Formulation and Optimization of Sustained Release Floating Matrix Tablets of Salbutamol Sulphate Using Xanthan Gum and Hydroxypropyl Methylcellulose Polymer Blend

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Abstract

Salbutamol sulphate is a directly acting sympathomimetic agent with selective action on $ß_2$-receptors. It is used as bronchodilator in the management of disorders involving reversible airways obstruction and in chronic obstruction pulmonary diseases. Oral salbutamol sulphate has site-specific absorption in the stomach and upper part of the small intestine. Its bioavailability is about 40% due to extensive hepatic first pass metabolism, sulphonation in intestinal fluid, degradation in colon and narrow absorption window. The aim of this study was to formulate and optimize a sustained release floating tablet of salbutamol sulphate using xanthan gum (XG) and hydroxypropyl methylcellulose (HPMC) as release retarding agents and sodiumbicarbonate ($NaHCO_3$) as floating aid in order to improve bioavailability, reduce dosing frequency, and increase patient compliance.

The sustained release floating tablets of salbutamol sulphate was prepared by wet granulation technique using XG and HPMC as release retarding polymers. The effects of formulation variables: percentage of polymer (XG, HPMC, or XG/HPMC) and percentage of sodium bicarbonate on response variables: floating lag time, floating duration, cumulative release within 1 hr, and release rate were investigated. Preliminary studies revealed that the percentage of sodium bicarbonate, percentage of polymer (XG, HPMC, or XG/HPMC) significantly affected the floating lag time, cumulative release within 1 hr and release rate ($P < 0.05$), but not floating duration. Among the polymers used, the one with 1:3 (XG:HPMC) ratio was selected for further optimization purpose due to that it contains relatively high amount of HPMC, which has low

hydration power than XG, that can release enough amount of drug in the first 1 hr which can be used as bolus dose for rapid relief of asthma. The effect of formulation variables on floating lag time was significant, but all formulations floated below 10 seconds and not considered during optimization. The effects of percentage of $NaHCO_3$ and percentage of XG/HPMC (1:3) were studied and optimized for maximum desired output of drug release rate and cumulative release within 1 hr using central composite design statistical approach. Design-Expert 8.0.7.1 software was employed to carry out the experimental design, statistical analysis, and numerical and graphical optimization.

Linear and quadratic models were developed as best fit models for release rate and cumulative release at 1 hr, respectively. The analysis of variance (ANOVA) of the models showed that the linear effects of both parameters were significant for the linear model of release rate; and all the linear, interaction and quadratic effects were significant for the quadratic model of cumulative release at 1 hr. The effect of percentage of XG/HPMC was more pronounced than the effect of percentage of $NaHCO_3$ on both models. Finally, simultaneous optimization of cumulative release at 1 hr and release rate was performed and the most desirable representative optimal point was obtained to have release rate of 28.49 $hr^{-1/2}$ and cumulative release at 1 hr of 24% at corresponding levels of 24.79% of XG/HPMC and 5% of $NaHCO_3$ with desirability of 0.756. The validity of this optimal point was confirmed by the low magnitude of percent prediction error. Evaluation of the optimized formulation showed successful formulation of the floating tablets with excellent granule and tablet property. Comparison of the release profiles of three different batches of the optimized formulation by dissolution efficiency revealed that there was no statistically significant difference ($p > 0.05$) in release profiles of the formulations. In addition, drug release kinetics and drug release mechanism studies indicated that the optimized formulation followed Higuchi square root kinetic model with non Fickian diffusion release mechanism. In conclusion, this study has come up with an optimum formulation for the development of floating tablet of salbutamol sulphate that could remain buoyant and release the drug over a period of 12 hr in a sustained manner *in vitro*.

***Keywords*:** GRDFs; Floating tablet; Salbutamol sulphate; Xanthan gum; HPMC; Optimization