

FORMULATION OF SUSTAINED RELEASE ATENOLOL MATRIX TABLETS THROUGH OPTIMIZATION AND THEIR EVALUATION

Masheer Ahmed Khan *

School of Pharmacy, Devi Ahilya Vishwavidyalaya, Takshshila Campus, Khandwa Road,
Indore-452001, India

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***Correspondence for
Author:**

Dr. Masheer Ahmed Khan

School of Pharmacy, Devi
Ahilya Vishwavidyalaya,
Takshshila Campus,
Khandwa Road, Indore,
452001, India

masheerak@yahoo.com

ABSTRACT

The object of the present study is to develop sustained release system of the Atenolol which is β -1 cardio selective adrenergic receptor blocker, widely used in the treatment of hypertension. The drug has a short biological half-life of six to eight hours with oral bioavailability of 50% and smaller dose of drug 50 mg. Once daily Sustained release matrix tablets of Atenolol reduces the frequency of administration and improves the patient compliance. Sustained release of the drug is devised from the matrix tablet dosage form. Atenolol matrices were prepared from different grades of hydroxylpropyl methylcellulose (HPMC) viz. combination of polymers HPMCK4M and HPMCK15M. Optimization techniques using factorial design for two factors at three levels (3^2) was selected to optimize varied response variables viz. release rate exponent (n), k, amount of drug released in 12h (Rel12h)

and mean dissolution time MDT. The optimum formulation was selected and the results obtained with the experimental values were compared with the predicted values. In conclusion, the results suggest that the developed sustained-release matrix tablets could provide quite regulated release of the drug over an extended period of time.

Key words: Atenolol, Sustained release, HPMC.

INTRODUCTION

A computer optimization technique, based on response-surface methodology has proven to be a useful approach for selecting pharmaceutical formulations. Factorial designs are the most popular response surface designs¹⁻². A factorial design for two factors at three levels (3^2) which is equivalent to a central composite design (CCD) for two factors was selected to

optimize varied response variables viz. release rate exponent (n), k, amount of drug released in 12h (Rel12h) and mean dissolution time MDT³⁻⁵.

Atenolol is a β -blocker, prescribed widely in hypertension, angina pectoris, arrhythmias, and myocardial infarction. It has been reported that atenolol undergoes extensive hepatic first-pass metabolism following oral administration and has a short biological half-life. Administration of conventional tablets of Atenolol has been reported to exhibit fluctuations in the plasma drug levels, results either in manifestation of side effects like nausea, diarrhea, ischemic colitis, and mesenteric arterial thrombosis or reduction in drug concentration at the receptor site. To reduce the frequency of administration and to improve the patient compliance, a once daily sustained release formulation of atenolol is desirable⁶⁻⁷.

Matrix tablet is the least complicated approach in devising a sustained release dosage form and involves the direct compression of blend of drug, retardant material and additives to form a tablet in which the drug is embedded in a matrix core of the retardant. Hydrophilic matrices are well mixed composite of one or more drugs with a hydrophilic polymer. Hydrophilic matrices possesses major advantages over other alternatives in developing oral controlled release drug delivery as they have a capacity to incorporate large doses of drugs, these can't be disintegrated throughout the GI tract so the dose dumping is not there⁸⁻¹².

In the current study different grades of HPMC like K4M, K15M and K100M were selected during preliminary studies for regulating the release of the drug atenolol. Two polymers HPMCK4M and HPMCK15M were further selected for optimization studies.

The raw data obtained from in vitro dissolution was analyzed using the software. The software has in built provisions for calculating the values of amount of drug release, percentage of drug release, log fraction released at various time intervals, log time, mid-point of time intervals and rate of drug release¹³⁻¹⁴.

Sustained release of drug is required to reduce the frequency of administration. Therefore the object of present study is to enable a simpler method of manufacture of tablets to provide sustained release of the drug content up to 12 hrs.

MATERIALS UNDER METHODS

Atenolol was obtained as a gift sample, HPMC (K4M, K15M, and K100M) were provided by Colorcon India Ltd., Goa, dicalcium phosphate, microcrystalline cellulose (Avicel PH101), purified talc, magnesium stearate and all other reagent used were of analytical grade.

Pre-optimization studies

Nine formulations employed for pre-optimization investigations containing different ratios of HPMCK4M, HPMCK15M and HPMCK100M, keeping the total tablet weight constant at 120 mg. The tablets were prepared by direct compression. The values of response variables viz. n , $rel12h$, MDT were studied to help in choosing the best possible combination for further optimization studies.

Factorial Design

The 3^2 factorial designs were selected using two factors (polymers) at three levels and the factor levels were suitably coded. Nine formulations were prepared as per the design and coded F1-F9. The two polymers HPMC K4M and HPMC K15M were selected and their limits were chosen for subsequent detailed studies using the factorial design. The amount of drug, magnesium stearate, MCC and talc were kept constant while dicalcium phosphate was taken in sufficient quantity to maintain a constant tablet weight of 120 mg. The translation of the coded factor level as amount of ingredients is listed in Table (1).

Table (1) Translation of experimental conditions into physical units

Coded Factor	Level	Factor(X1)	Factor (X2)	Units
		HPMC K ₄ M	HPMC K ₁₅ M	
-1	Low	25	15	mg
0	Intermediate	35	22.5	mg
1	High	45	30	mg

Preparation of Tablets and Physical Evaluation

Tablet batches consisting of 100 tablets were prepared by direct compression method. All the product and process variables other than the concentration of two polymers were kept constant. The composition of nine formulations F1-F9 as per factorial design during optimization studies are shown in Table (2). Ten tablets from each batch were weighed individually and subjected to physical evaluation.

Table (2): Composition of different formulations as per factorial design of optimization

Formulation Code	HPMCK4M	HPMCK15M	Total Polymer Content	Units
F1	25	15	40	mg
F2	25	22.5	47.5	mg
F3	25	30	55	mg
F4	35	15	50	mg
F5	35	22.5	57.5	m g
F6	35	30	65	mg
F7	45	15	60	mg
F8	45	22.5	67.5	mg
F9	45	30	75	mg

Dissolution Studies

The dissolution studies were performed in triplicate for all the batches in a USP XXIII dissolution rate test apparatus (type II). The release studies were performed at 50 rpm in 900 ml of 0.1N HCL for 2hrs followed by phosphate buffer pH 6.8 at $37 \pm 0.2^{\circ}\text{C}$. Five milliliters aliquots were withdrawn at predefined intervals, and the volume of the dissolution medium was maintained by adding the same volume of fresh pre warmed dissolution medium. The absorbance of the withdrawn samples was measured using spectrophotometer at 224 nm.

Data Analysis

The software calculates the response variables, which were considered for optimization included, n, mean dissolution time (MDT) and release at 12th hr (rel_{12h}). Finally, the prognosis of optimum formulation was conducted in feasible region to predict the possible solutions. The optimum formulation was selected by the critical evaluation of the tabulated search values.

Preparation of Predicted optimum Formulation

The tablet formulations were compressed using the chosen optimal composition and evaluated for physical test, tablet assay and dissolution performance. The observed and predicted responses were critically compared.

RESULTS

Pre-optimization Studies Results

The data obtained during the pre-optimization studies reveals that as the molecular weight or the viscosity of the polymer increases, release rate of the drug from the formulation decreases. These studies help in the selection of the appropriate range of polymer for the further optimization studies.

Physical Evaluation and Assay of Tablet

The tablet weights of all the nine batches vary between 120-121mg, and tablet hardness between 5.5 to 5.8 Kg. The assay values varied between 95.86% to 98.65%. The tablet friability ranged between 0.5 to 0.8%. The physical parameters of the manually compressed tablets were found within control.

Release Profile Studies

The dissolution parameters of nine formulations as per design containing HPMCK4M and HPMCK15M polymer combination with different ratios, obtained are shown in the Table (3). The release pattern between percent drug release vs. time is shown in Fig. (1).

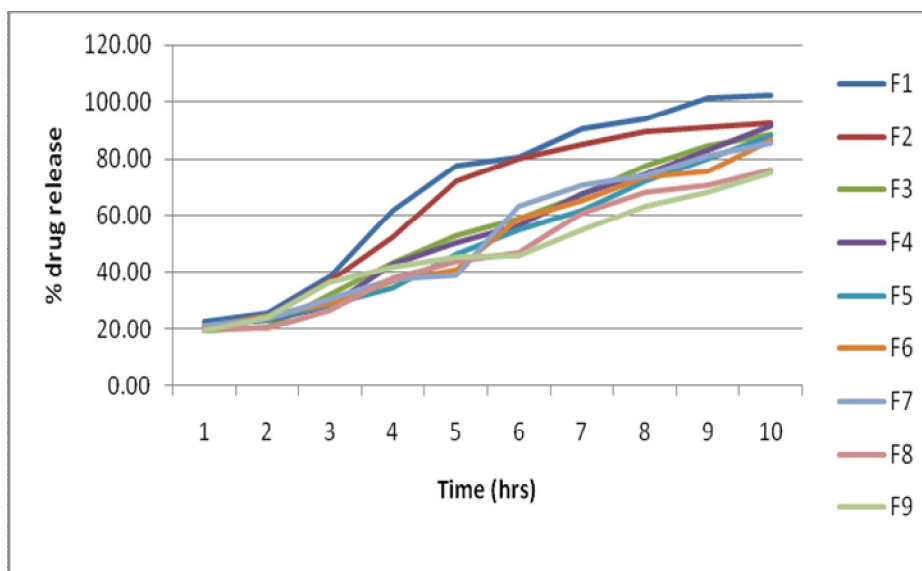


Fig.(1) Plot between percent drug release and time for formulations as per Factorial design

Table (3) Dissolution parameters of HPMCK4M-HPMCK15M polymer combinations with different ratios during optimization studies using 3² factorial design.

Formulation Code	n	k	MDT	Rel 12 hr
F1	0.550	0.288	3.246	102.35
F2	0.512	0.286	3.685	92.50
F3	0.508	0.266	5.047	88.67
F4	0.504	0.256	5.219	91.50
F5	0.479	0.245	5.807	88.06
F6	0.471	0.250	6.003	86.25
F7	0.475	0.245	6.148	85.47
F8	0.454	0.235	7.845	76.26
F9	0.432	0.245	7.495	75.30

Response Surface Analysis -Calculation of Coefficient

The coefficients of the polynomial equations for responses n, k, Rel 12hr and MDT along with their values of R². Coefficients (B₁-B₄) were calculated with B₀ as the intercept using the polynomial equation

$$Y=B_0 + B_1X_1 + B_2X_2 + B_3X_1^2 + B_4X_2^2 + B_5X_1X_2 + B_6X_1X_2^2 + B_7X_1^2 X_2$$

The coefficient of the above equation was calculated by regression using the transformed data taken for Factor X₁(HPMCK4M) and Factor X₂ (HPMCK15M) as shown in Table (1).The value of R² is quite high for Rel12h, n and MDT so for these responses, the polynomial equations form excellent fits to all the experimental data and statistically valid.

Search for Optimum Formulations

The criterion for selection of suitable feasible region was primarily based on highest possible values of n, Rel 12 hr and MDT . Two regions were selected on the basis of dissolution parameters obtained during optimization studies of formulations F1-F9. The excel sheet was used to predict and determine the responses between feasible regions for factorX₁ and FactorX₂ (HPMCK4M and HPMCK15M).

Feasible Region

$n > 0.460$; $\text{rel } 12 \text{ hr} > 90\%$; $\text{MDT} > 3.6$

The predicted values for the responses were noted and are shown in Table (4). Based on the predicted values the levels were decoded and factor values were determined (refer Table 1). Tablets of optimum formulation was prepared and subjected to dissolution studies. The dissolution parameters obtained for optimum formulation are shown in Table (5).

Table (4) Predicted values of optimum formulations.

n	k	MDT	Rel12hr
0.507	0.289	3.866	93.45

Comparison of Optimum Formulation

The results of the physical evaluation and tablet assay of the optimum formulation were within limits. Dissolution parameters like n, MDT and Rel 12n were tabulated for optimized matrix tablets formulation and shown in Table (5). The plot between percent drug release and time of the optimized formulation is shown in Fig. (2). The comparison of the observed responses with anticipated responses along with percent error were done. The results obtained of the experimental values are very much close to the predicted values for the two responses n and Rel12hr.

Table (5) Dissolution parameter for optimum formulation

n	k	MDT	Rel12hr
0.505	0.286	3.885	93.56

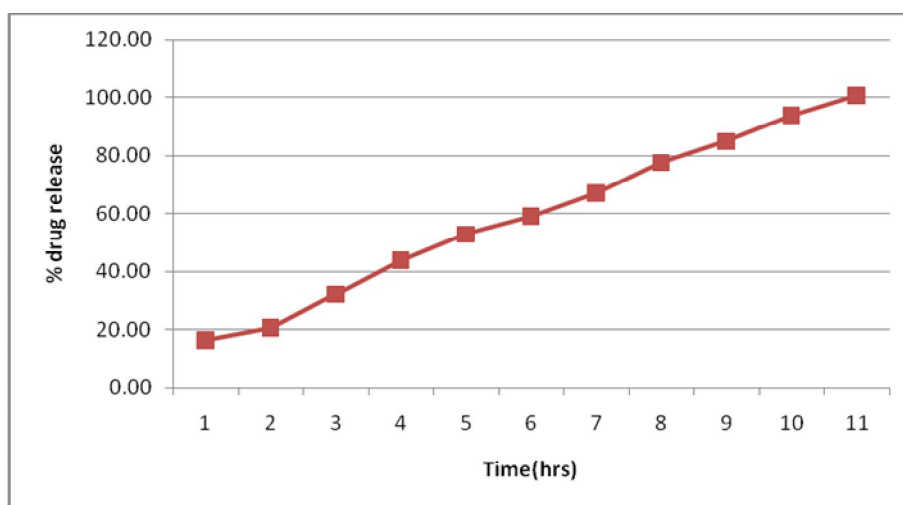


Fig.(2) Plot between percent drug release and time of the optimum formulations.

DISCUSSION

The dissolution data indicates that as the content of HPMCK4M and HPMCK15M increased, the value of n was found to decrease, except when HPMCK4M content increased from intermediate to high level. By and large the table delineates a decreasing trend in the value of n as the ratio of total polymer content to drug increased. In general the release pattern tends to approach Fickian release with increase in polymer content.

The values of k showed however no distinct trend with increase in concentration of polymers. The values of Rel_{12h} showed that with an increasing total polymer content resulted in the decrease in the drug release. The inverse relationship is there between the total polymer content and drug release.

The value of overall rate of release decreases with increasing concentration of HPMCK4M and HPMCK15M from low to intermediate levels. Increasing the concentration to high level of HPMCK4M and HPMCK15M did not have any significant effect on release rate, in accordance with the previous reports, wherein a saturation effect occurred at high concentration. The general pattern was a decrease in release rate with an increase in amount of total polymer content. This is in clear accordance with earlier findings.

The values of MDT showed that with increasing total polymer content resulted in the increase of mean dissolution time. MDT is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer.

Comparisons of the observed responses with that of the anticipated responses along with percentage error for dissolution parameters like n and Rel_{12h} of optimized matrix tablets formulation shows the prognostic ability of matrix tablet formulations of atenolol using optimization method.

CONCLUSION

Atenolol matrix tablets containing combination of polymers HPMCK4M and HPMCK15M shows sustained release over an extended period of time. Results of the studies for optimized formulation fulfilled maximum requisites because of better regulation of release rate. Rational use of optimization methodology helped to predict the best possible formulations and confirms the prognostic ability of optimization method. Conclusively, the current study attained the successful design, development, optimization and formulation of atenolol tablets.

REFERENCES

1. Swarbric J, and Boylan J.C.; Encyclopedia of Pharmaceutical Technology, Marcell Dekker, New York, 1995.
2. Bolton S.; Pharmaceutical Statistics: Practical and Clinical Applications. 2nd Ed., Marcel Dekker Inc, New York, 1990, 308-570.
3. Banker G., Rhodes C.; Modern Pharmaceutics, Marcel Dekker, New York, 1996, 247-289
4. Lewis GA, Mathieu D. and Phan-Tan-Luu R.; Pharmaceutical Experiment Design (Drugs and Pharmaceutical Sciences), Marcel Dekker, Inc., New York, 1999.
5. Box G., Connor C., Cousins W., Davies O, Himsworth F and Sillito G.; The Design and Analysis of Industrial Experiments Davies, O.L., (Ed) 2nd edition, Oliver and Boyd, London, 1960, 495-565.
6. Baisya O, Deb J, and Bhowmik M, Formulation and evaluation of sustained release matrix tablet of atenolol based on natural polymer, Research Journal of Pharmaceutical, Biological and Chemical Sciences (RJPBCS), Vol. 3, Issue- 4 (2012).
7. Khan M.A., Effect of pH on dissolution profile of atenolol sustained release matrix tablets, Research J. Pharma Dosage forms and Tech. 2013, 5(5), 275-277.
8. Khan M A, Formulation of sustained release diltiazem hydrochloride matrix tablets through optimization and their evaluation, Research Journal of Pharmaceutical, Biological and Chemical Sciences (RJPBCS), Vol. 4, Issue- 2 (2013) 1317-1325.
9. Khan M A, Formulation of sustained release chlorpheniramine maleate tablets through optimization and their evaluation, Journal of drug delivery and therapeutics, 2(5),45-49,(2012).
10. Khan MA , and Chaturvedi SC , Swelling and Drug Release Studies from Hydrophilic Matrices Containing Combination of Different Grades of Hydroxyl Propyl Methylcellulose, Asian Journal of Chemistry, Vol. 23,Issue8(2011),3566 - 3568
11. Khan M.A., and Chaturvedi S.C., Formulation of Sustained Release Zolpidem tartrate Matrix Tablets through Optimization and their Evaluation Asiaan Journal of Chemistry, Vol. 22,Issue 6(2010),4749-4762.
12. Liberman H, Lachman L and Schwartz J, Pharmaceutical Dosage Forms: Tablets. vol.1, 2nd edition revised and expanded, Dekker, New York, 2005.
13. Singh B and Singh S, A comprehensive computer program for the study of drug release kinetics from compressed matriceses, *Ind. J. Pharm. Sci.*, 60(6), 358-362 (1998).

14. Singh B and Gupta R.K., FACTOP: A Software Aid to Optimize Pharmaceutical Dosage Forms through Factorial Design in 4^{8th} Indian Pharmaceutical Congress, Chennai. 1996, AP 63.