ABSTRACT

Objective

The objective of the present study was to investigate the effect of various polymers on the release of bioactives like Dalfampridine and Tramadol HCl by formulating and optimizing their matrix tablets by using Eudragit RSPO, Eudragit RLPO and HPMC K100M for Dalfampridine and HPMC K100M, HPMC K100LVP, HPMC K15M for Tramadol HCl respectively by 3 level factorial designs i.e., response surface methodology (Box-Behnken design).

Method

Preliminary experiments were conducted to screen the main variables and the operable ranges of them in which the optimum response lied. The effect of concentration of various polymers like Eudragit RSPO, Eudragit RLPO, HPMC K100M for Dalfampridine and HPMC K100M, HPMC K100LVP, HPMC K15M for Tramadol HCl as independent variables on the in vitro % drug release at various time points as dependent variables. Through preliminary screening, it was identified that the concentrations of selected polymers were significantly affecting the responses. Based on the results of the preliminary studies a response surface method i.e., Box-Behnken design [Table 4.7 & 4.9] was selected to investigate the effect of each independent variable (polymer concentration) on dependent variables (% drug release at various time points and time taken to release 50% of the drug). This statistical design was employed for developing quadratic response surfaces and second-order polynomial models. The generated polynomial equations were used to optimize the response by considering the sign and magnitude of the variables. The independent variables and the dependent variables used in the design were shown in Table 4.4 & 4.5. The experiments were performed as for the design and the responses were tabulated in Table 4.4 & 4.5. The responses were mapped over the experimental domain to select optimum formulation by
using Stat-Ease Design Expert® software V9.0.4. Three experiments were additionally conducted to verify the validity of the statistical experimental strategies.

Prior to the design of formulations, the raw materials were subjected to preformulation studies. The designed 17 formulations of Dalfampridine were prepared by direct compression technique and formulations of Tramadol HCl were prepared by non aqueous wet granulation technique. The formulated blend or granules were subjected to Precompression parameters like angle of repose, tapped density, bulk density, compressibility index and Hausner’s ratio. The prepared tablets were subjected to post compression evaluations like weight variation, hardness, and friability. The formulations were further evaluated for in vitro drug release studies. Based on the results of dissolution parameters and applying optimization principles, one formulation from each of Dalfampridine and Tramadol HCl were selected for further stability and in vivo studies. The stability studies were carried out as per ICH guideline and these formulations were analyzed by in vivo animal studies to estimate pharmacokinetics parameters like AUC, AUMC, $C_{max}$, $T_{max}$, $t_{1/2}$, MRT & clearance. The pharmacokinetic parameters were estimated by using PK Solver Version 4.0 software

Results

The design and optimization of Dalfampridine and Tramadol HCl sustained release tablets were performed by applying one of the response surface method i.e., Box-Behnken design. The software generated 17 formulations for each drug by varying the concentration of independent variables i.e., rate retarding polymers. The formulae for drugs were developed based on the design and blend or granules were prepared as per the designed formulae. The estimated Precompression parameters like bulk density, tapped density, angle repose and Hausner’s ratio were in compliance with the sustained release tablets criteria as per USP specifications. The blend or granules were prepared into matrix tablets and the developed tablets were subjected to post compression parameters to assess the quality of tablets. The post compression parameters were in compliance with the standards of the sustained release tablets. The developed formulations were shown to
control the drug release over the period of 12 hours. The best formulations were selected after applying statistical optimization techniques like Box-Behnken design by considering various dissolution parameters like % drug release at various time points and time to release 50% of the drug. From the above design F13 of Dalfampridine and F10 of Tramadol HCl were selected as optimized formulations. The selected formulations were subjected to stability studies and were found to be stable which was confirmed observing the results before and after stability studies. The stable formulations were evaluated for pharmacokinetic parameters i.e., AUC, AUMC, $C_{\text{max}}$, $T_{\text{max}}$, $t_{1/2}$, MRT & clearance and results showed that pharmacokinetic parameters were found to be improved with sustained release formulations of selected bioactives.

**Conclusion**

In the present investigation the sustained release matrix tablets of two bioactives, Dalfampridine and Tramadol HCl using various polymers viz, Eudragit RSPO, Eudragit RLPO, HPMC K100M, Methocel K100M, Methocel K100LVP and Methocel K15M in various combinations were successfully prepared. All the developed formulations were optimized for optimum levels of polymers should be used to develop matrix tablets which meet USP SR drug release requirements using statistical Box-Behnken design. The prepared optimized tablets were stable and could control the drug release up to 12 hrs period following non-Fickian diffusion. *In vivo* pharmacokinetic studies revealed that the developed optimized matrix tablets were successful in increasing the $t_{1/2}$, AUC and MRT of pure bioactives. Hence the selected polymers (Eudragits and HPMC) are the right choice in developing of SR matrix tablets of chosen bioactives as they were successful in controlling release and absorption of drugs for prolonged period of time. Hence it can be concluded that the designed matrix tablets are the promising formulations to meet continuous needs of suffering society and the developed formulations would be the successful generic versions of the innovator products.