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

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ABSTRACT

The object of the present study was to develop once daily sustained release matrix tablets of Stavudine a thymidine analog approved for the treatment of HIV infection. Stavudine has a short half life of 1 to 1.6hrs and 40mg twice daily dose. Converting twice daily regimen of stavudine into once daily improves adherence and, therefore, enhances the effectiveness of antiretroviral therapy. Matrix tablets which is the least complicated approach is used to device sustained release of the drug candidate. Different grades of polymers HPMC viz HPMCK4M and HPMCK15M were selected to sustain the release of the drug up to 12 hrs. 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 stavudine over an extended period of time.

Key words: Stavudine, Matrix tablets, 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 designs [1-2]. 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, mean dissolution time MDT and amount of drug released in 12h (Rel12h) [3-5].

Stavudine, 2',3'-didehydro-3'-deoxythymidine (D4T) is a thymidine analog approved for the treatment of HIV infection [6] like other member of this class of antiretrovirals, its purported active metabolite, D4T-5'-triphosphate, is an inhibitor of the HIV reverse transcriptase and acts as a chain terminator during DNA synthesis [7]. Stavudine is currently approved by US-FDA for the treatment of patients who have become intolerant to or failed to response to zidovudine, didanosine or zalcitabine therapy. The mean serum elimination half life reported ranges between 1 to 1.67 hr in adults. It is given twice daily 40 mg. Main dose related adverse effect is peripheral neuropathy. Converting twice daily regimen of stavudine into once daily improve adherence and, therefore, enhances the effectiveness of antiretroviral therapy [8-9].

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 there[10-14] .

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 stavudine. 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 release [15-16].

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

Stavudine was obtained as a gift sample from Cipla Pharmaceuticals, Mumbai, HPMC(K4M, K15M, 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 290 mg. The tablets were prepared by direct compression. The values of response variables viz. n, k, MDT and rel12h 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 290mg. 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_4M	HPMC $K_{15}M$	
-1	Low	40	20	mg
0	Intermediate	60	30	mg
1	High	80	40	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	40	20	60	mg
F2	40	30	70	mg
F3	40	40	80	mg
F4	60	20	80	mg
F5	60	30	90	m g
F6	60	40	100	mg
F7	80	20	100	mg
F8	80	30	110	mg
F9	80	40	120	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 75 rpm in 900 ml of the medium 0.1 N hydrochloric acid for the first 2hrs followed by the medium of phosphate buffer pH 7.4 at 37 ± 0.2 ^{o}C for rest of the study time. 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 spectrophotometrically at 266 nm.

Data Analysis

The software calculates the response variables, which were considered for optimization included, n, mean dissolution time (MDT), k and release at 12^{th} hr (rel12h). 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 290 and 300 mg, and tablet hardness between 5.8 to 6.1 Kg. The assay values varied between, 95.86% to 98.95%. 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).

Table (3): Dissolution parameters of (HPMCK4M - HPMCK15M) polymer combinations with different ratios during optimization studies using 3^2 factorial design.

Formulation Code	n	k	MDT	Rel 12 hr
F1	0.552	0.288	3.246	102.46
F2	0.514	0.288	3.865	92.54
F3	0.510	0.266	5.047	88.86
F4	0.501	0.252	5.219	91.25
F5	0.476	0.250	5.907	88.08
F6	0.469	0.251	6.063	86.23
F7	0.476	0.247	6.248	84.47
F8	0.456	0.229	7.945	75.16
F9	0.436	0.250	7.595	74.69

Response Surface Analysis -Calculation of Coefficient

The coefficients of the polynomial equations for responses n, k, MDT and Rel 12hr along with their values of R^2. Coefficients (B_1-B_5) were calculated with B_0 as the intercept using the

polynomial equation

$$Y=B0 + B1X1 + B2X2 + B3X1^2 + B4X2^2 + B5X1X2 + B6X1X2^2$$

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 R^2 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, k, MDT and Rel 12 hr. 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 > 0.470; MDT > 3.6; rel 12 hr >90%

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
0.501	0.252	5.219	91.25

Table (5): Dissolution parameter of optimum formulation.

n	k	MDT	Rel12hr
0.502	0.262	5.187	91.21

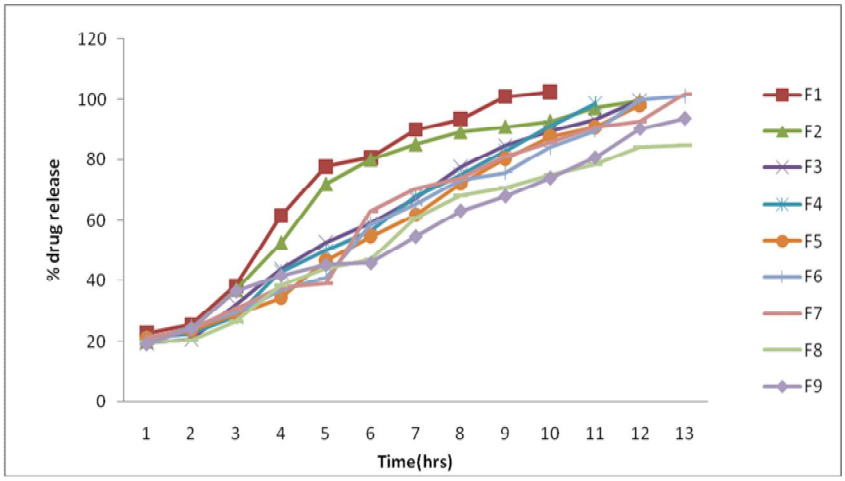

Fig.(1) Plot between percent drug release and time for formulations as per Factorial design

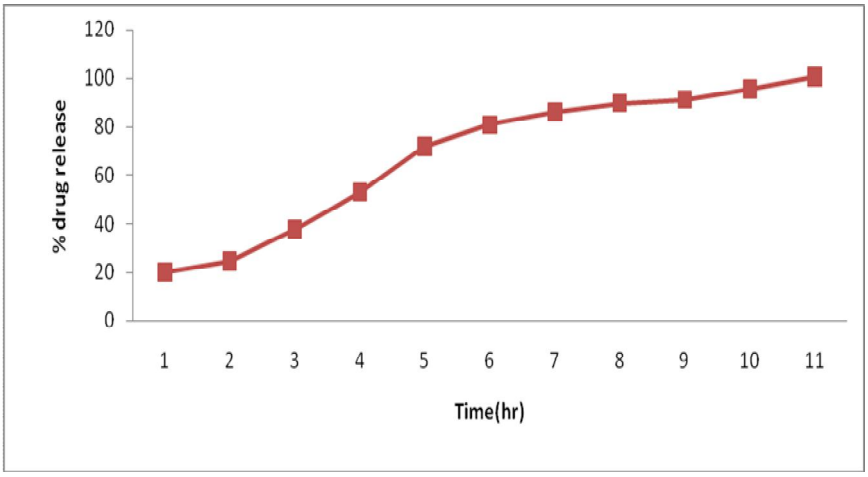

Fig.(2) Plot between percent drug release and time of the optimum formulations.

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, Rel 12n and k 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.

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 Rel12h 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 or 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 stavudine using optimization method.

CONCLUSION

Stavudine matrix tablets containing combination of polymers HPMCK4M and HPMCK15M, confirms excellent promises for drug release prolongation. Results of the dissolution 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 Stavudine sustained release matrix tablets.

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