ABSTRACT

Significant progress has been made towards achieving pulsatile drug delivery systems with different routes of administration considering patient need and safety. The growing interest in this research area is primarily related to the pursuit for high compliance of drug treatments that may accomplish chronotherapeutical requirements highlighted for a number of prevalent pathologies including arthritis. The present study was aimed to develop the best treatment for arthritis patient using chronobiological approach.

Combination treatment using one anti-inflammatory drug and one disease modifying drug (DMD) was selected for arthritis through pulsatile drug delivery system. Aceclofenac (ACE) was selected as a NSAID and Leflunomide (LEF) and Diacerein (DIA) were selected as DMD. Compression coating formulation approach was selected with inner tablet of disease modifying drug and outer of anti-inflammatory drug. Two coating approaches were selected to provide the desired lag phase i.e. one by using pH sensitive coating polymer and other by use of surface eroding polymer system. Eudragit S 100 and Eudragit L 100 were selected as pH sensitive polymers and Ethyl cellulose 10 cps and Lactose were selected as surface eroding systems. Further two pulses drug delivery was developed to provide drug release in two separate phases i.e. after desired lag phase in early morning NSAID was released to provide symptomatic treatment, followed by second pulse of DMD after 2-3 hrs to bring about remission to disease condition. Tablets in capsule (TIC) formulation were also evaluated as one formulation approach. Herbal formulation consisting salai gugul was also developed in form of pulsatile drug delivery and characterized subsequently.

All final formulations at each development stage were studied for 6 months stability study at 40°C/75% RH and evaluated for drug release, drug content etc. Further X-ray examination was carried out for the double pulse release system and study showed that desired two pulse delivery was achieved in vivo i.e. after 7 hrs first coating was removed and released outer fraction followed by at around 9.5 hrs 2nd coating removed and released inner tablet.

Comparative dynamic study was carried out by developing arthritis models in rats to select the best possible treatment for arthritis. Combination of ACE+LEF in double pulse pulsatile release system proved best treatment amongst the developed dosage forms. Best formulation was
studied for in vivo pharmacokinetic study and showed desired lag phase and plasma concentration in double pulse release pattern.

**KEY WORDS**

Chronotherapy, pulsatile drug delivery, multi-pulse delivery, pH sensitive polymers, surface eroding polymers, Tablet in Tablet formulation