PULSATILE DRUG DELIVERY SYSTEM

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ABSTRACT

Pulsatile drug delivery systems (PDDS) are gaining importance in the field of pharmaceutical technology as these systems deliver the right dose at specific time at a specific site. It is gaining increasing attention as it offers a more sophisticated approach to the traditional sustained drug delivery i.e. a constant amount of drug released per unit time or constant blood levels. Pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. Diseases wherein PDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children, and hypercholesterolemia. In addition, time-based colonic release can be attained when pulsatile delivery systems are properly adapted to overcome unpredictable gastric emptying and provide delay phases that would approximately match the small intestinal transit time. PDDS can be classified into time controlled systems wherein the drug release is controlled primarily by the delivery system, stimuli induced PDDS in which release is controlled by the stimuli, such as the pH or enzymes present in the intestinal tract and externally regulated system where release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. The current article focuses on the diseases requiring PDDS, methodologies involved for the existing systems, recent update and PDDS product currently available in the market.

Keywords: Chronotherapeutics, pulsatile drug release, lag time, time controlled systems, stimuli induced system.

INTRODUCTION

Controlled drug delivery systems have gained very important role in pharmaceutical Research and Development (R&D) business. Such systems offer control over the release of drug and grant a new lease on life to a drug molecule in terms of patentability. These dosage forms offer many advantages over the conventional drug delivery systems as follow

- Constant drug level at the site of action
- Prevention of peak-valley fluctuations
- Reduction in dose of drug
- Reduced dosage frequency
- Avoidance of side effects
- Improved patient compliance

The oral controlled-release system shows 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. However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release. Recent studies have revealed that diseases have a predictable cyclic rhythm and that the timing of medication regimens can improve the outcome of a desired effect. This condition demands release of drug as a "pulse" after a time lag and such system has to be designed in a way that complete and rapid drug release should follow the lag time. Such systems are known as pulsatile drug delivery systems (PDDS), time-controlled systems, or sigmoidal release systems (Fig 1). PDDS have been developed in close connection with emerging Chronotherapeutics views. In this respect, it is well established that the symptoms of many pathologies, as well as the pharmacokinetic and pharmacodynamics profiles of most drugs, are subject to circadian variation patterns.

![Figure 1: Schematic representation of different drug delivery systems where (1) sigmoidal release after lag time (2) delayed release after lag time (3) sustained release after lag time (4) extended release without lag time.](https://www.globalresearchonline.net)

As far as widespread chronic pathologies with night or early morning symptoms are concerned, such as cardiovascular disease (CVD), bronchial asthma and rheumatoid arthritis (RA), remarkable efficacy, tolerability and compliance benefits could arise from modified release medications. After bedtime administration, would
allow the onset of therapeutic drug concentrations to coincide with the time at which disease manifestations are more likely to occur. Performance of pulsatile delivery fulfills such goals. In addition to being potentially suitable for chronotherapy, pulsatile release is also exploited to target proximal as well as distal colonic regions via the oral route. Colon delivery is being extensively investigated as it may yield improved topical inflammatory bowel disease (IBD) treatments and is even suggested as one means of enhancing the poor oral bioavailability of peptides, proteins, oligonucleotides and nucleic acids. For the purpose of time-controlled colon targeting, delayed-release systems have to be presented in an enteric-coated configuration so that the high intra- and inter-subject variability in gastric residence may be overcome, and provide, following stomach emptying, a lag phase roughly corresponding to fairly reproducible small intestinal transit time.

**DISEASES REQUIRED FOR PULSATILE TECHNOLOGY**

There are number of diseases which required to be formulated as PDDS as like: 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 for each of these diseases will be briefly reviewed in tabular and text form.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chronological behaviour (category of drugs used)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>Pain in the morning and more pain at night (NSAIDs, Glucocorticoids)</td>
</tr>
<tr>
<td>Asthma</td>
<td>Precipitation of attacks during night or at early morning hour (Antihistamines and β agonist)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period (Nitroglycerine, calcium channels blockers)</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Increase in the blood sugar level after meal (sulfonylurea, biguanide, insulin)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Cholesterol synthesis is generally higher during night than during day time (HMG Co-A reductase enzyme)</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>Acid secretion is high (H₂ blockers)</td>
</tr>
</tbody>
</table>

1. Lipidemic Disease

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. 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. Studies with HMG Co-A reductase inhibitors have suggested that evening dosing was more effective than morning dosing.

2. Pulmonary disease

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, which reaches a low point in the early morning hours. As 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 β2-agonists.

3. 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 tumor cell cycles while less toxic to normal tissue. The blood flow to tumors was threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase. 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.

4. GI 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.

5. Rheumatoid Arthritis (RA)

The chronobiology, chronopharmacology and chronotherapeutics of pain have been extensively reviewed. For instance, there is a circadian rhythm in the plasma concentration of C-reactive protein and interleukin-6 of patients with rheumatoid arthritis. 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 Ibufrofen should be timed to ensure that the highest blood levels of the drug coincide with peak pain.

6. Diabetes mellitus (DM)

The circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical
importance in case of insulin substitution in type I diabetes have been studied\textsuperscript{28, 29}. 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.

7. CNS disorder

As an integrative discipline in physiology and medical research, chronobiology renders the discovery of new regulation processes regarding the central mechanisms of epilepsy. Chronophysiologic investigations considered at a rhythmeric level of resolution suggest several heuristic perspectives regarding (i) the central pathophysiology of epilepsy and (ii) the behavioral classification of convulsive events\textsuperscript{30}.

8. CVS Disease

Several functions such as Blood pressure (BP), heart rate, stroke volume, cardiac output, blood flow of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregation is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood\textsuperscript{31, 32}. It was postulated that modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events\textsuperscript{33}. 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, although hypertensive patients have an upward shift in the profile\textsuperscript{34}.

9. 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. This time is difficult to predict in advance, although a time lag of five hours is usually considered sufficient, given that small intestinal transit time is reported to be relatively constant at three to four hours\textsuperscript{35}. All of these conditions demand a time-programmed therapeutic scheme releasing the correct amount of dose of the drug at the appropriate time. This requirement is usually fulfilled by PDDS

Methodology

(1) Time controlled delivery system

The principle of time controlled drug delivery systems is that the release of the drug happens according to a predetermined rate so to achieve maximum therapeutic and minimum toxic effect. Systems having a lag phase (delayed release systems) and systems where the release is following a biological circadian rhythm are the most commonly used controlled release systems. As already mentioned the delayed drug release for meeting chronotherapeutical needs provides optimum drug delivery for a number of widespread chronic pathologies. Most delayed release delivery systems are reservoir devices covered with a barrier coating, which dissolves, erodes or ruptures after a lag phase. Well known coating techniques are applied to pellets and tablets to delay drug’s release. Conventional coatings dissolve slowly to release drugs into the intestine. Another well-known coating technique employs a water-permeable but insoluble film which encloses the active ingredient and an osmotic agent. As water from the gut slowly diffuses through the film into the core, the core swells until the film bursts, releasing the drug. The film coating may be adjusted for selecting suitable rates of water permeation, and thereby, release time. Alternatively, the tablet coating may be impermeable, and water enters through a controlled aperture in the coating until the core bursts. When the tablet bursts, the content is released immediately or over a longer period of time. These and other techniques may be employed to formulate tablets or capsules with the requisite time interval before drug release. An excellent example of a time controlled delivery system is a three pellet pulsatile delivery system of diltiazem consisting of a fast release fraction, a medium release fraction and a slow release fraction, patented by Sharma and co-workers in 2003\textsuperscript{36}. The fast release membrane composition includes an anionic surface active agent which assures complete drug release after providing a desired lag time. The medium and slow release fractions are plasticized with decreased concentration of triethyl citrate and increased concentrations of silicone dioxide powder for improved

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process performance. Diltiazem is release from the system in three well defined pulses over 30 hours Fig. (2).

![Figure 2: In-vitro drug release profile of the formulation](image)

Ting described a press coated, pulsatile drug delivery system suitable for oral administration, having an immediate-release compartment, made by a compressed blend of an active agent and one or more polymers, enveloped by an extended-release compartment, made by a compressed blend of the active agent and hydrophilic and hydrophobic polymers, able to provide a first order delivery of the active agent, interrupted by a timed, pulsed delivery of an increased amount of the active agent. When the extended release compartment is enveloped by an optional instant release compartment, can provide a dose sufficient to exceed the liver’s metabolic capacity and to maintain therapeutic levels, preferably throughout a 24-hour period Fig. (3).

![Figure 3: Press coated drug delivery system described by ting](image)

(2) Stimuli or Site Specific Delivery Systems

a) Release Using pH of Target Site

The pH differential between the stomach and small intestine has historically been exploited in oral drug delivery. Significant variations in the pH occur in the GI tract with values ranging from approximately 1.2 in the stomach, to 6.6 in the proximal small intestine and a peak of about 7.5 in the distal small intestine followed by a sharp decline in colon where the luminal pH is below 7.38. Delivery of drugs to sites beyond the stomach are especially desirable for drugs that are destroyed by the acid conditions or enzymes of the stomach, or for drugs that cause adverse events by local activity in the stomach. The low stomach pH and presence of gastric enzymes have led to the development of oral drug dosage forms in which the drug is provided with an enteric coating. Enteric coating materials exhibit resistance to acidic gastric fluids yet are readily soluble or permeable in intestinal fluid. Enteric polymeric materials are primarily weak acids containing acidic functional groups, which are capable of ionization at elevated pH. In low stomach pH, the enteric polymers are protonized, and therefore, insoluble. As the pH increases in the intestinal tract, these functional groups ionize, and the polymer becomes soluble in the intestinal fluids. Thus, an enteric polymeric film coating allows the coated solid to pass intact through the stomach to the small intestine where the drug is then released in a pH controlled fashion and either become available for absorption or exerts a pharmacologic effect locally. Targeting drugs to specific regions along the GI tract provides the ability to locally treat GI diseases, thus reducing side effects of drugs or inconvenient and painful direct delivery of drugs. Such specific delivery also potentially increases the efficiency of the drug and enables a reduction of the minimum effective dose of the drug. Furthermore, targeted delivery to certain parts in the GI tract may be advantageous when the absorption of a drug into the systemic circulation is limited to only a part of the GI tract. In such cases, the absorption may be increased when the drug is delivered in a pulsatile and complete way within the GI absorption window, since it would increase the driving force for absorption at the site where it is specifically needed. Sharma described a delayed release drug delivery system containing an acid sensitive drug which is stable at pH levels above 9.0, such as omeprazole. The delayed release drug delivery system is comprised of an alkaline core structure, layered omeprazole dispersion (aqueous dispersion of a water soluble binder), a separation barrier, (a non-enteric moisture barrier) and a delayed release enteric barrier providing gastro-resistant behaviour to deliver omeprazole in the proximal segment (pH 5-6) of the gastrointestinal tract. The goal is to take advantage of the alkaline core structure for optimization of release and stability of acid sensitive drugs and so to provide a delayed release dosage form of an acid sensitive drug, such as omeprazole which is resistant to dissolution in acidic media. Another aspect is to provide a sub-separation layer in the pellets adjacent to a layer containing the active acid sensitive material, the subseparation layer comprising water soluble/water dispersible polymer and a pharmaceutically acceptable water soluble buffer which can provide a pH of at least 9.0. The use of the high pH buffer materials assures that even in the presence of moisture which could cause migration of acid within the pellets, the high pH buffer would reduce any effect that Migratory acid could have on the system. Rigassi described a pharmaceutical composition which is capable of releasing a drug at a specific time, independently of the concentration and type of ions present in the gastro-intestinal environment, and also independently of enzymes, present into the surrounding body fluids. The pharmaceutical composition comprises a pharmaceutically active agent, a core and a
coating comprising an inner film of cellulose acetate and HPMC and an outer film of ethylcellulose and HPC.

b) Enzymes Present in the Intestinal Tract

Several prodrugs rely on colonic bacteria for release. In these systems, colonic bacteria are utilized to degrade the substrate. The bacterial amount has been estimated about 1011 per gram in the colon. The bacterial species in the colon have been estimated to be around 400 (anaerobic in nature) 41. In the past, polymers cross linked with azo-aromatic groups have been used to achieve colonic drug delivery. The first such compound that came out in the market was sulphasalazine, a prodrug consisting by 5 aminosalicylic acid linked by an azo bond to sulphapyridine. When the chemical entity was reaching the site of action (colon) a reduction reaction was taking place and the 5 aminosalicylic acid was becoming available. However, due to potential carcinogenic activity azo-aromatic compounds have now replaced with natural polysaccharides. Natural polysaccharides such as amylose chitosan, dextran, guar gum, and pectin are currently investigated for colonic delivery. To overcome problems of premature release due to their hydrophilic nature they are usually mixed with water insoluble polymers. Nevertheless, no granted patents on enzymatic drug delivery have been found.

c) Transit Time/Pressure of Various Part of the Intestine

Delivery systems with lag times of approximately 5 hours are generally considered sufficient to target API’s delivery in colon, and thus achieving site specific delivery using time controlled release. On the other hand, the pressure exerted to an undigested dosage form varies significantly according to the exact location of the formulation. For example, luminal pressure is higher in the pylorus due to mechanical stress and to the colon due to reabsorption of water in this region. A drug dispersed in a suppository base and coated with ethyl cellulose could take advantage of pressure differential in the GI lumen so to achieve site specific drug delivery. Temperature of body is responsible for suppository base to melt and increase in volume. Ethyl cellulose then forms a balloon filled with liquid capable to withstand small intestinal contractions (peristalsis) but ruptures in the colon when subjected to intensive contraction and contents of thicker viscosity. This system is used for the production of single unit system 42.

d) 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 inflammatory induced 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 patient with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated HA gels as new implantable drug delivery systems. 43

e) 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. 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. 44

f) 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. 45

3) 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. 46

B) CLASSIFICATION OF PDDS DEPENDING ON THE TECHNOLOGY USED

From technological point of view pulsatile drug release system are further divided to single and multiple units system.

Single unit system

a) Capsule Based

Amidon and Leesman 47 described a drug delivery system for administering a drug in controlled pulse doses to an aqueous environment in the body of a living being. The formulation comprises of one or more, and preferably less than ten, individual drug-containing subunits in a unitary drug depot, such as a tablet or capsule. The individual subunits are designed to dissolve at different
sites and/or times in the gastrointestinal tract to release pulse doses of drug into the portal system in an analogous manner to the rate of release from an immediate release dosage form administered according to an appropriate dosing schedule. The dissolution time of the individual subunits can be controlled by several methods including the provision of pH sensitive enteric coatings and permeability-controlled coatings. The drug delivery system has significant advantages for the oral administration of first-pass metabolized drugs which exhibit a non-linear relationship between input rate of the drug into the portal system and bioavailability.

Figure 4: Schematic diagram of capsular system

Percol and coworkers described a capsule capable of delivering therapeutic agents in the body in a time-controlled or position-controlled pulsatile release fashion, composed of one or more populations of multicoated particulates (beads, pellets, granules, etc.). Each bead has been prepared by coating an inert particle such as a nonpareil seed (sugar sphere), with a drug and a polymeric binder or by preparing a drug containing particle by granulation and/or extrusion-spheronization, coating the active drug particle with a plasticized enteric coating, and coating plasticized enteric coated drug particle with a mixture of a water insoluble polymer and an enteric polymer. One of the membrane barriers is composed of an enteric polymer while the second membrane barrier is composed of a mixture of water insoluble polymer and an enteric polymer. The composition and the thickness of the polymeric membrane barriers determine the lag time and duration of drug release from each of the bead populations. Optionally, an organic acid containing intermediate membrane may be applied for further modifying the lag time and/or the duration of drug release.

Jenkins et al. described a Multiparticulate modified release composition in an erodable, diffusion controlled or osmotic form designed to release the active ingredients at about six to twelve hours so that the resulting plasma profile is substantially similar to the plasma profile produced by the administration of the two or more immediate release dosage forms given sequentially. The composition can be in the form of an erodable formulation in which the structural integrity of the particulates deteriorates within the body over time, in the form of a diffusion controlled formulation in which the particulates are dispersed in a liquid medium or in the form of an osmotic controlled formulation in which the release of the active ingredient from the composition is controlled by osmosis.

b) Osmotic based pump capsule

Osmotic delivery capsules ("osmotic pumps") function by virtue of walls which selectively pass water into the capsule reservoir. Absorption of water by the capsule through these walls is driven by a water-attracting agent in the capsule interior which creates osmotic pressure across the capsule wall. The water-attracting agent may be the beneficial agent itself whose controlled release is sought, but in most cases, it is a separate agent specifically selected for its ability to draw water, and this separate agent is being isolated from the beneficial agent at one end of the capsule. In either case, the structure of the capsule wall does not permit the capsule to expand, and as a result, the water uptake causes discharge of the beneficial agent through an orifice in the capsule at the same rate that water enters by osmosis.

Figure 5: Different type of osmotic pumps used for PDDS

Linkwitz and coworkers proposed a drug delivery capsule where drug delivery is driven by the osmotic infusion of moisture from a physiological environment. The capsule has a delivery orifice which opens intermittently to achieve a pulsatile delivery effect. The wall in which the orifice is formed is constructed of an elastic material (elastomer) which stretches under a pressure differential caused by the pressure rise inside the capsule as the osmotic infusion progresses. The orifice is so small that when the elastic wall is relaxed, the flow rate of drug through the orifice is substantially zero, but when the elastic wall is stretched due to the pressure differential across the wall exceeding a threshold, the orifice expands sufficiently to allow the release of the drug at a physiologically beneficial rate. The selection of the materials from which the device is constructed and the configuration of the device and its dimensions controls the length of time between pulses.

c) Erodable Barrier System

Kim described a formulation of coated Donut Shaped Tablet (DST) and multi-layer DST so that immediate release of or time-delayed release can be achieved Fig. (7). Both zero order or first order extended release kinetics are possible, depending on the excipients and types of drugs in the tablet formulation. The coating layer for time delay is made of high molecular weight water soluble polymers so that the dose dumping can be minimized.
even when the hydrated surface of the DST and MLDST peels off. Low molecular weight water soluble polymer coatings having a drug dispersed may be employed to provide a pulsatile release of a drug.

Figure 6: a) Coated Donut Shaped Tablet (DST) and b) multi-layer DST MLDST’s so that immediate release or time-delayed release of a drug proposed by Kim. Kohn and coworkers uses the degradation products of one polymer to trigger the release of the active compound from another polymer. The delayed release of the active compound was achieved without using a barrier system that requires complex and sophisticated formulation techniques.

Figure 7: Schematic diagram of delivery system of erodible coating layer

The proposed formulation comprises the biologically active compound having a chemical structure with hydrogen bonding sites dispersed in a biocompatible, hydrolytically degrading polyarylates. In the case of peptide drugs, interactions between the peptide and the first polymer inhibit the release of the peptide. Bonding interactions between the polymer and the active compound are used to lock the active compound into the polymeric matrix. In order to control the time of peptide release from polyarylates, a second biocompatible polymer but less hydrophobic than polyarylates is also used. The second polymer can be degraded into acidic byproducts into the matrix. This is necessary because the hydrogen bonding interactions can be weakened under conditions of low pH, resulting in the release of the peptide. Degradation products lower the pH of the matrix, causing an interruption in the interactions and the subsequent release of the peptide.

d) Rupturable Layers

A novel formulation for once daily administration (prior to sleeping) that provides an initial delay followed by controlled release of the drug. A method for preparing a time specific delayed, controlled release formulation of dosage is also provided which method includes coating a single pellet with at least one dosage layer, which is coated by at least one seal coat and at least one outer rate controlling layer of a water soluble polymer coat. The formulation affords excellent bioavailability while avoiding fluctuating blood levels. By that way, it is possible to maintain drug plasmatic concentrations in a desired, effective range in a circadian fashion while simplifying the administration of the drug to only once daily.

Figure 8: Schematic diagram of delivery system with rupturable coating layer

B) Multiple Units

a) Systems Based on Change in Membrane Permeability

Numerous pharmaceutical forms with delayed release for oral administration are available. As already mentioned the release of the drug must be controlled according to therapeutical purpose and the pharmacological properties of the active ingredient. In consequence, it is not always desirable the blood levels to be constant. On the contrary, in order to avoid any habituation and in order to limit the side effects provoked by the active ingredient, it would be absolutely advantageous for the plasmatic rate to follow the metabolic rhythm and the specific needs of the patient during certain periods. For instance, in order to diminish the nocturnal symptoms or the symptoms upon awakening in the case of certain chronic diseases such as ischemic heart disease, asthma and arthritis, the drugs should be administered in such a way that the desired therapeutical plasmatic level is reached only at the desired moment, i.e. during sleep or at the moment of awakening Dosage form for Pulsatile release proposed by Chen containing a plurality of different pellets composed with a core and several coating layers.

Chen described a dosage form for delivering drugs into the body in a series of sequential, pulsatile releasing events. The system can be used with drugs which cannot be released by diffusion through a porous coating, such as water insoluble drugs. A plurality of populations of pellets is provided within a unit dosage form such as a capsule or tablet Fig. (9).

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Dosage form for pulsatile release proposed by Chen⁵³ containing a plurality of different pellets composed with a core and several coating layers. The pellets are composed of a core containing the drug and a swelling agent which expands in volume when exposed to water. The core is enclosed within a membrane or coating which is permeable to water. The membrane is composed of a water insoluble and permeable film forming polymer, a water soluble film forming polymer and a permeability reducing agent. When the unit dose releases the pellets into the digestive tract, water diffuses through the coating and into the core. As water is taken up by the swelling agent, the core expands, exerting force on the coating until it bursts, releasing the drug. The permeability reducing agent reduces the rate at which water reaches the swelling agent, thereby delaying release time. The water soluble polymer dissolves, weakening the coating so that it bursts sooner. By varying the proportions of the three coating ingredients and/or coating thickness from one pellet population to another, the release timing of the pellets can be very effectively controlled⁵³.

Application or recent advances in the pulsatile drug delivery

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-particle 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 time26. Multiparticle 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. Gastro retentive drug delivery system is an approach to prolong gastric residence time, thereby targeting site specific 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 system developed multiparticulate floating pulsatile drug delivery system using porous calcium silicate and sodium alginate for time and site specific drug release.

Marketed technology of pulsatile drug delivery⁵⁴

<table>
<thead>
<tr>
<th>Technology</th>
<th>Mechanism</th>
<th>Brand name and dosage form</th>
<th>API</th>
<th>Disease</th>
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<tbody>
<tr>
<td>Pulsincap™</td>
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<td>Pulsincap™</td>
<td>Dofetilide</td>
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<td>OROS®</td>
<td>Osmotic mechanism</td>
<td>Covera-HS™; XL tablet</td>
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<td>Verelan® PM; XL release system</td>
<td>Verapamil HCl</td>
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<td>DIFFUCAPS®</td>
<td>Multi-particle system</td>
<td>Innopropan™; XL tablet</td>
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Current and future developments

The future of chronotherapeutics and more specifically the future of delivering drugs in a pulsatile manner seem to be quite promising as in certain disease states pulsatile release exhibit several advantages over the traditional zero or first order drug delivery mechanisms. Pulsatile drug delivery systems can be either time controlled or site-specific, single or multiple units. At the moment pulsatile release (site or time specific) most often is achieved by using different polymers in coating layers or by changing the coating thickness. From technological point of view, Multiparticle systems seem to be more efficient than single-unit dosage forms in achieving Pulsatile drug delivery and it can become even more sophisticated when coating technologies are incorporated. The authors of this paper believe that an increasing number of multiparticulate coated systems would become commercially available in the years to come.

Futuristic Prospect of PDDS

The development of PDDS is very challenging. Multiparticle PDDS offer more advantages when compared with the single-unit pulsatile systems since it has predictable, reproducible and short gastric empty time with no risk of dose dumping. However, the novel PDDS pays more attention on site and time-specificity. It is believed that in the near future novel PDDS will be explored in the treatment or management of some other chronic and terminal disease conditions.

CONCLUSION

Delayed release formulations are not enough in treating the diseases especially diseases with chronologial pathophysiology, for which, PDDS is beneficial. Various methodologies are employed for developing pulsatile drug delivery like time controlled Pulsatile drug delivery system which includes delivery systems with rapturable coating layer or with erodible coating layers or with release controlling plug, stimuli induced Pulsatile drug
delivery systems less temperature induced and chemical stimuli induced systems and externally regulated systems. Multiparticulate systems are useful for treatment of patients; due to their resulting high efficiency and efficacy. There are various technologies present in the market based on the various methodologies. Pulsatile release systems should be very beneficial and helpful in treatment of various diseases.

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