2.0 RATIONALE AND HYPOTHESIS

Current treatment of arthritic includes pain relievers, group of medications known as non-steroidal anti-inflammatory drugs (NSAIDs). These drugs interfere with chemicals called prostaglandins in the body, which trigger pain, inflammation, and fever. NSAIDs can be very helpful for relieving pain and swelling in all types of arthritis. If patients already tried a variety of pain relievers and joints are still throbbing, or just can't tolerate NSAIDs, doctor may recommend stronger opioid or narcotic pain relievers. These drugs can become habit-forming, so it's important that you keep in close touch when using opioids. Pain relievers can make you feel better, but they're not going to change the course of your arthritis. Disease-modifying anti-rheumatic drugs (DMARDs) can actually slow joint damage in people with arthritis from an overactive immune system such as rheumatoid arthritis and psoriatic arthritis.

Current treatment not includes combination of NSAIDs and DMDs. Further combination treatment with timely release of drugs can serve the best treatment for arthritis patients.

a) Disease like arthritis follow a circadian rhythm so should be better handled by chronotherapy. As discussed earlier, arthritis follows circadian pattern and patient suffers from early morning stiffness. Such a disease pattern is better managed by pulsatile drug release i.e. dosage regimen releases the drug after desired lag phase.

b) Arthritis treatment should be better treated if a combination of drugs i.e. one which gives symptomatic relief and the other that gives remission of disease is given. The major complaint by individuals who have arthritis is joint pain. Pain is often constant, and may be localized to the joint affected. The pain from arthritis is from inflammation around the joint, damage to the joint from disease, daily wear and tear of the joint, muscle strains caused by forceful movements against stiff and painful joints, and from fatigue. Better treatment for the arthritic patient includes combination therapy which includes (i) one drug provides relief from joint pain and (ii) second drug will bring about remission in disease condition. This combination therapy will reduce the pain and heal the disease condition on treatment and bring about reduction in dosing frequency on treatment.
Considering the chronobiological pattern of the disease, dosage regimen selected for the treatment included one NSAID and one Disease Modifying Drug (DMD). Aceclofenac (ACE) was selected as NSAID and Leflunomide (LEF) and Diacerein (DIA) were selected as DMD drugs. NSAID will give the symptomatic relief from the arthritic pain and DMD will bring about remission in the disease condition. The combination treatment will work as a best treatment which will result in dose reduction or complete cure of arthritic patient. One Herbal formulation consisting salai gugul as an active component was also evaluated for the arthritic treatment.

For the treatment of Arthritis (particularly Rheumatoid Arthritis), 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 now a day favored, and combination of these drugs with NSAIDs is better way to treat the arthritis patient.

Hence present work was embarked on to develop a combination drug therapy of NSAID and DMD to treat Rheumatoid Arthritis with the following objectives:

1. To take care of early morning stiffness and immobility by preparing delayed release system.
2. The release of NSAID after a predetermined lag time (correlates with the difference in time of administration and time of required effect) to give symptomatic relief.
3. Additional release of DMD so as to arrest the progress of disease.
4. Since the two drugs are combined in single system, it will reduce the number of tablets the patient (pill burden) has to take at a time.
5. The combination should therefore increase patient compliance and should give better control over the disease management.

Based on lag phase required for the early morning release of drug following release profile for the pulsatile treatment are desired. Considering the combination therapy and double pulse approach (first pulse of NSAID and Second pulse of DMD), following is the desired drug release profile for single pulse (Fig 2.1) and multi pulse system (Fig 2.2)
Figure 2.1: Desired Dissolution profile for pulsatile drug delivery system - Single pulse

Figure 2.2: Desired Dissolution profile for pulsatile drug delivery system - Multi pulse

Where Pulse 1 - ACE (NSAIDs), Pulse 2 – DIA/LEF (DMDs)
Further diagrammatic representation of single pulse and double pulse systems were shown below in Figure 2.3,

<table>
<thead>
<tr>
<th>Single Pulse System</th>
<th>Double Pulse System</th>
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<tbody>
<tr>
<td>Outer coat dissolves after desired time</td>
<td>Outer coat dissolves and releases the outer fraction</td>
</tr>
<tr>
<td>Tablet disintegrates and releases drug</td>
<td>Tablet disintegrates after desired time</td>
</tr>
</tbody>
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Figure 2.3: Diagrammatic representation of single and double pulse system

Where inner tablet is of ACE (NSAIDs) and outer is of DIA/LEF (DMDs).