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Research Article

Pulsatile Drug Delivery System: An Overview

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Abstract

Pulsatile drug delivery systems (PDDS) are gaining importance as they deliver a drug at specific time as per the pathophysiological need of the disease, resulting in improved therapeutic efficacy as well as compliance. Diseases wherein PDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children, and hypercholesterolemia. These delivery systems can be classified into time controlled wherein the drug release is governed primarily by the delivery system; stimuli induced in which release is controlled by a stimuli, like the pH or enzymes present in the intestinal tract or enzymes present in the drug delivery system and externally regulated system where release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. The current article focuses on the review of literature concerning the disease requiring PDDS, methodologies involved in the existing systems, recent update and product currently available in the market.

Key words: Lag time, pulsatile release, multiple unit-systems, chronotherapy, regulatory aspect.

INTRODUCTION

Daily rhythms in life form including plants and animals have been observed since early times. As early as the fourth century BC, Alexander the Great's scribe Androsthenes noted that the leaves of certain trees opened during the day and closed at night showing a clear rhythmicity. In 1729, the French astronomer Jean Jacques d'Ortous deMairan conducted the first known experiment on biological rhythms [1]. With the advancement of the technologies in the pharmaceutical field, drug delivery systems have drawn an increasing interest over the

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last few decades. Nowadays, the emphasis of pharmaceutical galenic research is turned towards the development of more efficacious drug delivery systems with already existing molecules rather than going for new drug discovery because of the inherent hurdles posed in drug discovery and development process [2]. Traditionally, drug delivery has meant a simple chemical absorbed predictably from the gut or from the site of injection. A second-generation drug delivery goal has been the perfection of continuous, constant rate or "zero order" delivery of the bioactive agents. However, living organisms are not essentially ''zero-order'' in their requirement or response to drugs. They are predictable resonating dynamic systems, which require different amounts of a drug at predictably different times within the circadian cycle which will maximize desired and minimize undesired drug effects [3-4].

Till early nineties efforts have been made to design the drug delivery system which would release the drug at fairly constant rate. In fact these systems turned to be one of the most successful systems in delivering the drug molecule. But still for many of the drugs, use of such systems is not suitable because of a number of reasons. This is particularly true in cases where the drug is subjected to large metabolic degradation. Due to 'first pass effect' there will be reduction in the bioavailability of the drug because gradual release can result in greater degradation [5]. Secondly drugs with short half-life need to be administered repeatedly which results in patient non-compliance. Further, in case of a chronic treatment, where the drug is given in sustained release dosage form, continuous exposure of the drug to body may lead to adverse effects. For example, diabetes mellitus requires long term treatment with sustained release formulations of drugs like sulfonylurea which may damage the pancreas earlier than the corresponding immediate release dosage form. Lastly, drugs which exhibit tolerance should not be delivered at a constant rate, since the drug effect decreases with time at constant drug level. In addition drug toxicity may increase with time when drug levels are held constant. In such cases it is preferable to opt for dosage form which will provide desired concentration of drug at particular time point only [6]. Nowadays, concept of chronopharmaceutics has emerged, wherein, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Diseases where constant drug levels are not preferred, but a need for pulse of therapeutic concentration in a periodic manner exists act as a push for the development of "Pulsatile Drug Delivery Systems". In these systems, there is rapid and transient release of a certain amount of drug within a short time-period immediately after a predetermined no release period. Modified release polymeric multiparticulate systems of theophylline were prepared by mixing the drug and powdered

carnauba wax copolymer, which were then compressed at room temperature for desired release [7, 8].

The focus of the present review is primarily on the pulsatile drug delivery methodologies and the up coming technologies, which are being exploited on an industrial scale.

Diseases requiring pulsatile drug delivery

Thorough understanding of the pathophysiology of disease is required before designing a suitable drug delivery system. Diseases where rhythmic circadian organization of the body plays an important role, pharmacokinetics and/or pharmacodynamics of the drugs is not constant within 24 hours. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. In case of cardiovascular diseases, several functions (e.g. BP, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms as shown in **Fig. 1.** 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 [9]. 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 exploited. Furthermore diverse directions of circadian changes in lipid fractions where patients and normal subjects may contribute to alteration in the rhythmicity of other metabolisms and in the blood coagulation system, may lead to various complications. A circadian rhythm occurs during hepatic cholesterol synthesis. In case of arthritis there is a circadian rhythm in the plasma concentration of C - reactive protein and interleukin-6 of patients with rheumatoid arthritis [10].

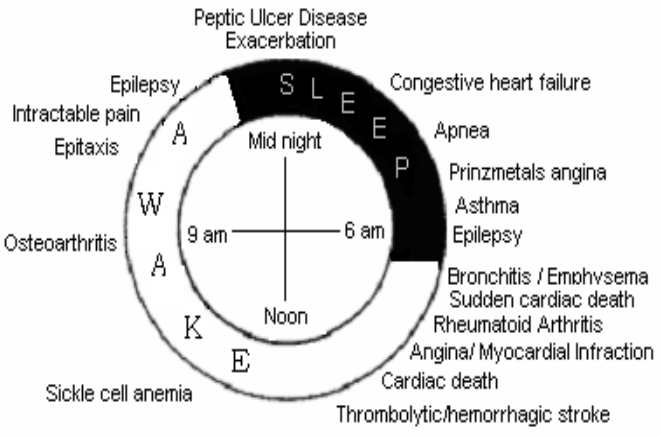

Figure 1: Cycle of circadian rhythm

Basic physiology, challenges, and approaches:

It is well recognized that the stomach may be used as a 'depot' for sustained-release (SR) dosage forms, both in human and veterinary applications. The stomach is anatomically divided into three parts: fundus, body, and antrum (or pylorus). The proximal stomach, made up of the fundus and body regions, serves as a reservoir for ingested materials while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying. The process of gastric emptying occurs both during fasted and fed states; however, the pattern of motility differs markedly in the two states. In the fasted state, it is characterized by an interdigestive series of electrical events which cycle both through the stomach and small intestine every 2–3 h. This activity is called the interdigestive myoelectric cycle or migrating myoelectric complex (MMC), which is often divided into four consecutive phases. As described by Wilson and Washington, phase I is a quiescent period lasting from 40 to 60 min with rare contractions. Phase II is a period of similar duration consisting of intermittent action potentials and contractions that gradually increase in intensity and frequency as the phase progresses. Phase III is a short period of intense, large regular contractions lasting from 4 to 6 min. It is this phase, which gives the cycle the term 'housekeeper' wave, since it serves to sweep undigested materials out of the stomach and down the small intestine. As phase III of one cycle reaches the end of the small intestine, phase III of the next cycle begins in the duodenum. Phase IV is a brief transitional phase that occurs between phase III and phase I of two consecutive cycles. In the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. In other words, feeding results in a lag time prior to the onset of gastric emptying [12-14].

Various techniques are available for the pulsatile delivery like pH dependent systems, time dependent systems, micro-flora activated systems, etc. which can be designed as per the physiology of disease and properties of the drug molecule. Functional membranes for lag time of a typical pulsatile drug delivery system with unit and bi-modal pulse is shown in **Fig. 2.** It comprises of an external water-insoluble polymer (e.g.ethylcellulose) or enteric polymer (e.g. hypromellose phthalate) over an immediate release drug layer, followed by a release control polymer over the timed pulsatile release drug layer applied on core granules

New global trends in drug discovery and development

In this century, the pharmaceutical industry is caught between pressure to keep prices down and the increasing cost of successful drug discovery and development. The average cost and time for the development of a new chemical entity are much higher (approximately $500 million and 10–12 years) than those required to develop a novel drug delivery system (NDDS or PDDS) ($20–$50 million and 3–4 years). In the form of PDDS, an existing drug molecule

can ‘‘get a new life’’, thereby increasing its market value and competitiveness and extending patent life. According to IMS Health, retail growth for major generics markets (1999–2004) was forecasted to reach 13% in 2005. Of the leading 35 molecules worldwide in US dollars terms, 13 will lose their patent protection over the next 5 years. Major patents expiring during this period would be may only covering categories including major therapy classes: central nervous system (anti-depressants), cardiovascular system (ACE Inhibitors), alimentary tract (proton pump inhibitors), and respiratory system (antihistamines) [15]. It is important to point out most of the diseases targeted by these drugs have been shown to have a chronobiological pattern in their pathogenesis. The key issues impacting the generic growth, especially in USA and Europe, include: economic growth, cost-containment reinforcement including reference price cuts and stringent reimbursement conditions, governmental promotion of rational prescribing (generic interchangeability), emphasis on cost-effectiveness and integrated care, and encouraged use of generics (mandatory substitution and prescribing guidelines). In addition to scientific evidence demonstrating the usefulness of PDDS, these market constraints (cost, patent expiration and political pressure) are the key driving forces for the pharmaceutical industry to consider chronopharmaceutical formulations in order to maintain competitiveness [16].

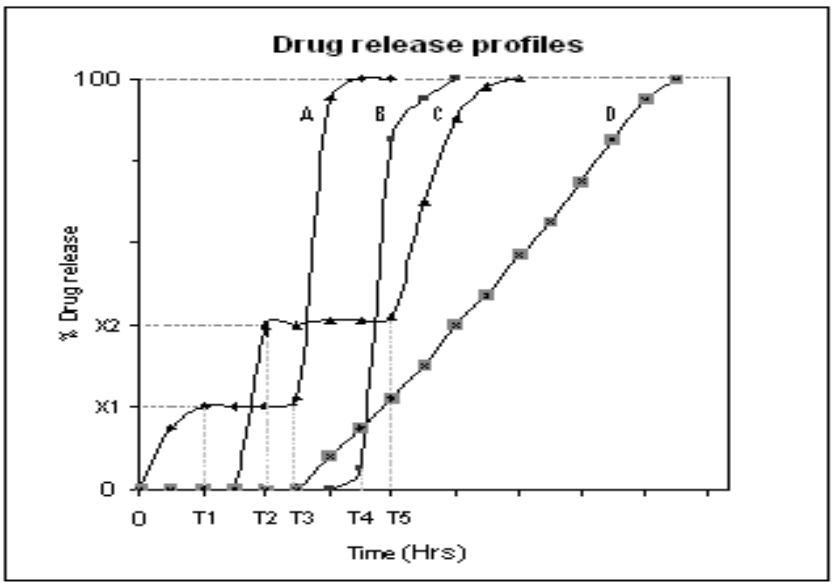

Figure 2: Conceptual *in-vitro* drug release profiles from pulsatile drug delivery system: (A) Initial release followed by lag and then quick release, (B) Quick release after lag time, (C) Multiple lags & quick releases and (D) Sustained release after lag time.

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 disorderes. 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 [17, 18]. 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.

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 [19-22].

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 [23-24]. The exact dose would depend on the severity of the patient's pain and his or her individual physiology.

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 [25]. Theoretical problems associated with a sustained or profound decrease of 24-h 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 [26].

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 rhythmic circadian changes in tumor blood flow and cancer growth are relevant both when tumors are small and growing most rapidly and when they are larger and growing more slowly. The blood flow to tumors and

tumor growth rate are each up to threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase. Clinical studies indicating whether circadian chemotherapy timing meaningfully affects drug toxicity patterns and severity, maximum tolerated dose, average dose intensity, tumor response quality and frequency and the survival of patients with cancer, have been indicated since the pioneer work of Haus et al. on leukemic mice. 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 [27, 28].

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 [29]. 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 [30].

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 [31]. 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 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 [32, 33].

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 [34-36]. Exogenous administration of mealtime doses promotes peripheral glucose uptake (i.e. it prevents postprandial increases in blood glucose concentration) as well as reducing hepatic glucose release.

Classification of pulsatile systems

In this review attempt is made to review various time controlled drug delivery system based on rupturing of membrane or erosion of membrane. Time dependent dosage forms are formulated to release their drug load after a predetermined lag time. Alternative terms used are pulsatile release, delayed or sigmoidal release. Besides one-pulse systems, multiple systems release the drug in subsequent pulses. The application of pulsatile release systems can be advantageous to adapt a drug therapy to chronopharmacological needs or to target a drug specific site in the gastrointestinal tract, e.g. to the colon. Lag time of 4-6 hours generally considered sufficient, since small intestine transit is about 3-4 hours, which is relatively constant. Formulation in which drug release is independent of the environmental factors like PH, enzymatic activity, intestinal motility, pressure etc. can be achieved by incorporating a lag-time into the formulation equivalent to mouth to colon transit time. The pulsatile drug delivery systems are of two types –

- Single unit system
- Multiple unit system

Single Unit System

Capsular system – Architecture of these systems generally consists of insoluble capsule body housing, a drug & a plug. After a predetermined lag-time plug was removed because it undergoes swelling, erosion or dissolution. Example: pulsincap R system – In this system a water insoluble body containing the drug formulation, system is closed with a swell able hydrogel. Plugged (insoluble but permeable & swellable) at open end [37]. Upon contact with,

gastro-intestinal fluid or dissolution medium the plug swells pushing itself out of the capsule after lag-time. Position & dimensions of plug control lag-time. For rapid release of water insoluble drug effervescent or disintegrating agents are added. No gastrointestinal irritation can be observed in both human & animal [38].

Pulsatile delivery by osmosis – The Port R system consists of gelatin shell filled with osmotically active ingredient along with drug & also having an insoluble lipidic plug. Shell is coated with semi permeable membrane (cellulose acetate) then plugged with insoluble plug as well as system comes in contact with aqueous medium the water moves across semi-permeable membrane & exert pressure which remove the plug after lag-time. System shows good in-vivo & in-vitro correlation in humans & used to deliver methylphenidate to school age children for the treatment of attention deficit hyper activity disorder (ADHD) [39].

Another system is also based on expendable orifice that contain capsular system in which liquid drug is absorbed on highly porous particles. Drug releases through orifice of a semipermeable capsule supported by an expending osmotic layer after the barrier layer is dissolved.

Still another system is based on delivery by a series of stop. In this system the capsule contains a drug & water absorptive water engine that are placed in compartment separated by a movable partition. These stops obstruct the movement of partition but are overcome in succession when osmotic pressure rises above threshold level.

System with solublization of coating: Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after specified lag period & drug is subsequently released rapidly. The lag time depends on the thickness of the coating layer. Example: The Time Clock system consists of solid dosage form coated with lipid barriers such as carnauba wax & beeswax along with surfactants like polyoxyethylene sorbitan monooleate. When this system comes in contact with the aqueous medium the coat emulsifies or erodes after the lag-time depending on the thickness of coat. The lag time of system is independent of the gastrointestinal motility, PH, enzyme & gastric residence time [40].

Reservoir system with rupture of membrane – The other class of the reservoir type pulsatile system is based on rupturable coatings. The drug release from the core occurs when

surrounding polymeric membrane undergo ruptured due to inbuilt pressure within system. The effervescent excipients produces gas or osmotic agent produces osmotic pressure or swelling agent causes swelling, one of these is necessary for rupture of coating. Citric acid & sodium bicarbonate is incorporated as effervescent mixture in tablet core coated with ethyl cellulose, when system comes in contact with water it produces carbon dioxide gas which exerts pressure & after lag time rupture the membrane & rapid release of drug occurs. A reservoir system with a semi permeable coating is proposed especially with drugs with high first pass effect in order to obtain in-vivo drug pattern similar to the administration of several immediate release doses croscarmellose sodium starch glycollate or low substituted hydroxy propyl cellulose were used as swelling substances, which resulted in complete film rupture followed by rapid drug release [41]. The lag time is controlled by composition of outer polymeric membrane (HPMC water soluble polymer increased permeability decreased lag-time)

Multiple unit System

Multiparticulate systems are reservoir type of devices with a coating, which either ruptures or changes its permeability. Drug is coated over sugar seeds these granules may then be packaged in a capsule or compressed with additional excipients to form a tablet. The active pharmaceutical ingredient may also be blended or granulated with polymers before coating to provide an additional level of control. However, drug loading in this type of system is low due to higher need of excipients.

System with rupturable polymeric coating

In these multiparticulate system drugs is coated on sugar seeds & then coated with insoluble & swellable top layer [42]. The swelling agent includes super disintegrents like carboxy methylcellulose, sodium starch glycollate, L-hydroxy propyl cellulose. Polymers like polyacrylic acid, polyethylene glycol etc. alternatively comprising of a mixture of tartaric acid & sodium bicarbonate that used as effervescent agent. Water ingress to system causes the coating to swell, rupture & release of drug occurs. Release of drug is independent of pH or solubility of drug. Lag-time can be varied by varying thickness of coating or by changing amount of plasticizers in the outermost layer. If concentration of osmotic agent increases rapid release of drug after lag-time can be observed. In-vivo studies of time controlled explosion system with an in-vitro lag-time of three hours showed appearance of drug in blood after 3 hours, and maximum level after 5 hours [43, 44].

Reservoir system with soluble or eroding polymer coating

These system contains core having drug (low bulk density solid or liquid lipid material) & disintegrant. Core is coated with cellulose acetate polymer. System is combination of swelling & osmotic effect, upon immersion in aqueous medium, water penetrates the core, displaces the lipid material, after depletion of lipid material internal pressure increases until a critical stress is reached, which causes rupture of coating. Another type of system is one in which tablet or capsule is composed of large number of pellets (two or more pellets). Single pellet of this system contains drug plus osmotic agent & coated with water permeable, water insoluble polymer. In film hydrophobic agent (water insoluble) is incorporated which alters permeability. The rate of water influx & drug efflux causes the film coating of each population to differ from any other pellet coating in the dosage form. Pellet gets swelled due to dissolution of osmotic agent as it comes in contact with water resulting in regulation of diffusion & release of drug content from pellet [45]. Each pellet population of system shows this effect. The coating thickness may vary & this system is used for antihypertensive drug diltiazem. Osmotically active compound don't undergo swelling, the use of osmotic active agent was reported by Shultz & Kleinbudde. The pellet core made up of drug, sodium chloride & coated with semi permeable cellulose acetate polymer (permeable to water & not to drug). Varying thickness of coating & amount of plasticizer in coating can vary lag-time of system. Sodium chloride provides fast release of drug if it is absent in core then a sustained release was observed after lag-time due to lower degree of swelling & generation of small fissures in core. Chen has also reported a system-containing core of drug & osmotically active agent coated with insoluble permeable membrane.

Change in membrane permeability based system

The permeability & water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter ions. Several delivery system with sigmoidal or pulsatile release based on these ion exchange have been developed Eudragit RS 30D is polymer of choice, it contains positively polarized quaternary ammonium group in the polymer side chain & also negative hydro chloride counter ions. The ammonium group is hydrophilic causes interaction with water & changes in permeability of it in controlled manner. In these system core containing drug & sodium acetate coated with four different layer of Eudragit RS30D. Small amount of sodium acetate dramatically change the permeability of eudragit film. After lag time permeability increases due to increase in interaction between eudragit & acetate, resulting in entire drug release within few minutes. Increase in lag-time occurs as thickness increases but it has no effect on release [46].

Sigmoid release system consists of drug & succinic acid core coated with ammonio-methacrylate copolymer USP/NF TYPE B. The lag-time is controlled by the rate of water influx through polymer membrane. Succinic acid dissolves by the water causes increase in permeability of hydrated polymer film that increases free volume. These findings were used to design acid containing core that is coated by polymeric membrane.

Low density floating multiparticulate pulsatile system

Conventional multiparticulate pulsatile release dosage forms mentioned above are having longer residence time in the gastrointestinal tract and due to highly variable nature of gastric emptying process, may resulted in in vivo variability and bioavailability problems. In contrary, low density floating multiparticulate pulsatile dosage forms reside in stomach only 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. Overall, these considerations led to the development of multiparticulate pulsatile release dosage forms possessing gastric retention capabilities. A multiparticulate floating-pulsatile drug delivery system was developed using porous calcium silicate (Florite RE) and sodium alginate, for time and site specific drug release of meloxicam for chronopharmacotherapy of rheumatoid arthritis. Meloxicam was adsorbed on the Florite RE (FLR) by fast evaporation of solvent from drug solution containing dispersed FLR. Drug adsorbed FLR powder was used to prepare calcium alginate beads by ionotropic gelation method, using 3(2) factorial designs. The floating time for this system was controlled by density of beads and hydrophobic character of drug. Polysaccharides are widely used in oral drug delivery systems because of the simplicity to obtain the desired drug delivery system and drug release profile, by the control of cross-linking, insolubility of crosslinked beads in gastric environment and broad regulatory acceptance. Badve et al developed hollow calcium pectinate beads for floating-pulsatile release of diclofenac sodium intended for approaches for imparting buoyancy, hollow/porous calcium pectinate beads were prepared by simple process of acid-base reaction during ionotropic crosslinking. The floating beads provided two-phase release pattern with initial lag time during floating in acidic medium followed by rapid pulse release in phosphate buffer [47, 48]. This approach suggested the use of hollow calcium pectinate microparticles as promising floating-pulsatile drug delivery system for site- and time specific release of drugs for chronotherapy of diseases. Further, combined floating and pulsatile principles were achieved using a specific technology, in which low density

microporous polypropylene, Accurel MP 1000, were used as a multiparticulate carrier for ibuprofen. Ibuprofen was adsorbed on the polymer by solvent evaporation technique; a single step method resulted in to different porous particles. This drug delivery system showed distinct behaviour from other approaches in chronotherapy with desired low drug release in acidic medium, reduced time consumption due to single step process, and even overcame the limitations of process variables caused by multiple formulation steps.

Methodologies for pulsatile drug delivery

Methodologies for the pulsatile drug delivery system can be broadly classified into three classes.

Time controlled systems

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. Various methodologies that can be used for time controlled pulsatile release systems are discussed in following section.

Delivery systems with rupturable coating

Delivery systems with rupturable 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. 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. Further 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 [49].

Delivery systems 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 [50]. 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.

Capsule shaped system provided with release controlling plug

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 [51].

Stimuli induced systems

In these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli. These systems are further classified in to temperature induced systems and chemical stimuli induced system, on the basis of stimulus.

7.2.1 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 20^0C and 30^0C 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 [52, 53].

Chemical stimuli induced pulsatile systems.

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 there by 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 [54]. 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.

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 [55].

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 [56]. 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.

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, sodium carboxymethylcellulose. 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, Hydroxypropylmethylcellulose phthalate and Hydroxypropylmethylcellulose 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 [57].

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 [58]. Magnetically regulated system contain 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, ultrasonic waves 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 waves24. 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 [59].

Mechanism of drug release from pulsatile drug delivery system

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.

Erosion

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

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.

Evaluation of pulsatile drug delivery system

In vitro and in vivo correlation ((IVIVC)

Correlations between in vitro and in vivo data (IVIVC) are often used during pharmaceutical development in order to reduce development time and optimize the formulation. A good correlation is a tool for predicting in vivo results based on in vitro data. IVIVC allows dosage form optimization with the fewest possible trials in man, fixes dissolution acceptance criteria, and can be used as a surrogate for further bioequivalence studies; it is also recommended by regulatory authorities [60].

For the optimum design of a modified release oral dosage form, the key step is to understand the principles of GI dynamics such as gastric emptying, small intestinal transit, colonic transit, etc. Acquiring knowledge about the rate and extent of drug absorption from different sites of GI tract, and factors that can alter or limit the absorption further aid in designing the type of dosage form that is needed for a particular drug. For instance, with drugs such as sulpiride, furosemide, theophylline and albuterol which are predominantly absorbed from the upper part of the GI tract, designing a gastroretentive dosage form is a logical strategy for improving and extending their limited oral bioavailability. With the advent of g-scintigraphy, it is now possible to understand the various physiological and pharmaceutical factors involved in oral drug delivery. One of the most reliable and novel approaches includes the use of the InteliSiteE Capsule, which provides quick assessment of the oral absorption of

drugs within specific regions of the GI tract. The method is simple, operator-controlled, non-invasive, and leads to cost-effective development of novel oral PDDS [61].

Table 1: Parameters Used In IVIVC correlation

Level	In vitro	In vivo
A	Dissolution curve	Absorption curves
B	Statistical moments:MDT	Statistical moments:MRT, MAT,etc
C	Disintegration time, Time to have 10,50,90% dissolved, Dissolution rate, Dissolution efficiency	Cmax, Tmax, Ka, Time to have 10,50,90 % absorbed, AUC (total or cumulative),

Note: MDT- mean dissolution time, MRT - the mean residence time, MAT- the mean absorption time.

Recent advances in the pulsatile drug Delivery:

Nowadays pulsatile drug delivery systems are gaining importance in various disease conditions specifically in diabetes where dosing is required at different time points. 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 them with different release patterns, as well as short and reproducible gastric residence time. 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 [62]. Gastroretentive 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 [63].

Advantages, future potential of PDDS

Multiphase oral delivery is at another exciting stage in its history. The development of products and manufacturing systems continues according to classical needs; for example, the provision of varying in vitro and in vivo release profiles and for the delivery to local absorption sites such as the colon. However, new technologies are exploring the more

complex needs of bio chemical processes, seeking to alter and exploit their mechanism. These routes take advantage of increased understanding of biological processes and offer new possibilities for drug delivery systems. It is worth noting that many of the applications described here relate to the manipulation of compounds arising from synthetic chemistry laboratories. There should be ample scope for potential application of some of the newer techniques to the large number of development products that arise from the biotech industry. Oral drug candidates such as oligopeptides are most likely to require delivery targeting in order to avoid degradation and/or meet specific absorption mechanisms.

Here, multi-step approaches, such as those being explored by Junginger, may present powerful tools in their oral delivery. It is significant that materials already found to be of use in the manipulation of the absorption process, for example poly carbomers, are currently in use in other applications. This should minimize regulatory requirements in assessing their long-term safety, and recognize that they have more than a purely passive role in drug delivery. It will minimize the time involved in taking specific products to market. In addition, the early identification of their activity will facilitate their use as models in the development of carriers with wider application and greater absorption enhancement. This will benefit development companies in opening up new markets, thus facilitating the oral delivery of compounds currently restricted to routes that are less convenient to patients. It will also benefit patients directly in terms of reliable oral delivery of potent new clinical agents. Other direct patient benefits will arise from minimizing dosing regimens and the related reduction in clinical side-effects. It is clear that some of the novel solutions in development will be relevant. These are exciting times for imaginative formulators and products.

Commercial products:

A major objective of chronopharmaceutics is to deliver the drug in higher concentrations during the time of greatest need and in lesser concentrations when the need is less to minimize unnecessary side effects.

Their approval dates, proprietary name and technology, indications and rationale for chronotherapy in each case are given in table 1. The selected dosage forms are claimed by the marketer developer as exhibiting chronotherapeutic effects. Most data were compiled from FDA electronic orange book, specific product package inserts and United States patents and specific pharmaceutical company websites.

Regulatory aspects:

Perhaps the most complex controlled-release profile is the pulsatile profile. Pulsatile release

Table: 2: Advantages of Technology

Technology	Mechanism	Proprietary name and Dosage form	API	Disease	Advantage
OROS	Osmotic mechanism	Covera-HS®; XL Tablet	Verapamil HCl	Hypertension	Prevent the dangerous surge of BP in the early morning
CODAS	Multiparticulate, pH dependent system	Verelan® PM; XL Release Capsule	Verapamil HCl	Hypertension	Early morning peaks plasma concentration after bed time dosing
DIFFUCAPS	Multiparticulate system	Innopran®; XL tablets	Propranolol HCl, Verapamil HCl	Hypertension	Lag time is 4-5 hours. Release is pH independent
Three dimensional Printing	Externally reglated system	TheirForm®	Diclofenac Sodium	Inflammation	Complex, computer generated delivery system.
CONTIN®	Extended release tablet	Uniphyl® extended release tablet	Thiophylline	Asthma	Early morning Peak plasma concetration following by bed time dosing

may be desirable where tolerance to a drug is likely to develop, or where the drug is administered to mimic natural secretion within the body. In cases such as these, drug delivery technologies can imitate the effect of administering the drug at discrete intervals throughout the day, without inconvenience to the patient because of a cumbersome dosage regime.

More than 30 years have been devoted to characterizing the biopharmaceutical properties of drug products. The numerous tests developed are generally based on two distinct methodologies--a closed system (beaker method) and an open system (flow-through method). Selected methods were finally standardized and described in such pharmacopoeias as Ph. Eur. 2, USP XXII and Ph. Jap. XII. The most common procedures are the paddle and basket methods. An alternative method--the flow--through method--was also introduced into the pharmacopoeias Ph. Eur. 2 and USP XXII. The advantages of the flow-through method are evident with regard to testing and assessing different types of dosage forms and active ingredients of very slight solubility. Changes of testing fluids (e.g. change to the pH) can be

easily performed during the test. Another advantage is seen in the positioning of the specimen. Capsules, even when floating initially, or pellets can be tested using the same equipment and require no additional devices such as sinkers. With slight changes to the cell design, the same apparatus can be used for the testing of powders, or even non-solid dosage forms such as suppositories or soft-gelatine capsules. For long-term testing necessary for extended release products, flow-through apparatus offers a considerable number of advantages for routine work. Irrespective of the methodologies used, dissolution tests should be validated with regard to analytical methods, testing conditions and specifications. The validation of the analytical method should follow EC guidelines. Testing conditions should take into account the choice of the correct apparatus, dissolution media and agitation. The results of in vitro dissolution should be validated by in vivo data in an analogous sense. The practical application of flow-through apparatus is presented on the basis of various examples regarding development and batch control.

CONCLUSION

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. Moreover, the circadian clock of the suprachiasmatic nucleus (SCN) is thought to drive daily rhythms of behavior by secreting factors that act locally within the hypothalamus. Epidermal growth factor receptors signaling have been implicated in the daily control of locomotor activity, and neural circuit in the hypothalamus that likely mediates the regulation of behavior both by the SCN and the retina have been identified. Clearly, mammals possess a rationally based light-detection system that has component (e.g. melanopsin, cryptochromes) that may be potential target for efficient chronopharmaceutical drug development. Because we are moving smaller in drug discovery and development engineered nanomaterials for biophotonics applications may also be used to develop optically controlled PDDS. The overall success of

chronopharmaceutics will depend on the successful integration of knowledge from future advances in development timing, system biology and nanomedicine. The selection of the appropriate chronopharmaceutical technology should take into considerations the application range (e.g. targeted drugs of different physico-chemical properties), the ease of manufacturing, the cost-effectiveness, and the flexibility in the pharmacokinetic profile.

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.

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