Pulsatile Drug Delivery with Press Coated Techniques

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Abstract

Pulsatile drug delivery systems (PDDS) have attracted attraction because of their multiple benefits over conventional dosage forms. They deliver the drug at the right time, at the right site of action and in the right amount, which provides more benefit than conventional dosage and increased patient compliance. The past several decades have seen the development of many controlled-release preparations constant release rates to maintain drug concentrations in the human body, according of the patient’s physiological condition. Person to person different physiological and biochemical conditions during any 24 h period, due to the circadian rhythm, and thus, the constant delivery of a drug into the body. Pulsatile drug delivery system which promises the predetermined Lag-time followed by the immediate release of drug. So optimizing the therapeutic effect while minimizing side effects. Various methods describes in review in which press coating technique is a simple and unique technology used to provide tablets with a programmable lag phase, followed by a fast, or rate-controlled, drug release after administration. The technique offers many advantages, and no special coating solvent or coating equipment is required for manufacturing this type of tablet. The contents of this article include biological rhythms and the reasons for using pulsatile drug delivery for disease treatment, and press-coated delivery techniques, factors affecting the performance and drug release characteristics of press-coated delivery systems.

Keywords: Circadian rhythm, chronodelivery, lag time, time controlled PDDS, press coated tablet

INTRODUCTION

During the past several decades, conventional drug dosage forms have been widely used for treatment of various conditions. These drug dosage forms typically provide an immediate or rapid medication release, and supply a given concentration or quantity of the drug to the body’s systemic circulatory system without any rate control. To maintain the effective plasma drug concentration, administration is required. Due to poor drug efficacy, the incidence of side effects, frequency of administration and patient compliance of these conventional drug preparations, many traditional drug dosage forms are undergoing replacement by second-generation, modified drug-release dosage forms (Fig. 1). Treatment of numerous diseases using traditional drug products is often inconvenient and impractical if disease symptoms occur during the night or early morning.

During the early 1990’s Second-generation modified-release drug preparations achieved continuous and constant-rate drug delivery, in which constant or sustained drug output minimize drug concentration “peak and valley” levels in blood, so promoting drug efficacy and reducing adverse effects. Modified-release drug preparations are expected to provide reduced dosing frequency and improved patient compliance compared to conventional release preparations. Second-generation modified-release dosage includes slowed-release, delayed-release, prolonged-release, extended-release, repeated-release, sustained-release and controlled-release drug preparations [1].

Various modified release drug products [2]

Controlled and sustained releases, both are used in consistent and confusing manner. Both represent separate delivery process.
Extended Release:
It leads to two fold reductions in dosing frequency compared to immediate release dosage forms.

Controlled Release:
This system allows slow drug release over extended period of time but not at predetermined rate.

Sustained Release:
This system delivers drug at predetermined rate over a long period.

Delayed Release:
This dosage form releases discrete portion of drug at a time other than rapidly after administration, although one portion may be released promptly after administration.

Targeted Release:
These delivery systems deliver drug at or near the intended site of action and may have extended release characteristics.

Repeated Action:
This product is designed to release first dose initially, followed by second dose of drug at a later time.

Prolonged Action:
This dosage form releases drug slowly and provide continuous supply of drug over an extended period. Controlled-release medications deliver continuous treatment, rather than providing relief of symptoms and protection from adverse events solely when necessary, the development of a third-generation of advanced drug delivery systems (DDSs) to optimize and create new innovative DDS which provide a defined dose, at a chosen rate, at a selected time, to a targeted site is now a growing challenge. A chronodelivery system, based on biological rhythms, is a state-of-the-art technology for drug delivery; chrono-modulated DDSs not only increase safety and efficacy levels, but also improve overall drug performance [3,4].

Chronopharmaceutics [5,6]
During the past two decades, diseases that follow rhythmic patterns have given rise to the creation of new drug delivery dosage forms, called chronopharmaceuticals chronotropic DDS technology for delivering drugs precisely in a time-controlled fashion in accordance with circadian rhythms may be developed as a chrono pharmaceutical product to treat different human diseases, as proposed by (Fig. 2).

Chronopharmaceutics includes the fundamentals and research into various aspects [7]

1) Chronobiology:
Chronobiology is the science concerned with the biological mechanism of the diseases according to a time structure “Chrono” pertains to time and “biology” pertains to the study, or science, of life.

2) Chronopharmacology [8]
Chronopharmacology is the science concerned with the variations in the pharmacological actions of various drugs over a period of time of the day.

3) Chronopharmacokinetics [8,9]
Chronopharmacokinetics involves study of temporal changes in drug abortion distribution metabolism and excretions, pharmacokinetics parameters, which are conventionally considered to be constant in time, are influenced by different physiological functions displaying circadian rhythm. Circadian changes in gastric acid secretion, gastrointestinal blood flow, drug

Figure 1: Progress of pharmaceutical preparations

<table>
<thead>
<tr>
<th>Conventional dosage forms</th>
<th>Modified-release dosage forms</th>
<th>New drug delivery system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syrup</td>
<td>Slowed-release</td>
<td>Inhalation delivery</td>
</tr>
<tr>
<td>Tablet</td>
<td>Delayed-release</td>
<td>ODT delivery</td>
</tr>
<tr>
<td>Capsule Injection</td>
<td>Prolonged-release</td>
<td>Chronodelivery</td>
</tr>
<tr>
<td>Ointment</td>
<td>Extended-release</td>
<td>Nanodelivery</td>
</tr>
<tr>
<td>Solution</td>
<td>Repeated-release</td>
<td>Targeting delivery</td>
</tr>
<tr>
<td>Syrup</td>
<td>Sustained-release</td>
<td>Gene delivery</td>
</tr>
<tr>
<td>Suppository</td>
<td>Controlled-release</td>
<td>Stem cell therapy</td>
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protein binding, liver enzyme activity, renal blood flow and urinary pH can play role in
time dependent variations of drug plasma concentrations.

<table>
<thead>
<tr>
<th>Circadian Rhythm</th>
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<tbody>
<tr>
<td>Biochemical</td>
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<tr>
<td>Physiological</td>
</tr>
<tr>
<td>Process</td>
</tr>
</tbody>
</table>

Chronopharmacology
Chronopharmacokinetics
Chronopharmacodynamics

Chronopharmacotherapeutic Concept

Drug

Chronotrophic Drug Delivery Strategy
- Functional Design
- Formulation Design
- Process Design
- Package Design

Quality by Design

Optimal dosing time

Time-control

Site-control

Compliance

Ideal Chronotherapy

QOL

Efficacy

Side effect

Figure 2: Design and development of new Chronotropic DDSs in accordance with
circadian rhythm of human body

4) Chronotherapy:
Co-ordination of biological rhythms and medical treatments is called Chronotherapy.

5) Chronotherapeutics
Chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. It is becoming increasingly more evident that the specific time that patients take their medication may be even more significant than was recognized in the past.

Biological rhythm [10]

1. Ultradian rhythm: Oscillations of shorter duration are termed ultradian rhythms (more than 1 cycle per 24 h), e.g., 90 minutes sleep cycle.

2. Infradian
Oscillations that are longer than 24 hours are termed as Infradian rhythms (less than 1 cycle per 24 h), e.g., monthly menstruation.

3. Circadian
Circadian rhythms are self-sustaining endogenous oscillations.

Circadian variation [11]
Many common diseases also display a marked circadian variation during onset or exacerbation of symptoms, as shown in (Fig. 3). Since the circadian rhythm influences normal biological processes, the occurrence or intensity of symptoms.
Figure 3: The circadian pattern of diseases

Normal physiological condition
The body varies greatly in physiological and biochemical status over a 24-hour period due to circadian rhythm (Table 1)
Traditionally, drug delivery has meant a simple chemical absorbed from the gut or from the site of injection. A second-generation drug delivery goal has been perfection of continuous, constant rate delivery of bioactive agents but living organisms are not “zero-order” in their requirement or response to drugs. They are predictable resonating dynamic circadian cycle which will maximize desired and minimize undesired drug effect. So have been made to design the drug delivery system which will release the drug at constant rate. But still for many of the drugs, use of such systems is not suitable because of a number of reasons.

Table 1: Circadian rhythm influences on physiological process

<table>
<thead>
<tr>
<th>Physiological functions</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body temperature</td>
<td>Sleep ↓ wakefulness ↑</td>
</tr>
<tr>
<td>Breathing</td>
<td>Sleep ↓ wakefulness ↑</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Sleep ↓ wakefulness ↑</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>pm 11:00 secretion ↑</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>pm 11:00 secretion ↑</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Sleep ↓ wakefulness ↑</td>
</tr>
<tr>
<td>Plasma catecholamines</td>
<td>Increase in morning</td>
</tr>
<tr>
<td>Plasma agreeability</td>
<td>Increase in morning</td>
</tr>
<tr>
<td>Fibrinolytic activity</td>
<td>Decrease in morning</td>
</tr>
<tr>
<td>Gastric acid secretion</td>
<td>Highest in evening</td>
</tr>
<tr>
<td>Gastric emptying</td>
<td>More rapid in morning</td>
</tr>
</tbody>
</table>

Note: ↓ down ↑ up

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. Secondly drugs with short half-life need to administered repeatedly which results in patient non-compliance. In case of chronic treatment, where the drug is given in sustained release dosage form, and continuous exposure of the drug to body may lead to adverse effect. For example, diabetes mellitus requires chronic treatment with sustained release formulations of drugs like sulfonylurea which will 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 increases with time when drug levels are held constant. Dosage form which will provide desired concentration of drug at particular time point only. [12]

Pulsatile drug delivery system has fulfilled this requirement. Pulsatile drug release is such a system where drug is released suddenly after well-defined lag time or time gap according to circadian rhythm of disease states. No drug is released from the device within this lag time. This delivery system is true for cases where drugs including proteins and peptides undergo through large metabolic degradation. In case of chronic treatment drug resistance may grow and adverse effect may be seen. Here chances are less because the desired concentration of drug at certain time point is available. This method is good for the drugs with extensive first pass metabolism and targeted to specific site in the intestinal tract [13]. Drug release pattern from the device with pulsatile effect is shown in. In these systems, there is rapid and transient release of a certain amount of drug molecules within a short time period immediately after a predetermined off release period, i.e lag time. Lag time is defined as the time between when a dosage form is placed into an aqueous environment and the time at which the active ingredient begins to get released from the dosage form. [14]

![Diagram of Pulsatile Drug Release](image)

**Figure 4: Pulsatile drug release pattern**

**Diseases requiring pulsatile drug delivery** [15]

Thorough understanding of the disease physiology is required before designing the pulsatile 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 h. (Table 2) enumerates various diseases showing such a chronological behavior.

**Advantages of Pulsatile drug delivery** [16]

- Increases absorption and bioavailability than conventional immediate release or sustained release drug due to its ability to release drug in a burst manner, at target site of absorption.
- Site targeting allows delivery of poorly bioavailable drugs that would get destroyed in higher GI tract environment. E.g., peptide and protein molecules.
- Reduces dose of drug without decrease in therapeutic effects.
- Decreases side effects.
- Decreases drug interaction due to lower cytochrome P450 isoenzymes.
- Decreases food effect (change occurring in bioavailability of drug when given with food).
- Improved compliance.
• Chronotherapy, programmed delayed release provides optimal treatment of diseases.
• Pulse release allows multiple dosing in a single dosage form.
• Allows site specific release for local treatment of diseases. Drug release is not affected by change in pH of the gastrointestinal tract, viscosity of lumen contents, and agitation rate of GI tract.
• The system can be utilized for many solid dosage forms like granules, microspheres, microparticles, tablets, capsules, and pellets.

Disadvantages of PDDS [17]
• It develops a non 24 hours sleep wake syndrome after the treatment as the person sleeps for over 24 hours during the treatment. It's not quite common but the degree of risk is not known.
• Person may also be sleep deprived sometimes.
• Person become less productive during chronotherapy and staying awake till the other schedule will be bit uncomfortable.
• You will have to take some time off from your busy normal schedule as its time taking therapy.
• Medical supervision is mandatory for this therapy. And regular consulting of sleep speacitists is recommended.
• One has to keep himself awake till the next sleep schedule.so he have to get himself busy so that he stay awake till the other schedule.
• Person going through the therapy may feel unusually hot or cold sometimes. Have to consult the doctor regularly to avoid side effects.

Table 2: Various diseases showing such a chronological behavior

<table>
<thead>
<tr>
<th>DISEASES</th>
<th>CHRONOLOGICAL BEHAVIOUR</th>
<th>DRUGS USED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer</td>
<td>Acid secretion is high in the afternoon and at night</td>
<td>H₂ blockers</td>
</tr>
<tr>
<td>Asthma</td>
<td>Precipitation of attacks during night or at early morning hour</td>
<td>β₂ agonist, Antihistaminic</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</td>
<td>Nitroglycerin, Calcium channel blockers, ACE inhibitors etc.</td>
</tr>
<tr>
<td>diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>Pain in the morning and more pain at night</td>
<td>NSAIDs, Glucocorticoids</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Increases in the blood sugar level after meal</td>
<td>Sulfonylurea, Insulin, Biguanide</td>
</tr>
<tr>
<td>Attention</td>
<td>Increase in DOPA level in afternoon deficit syndrome</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Hyper cholesterol</td>
<td>Cholesterol synthesis is generally higher during night than during day time</td>
<td>HMG CoA reductase inhibitors</td>
</tr>
</tbody>
</table>

Diseases with established circadian rhythms [18-20]
All endogenous biological processes and functions are programmed in time during the 24 hour for the conduct of specific activities at discrete times. A number of diseases show their pathognomonic following a biological rhythm:

Asthma:
Circadian changes are seen in normal lung function, which drops in the early morning hours. The decreased lung function is more pronounced in people with asthma. It is usually highest at 4 pm and lowest at 4 am. It is the 4 am when asthma is more prevalent.

Duodenal Ulcer:
Gastric acid secretions are highest at night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing, once daily bed time dosage regimen is recommended for H₂ antagonists

Cancer:
Chemotherapy may be more effective and less toxic if anticancer agents are administered keeping in mind the tumor cell cycles. This way it will be less toxic to normal tissue. Blood flow to tumors and
tumor growth rate are each up to three fold greater during each daily activity phase of circadian cycle than during daily rest phase. Chronotherapy concept offers promise for improving current cancer treatment options. However Chronotherapy is still uncommon, limited to only 50 cancer centers throughout world. For Chronotherapy to be widely accepted additional randomized clinical trials is needed to be conducted.

**Diabetes:**
Circadian behavior in glucose and insulin secretion in diabetes was revealed and studied. Increase in blood sugar level is found after meal.

**Hypercholesterolemia:**
Hepatic cholesterol synthesis is also found to follow circadian rhythm. But the rhythmicity varies according to individuals. There is a large difference in plasma mevalonate concentration between individuals. However cholesterol synthesis is generally higher during the night than during daylight. Diurnal synthesis is only 30-40% of daily cholesterol synthesis. Maximum production occurs early in the morning i.e. 12 hours after the last meal. The evening dose of HMG CoA reductase inhibitors is more effective than morning dose.

**Neurological Disorder:**
Investigation on epilepsy and convulsion demonstrate chronological rhythm. It is mentioned that brain area with highest concentration in noradrenergic nerve terminals and noradrenalin have a circadian rhythm in their content of noradrenalin.

**Myocardial Infarction:**
Onset of myocardial infarction has been shown to be more frequent in the morning with 34% events occurring between 6 A.M. and noon. Acute cardiac arrest and transient myocardial ischemia shows an increased frequency in morning. The causes for these findings have been suggested to be release of catecholamines, cortisol, increase in the platelet aggregation and vascular tone.

**Cerebrovascular accidents:**
The cerebrovascular accidents have been shown to occur on the first hours of morning between 10 A.M. and 12 noons, and the incidence declines steadily during the evening and the midnight. A major objective of chronotherapy for cardiovascular disease is to deliver the drug in higher concentration during time of greatest need and in lesser concentrations when the need is less. ACE inhibitors are more effective when administered during night. Atenolol, Nifedipine and amolodipine are more effective when administered at night. The first chronotherapeutic therapy for hypertension and angina pectoris has recently been developed which matches drug delivery to the circadian pattern of blood pressure and rhythm of myocardial ischemia. Verapamil has been employed in this system where release is observed after 4-5 hours an continues for 18 hours. Taken at bedtime, this provides optimal blood concentration between 4 A.M. and afternoons.

**Pain:**
It was reported that the highest threshold occurred at the end of the resting period, while the least threshold seen at the end of the activity period. In arthritis there is circadian rhythm in the plasma concentration of C-reactive protein and interleukin-6 of patient with rheumatoid arthritis. It was reported that levels of endogenous opioid peptides are higher at the starting point of the day and lower in the evening both in neonate and adult human volunteers. Patients with osteoarthritis tend to have less in the morning and more at night. While patients with rheumatoid arthritis have pain that usually peaks in the morning and decreases throughout day.

**Sleep disorder:**
Many biological signalings e.g. sleep disorder occurring in the central and autonomous nervous systems show complex time structure with rhythm and pulsatile variations in multiple frequencies. The time of sleep required by each person is usually constant, although there is a wide variation among individuals.

**Alzheimer's disease:**
Individuals with Alzheimer's show less diurnal motor activity, a higher percentage of nocturnal activity, lower interdaily stability of motor activity, and a later activity acrophase (time of peak) than normal healthy individuals. Alzheimer's disease leads to pathological changes in the suprachiasmatic nucleus and thus it disrupts circadian rhythms of the brain's function. The core body temperature is also higher in
patients with this disease. The circadian abnormalities are seen together with cognitive and functional deterioration in this disease.

**Infectious diseases:**
Periodic time-dependent changes in the incidence of infectious diseases are well known. The elevation of body temperature, fever due to bacterial infections is higher in the evening while that due to viral infections is more likely in the morning. Influenza is epidemic in the winter season. It was reported that the morbidity and the mortality were greatest during the winter and least during the summer both in the Northern and Southern Hemispheres. The weight of the nasal secretions is highest in the morning in patients with cold and decreased over the day and increased again somewhat in late evening.

**Methods of Pulsatile drug delivery system [21-24]**
Pulsatile systems are basically time controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastro-intestinal motility, etc. classification of pulsatile drug delivery.

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**Figure 5: Classification of pulsatile drug deliver**

1. **Time Control Pulsatile Drug Delivery**
   1. **Capsule based systems:**
      Single unit systems are mostly developed in capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion, and the drug is released as a “Pulse” from the insoluble capsule body. Pulsincap is one such system that comprises of a water-insoluble capsule enclosing the drug reservoir. When this capsule came in contact with dissolution fluid, it swelled; and after a lag time, the plug pushed itself outside the capsule the rapidly released the drug. The...
lag time can be controlled by manipulating the dimension and the position of the plug [25,26].

**Figure 6: Design of Pulsincap system**

Polymers used for designing of the hydro gel plug
1) Insoluble but permeable and swellable polymers e.g. polymethacrylates
2) Erodible compressed polymers e.g. hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide
3) Congealed melted polymers e.g. saturated polyglycolated glycosides, glycerin monooleate
4) Enzymatically controlled erodible polymer e.g. pectin [27,28].

The preparation and invitro release of tetramethylpyrazine phosphate Pulsincap capsule has been reported. It was prepared by sealing the drug tablet and fillers inside an impermeable capsule body with erodible plug. To meet the chronotherapeutic requirements, a suitable lag time can be achieved by adjusting the content of gel-forming polymer (HMPC) and the erodible plug weight.

**Capsular System based on Osmosis:**

**a) PORT system**

Consists of a capsule coated with a semi permeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation. When this capsule came in contact with the dissolution fluid, the semi permeable membrane allowed the entry of water, which caused the pressure to develop and the insoluble plug expelled after a lag time. Such a system was developed to deliver methylphenidate used in the treatment of attention deficit hyperactivity disorder as the pulsatile port system. This system avoided second time dosing, which was beneficial for school children during daytime.

**Figure 7: Drug release mechanism from**
b) System based on expandable orifice:
To deliver the drug in liquid form, an osmotically driven capsular system was developed in which the liquid drug is absorbed into highly porous particles, which release the drug through an office of a semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved.

Figure 8: System based on expandible orifice

The capsular system delivers drug by the capsule's osmotic infusion of moisture from the body. The capsule wall is made up of an elastic material and possesses an orifice. As the osmosis proceeds, the pressure within the capsule rises, causing the wall to stretch. The orifice is small enough so that when the elastic wall relaxes, the flow of the drug through the orifice essentially stops, but when the elastic wall is distended beyond threshold value, the orifice expands sufficiently to allow drug release at a required rate. E.g. Elastomers, such as styrene-butadiene copolymer have been suggested. [29] Pulsatile release was achieved after a lag times of 1 to 10 hrs, depending on the thickness of the barrier layer and that of semi permeable membrane. A capsule designed for implantation can deliver drug intermittently at intervals of 6 hours for 2 days.

c) Delivery by series of stops:
This system is described for implantable capsules. The capsule contains a drug and a water-absorptive osmotic engine that are placed in compartments separated by movable partitions. The Pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level. The number of stops and the longitudinal placements of the stops along the length of the capsule dictate the number and frequency of the pulses, and the configuration of the partition controls the pulse intensity. This system was used to deliver porcine somatotropin.

d) Pulsatile delivery by solubility modulation:
Such systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate. [30] The composition contains the drug (salbutamol sulphate) and a modulating agent (sodium chloride). The amount of NaCl was such that it was less than the amount needed to maintain saturation in a fluid that enters the osmotic device. The pulsed delivery is based on drug solubility. Salbutamol has solubility of 275 mg/ml in water and 16 mg/ml in saturated solution of NaCl has solubility of 321 mg/ml in water, and its saturation solubility is 320 mg/ml.

3. Pulsatile system with Erodible or soluble barrier coatings:
Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly from
reservoir core. The lag time depends on the thickness of the coating layer.

a) The Chronotropic system:

![Image of Chronotropic system]

**Figure 9: The chronotropic system**
The Chronotropic system consists of a drug containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of release [31,32]. In addition, through the application of an outer gastric-resistant enteric film, the variability in gastric emptying time can be overcome, and a colon-specific release can be obtained, relaying on the relative reproducibility of small intestinal transit time. The lag time is controlled by the thickness and the viscosity grades of HPMC [33]. Both in-vitro and in-vivo lag times correlate well with the applied amount of the hydrophilic retarding polymer. The system is suitable for both tablets and capsules [34].

b) Time clock system:

![Image of Time clock system]

**Figure 10: 'Time clock' System**
The time clock is a delivery device based on solid dosage form that is coated by an aqueous dispersion. This coating is hydrophobic-surfactant layer to which a water soluble polymer is added to improve adhesion to the core. Once in contact with the dissolution fluid, the dispersion rehydrates and redisperses. The lag time could be controlled by varying the thickness of the film. After the lag time, i.e., the time required for rehydration, the core immediately releases the drug. This system has shown reproducible results in-vitro and in-vivo. The effect of low calorie and high calorie meal on the lag time was studied using gamma scintigraphy. The mean lag time of drug release was 345 and 333 min respectively.

C) Compressed Tablets:
Compression coating can involve direct compression of both the core and the coat, obviating needs for separate coating process and use of coating solutions. The outer tablet of the compression-coated tablet provides the initial dose, rapidly disintegrating in the stomach and the inner layer is formulated with components that are insoluble in gastric media but are released in the intestinal environment [35]. Materials such as hydrophilic cellulose derivates can be used. Compression is easy on laboratory scale. The major drawbacks of the technique are that relatively large amounts of coating...
materials are needed and it is difficult to position the cores correctly.

**Press-coated pulsatile drug delivery system:**

1) Press-coated pulsatile drug delivery systems can be used to protect hygroscopic, light sensitive, oxygen labile or acid-labile drugs.
2) Press-coated pulsatile drug delivery systems are relatively simple and cheap.
3) These systems can involve direct compression of both the core and the coat.
4) Materials such as hydrophobic, hydrophilic can be used in press-coated pulsatile drug delivery system.
5) Press-coated pulsatile drug delivery systems involve compression which is easy on laboratory scale.
6) Press-coated pulsatile formulations release drug after “lag time”.
7) Press-coated Pulsatile drug delivery formulations can be used to separate incompatible drugs from each other or to achieve sustained release.

**d) Multilayered Tablets:**
A release pattern with two pulses was obtained from a three layered tablet containing two drug containing layers separated by a drug-free gellable polymeric barrier layer [36]. This three-layered tablet was coated on three sides with impermeable ethyl cellulose, and the top portion was left uncoated. Upon contact with dissolution medium, the initial dose incorporated into the top layer was released rapidly from the non-coated surface. The second pulse was obtained from the bottom layer after the gelling barrier layer of HPMC was eroded and dissolved. The rate of gelling and/or dissolution of the barrier layer control the appearance of the second pulse. The gelling polymers reported include cellulose derivatives like HPMC, methyl cellulose, or polyvinyl alcohols of various molecular weights and the coating materials include ethyl cellulose, cellulose-acetate-propionate, methacrylic polymers, acrylic and methacrylic copolymers, and polyalcohol.

**Figure 11: Multilayered Tablets**

**3. Pulsatile system with Rupturable coating:**
These systems depend on the disintegration of the coating for the release of drug. The pressure necessary for the rupture of the coating can be achieved by the effervescent excipients, swelling agents or osmotic pressure. An effervescent mixture of citric acid and sodium bicarbonate was incorporated in a tablet core coated with ethyl cellulose. The carbon dioxide developed after penetration of water into the core resulted in a Pulsatile release of drug after rupture of the coating [37]. The release may depend on the mechanical properties of the coating layer. The lag time increases with increasing coating thickness and increasing hardness of the core tablet. The highly swellable agents, also called superdisintegrants, were used to design a capsule-based system comprising a drug, swelling agent, and Rupturable polymer layer [38].

**B. Multiparticulate/Multiple unit systems:**
Multiparticulate systems (e.g. pellets) offers various advantages over single-unit systems. These include,
1) No risk of dose dumping
2) Flexibility of blending units with different release pattern
3) Reproducible and short gastric residence time

The drug-carrying capacity of Multiparticle systems is lower due to presence of higher quantity of excipients. Such systems are invariable a reservoir type with either Rupturable or altered permeability coating.

1. Pulsatile system based on Rupturable coating:
E.g. Time-controlled Explosion system (TCES):
This is Multiparticle system in which drug is coated on non-parcel sugar seeds followed by a swellable layer and an insoluble top layer [39,40]. The swelling agents used include superfidintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose. Polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc. Alternatively, an effervescent system comprising a mixture of tartaric acid and sodium bicarbonate may also be used. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The release is independent of environmental factors like pH and drug solubility. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer. A rapid release after the lag phase was achieved with increased concentration of osmotic agent [41].

![Figure 12: Time-controlled Explosion system (TCES)](image)

2. Osmotic based Rupturable coating system:
This system is based on a combination of osmotic and swelling effects. The core containing the drug a low bulk density solid and/or liquid lipid material (e.g. mineral oil) and a disintegrate was prepared. This core was then coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of coating [42].

Another system is based on capsule or tablet composed of a large number of pellets consisting of two or more pellets or parts (i.e. populations) [43]. Each pellet has a core that contains the therapeutic drug and a water-soluble osmotic agent. Water-permeable, water insoluble polymer film encloses each core. A hydrophobic water-insoluble agent that alters permeability (e.g. a fatty acid, wax, or a salt of fatty acid) is incorporated into the polymer film. The rate of water influx and drug efflux causes the film coating of each population to differ from any other pellet coating in the dosage form. The osmotic agents dissolve in the water causing the pellets to swell, thereby regulating the rate of drug diffusion. The effect of each pellet population releasing its drug content sequentially provides a series of pulses of drug from a single dosage form. The coating thickness can be varied amongst the pellets. This system was used for the delivery of antihypertensive drug, diltiazem.

2. Pulsatile delivery by change in membrane permeability
The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium [44]. Several delivery systems based on this ion...
exchange have been developed. Eudragit RS 30D is reported to be a polymer of choice for this purpose. It typically contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions. The ammonium group being hydrophilic facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner. This property is essential to achieve a precisely defined lag time. The cores were prepared using theophylline as model drug and sodium acetate. These pellets were coated using Eudragit RS30D (10% to 40% weight gain) in four different layer thicknesses. A correlation between film thickness and lag time was observed.

I. Sigmoidal Release System:
A Sigmoidal release system (SRS) is reported which is based upon the interaction of acrylic polymers with quaternary ammonium groups in the presence of different counter-ions. SRS system consists of pellet cores having dug and succinic acid coated with ammonim-methacrylate copolymer USP/NF type (B). The water in the medium dissolves succinic acid. The drug inside and the acid solution increase the permeability of the polymer film. This system was useful for design an acid containing core. Good in-vitro and in-vivo correlation of lag time was observed.

II Stimuli induced Pulsatile drug delivery
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 classified into temperature induced systems and chemical stimuli induced system, on the basis of stimulus.
1) Temperature induced systems
2) Chemical stimuli induced Pulsatile systems
a. Glucose-responsive insulin release devices
b. Inflammation-induced Pulsatile release
c. Drug release from intelligent gels responding to antibody concentration
d. pH sensitive drug delivery system [45].

III Eternally regulated pulsatile drug delivery:
For releasing the drug in a pulsatile manner, another way can be the externally regulated system in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. Manetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads.

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<th>Table 3: Marked Technologies of Pulsatile drug deliver [46]</th>
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<td><strong>Technology</strong></td>
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1. Pharmaceutical coating
Pharmaceutical coating is an important technique for the preparation of solid dosage
forms; the main technique employed in the preparation of coated solid dosage forms is based on the deposition of different materials from solution, suspensions, or powders. There are four major coating techniques for applying coatings to pharmaceutical solid dosage forms: (1) sugar coating, (2) film coating, (3) microencapsulation, and (4) press coating. The first three items for the coating of solid dosage forms are classified under liquid coating technology by solution or suspension, these present some disadvantages: they are time consuming, drug stability for heat labile and hydrolysis, and environmental pollution becomes a problem. Therefore, non-solvent or solventless coating methods, such as press coating, are used as alternative coating techniques, to avoid disadvantages in the pharmaceutical coating of many drugs.

2. Solventless coating technology
Solventless coating technology can avoid problems of solvent exposure, solvent disposal, and residual solvent in the product. Solventless processing enables a reduction in costs, by eliminating the slow and expensive processes associated with solvent treatment. Moreover, the technology can significantly reduce processing times because there are no drying and evaporation steps. In particular, the solventless coating process without any heating source in most cases can provide an alternative method to coat the temperature-sensitive drugs. Among these techniques, press coating has recently been adopted as a means of special coating for specific drug delivery applications. Press coating involves the use of modified tableting machines, which allow the compaction of a dry-coat around a tablet core produced on the same machine.

3. Press coating technology
Press coating, also referred to as double compression coating, compression coating, or dry coating, is an old technique. Press coating found increasing application during the past two decades; the process does not require solvents, has a relatively short manufacturing process, and achieves a greater increase in mass of the core tablet than solvent-based methods do. Although it is an old concept, press coating is a novel technology for the formulation of new DDS systems. The technique requires a specific tablet press, with compression coating capability.

The press coating technique offers many advantages, such as protection of hygroscopic, light sensitive, oxygen labile, and acid-labile drugs, isolation of incompatible drugs from each other, and provides a method for both sustained drug release and modification of the drug release profile. The press-coating technique has been used to modify the drug release of many drugs, mask a medication's bitter taste, and protect volatile substances. The technique offers several unique features, such as no requirement for special coating solvents or coating equipment and short manufacture times.

In general, a press-coated tablet consists of an inner core tablet and an outer coating shell. The outer layer surrounds the inner core, and so selection of outer layer materials has a significant impact on the performance of the tablet, including the coating's mechanical strength, drug release characteristics, and tablet stability. It is also possible to produce combination dosage forms, in which two active substances target different areas of the gastrointestinal tract. Press coating allows the physical separation of incompatible drugs in the core and coat within the same dosage form. Direct compression of both the core and the coating shell can remove the necessity for a separate coating process. Any type of material with adequate compaction properties can be used for the coating shell. More recently, DDSs based on press-coated functional layers have been proposed for delayed, pulsatile, and programmable release of different drugs in a single tablet. The press-coating technique has been used to modify the drug release of many drugs, mask a medication’s bitter taste, and protect volatile substances. The technique offers several unique features, such as no requirement for special coating solvents or coating equipment and short manufacture times. Recently, the application of this technology was investigated in the development of timed release dosage forms, time clock systems, and delayed-release tablets [24,48]. The press-coated tablet may consist of a fast disintegration or modified...
release core, coated by compression with a solid barrier, commonly made of polymeric material, a diluent (as a release modifier) and drug (for both rapid or extended release) [48,49]. Press-coated tablets may be modified to provide different release patterns, by varying the drug distribution and type of polymers used in the core and outer coating shell. The resulting modified drug release may be dependent on the time, pH, or microbial control to target a specific region in gastrointestinal tract. Thus, press-coating may be classified as a chronopharmaceutical technology [47,50, 51], in that it provides a solid dosage form for drug delivery in a pulsatile fashion rather than continuously, and at predetermined times and sites following oral administration.

4. Manufacturing process of press coating

The press-coating manufacturing processes employ several steps. The inner core tablet is formulated, and then compressed under appropriate conditions. The tableting machine die is pre-filled with shell-coating materials to form a powder bed, the compressed inner core tablet is placed at the center of the bed, and any remaining outer coating shell materials added. Finally, the outer coating shell is compressed around the inner core tablet [52].

**Figure 13: Manufacturing process of press coating**

I. Prefilling the half amount of outer coating materials into the die.
II. Putting the inner core tablet on the powder bed of outer coating materials
III. Centering.
IV. Filling the residual half amounts of outer coating materials.
V. Compression.
VI. Ejection of press coated tablet from the die.

**Different types of press coated tablets:**

**Figure 14: Different types of press coated tablets**

IR core - Immeadiate release core
IR layer - Immeadiate release layer with or without drugs
Factors affecting performance and drug release of press-coated delivery systems

Several factors that affect performance and drug release behavior of the press-coated tablets, and we discuss these in detail, below. Press-coated tablets have two layers, an inner core compressed as a small tablet and an outer shell. The core tablet may additionally be dry-coated with rate controlling materials such as controlled release polymers and fillers [47,53]. The press-coated assemblage comprising core and shell may provide both rate-control and time-control to drug release. The drug release rate is influenced by various factors including the thickness and porosity of the outer shell, type of material used to compress the inner core and outer shell, excipient particle size, force used to compress each layer, and position of the inner core within the tablet.

1. Inner core tablet
The inner core of the press-coated tablet may comprise pure drug crystals, drug-excipient blends, granules, microspheres and beads. It is also possible to incorporate materials into the core tablet to facilitate disintegration, or otherwise modify the drug release.

1.1. Drug solubility
The solubility of a drug embedded within the inner core of a press-coated tablet is also a major parameter to monitor along with the dissolution behavior of the drug.

1.2. Core composition variables
The influence of different core compositions on drug release using spray-dried chitosan acetate and HPMC compression-coated tablets. Soluble diluents and an appropriate amount of super disintegrant in core tablets enhanced drug release, while using sodium chloride as an osmotic agent slightly retarded drug release.

1.3. Amounts of inner core
To maximize potential drug loading, Rujivipat and Bodmeier investigated the effect of different inner core:outer shell ratios. Three ratios were used, 3:1 (9mm core in 11 mm press-coated tablet), 1:1 (6mm core in 8 mm press-coated tablet) and 1:2 (6mm core in 9 mm press-coated tablet).

None of the formulations released at pH 1.0 for 20 h, but a pulsatile release occurred after a distinct lag time at pH 7.4. The rate of drug release was increased with an increase in the inner core:outer shell ratio, due to faster erosion and the thinner press coating, while increasing the compression force and decreasing the inner core:outer shell ratio caused the lag time to increase.

1.4. Compression pressure
The compression force plays an important role in the tablet manufacturing process, particularly in the fabrication of time controlled press-coated tablets. a constant compression pressure of 300 kg/cm² for the outer coating layer, and studied the influence of varying the inner core tablet compression pressure between 50 and 200 kg/cm² on the release profile of sodium diclofenac. Inner core tablets prepared using a compressive force between 50 and 150 kg/cm² all exhibited similar release profiles, and the slopes of the lines for all three products appeared identical, with lag times of around 12.5 h. However, at inner core compression forces greater than 200 kg/cm², the lag time increased from 12.5 to 16.3 h implying that the compression force applied to the inner core tablet has less influence on drug release after application of a constant compression force to form the outer shell.

1.5. Location of inner core
Correct centering of the inner core within the press-coated tablet is essential, and the exact centralization of the press-coated tablet core is a common cause of complication and failure for the press coating process. The press-coated tablet drug-release reproducibility is always poor, since problems and mistakes can arise from unequal coating or off-center positioning of the core, or both. However, a novel compression tool of the OSDRC-system and a non-invasive Xray computed tomography have recently overcome this problem.

2. Outer coating shell
To design a press-coated tablet, the outer shell is key in ensuring that medication will reliably reach the predetermined site...
following oral administration. Press coating involves direct compression of both the inner core and the outer coating shell, without separate coating processes or the use of coating solutions. The drug form is manufactured by compressing a tablet within a tablet, so that the outer shell becomes a coating layer. Various drug release mechanisms become available by incorporating different polymers or other materials into the outer shell formulation, or by increasing the layer’s thickness. An outer shell made of a rupturable, swellable, or erodible coating, or a permeation coating using combinations of hydrophilic and hydrophobic polymers, can modulate the speed of water penetration into the outer layer to control drug release. The outer coating shell of the press-coated tablet may also provide the initial dose of drug.

2.1. Polymer particle size
The drug release from these tablets exhibited an initial lag period, dependent on the EC particle size, followed by rapid drug release. Various lag times, ranging from one to 20 h, were obtained for different EC particle sizes, with smaller particle sizes providing greater lag times. The finer the particle size, the less residual porosity will remain in the coating shell due to more efficient consolidation of the polymer powder. Smaller EC particle sizes in the shell provide the fabrication of time-controlled press-coated tablets with less porosity and a more tortuous path for medium infiltration, and so greater lag times of drug release are obtained.

2.2. Formulation variables
Many pharmaceutical polymers, including cellulose derivatives EC, HPMC hydroxypropylcellulose (HPC), hydroxyethyl cellulose (HEC), and hydroxypropylmethylcellulose acetate succinate (HPMCAS); polysaccharides guar gum, sodium alginate, and pectin; water soluble polymers (polyethylene oxide, PEO), gellable or swellable (high molecular weight HPMC, gums), pH-dependent soluble (HPMCAS, Eudragit copolymers), waxy and bacterial digestible. Both controlled and modulated drug release behavior from press-coated tablets by varying the type and molecular weight of the polymer used to form the outer coating shell [54]. Drug release starts when the shell is completely eroded, swollen, or dissolved. A purely erodible coating prevents drug release from the inner core until it is removed by the dissolution medium. An erodible shell coating does not modify the release behavior of the inner core; however, a gellable coat can delay and alter the presscoated tablet release performance. Release rate from a gellable coat increases with decreasing molecular weight, for example a low molecular weight polymer, such as HPMC 2208, provides a greater release rate following the lag time than a higher molecular weight does [55]. Hydrophilic excipients incorporated into an insoluble outer shell possibly act as pore-forming agent to aid water penetration; lag time decreases as water soluble excipient content in the coating shell is increased. Different drug release behaviors from press-coated tablets containing various hydrophilic excipients were observed for various physiochemical properties.

2.3. Compression pressure
The compression force used in the fabrication of the press-coated tablet is a critical parameter influencing the dosage form design performance. the influence of the compression force applied to the outer coating shell on drug release. When various forces were applied to an insoluble, rupturable coat made of EC, the lag time and drug release rate were markedly altered. It is evident that lag time is significantly dependent on the compression force applied to the outer coating layer. After expiry of the lag period, the outer shell broke into two halves and yielded a fast drug release. Both lag time and the rapid release were dependent on the applied compression force, providing for different time-controlled release characteristics.

2.4 Amounts of outer shell
The amount of material in the outer coating shell is a key parameter in achieving a
uniform coating for press-coated tablets. The tablet requires an outer coat, which is about twice the mass of the inner core tablet or more, however, the volume must be greater than that of the inner core itself. If the inner core mainly consists of low-density materials, such as fats and waxes, the mass of the coating shell must be greater to assure a uniform covering for the inner core, and provide adequate adhesion between the inner core and outer coating shell. The outer coating layer controls the swelling, erosion, disintegration, and dissolution behavior of the press-coated tablet, and so the amount of material in this layer plays a unique role in the performance of these dosage forms. The effect of the amount of coating material on the release profile of press-coated tablets. Greater quantities of outer coating were found to prolong the lag time before drug release. Press-coated tablets prepared using 160 mg of EC as the outer coating shell had a shorter time lag, and exhibited a different initial release profile compared to tablets prepared using greater than 200 mg of EC.

**CONCLUSION**

The review considers biological rhythms and describes the benefits of pulsatile drug delivery for disease treatments. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place, and in right amounts when the patients suffering from chronic problems like diabetes mellitus, cardiovascular diseases and peptic ulcer. The review provides different pulsatile system and press-coated delivery techniques, factors affecting performance and drug release of press coated delivery systems technique. Pulsatile release systems should be promising in the future. The present review article introduces chronopharmaceutical press-coated products from a patient physiological needs perspective.

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