PULSATILE DRUG DELIVERY SYSTEMS USING NATURAL POLYMERS AS RELEASE MODIFIERS
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ABSTRACT
Sustained and controlled drug delivery system release the drug at a substantially steady rate of release per unit of time. However, there are instances where maintaining a constant blood level of a drug is not desirable. In such cases a pulsatile drug delivery may be more advantageous. Pulsatile drug delivery system (PDDS) is the most interesting time and site-specific system. This system is designed for chronopharmacotherapy which is based on circadian rhythm. Pulsatile drug delivery systems are gaining importance as these systems deliver the drug at specific time as per the pathophysiological need of the disease resulting in improved patient therapeutic efficacy and compliance. The current article focuses on the need for pulsatile drug delivery system, diseases requiring pulsatile drug delivery system, methodologies involved for the existing systems, application of natural polymers as drug release modifiers for pulsatile drug delivery systems with supportive studies on natural polymers as suitable candidates for pulsatile drug delivery systems and pulsatile drug delivery product currently available in the market.

Keywords: Pulsatile drug delivery system, chronopharmacotherapy, circadian rhythm, natural polymers.

INTRODUCTION
A delivery system with a release profile that is characterized by a time period of no release (lag time) followed by a rapid and complete drug release (pulse release) can be called as an ideal pulsatile drug delivery system. In other words, it is required that a drug should not be released during the initial phase of dosage form administration. 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. A Pulsatile drug delivery system is characterized by a lag time that is an interval of no drug release followed by rapid drug release3. A timed, pulsatile delivery system provides one or more rapid release pulses at predetermined lag times or at specific sites resulting in better absorption of the drug, and thereby providing more effective plasma concentration time profile2.

Merits of pulsatile drug delivery system:
- Predictable, reproducible and short gastric residence time
- Improved bioavailability
- Extended day time night time activity
- Drug adapts to suit cardiac rhythms to body function or disease
- Drug targeting to specific site like colon
- Protection of mucosa from irritating drugs

Limitations of pulsatile drug delivery system:
- Lack of manufacturing, reproducibility and efficacy
- Batch manufacturing process
- Higher cost of production
- Trained/skilled personnel needed for manufacturing
- Low drug load
- Immediate withdrawal of drug is not possible

Circadian rhythms and their implications3,4:
Circadian rhythms are self-sustaining, endogenous oscillation, exhibiting periodicities of about one day or 24 hrs. Normally, circadian rhythms are synchronized according to the body’s pacemaker clock, located in the suprachiasmatic nucleus of the hypothalamus.

The physiology and biochemistry of human being is not constant during the 24 hrs, but variable in a predictable manner as defined by the timing of the peak and through of each of the body’s circadian processes and functions. The peak in the rhythms of basal gastric and secretion, white blood cells, lymphocytes, prolactin, melatonin, eosinophils, adrenal corticotropic hormone (ACTH), follicle stimulating hormone (FSH) and luteinizing hormone (LH), is manifested at specific times during the nocturnal sleep span. The peak in serum cortisol, aldosterone, testosterone plus platelet adhesiveness and blood viscosity follows later during the initial hours of diurnal activity. Hematocrit is the greatest and airway caliber the best around the middle and afternoon hours, platelet numbers and uric acid peak later during the day and evening. Hence, several physiological processes in humans vary in a rhythmic manner, in synchrony with the internal biological clock.

Through a number of clinical trials and epidemiological studies, it has become evident that the levels of disease activity of number of clinical disorders have a pattern associated with the body’s inherent clock set according to circadian rhythms. Infact just as the time of day influences normal biologic processes, so it affects the pathophysiology of disease and its treatment.

Chronotherapeutic: Therapy in synchrony with biorhythms
Chronotherapy coordinates drug delivery with human biological rhythms and holds huge promise in areas of pain management and treatment of asthma, heart disease and cancer. The coordination of medical treatment and drug delivery with such biological clocks and rhythms is termed chronotherapy5.

Chronotherapeutics or delivery of medication in concentrations that vary according to physiological need at different times during the dosing period; is a relatively new practice in clinical medicine and thus many physicians are unfamiliar with this intriguing area of medicine. It is important that physicians understand the advantages of chronotherapy so that they can make well-informed decisions on which therapeutic strategies are best for their patients-traditional ones or chronotherapies.

The goal of chronotherapeutics is to synchronize the timing of treatment with the intrinsic timing of illness. Theoretically, optimum therapy is more likely to result
when the right amount of drug is delivered to the correct target organ at the most appropriate time. In contrast, many side effects can be minimized if a drug is not given when it is not needed.

**Need for pulsatile drug delivery system**

There are many conditions and diseases where sustained release formulations do not show good efficacy. The shift from conventional sustained release approach to modern pulsatile delivery of drugs can be credited to the following reason(s):

1. Chronopharmacological need
2. Biological tolerance
3. Gastric irritation or drug instability in gastric fluid
4. Local therapeutic need
5. First pass metabolism

**Classification of pulsatile drug delivery system**

Methodologies for the pulsatile drug delivery system can be broadly classified as following three types:

I. Time controlled pulsatile release system
II. Stimuli induced pulsatile release system
III. External stimuli pulsatile release

I. Time controlled pulsatile release system:

These time-controlled systems can be classified as single unit (e.g., tablet or capsule) or multiple unit systems.

- **A. Single unit systems**
- **B. Multi-particulate systems**
  - **A. Single unit system**
  - **i) Pulsatile system based on capsule:**
    A general architecture of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined lag time owing to swelling, erosion, or dissolution. Manipulating the dimension and the position of the plug can control the lag time.
  - **ii) Port system:**
    The Port® system consists of a gelatin capsule coated with a semipermeable membrane (e.g., cellulose acetate) housing an insoluble plug (e.g., lipidic) and an osmotically active agent along with the drug formulation. Coating thickness controls the lag time.
  - **iii) Delivery by a series of stops:**
    This system is described for implantable capsules. The capsule contains a drug and a water-absorbive osmotic engine that are placed in compartments separated by a movable partition. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule.
  - **iv) Delivery by solubility modulation:**
    These systems contain a solubility modulator for pulsed delivery of variety of drugs. The compositions contain the drug and a modulating agent, sodium chloride (NaCl). 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.
  - **v) Delivery by reservoir systems with erodible or soluble barrier coatings:**
    Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. Barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly. The time lag depends on the thickness of the coating layer.

B. Multiparticulate systems:

- **Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, in which the active substance is present as a number of small independent subunits.**

There are different types of multiparticulate systems and these are enumerated and explained below:

- **i) Pulsatile system based on rupturable coating:**

  This is a multiparticulate system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer. The 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.

- **ii) Time controlled expulsion system:**

  This system is based on a combination of osmotic and swelling effects. The core contains the drug, a low bulk density solid and/or liquid lipid material (e.g., mineral oil) and a disintegrant. The core is further coated with cellulose acetate.

- **iii) Sigmoidal release system:**

  This consists of pellet cores comprising drug and succinic acid coated with ammonia-methacrylate copolymer USP/NF type B. The time lag is controlled by the rate of water influx through the polymer membrane. The water dissolves acid and the drug in the core. The acid solution in turn increases permeability of the hydrated polymer film.

- **iv) Low density floating multiparticulate pulsatile systems:**

  Low density floating multiparticulate pulsatile dosage forms reside only in stomach and are 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.

II. Stimuli induced pulsatile release system:

The mechanisms of drug release include ejection of the drug from the gel as the fluid phase synergizes out, drug diffusion along a concentration gradient, electrophoresis of charged drugs towards an oppositely charged electrode and liberation of the entrapped drug as the gel or micelle complex erodes. It further includes chemical stimuli induced pulsatile systems subclassified into the following:

- **i) Glucose-responsive insulin release devices**
- **ii) Inflammation-induced pulsatile release**
- **iii) Drug release from intelligent gels responding to antibody concentration**

III. External stimuli pulsatile release:

This system is not self-operated, but instead requires externally generated environmental changes to initiate drug delivery. These can include magnetic fields, ultrasound, electric field, light and mechanical force. It include:

- **i) Electro responsive pulsatile release**
- **ii) Magnetically induced pulsatile release**

**Natural polymers as release modifiers for pulsatile drug delivery system**

Polymers have been successfully investigated and employed in the formulation of solid, liquid and semi-solid dosage forms and are specifically useful in the design of novel drug delivery systems. Synthetic polymers are toxic, expensive, have environment related issues, need long development time for synthesis and are freely available in comparison to naturally available polymers. However the use of natural polymers for pharmaceutical applications is attractive because they are economical, readily available, non-toxic and capable of chemical modifications, potentially biodegradable and with few exceptions and also biocompatible.

A large number of plant-based pharmaceutical excipients are...
Vidyadhara S, Prasad SS, Devi VA, Chowdary YA have formulat hydrochloride matrix tablets were prepared by direct system was studied, with a view to develop slow release different concentrations of polymer on erosion of matrix developed an oral monolithic controlled dosag and applicability and efficacy has been proven. These has also been utilized as viscosity enhancers, stabilisers, disintegrants, solubilisers, emulsifiers, suspending agents, gelling agents and bioadhesives, binders in the above mentioned dosage forms.

Some natural polymers selected as suitable candidates for PDDS are: Karaya gum, tragacanth gum, copal gum, tamarind seed polymer, locust bean gum, dammar gum, xanthan gum, gaur gum, chitosan etc.

Vidyadhara S, Prasad SS, Devi VA, Chowdary YA have developed an oral monolithic controlled dosage form of dilatiazem hydrochloride with dammar gum as controlled release polymer. In the present study, the influence of different concentrations of polymer on erosion of matrix system was studied, with a view to develop slow release formulation of dilatiazem hydrochloride. The dilatiazem hydrochloride matrix tablets were prepared by direct compression and wet granulation methods. Various formulations were prepared; DTZ-1 to DTZ-6. The results from the in-vitro drug release studies indicated that, the formulations DTZ-5 and DTZ-6 with drug: polymer concentrations, 1:1 and 1:1.5 respectively, prepared by wet granulation method using distilled water as solvent were found to release the drug at a steady state over an extended period of time up to 12 hours.

Selvar, Ashutosch KP, Jayakandan M, Ashok KM have studied formulations and evaluation of chitosan matrix tablets of tinidazole. The study consist of sustained release matrix tablets of tinidazole with chitosan in different proportions (1:0.1, 1:0.15, 1:0.2) prepared by wet granulation method using EC, CAP, HPMC and shellac solutions. 12 formulations were prepared TE-1 to TE-3, TC-1 to TC-3, THP-1 to THP-3, TS-1 to TS-3. It was observed that the integrity of the drug is not affected by formulation procedure. The result revealed that the drug polymer ratio (i.e. THP-1; 1:0.1) showed a greater drug release than other formulations.

Chavda HV, Patel MS, Patel CN have designed an oral controlled drug delivery system for diclofenac sodium using gaur gum as triple-layer matrix tablets. The design of the study was as follows; matrix tablet granules containing 30% (D1), 40% (D2) or 50% (D3) of guar gum were prepared by wet granulation technique. Matrix tablets of diclofenac sodium were prepared by compressing three layers one by one. Centre layer of sandwich like structure was incorporated with matrix granules containing diclofenac sodium which was covered on either side by gaur gum granule layers containing either 70, 80 or 87% of guar gum as release retardant layers. D3, containing 87% of guar gum in guar gum layers and 50% of guar gum in diclofenac sodium matrix granule layer was found to provide the release rate for prolonged period of time. The results clearly indicate that guar gum could be a potential hydrophilic carrier in the development of oral controlled drug delivery systems.

Vishnumurthy V, Dheeraj N have formulated and evaluated sustain release tablets of frusemide using natural hydrophilic polymers like Guar gum, Pectin, Tragacanth gum and Xanthan gum. The study consist of total 16 formulations prepared using different quantities of Guar gum, Pectin, Tragacanth gum and Xanthan gum; formulations G1 to G4, P1 to P4, T1 to T4, X1 to X4. Result of the present study ascertains that natural gums employed were found to be successful in formulating the sustained-release matrix tablets of Frusemide. It was evident that the concentration of gums up to 47% was capable of prolonging the release of drug for 16hrs. Among the natural gums used, Guar gum was found to be more effective than others in sustaining the drug release. The observed sustaining performance order was as follows: Guar gum > Xanthan gum > Tragacanth gum > Pectin.

### Table 1: Circadian rhythm and manifestation of Clinical diseases

<table>
<thead>
<tr>
<th>Disease or syndrome</th>
<th>Circadian rhythm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic Rhinitis</td>
<td>Worse in the morning/ upon rising</td>
</tr>
<tr>
<td>Asthma</td>
<td>Exacerbation more common during the sleep period</td>
</tr>
<tr>
<td>Angina Pectoris</td>
<td>Chest pain and ECG changes more common in early morning</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>Incidence greatest in early morning</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>Symptoms worse in the middle/ later portion of the day</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>Worse in late evening and early morning hours</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>Increased stiffness early in the morning which typically lasts for more than an hour and decrease later in day</td>
</tr>
<tr>
<td>Stroke</td>
<td>Incidence higher in the morning after awakening</td>
</tr>
</tbody>
</table>

### Table 2: Diseases requiring Pulsafile drug delivery

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Chronological behaviour</th>
<th>Drugs used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>Pain in the morning and more pain in the night</td>
<td>NSAIDs, Glucocorticoids</td>
</tr>
<tr>
<td>Asthma</td>
<td>Precipitation of attacks during night or at early morning hours</td>
<td>β2 agonists, Antihistaminics</td>
</tr>
<tr>
<td>Attention deficit syndrome</td>
<td>Increase in DOPA level in noon</td>
<td>METHYLPHENIDATE</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>BP is at its lowest during sleep cycle and rises steeply during early morning awakening period</td>
<td>Nitroglycerin, Calcium channel blocker, ACE inhibitors etc</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Increase in blood sugar level after meal</td>
<td>Sulfonylurea, Insulin, Biguanide</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Cholesterol synthesis is generally higher during night than day</td>
<td>HMG CoA reductase inhibitors</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>Acid secretion is high in the noon and at night</td>
<td>H2 blockers</td>
</tr>
</tbody>
</table>
CONCLUSION
Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. There is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension etc. Thus designing of proper pulsatile drug delivery will enhance the patient compliance, optimum drug delivery to the target site and minimize the undesired effects. The approaches in this article represent application of natural polymers as drug release modifiers with a view to design pulsatile drug delivery systems keeping in mind the toxic effects of the drugs incorporated and to maintain the overall stability of the product on account of the properties of natural polymers. There are various technologies present in the market based on the various methodologies. Pulsatile release systems with natural polymers as drug release modifiers should be promising in the future.

REFERENCES

Table 3: Marketed technologies of Pulsatile drug delivery system

<table>
<thead>
<tr>
<th>Technology</th>
<th>Mechanism</th>
<th>API</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulsys®</td>
<td>Timed-controlled System</td>
<td>Amoxicillin</td>
<td>Pharyngitis/Tonsillitis</td>
</tr>
<tr>
<td>Umphyl®</td>
<td>Externally regulated System</td>
<td>Theophylline</td>
<td>Asthma</td>
</tr>
<tr>
<td>Ritalma®</td>
<td>Osmotically Regulated</td>
<td>Methyl Phenidate</td>
<td>Attention deficit hyperactivity disorder</td>
</tr>
<tr>
<td>Opana®ER</td>
<td>Timed-controlled System</td>
<td>Oxymorphone</td>
<td>Pain medicine</td>
</tr>
<tr>
<td>TherForm®</td>
<td>Externally regulated System</td>
<td>Diclofenac sodium</td>
<td>Inflammation</td>
</tr>
</tbody>
</table>

Figure 1: Schematic diagram of circadian rhythm showing diseases require pulsatile drug delivery system