INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

ISSN: 2320-2831

IJPAR |Vol.10 | Issue 3 | July - Sep -2021
Journal Home page: www.ijpar.com

Research Study *Open Access*

Formulation and evaluation of bilayer matrix tablets of rosuvastatin calcium and glimipiride for type II diabetes mellitus

Neethu Vijayan [1*],Jacob P[2],Jose S [3], Sari S Nair[4], Meena Kurup[5]

[1]Assistant professor, Al AzharCollege of pharmacy, Perumpillichira p o, Thodupuzha, Kerala, India.*
[2]Associate Professor, Department of pharmaceutical sciences, Regional institute of medical sciences, Centere for professional and advanced studies, Rubber board P O, Kottayam, India.
[3]Professor, Caritas College of pharmacy, Caritas educity, 101 junction, Ettumanoor, Kerala 686 631, India.
[4]Associate professor, Al Azharcollege of pharmacy, Perumpillichira P O, Thodupuzha, Kerala, India.
[5]PhD scholar , vinayaka missions college of pharmacy, Salem, Tamilnadu, India

[*]**Address for correspondence: Neethu Vijayan**
Email: neethuvijayankr1991@gmail.com

ABSTRACT

Theaim of the present work was to develop a bilayer matrix tablet for type II diabetes mellitus which contain Glimepiride sustained release layer and Rosuvastatin Calcium immediate release layer. Sustained release layer of Glimepiride was optimised using Box-behnkendesign, a common analytical method for quantitative combined drug estimation was employed and evaluated. Hydroxy propyl methyl cellulose and Ethyl cellulose were used as polymers inorder to get the sustained release profile over a period of 12 h. Tablets were evaluated for physical properties, drug content and in vitro drug release. The excipients used in this formulation did not alter physicochemical properties of drug as tested by FTIR. Stability of the formulation at 60 days in room temperature shows no significant variation in appearance, hardness, drug content and in vitro drug release. This formulation also exhibited the best fitted formulation in zero order kinetics and non-Fickian transport. Bilayer tablet prepared from the optimised formula was found to be best suited method for fixed dose combination of sustained release Glimepiride and immediate release Rosuvastatin Calcium for type II diabetes mellitus.

Keywords: Bilayer matrix tablet, Glimepiride, Rosuvastatin Calcium, sustained release, Box-behnken design

INTRODUCTION

Type II Diabetes mellitusis characterized by insulin resistance, a condition in which cells fails to respond to insulin properly[1]. Stat in treatment is beneficial in managing patients with diabetic mellitus, which are able to control the multi factorial atherosclerosis observed in diabetes. Combination of statin with antidiabetic drug is more beneficial in reducing the morbidity and mortality associated with diabetes. But the low patient compliance and high cost are the main barriers for multiple drug therapy.[2,3]

In the last decades interest in developing a combination of two or more Active Pharmaceutical Ingredients in a single dosage form (bi-layer tablet)

has increased in the pharmaceutical industry, promoting patient compliance and convenience.[4] Glimepiride is an antidiabetic drug which provide a brisk release of insulin from pancreas, Glimepiride also produces an increase in sensitivity of peripheral tissues to insulin via extra pancreatic mechanism[5]. Rosuvastatin calcium is a hypolipidemic agent, which is a competitive in hibitor of HMG-CoAreductase. The overall effect of Rosuvastatin calcium is a decrease in plasmaLDL and VLDL.[6]

In the present work bi-layer tablet of Rosuvastatin calcium as an immediate release and Glimepiride as sustained release was prepared by wet granulation and direct compression method respectively. Box-behkendesignwasappliedtostudytheeffectofformulationandprocessvariables.Concentration of HPMC, EC and MCC were selected as independent variables. The R^2 value of zero order release kinetics and % cumulative drug release at 11-12 hour were selected as dependent variables.

MATERIALS AND METHODS

Rosuvastatin Calcium was a gift sample from CTX Life sciences pvt.ltd, Surat. Glimepiride and MCC were received as a gift sample from Sangrose lab pvt.ltd, Mavelikkara. HPMC was a gift sample from Sancepvt.ltd, Koyttayam. Ethyl cellulose was purchased from Yarrowchemprdts, Mumbai.

Preformulation studies

Compatibility studies

The compatibility studies were carried out at room temperature by FTIR to determine the interaction of Rosuvastatin calcium with Glimepride and both drugs with the polymers used in the formulation. The FTIR Spectra of drugs alone, combination of drugs and combination of drugs with polymers were taken. The samples were analyzed in Shimadzu IR Spectra Analyzer.

Angle of repose

A funnel was filled to the brim and the powder blends were allowed to flows moothly through the orifice under gravity. From the cone formed on a graph sheet was taken to measure the area of pile, thereby evaluating the flow ability of the granules. Height of the pile was also measured.

$$\theta = \tan^{-1}(h/r)$$

Where, θis the angle of repose, his height of pile
ris radius of the base of pile

Bulk density (Db)

The weighed amount of powder blends were passed through sieve No.18 transferred into a dry 25 mL cylinder. Carefully levelled the powder without compacting and read the unsettled apparent volume, V_0, to the nearest graduated unit and calculated the bulk density in g per mL by the formula.

$$\text{Bulk Density, } Db = M/V_0$$

Where M = mass of the powder sample
V_0 = unsettled volume

Tapped density (Dt)

The weighed amount of powder blends was passed through Sieve No.18 and transferred into a dry 25 mL glass graduated cylinder. The cylinder was tapped initially 200 times from a distance of 14 ± 2 mm. The tapped volume (V_a) was measured to the nearest graduated unit. The tapping was repeated additional 200 times. Again the tapped volume (V_b) was measured to the nearest graduated unit. Asthe difference between the two volumes is less than 2%, V_{bis} the final tapped volume,V_f. the tapped density was calculated, in g per mL, by the formula.

$$\text{Tapped Density, } Dt = M/Vf$$

Where M = mass of the powder sample
Vf = Final tapped volume

Carr's compressibility index(I)

Carr's compressibility index (I), is an indication of the ease with which a material can be induced to flow. It is expressed in percentage. Carr's "percent compressibility" is calculated by the equation,

$$compressibilityIndex, I = \frac{TappedDensity - BulkDensity \text{X} 100}{TappedDensity}$$

Hausner's ratio

Hausner's ratio is an index of ease of powder flow; it is calculated using the formula,

Hausner's ratio =Tapped density/Bulk density

Preparation of immediate release layer

The immediate release tablets of Rosuvastatin calcium were designed as per the composition given in Table 1 and prepared by wet granulation method. All the ingredients were passed through sieve No. 40 separately. The drug, half of the quantities of super disintegrant (crospovidone) and other ingredients were mixed geometrically. This premix blend was wet granulated with 10% of maize starch. The wet mass was passed through sieve No. 10. The wet granules were air dried for 1 hour and the dried granules were sieved through sieve No 16. Granules were evaluated for pre-compression properties and these granules were blended with other half of crospovidone, magnesium stearate and talc.[7, 8]

Table.1: Composition ofimmediate release layer

Ingredients	Amount (mg)
Rosuvastatin calcium	10
Maize starch	40
MCC	120
Trisodium citrate	10
$CaCO_3$	30
Mg.sterate	3
Cros povidone	40
Talc	3
Lactose	93
Synthetic food color	1
TOTAL	**350**

Preparation of sustained release layer

Sustained release layer was prepared by direct compression according to the formulas given in Table 2. Sustained release matrix tablet of Glimepiride were prepared by using HPMC (K15M), and ethyl cellulose as matrix forming materials, while lactose as diluent, magnesium stearate as lubricant and talc as anti-adherent. All ingredients used were passed through # 100 sieve, weighed and blended.[8, 9]

Table.2: Composition of sustained release layer

Formulation code	Ingredients(mg)						
	Glimepiride	HPMC	EEC	MCC	Mg. sterate	Lactose	Talc
F1	4	60	40	100	3	40	3
F2	4	60	40	140	3	-	3
F3	4	60	20	120	3	40	3
F4	4	40	20	140	3	40	3
F5	4	40	20	100	3	80	3
F6	4	40	60	100	3	40	3
F7	4	40	40	120	3	40	3
F8	4	20	40	100	3	80	3
F9	4	40	40	120	3	40	3
F10	4	20	60	120	3	40	3
F11	4	40	40	120	3	40	3
F12	4	20	40	140	3	40	3
F13	4	20	20	120	3	80	3
F14	4	60	60	120	3	-	3
F15	4	40	60	140	3	-	3
F16	4	40	40	120	3	40	3
F17	4	40	40	120	3	40	3
TOTAL = 250 mg							

Bilayer Tablet Compression

The tablets were compressedusing 12.7 mm diameter flat circular punch in multi station compression machine (KarnavatiMinipress, India). The lower layer, Rosuvastatin calcium granules were introduced first and a slight compression was made so that the layer wasuniformly distributed. After that the second layer Glimepiride was added and the final compression was made with complete force.[7]

Evaluation of bilayered tablets

Post compression parameters

Formulated tablets were evaluated for their post compression parameters like thickness, weight variation, hardness and friability.

Drug content estimation

One tablet was powdered finely in a glass mortar and transferred in to a 50 ml volumetric flask and made up the volume with 0.1 N NaOH. 5 ml of the above solution was diluted to 50 ml with 0.1 N NaOH. 5 ml of the above solution was further diluted in to a 50 ml volumetric flask with 0.1 N NaOH. Absorbances were read at 241 nm and 231 nm. Concentrations of Rosuvastatin calcium (CX) and Glimepiride (CY) were determined by simultaneous equation method (vierodt's method)[10, 11]

CX= A2ay1-A1ay2/ax2ay1-ax1ay2 ---------- (1)
CY= A1ax2-A2ax1/ax2ay1-ax1ay2 ---------- (2)

In-vitro drug release study

The in vitro dissolution study of bilayer tablet of Rosuvastatin calcium and Glimepiride were carried out in USP type II dissolution test apparatus (paddle type). The drug release study was carried out in 900 ml 0.1 N Hcl as the dissolution medium with agitation speed 50 rpm, maintained at 37±0.5°c. At predetermined time intervals 1 ml sample were withdrawn and filtered by whatmann filter paper. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The samples were analyzed for drug release by measuring the absorbance at 241 nm and 231 nm in UV- spectrophotometer. The amount of drug present in the sample was calculated with the help of simultaneous equation method (Vierodt's method)developed by Ashraful Islam *et al* 2011 [10, 11, 12]

Experimental design for optimization

Sustained release layer of Glimepiride were prepared and evaluated using Box-behnken experimental design. Aim of this study is to statistically optimize the formulation parameters of sustained release layer for the maximum value of zero order release kinetics and percentage cumulative drug release at 11-12 hour. Variables selected were amount of HPMC (X1), amount of EC (X2), and amount of MCC (X3). The response variables were R^2 value of zero order release kinetics and % cumulative drug release at 11-12 hour. The levels of these variables were determined from the preliminary trials and shown in table 3.

Box-Behnken design was used to statistically optimize the formulation factors and evaluate effects such as main, interaction and quadratic; on the R^2valueof zero order release kinetics and cumulative drug release at 11-12 hour. A three factor, three-level Box-Behnken statistical experimental design as the Response Surface Methodology requires 17 runs and these 17 runs with triplicate centre points were generated. The full factorial design and layout with coded values of variables for each batch and responses are shown in Table 4. The ranges of Y1 and Y2 for all batches were 0.98-1and 92-99%, respectively.[13]

Table. 3 Optimization levels

Factors	Levels used		
	-1	**0**	**1**
X1=Amount of HPMC (mg)	20	40	60
X2= Amount of ethyl cellulose (mg)	20	40	60
X3= Amount of micro crystalline cellulose(mg)	100	120	140
Responses	**Constraints**		
Y1 = R^2 value of zero order release kinetics	0.98-1		
Y2 = Cumulative drug release at 11-12 hour	92-99		

Table. 4: Design matrix

Formulation code	Factors		
	Amount ofHPMC (mg) X_1	Amount ofEC (mg) X_2	Amount of MCC (mg) X_3
F1	60	40	100
F2	60	40	140
F3	60	20	120
F4	40	20	140
F5	40	20	100
F6	40	60	100
F7	40	40	120
F8	20	40	100
F9	40	40	120
F10	20	60	120
F11	40	40	120
F12	20	40	140
F13	20	20	120
F14	60	60	120
F15	40	60	140
F16	40	40	120
F17	40	40	120

Evaluations of the optimmized formula

The optimum formula suggested by the software was evaluated for various parameters like, thickness, hardness, friability, weight variation and drug content. The in vitro dissolution studies were also performed.

Kinetics of in-vitro drug release

The data obtained from the release studies were kinetically analyzed to determine the mechanism and the order of drug release from various formulations. Linear regression analysis was done to fit the data to various models like zero order, first order, Higuchi and Korsemeyer-Peppas.[14]

Stability studies

The optimized batch of the tablet was monitored up to 60 days at room temperature. After 60 days tablets were evaluated for hardness, % drug content, and *in vitro* drug release study by procedure stated earlier.

RESULTS AND DISCUSSION

Drug– drugand drug – polymerinteraction was studied by FTIR spectroscopy. No interaction between drugs and between drugs and polymers were seen, which can be interpreted from fig1, as there is no shift in the peaks of drug spectra.

Flow properties of 17 batches of sustained release layer and immediate release layer were carried out and results are depicted in table5, which shows all the values are within in the standard limits prescribed by the official text books.

Table 5.Flow properties of sustained release layer and immediate release layer

Formulation	Angle of Repose(^{0})	Bulk	Tapped	Carr's index (%)	Hausner's
F1	28.87	0.3645	0.3945	7.60	1.08
F2	23.84	0.3345	0.3628	7.80	1.08
F3	24.36	0.3256	0.3534	7.86	1.08
F4	24.96	0.3812	0.4097	6.95	1.07
F5	29.71	0.4289	0.4854	11.63	1.13
F6	30.76	0.4038	0.4276	5.56	1.05
F7	27.47	0.3925	0.4309	8.91	1.09
F8	26.22	0.3812	0.4398	13.32	1.15
F9	30.04	0.4301	0.4602	6.54	1.06
F10	25.84	0.3845	0.4293	10.43	1.11

F11	30.64	0.3996	0.4532	11.82	1.13
F12	27.39	0.4293	0.4588	6.42	1.06
F13	29.33	0.3212	0.3764	14.66	1.17
F14	27.89	0.3712	0.3995	7.08	1.07
F15	26.31	0.3490	0.3734	6.53	1.06
F16	30.02	0.3466	0.3967	12.62	1.14
F17	29.49	0.3875	0.4276	9.37	1.10
Rosuvastatin	24.67	0.3865	0.4354	11.23	1.12

Bi layer tablets were prepared by using the formulas given in table1 and table 2. Post compression parameters of the prepared bilayer tablets like thickness, average weight, weight variation, hardness and friability were carried out and results of these parameters are depicted in table 6.

Table 6.Post compression parameters of bilayer matrix tablet

Formulation code	Thickness* (mm)	Average weight of one tablet** (%)	Weight variation as per USP	Hardness* (kg/cm^2)	Friability (%)
F1	5.46±0.34	598.34±0.56	Pass	6.23±0.98	0.16
F2	5.85±0.21	600.55±0.88	Pass	5.94±0.66	0.56
F3	5.78±0.76	598.67±0.34	Pass	6.78±0.65	0.41
F4	5.67±0.98	605.64±0.17	Pass	6.32±1.23	0.21
F5	5.93±1.98	610.34±0.84	Pass	6.76±0.37	0.32
F6	5.86±0.54	600.98±0.23	Pass	7.12±0.86	0.62
F7	5.86±0.04	597.90±0.09	Pass	6.34±1.98	0.62
F8	5.89±0.47	599.45±0.06	Pass	6.27±0.54	0.49
F9	5.91±0.67	597.89±0.54	Pass	5.97±0.42	0.29
F10	5.90±1.06	600.32±0.28	Pass	7.10±0.98	0.69
F11	5.76±0.37	600.43±0.29	Pass	6.43±0.76	0.21
F12	5.67±0.56	609.56±0.07	Pass	6.26±0.42	0.87
F13	5.87±0.47	612.38±0.03	Pass	5.60±0.43	0.61
F14	5.85±1.06	605.97±0.56	Pass	5.78±0.57	0.34
F15	5.95±1,23	599.45±0.49	Pass	5.87±0.47	0.36
F16	5.82±0.99	594.56±0.37	Pass	6.98±1.23	0.49
F17	5.79±0.53	606.45±0.74	Pass	6.34±0.29	0.57

From table7, percentage drug content of Glimepiride was in the range of 95-99 and Rosuvastatin calcium was 96.63.

Table 7.Drug content estimation of bi layer tablet

Formulation code	% drug content
Glimepiride	
F1	99.45±0.23
F2	98.76±0.73
F3	98.18±1.23
F4	95.33±0.76
F5	95.99±0.45
F6	97.19±1.56
F7	97.59±0.67
F8	97.98±0.39
F9	96.74±0.74
F10	99.12±1.34
F11	99.19±0.02
F12	95.34±1.09
F13	96.45±0.76

F14	95.77±1.22
F15	95.64±0.37
F16	95.46±0.95
F17	98.56±0.65
Rosuvastatin Calcium	**96.633±1.165**

In vitro drug release study of 17 batches were performed, and the results were depicted infigure 2, figure 3, figure 4 and figure 5, which shows F4, F9 and F17 shows maximum percentage release up to 12 hours and F5 and F13 shows minimum percentage release.

ANOVA summery of the responses Y1 and Y2 were shown in table 8 and 9 respectively. Data from the table 8 shows thatthe model F -value of 21.97 implies the model is significant. Values of "Prob>F" less than 0.0500 indicate model terms are significant. The lack of "Lack of Fit F-value" of 1.90 implies the Lack of Fit is not significant relative to the pure error. Data from the table 9 shows that the model F -value of 27.58 implies the model is significant. Values of "Prob>F" less than 0.0500 indicate model terms are significant. The "Lack of Fit F-value" of 0.031 implies the Lack of Fit is not significant relative to the pure error.

Table 8 ANOVA summery of response Y1

Source	F-value	P-value	Remarks
Model	21.97	0.0003	Significant
X1	94.24	<0.0001	
X2	2.62	0.1497	
X3	1.28	0.2947	
X1X2	0.21	0.6611	
X1 X3	0.84	0.3905	
X2 X3	2.57	0.1533	
X_1^2	3.02	0.1259	
X_2^2	9.90	0.0162	
X_3^2	77.09	<0.0001	
Residual	Nd	Nd	
Lack of Fit	1.90	0.2715	not significant
Pure Error	Nd	Nd	
Cor Total	Nd	Nd	

* Significant at 5% level
Nd = not defined

Table 9 ANOVA summery of response Y2

Source	F-value	P-value	Remarks
Model	27.58	0.0001	Significant
X1	27.22	0.0012	
X2	24.16	0.0017	
X3	35.64	0.0006	
X1X2	41.65	0.0003	
X1 X3	7.47	0.0292	
X2 X3	36.40	0.0005	
X_1^2	2.97	0.1284	
X_2^2	52.43	0.0002	
X_3^2	18.62	0.0035	
Residual	Nd	Nd	
Lack of Fit	0.31	0.8162	Not significant
Pure Error	Nd	Nd	
Cor Total	Nd	Nd	

* Significant at 5% level
Nd = not defined

Response surface plot for the effect of HPMC, EC and MCC on R^2 value of zero order release kinetics were shown in figure 11, and Response surface plot for the effect of HPMC, EC and MCC on cumulative percentage release at 11-12 hours were shown in figure 12

After generating the polynomial equation relating to the dependent and independent variables, the formulation was optimized for the responses. The desirable range of the responses was restricted to maximize theR^2 value of zero order release kinetics in the range of 0.92-0.99 and cumulative drug release at t90 in the range of 90-99%.The optimum values of the variables were obtained by the numerical analysis based on the criterion of desirability. Therefore a new batch of tablets with the predicted levels of formulation factors was prepared to confirm the validity of the optimization procedure.

Based on the statistical evaluations the software gave 27 solutions for the optimization of the batches and selected one optimum batch. The formula for the optimum batch is given in table10.

Table 10.Actual formula of optimized batch of sustained layer

Ingredients (mg)						
Glimepiride	**HPMC**	**EC**	**MCC**	**Mg.stearate**	**Talc**	**Lactose**
4	59.40	37.38	100.28	3	3	37

The prepared tablets were then evaluated for the various parameters including thickness, weight variation, friability, hardness, percentage drug content (Table 11)and in-vitro dissolution testing(Table 12). These parameters were found to be within acceptable limits. In Vitro dissolution study of optimized batch were shown in figure 6.

Table 11. Evaluation of the optimized batch

***Thickness (mm)**	****Average weight of one tablet (mg)**	**Weight variation as per USP**	**Friability**	*** Hardness (kg/cm^2)**	**%Drug Content**
5.96±0.93	600.54±0.23	pass	0.58	6.43±0.53	99.72±0.72

*Mean±SD; n=3 **Mean±SD; n=10

The R^2 values suggested that the drug release from the system predominately followed Higuchi's square root of time kinetics, as the values for Q vs. t1/2 was always higher. Release exponent, n, was >0.5, but <1 for the batch indicating an anomalous or non-Fickian release, suggesting a coupled erosion– diffusion transport mechanism. Plots of various models for the optimized batch are represented byfigures7, figure 8, figure 9, and figure 10**.**

The stability of the optimized batch up to 60 days at room temperature (table 12) shows no great differences in physical appearance, hardness, and percentage drug content and dissolution profiles.

Table 12. Results of stability study

Numberof days	**Physical appearance**	**Hardness (kg/cm^2)**	**% drug content**		**% drug release**	
			Glimepiride (%)	**Rosuvastatin Calcium (%)**	**Glimpiride at 12^{th} hour (%)**	**Rosuvastatin calcium at 2^{nd} hour (%)**
0	No change	6.43±0.53	99.72±0.72	96.633±0.165	99.89	98.99
60	No change	6.39±0.32	98.71±0.35	94.851±0.284	98.57	96.12

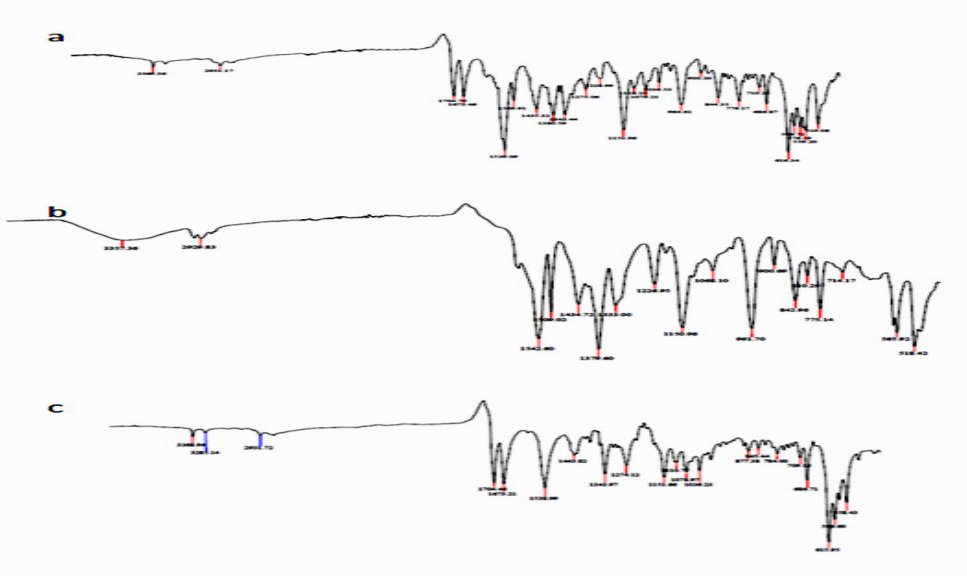

Figure 1: FTIR Spectrum of a) mixture of Rosuvastatin Calcium and Glimepiride b) mixture of Rosuvastatin Calcium and mixture of Polymers c) Glimepiride and mixture of Polymers

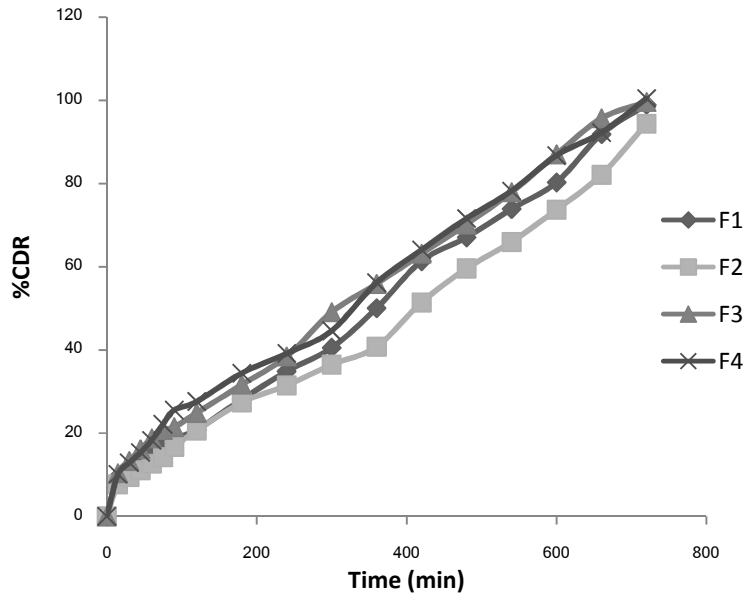

Figure 2: IN Vitro dissolution study of F1- F4

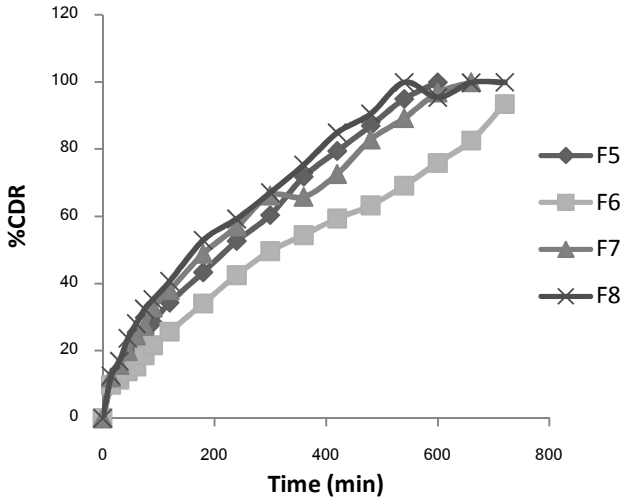

Figure 3: In Vitro dissolution test of F5- F8

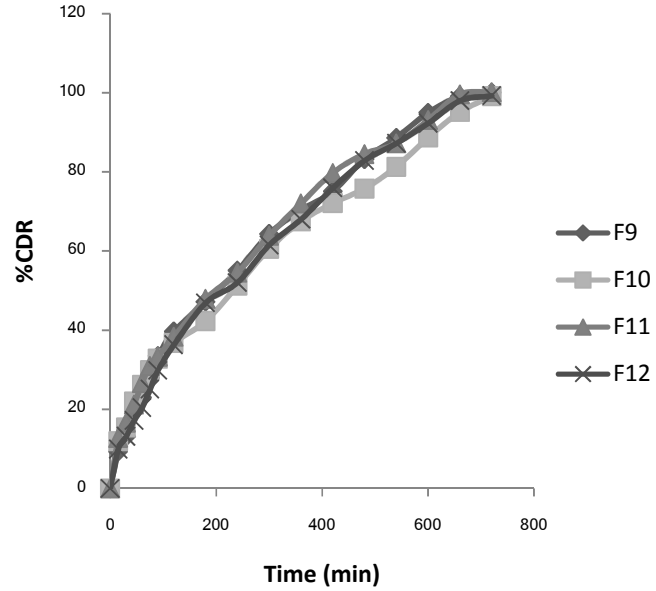

Figure 4: In Vitro dissolution test of F9-F12

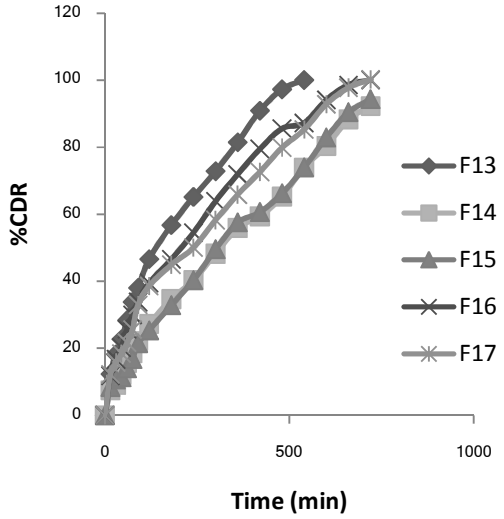

Figure 5: In Vitro dissolution of F13-F17

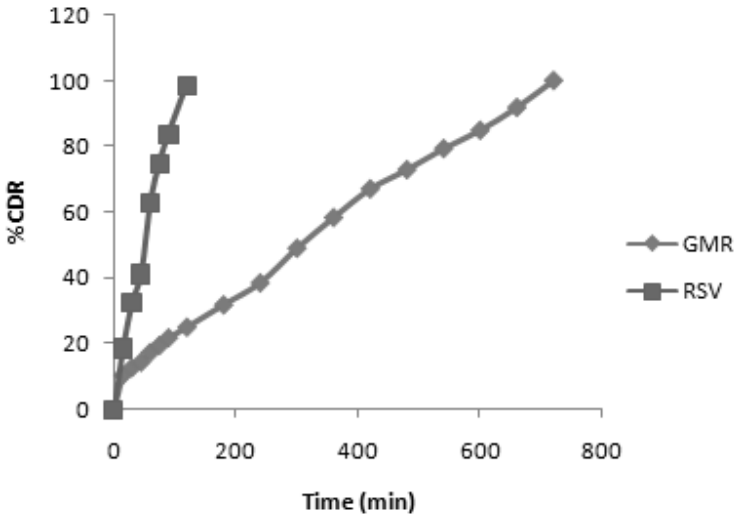

Figure 6: In Vitro dissolution study of optimized batch

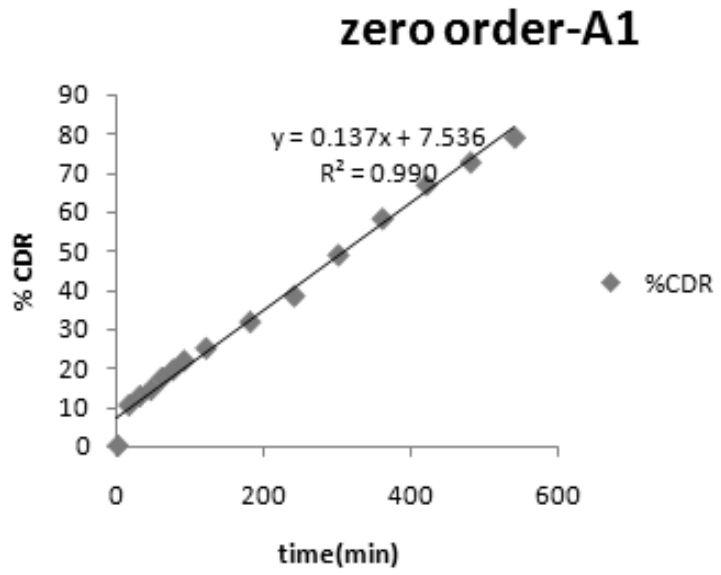

Figure 7: Zero order release kinetics of Sustained release layer

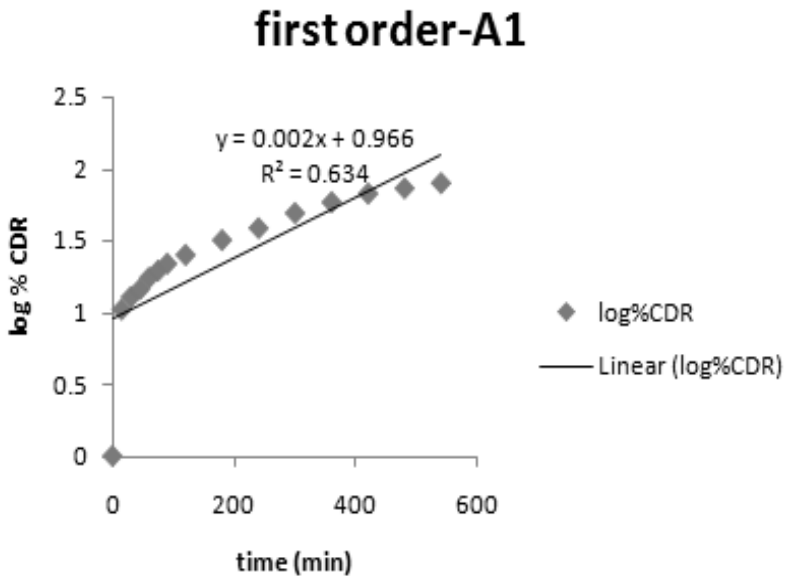

Figure 8: First order release kinetics of sustained release layer

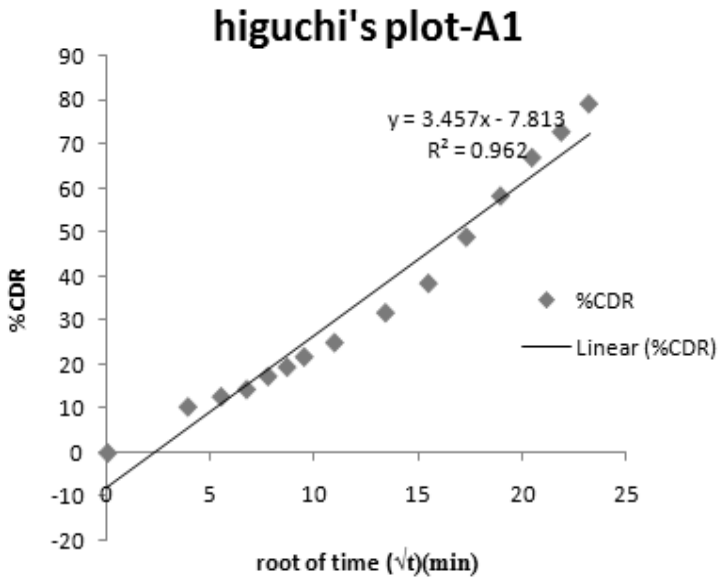

Figure 9: Higuchi's plot of sustained release layer

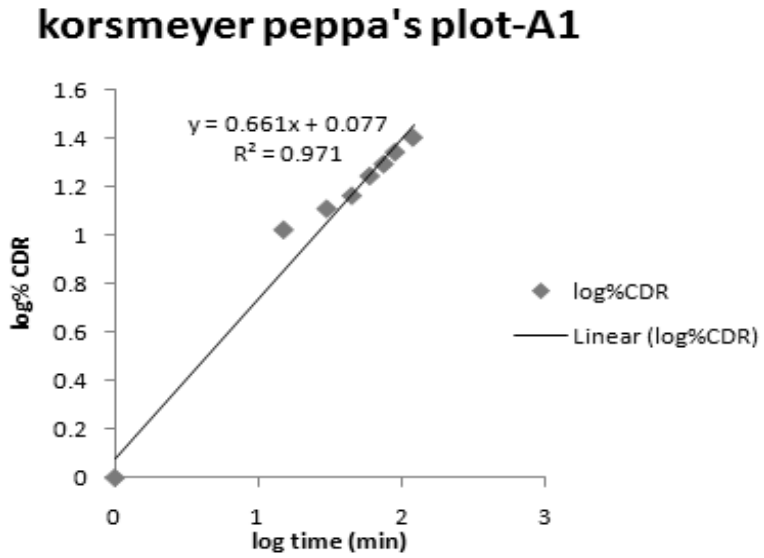

Figure 10: Korsmeyerpeppa's plot of sustained release layer

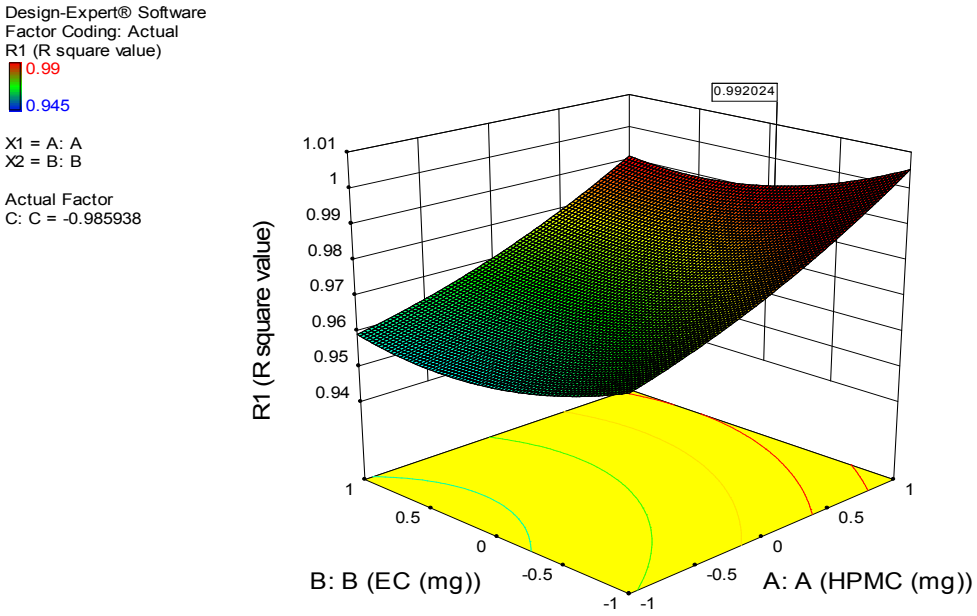

Figure 11: Response surface plot for the effect of HPMC, EC and MCC on R^2 value of zero order release kinetics

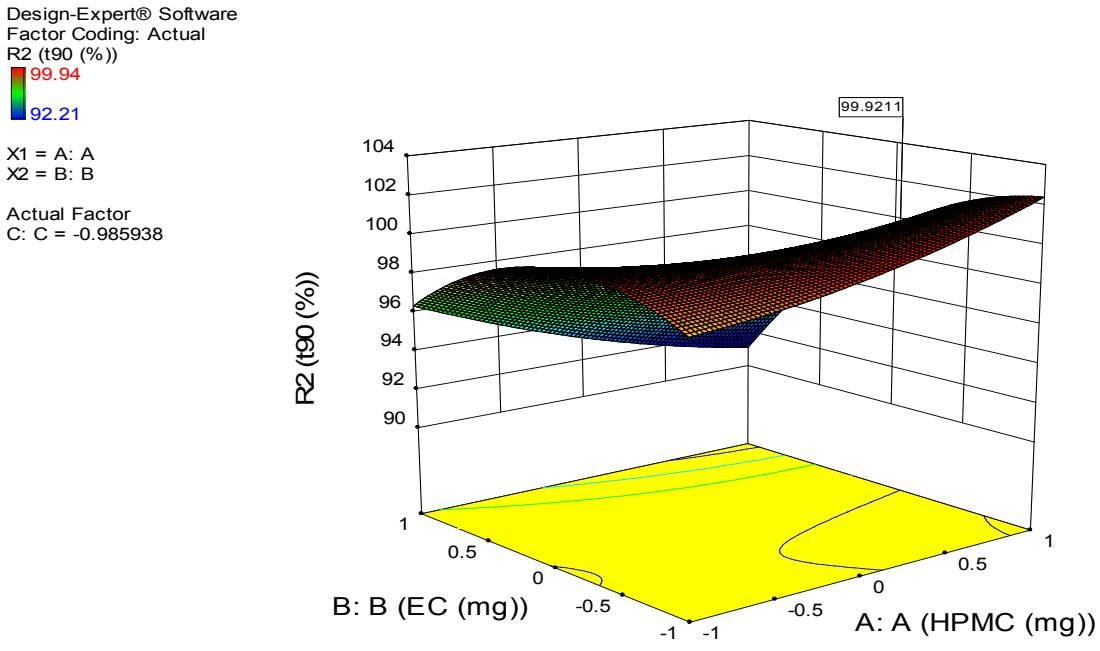

Figure 12: Response surface plot for the effect of HPMC, EC and MCC on cumulative percentage release at 11-12 hours

CONCLUSION

From the present study, it can be concluded that bilayer tablets containing immediate releasing Rosuvastatin calcium and sustain releasing Glimepiride can be prepared for the treatment of Diabetes mellitus. FT-IR of Rosuvastatin calcium and Glimepiride drug mixture show no interference between the two drugs and also found that Rosuvastatin calcium and Glimepiride drugs did not interfere with the polymers used. The responses obtained from the design matrix i.e., R^2 value of zero order release kinetics, cumulative percentage release at 11-12 hours of the sustained release layer were statistically evaluated. Thus an optimum formula was obtained.The optimum formulation was prepared and performed the in- vitro dissolution studies. The dissolution study of bilayer tablets showed that, the drug Glimepiride was effective in providing sustained action i.e., up to12 hours andthe drug Rosuvastatin calcium was effective in providing immediate action within 2 hours. The drug release from the Glimepiride sustain release layer followed Higuchi kinetic model, which indicated that drug release occurs by a diffusion controlled mechanism. Since 'n' value is between 0.5 and 1, it follows non-Fickian release. According to stability studies it was found that there was no significant variation in hardness, percentage drug content and *in-vitro* drug release profile of optimized formulation. For further development of the drug delivery system evaluation of the biopharmaceutical and should be done by performing *in-vivo* animal studies. The scale up of the formula, process and equipments can be done for the large scale manufacturing of the product.

ACKNOWLEDGEMENT

We are thankful to CTX life sciences pvt ltd, Mumbai. for providing Rosuvastatin calcium drug as gift samples for this work. We also thank Sangrospvt ltd, Mavelikkara for providing Glimepiride drug as gift sample. We are thankful to Department of chemical sciences, M G University for providing the facility for taking IR spectroscopy.

REFERENCES

[1] *"Diabetes Fact sheet N°312". WHO. October 2013. Retrieved 25 March 2014.*

[2] Gillian Marshall, Claire McDougall, Adraian J B Brady, Miles Fisher, Should all diabetic patients receive a statin? Results from recent trials, British Journal of Cardiology, 2014, 11(6):445-460.

[3] MRC/BHF Heart Protection Study of Cholesterol lowering with Simvastatin in 5963 people with Diabetes; a randomised placebo-controlled trial. Lancet 2003, 361:2005-2016

[4] Maggi L, Segale L, Conti S, Ochoa Machiste E and Conte U. Preparation and evaluation ofrelease characteristics of 3TabGum, a novel chewing device. Eur J Pharm Sci 2005, 24:487- 493.

[5] Drug bank. Open data drug and drug target database .Available from: http://www.drugbank.ca/drugs/DB01016.

[6] Laufs U, Gertz K, Dirnagl U, Bohm M, Nickenig G, Endres M: Rosuvastatin, a new HMG-CoA reductase inhibitor,Brain Res. 2002;942(1-2):23-30.

[7] M. SambasivaRao, A. Sunil kumar Reddy, A. Ashok Kumar, Formulation and evaluation of Metformin and Rosuvastatin calcium bilayered tablets, journal of pharmacreations, 2016;3: 26-39

[8] Mohd Abdul Khadi, V LokeswaraBabu and Narottan Pal, Formulation and evaluation of sustained release matrix tablets of Glimepiride based on combination of Hydrophilic and Hydrophobic polymers, Journal of applied pharmaceutical science 2012;02(06):101-107

[9] Durga Prasad Pattanayak and Subash C Dinda, Bilayer tablet of formulation of Metformin Hydrochloride and Glimepiride ; a novel approach to improve therapeutic efficacy, International Journal of drug discovery and herbal research 2011;1(1): 1-4.

[10] AsmaAfroz, TasnuwaHaque, MdMesbah, UddinTalukder and S M Ashraful Islam, Spectrophotometric estimation of Rosuvastatin Calcium and Glimepiride in tablet dosage form, Asian journal of Pharmaceutical Analysis 2011;1(4): 74-78

[11] A H Beckett and Stenlake , practical pharmaceutical chemistry ; 2: 284-285

[12] Costa P and Susa Lobo, modelling and comparison of dissolution profiles, European Journal of Pharmaceutical sciences 2001;13(3): 123-133

[13] S Y Rai and PadminiRavikumar, development and evaluation of microsphere based topical formulation using design of experiments, Indian journal of pharmaceutical sciences 2016;78(2):182-192

[14] Rawe RC, Sheskey PG, Quinn ME. Handbook of Pharmaceutical Excipient, 2009; 6: 129, 315, 206, 663, 728.