Abstract

Co-existence of asthma with allergic rhinitis and their shared pathophysiology have led to the concept of “one airway, one disease” and the need for a common therapeutic approach. Montelukast sodium (MKS), a leukotriene receptor antagonists (LTRAs) considered as a useful common therapy to treat both asthma and allergic rhinitis, with clinical evidence for their efficacy and tolerability. The purpose of this study was to develop chronomodulated drug delivery systems of MKS for the chronic management of asthma and associated allergic rhinitis, symptoms for which mostly aggravates in the early morning and morning hour respectively. Time controlled pulsatile release tablets, osmotically controlled pulsatile release capsules, delayed release beads of MKS were developed and studied for physical characteristics, in vitro release study, stability study and in vivo study. A sensitive and specific RP-HPLC analytical and bioanalytical methods with UV detection were developed and validated as per the ICH and USFDA guidelines respectively to quantitate MKS in the developed formulations and in plasma. Central composite design (CCD) was introduced to execute the experiments and polynomial equation was generated to predict and assess the independent variables with respect to the dependent variables. The composition of optimal formulation for time controlled pulsatile release tablets 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 the lag time of 4.5 h, release at 6 h and 12 h are 84.14% and 95.32% respectively. The composition of optimal formulation for osmotically controlled pulsatile release capsules 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 the lag time of 4.5 h, release at 6 h and 12 h are 61.95% and 96.29% respectively. The composition of optimal formulation for delayed release beads was determined as 23.33% w/w (coded value -0.66) eudragit RLPO in coating composition and 9.84% w/w (coded value -0.08) coating weight gain. The results showed the lag time of 4.5 h and release at 6 h is 74.9%. In vivo pharmacokinetic study in rabbits revealed T_{max} of 2 h for marketed tablets and 7 h for optimised formulations. The present study demonstrated successful formulation development of chronomodulated delivery system of MKS which releases the drug after a predetermined lag time consistent with requirements for chronotherapy of asthma and allergic rhinitis. This approach will provide a useful means for better management of asthma and allergic rhinitis.