Vol 1, Issue 2, 2014 ISSN – 2349-7041

Original Article

APPLICATION OF RESPONSE SURFACE METHODOLOGY (RSM) IN STATISTICAL OPTIMIZATION AND PHARMACEUTICAL CHARACTERIZATION OF A MATRIX TABLET FORMULATION USING METFORMIN HCL AS A MODEL DRUG

SHUBHASIS DAN[1], NIRNOY DAN[2] AND TAPAN KUMAR PAL[1]*

[1]Bioequivalence Study Centre, Department of Pharmaceutical Technology, Jadavpur University, Kolkata-700 032, India.[2.] Birla Institute of Technology, Mesra, Ranchi, Jharkhand-835215, India.

Email: tkpal12@gmail.com

ABSTRACT

The present study is about the application of a statistical optimization tool in the pharmaceutical tablet formulation. The toil of numerous scientists for years resulted in evolvement of the modified application based on the Response Surface Methodology (RSM). It has been found constructively eloquent in overcoming the problems of optimization regarding formulation of a sustained release tablet. In this study Metformin HCl is chosen as a model drug. In different time-points, experimental data are tabulated and graphically plotted. Depending upon the process variables, the predicted data obtained by RSM were compared with the experimental data. The result showed that the statistical optimization decreases the number of trial batches which is undoubtedly helpful in curtailing the resources i.e. principal, time and human effort.

Keywords: Response Surface Methodology (RSM), Metformin Hydrochloride (Met-HCl), HPMC, PVP, Contour Plots, Process Variables.

INTRODUCTION

In the modern days, pharmaceutical industries have adapted statistical process control and design of experiments with a target to save time and money during product and process development. This helps them in various ways such as ease in manufacturing process, scale ups from pilot studies along with reduction cost with a better management of manufacturing process. Response Surface Methodology (RSM) is an important engineering tool in process development through experimental design. It contributes to the industries in various aspects such as pharmaceutical product design, process development, quality, manufacturing engineering and operations by improving their performances, design of the formulations and also the intermediate as well as final products [1-3].

In the development of a sustained release dosage form, an important issue encountered is to design and optimize pharmaceutical formulation with an appropriate dissolution rate in shorter time period and with a minimum number of trials. For resolving this issue, a computer based polynomial equation and Artificial Neutral Network (ANN) are widely used [4, 5]. The optimization procedure involves systematic formulation design to minimize the number of trials, analysis of the response surfaces in order to facilitate understanding of the effect of independent factors, obtaining appropriate formulation with the achievement of target goals and also with the acceptable component region as process control condition in practical preparation [6-8].

Sustained matrix tablet is the one which delivers the drug at a predetermined rate, locally or systematically for a specified period of time. Sustained release tablet prolongs the drug release and hence maintains almost constant plasma drug level for an extended period of time. In the present study, Metformin Hydrochloride (Met-HCl) has been used as a model drug [9, 10]. The primary purpose of the study was to develop and to optimize Met-HCL sustained release formulation within the range of release profile using Response Surface Methodology (RSM) utilizing different kind of polynomial by which the design models has been made significant ($P \leq 0.05$). Under the foregoing circumstances, the drug kinetics can be characterized by three parameters; the elimination rate constant (K_e or biologic half-life ($t_{½} = 0.693/ke$), the absorption rate constant (K_a), and the apparent distribution volume (V_d), which defines the apparent body space in which drug is distributed. To attain a constant drug level, the rate of drug absorption must be equal to its rate of elimination [11, 12].

Response surface methodology (RSM) is a collection of statistical and mathematical techniques useful for developing, improving, and optimizing processes. It also provides important applications in the design, development, and formulation of new products, as well as in the improvement of existing product designs. The most extensive applications of RSM are in the industrial world, particularly in the situations where several input variables potentially influence some performance measure or quality characteristic of the product or process [13-16]. This performance measure or quality characteristic is called the response. It is typically measured on a continuous scale, although its application attributes to responses, ranks, and sensory responses which are not unusual. Most real world applications of RSM involve more than one response. The input variables are sometimes called independent variables and they are subjected to be controlled by the engineer or scientist, at least for purpose of a test or an experiment [17, 18].

Various RSM computations for the current optimization study has been performed employing Design Expert Software (Trial Version 7.1.1 State – Ease Inc., Minneapolis MN). Polynomial models including quadratic terms have been generated for the entire response variable using multiple liner regeneration analysis approach. The general form of the MLRA model is represented as equation no.1.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \beta_6 X_1 X_2^2 + \beta_7 X_1^2 X_2 \quad \text{---------- (1)}$$

Here β_0 is the intercept representing the arithmetic average of all quantitative outcomes, β_1 to β_7 are the coefficient computed from the observed experimental values of Y, and X_1, X_2 are the coded levels of the independent variables. Many statistical experimental designs have been recognized as useful techniques to optimize the process variables. Different type of screening designs such as--- fractional and Plackett Burman screening design have been used for prefomulation evaluation. RSM is applied when only a few significant factors are involved in optimization. Different types of RSM techniques, including 3-level factorials design, central composite design (CCD), Box- Behnken

design,composite design and D-optimal design are helpful for statistical optimization [19-21].

In modern well-furnished laboratories, the computer-controlled intricate instruments have wiped out the common problems of chemists, where the practical experiments generally used to cause the major limitation in obtaining relevant information. Therefore, a large investment was required in terms of time and energy to design and execute those experiments whereas in the modern laboratory those ones can be performed in a fast, reproducible way. Optimization can be defined as the search for a maximum or minimum in terms of value of a certain response function.

Traditionally pharmaceutical formulations are developed by changing one variable at a time. The method is time consuming and difficult enough to evolve an ideal formulation using this classical technique since the combined effects of the independent variables is not considered. It is therefore important to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design [22, 23]. The number of experiments required for these studies is dependent on the number of independent variables selected.

In the present study, attempts have been made to establish the application of RSM as a statistical optimization tool for the sustained release matrix tablet formulation using Met-HCl as a model drug.

MATERIALS

Raw Met-HCl was gifted by **Stadmed Pvt. Ltd.,** Kolkata, India. Hydroxypropyl Methyl Cellulose K-15M (HPMC K-15M), Polyvinyl Pyrrolidone K-30 (PVP K-30) was purchased from Colorcon Asia Private Ltd., and SD Fine Chemicals, India Respectively. Magnesium stearate and Talc was purchased from Mohanlal Doyaram and Concern, India. For all experimental runs, these chemicals used were obtained from the same batch.

METHODS

Full factorial Design

3-level-2-factor factorial design was prepared as per the standard protocol. The amount of HPMC K-15M (X1) and PVP K-30 (X2) has been selected as the casual factors [24]. All the other formulation and processing factors have been kept invariable. The constraints of the dependent responses are shown in the Table-1.Table-2 summarizes an account of total 9 experimental runs studied, their factor combination and the translation of coded levels to the experimental unit employed during the study.

Table 1: Variables in full factorial design.

Variables	**Levels Used**		
Independent Variables	**Low (-1)**	**Medium (0)**	**High (+1)**
X1= HPMC K 15M	100	300	500
X2= PVP K30	50	75	100
Dependent Variables			
Y1	Not more than 30percentage		
Y2	Not more than 40percentage		
Y3	Not more than 60percentage		
Y4	Not more than 70percentage		
Y5	Not less than 80percentage		

Table 2: Factor combinations as per the chosen experimental design.

Trial No	**Coded factor Levels**	
	X1 (HPMC K15M)	**X2 (PVP K30)**
F1	-1	-1
F2	-1	0
F3	-1	1
F4	0	-1
F5	0	0
F6	0	1
F7	1	-1
F8	1	0
F9	1	1

Preparation of Matrix Tablet

Met-HCl, HPMC K-15 and PVP were weighed and mixed well. 3ml of isopropyl alcohol was taken and poured into the bulk of the mixture and mixed for 10mins to prepare a wet mass. Granules were prepared by passing the wet mass through the mesh #16. The granules were dried in an oven for half an hour at 40 degree centigrade and then passed through the mesh #22. The dried granules were blended with 1percentage Mg-stearate and 1 percentage talc, which act as glidant and lubricant respectively. Tablets containing 500mg Met-HCl were compressed using 19.5 X 8.9 mm tablet tooling at rotational speed 40 r.p.m. The average hardness of the tablet was 6-7kg/cm^2. The trials were performed in a randomized order. The total weight of each tablet was fixed at 1110 mg by using starch as diluents. All of the ingredients used in this study came from the same lot as well as from the same manufacturer and same equipments were used throughout the production and testing of the tablets.

Determination of Drug release from Matrix Tablet

Release of Met-HCl from the tablet was determined using USP standard dissolution apparatus Type-1(with basket). The dissolution medium used was 900 ml of distilled water maintained at a temperature of 37± 0.05 degree centigrade and at a rotational speed 100 r.p.m. from each batch of formulation 6 tablets were tested. Sample aliquots were withdrawn manually at the time intervals of 1hr., 2hr., 4hr., 6hr., and 8hr. Then it was diluted with 0.2ml to 10ml of distilled water. The samples were analyzed by using UV-Spectrophotometer at 232nm.

RESULT

Response data of all 9 experimental runs of full factorial design (F1- F9) performed in accordance with table 2 is presented in figure 1. The response data are given in table 3.

Fig. 1: Release profiles with respective standard deviation of Met-HCl in accordance with Full Factorial Experimental Design runs F1 – F9.

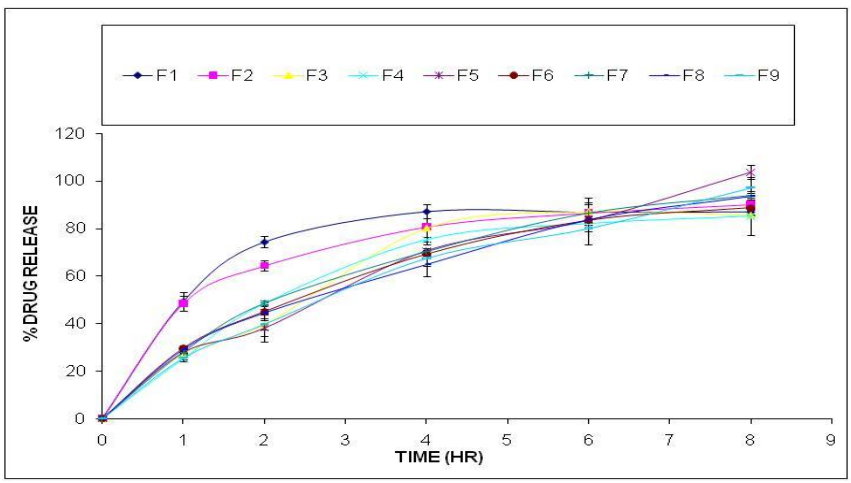


Table 3: The responses of model formulation of Metformin HCl sustained release matrix tablets utilizing full factorial experimental design.

Formulation Code	Y1 percentage Release 1 hr	Y2 percentage Release 2 hrs	Y3 percentage Release 4 hrs	Y4percentage Release 6 hrs	Y5 percentage Release 8 hrs
F1	49.39±3.94	74.45±2.21	87.28±2.81	87.03±3.04	87.18±1.58
F2	48.37±3.21	64.27±2.18	80.64±1.09	86.47±1.51	90.05±1.70
F3	27.30±3.08	39.57±4.80	80.23±7.06	87.13±5.70	85.65±8.28
F4	25.29±1.11	48.47±1.32	75.34±0.91	82.09±8.89	85.22±0.58
F5	27.90±0.18	38.17±5.68	70.72±1.01	83.55±3.43	103.8±2.96
F6	29.68±0.20	45.01±0.96	69.131±0.69	83.32±0.61	88.60±0.87
F7	28.01±0.56	48.55±0.38	70.30±0.74	86.46±3.65	93.86±0.79
F8	29.14±1.68	44.53±2.99	64.88±5.01	83.74±3.11	93.51±1.33
F9	25.53±1.58	39.81±2.25	67.58±3.24	80.12±1.25	97.23±4.25

RSM Optimization Results

3-Dimentional (3-D) Response Surface Plots and Contour Plots for the measured responses were formed based on the model polynomial function. The relationship between the dependent and independent variables can be clearly understood by these plots. Since the model has only 2 factors, total 5 surface plots and 5 Contour plots were produced. For each response one 3-D response plot and one Contour plot were produced. The responses—Y1, Y2, Y3, Y4 and Y 5 are further presented.

$Y1= +29.23-6.55X_1+2.19X_2+3.66X_1X_2+4.84X_1^2 -2.41X_1^2-9.58X_1^2 X_2$

$Y2= +49.21-7.57X_1-7.85X_2+6.53X_1X_2$

$Y3=+69.80-7.57X_1-2.67X_2+1.08X_1X_2+3.42X_1^2 +2.90X_2^2$

$Y4=+84.44-1.72X_1-0.83X_2-1.61\ X_1X_2$

$Y5=+96.65111+3.62033X_1+0.86783X_2+1.22400\ \ X_1X_2-1.29467\ \ X_1^2-6.15917X_2^2$

Response surface plot and Contour plot show the effect of amount of HPMC-K (X1) and amount of PVP (X2) on the response Y1. This figure shows that at a lower level of X2, the drug release at 1 hr (Y1) decreases with an increase in the level of X1 to a sum extent and then Y1 increase up to its highest level that means that effect of polymer on Y1 is not linear. However at the lowest level of X_1 the percentage of drug release at 1hr decreases with an increase in the level of X2. It signifies that the effect of binder on the drug release on the (Y1) is near about linear which implies that the increase of binder decreases the percentage of drug release. So the amount of binder for a particular sustained release formulation should be optimized.

In case of sustained release matrix tablet dosage form loading dose should be an important parameter, because this amount of drug contained at loading dose should be released at one hr. In case of Met-HCl sustained released tablet, release at 1st hr should be within the 25%--30% as per USP guideline. So amount of drug released at 1st hr should be reasonably high.

Figure 2: (A and B): RSM (3D) and contour plots showing the effect of the amount of HPMC K-15M (X1) and the amount of PVP K30 (X2) on the response Y1 (percentage of Met-HCl released in 1 hr).

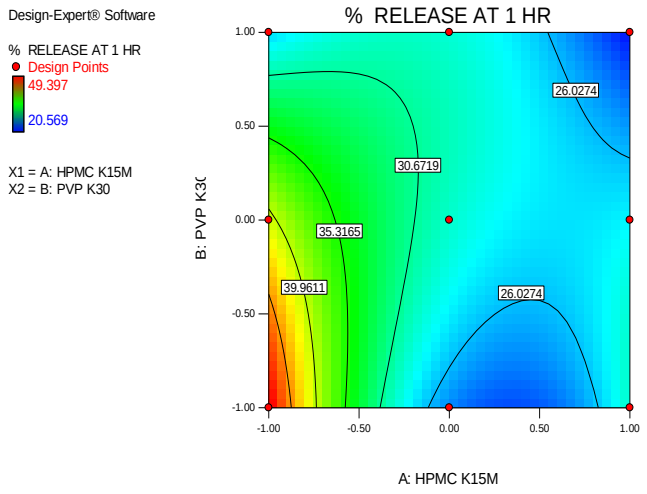


Figure-2(A)

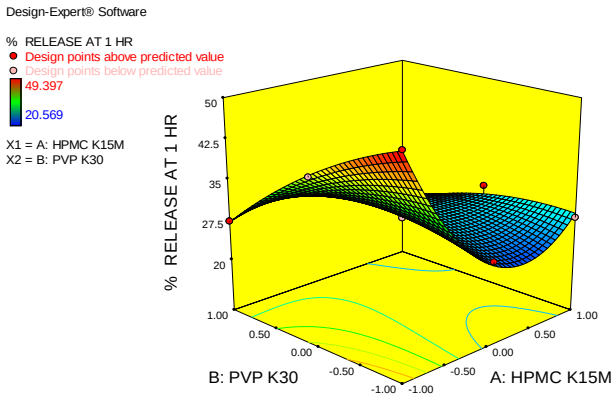


Figure-2(B)

The response surface plot (3-D) and the contour plot signify the effect of the amount of HPMC K-15M (X-1) and the PVP K-30 (X-2) on the response Y-2 (percentage of Met-HCl released in 2nd hr.). By keeping the amount of HPMC k-15M (X1) constant at the lowest level, increasing the level of PVP K-30 (X2), Y2 (percentage of released Met-HCl in 2nd hr.) decreases gradually.

Concurrently in the level of HPMC K-15M (X1), Y2 (percentage of released Met-HCl in 2nd hr.) decreases gradually. Therefore from the above observation it is clear that the effect of HPMC K-15M (X1) and PVP K-30 (X2) greatly affect Y2. So the formula should be optimized for controlling the release pattern.

Fig 3: RSM (3D) and contour showing the effect of the amount of HPMC K-15M (X1) and the amount of PVP K30 (X2) on the response Y2 (percentage of Met-HCl released in 2 hr).

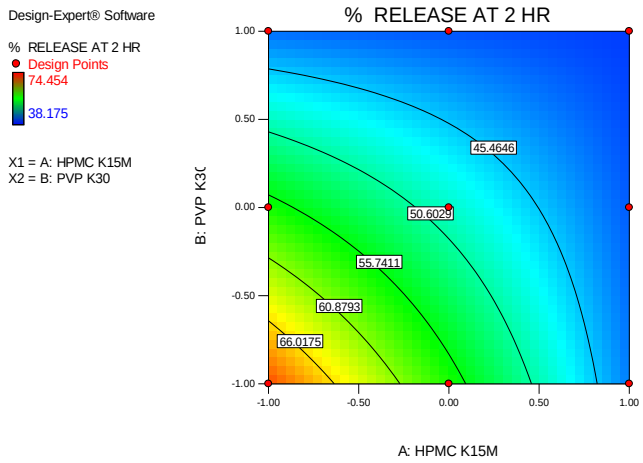


Figure-3(A)

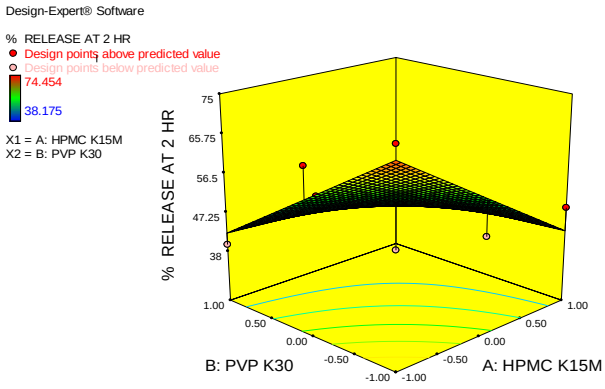


Figure-3(B)

The response surface plot (3D) and the contour plot signify the effect of the amount of HPMC K-15M (X-1) and PVP K-30 (X-2) on the response Y-3 (percentage of Met-HCl released in 4th hr.). By keeping HPMC K-15M (X-1) constant at the lowest level, increase of the level of PVP K-30 (X-2), Y-3 (percentage of Met-HCl released in 4th hr.) decreases gradually. Concurrently by keeping constant PVP K-30 (X2) at the lowest level, increase in the level of HPMC K-15M (X-1), also decreases Y-3 (percentage of Met-HCl released in 4th hr) gradually. Therefore from the above observation it can be said that the effect of HPMC K-15M (X-1) and PVP K-30 (X-2) greatly affect Y-3. So the formula should be optimized for controlling the release pattern.

Fig 4: RSM (3D) and contour showing the effect of the amount of HPMC K-15M (X1) and the amount of PVP K30 (X2) on the response Y3 (percentage of Met-HCl released in 4 hr).

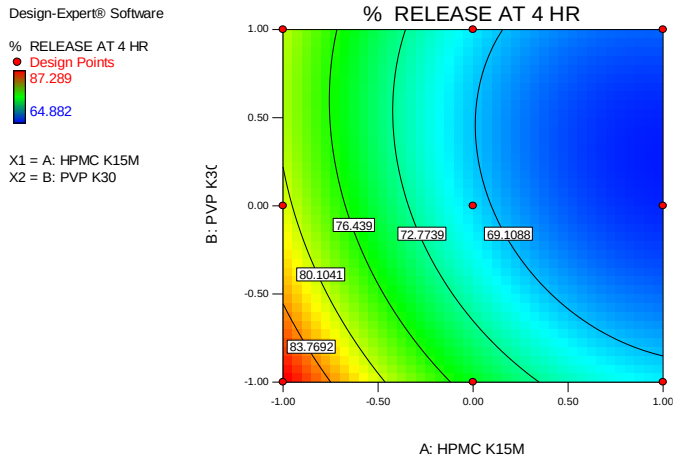


Figure-4(A)

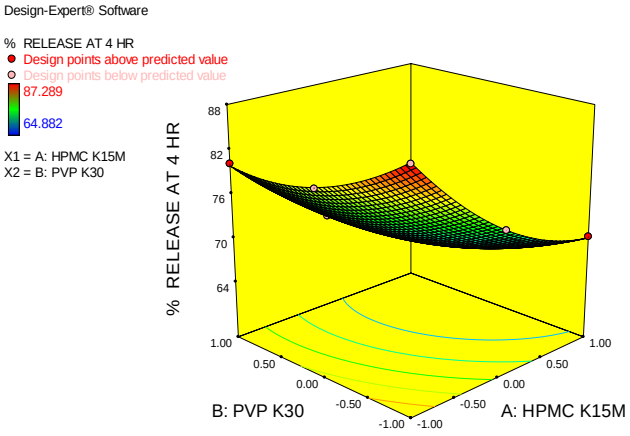


Figure-4 (B)

The response surface plot (3D) and the contour plot signify the effect of the amount of HPMC K-15M (X-1) and the PVP K-30 (X-2) on the response Y-4 (percentage of Met-HCl released in 6th hr.). This figure show with the increase in the level of (X1) keeping the level of (X2) fixed the percentage drug release at 6th hour increases. Similarly with the increase in the level of (X2), keeping the level of (X1) constant, the percentage drug release at 6th hour Y-4 also gradually increases. So it describes the effect of X1 and X2 on the percentage drug release (Y-4) affects greatly. Therefore the formulation should be optimized for controlling the release pattern.

Figure 5: RSM (3D) and contour showing the effect of the amount of HPMC K-15M (X1) and the amount of PVP K30 (X2) on the response Y4 (percentage of Met-HCl released in 6 hr)

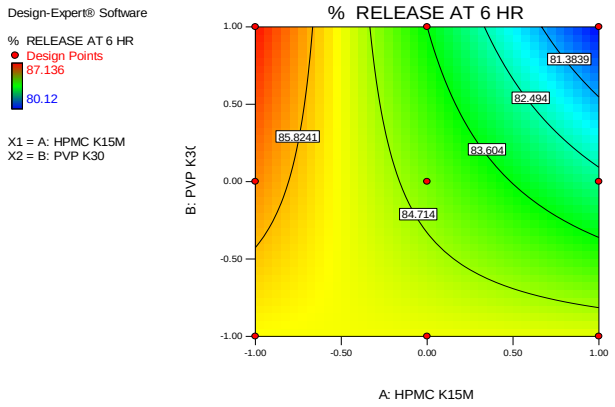


Figure-5(A)

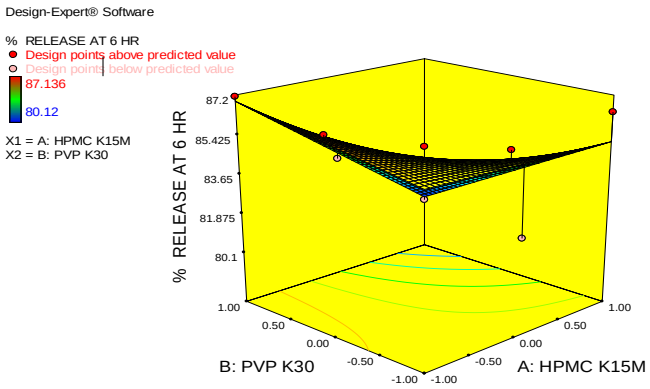
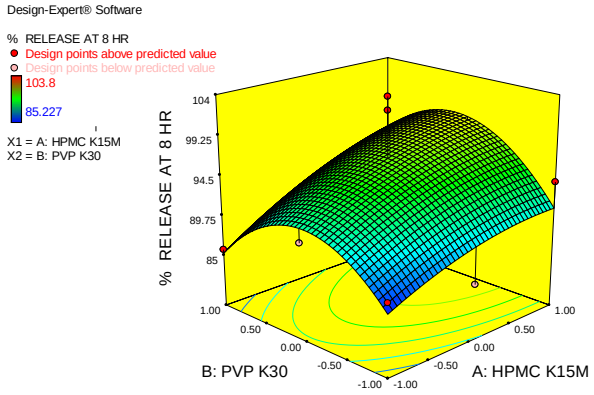


Figure-5(B)

The response surface plots (3D) and the contour plot signify the effect of the amount of HPMC K-15M (X-1) and the PVP K-30 (X-2) on the response Y-5 (percentage of Met-HCl released in 4th hr.). This figure shows that with the increase in the level of (X1) while keeping the level of (X2) fixed at the lowest level the percentage drug release at 8th hr. (Y-5) increases. Concurrently with the increase in the level of (X2), keeping the level of (X1) constant, the percentage drug release at 6th hour Y-5 increases up to a certain level and decreases after that. It signifies the effect of X1 and X2 on the percentage of drug released at 8th hr. (Y-5). So the formula should be optimized for controlling the release pattern.

Figure 6: RSM (3D) showing the effect of the amount of HPMC K-15M (X1) and the amount of PVP K30 (X2) on the response Y5 (percentage of Met-HCl released in 8 hr).



Formulation Optimization

After generating the model polynomial equation to relate the dependant and independent variable, the combination was optimized for all 5 responses. The final optimal experimental parameter were calculated using the optimization technique in this design expert software which allows to compromise among various responses and searches for a combination of factor level that jointly optimize a set of responses by satisfying the requirement of each responses in the set. In the study the optimization was performed with constraints for all five responses, present in Table-1. The optimal level and amount of two independent variable is given in the Table-4.

Table 4: Optimal level and amount of two independent variables.

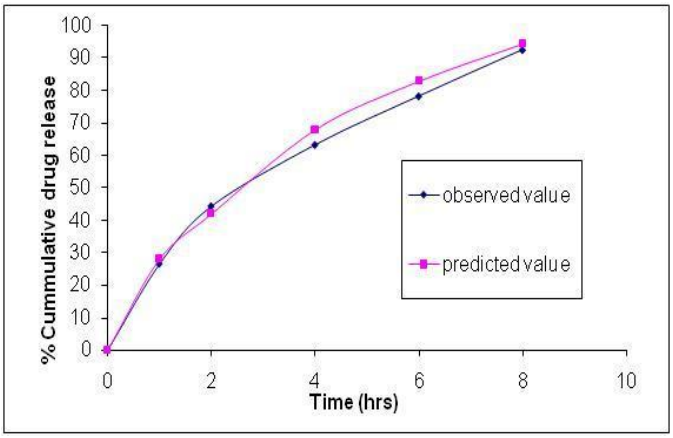
Independent Factor	Optimum Level	Optimum Amount
HPMC K-15M	0.30	360 mg
PVP K-30	0.84	96 mg

The observed and predicted responses along with the residual values for the drug release are summarized in the Table-5. Tests performed at optimal values of the analytical parameters had been investigated in the study. From the result presented in the table-5, it can be concluded that the optimized formulations ensure the release profile, which are reasonably close to the predicted values. Figure-7 represents the dissolution profile of observed and predicted values of optimal formulation.

Table 5: Observed and predicted responses (Y1, Y2, Y3, Y4 and Y5) and residual values for the drug test performed at optimal values of factors investigated

Response	Observed Response	Predicted Response	Residual Value
Y1	0	0	0
Y2	26.5321	28.0122	-1.4801
Y3	44.3258	41.9672	2.3586
Y4	63.2587	67.9032	-4.6445
Y5	78.2564	82.798	-4.5416

Figure 7: Comparison of observed dissolution profile and predicted dissolution of the optimal formulation obtained from the response surface methodology.



Validation of RSM Results

For all the checkpoint formulation, the results of all dependent response are found to be within in limits. Table -6 lists the level of the independent variables, their predicted and observed values of the percentage error in prognosis. Upon comparison of observed response with predicted response, percentage error views within the limits. The linear correlation plots drawn between the predicted observed responses demonstrated high value of R^2. Thus, the low magnitude of error as well as significant value of R^2 in the current study indicates a high prognostic ability of RSM.

DISCUSSIONS AND CONCLUSION

The method for drug release of Met-HCl from sustained release matrix tablet with optimum release properties was determined using experimental design methodology. After determination of significant parameters, the 3-level-2-factor full factorial experimental design was applied. Independent variables involved in the study were: amount of HPMC K-15M (X1) and PVP K-30 (X2). The chosen responses were a cumulative percentage of released Met-HCl in 1hr., 2hr, 4hr., 6hr., and 8hr. The levels of the factors were predicted to obtain an optimal response with reference to constraints. The observed responses were found to be sufficiently close to the predicted values for the optimized drug release method.

It was concluded that the Response Surface Methodology (RSM) and multiple response optimization utilizing a polynomial equation can be successfully used to design a sustained release formulation containing water soluble drug for predetermined release profile in a very short period of time and with less number of experimental runs. Therefore the final sustained release Met-HCl formulation with satisfactory release properties prepared with HPMC K-15M, PVP K-30 and other ingredients (Mg-stearate, Talc and starch) will be 500 mg, 360 mg, 96 mg, 5mg, 5 mg and q.s. appropriately to produce a total tablet weight of 1110 mg.

ACKNOWLEDGEMENT

The authors would like to thank M/s Stadmed Pvt. Ltd., Kolkata, India for providing API of Metformin HCl. Author Shubhasis Dan is acknowledging University Grants Commission (UGC) for financial support through UGC-BSR fellowship scheme.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

REFERENCE

1. Khuri AI, Cornel A.Response Surface, Design and Analysis. Journal of Pharmaceutical Science. 1987; 58.
2. Fonner DE, Buck BJ. Mathematical optimization technique in drug product. Design and process analysis. J. Pharm. Sci. 2006; 59:1587-1596.DOI: 10.1002/jps.2600591110
3. Singh B, Kumar R, Ahuja N. Optimizing drug delivery systems using systematic "Design of Experiments". Part 1: Fundamental aspects. Critical Rev Therapeutic Drug Carrier Syst. 2005; 22:27-105.
4. Streubel A, Siepmann J, Dashevsky A, Bodmeier R.pH-independent release of weakly basic drug from water insoluble and water soluble matrix tablets. J Control Release. 2000; 67:101-110.
5. Emami J. Taj AM, Ahmadi F.Preparation and In Vitro Evaluation of Sustained-Release Matrix Tablets of Flutamide Using Synthetic and Naturally Occurring Polymers.Iranian Journal of Pharmaceutical Research. 2008; 247-257.
6. Dan S, Pal TK. Sustained Release Matrix Tablet of Diltiazem Hydrochloride: Formulation Development, in-vitro Evaluation and Statistical Optimization by Response Surface Methodology (RSM). Electronic Journal of Biosciences. 2013; 1: 06-22.
7. Mondal U, Gouda 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.The Pharmaceutical Society of Japan. 2007; 1281-1290.
8. Khuri AI, Mukhopadhyay S. Response surface methodology.WIREs Comp Stat. 2010 ; 2 : 128–149.
9. Dzido TH, Soczewinski E, Gudej J. Computer-aided optimization of high-performance liquid chromatographic analysis of flavonoids from some species of the genus. J Chromatogr A. 1991; 550: 71-76.
10. Singh B, Ahuja N, Pahuja S, Kapil R. Formulation development of oral controlled release tablets of hydralazine: Optimization of drug release and bioadhesive characteristics.Acta. Pharm. 2009; 59. 1–13.
11. Hussen AS, Yu X, Johnoson RD. Application of neural computing in pharmaceutical product development. Pharma.res. 1991; 8; 1248-1252.
12. Takahara J, Takayama K, Nagai T.Multi-objective simultaneous optimization based on artificial neural network in sustained released formulation.J.Contr. Rel. 1997;49: 11-20.
13. De Boer JH, Bolhuis GK, Doornbos DA.Comparative evaluation of multicriteria decision aking and combined contour plots in optimization of directly compressed tablets.Eur. J. Pharm. Biopharm. 1991; 37.
14. Baba Y, Kura G.Computer-assisted retention prediction system for inorganic cyclic polyphosphates and its application to optimization of gradients in anion-exchange chromatography.J Chromatogr A, 1991; 550: 5—14.
15. Adinarayana K, Ellaiah P. Response surface optimization of the critical medium components for the production of alkaline protease by a newly isolated bacillus sp. J. Pharm Pharmaceut Sci. 2002; 5(3): 281- 287.
16. Vining GG, Myers RH.A graphical approach for evaluating response surface designs in terms of the mean squared error of prediction. Technometrics.1991; 33:315–326.
17. Singh B, Dahiya M, Saharan V, Ahuja N. Optimizing Drug Delivery Systems Using Systematic "Design of Experiments." Part II: Retrospect and Prospects. Critical Reviews in Therapeutic Drug Carrier Systems. 2005; 22(3):215–293.
18. Merchant HA, Harris M, Jaweria T. Once-Daily Tablet Formulation and In Vitro Release Evaluation of Cefpodoxime Using Hydroxypropyl Methylcellulose: A Technical Note.AAPS Pharm Sci Tech. 2006; 78.
19. Higuchi T. Rate of release of medicaments from ointment base containing drugs in suspension. J. Pharm. Sci. 1961; 50:874–875.
20. Wu T. Pan W, Chen J, Zhang R. Formulation optimization technique based on artificial neural network in salbutamol sulfate osmotic pump tablets. Drug. Dev. Ind. Pharm. 2000; 26:211-215.
21. B Schwartz, Flamholz JR, Press RH.Computer optimization of pharmaceutical formulations I: General procedure. J.Pharm.Sci. 1973; 62:1165-1170.
22. Sharma RN, Pancholi SS. Optimization techniques in pharmaceutical industry: A Review. Journal of Current Pharmaceutical Research. 2011; 7 (1): 21-28.
23. Fonner DE, Buck BJ. Mathematical optimization technique in drug product. Design and process analysis. J.Pharm.Sci. 2006; 59: 1587-1596.
24. Xu G, Sunada H. Influence of formulation change on drug release kinetics from hydroxypropyl methylcellulose matrix tablet. Chem Pharm Bull. 1995; 43:483-487.