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DESIGN AND EVALUATION OF BI-LAYER DRUG DELIVERY SYSTEM OF ATORVASTATIN AND GLIPIZIDE

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ABSTRACT

The main focus of this study is to develop bi-layer tablets containing immediate release (I. R.) layer of atorvastatin and extended release (E. R.) layer of glipizide. atorvastatin I. R. tablets and glipizide E. R. tablets were prepared separately and were evaluated. From the *in vitro* dissolution studies, the I. R. formulation (A3) and the E. R. formulation (K1) were selected for further formulation into bi-layer tablets. The *in vitro* dissolution study of the bi-layer tablet showed that the percentage of atorvastatin released from I. R. layer was 76.9% within 45 min and the percentage of glipizide released from the E. R. layer was 31.64% in 8 hrs. All the formulations showed no change in physical appearance and in drug content after storage at 40 ± 2°C / 75 ± 5%RH for 3 months. DSC studies indicated no possibility of interaction between drugs and other formulation excipients.

Key words : Atorvastatin, Glipizide, Bi-layer tablets, Immediate release, Extended release, Swellable polymer, Non-swellable polymer, Disintegrant.

INTRODUCTION

An approach, which is new to achieve bimodal drug release (I. R. and E. R.) based on matrix tablet, is followed in formulating bi-layered tablets[1]. The design of bi-layer tablet is usually introduced to provide patient compliance and convenience, to eliminate frequent dosing and fluctuation in plasma drug concentrations and to achieve rapid and extended delivery of drug or drugs present in the formulation[2]. Immediate release layer applies the techniques of conventional tableting and the extended release layer applies the techniques of extended release tableting using release retardant matrix. In bimodal drug delivery in bi-layer tablet, the I. R layer can be fabricated with the drugs, which are needed to be taken once daily and the E. R layer can be fabricated for those drugs, which needs frequent dosing to achieve desired blood concentrations[3].

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Type 2 diabetes, formerly known as non–insulin dependent diabetes mellitus represents about 98% of all diabetes cases among persons older than 45 years of age, which also leads to micro and macro vascular complications[4]. glipizide is more efficacious in enhancing meal-stimulated insulin secretion and generally have a lower risk of hyper glycemia but often needed to be taken more than once per day, which may decrease patient compliance and produce great change in plasma drug levels both; above and below the therapeutic range. So the drug can be given as E. R. formulation for better results. National Institute for Clinical Excellence (NICE) guidelines recommends lipid lowering drugs for peoples with Type 2 diabetes based on their absolute risk of a coronary event and whether or not, they have adverse lipid profile[5]. Collaborative Atorvastatin Diabetes Study (CARDS) proved that atorvastatin 10 mg daily is safe and efficacious in reducing the risk of first cardiovascular disease events[6]. Hence, formulating a bi-layer tablet containing I. R. layer of atorvastatin and an E. R layer of glipizide offers a better compliance and other benefits to the patients.

EXPERIMENTAL

Materials

Glipizide and atorvastatin calcium was obtained as gift sample from USV Ltd and Arabindo Remedies, respectively. Eudragit RSPO was obtained from Axon Drugs. The polymers and other materials namely lactose, PVP K30, talc and magnesium stearate were of AR grade.

Methods

Formulation of atorvastatin calcium immediate release tablets

Three formulations of atorvastatin calcium I. R. tablets were prepared (Table 1). Micro crystalline cellulose, sodium starch glycolate and primellose were used as tablet disintegrants. The granules prepared by wet granulation method were evaluated and then compressed into tablets using Cadmach single punch tablet machine fitted with 8 mm concave punches.

Formulation of glipizide extended release tablets

Fourteen formulations of glipizide E. R. tablets were prepared (Table 2). Sodium CMC, Eudragit RSPO, HPMC K_4M and HPMC $K_{100}M$ were used as polymers. The granules prepared by wet granulation method were evaluated and then compressed into tablets using Cadmach single punch tablet machine fitted with 8 mm concave punches.

Table 1 : Formulation of atorvastatin calcium immediate release tablets

S. No.	Ingredients	Amount of ingredients in % per tablet		
		A1	**A2**	**A3**
1	Atorvastatin calcium	8.66	8.66	8.66
2	$CaCO_3$ (Light)	36	36	22
3	Dicalcium phosphate	12.2	12.2	-
4	Micro crystalline cellulose	31.2	31.2	40
5	Aerosil	2.4	2.4	-
6	Talc	3.6	3.6	-
7	Sodium starch glycolate	6	-	-
8	Primellose	-	6	6
9	Lactose	-	-	20.44
10	Hydroxy propyl cellulose	-	-	2
11	Tween 80	-	-	0.4
12	Magnesium stearate	-	-	0.5
13	Coloring agent	Q. S	Q. S	Q. S
14	Isopropyl alcohol	Q. S	Q. S	Q. S
	Total %	**100%**	**100%**	**100%**

Evaluation of atorvastatin calcium I. R. and glipizide E. R. single layer tablets[7-9]

The prepared tablets were evaluated for hardness, thickness, diameter, friability, weight variation and drug content. *In vitro* release studies were carried out for all formulated atorvastatin I. R. tablets and glipizide E. R. tablets in a USP type II (paddle) dissolution apparatus at 37 ± 0.5ºC at 50±1 rpm in 900 mL of phosphate buffer pH 6.8 for about 2 hrs and 8 hrs, respectively. Samples were withdrawn at pre-determined time intervals and the amount of atorvastatin and glipizide released was determined by measuring the absorbance of the samples using UV-Visible spectrophotometer at λ_{max} 241.5 nm and 275 nm, respectively.

Table 2: Formulation of glipizide extended release tablet

Ingredients	Amount of ingredients in % per tablet													
	F1	**F2**	**F3**	**E1**	**E2**	**E3**	**K1**	**K2**	**K3**	**L1**	**L2**	**L3**	**L4**	**L5**
Glipizide	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Sodium CMC	16	32	48	-	-	-	-	-	-	-	-	-	-	-
Eudragit RSPO	-	-	-	16	32	48	-	-	-	-	-	-	-	-
HPMC K_4M	-	-	-	-	-	-	16	32	48	-	-	-	-	-
HPMC $K_{100}M$	-	-	-	-	-	-	-	-	-	4	6	16	32	48
PVPK-30	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Dicalcium phosphate	67	51	35	67	51	35	67	51	35	79	75	67	51	35
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Isopropyl alcohol	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

Selection of best formula for I. R. layer and E. R. layer for the preparation of bi-layer tablets

From all the formulated atorvastatin I. R. tablets and glipizide E. R. tablets, the best formula was selected for I. R. layer and E. R. layer, respectively, which were then compressed into bi-layer tablets using Cadmach single punch tablet machine fitted with 8 mm concave punches.

Evaluation of bi-layer tablets[7, 8, 10]

The bi-layer tablets were evaluated for hardness, thickness, diameter, friability and weight variation. The drug content of the bi-layer tablets were estimated by RP-HPLC method using C_{18} column on Shimadzu LC-10 AT VP instrument. The *in vitro* release study was done in a USP type II (paddle) dissolution apparatus at 37±0.5ºC at 50±1 rpm in 900 mL of phosphate buffer pH 6.8 for about 8 hrs. 1 mL sample was withdrawn at pre-determined time intervals and then filtered through Whatman filter paper using vacuum. From this, 20 µL of sample was withdrawn and the chromatogram was recorded. The amount of drug released from the tablet was calculated.

Differential scanning calorimetry (DSC)[11]

DSC examination was conducted for the pure and physical mixture of the 2 drugs and also for the finished bi-layer tablets using Shimadzu 60 DSC instrument.

Stability studies[11]

Stability studies were conducted on all the formulated tablets by storing at 40 ± 2°C/75 ± 5%RH for 3 months. The drug content was evaluated periodically using UV-Visible Spectrophotometer.

RESULTS AND DISCUSSION

Evaluation of granules

The angle of repose valued between 23° to 26° and the percentage compressibility valued in the range of 12.5 to 17.8 %. The bulk density and tapped density were in the range of 0.41-0.60 g/mL and 0.45-0.62 g/mL, respectively. These values indicated that the granules of all the formulations had good flow properties. The drug content of the granules was found in the range of 99.01% to 103.23% (Table 3).

Table 3: Evaluation of atorvastatin calcium I. R. and glipizide E. R. single layer tablets

Formulation code	LBD* (g/mL)	TBD* (g/mL)	C. I.* (%)	A. O. R.* (θ)	Hardness* (Kg/cm^2)	Thickness* (mm)	Diameter* (mm)	Friability (%)	Drug content (%)
F1	0.4148	0.4741	12.50	23° 75'	6-7	2.1	8	0.052	110.50
F2	0.4468	0.4821	12.80	24° 78'	6-7	2.0	8	0.061	100.10
F3	0.4512	0.4999	13.20	26° 28'	6-7	2.2	8	0.090	99.00
E1	0.4412	0.4572	12.20	25° 21'	6-7	2.0	8	0.120	100.80
E2	0.4512	0.4752	12.31	26° 10'	6-7	2.1	8	0.140	101.00
E3	0.4522	0.4813	12.82	26° 71'	6-7	1.9	8	0.080	102.10
K1	0.5123	0.5272	13.80	23° 62'	6-7	2.0	8	0.020	100.10
K2	0.5432	0.5500	14.21	24° 31'	6-7	2.1	8	0.010	99.80
K3	0.5555	0.6123	14.71	25° 40'	6-7	2.0	8	0.010	99.10
L1	0.5213	0.5382	15.13	22° 11'	6-7	2.1	8	0.080	102.10
L2	0.5312	0.5360	15.78	22° 24'	6-7	2.2	8	0.060	99.90
L3	0.5514	0.5818	16.01	22° 64'	6-7	2.1	8	0.020	101.20
L4	0.5800	0.6100	17.20	25° 71'	6-7	2.0	8	0.010	100.20
L5	0.6002	0.6188	17.80	25° 12'	6-7	1.9	8	0.010	98.90
A1	0.4512	0.4762	12.81	23° 21'	6-7	2.0	8	0.090	102.10
A2	0.4415	0.4678	13.12	24° 32'	6-7	2.0	8	0.120	98.10
A3	0.4310	0.4512	13.72	25° 01'	6-7	2.0	8	0.140	100.20

LBD - Loose bulk density; TBD - Tapped bulk density; C. I. - Compressibility index; A. O. R. - Angle of repose; *n = 3

Evaluation of atorvastatin calcium I. R. and glipizide E. R. single layer tablets

The hardness, thickness, diameter and friability of all the tablet formulations were observed in the range of 6-7 kg/cm^2, 2-2.1 mm, 8 mm and 0.01-0.14%, respectively. Weight variation was found to be within the I. P. limits. The disintegration time of the I. R. tablets were found within the range of 25-35 s. Hence, these formulations may release the drug immediately. The drug content of all the formulations was found within the range of 98.1-102.1 %, which showed that the drug was uniformly distributed in all the formulations (Table 3).

In vitro release studies of atorvastatin calcium I. R. tablets

In vitro release studies of atorvastatin calcium I. R. tablets showed that the formulations A1, A2 and A3 released 32%, 43% and 70% of drug, respectively after 45 min. and released 45%, 56% and 77% of drug, respectively after 2 hrs (Fig. 1). This showed that the formulated I. R. tablets disintegrated rapidly and released the drug immediately.

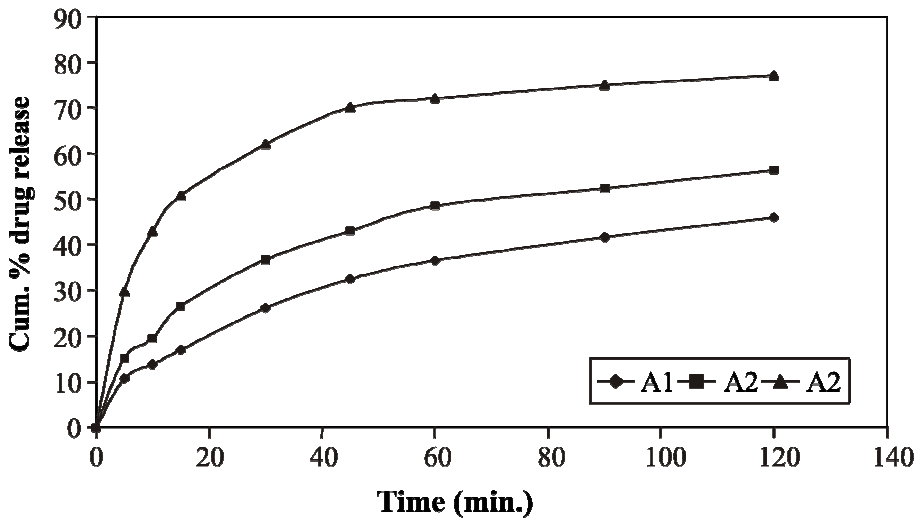

Fig. 1 : *In vitro* dissolution studies of atorvastatin I. R. tablets *in vitro* release studies of glipizide E. R. tablets

In vitro release studies of glipizide E. R. tablets were conducted for a period of 8 hrs. The formulations F1, F2 and F3 containing sodium CMC polymer released 78.8%, 53.6% and12.5% of drug, respectively (Fig. 2). The formulations E1, E2 and E3 containing Eudragit RSPO polymer released 8.5%, 5.9% and 2.5% of drug, respectively (Fig. 3). The

formulations K1, K2 and K3 containing HPMC K_4M polymer released 30.4%, 26.78% and 21.98% of drug, respectively (Fig. 4). The formulations L1, L2, L3, L4 and L5 containing HPMC $K_{100}M$ polymer released 17.6%, 12.18%, 10.4%, 23.69% and 18.2% of drug, respectively (Fig. 5). All the formulations of glipizide E. R. tablets showed sustained release of the drug for 8 hrs.

The drug release was controlled in the following order –

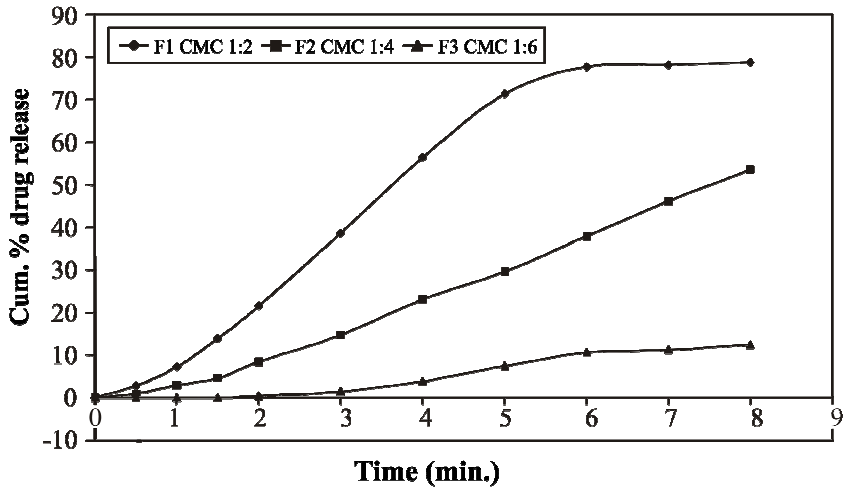

Fig. 2 : *In vitro* dissolution studies of the glipizide E. R. tablets with sodium CMC

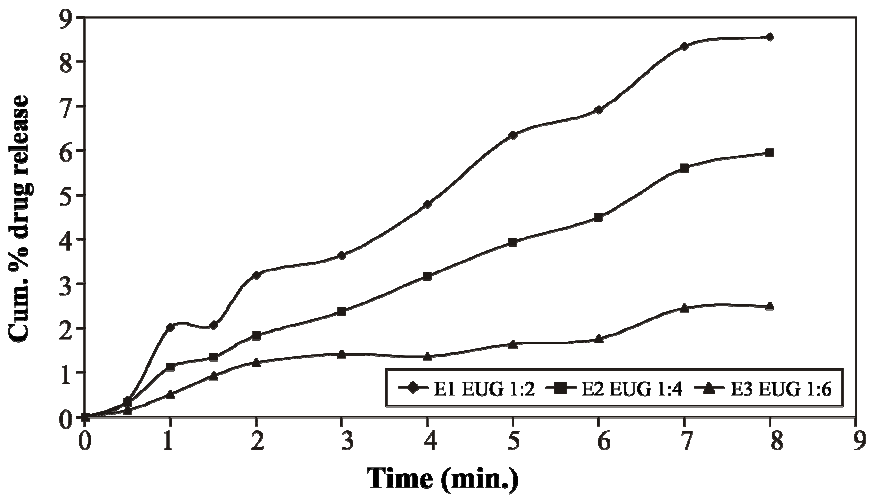

Fig. 3 : *In vitro* dissolution studies of the glipizide E. R. tablets with Eudragit RSPO

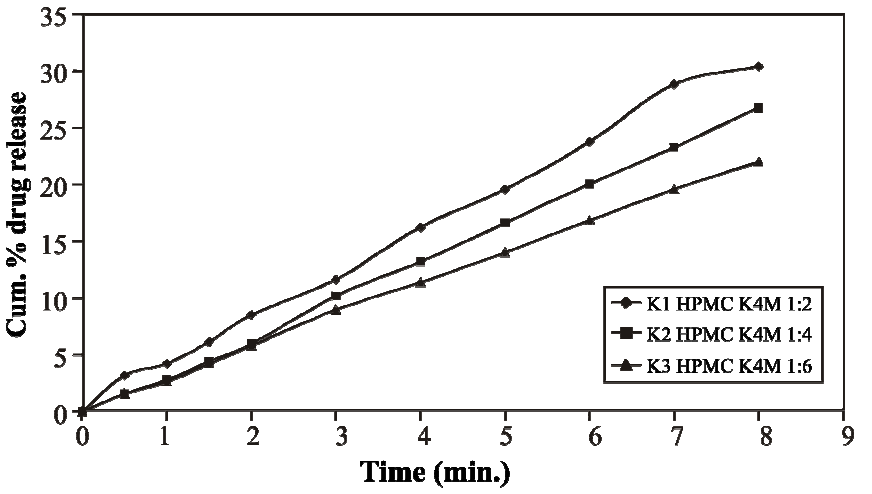

Fig. 4 : *In vitro* dissolution studies of glipizide E. R. tablets with HPMC K_4M

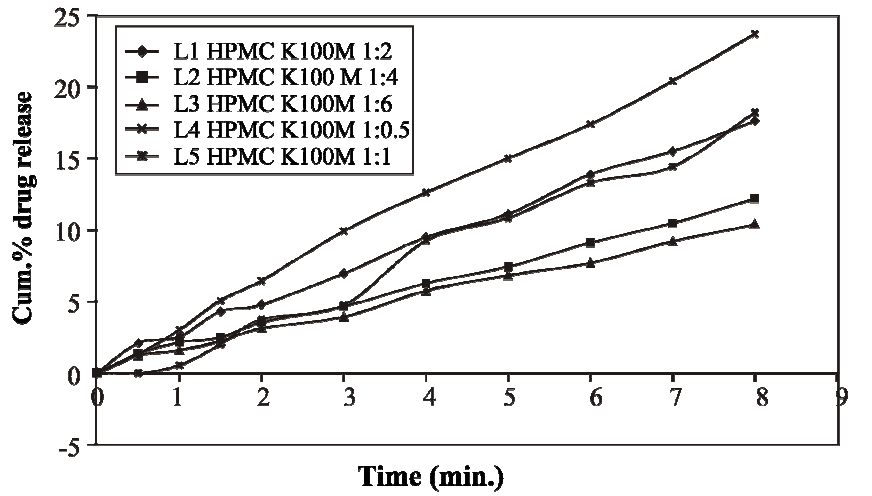

Fig. 5 : *In vitro* dissolution studies of glipizide E. R. tablets with HPMC K_{100} M

Eudragit RSPO > HPMCK_{100}M > HPMCK_4M > Sodium CMC

Kinetics of drug release

All the E. R. formulations fitted well into zero order kinetics and first order kinetics, which is evident from the highest correlation coefficient (R^2) value (Table 4).

Selection of best I. R. and E. R. layer for the formulation of bi-layer tablets

As per I. P specifications, the I. R. formulation A3 showed 70% of drug release within 45 min. (Fig. 1). Hence, this formulation was selected for further formulation into bi-layer tablets.

The E. R. formulation K1 showed maximum similarity factor F_2 of 78, when compared to marketed product (Table 4). More over, the marketed as well as the formulation K1 follows similar pattern of drug release (Fig. 6). Hence, this formulation was selected for formulation of bi-layer tablets.

Table 4 : Release profiles of E. R. formulation and similarity factor values compared with marketed E. R. product

Formulations	F2	Zero order-Kr	R^2	1st order-Kr	R^2
Marketed Product		3.9	0.9933	0.048	0.9936
CMC 1 : 2 (F1)	21	11.6	0.9449	0.22	0.9128
CMC1 : 4 (F2)	46	6.9	0.9912	0.099	0.9787
CMC 1 : 6 (F3)	51	1.9	0.9286	0.02	0.9421
HPMC K_{100} M 1 : 0.5 (L4)	73	2.9	0.9937	0.03	0.9934
HPMC K_{100} M 1 : 1 (L5)	59	2.3	0.9881	0.026	0.9888
HPMC K_{100} M 1 : 2 (L1)	61	2.2	0.9963	0.024	0.9963
HPMC K_{100} M 1 : 4 (L2)	51	1.45	0.99	0.02	0.9889
HPMC K_{100} M 1 : 6 (L3)	49	1.25	0.991	0.013	0.9924
Eutragit RSPO 1 : 2 (E1)	48	1.12	0.9829	0.01	0.9832
Eutragit RSPO 1 : 4 (E2)	46	0.89	0.9564	0.01	0.9499
Eutragit RSPO 1 : 6 (E3)	46	0.77	0.9105	0.01	0.9076
HPMC K_4M 1 : 2 (K1)	78	3.9	0.9951	0.046	0.9934
HPMC K_4M 1 : 4 (K2)	74	3.4	0.998	0.04	0.9959
HPMC K_4M 1 : 6 (K3)	70	2.8	0.9982	0.03	0.9973

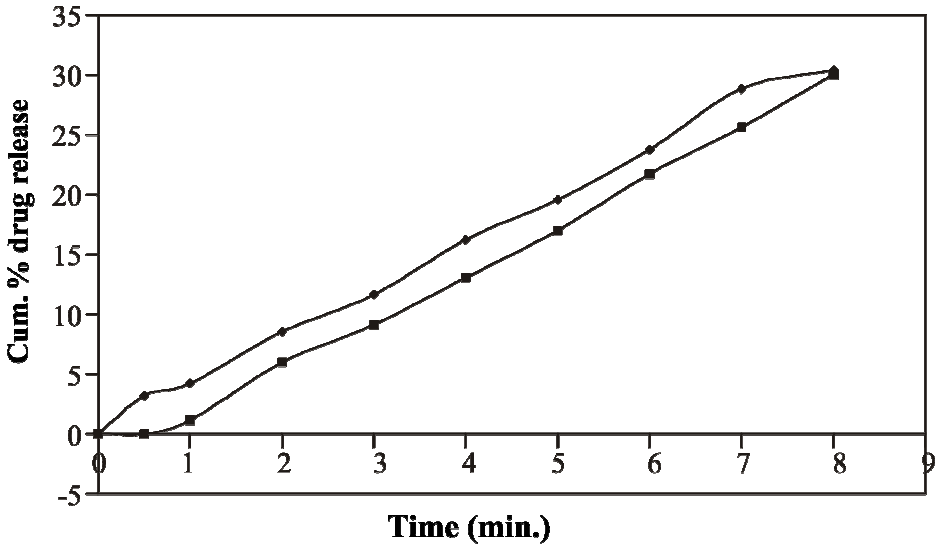

Fig. 6 : Comparison of drug release of K1 formulation and marketed formulation

Formulation and evaluation of atorvastatin calcium and glipizide bi-layer tablets

The bi-layer tablets were prepared by using the composition of the formulations A3 and K1 as the formula for I. R. layer and E. R. layer, respectively.

Table 5 : Evaluation of atorvastatin calcium and glipizide bi-layer tablets

Formulation parameters	Average values	
Thickness* (mm)	4	
Diameter* (mm)	8	
Average weight (mg)	246.33	
Hardness* (Kg/cm^2)	6-7	
Friability (%)	0.18	
Disintegration time (sec.)	35	
Drug content (%)	Atorvastatin calcium	Glipizide
	100.29	101.77

*n = 3

The hardness, thickness, diameter and friability of the bi-layer tablets were 6-7 kg/cm^2, 4 mm, 8 mm and 0.18%, respectively indicated the robustness of the product, which may be able to withstand the mechanical stress. Weight variation was found to be within the I. P. limits. The disintegration time of the I. R. layer was found to be 35 seconds and it indicates that the I. R layer may release the drug within short period of time. Further, the drug content of atorvastatin and glipizide was found to be 100.29% and 101.77%, respectively, which showed that the drugs were uniformly distributed in the formulations (Table 5).

In vitro release studies of atorvastatin calcium and glipizide bi-layer tablets

The *in vitro* release study was performed using USP type II (paddle) apparatus. The percentage of atorvastatin released from I. R. layer was found to be 76.9% within 45 min. and the percentage of glipizide released from the E. R. layer was found to be 31.64% in 8 hrs (Fig. 7).

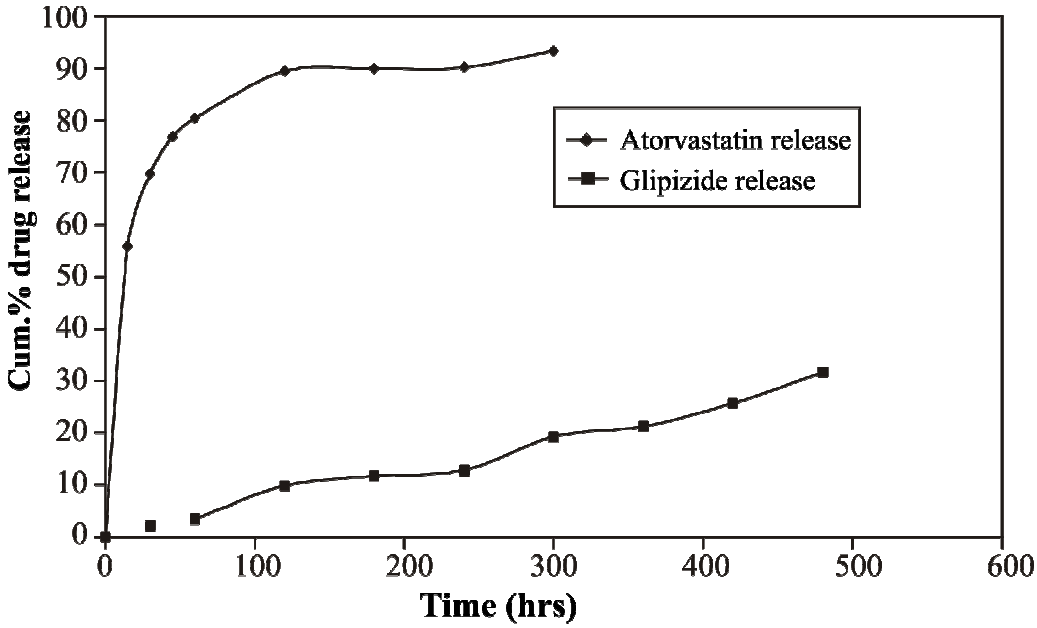

Fig. 7 : *In vitro* release profile of the formulated bi-layer tablet differential scanning calorimetry (DSC)

Table 6: Stability studies data of the formulations stored at 40 ± 2ºC / 75 ± 5 % RH

	Percentage of drug content (weeks)												
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
F1	100.50	100.38	100.31	99.87	100.80	100.20	100.72	100.31	99.87	100.31	10.31	99.87	99.21
F2	100.10	99.23	100.12	100.72	99.71	98.71	99.10	100.12	100.72	100.12	100.12	100.72	98.71
F3	99.80	99.71	99.31	100.10	100.21	99.21	98.98	99.31	100.10	99.31	99.31	100.10	98.98
E1	100.80	100.90	99.98	101.00	100.28	100.21	100.71	99.98	101.00	99.98	99.98	101.00	99.21
E2	101.00	100.05	100.18	101.13	101.21	100.20	99.89	100.18	101.13	100.18	100.18	101.13	100.22
E3	102.10	101.81	100.28	102.13	101.01	100.80	100.78	100.28	102.13	100.28	100.28	102.13	100.21
L1	102.10	103.23	101.78	102.31	101.02	100.88	99.98	101.78	102.31	101.78	101.78	102.31	100.42
L2	99.20	10.10	99.27	99.78	100.17	100.72	99.38	99.27	99.78	99.27	99.27	99.78	99.81
L3	101.20	100.20	101.31	101.48	101.72	100.42	100.71	101.31	101.48	101.31	101.31	101.48	100.98
L4	100.20	100.11	100.31	100.13	99.98	99.78	99.51	100.31	100.13	100.31	100.31	100.13	100.34
L5	98.90	99.81	98.21	98.78	98.21	99.70	98.21	98.21	98.78	98.21	98.21	98.78	98.29
K1	**100.10**	**108.81**	**100.26**	**99.78**	**99.60**	**99.78**	**98.90**	**100.26**	**99.78**	**100.26**	**100.26**	**99.78**	**99.50**
K2	99.80	99.50	100.12	100.19	99.61	99.71	98.29	100.12	100.19	100.12	100.12	100.19	98.89
K3	99.10	99.71	100.12	100.87	100.18	98.12	98.20	100.12	100.87	100.12	100.12	100.87	98.71
A1	102.10	102.22	101.78	101.21	101.31	102.32	100.87	101.78	101.21	101.78	101.78	101.21	101.21
A2	98.10	98.21	97.91	97.80	98.78	98.76	98.26	97.91	97.80	97.91	97.91	97.80	98.40
A3	**100.20**	**99.21**	**101.12**	**101.12**	**100.31**	**99.72**	**99.88**	**101.12**	**101.12**	**101.12**	**101.12**	**101.12**	**99.91**

DSC studies indicated no interaction between drugs and polymer / other excipients.

Stability studies

All the separate layer tablets of atorvastatin and glipizide showed no significant change in the physical appearance and drug content after storing them at 40 ± 2 °C / 75 ± 5 % RH for 3 months (Table 6).

CONCLUSION

The bi-layer tablets containing one I. R. layer of atorvastatin and another E. R. layer of glipizide were formulated, which offers better patient compliance of once daily dosing. The *in vitro* release studies of single layer tablets showed that the I. R. tablets of atorvastatin rapidly disintegrates and dissolves and the E. R. tablets of glipizide released the drug at constant rate till the end of the dissolution process. The simultaneous *in vitro* evaluation of the formulated bi-layer tablet by RP HPLC method also proved the same. Thus, the formulated bi-layer tablets may be considered for further bio- availability studies and other regulatory affairs required by the Government, to treat the patients suffering from Type II diabetes mellitus with or without adverse lipid profile.

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