1.0 INTRODUCTION

Oral-controlled and modified-release drug delivery systems with zero-order sustained-release kinetics have been developed and proven suitable for meeting increasingly sophisticated therapeutic needs. Nevertheless, the impact of basic chronobiology concepts on the practice of medicine is still ongoing and to address chronotherapy needs, various types of pulsatile drug delivery systems have been innovated. There has been a growing interest in pulsatile delivery, which generally refers to the liberation of drugs following a programmable and well-defined lag phase from the time of administration.

1.1 Introduction to Chronotherapeutics and pulsatile drug delivery

Chronobiology

Biological rhythms, fundamental attributes of all living organisms, are serving time to run physiological functions in a preventive way to the environment that displays prominent, predictable-in-time changes. Biological rhythms exist at any level of living organisms and, according to their cycle length, may be divided into: i) circadian rhythms (period of approximately 24 h); ii) ultradian rhythms (period shorter than 24 h); and iii) infradian rhythms (period longer than 24 h). During the last few years, chronobiology has aimed at studying these biological rhythms, explaining most of the biological mechanisms of: i) the endogenous circadian rhythmicity; ii) the neurophysiological mechanisms of the photic system that allows its external resetting; and iii) the neuroendocrine mechanisms of internal rhythm synchronization. All these mechanisms are programmed-in-time during 24 h for the conduct of specific activities at discrete time points. Moreover, the description of specific biological rhythm disorders and rhythm problems at the cellular and even the molecular level has prompted the emerging fields of chronopharmacology and chronotherapeutics.

Chronotherapeutics and Pulsatile drug delivery: definition and concepts

Chronotherapeutics, dosage forms designed to elicit a programmed liberation of drugs after lag phases that commence upon administration are recognized as potentially suitable tools for meeting chronopharmaceutical demands. It takes into account rhythm determinants in disease pathophysiology, chronopharmacology of medications and the human circadian time structure to determine the drug-delivery pattern, dose and administration time to optimize desired and/
or minimize adverse effects. Such a release mode is commonly referred as pulsatile release or time-controlled release. Broadly, methodologies for release mechanisms include time-controlled, stimuli-induced and externally regulated systems. Time-controlled systems include bulk erosion of polymers in which drug release by diffusion is restricted, surface erosion of layered devices composed of alternating drug containing and drug-free layers, and osmotically controlled rupture. Stimuli-induced systems consist of stimulation by any biological factor like temperature, or any other chemical stimuli. Chemical stimulation may be from glucoseresponsive insulin release devices, inflammation-induced, gels or its derivatives responding to antibody concentration and pH-sensitive systems. [1]

Pulsatile delivery generally refers to release of a portion of the total payload in a burst or in a constant manner, followed by periods of little or no release (lag phase) in a defined temporal pattern as shown in Figure 1.1.

![Pulsatile release pattern](image.jpg)

**Figure 1.1: Pulsatile release pattern-typical** [2]

A circadian rhythm is a 24-hour cycle in the biochemical, physiological or behavioral processes of living entities. For example, many body functions and diseases follow a circadian rhythm. So, by timing administration of a programmed release device, therapeutic plasma concentration can be obtained at an optimal time to counter the diurnal nature of certain diseases, such as angina, hypertension, asthmatic attacks and stiffness of arthritic patients during early morning
hours, and heart attacks at night etc. Further following table indicated the various disease conditions, daily variations and medications.

Below table (Table 1.1) describes various diseases following circadian changes

Table 1.1: Overview of most serious diseases displaying significant daily variations [3]

<table>
<thead>
<tr>
<th>Medical condition</th>
<th>Circadian changes in body</th>
<th>Medications used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Joint pain and stiffness early in morning</td>
<td>NSAIDs, DMDs, glucocorticoids</td>
</tr>
<tr>
<td>Allergic rhinitis and bronchial asthma</td>
<td>Precipitation of attacks during night or at early morning hours</td>
<td>β2 agonist, antihistaminics</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>BP-lowest during the sleep cycle, rises steeply during the early morning awakening</td>
<td>Nitroglycerin, calcium channel blocker</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Increase in the blood sugar level after meal</td>
<td>Sulfonylurea, insulin, biguanide</td>
</tr>
<tr>
<td>Attention deficit syndrome</td>
<td>Increase in 3,4-dihydroxyphenylalanine level in afternoon</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Cancer</td>
<td>Rhythm-dependent differences in drug toxicity</td>
<td>5-fluorouracil and leucovorin</td>
</tr>
<tr>
<td>Migraine</td>
<td>Alteration of vasomotor tone</td>
<td>Anti-migraine drugs</td>
</tr>
<tr>
<td>Seizures</td>
<td>Nocturnal or early-morning seizures</td>
<td>Anti-epileptic drugs</td>
</tr>
<tr>
<td>Gastroenteric disorders</td>
<td>Increased gastric acid secretion at midnight</td>
<td>H2 receptor antagonist</td>
</tr>
</tbody>
</table>
Various patents worldwide were reported (Table 1.2) involving different approaches for pulsatile drug delivery.

**Table 1.2: Patents involving different approaches for pulsatile drug delivery technologies.** [3]

<table>
<thead>
<tr>
<th>Mode of drug delivery</th>
<th>Title (number)</th>
<th>Rationale for chronotherapy and features of patented systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral capsular based</td>
<td>Pharmaceutical dosage form for pulsatile delivery of methylphenidate (US65550136)</td>
<td>Attention deficit disorder, System with three pulses of release at different time points (Combination of immediate and delayed release tablets)</td>
</tr>
<tr>
<td>Oral capsular based</td>
<td>Timed pulsatile drug delivery systems (US6627223)</td>
<td>Arrhythmia, capable of delivering therapeutic agent in position or time controlled fashion with multi-particulate-coated system</td>
</tr>
<tr>
<td>Oral capsular based</td>
<td>Pulsatile particles drug delivery system (US5472708)</td>
<td>Angina and hypertension, time-controlled system able to release drug at intestine with release controlled polymers</td>
</tr>
<tr>
<td>Oral tablet based</td>
<td>Tablet for pharmaceutical use able to release active substances at successive times (US4865849)</td>
<td>Morning pain in rheumatic illness, system enables release of drug in successive spaced apart stages to obtain high hematic drug levels at different time intervals</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Oral tablet based</td>
<td>Delayed total release two pulse gastrointestinal drug delivery system (US6632451)</td>
<td>Analgesic and anti-inflammatory, a two pulse delivery device for delivering one or more active agents at colon</td>
</tr>
<tr>
<td>Transdermal device</td>
<td>Medical device for pulsatile transdermal delivery of biologically active agents (US4698062)</td>
<td>Angina pectoris and chronic heart failure, delivery device relates delivery of nitroglycerin in steady state flux for two time period</td>
</tr>
<tr>
<td>Hydrogel system</td>
<td>Pulsatile drug delivery device using stimuli sensitive hydrogel (US5226902)</td>
<td>Diabetes mellitus, invention relates to delivery of drug laden hydrogels which deswell and gives pulsatile release of drugs in response to external or internal stimuli such as temperature or pH changes, or chemical reactions.</td>
</tr>
</tbody>
</table>
1.2 *Time controlled pulsatile release system*

Time-dependent dosage forms are formulated to release their drug load after a predetermined lag time. The action of a certain drug should coincide with the proper site and time for optimal effect. Therefore, the development of a time-controlled release system is desired for the treatment of patients. These systems are designed to release drug in pulses governed by the device fabrication and ideally, independent of the environment. The release mechanisms employed include bulk erosion of the polymer in which drug by diffusion is restricted, surface erosion of layered devices composed of altering drug containing and drug free layers, osmotical controlled erosion coating layer.

**Delivery system provided with erodible coating layers**

In such systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing drug. Time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer coat is shown in Figure 1.2

![Erodible coating layer](image)

**Figure 1.2: Schematic diagram of drug delivery with erodible coating layer**

**pH sensitive drug delivery system**

pH-sensitive polymers are polyelectrolytes that bear in their structure weak acidic or basic groups that either accept or release protons in response to changes in environmental 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 carboxy methyl cellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine [4-5].

**Reservoir systems with soluble or eroding polymer coatings**

Another class of reservoir-type multiparticulate pulsatile systems is based on soluble / erodible layers in place of rupturable coatings. The barrier dissolves or erodes after a specific lag time followed by burst release of drug from the reservoir core. In general, for this kind of systems, the lag time prior to drug release can be controlled by the thickness of the coating layer. However, since from these systems release mechanism is dissolution, a higher ratio of drug solubility relative to the dosing amount is essential for rapid release of drug after the lag period.

**Osmotic drug delivery system**

OROS (Osmotic [Controlled] Release Oral [Delivery] System) is an advanced controlled release oral drug delivery system in the form of a rigid tablet with a semi-permeable outer membrane and one or more small laser drilled holes in it. As the tablet passes through the body, water is absorbed through the semipermeable membrane via osmosis, and the resulting osmotic pressure is used to push the active drug through the opening in the tablet. Osmotic release systems have a number of major advantages over other controlled-release mechanisms. They are significantly less affected by factors such as pH, food intake, GI motility, and differing intestinal environments. Using an osmotic pump to deliver drugs has additional inherent advantages regarding control over drug delivery rates. This allows for much more precise drug delivery over an extended period of time, which results in much more predictable pharmacokinetics. However, osmotic release systems are relatively complicated, somewhat difficult to manufacture, and may cause irritation or even blockage of the GI tract due to prolonged release of irritating drugs from the non-deformable tablet.
Compression coated tablets as drug delivery system
Pharmaceutical coatings are an essential tool to achieve the desired formulation of pharmaceutical dosage forms. Coatings are applied to achieve superior aesthetic property of a dosage form (e.g. Color, texture, mouth feel and taste masking), physical and chemical protection for the drugs in cores, and modified drug release characteristics. Coating techniques mostly used in pharmaceutical industry are aqueous or organic coating, which present some disadvantages: time consuming, stability for heat labile and hydrolysis of degradable drug and polluted environment problem. Thereby, non-solvent coating is introduced as alternative coating technique to overcome these disadvantages. Non-solvent coatings have been categorized as press coating, hot melt coating, supercritical fluid spray coating, electrostatic coating, dry powder coating and photo curable coating [6]. Among these techniques, compression coating is the absolute dry coating without solvent and heat use. Additionally, compression coating has no limitation for the cores and hence overcomes the adhesion problem found in spraying methods. Tablets with cylinder or special shapes can be press-coated. [6-9]

1.3 Introduction to Arthritis [10-13]
Arthritis (from Greek arthro-, joint + -itis, inflammation; plural: arthritides) is a group of conditions involving damage to the joints of the body. There are over 100 different forms of arthritis. The most common forms are osteoarthritis (OA) (degenerative joint disease), rheumatoid arthritis (RA) (joint inflammation of, synovial proliferation and destruction of articular cartilage) and psoriatic arthritis (inflammatory arthritis).
RA typically manifests with signs of inflammation, and the affected joints are swollen, warm, painful and stiff early in the morning on waking and following prolonged inactivity. The main symptom in OA is acute pain, causing loss of ability and often stiffness with affected joints. Rheumatic conditions are typically characterized by pain, aching, stiffness and swelling in and around one or more joints. The symptoms can develop gradually or suddenly. Certain rheumatic conditions can also involve the immune system and various internal organs of the body. Some forms of arthritis, such as rheumatoid arthritis and lupus, can affect multiple organs and cause widespread symptoms.
Arthritis is more common among adults aged 65 years or older, but people of all ages (including children) can be affected.

**Current Treatment of Arthritis**

Whether you have a non-inflammatory or inflammatory type of arthritis or even a painful case of gout, there are numerous medications and recommendations to relieve pain and ensure that your joints do not become damaged further. The focus of treatment for arthritis is to control pain, minimize joint damage and improve or maintain function and quality of life. According to the American College of Rheumatology, the treatment of arthritis might involve the following:

- Medications
- Non-pharmacologic therapies
- Physical or occupational therapy
- Splints or joint assistive aids
- Patient education and support
- Weight loss
- Surgery - joint replacement and joint surgery

These treatments are also applied to inflammatory types of arthritis (such as RA) along with anti-inflammatory medications such as corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) and a relatively new class of drugs known as biologics.

Medications that are used to treat arthritis depend on the type of arthritis. Commonly used arthritis medications include:

- Analgesics: these reduce pain, but have no effect on inflammation. Examples include acetaminophen (Tylenol), tramadol (Ultrag) and narcotics containing oxycodone (Percocet, Oxycontin) or hydrocodone (Vicodin, Lortab)
- Non-steroidal anti-inflammatory drugs (NSAIDs): these reduce both pain and inflammation. Over-the-counter NSAIDs include ibuprofen (Advil, Motrin IB) and naproxen sodium (Aleve). Some NSAIDs are available as creams, gels or patches which can be applied to specific joints
• Counterirritants: some varieties of creams and ointments contain menthol or capsaicin, the ingredient that makes hot peppers spicy. Rubbing these preparations on the skin over a painful joint can modulate pain signals from the joint and lessen pain.

• Disease-modifying antirheumatic drugs (DMARDs): used to treat RA, DMARDs slow or stop your immune system from attacking your joints. Examples include methotrexate (Trexall), hydroxychloroquine (Plaquenil), leflunomide and Diacerein.

• Biologics: used in conjunction with DMARDs, biologic response modifiers are genetically engineered drugs that target various protein molecules involved in the immune response. Examples include etanercept (Enbrel) and infliximab (Remicade).

• Corticosteroids: includes prednisone and cortisone, this class of drug reduces inflammation and suppresses the immune system.

NSAIDs are used first; they afford symptomatic relief (pain, swelling, morning stiffness, immobility) but do not arrest the disease process.

The disease modifying drugs (DMDs) are added if deformity and bony changes progress rapidly. Early introduction of these drugs is nowadays favored.

Sometimes, Corticosteroids are also employed as an adjuvant to NSAIDs or with DMDs.

Symptoms of rheumatoid arthritis (RA) frequently show diurnal variation, with exacerbations in the morning (Fig 1.3). This variation in disease expression is accompanied by daily oscillations in circulating concentrations of disease-mediating cytokines. In particular, IL-6 shows robust oscillations, and fluctuations in serum IL-6 levels correlate with changes in disease symptoms.
Figure 1.3: Diurnal variation in Rheumatoid arthritis [1]

This correlates with the early morning rise in plasma IL-6 levels. The circadian hormone melatonin (which is considered to exacerbate the inflammatory response) is released only during the night, and circulating levels peak in the mid-night. The anti-inflammatory glucocorticoid - cortisol - is also under circadian control, peaking in the early morning.

Many herbal constituents also show the anti-arthritic activity. Boswellia (Boswellia serrata)/Salai gugul is a fragrant tree resin used extensively to support normally functioning joints.

Pharmacology of Salai gugul: Boswellia serrata gum resin has been reported to have analgesic, anti-inflammatory, anti-arthritic and anti-pyretic activity. [14]

Key benefits of Salai gugul

- Supports normally functioning joints
- Supports normal flexibility of the body
- Supports normal and comfortable range of movement
- Supports the normal function of the body's connective tissues

Dosage: 150 mg of boswellic acid two times a day

(Ref.: Product label of Himalaya Herbal Health Care)
1.4 Introduction to Drug and Key Excipients Profile [15-17]

Drugs profile and key excipients profiles are provided as Annexure. (Annexure 1 & 2)
Vendor COA of APIs and key excipients are also provided as Annexure. (Annexure 3)