WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 17, 838-845. Research Article ISSN 2277–7105

# COMPARISON STUDY SHOWING RATIONAL USE OF OPTIMIZATION METHODOLOGY IN PREDICTING THE BEST POSSIBLE FORMULATIONS OF SUSTAINED RELEASE DOSAGE FORMS

**Masheer Ahmed Khan***

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

Article Received on
24 Oct. 2017,

Revised on 15 Nov. 2017,
Accepted on 06 Dec. 2017,

DOI: 10.20959/wjpr201717-10394

***Corresponding Author**
**Masheer Ahmed Khan**
School of Pharmacy, Devi Ahilya Vishwavidyalaya, Takshshila Campus, Khandwa Road, Indore-452001, India.

## ABSTRACT

A computer optimization technique, based on response-surface methodology has proven to be a useful approach for selecting pharmaceutical formulations. The present study examines comparison showing rational use of optimization methodology in predicting the best possible formulations of sustained release dosage forms. Optimization methodology using 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) in two different drugs, diltiazem hydrochloride and metformin hydrochloride. The optimum formulation was selected using software for both the drugs and the results obtained with the experimental values were compared with the predicted values. Comparison study for both the drugs formulations suggests the rational use of optimization methodology and can be successfully utilized further in other sustained release drug formulations.

**KEYWORDS:** Optimization, Methodology, 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]

Metformin hydrochloride is an oral anti-hyperglycemic agent, acts by decreasing hepatic glucose output and peripheral insulin resistance in patients with Type 2 diabetes mellitus. It 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. 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.[6-8]

Diltiazem hydrochloride which is a calcium channel blocker widely used for its peripheral and vasodilator properties. It is also used for lowering blood pressure and has some effect on cardiac induction. It is given as oral dosage form in the treatment of angina pectoris and the management of hypertension. Its short biological half life (3-5 h), high aqueous solubility, and frequent administration (usually three to four times a day) make it a potential candidate for sustained release preparations.[9-11]

In the present work, an attempt has been made to formulate the sustained release matrix tablets of diltiazem hydrochloride using different grades of HPMC like K4M, and K15M and sustained release matrix tablets of metformin hydrochloride using hydrophilic matrix material HPMC K15M in combination with hydrophobic ethyl cellulose release.[12-13]

The raw data obtained from in-vitro dissolution can be analyzed using 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.[14-19]

## MATERIALS UNDER METHODS

Diltiazem hydrochloride was obtained as a gift sample from Promed Labs. Ltd, Indore, (M.P.) Metformin hydrochloride was obtained as a gift sample from Cipla Pharmaceuticals, Mumbai, (HPMCK4m, HPMC K15M, and 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.

**Factorial Design**

The $3^2$ factorial designs were selected using two factors (polymers) at three levels and the factor levels were suitably coded Table (1). Nine formulations were prepared as per the design and coded F1 to F9 for diltiazem hydrochloride and F1 to F9 for metformin hydrochloride tablets. Diltiazem hydrochloride matrices were prepared using HPMC K4M and HPMC K15M polymers and 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.

**Dissolution Studies**

The dissolution studies for diltiazem hydrochloride matrix tablets 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 phosphate buffer pH 7.4 at 37 ± 0.2$^{o}$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 spectrophotometrically at 237 nm. Similarly dissolution studies for metformin hydrochloride were performed using 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. 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$^{th}$ hr (rel12h). Finally, the prognosis of optimum formulation for both the drugs 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 for both the drugs 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

**Table. (1): Translation of experimental conditions into physical units**

| Coded Factor Diltiazem HCL | Level | Factor(X1) HPMC $K_4M$ | Factor (X2) HPMC $K_{15}M$ | Units |
|---|---|---|---|---|
| -1 | Low | 40 | 20 | mg |
| 0 | Intermediate | 60 | 30 | mg |
| 1 | High | 80 | 40 | mg |
| **Coded Factor Metformin HCL** | **Level** | **Factor(X1) HPMC K15M** | **Factor (X2) Ethyl Cellulose** | **Units** |
| -1 | Low | 90 | 40 | mg |
| 0 | Intermediate | 120 | 60 | mg |
| 1 | High | 150 | 80 | mg |

**Table. (2): Dissolution parameters of Diltiazem hydrochloride matrix tablets during optimization studies using $3^2$ factorial design.**

| Formulation Code | n | k | MDT | Rel 12 hr |
|---|---|---|---|---|
| F1 | 0.556 | 0.298 | 3.148 | 103.35 |
| F2 | 0.509 | 0.289 | 3.885 | 93.06 |
| F3 | 0.505 | 0.249 | 5.247 | 89.67 |
| 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 | 0.471 | 0.247 | 6.248 | 84.47 |
| F8 | 0.450 | 0.229 | 7.945 | 75.26 |
| F9 | 0.428 | 0.250 | 7.595 | 74.39 |

**Table. (3): Dissolution parameters of Metformin hydrochloride matrix tablets during optimization studies using $3^2$ 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 |

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

| Formulation | n | k | MDT | Rel12hr |
|---|---|---|---|---|
| Diltiazem HCL | 0.508 | 0.288 | 3.885 | 93.05 |
| Metformin HCl | 0.484 | 0.252 | 5.249 | 94.68 |

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

| Formulation | n | k | MDT | Rel12hr |
|---|---|---|---|---|
| Diltiazem HCL | 0.507 | 0.289 | 5.187 | 91.10 |
| Metformin HCl | 0.480 | 0.254 | 5.07 | 93.86 |

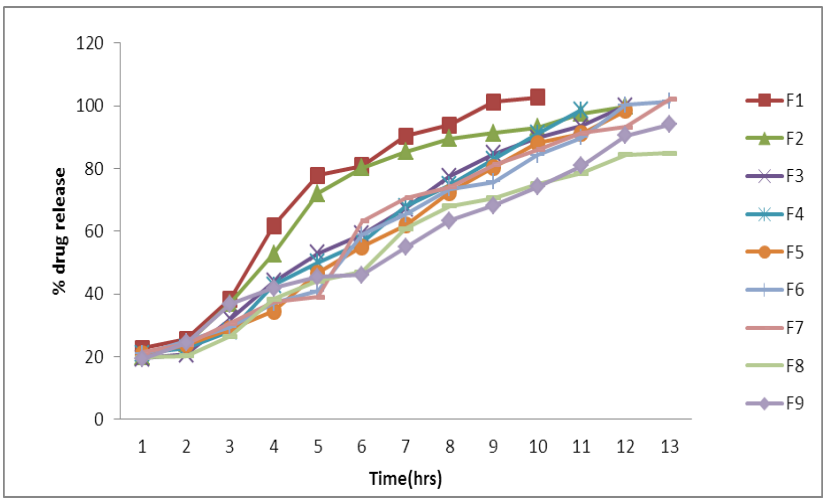


**Fig. (1): Plot between percent drug release and time for diltiazem Hhdrochloride matrix tablet formulations as per Factorial design.**

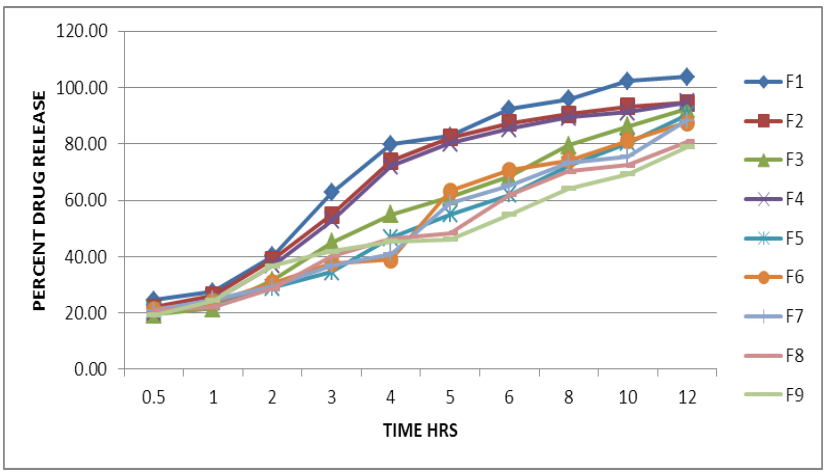


**Fig. (2): Plot between percent drug release and time for formulations Metformin hydrochloride matrix tablet as per Factorial design.**

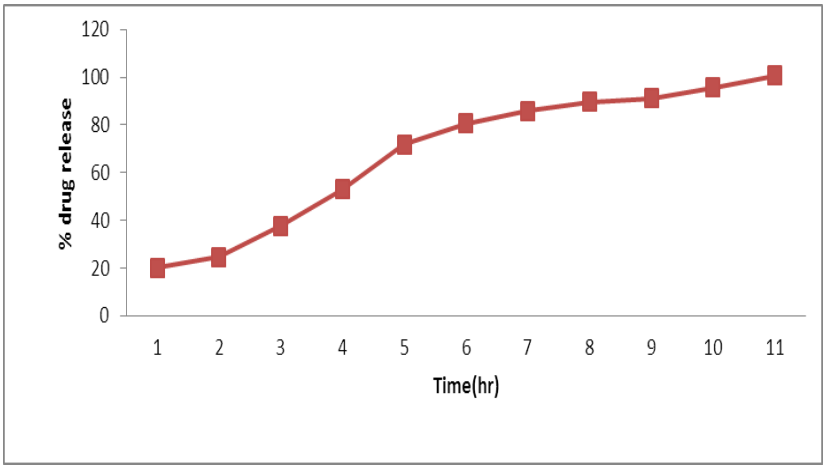


**Fig. (3): Plot between percent drug release and time of the diltiazem Hhdrochloride matrix tablet optimum formulations.**

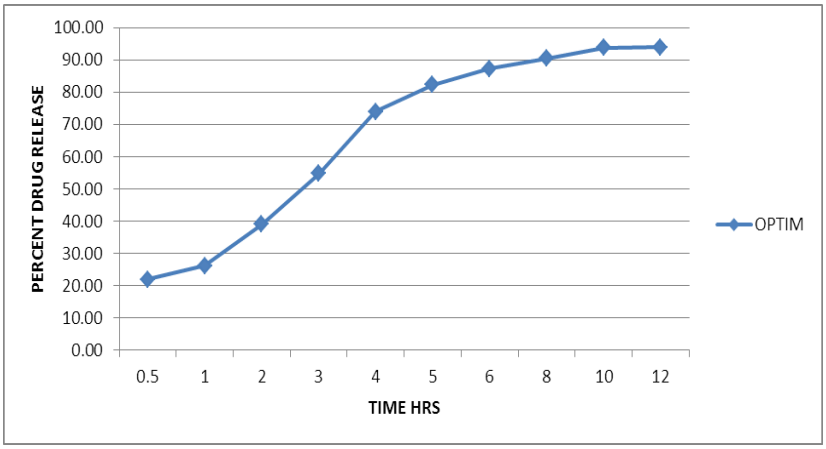


**Fig. (4): Plot between percent drug release and time of the Metformin hydrochloride matrix tablet optimum formulations.**

**Release Profile Studies:** The dissolution parameters of diltiazem hydrochloride formulations as per design, obtained are shown in the Table (2) and for metformin hydrochloride formulations as per design are shown in the Table (3).

The release pattern between percent drug release versus time is shown in Fig. (1) for diltiazem hydrochloride formulations and for metformin hydrochloride formulations are shown in Fig (2).

**Feasible Region**

Diltiazem Hydrochloride matrices , n > 0.460; MDT > 3.6; rel 12 hr >90%

Metformin hydrochloride matrices, n > 0.470; MDT > 5.01; rel 12 hr >93%

The predicted values for the responses of both the drugs 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 of both the drugs are shown in Table (5). The plot between percent drug release and time of the optimized formulation for both the drugs are shown in Fig. (3) and Fig. (4) respectively.

## CONCLUSION

The optimum formulation was selected using software for both the drugs and the results obtained with the experimental values were compared with the predicted values. Comparison study for both the drugs formulations suggests the rational use of optimization methodology and can be successfully utilized further in other sustained release drug formulations.

## 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. 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; 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. Saleh M Al-Saidan et al, in vitro and in vivo evaluation of guar gum matrix tablets for oral controlled release of water soluble diltiazem hydrochloride, AAPS PharmSciTech, 2005; 6(1): E14-21.
10. Mickey.LW and Eugene LP, Models for release of chlorpheneramine and a noninteracting compound from an inert heterogenous matrix containing an anionic surfactant, Drug development and Industrial Pharmacy, 1992; 18(3): 265-284.
11. 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, 2011; 23(8): 3566-3568.
12. 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), 2013; 4(2): 1317-1325.
13. Khan M.A., Formulation of Sustained Release metformin hydrochloride Matrix Tablets through Optimization and their Evaluation, World Journal of Pharmaceutical Research, 2013; 2(6): 2985-2995.
14. 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.
15. Khan M A, Formulation of sustained release chlorpheniramine maleate tablets through optimization and their evaluation, Journal of drug delivery and therapeutics, 2012; 2(5): 45-49.
16. 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, 2011; 23(8): 3566-3568.
17. Khan M.A., and Chaturvedi S.C., Formulation of Sustained Release Zolpidem tartrate Matrix Tablets through Optimization and their Evaluation Asiaan Journal of Chemistry, 2010; 22(6): 4749-4762.
18. Singh B and Singh S, A comprehensive computer program for the study of drug release kinetics from compressed matrices, Ind. J. Pharm. Sci., 1998; 60(6): 358-362.
19. 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.