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Formulation of Sustained Release Zolpidem Tartrate Matrix Tablets Through Optimization and Their Evaluation

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The object of the present study is to develop sustained release system of the hypnotic agent zolpidem useful for the treatment of insomnia. Matrix tablet is the least complicated device to sustain the release of drug candidates. Two polymers HPMCK4M and HPMCK15M were selected to sustain the release up to 12 h. 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), t_{50} %, k, amount of drug released in 12 h and mean dissolution time. Software Zorel was used to calculate the release kinetics. The design expert software was used to generate ANOVA for selected five responses. The optimum formulations were selected and the results obtained with the experimental values were compared with the predicted values. Furthermore, the *in vitro* and *in vivo* studies were performed with newly formulated sustained-release zolpidem tablets and were compared with conventional marketed tablet (zoldem). *In vivo* investigation in rabbits showed sustained-release pharmacokinetic profile of zolpidem from the matrix tablets formulated using combination of HPMCK4M and HPMCK15M. In conclusion, the results suggest that the developed sustained-release matrix tablets could provide quite regulated release of zolpidem tartrate up to nearly 12 h.

Key Words: Zolpidem tartrate, Matrix tablets, Sustained release, HPMC, Polymer, Factorial design.

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[1-3]. 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), t_{50} %, k, amount of drug released in 12 h and mean dissolution time (MDT)[4,5].

In particular zolpidem (ZP), N,N,6-trimethyl-2-*p*-tolylimidazol[1,2-a]pyridine-3-acetamide-L-(+)-tartrate (2:1), exhibits strong hypnotic and sedative action with negligible anxiolytic, muscle relaxant or anticonvulsant properties and is widely

prescribed for the treatment of the insomnia and sleep disorders. It binds in the central nervous system to GABAa receptors. The pharmacokinetic profile of zolpidem is characterized by rapid absorption from gastro intestinal tract and a short elimination half-life (2.5 h). Due to the short elimination half-life, the plasma drug concentration cannot be achieved during late hours of sleep. It could be useful to develop formulations enabling sustained release of this drug for elucidating the potential of zolpidem in the treatment of different insomnia categories.

Zolpidem is marketed in US, India and elsewhere in immediate release tablets. More recently, controlled release tablets have been introduced into the US market, which are two layer tablets and require use of specialized equipments.

Therefore, the object of the present study is to develop matrix tablets to provide sustained release of the drug content up to 12 h[6-11].

Matrix tablet is the least complicated approach in devising a sustained release dosage form. This 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[12-15].

In the current study different grades of HPMC like methocel K4M, K15M and K100M were selected during preliminary studies for regulating the release of zolpidem tartrate. Two polymers HPMCK4M and HPMCK15M were further selected for optimization studies[16,17].

EXPERIMENTAL

Zolpidem tartrate was obtained as a gift sample from Ranbaxy Labs. Ltd., Dewas, (M.P.), methocel (K4M, K15M, K100M) were provided by Colorcon India Ltd., Goa, dicalcium phosphate, microcrystalline cellulose (Avicel), 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 HPMC of different grades, keeping the total tablet weight constant at 120 mg. The tablets were prepared by direct compression. The values of response variables *viz*. n, released in 12 h, mean dissolution time, t_{50}, t_{70} and t_{80} % were studied to help in choosing the best possible combination for further optimization studies.

Factorial design: The 3^2 factorial design was 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, F2, F3, …, F9. The two polymers HPMCK4M and HPMCK15M were selected and their limits were chosen for subsequent detail studies using the factorial design. The amount of drug, magnesium stearate and talc were kept constant while dicalcium phosphate was taken in sufficient

quantity to maintain a constant tablet weight of 120 mg. 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) HPMC K4M	Factor (X2) HPMC K15M	Units
-1	Low	15	10	mg
0	Intermediate	20	15	mg
1	High	25	20	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) like mixing time, compaction force, *etc.*, were kept constant. Ten tablets from each batch were weighed individually and subjected to physical evaluation.

Dissolution studies: Dissolution studies were carried out for all the nine formulations in triplicate, employing dissolution apparatus, using distilled water pH 6.3 as the dissolution medium at 50 rpm and 37 ± 0.5 ºC. An aliquot of sample was periodically withdrawn at suitable time intervals and volume replaced with equivalent amounts of plain dissolution medium. The samples were analyzed at 245 nm.

Data analysis: The raw data obtained from *in vitro* dissolution was analyzed using the ZOREL 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 interval, log time, mid-point of time intervals and rate of drug release[18-20].

The software also calculates the kinetic constant (K), the diffusional release exponent (n) using logarithmic transformation, based on phenomenological analysis, the type of release, whether Fickian, non-Fickian (anomalous) or zero-order, was predicted. The software also calculates coefficient of determination (R^2), standard error of estimation (SEOE), significance test, 't' values and 'p' values. The response variables, which were considered for optimization included, n, mean dissolution time (MDT), release at 12 h, t_{50} %.

The design expert software generates the second order polynomial equation with added interaction terms to correlate the studied responses with the examined variables. The polynomial regression results were demonstrated using 3-D plots and contour plots.

Finally, the prognosis of optimum formulation was conducted in two stages. First, a feasible space was located and second, an exhaustive grid search was conducted to predict the possible solutions. Six optimum formulations were selected by the critical evaluation of the tabulated grid search values.

Validation of the predicted 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.

***In vivo* evaluation:** *In vivo* evaluation was carried out in rabbits for selected optimized formulation of zolpidem tartrate tablet in comparison with one marketed conventional formulation. Evaluation was carried by established HPLC method to check the bioavailability of the formulation[21,22]. Analyses were performed on a Shimadzu (Japan) liquid chromatographic system composed of SPD-M 10 AVP variable wavelength detector, LC-10 ATVP pump and analytical column C_{18}.

Rabbits of either sex weighing (2.2-2.6 kg) were divided into two groups each consisting of three animals. First group received marketed tablets and second group received the formulated optimized tablets. Food was withdrawn from the rabbit 12 h before drug administration. All rabbits had free access to water throughout the study. The institutional animal ethical committee approved the protocol for this study.

HPLC assay: The quantitative determination of drug in plasma was performed by HPLC assay using the mobile phase acetonitrile and disodium hydrogen phosphate in the ratio 40:60. Before analysis, the mobile phase was filtered and degassed. The flow rate was adjusted at 1.2 mL/min. All determination was performed at 245 nm wavelengths at room temperature.

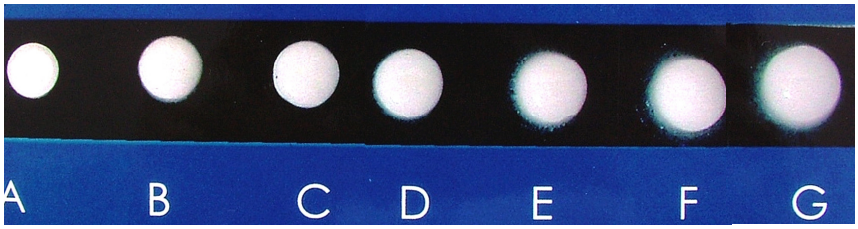
Bioavailability studies: Blood samples were collected in tubes from marginal ear vein at defined time intervals. Collected blood was centrifuged at 5000 rpm for 5 min (Remi equipment, Mumbai, India). Plasma was separated then acetonitrile was added for protein precipitation. The tubes were centrifuged for 5 min at 5000 rpm. The supernatant layer was filtered through 0.45 μm filter and the sample was reconstituted with 500 μL of mobile phase and again agitated for 30 s. The drug concentration in the sample was then determined by assay.

***In vitro-in vivo* correlations:** Model independent pharmacokinetic parameters were computed from blood level data. Subsequently by plotting per cent of drug release *versus* per cent of drug absorbed the *in vitro-in vivo* correlation performed.

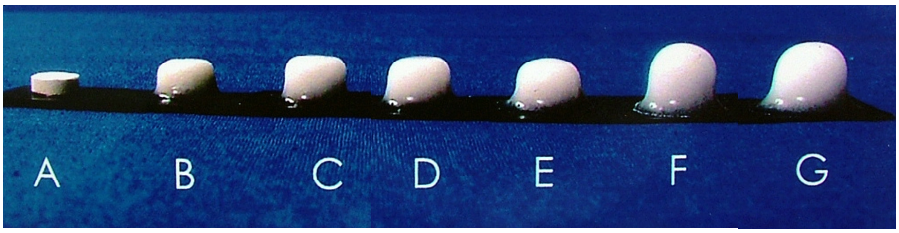
RESULTS AND DISCUSSION

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.

Fig. (1a and 1b) shows the swelling behaviour of zolpidem matrix tablet formulations at different time intervals, the top view and side view, respectively. The top view shows the radial swelling increase and the side view indicates the axial swelling increase with the increase in dissolution time (coded in Fig. 1 as A-G from 1-12 h time intervals).



(a) To view



(b) Side view

Fig. 1. Swelling behavior of zolpidem, matrix tablet formulations at different time intervals

Physical evaluation and assay of tablet: The tablet weights of all the nine batches vary between 120 and 125 mg, diameter between 6.8-6.81 mm, thickness between 2.8-2.81 mm and tablet hardness between 5.5-5.9 Kg. The assay values varied between 95.83-98.75 %. The tablet friability ranged between 0.5-0.8 %. 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-2. Fig. 2 shows the release pattern between per cent drug releases *versus* time.

TABLE-2
DISSOLUTION PARAMETERS OF (K4M-K15M) POLYMER COMBINATIONS WITH DIFFERENT RATIOS DURING OPTIMIZATION STUDIES USING 3^2 FACTORIAL DESIGN

Formulation code	n	K	MDT	Released in 12 h	Released in 24 h	t_{50} %	t_{60} %	t_{80} %	t_{90} %	da/dt
F1	0.556	0.298	3.148	103.35	–	2.529	3.509	5.885	7.272	1.457
F2	0.529	0.279	3.827	93.71	–	2.987	4.214	7.251	9.056	1.244
F3	0.514	0.243	5.302	89.90	–	4.057	5.782	10.116	12.719	1.013
F4	0.501	0.252	5.219	91.25	–	3.918	5.639	10.019	12.677	1.167
F5	0.476	0.250	5.907	88.08	–	4.268	6.261	11.464	14.686	1.009
F6	0.471	0.247	6.248	84.47	102.62	4.479	6.597	12.149	15.600	0.955
F7	0.469	0.251	6.063	86.23	103.34	4.338	6.395	11.797	15.158	0.977
F8	0.450	0.229	7.945	75.26	86.18	5.536	8.266	15.559	–	0.834
F9	0.428	0.250	7.595	74.39	94.50	5.018	7.683	15.045	19.811	0.862

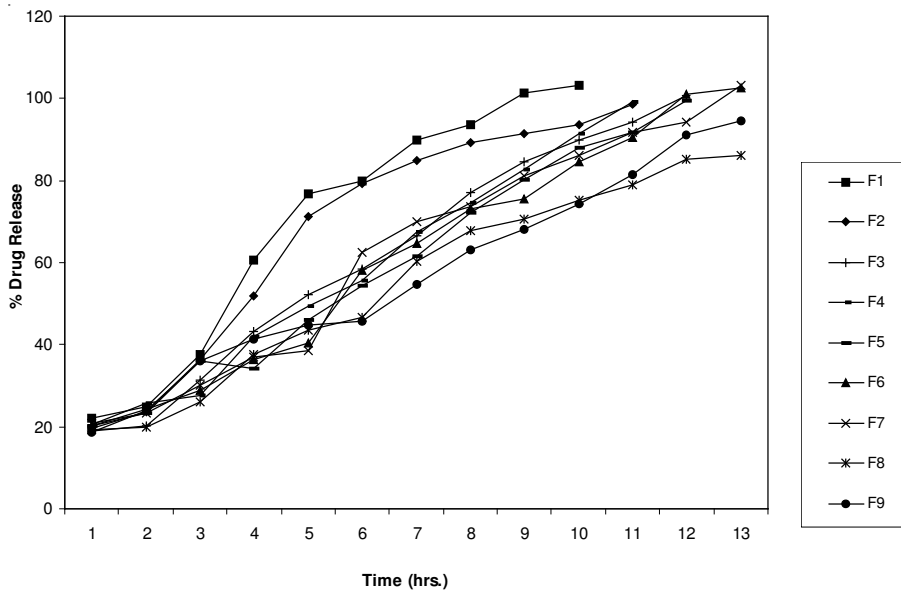


Fig. 2. Plot between per cent drug release and time for combinations as per factorial design

Response surface analysis-calculation of coefficient: The coefficients of the polynomial equations for five responses n, k, released in 12 h, mean dissolution time and t_{50} % are listed Table-3 along with their values of R^2. Five coefficients (B_1-B_4) were calculated with B_0 as the intercept. Since the values of R^2 are quite high for released in 12 h, t_{50} %, n and mean dissolution time, so for these responses, the polynomial equations form excellent fits to all the experimental data and statistically valid.

TABLE-3
VALUES OF THE COEFFICIENT FOR THE POLYNOMIAL EQUATIONS AND R^2 FOR VARIOUS RESPONSE VARIABLES OF THE FORMULATIONS

Coefficient	n	MDT	Released in 12 h	t_{50} %	k
B_0	0.490	5.700	87.400	4.130	0.260
B_1	-0.038	1.510	-8.780	0.840	-0.012
B_2	-6.156	0.097	0.530	0.096	-6.078
B_3	-0.018	0.690	-4.480	0.390	-8.844
B_4	-1.989	0.200	-1.720	0.140	-2.578
R^2	0.989	0.944	0.967	0.891	0.637

MDT = mean dissolution time

Further the model diagnostic plots are plotted to investigate the goodness of fit of the proposed model. Actual *versus* predicted, graph was plotted between the actual and the predicted response values. Residual *versus* predicted, graph was also plotted. Residual (or error) is the magnitudinal difference between the observed and the predicted response(s). These plots were obtained by use of software and shown in Fig. 3 for various responses.

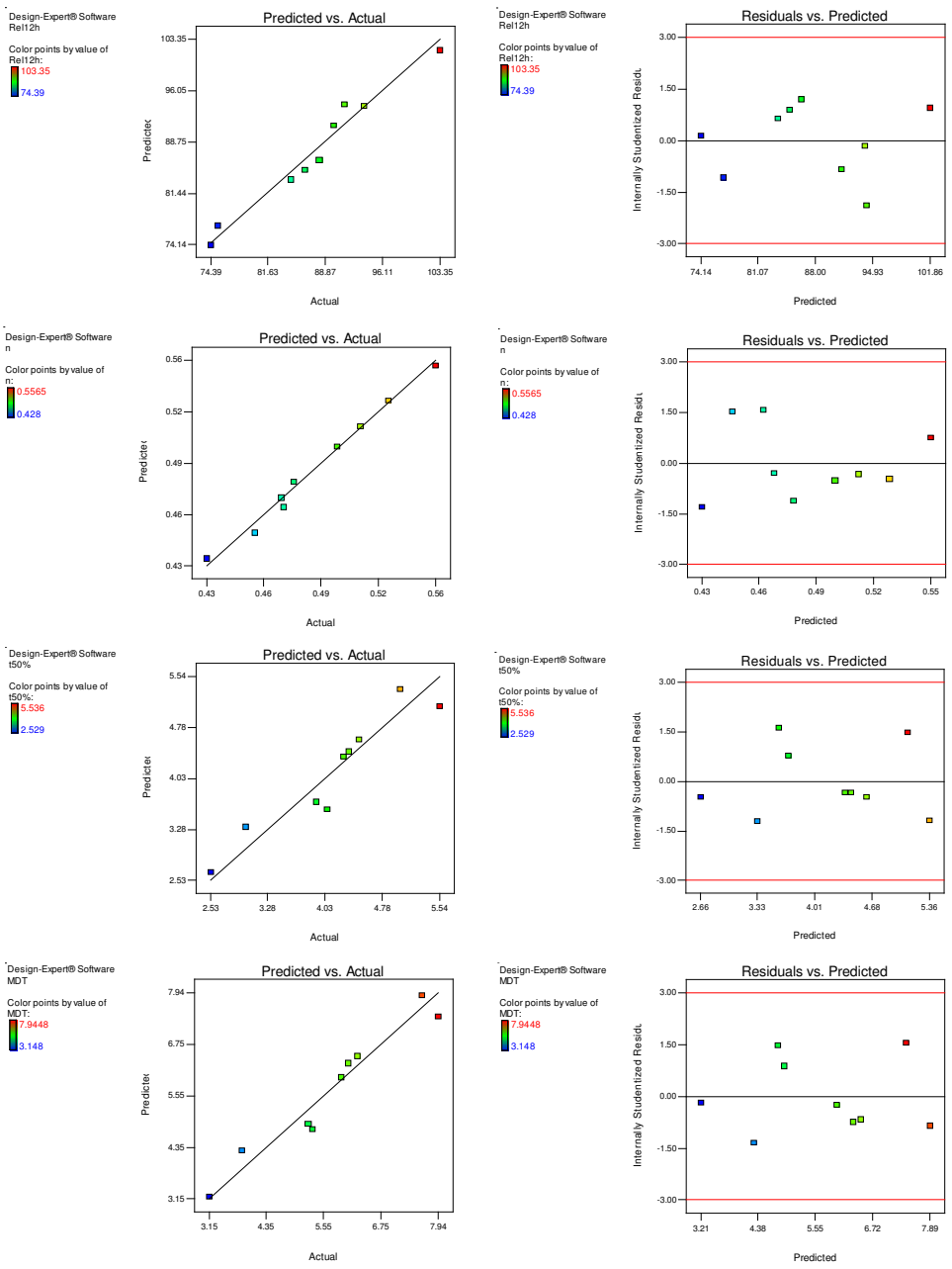
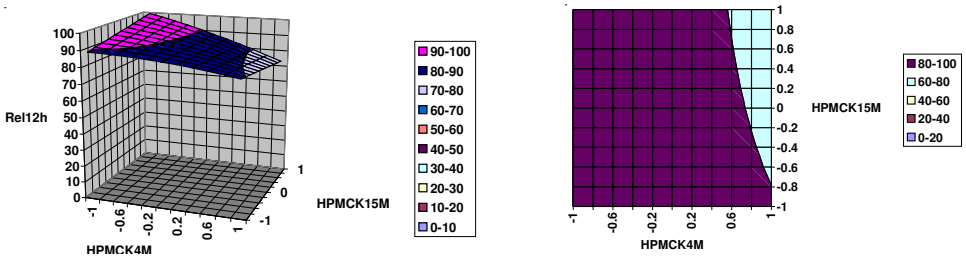


Fig. 3. Plots between actual and predicted responses

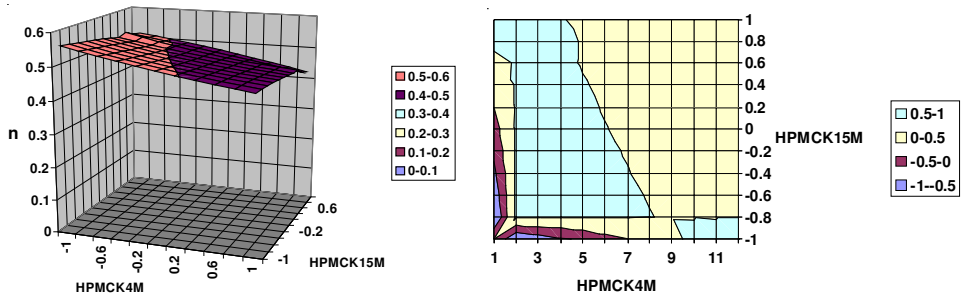
Search for optimum formulations: The criterion for selection of suitable feasible region (shown with highlighted cells) was primarily based on highest possible values of n, released in 12 h, mean dissolution time and t_{50} %. Two regions were selected on the basis of following criteria.

Region 1: Released in 12 h > 95 %; n > 0.50; MDT > 3.1; t_{50} % > 2.5 h
Region 2: Released in 12 h > 96.9 %; n > 0.52; MDT > 4.1; t_{50} % > 3.5 h

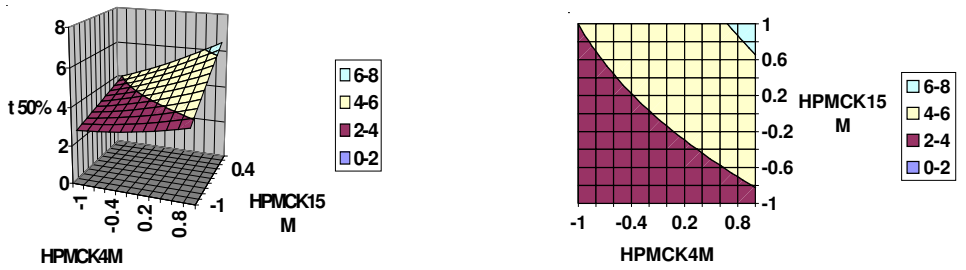
The response surface plot and contour plots known to facilitate an understanding of the contribution of the variables and there interactions are shown in Fig. 4.



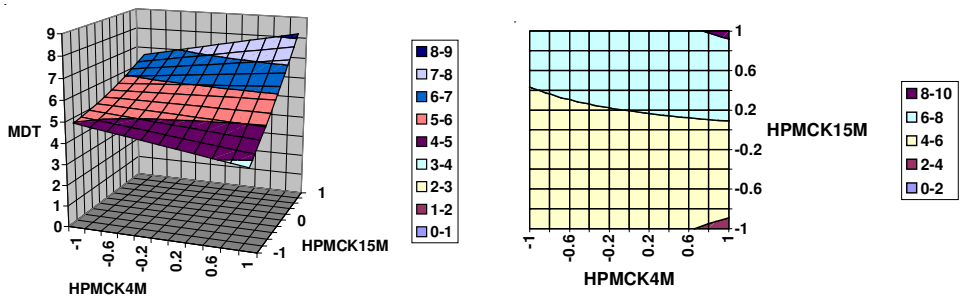
Response surface and contour plots for values of released in 12 h



Response surface and contour plots for values of n



Response surface and contour plots for values of t_{50} %



Response surface and contour plots for values of MDT

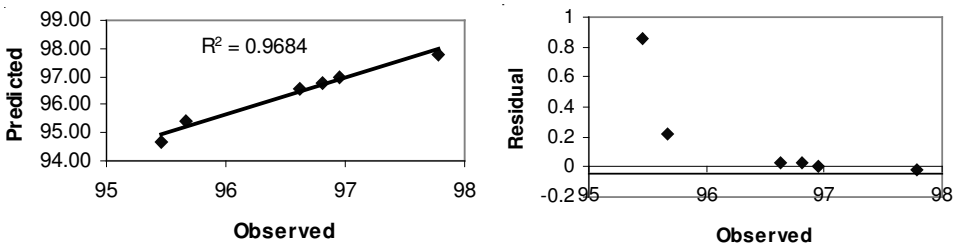
Fig. 4. Response surface and contour plots for various responses

Validation of optimum formulation: The results of the physical evaluation and tablet assay of the optimized formulation were within limits. Dissolution parameters like n, k, mean dissolution time, released in 12 h and k were tabulated for six optimized matrix tablets formulation coded A-F and shown in Table-4.

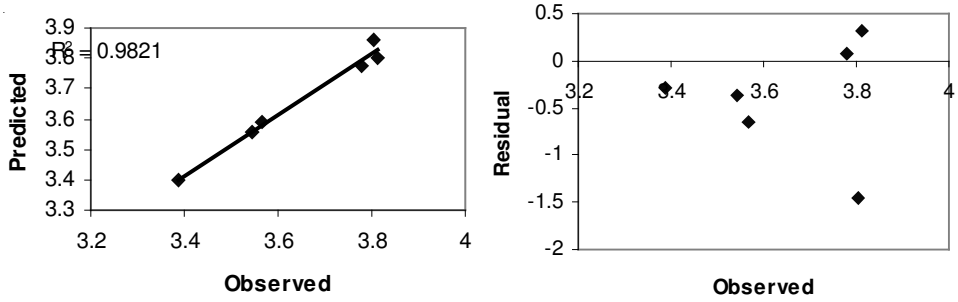
TABLE-4
VALUES OF RELEASE PARAMETERS OF SIX OPTIMIZED MATRIX TABLET FORMULATIONS OF ZOLPIDEM TATRATE USING DIFFERENT AMOUNTS OF HPMCK4M AND HPMCK15M

Formulation composition			n	k	MDT	Released in 12 h	t_{50} (%)
HPMC K4	HPMC K15	Code					
14.4	12.0	A	0.522	0.260	4.090	97.80	3.859
14.4	11.2	B	0.521	0.249	4.118	96.94	3.777
15.0	4.0	C	0.533	0.242	4.271	94.65	3.557
15.0	4.8	D	0.531	0.237	4.246	95.45	3.589
13.8	12.0	E	0.538	0.246	4.149	96.79	3.675
13.8	11.2	F	0.519	0.253	4.175	96.60	3.800

Actual *versus* predicted and residual *versus* observed, graph was also plotted between the actual and the predicted responses of optimized formulations Fig. (5a-5d). Comparisons of the observed responses with that of the anticipated responses along with percentage error were done (Table-5). As per cent error in prognosis was minimum, hence the prognostic ability of matrix tablet formulations of zolpidem tartrate using RSM optimization validated.



(a)



(b)

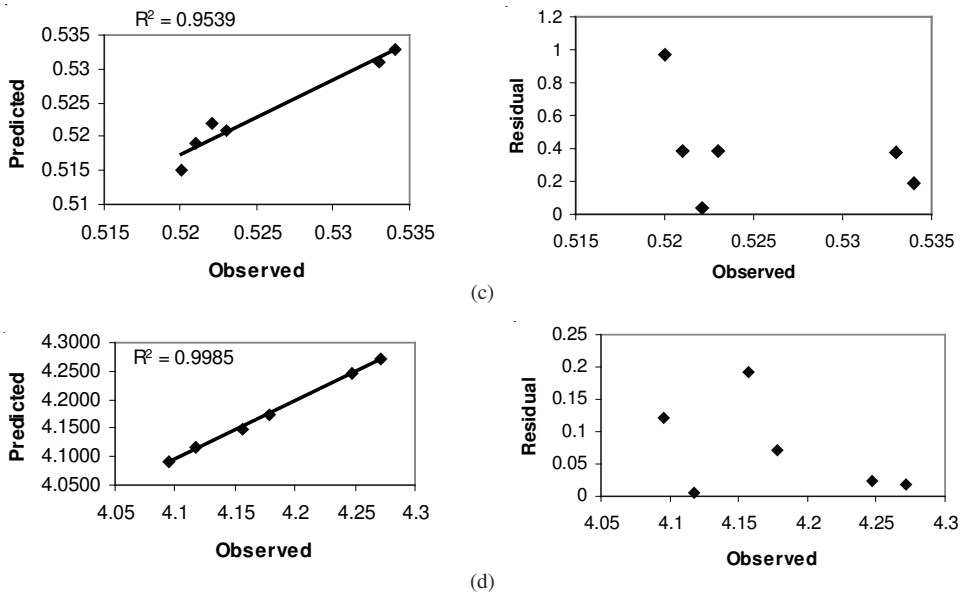
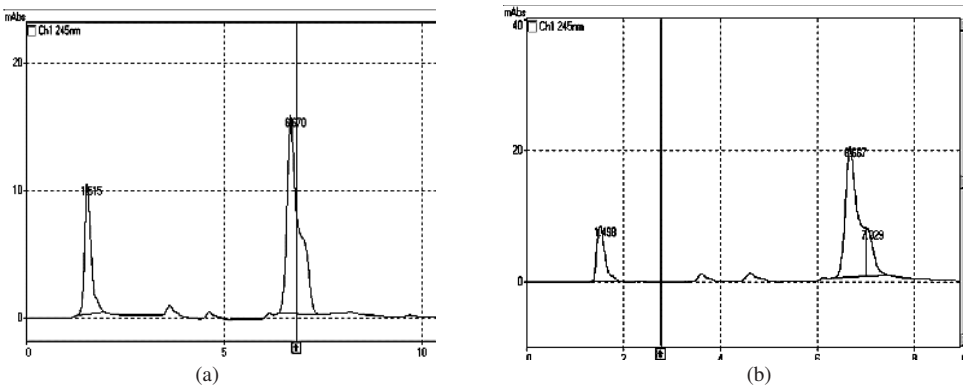


Fig. 5. (a) Linear and residual plots between observed and predicted values of released in 12 h. (b) Linear and residual plots between observed and predicted values of t_{50} %. (c) Linear and residual plots between observed and predicted values of n. (d) Linear and residual plots between observed and predicted values of mean dissolution time

***In-vivo* evaluation:** Plasma concentration and pharmacokinetic parameters after oral administration of one optimized matrix tablets and conventional tablets were summarized (Table-6). Chromatogram and peak reports of plasma concentration were obtained by HPLC at different intervals [Fig. (6a-6e)]. The following parameters were calculated using non compartmental model: area under the plasma concentration-time curve from zero to last measurable zolpidem concentration sample time, maximum plasma drug concentration (C_{max}) and time to reach C_{max} (T_{max}). The values of C_{max} and T_{max} were obtained directly from the concentration curve and AUC was calculated (Fig. 7).



(a) (b)

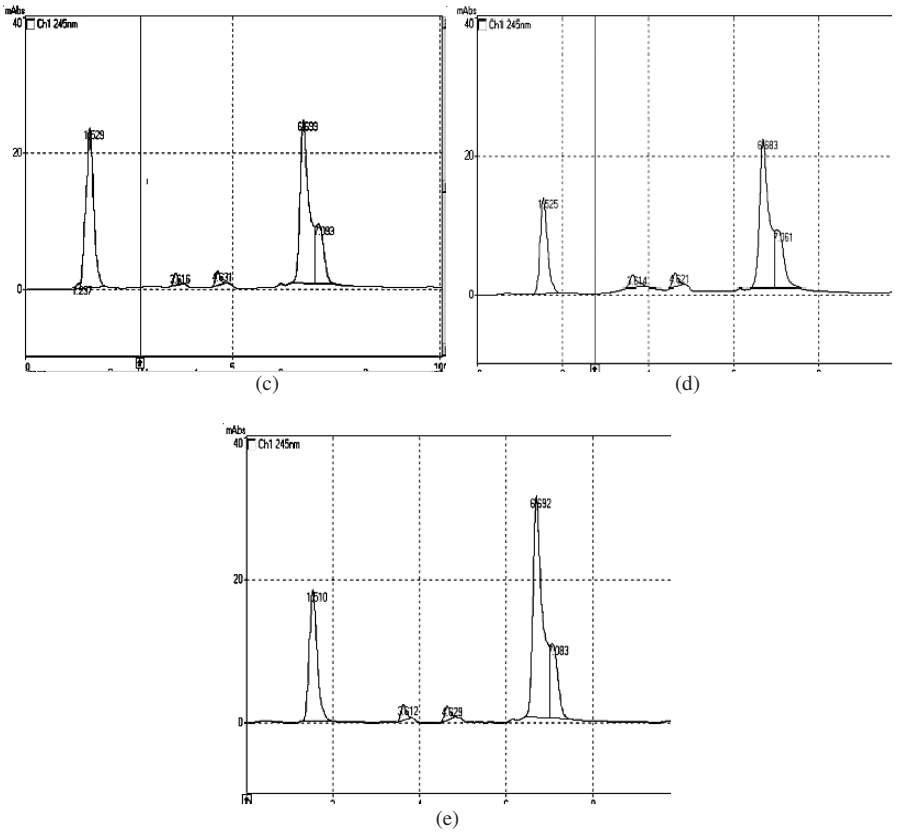


Fig. 6. Chromatogram of plasma concentration by HPLC at different intervals

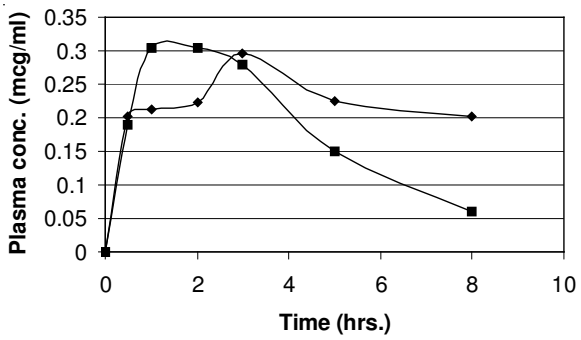


Fig. 7. Plasma concentration time profile of optimized batch of matrixtablet and conventional tablet after oral administration

***In-vitro-in-vivo* correlation:** A good correlation between the dissolution profile and bioavailability was observed. *In vitro-in vivo* correlation was determined by plotting a graph showing the fraction of drug absorbed *versus* the fraction of drug released *in vitro* (Fig. 8).

TABLE-5
COMPARISON OF EXPERIMENTAL RESULTS WITH PREDICTED RESPONSES FOR ZOLPIDEM TABLETS

Composition HMPCK4/ HPMCK15M	Response	Predicted value	Experimental value	Percentage error
14.4/12	Released in 12 h	97.78	97.800	-0.020
	t_{50} %	3.803	3.859	-1.451
	n	0.522	0.521	0.038
	MDT	4.095	4.090	0.122
14.4/11.2	Released in 12 h	96.949	96.94	0.009
	t_{50} %	3.780	3.777	0.079
	n	0.523	0.521	0.384
	MDT	4.118	4.117	0.005
15/4	Released in 12 h	95.46	94.65	0.858
	t_{50} %	3.544	3.557	-0.365
	n	0.534	0.533	0.188
	MDT	4.271	4.270	0.019
15/4.8	Released in 12 h	95.660	95.45	0.223
	t_{50} %	3.566	3.589	-0.641
	n	0.533	0.531	0.377
	MDT	4.247	4.246	0.024
13.8/12	Released in 12 h	96.812	96.790	0.023
	t_{50} %	3.386	3.396	-0.294
	n	0.520	0.515	0.971
	MDT	4.157	4.149	0.193
13.8/11.2	Released in 12 h	96.626	96.600	0.027
	t_{50} %	3.812	3.800	0.316
	n	0.521	0.529	-1.512
	MDT	4.178	4.175	0.071

TABLE-6
PHARMACOKINETIC PARAMETERS

	AUC	C_{max}	T_{max}
Conventional tablet	0.154 ± .01	0.305 ± 0.3	1.8 ± 0.2
Optimized tablet	0.179 ± 0.2	0.296 ± 0.1	2.5 ± 0.3

The dissolution data indicates that as the content of HPMCK4M and HPMCK15 increased, the value of n was found to decrease, except when HPMCK4M content increased from intermediate to high level. 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 value remained practically invariant ranging from 0.2295-0.2983. This is in accordance with the characteristic nature of the kinetic constant, which is a function of the proportion of the matrix polymer *viz.*, solubility, molecular weight, viscosity, *etc*. It depicts insignificant change in overall polymer characters.

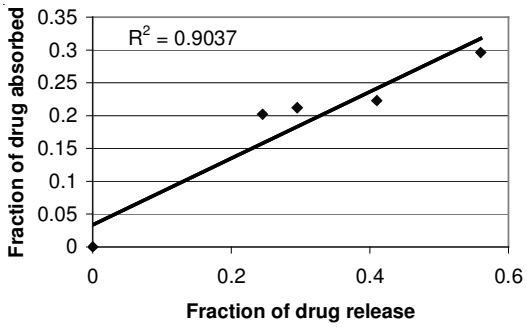


Fig. 8. Fraction of drug absorbed *versus* fraction of drug release (*in vitro-in vivo*) co-relation for optimized batch of matrix tablets

The values of drug released in 12 h 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 HPMCK15 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 mean dissolution time showed that with increasing total polymer content resulted in the increase of mean dissolution time. Mean dissolution time is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. The 3D response surface plots and contour plots demonstrated the graphical representation of results.

Comparisons of the observed responses with that of the anticipated responses along with percentage error for dissolution parameters like n, k, mean dissolution time, drug released in 12 h and k of six optimized matrix tablets formulation shows the prognostic ability of matrix tablet formulations of zolpidem tartrate using RSM optimization method and is validated.

Bioavailability studies shows that no sustained blood level of zolpidem was evident after oral administration of the conventional formulation. Although, plasma concentration time was characterized significantly by higher plasma concentration after 2 h of administration followed by decline in plasma concentration.

The formulated matrix tablets showed significantly lower C_{max} then conventional tablet and required significantly more time to reach C_{max} (T_{max} 2.5 h) as compared with conventional tablets (T_{max} 1.8 h). However the tablets maintained extended constant plasma concentration up to 12 h.

A high value of correlation R^2 (0.9037) suggested good correlation between *in vitro-in vivo* data.

Conclusion

Zolpidem tartrate 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 RSM optimization method and validated. Results of bioavailability studies confirm lower C_{max} and significant more T_{max} (2.5 h) of formulated matrix tablets in comparison to conventional tablets. A high value of R^2 0.9037 confirms the *in-vivo-in-vitro* correlation at level A between fraction of drug absorbed and fraction of drug release.

Conclusively, the current study attained the successful design, development and optimization of formulation of zolpidem tartrate matrix tablets.

REFERENCES

1. J. Swarbric and J.C. Boylan, Encyclopedia of Pharmaceutical Technology, Marcel Dekker, New York (1995).
2. S. Bolton, Pharmaceutical Statistics: Practical and Clinical Applications, Marcel Dekker Inc, New York, edn. 2 (1990).
3. G. Banker and C. Rhodes, Modern Pharmaceutics, Marcel Dekker, New York (1996).
4. G.A. Lewis, D. Mathieu and R. Phan-Tan-Luu, Pharmaceutical Experiment Design (Drugs and Pharmaceutical Sciences), Marcel Dekker, Inc., New York (1999).
5. G. Box, C. Connor, W. Cousins, O. Davies, F. Himsworth and G. Sillito, The Design and Analysis of Industrial Experiments, in eds.: O.L. Davies, Oliver and Boy, London, edn. 2 (1960).
6. G. Trapani, A. Lopedota, G. Boghetich, A. Latrofa, M. Franco, E. Sanna and G. Liso, *Int. J. Pharm.*, **268**, 47 (2003).
7. G. Trapani, M. Franco, A. Latrofa, M.R. Pantaleo, M.R. Provenzano, E. Sanna, E. Maciocco. and G. Liso, *Int. J. Pharm.*, **184**, 121 (1999).
8. D.J. Greenblatt, E. Legangneux, J.S. Harmatz, E. Weinling, J. Freeman, K. Rice and G.K. Zammit, *J. Clin. Pharmacol*., **46**, 1469 (2006).
9. E. Weinling, S. McDougall, F. Andre, G. Bianchetti and C. Dubruc, *Fundam. Clin. Pharmacol.*, **20**, 397 (2006).
10. R.L. Barkin, *Am. J. Ther.*, **14**, 299.
11. G. Zammit, *Exp. Opin. Drug Toxicol.*, **4**, 325 (2008).
12. H. Liberman, L. Lachman and J. Schwartz, Pharmaceutical Dosage Forms: Tablets, Vol. 1, edn. 2 Revised and Expanded, Dekker, New York (2005).
13. H. Liberman, L. Lachman and J. Schwartz, Pharmaceutical Dosage Forms: Tablets, Vol. 3, edn. 2 Revised and Expanded, Dekker, New York (2005).
14. Remington, The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, Vol. 1, edn. 20 (2000).
15. A. Kuksal, A.K. Tiwary, N.K. Jain and S. Jain, *AAPS Pharm. Sci. Tech*., 7(1): Article, (2006).
16. K.V.R. Rao and K.P. Devi, *Int. J. Pharm*., **48**, 1 (1988).
17. M. Efentakis, M. Vlachou, N.H. Choulis, *Drug Dev. Ind. Pharm.*, **23**, 107 (1997).
18. B. Singh and S. Singh, *Ind. J. Pharm. Sci*., **60**, 358 (1998).
19. B. Singh and N. Ahuja, *Drug Dev. Ind. Pharm*., **28**, 431 (2002).
20. B. Singh and R.K. Gupta, FACTOP: A Software Aid to Optimize Pharmaceutical Dosage Forms through Factorial Design in 48th Indian Pharmaceutical Congress, Chennai, p. AP63 (1996).
21. B.A. El Zeany, A.A. Moustafa and N.F. Farid, *J. Pharma. Biomed. Anal.*, **33**, 393 (2003).
22. L. Laviana, C. Mangas, F. Fernandez-Mari, M. Bayod and D. Blanco, *J. Pharma. Biomed. Anal*., **36**, 925 (2004).

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