm, Pulsatile, Chronotherapy

INTRODUCTION

Oral drug delivery is the most preferred route for drug administration. The oral controlled-release systems show a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time, thereby ensuring sustained therapeutic action. There are certain conditions for which such a release pattern is not suitable that demand release of a drug after a lag time. In other words, they require pulsatile drug delivery system. The pulsatile system is gaining a lot of interest, as the drug is released completely after defined lag time. Pulsatile drug delivery is time and site-specific drug delivery, thus providing spatial and temporal delivery and increasing patient compliance[1, 2]. 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. Pulsatile release is commonly found in the body, for example during hormone release, in which a baseline release is combined with pulsed, one-shot type release within a short time range[2, 3]. Humans exhibit endogenous circadian rhythms that are regulated by the master circadian clock of the body, the suprachiasmatic nucleus. Chronopharmacotherapy of diseases (cardiovascular diseases, arthritis, asthma, cancer, hypercholesterolemia, duodenal ulcer, neurological disorders and diabetes) that 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[4, 5]. There are many other conditions that demand pulsatile release, like many body functions that follow circadian rhythms, such as secretion of hormones [including follicle stimulating hormone (FSH), luteinizing hormone (LH), luteinizing hormone releasing hormone (LHRH), estrogen and progesterone], acid secretion in the stomach, gastric emptying and gastrointestinal blood transfusion. Drugs that produce biological tolerance demand a system that will prevent their continuous presence at the biophase, as this tends to reduce their therapeutic effect. The lag time is essential for drugs that undergo degradation in gastric acidic medium (e.g., peptide drug) and irritate the gastric mucosa or induce nausea and vomiting. Targeting a drug to a distal organ of gastrointestinal tract (GIT), like the colon, requires that the release is prevented in the two-third portion of the GIT. Drugs (β-blockers or β-estradiol) that undergo first-pass metabolism, resulting in reduced bioavailability, altered steady-state levels of drug and metabolite and potential food drug interaction, require delayed released to the extent possible. All the above attributes can be taken into account in designing a delivery system that exhibits pulsatile release characteristics and releases the drug in a predetermined fashion at a particular site[6-8]. These systems will have application in fields such as insulin delivery, contraception, controlled animal breeding and growth promotion[3].

ADVANTAGES[3, 9]

1. Predictable, reproducible and short gastric residence time
2. Used for extended day time or night time activity.
1. Less inter- and intra-subject variability
2. Improve bioavailability
3. Reduced side effects and improved tolerability
4. Flexibility in design
5. Limited risk of local irritation
6. Extend patent protection, globalize product, and overcome competition
7. No risk of dose dumping
8. Improve stability
9. Improve patient comfort and compliance
10. Achieve a unique release pattern

DISADVANTAGES[3, 9]

1. Higher cost of production
2. Lack of manufacturing reproducibility and efficacy
3. Large number of process variables
4. Multiple formulation steps
5. Trained/skilled personal needed for manufacturing
6. Low drug loading capacity and incomplete release of drug.
7. Need of advanced technology

LIST OF DISEASES REQUIRING PULSATILE DRUG DELIVERY

The diseases currently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify PDDS compared to the conventional

drug administration approach. These include: asthma, arthritis, duodenal ulcer, cancer, diabetes, cardiovascular diseases (e.g. hypertension and acute myocardial infarction), hypercholesterolemia, and ulcer and neurological disorders. The rationale for chronotherapy for each of these diseases will be briefly reviewed below. Reader having further interest may find a comprehensive coverage of the topics in several excellent reviews and references provided.

Cardiovascular diseases
In cardiovascular disease capillary resistance and vascular reactivity are higher in the morning and decreases latter in the day. Platelet agreeability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. Because of this reason the frequencies of myocardial infarction and of sudden cardiac death are more during a period from morning to noon. Ambulatory blood pressure measurements show a significant circadian variation to characterize blood pressure. This variation is affected by a variety of external factors such as ethnicity, gender, autonomic nervous system tone, vasoactive hormones, hematological and renal variables. Increased heart rate, blood pressure, imbalanced autonomic tone, circulating level of catecholamine controlling the cardiac arrhythmias show important circadian variation and trigger the genesis of the circadian pattern of cardiac arrhythmias. Atrial arrhythmias appear to exhibit circadian pattern usually with a higher frequency in the daytime and lower frequency in the night time with the abnormal foci under the same long-term autonomic regulation as normal pacemaker tissue. According to study ventricular tachyarrhythmias shows late morning peak in the patients with myocardial infarction sometime in the distant past morning peak and afternoon peak in patients with recent myocardial infarction[10, 11].

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. The exact dose would depend on the severity of the patient's pain and his or her individual physiology[12, 13].

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. Circadian changes are seen in normal lung function, the later reaches a low point in the early morning hours. This dip is particularly pronounced in people with asthma. Because bronchoconstriction 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 B2-agonists[14, 15].

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 with HMG COA reductase inhibitors have suggested that evening dosing was more effective than morning dosing[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. These biorhythms have important implications in the pharmacokinetics of orally administered drugs. At nighttime, 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 H2 antagonists. Theoretical problems associated with a sustained or profound decrease of 24 hours intra gastric acidity include the threat of enteric infection and infestation, potential bacterial overgrowth with possible N-nitrosamine formation, drug-induced hyper gastrinaemia and disturbed protein digestion. In light of these potential problems, for the management of simple peptic ulceration, it appears sensible to use the minimum intervention required. Bedtime H2-receptor blockade is one such regimen[17, 18].

Neurological disorders
As an integrative discipline in physiology and medical research, chronobiology renders possible 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 behavioral classification of convulsive events. Such circadian studies also show that chronobiology raises some working hypotheses in psychophysiology and permits the development of new theoretical concepts in the field of neurological science. It is also well known that the brain area with the highest concentration in noradrenergic nerve terminals and noradrenaline (NA) have a circadian rhythm in their content of NA. Moreover, it has been shown that the human sleep, its duration and organization depend on its circadian phase. A breakthrough chronopharmaceutical formulation against insomnia that plagues many people would be one that addresses the entire oscillatory cycle of human sleeping process[19, 20].

Diabetes

There circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance in case of insulin substitution in type 1 diabetes has been well established. 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. Providing basal insulin exogenously to patients with diabetes inhibits hepatic glucose production. Exogenous administration of mealtime doses promotes peripheral glucose uptake as well as reducing hepatic glucose release[21].

METHODOLOGIES FOR PULSATILE DRUG DELIVERY

Methodologies for the pulsatile drug delivery system can be broadly classified into four classes.
1. Time controlled pulsatile release system
2. Internal stimuli induced pulsatile release system
3. Externally regulated pulsatile release
4. Multiparticulate pulsatile drug delivery system

Time controlled pulsatile release system

In time controlled drug delivery systems pulsatile release is obtained after a specific time interval in order to mimic the circadian rhythm. Such type of pulsatile drug delivery system contains two components: one is of immediate release type and other one is a pulsed release type. These systems are designed to release drug in pulses governed by the device fabrication and ideally, independent of the environment. The release mechanisms employed include bulk erosion of the polymer in which drug by diffusion is restricted, surface erosion of layered devices composed of altering drug containing and drug free layers, osmotically controlled erosion coating layer. Various methodologies are:

Delivery system provided with erodible coating layers

In these systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing a drug. Time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer coat. Sangalli et al. developed an oral dosage form devised to release drugs following a programmed time period after administration based on this concept. The system is composed of a drug-containing core and a hydrophilic swellable polymeric coating of HPMC which is capable of delaying the drug release through slow interaction with aqueous fluids[11, 22]. Zema et al. when used as release-controlling coating agents for tableted core-based pulsatile delivery systems, three different HPMC grades, Methocel® E5, E50, and K4M, provided lag phases of varying duration (Methocel® K4M > E50 > E5) and a prompt and quantitative model drug release. Dissolution/mechanical erosion, permeability increase and disruption of the hydrated polymeric layer were assumed to participate in the definition of the overall release pattern. The polymers were evaluated for dissolution and swelling, while the finished systems were concomitantly evaluated for drug release and polymer dissolution. This polymer indeed proved to yield higher viscosity and slower dissolving gel layer, which was able to withstand extensive dissolution/erosion for periods that exceeded the observed lag phases. The particular characteristics of swollen Methocel® K4M were shown to be associated with possible drug diffusion phenomena, which might impair the prompt and quantitative release phase that is typical of pulsatile delivery. Zema et al. when used as release-controlling coating agents for tableted core-based pulsatile delivery systems, three different HPMC grades,

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Delivery system provided with reputable coating layer

These systems consist of an outer release controlling water insoluble but permeable coating subject to mechanically induced rupture phenomenon. Recently different systems based on hard gelatin capsules and tablet core were described, all coated by inner swellable and outer rutpurable layer. The film rupture may be attained by including swelling, osmotic or effervescent additives in the reservoir. By optimizing the system, drug release can be obtained at specific time interval. Thombre et al. developed osmotic drug delivery using swellable core technology wherein formulations consists of a core tablet containing the drug and a water swellable component, and one or more delivery ports[24]. Sungthongjeen et al. developed a tablet system consisting of core coated with two layers of swelling and rupturable coatings wherein they used spray dried lactose and microcrystalline cellulose in drug core and then core was coated with swelling polymer croscarmellose sodium and an outer rupturable layer of ethylcellulose[11, 24].

Capsule shaped system provided with release controlling plug

Several pulsatile dosage forms with a capsular design have been developed. These systems contain 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 lag time is provided by the plug which is inserted in to the body. In an approach used by Jimoh et al. pulsatile release was achieved by generation of hydrostatic pressure inside the capsule. A hollow biodegradable capsule of poly (lactic acid) (PLA) containing the drug along with citric acid / sodium bicarbonate and glucose was prepared. Thin poly (lactide-co-glycolide) (PLGA) membrane (to allow water penetration inside the capsule) was utilized on one end. Water penetrates into the capsule through the thin poly (lactide-co-glycolide) (PLGA) membrane side, which generates effervescence due to reaction caused between the citric acid and sodium bicarbonate, generating carbon dioxide gas that accumulates in the capsule and finally ruptures the thin membrane[25]

Internal stimuli induced pulsatile release system

In these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli. Soppimath et al. had done research activity in the development of stimulus-responsive polymeric hydrogels. These hydrogels are responsive to external or internal stimuli and the response can be observed through abrupt changes in the physical nature of the network. The stimuli can be temperature, pH, ionic strength, etc[26]. These

systems are further classified in to temperature induced systems and chemical stimuli induced system, on the basis of stimulus.

Temperature induced 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 20°C and 30 C 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 end functionalized poly (*N*-isopropylacrylamide) (PIPAAm) to prepare corona of the micelle which showed hydration and dehydration behavior with changing temperature[27, 28].

Chemical stimuli induced pulsatile systems.

In these systems the polymer undergoes swelling or deswelling phase in response of chemical reaction with membrane, alteration of pH and Inflammation induce, release drug from polymer by swelling the polymer.

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. Obaidat and Park prepared a copolymer of acryl amide and allyl glucose. The side chain glucose units in the copolymer were bound to concanavalin A. These hydrogels showed a glucose-responsive, sol–gel phase transition dependent upon the external glucose concentration. Okano et al. developed the system based upon the fact that boronic acid moiety forms reversible bonds with polyol compounds including glucose. They used water-soluble copolymers, containing phenylboronic acid side chains which showed formation of a reversible complex gels with polyol compounds such as poly(vinyl alcohol) (PVA). Such complexes dissociated after the addition of glucose in a concentration dependent manner[29].

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. Yui and co-workers focused on the inflammatoryinduced hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner. They used hyaluronic acid (HA) which is specifically degraded by the hyaluronidase or free radicals. Degradation of HA via the hyaluronidase is very low in a normal state of health. Degradation via hydroxyl radicals however, is usually dominant and rapid when HA 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[30].

pH sensitive drug delivery system

Such type of pulsatile drug delivery system contains two components one is of immediate release type and other one is pulsed release which releases the drug in response to change in pH. In case of pH dependent system advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. 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 carboxy methyl cellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine. Yang et al. developed pH-dependent delivery system of nitrendipine in which they have mixed three kinds of pH dependent microspheres made up of acrylic resins Eudragit E-100, Hydroxy propyl methyl cellulose phthalate and Hydroxy propyl methyl cellulose acetate succinate as pH dependent polymers. In one of the study carried out by Mastiholimath et al. attempt was made to deliver theophylline into colon by taking the advantage of the fact that colon has a lower pH value (6.8) than that of the small intestine (7.0–7.8). So, by using the mixture of the polymers, i.e. Eudragit L and Eudragit S in proper proportion, pH dependent release in the colon was obtained[31].

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 interactions are very specific[32].

Externally regulated systems

For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads. Saslawski et al. developed different formulation for in vitro magnetically triggered delivery of insulin based on alginate spheres. In case of ultrasonically modulated systems, an ultrasonic wave causes the erosion of the polymeric matrix thereby modulating drug release. Miyazaki et al. evaluated the effect of ultrasound (1 MHz) on the release rates of bovine insulin from ethylene vinyl alcohol copolymer matrices and reservoir-type drug delivery systems in which they found sharp drop in blood glucose levels after application of ultrasonic waves. Also irradiation with light rays the desired drug release pattern. Mathiowitz et al. developed photo chemically controlled delivery systems prepared by interfacial polymerization of polyamide microcapsules. For this purpose, azobisisobutyronitrile (AIBN), a substance that photo chemically emanates nitrogen gas, was incorporated. Due to exposure of azo bis isobutyronitrile to light, causing release of nitrogen and an increase in the pressure which ruptures the capsules thereby releasing the drug[9, 11].

Externally regulated pulsatile release

In this drug delivery are not self-operated, but instead required externally generated environmental changes to

initiate drug delivery. These can include magnetic fields, ultrasound, electric field, light, and mechanical force.

Magnetic induces 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. Christopher Brazel et al. have development of magnetothermally- triggered drug delivery systems, whereby magnetic nanoparticles are combined with thermallyactivated materials. By combining superparamagnetic nanoparticles with lower critical solution temperature (LCST) polymers, an alternating current magnetic field can be used to trigger localized heating *in vivo*, which in turn causes a phase change in the host polymer to allow diffusion and release of drugs[32]. The use of magnetic nanoparticles for biomedical applications as well as the design of thermally-activated polymeric systems. Magnetic-sensitive behavior of intelligent ferrogels for controlled release of drug 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[31]. Although the external direct current magnetic field was applied to the ferrogel, the drug was accumulated around the ferrogel, but the accumulated drug was spurt to the environment instantly when the magnetic fields instantly switched "off". Furthermore, rapid to slow drug release can be tunable while the magnetic field was switched from "off" to "on" mode. The drug release behavior from the ferrogel is strongly dominated by the particle size of Fe_3O_4 under a given magnetic field. The best "magnetic-sensitive effects" are observed for the ferrogels with larger Fe_3O_4 particles due to its stronger saturation magnetization and smaller coercive force. Saslawski et al. has developed different formulations for *in vitro* magnetically triggered delivery of insulin based on alginate spheres[33]. In an experiment, ferrite microparticles (1 mm) and insulin powder were dispersed in sodium alginate aqueous solution. The ferrite-insulin-alginate suspension was later dropped in aqueous calcium chloride solution which causes the formation of cross linked alginate spheres, which were further cross linked with aqueous solution of poly(llysine) or poly-(ethylene imine). Applications as high frequency gave a significant release enhancement for the second magnetic field application, after which the enhancement level decreased due to the faster depletion at these frequencies[3].

Ultrasound induces release

Husseini et al the high toxicity of potent chemotherapeutic drugs like doxorubicin (Dox) limits the therapeutic window in which they can be applied. This window can be expanded by controlling the drug delivery in both space and time such that non-targeted tissues are not adversely affected. Recent research has shown that ultrasound (US) can be used to control the release of Dox and other hydrophobic drugs from polymeric micelles in both time and space. Dox activity can be enhanced by ultrasound in one region, while in an adjacent region there is little or no effect of the drug. We review the *in vivo* and *in vitro* research being conducted in the area of micellar drug delivery and ultrasound to cancerous tissues[34]. The potential benefits of such controlled chemotherapy compels a thorough investigation of role of ultrasound (US) and the mechanisms by which US accomplishes drug release and/or enhances drug potency. 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. 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. With respect to drug delivery, these latter effects are probably not involved except to the degree that fluid or particle motion (via acoustic streaming or radiation pressure) increases convection and transport of drug. Bio-effects related to cavitation can produce strong stresses on cells, which may increase drug interactions with the cell, including increased transport toward and into the cell[35].

Electric field induces release

As an external stimulus have advantages such as the availability of equipment, which allows precise control with regards to the magnitude of current, duration of electric pulses, interval between pulses etc. 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 electroresponsive. Under the influence of electric field, electroresponsive hydrogels generally deswell or bend; depending on the shape of the gel lies parallel to the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes. Soon Hong Yuk et al. developed monolithic devices composed of sodium alginate and polyacrylic acid was prepared. A pulsatile drug release pattern was observed upon application of electrical current using the prepared monolithic devices. Two release patterns of hydrocortisone were achieved by proper design of the drug delivery devices, demonstrated the feasibility of achieving a pulsatile drug delivery system depending on the environmental conditions[36].

Light induces release

Light-sensitive hydrogels have potential applications in developing optical switches, display units, and opthalmic drug delivery devices. Since the light stimulus can be imposed instantly and delivered in specific amounts with high accuracy, light sensitive hydrogels may possess special advantages over others. The capacity for instantaneous delivery of the sol–gel stimulus makes the development of light-sensitive hydrogels important for various applications in both engineering and biochemical fields. Light-sensitive hydrogels can be separated into UV-sensitive and visible light-sensitive hydrogels. Unlike UV light, visible light is readily available, inexpensive, safe, clean and easily manipulated[37].

Multiparticulate pulsatile drug delivery 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. The release of drug from microparticles depends on a variety of factors including the carrier used to form the multiparticles and the amount of drug contained in them. Consequently, multiparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development. 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 behavior due to unit to unit variation[3, 38].

Recent innovations in multiparticulate systems for pulsatile delivery are:

a. Reservoir systems with rupturable polymeric coatings
b. Reservoir systems with soluble or eroding polymer coatings
c. Floating multiparticulate pulsatile systems

MECHANISM OF DRUG RELEASE FROM PULSATILE DRUG DELIVERY SYSTEM[11]

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

Diffusion

On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Osmosis

In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.

Erosion

Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.

MARKETED TECHNOLOGIES OF PULSATILE DRUG DELIVERY[9, 39]

Different marketed technologies have been developed for pulsatile drug delivery. These are:

1. PulsincapTM
2. Three-dimensional printing®
3. OROS®
4. Ritalina®
5. Opana®ER.
6. GEOCLOCK®
7. Diffucap®
8. CODAS®
9. IPDAS®
10. Uniphyl®

CONCLUSION

Rapid advancement and newer developments in the field of drug delivery have led to the formulation of the pulsatile drug delivery system, which, on one hand, can be formulated with ease and, on the other hand, provides a significant amount of therapeutic benefits. A significant amount of progress has been achieved towards pulsatile drug delivery systems that can effectively treat disease with non-constant dosing therapies such as diabetes. These systems deliver the drug at right time, place and amount in the patient's body. The circadian disorders generally require chronopharmacotherapy, which can be easily accomplished by pulsatile drug delivery system in a very organized manner. By selecting optimal time to achieve the desired effect, treatment opportunities may arise and undesired side effects can be minimized. These considerations, coupled with the potential therapeutic benefits of pulsatile drug delivery systems, should ensure that the current high level of interest in this would extend well in to future and result in the betterment of the quality of life. This review demonstrates that there are both experimental and theoretical backgrounds and market constraints as basis for the clinical relevance of chronopharmaceutics as an emerging approach to drug delivery. Chronopharmaceutics will certainly improve patient outcome and optimize disease management in the future. The major drawbacks of existing oral PDDS on the market are

that they rely on human action to trigger the drug administration for example on daily basis. Ideal PDDS should be self regulating, when taken any time of the day and should take environmental factors in account (e.g. awake-sleep, light–dark, activity–rest status). For example, the human body is comprised of molecules, hence the availability of molecular nanotechnology that facilitate self-regulation of PDDS based on body immune system and disease state will permit dramatic progress in human medical services.The approaches in this article represent attempts conducted over the past decade to achieve pulsatile release. It should be pointed that these drug delivery systems are still in the early developmental stage and much research will have to be conducted for such systems become practical clinical alternatives.

REFERENCES

1. Bussemer T, Otto I, Bodmeier R. Pulsatile drug delivery systems. Crit Rev Ther Drug Carrier Syst 2001; 18:433-58.
2. Kikuchi A, Okano T. Pulsatile drug release control using hydrogels. Adv Drug Deliv Rev 2002; 54:53-7.
3. Dalvadi H, Patel JK. Chronpharmaceutics, pulsatile drug delivery system as current trend. Asian Journal of Pharmaceutical Sciences 2010; 5(5): 207-230.
4. Santini JTJ, Cima MJ, Langer R. A controlled-release microchip. Nature 1999; 28:335-8.
5. Amy CRG, Insung SC, Betty MT, Paul PW, Henry B, Michael JC, et al. Multi-pulse drug delivery from a resorbable polymeric microchip device. Nat Mater 2003; 2:767-72.
6. Reddy RK, Jyothsna MV, Mohamed TSS, Chetty CMS. Review on: pulsatile drug delivery systems. J Pharm Sci Res 2009; 1:109-15.
7. Yang SY, Yang JA, Kim ES, Jeon G, Oh EJ, Choi KY, et al. ACS Nano 2010; 4:3817-22.
8. Ritschel WA, Forusz H. Chronopharmacology: a review of drugs studies, methods find. Exp Clin Pharmacol 1994; 16:57-75.
9. Jain D, Raturi R, Jain V, Bansal P, Singh R. Recent technologies in pulsatile drug delivery systems. Biomatter 2011; 1(1): 57-65.
10. Tofler GH, Brezinski D, Schafer AI, Czeisler CA, Rutherford JD, Willich SN, et al. Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. New Engl J Med 1987; 316: 1514-1518.
11. Singh DK, Poddar AS, Nigade SU, Poddar SS. Pulsatile drug delivery system: An overview. IJCPR 2011; 2(2): 55-80.
12. Auvil-Novak SE. The chronobiology, chronopharmacology, and chronotherapeutics of pai. Annu Rev Nurs Res 1999; 17: 133-153.
13. Tiran J, Galle KR, Porte JD. A simulation model of extra cellular glucose distribution in the human body. Ann Biomed Eng 1975; 3: 34-46.
14. Arkinstall WW. Review of the North American experience with evening administration of Uniphyl tablets, a once-daily theophylline preparation, in the treatment of nocturnal asthma. Am. J. Med. 1988; 85: 60-63.
15. Martin RJ, Banks-Schlegel S. Chronobiological of asthma, Am J Respir Crit Care Med 1998; 158: 1002-1007.
16. Goff WL, Guerin M, Chapman J, Bruckert E. Circadian and interindividual variations of cholesterol synthesis, Sang Thromb Vaiss 2001; 13: 461-467.
17. Hrushesky WJ, Lannin D, Haus E. Evidence for an ontogenetic basis for circadian coordination of cancer cell proliferation. J Natl Cancer Inst 1998; 90: 1480-1484.
18. Humphries TJ, Root JK, Hufnagel KK. Successful drug specific chronotherapy with the H2 blocker famotidine in the symptomatic relief of gastroesophageal reflux disease. Ann New York Acad Sci 1991; 618: 517.
19. Poirel C, Ennaji M. Chronobiological paradigms of mental life and clinical neurosciences. Encephale 2000; 26: 57-66.
20. Czeisler CA, Weitzman E, Moore-Ede MC, Zimmerman JC, Knauer RS. Human sleep: its duration and organization depend on its circadian phase. Science 1980; 210: 1264-1267.
21. Verrillo A, Teresa AD, Rucco E. Circadian variation in glucose tolerance and associated changes in plasma insulin and somatostatin levels in normal volunteers". Boll. Soc. Ital Biol Sper 1984; 60: 2261-2266.
22. Sangalli ME, Maroni A, Foppoli A. European Journal of Pharmaceutical Sciences 2004; 22: 469-476.
23. Sangalli ME, Maroni A, Foppoli A. Different HPMC viscosity grades as coating agents for an oral time and/or site-controlled delivery system: a study on process parameters and *in vitro* performances. Eur J Pharm Sci 2004; 22: 469-476.

24. Ueda Y, Hata T, Yamaguchi H, Ueda S, Kotani M. Time Controlled Explosion System and Process for Preparation for the Same. US Patent 4,871,549. 1989.
25. Jimoh AG, Wise DL, Gresser JD. Trantolo DJ. Pulsed FSH release from an implantable capsule system. J Control Release 1995; 34: 87-95.
26. Soppimath KS, Aminabhavi TM, Dave AM. Stimulus-responsive ''smart'' hydrogels as novel drug delivery systems. Drug Dev Ind Pharm 2002; 28: 957-974.
27. Kataoka K, Harada A, Nagasaki Y. Block copolymer micelles for drug delivery: design, characterization and biological significance. Adv. Drug Deliv Rev 2001; 47: 113-131.
28. Kikuchi A, Okano T. Pulsatile drug release control using hydrogels. Adv Drug Del Rev 2002; 54: 53-77.
29. Obadiah AA and Park K. Characterization of protein release through glucose sensitive hydrogel membranes. Pharm Res 1996; 13: 989-995.
30. Yui N, Okano T, Sakurai Y. Inflammation responsive degradation of cross linked hyaluronic acid gels. J Control Rel 1992; 22: 105-116.
31. Saslawski O, Weingarten C, Benoit JP, Couvreur P. Magnetically responsive microspheres for the pulsed delivery of insulin. Life Sci 1988; 42(16): 1521-1528.
32. Brazel CS. Magnetothermally-responsive nanomaterials: combining magnetic nanostructures and thermally-sensitive polymers for triggered drug release. Pharm Res 2009, 26: 644-656.
33. Liu TY, Hu SH, Liu TY. Magnetic-sensitive behavior of intelligent ferrogels for controlled release of drug. Langmuir 2006; 22: 5974-5978.
34. Husseini GA, Pitt WG. The use of ultrasound and micelles in cancer treatment. J Nanosci Nanotechnol 2008; 8: 2205-2215.
35. Nyborg WL. Biological effects of ultrasound: Development of safety guidelines. Part II: General review. Ultrasound Med Biol 2001; 27: 301-333.
36. Yuk SH, Hang S, Lee HB. Electric current-sensitive drug delivery system using sodium alginate/polyacrylic acid composites. Pharm Res 1992; 9: 955-957.
37. Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. Adv Drug Del Reviews 2001; 53: 321-339.
38. Dey NS, Majumdar S, Rao MEB. Multiparticulate drug delivery systems for controlled release. Tropi J Pharm Res 2008; 7: 1067-1075.
39. Survase S, Kumar N. Pulsatile Drug Dlivery: Current scenario. CRIPS 2007; 8: 23-7.