Vol 4 | Issue 1 | 2014 | 8-12.

e-ISSN 2248 – 9142
print-ISSN 2248 – 9134

International Journal of
Current Pharmaceutical & Clinical Research

www.ijcpcr.com

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

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ABSTRACT

The object of the present study was to prepare and evaluate sustained release zidovudine matrix tablets. Zidovudine, the first anti-HIV compound approved for clinical use is widely used for the treatment of AIDS either alone or in combination with other antiviral agents. However, the main limitation to therapeutic effectiveness of zidovudine is its dose-dependent hematological toxicity, low therapeutic index, short biological half-life, and poor bioavailability. Sustained release matrix tablets were prepared using combination of hydrophilic polymer HPMC K15M and hydrophobic polymer ethyl cellulose. 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 zidovudine over an extended period of time12 hrs leading to improve efficacy and better patient compliance.

Key words: Zidovudine, Matrix tablets, HPMC, Sustained release.

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].

Zidovudine, the first anti-HIV compound approved for clinical use is widely used for treatment of AIDS either alone or in combination with other antiviral agents. However, the main limitation to therapeutic effectiveness of it is its dose-dependent hematological toxicity, low therapeutic index, short biological half-life, and poor bioavailability.

After oral administration, it is rapidly absorbed from the gastrointestinal tract (GIT) exhibiting a peak plasma concentration of 1.2 μg/mL at 0.8 hours. In the systemic circulation, it is first converted to zidovudine triphosphate, which is pharmacologically active and prevents the replication of the HIV virus. The biological half-life of zidovudine -triphosphate is 4 hours, thus necessitating frequent administration (3 to 4 times a day) to maintain constant therapeutic drug levels. Since zidovudine acts as a metabolic antagonist of thymidine and its antiviral effect is time dependent, an adequate zero-order delivery of zidovudine is desired for maintaining anti-AIDS effect and avoiding the strong side effects. These side effects are usually associated with excessive plasma level of zidovudine immediately after intravenous or oral administration. Zidovudine is absorbed throughout the GIT. The drug is freely soluble at

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any pH and hence judicious selection of release retarding excipients is necessary for achieving constant in vivo release. The most commonly used method of modulating the drug release is to include it in a matrix system [5-10].

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 polymer matrix systems are widely used for designing oral controlled drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The hydrophilic polymers selected for the present study was HPMCK15M. These polymers provide pH-independent drug release to oral dosage forms that can be used for formulating the sustained-release dosage forms. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs it becomes essential to include hydrophobic polymers in the matrix system. Hence, in the present work, an attempt has been made to formulate the sustained release matrix tablets of zidovudine using hydrophilic matrix material (HPMC K15M) in combination with hydrophobic ethyl cellulose. Two polymers HPMCK15M and ethyl cellulose were selected for optimization studies [11-14].

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 [15-18]. 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

Zidovudine was obtained as a gift sample from Cipla Pharmaceuticals, Mumbai, (HPMCK15M, Ethyl cellulose) 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 HPMCK15M and ethyl cellulose, keeping the total tablet weight constant at 300 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 and limits 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 K15M and ethyl cellulose 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 300mg. The translation of the coded factor level as amount of ingredients is listed in Table (1).

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.

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 ± 0.2ºC 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 concentration 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 6.4 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 HPMCK15M and ethyl cellulose 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).

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(HPMCK15M) and Factor X2 (Ethyl Cellulose) 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 (HPMCK15M and Ethyl Cellulose).

Feasible Region

n > 0.480; MDT > 3.2; 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).

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.

Table 1. Translation of experimental conditions into physical units

Coded Factor	Level	Factor(X1)	Factor (X2)	Units
		HPMC K15M	Ethyl Cellulose	
-1	Low	40	20	mg
0	Intermediate	60	30	mg
1	High	80	40	mg

Table 2. Composition of different formulations as per factorial design of optimization

Formulation Code	HPMCK15M	Ethyl Cellulose	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

Table 3. Dissolution parameters of (HPMCK15M – Ethyl cellulose) polymer combinations with different ratios during optimization studies using 3^2 factorial design

Formulation Code	n	k	MDT	Rel 12 hr
F1	0.557	0.298	3.246	104.24
F2	0.505	0.288	3.865	94.5
F3	0.487	0.266	5.047	91.2
F4	0.494	0.252	5.219	92.5
F5	0.471	0.250	5.907	88.06
F6	0.457	0.251	6.063	85.47
F7	0.461	0.247	6.248	86.25
F8	0.420	0.236	7.545	78.68
F9	0.407	0.228	7.595	76.24

Table 4. Predicted values of optimum formulations

n	k	MDT	Rel 12hr
0.505	0.288	3.865	94.5

Table 5. Dissolution parameter of optimum formulation

n	k	MDT	Rel 12hr
0.510	0.288	3.685	95.46

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

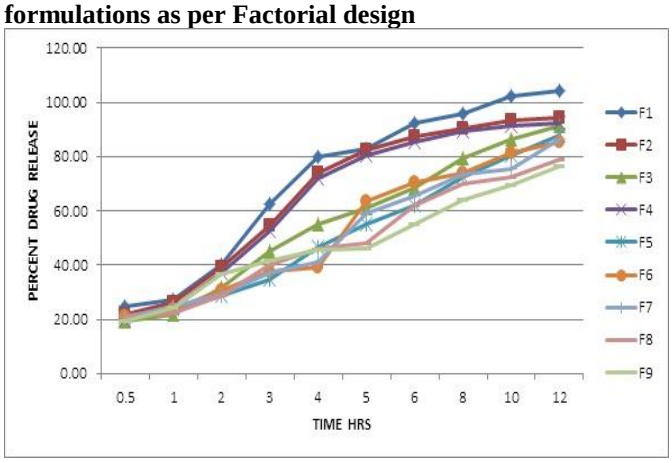
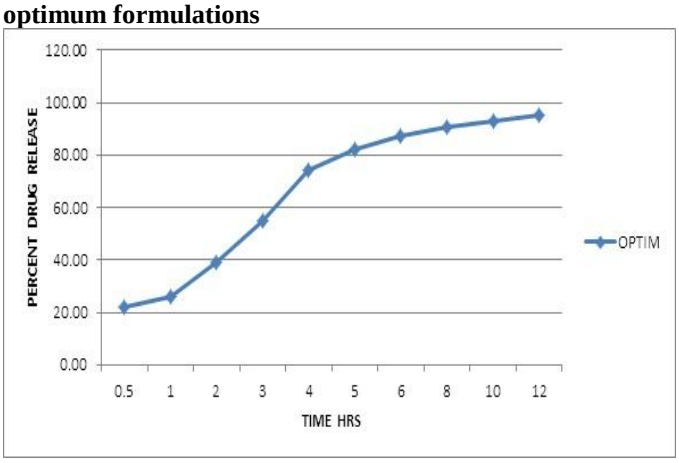


Fig 2. Plot between percent drug release and time of the optimum formulations



DISCUSSION

The dissolution data indicates that as the content of HPMCK15M and Ethyl Cellulose increased, the value of n was found to decrease, except when HPMCK15M 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 HPMCK15M and ethyl cellulose from low to intermediate levels. Increasing the concentration to high level of HPMCK15M and ethyl cellulose 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 zidovudine using optimization method.

CONCLUSION

Zidovudine matrix tablets containing combination of hydrophilic and hydrophobic polymers, 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 over an extended period of time 12hrs. 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, optimization, formulation and evaluation of zidovudine sustained release matrix tablets.

REFERENCES

1. Swarbric J and Boylan JC. 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. Kuksal A, Tiwary KA, Jain NK, Jain S. Formulation and in vitro, in vivo evaluation of extended- release matrix tablet of Zidovudine: Influence of combination of hydrophilic and hydrophobic matrix formers. *AAPS Pharm Sci Tech*, 2006, 7(1), E1-E9.
7. Ganesh S, Radhakrishnan M, Ravi M, Prasannakumar B, Kalyani J. *In vitro* Evaluation of the Effect of Combination of Hydrophilic and Hydrophobic Polymers on Controlled Release Zidovudine Matrix Tablets. *Indian J Pharm Sci*, 70(4), 2008, 461-5.
8. Salsa T, Veiga F, Pina ME. Oral controlled-release dosage forms. I. Cellulose ether polymers in hydrophilic matrices. *Drug Dev Ind Pharm*, 23, 1997, 929-938.
9. Huang P, Farquhar D, Plunkett W. Selective action of 2',3' didehydro-2',3'-dideoxythymidinetriphosphate on human immune deficiency virus reverse transcriptase and human DNA polymerases. *J. Biol. Chem*, 267, 1982, 1817-1822.
10. Kumar D, Dave V, Lewis S, Parmar B, Gajbhiye KR and Paliwal S. Design and evaluation of sustained release matrix once daily formulation of Stavudine. *International Journal of Drug Delivery*, 2, 2010, 125-134.
11. Liu J, Zhang F, McGinity JW. Properties of lipophilic matrix tablets, containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion. *Eur J Pharm Biopharm*, 52, 2001, 181-190.
12. Saravanakumar M, Venkateswaramurthy N, Dhachinamoorthi D, Perumal P. Extended release matrix tablets of Stavudine: Formulation and *in vitro* evaluation. *Asian J Pharm*, 4, 2010, 219-23.
13. Khan MA. Formulation of sustained release diltiazem hydrochloride matrix tablets through optimization and their evaluation. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 4(2), 2013, 1317-1325.
14. Khan MA. Formulation of sustained release chlorpheniramine maleate tablets through optimization and their evaluation. *Journal of drug delivery and therapeutics*, 2012, 2(5), 45-49.
15. 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*, 23(8), 2011, 3566 - 3568
16. Khan MA and Chaturvedi SC. Formulation of Sustained Release Zolpidem tartrate Matrix Tablets through Optimization and their Evaluation. *Asiaan Journal of Chemistry*, 22(6), 2010, 4749-4762.
17. Liberman H, Lachman L and Schwartz J. Pharmaceutical Dosage Forms: Tablets. vol.1, 2nd edition revised and expanded, Dekker, New York, 2005.
18. Singh B and Singh S. A comprehensive computer program for the study of drug release kinetics from compressed matrices. *Ind. J. Pharm. Sci*, 60(6), 1998, 358-362.