Introduction:

With the advancement of the technologies in the pharmaceutical field, drug delivery systems have drawn an increasing interest over the last few decades. Conventional controlled release drug delivery systems are based on single- or multiple-unit reservoir or matrix systems, which are designed to provide constant or nearly constant drug levels over an extended period of time. However, pulsatile delivery is desirable for drugs acting locally or having an absorption window in the gastro-intestinal tract or for drugs with an extensive first pass metabolism (Sunthongjeen S, 2004).

Nowadays, concept of chronopharmaceutics has emerged, wherein, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy (Botti, 2004).

Diseases where a constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of “Pulsatile Drug Delivery Systems” (Siegel RA, 1995). 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. Various techniques are available for the pulsatile delivery like pH dependent systems, time dependent systems, micro-flora activated systems, etc. which can be designed as per the physiology of disease and properties of the drug molecule. The focus of the present research work is primarily on the pulsatile drug delivery methodologies and the upcoming technologies, which can be being exploited on an industrial and commercial scale.

Diseases requiring pulsatile drug delivery:

Thorough understanding of the disease physiology is required before designing the pulsatile drug delivery system. Table 1 enumerates various diseases and their chronological behavior.
**Table 1: Various diseases and their chronological behavior.**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chronological behavior</th>
<th>Drugs used</th>
</tr>
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<tbody>
<tr>
<td>Peptic ulcer</td>
<td>Acid secretion is high in the afternoon and at night</td>
<td>H 2 blockers</td>
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<tr>
<td>Asthma</td>
<td>Precipitation of attacks during night or at early morning hour</td>
<td>B 2 agonist, Antihistaminics</td>
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<tr>
<td>Cardiovascular diseases</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 blocker, ACE inhibitors etc</td>
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<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>Increase in the blood sugar level after meal</td>
<td>Sulfonylurea, Insulin, Biguanide</td>
</tr>
<tr>
<td>Attention deficit syndrome</td>
<td>Increase in DOPA level in afternoon</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Cholesterol synthesis is generally higher during night than day time.</td>
<td>HMG CoA reductase inhibitors</td>
</tr>
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</table>

**Advantages and drawbacks of pulsatile drug delivery systems:** (Hitesh Dalvadia, 2010; P Roy 2009; Shiwani Sharma 2011)

**Advantages**

1. Predictable, reproducible and short gastric residence time
2. Less inter- and intra-subject variability
3. Improve bioavailability
4. Reduced adverse effects and For drugs which develop biological tolerance,
5. Limited risk of local irritation
6. No risk of dose dumping
7. Flexibility in design
8. Improve stability
9. Improve patient comfort and compliance
10. Achieve a unique release pattern
11. Extend patent protection, globalize product, and overcome competition.

**Drawbacks**

1. Lack of manufacturing reproducibility and efficacy
2. Large number of process variables
3. Multiple formulation steps
4. Higher cost of production
5. Need of advanced technology

**Methodologies for pulsatile drug delivery**

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

1. **Time controlled pulsatile release system:**
   A. Delivery systems with rupturable coating layer. (Sungthongjeen S, 2004; Inna K 1999).
   B. Delivery systems provided with erodible coating layers. (Gazzaniga A, 2007)
   C. Capsule shaped system provided with release controlling plug. (Ganiyu J A 1995; Joseph K 2001)

2. **Stimuli induced pulsatile system:**
   A. Temperature induced systems. (Siegel RA, 1995; Akihiko Kand, 2002; Kazunori K, 2001).
   B. Chemical stimuli induced pulsatile systems. (Aiman A, 1997)

3. **Externally regulated systems.** (Saslawski O, 1988)