

## **FORMULATION OF SUSTAINED RELEASE METFORMIN HYDROCHLORIDE 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 metformin hydrochloride matrix tablets. Metformin HCL, the only available biguanide, remains the first line drug therapy for patients with Type 2 diabetes mellitus acts by decreasing hepatic glucose output and peripheral insulin resistance. It has relatively short plasma half life, low absolute bioavailability. The need for the administration two to three times a day when larger doses are required can decrease patient compliance. This is improved by developing sustained release formulations of drug candidate. Sustained release matrix tablets were prepared using combination of hydrophilic polymer HPMC K15M and hydrophobic polymer ethyl cellulose as rate controlling factor. 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 metformin hydrochloride over an extended period of time 12 hrs leading to improve efficacy and better patient compliance.

**Key words:** Metformin hydrochloride, Matrix tablets, 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<sup>1-2</sup>. 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)<sup>3-5</sup>.

Type 2 diabetes mellitus (T2DM) is a worldwide public health challenge. The morbidity, mortality and economic consequences of T2DM are still a great burden to patients, society, health care systems and the economy. The existing treatments for glycaemic control have limitations either because of their side effects (particularly weight gain and hypoglycaemia) or contraindications that limit their use. Metformin HCL, the only available biguanide, remains the first line drug therapy for patients with T2DM, acts by decreasing hepatic glucose output and peripheral insulin resistance. The advantages of metformin are a very low risk of hypoglycaemia, weight neutrality and reduced risk of cardiovascular morbidity and mortality. It is an oral anti-hyperglycemic agent, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50% – 60 % with relatively short plasma half-life of 1.5 - 4.5 h. An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhoea that especially occur during the initial weeks of treatment. Side effects and the need for administration two or three times per day when larger doses are required can decrease patient compliance. A sustained-release formulation that would maintain plasma levels of the drug for 10 to 16 hours might be sufficient for once-daily dosing of metformin<sup>6-10</sup>.

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 metformin hydrochloride using hydrophilic matrix material (HPMC K15M) in combination with hydrophobic ethylcellulose. Two polymers HPMCK15M and ethyl cellulose were selected for optimization studies<sup>11-14</sup>.

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<sup>15-18</sup>. 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

Metformin hydrochloride 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 1000 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<sup>2</sup> 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 1000mg. 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 K15M	Ethyl Cellulose	
-1	Low	90	40	mg
0	Intermediate	120	60	mg
1	High	150	80	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	HPMCK15M	ETHYL CELLULOSE	Total polymer content	Units
F1	90	40	130	mg
F2	90	60	150	mg
F3	90	80	170	mg
F4	120	40	160	mg
F5	120	60	180	m g
F6	120	80	200	mg
F7	150	40	190	mg
F8	150	50	200	mg
F9	150	80	230	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  $37 \pm 0.2^{\circ}\text{C}$  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 233nm.

### Data Analysis

The software calculates the response variables, which were considered for optimization included, n, mean dissolution time (MDT), k and release at 12<sup>th</sup> 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 6.5 to 7.4 Kg. The assay values varied between, 96.86% to 98.55%. 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).

**Table (3): Dissolution parameters of (HPMCK15M – Ethyl cellulose) polymer combinations with different ratios during optimization studies using 3<sup>2</sup> factorial design.**

Formulation Code	n	k	MDT	Rel 12 hr
F1	0.545	0.298	3.266	103.82
F2	0.493	0.288	3.885	95.56
F3	0.476	0.266	5.067	92.42
F4	0.484	0.252	5.249	94.68
F5	0.471	0.250	5.937	90.26
F6	0.460	0.251	6.093	87.47
F7	0.451	0.247	6.268	88.25
F8	0.410	0.236	7.565	80.64
F9	0.401	0.228	7.562	78.86

### 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<sup>2</sup>. Coefficients (B<sub>1</sub>-B<sub>5</sub>) were calculated with B<sub>0</sub> as the intercept using the polynomial equation

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

The coefficient of the above equation was calculated by regression using the transformed data taken for Factor X<sub>1</sub>(HPMCK15M) and Factor X<sub>2</sub> (ETHYL CELLULOSE) as shown in Table (1).The value of R<sup>2</sup> 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 FactorX<sub>1</sub> and FactorX<sub>2</sub> (HPMCK15M and ETHYL CELLULOSE).

### Feasible Region

$n > 0.470$ ;  $MDT > 5.01$ ;  $rel\ 12\ hr > 93\%$

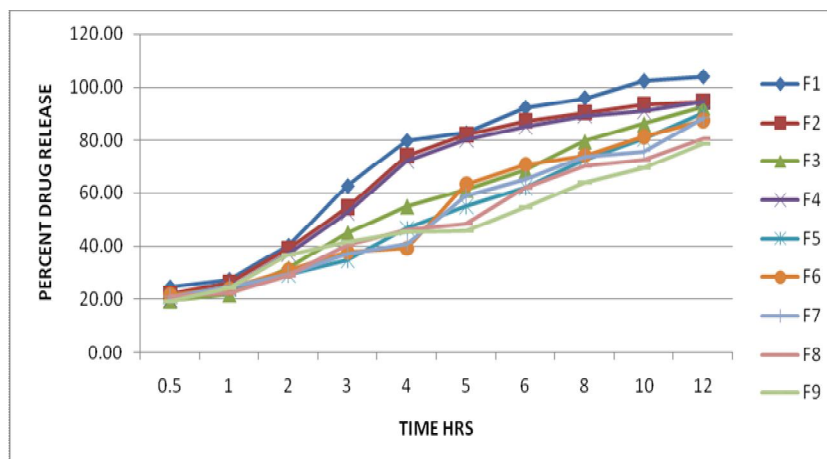
The predicted values for the responses were noted and are shown in Table (4). Based on the predicted values the levels were decoded and factor values were determined (refer Table 1). Tablets of optimum formulation was prepared and subjected to dissolution studies. The dissolution parameters obtained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

**Table (4): Predicted values of optimum formulations.**

n	k	MDT	Rel12hr
0.484	0.252	5.249	94.68

**Table (5): Dissolution parameter of optimum formulation.**

n	k	MDT	Rel12hr
0.480	0.254	5.07	93.86



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

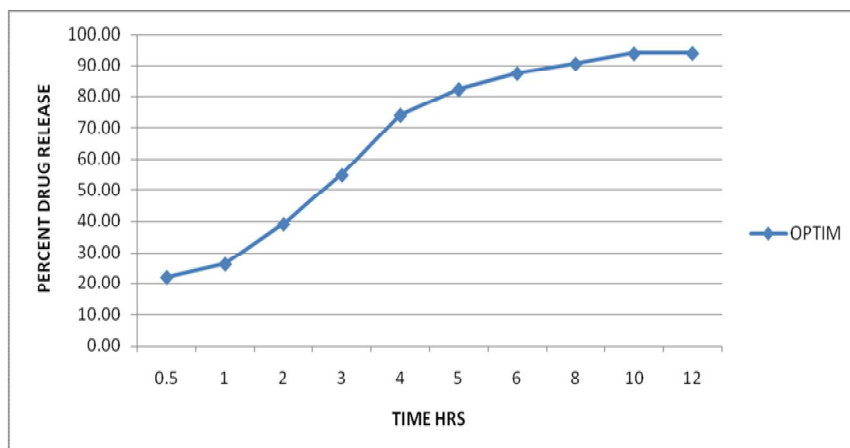


Fig.(2) Plot between percent drug release and time of the optimum formulations.

### 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, Rel12n 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 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 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 metformin hydrochloride using optimization method.

## CONCLUSION

Metformin hydrochloride 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 metformin hydrochloride sustained release matrix 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. 2<sup>nd</sup> 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) 2<sup>nd</sup> edition, Oliver and Boyd, London, 1960, 495-565.

6. Ken F., Miranda P., Steven J., Glycemic control in patients with type 2 diabetes mellitus switched from twice-daily immediate-release metformin to a once-daily extended-release formulation, *Clinical Therapeutics*, Volume 25, Issue 2, February 2003, Pages 515–529.
7. Mandal U, Gowda V, Ghosh A, Selvan S, Solomon S, Pal TK., Formulation and optimization of sustained release matrix tablet of metformin HCl 500 mg using response surface methodology, *Yakugaku Zasshi*. 2007 Aug; 127(8):1281-90
8. Wadher KJ, Kakde RB, Umekar MJ, Formulation and evaluation of a sustained-release tablets of metformin hydrochloride using hydrophilic synthetic and hydrophobic natural polymer, *Indian J Pharm Sci*. 2011 Mar;73(2):208-15
9. Wadher J.K., Kakde R.B., Umekar M.J., Formulation of sustained release metformin hydrochloride matrix tablets : influence of hydrophilic polymers on the release rate and invitro evaluation, *International Journal of rResearch in Controlled Release*, 2011,1(1) 9-16.
10. Wadher J.K., Kakde R.B., Umekar M.J., Effect of Hydroxypropyl Methylcellulose and Ethyl Cellulose polymer on Release Profile and Kinetics of Metformin HCl from Matrix Tablets, *International Journal of PharmTech Research CODEN (USA): IJPRIF ISSN : 0974-4304 Vol.3, No.3, pp 1850-1859 , July-Sept 2011*.
11. Liu J, Zhang F, McGinity JW. Properties of lipophilic matrix tablets, containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion. *Eur J Pharm Biopharm*. 2001; 52:181-190.
12. Kuksal A, Tiwary, K A, Jain N.K, 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.
13. 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.
14. 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).
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*, Vol. 23, Issue8(2011),3566 - 3568

16. 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.
17. Liberman H, Lachman L and Schwartz J, Pharmaceutical Dosage Forms: Tablets. vol.1, 2<sup>nd</sup> 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), 358-362 (1998).