8.1. Summary

Several drug delivery technologies based on physical and/or chemical activation for chronomodulated drug release that is intended for oral route of administration have been reported. Among emerging chronotherapeutic approaches, pulsatile drug delivery systems (PDDS) has attracted increasing interest among academic and industrial researchers for its ability to liberate medication following a programmed lag phase. Due to the co-existence of asthma with rhinitis and their shared pathophysiology, treatment strategies targeting both diseases are a major concern and there is need of a common therapeutic approach. Montelukast sodium a leukotriene receptor antagonist considered as a useful common therapy to treat both asthma and allergic rhinitis, with reported clinical evidence for their efficacy. So, in the present study different chronomodulated delivery systems of MKS such as time controlled pulsatile release tablets, osmotically controlled pulsatile release capsules and delayed release beads were prepared and their in vivo behaviour was studied in rabbits. Based on the results obtained as discussed in the earlier chapters, results are summarized below.

Analytical and bioanalytical method development

- The successful formulation development involved sensitive analytical method for the evaluation of drug in formulations and release media.
- Analytical methods such as UV and RP-HPLC methods were developed and validated as per the ICH guidelines to quantify drug.
- The sensitive bioanalytical method for the evaluation of drug in rabbit plasma was developed and validated as per USFDA guidelines. The method was successfully applied for the preclinical pharmacokinetic study.

Time controlled pulsatile release tablets

Time controlled pulsatile release tablets (TCRTs) were prepared by coating MKS containing core tablets with EC/HPMC in different ratio.

- Drug excipient compatibility study has shown no drug-polymer interaction as confirmed by physical observation for one month at stored at accelerated stability condition (40 ± 2 °C/75 ± 5% RH), DSC and FTIR study.
- The final blend ready for compression showed good flow and compression properties as confirmed by Angle of repose, Carr’s index and Hausner’s ratio.
• Core tablets containing 5% CCS and 10% L-HPC was found to be suitable for time controlled pulsatile release tablets.
• The core tablets coated with ethyl cellulose and eudragit L100 has shown pH dependent bursting time whereas ethyl cellulose and HPMC coated tablet has shown no effect of buffer pH on bursting time.
• The immediate release core tablets were coated with an outer rupturable layer of polymer blend EC/HPMC ratio (80:20, 70:30, 60:40) at different weight gain (8-12% w/w). A 2-factor 3-level, face centered CCD was designed to execute the experiments.
• The composition of optimal formulation was determined as 33.33% w/w (coded value +0.33) HPMC in coating composition and 9.42% w/w (coded value -0.29) coating weight gain. The results showed that the optimal formulation of TCRTs had lag time (4.5 h), release at 6 h and 12 h are 84.14% and 95.32% respectively.
• The optimized TCRTs (containing BaSO₄) were tested in vivo in New Zealand white rabbits for bursting time by X-ray imaging study. It was observed that tablet remained intact for 4 h, and at 5 h tablet was disintegrated.
• In vivo study revealed comparative pharmacokinetic profiles of marketed tablets, core tablets and TCRTs, however T_{max} of 2 h for marketed and core tablets and 7 h for TCRTs were observed. Thus, designed TCRTs found to be suitable in treating episodic attack of asthma in early morning and associated allergic rhinitis.

Osmotically controlled pulsatile release capsules
Assembly of the capsular systems consisted of push, active and plug tablet arranged from bottom to top in hard gelatin capsule. The capsule system was coated with a semi-permeable membrane of cellulose acetate and drilled towards plug side in cap.
• There was no interaction observed between the drug and the excipients.
• The prepared blend for compression showed good flow properties. The formulations were characterized by DSC and FTIR spectroscopy. No interactions between drug and additives used in the preparation were noted.
• A three-factor 3-level, face centered CCD was introduced to execute the experiments and quadratic polynomial model was generated to predict and assess the independent variables (i.e. lag time, release at 6 h and release at 12 h) with respect to the dependent variables (i.e. push, plug and coat weight).
• The composition of optimal formulation was determined as weight of push tablet 138 mg (coded value: +0.59), plug tablet 60 mg (coded value: +0.49) and coating weight gain of 8.4 mg (coded value: -0.82). The results showed that the optimal formulation of PRCs had lag time of 4.5 h and release at 6 h and 12 h are 61.95% and 96.29% respectively.

• The X-ray imaging study was carried out to monitor the *in vivo* behaviour of developed BaSO₄ loaded osmotically controlled PRCs in rabbits under fasting conditions. It was observed that middle layer (with BaSO₄) remained inside the capsule upto 4 h supported by bright spot region, after this it comes out as confirmed by scattered region of barium sulphate and completely disappears at 7 h.

• *In vivo* pharmacokinetic study of osmotically controlled PRCs revealed $T_{\text{max}}$ at 7 h with initial lag time of 4 h. Thus designed capsular system may be helpful for patients with episodic attack of asthma in early morning and associated allergic rhinitis.

**Delayed release beads**

Alginate beads of MKS were prepared by ionotropic gelation method and optimized beads were coated with mixture of eudragit polymers.

• There was no interaction observed between the drug and the excipients.

• There was no significant difference in release profile observed between Ca²⁺ & Zn²⁺ cross linked beads. Whereas, slight slow release was observed in case of chitosan reinforced beads.

• There is no release was observed in 0.1N HCl (pH 1.2) for all formulations. However, rapid release from cross linked beads in phosphate buffer, pH 6.8 has been presumed to be due to greater solvent penetration into the calcium alginate network, followed by greater ion exchange between Ca²⁺/Zn²⁺ and Na⁺/K⁺ ions.

• MKS release from cross-linked alginate beads were slightly altered with sodium alginate concentration, cross-linking time and talc. At higher concentration of alginate slow release was observed whereas addition of talc to alginate increased the release rate.

• The cross linked beads were coated with an outer rupturable layer of polymer blend eudragit RSPO/RLPO in different ratio (80:20, 70:30, 60:40) at different weight
gain (8-12% w/w). A 2-factor 3-level, face centered CCD was designed to execute the experiments.

- The composition of optimal formulation was determined as 23.33% w/w (coded value is -0.66) eudragit RLPO in coating composition and 9.84% w/w (coded value is -0.08) coating weight gain. The results showed that the optimal formulation of DRBs had lag time (4.5 h) and release at 6 h is 74.9%.
- \textit{In vivo} pharmacokinetic study of DRBs revealed \( T_{\text{max}} \) at 7 h with initial lag time of 4 h. Thus developed formulation may be helpful for patients with episodic attack of asthma in early morning and associated allergic rhinitis.

### 8.2. Conclusion

The present study demonstrated successful formulation development of chronomodulated drug delivery systems of MKS for chronic management of asthma and allergic rhinitis. Different dosage forms of MKS such as time-controlled pulsatile release tablets, osmotically controlled pulsatile release capsule and delayed release beads were developed and optimized to release the drug after a predetermined lag time and evaluated both \textit{in vitro} and \textit{in vivo}. Optimization of delivery system is a difficult process, which requires considering a large number of variables and their interactions with each other. This study decisively demonstrates that the optimal formulations may be effectively produced using the central composite design. Among all formulations in delayed release beads, it is the physiological pH which triggered the release of drug from cross linked beads. Eudragit RSPO/RLPO (pH independent) coating may have reduced the risk of variations in release properties due to individual GIT condition variations. Other developed systems are insensitive to variations in the gastro-intestinal transit time and minor variations in the pH of the GIT. The selection of the appropriate dosage form and technology should take into considerations about the ease of manufacturing, safe, cost-effectiveness, and the flexibility in the pharmacokinetic profile. Preparation of osmotically controlled pulsatile release capsules involve many steps in assembling the device and were tedious. The time controlled release tablets consist of fast disintegrating core coated with a mixture of pH independent polymeric film EC (water insoluble)/HPMC (water soluble) found to be potentially useful for chronotherapy of asthma and allergic rhinitis which can control the time and duration of plasma drug concentration better than conventional tablet. The \textit{in vivo} study indicates that developed formulations can release the drug in the GI tract after a predetermined lag
period of time in a manner similar to that in vitro as supported by X-ray imaging and pharmacokinetic study. Thus, the designed devices can be considered as promising delivery system in chronotherapeutic management of asthma and associated allergic rhinitis.

**Future scope**

- The pilot plant scale up studies are required for the optimized formulation to meet the industrial and regulatory requirements.
- The long term stability studies as per ICH guidelines are required to establish the stability data of these formulations.
- The pharmacokinetic study of optimized formulations should be carried out in healthy human subjects to establish the pharmacokinetic profile.
- The clinical study of optimized formulation should be carried in patient subject to establish the efficacy of designed delivery system.