Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2013, 5 (2):54-62
(http://scholarsresearchlibrary.com/archive.html)

Der Pharmacia Lettre
Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Development of bilayer tablets of lisinopril and gliclazide: *In vitro* and *in vivo* evaluation

[*1]Izhar Kasid, [1]M A Saleem, [2]Rozeena Parveen, [2]Nikhat Parveen and [3]Aijaz A Sheikh

[1]Department of Pharmaceutics, Luqman College of Pharmacy Gulbarga
[2]Department of Pharmaceutics, P. Wadhawani College of Pharmacy, Yavatmal
[3]Department of Pharmaceutics, Anuradha College of Pharmacy, Chikhli

---

ABSTRACT

Bilayer tablets were prepared by using combination of fast dissolving lisinopril along with sustained release gliclazide. The FTIR study conducted using a combination of drugs along with excipients and polymers revealed that combination can be safely prepared. The precompression parameter of powder blends for preparation of individual layers suggested good flowability and compressibility. Lisinopril was formulated as fast dissolving layer using sodium starch glycolate, croscarmellose sodium as superdisintegrants and evaluated for physical parameter and disintegration time. The optimized lisinopril fast dissolving layer (L-6) with highest in vitro release of 99.73% was selected. Gliclazide was formulated as sustained release layer using different polymer matrix like hydroxyethylcellulose, hydroxypropylcellulose, and ethylcellulose and evaluated for physical parameter along with in vitro release studies. The optimized sustained release layers (G-5) which extend the gliclazide release more than 8hrs was selected. Finally bilayer tablets were prepared by double compression of optimized gliclazide sustained release layer and lisinopril fast dissolving layer. Bilayer tablets were evaluated for hardness, thickness, weight variation, friability, in vitro disintegration time and in vivo antidiabetic activity using wistar rats. All the physical parameters were in acceptable limit of pharmacopeial specification. The in vivo antidiabetic activity suggested that lisinopril potentiate hypoglycemic effect of gliclazide and blood glucose level was constantly maintained upto 24 h. Hence bilayer tablets of lisinopril and gliclazide as fast and sustained release combination could be used to improve patient compliance towards the effective management of diabetes along with diabetic hypertension and nephropathy.

Keywords: Gliclazide; Lisinopril; bilayer tablets; fast release layer; sustained release layer; *in vivo* antidiabetic activity.

INTRODUCTION

Bi-layer tablets are the novel drug delivery system where combination of two or more drugs in a single unit having different release profile improves patient compliance, prolongs the drug action, avoid the saw tooth kinetics resulting in effective therapy along with better control of plasma drug level. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose[1]. Hence in the present work an attempt was made to formulate bilayer tablet of lisinopril and gliclazide as bimodal release system to manage diabetes mellitus and to overcome diabetic induced complications such as hypertension and nephropathy.

Patient with type I and II Diabetes mellitus represent a population at a high risk of the cardiovascular, cerebrovascular and renal effects of hypertension. Hypertension is twice as prevalent in people with diabetes as in the general population. In both type I and II diabetes, hypertension leads to a two or three fold increase in major cardiovascular events. In type II diabetes, stroke, coronary heart disease account for the majority of death with hypertension being associated with a four to five fold increase in mortality compared with normotensive type II diabetic patients. On average 75-80% of adult diabetic subject die from coronary heart disease, cerebrovascular and or peripheral vascular disease. Hypertension is a major contributor to large vessel disease, especially in type II diabetes and the level of urinary albumin, excretion has been shown to reflect the degree of macrovascular risk. Therefore monitoring of the cardiovascular risk factor in these patients is critical. Several studies have suggested that ACE inhibitor are superior to other classes of agent in conferring additional cardioprotection in hypertensive patient with type I or II diabetes as they decrease protienuria and preserve glomerular filtration rate in diabetic patient and they also potentiate the effect of sulphonyl urea and biguanides[2,3]. Lisinopril is ACE inhibitors which is widely used in the treatment of hypertension in diabetic patients and also play a vital role in the management of diabetes complication such as diabetic nephropathy. Half life of lisinopril is 11-12 h and given in a dose of 2.5–10 mg daily[4]. In the GISSI-3 trail, lisinopril treatment was associated with improved 30 day survival in diabetic patients after an acute myocardial infract. Gliclazide is a second generation sulphonyl urea, an antihyperglycemic agent that improves glucose tolerance and enhances peripheral insulin sensitivity in patient with type-II diabetics. Also the effect of gliclazide is potentiated by the lisinopril. Half life of gliclazide is 10-12 h and given in a dose of 80 mg daily[5]

MATERIALS AND METHODS

Lisisnopril was a kind gift from Ipca Laboratries Pvt Ltd, Dehradun and Gliclazide, was gifted from Astro Pharmaceuticals Pvt Ltd Daman. HEC, HPC, EC were purchased from Loba chemicals, Mumbai. Croscarmellose sodium and Sodium starch glycolate were purchased from Colorcon Asia Pvt Ltd, Goa. All other reagents used were of analytical grade.

Drug-polymer interaction study by Fourier-transformation infrared (FTIR) spectroscopy:
The drug-polymer and polymer-polymer interactions were studied by FT-IR, Spectrum RX1, Perkin Elmer Ltd Switzerland by scanning the sample in Potassium bromide discs. The samples of both pure drug and granules containing drugs with different polymer were scanned individually.

Precompression parameters for lisinopril and gliclazide layers[6]:
Prior to compression, granules were evaluated for their characteristic parameters, such as bulk density, tapped density, hausner ratio, compressibility index and angle of repose.

Preparation of Immediate Release layer of Lisinopril:
Lisinopril and microcrystalline cellulose were mixed with disintegrant for 15 min in porcelain mortar, passed through 60# sieve. This blend was mixed with colloidal silicon dioxide and magnesium stearate for 5min and processed for direct compression by using 8 mm round concave-faced punch at 10 station tablet press. Compression force was maintained at constant level and magnesium stearate as lubricant was fixed at 2% w/w for all formulations. Disintegrants are used at 4, 6 and 8% in tablets. Compositions of all batches are represented in table-2.

Preparation of Sustained Release layer of Gliclazide:
Sustained release tablet layer was prepared by direct compression method according to the formula given in table-3. All the ingredients including drug were weighed accurately and passed through 60# sieve separately. The drug and polymer was mixed by small portion of both each time and blend it to get a uniform mixture and kept aside. Then all the ingredients weighed are mixed in geometrical order excluding magnesium stearate to get a uniform blend. Finally mixture is blended with magnesium stearate and tablets were compressed of 8mm sizes concave round punch to get tablet using Rimek Compression Machine.

Evaluation parameter for lisinopril and gliclazide layers: Standard physical test (hardness, thickness, friability, weight variation) for immediate release lisinopril layer and sustained release gliclazide layer were performed and average values were calculated according to pharmacopeial standard [7]. Drug content uniformity of lisinopril layer was determined by using 0.1N HCl as the extracting solvent, and the samples were analyzed spectrophotometrically at 258 nm. *In-vitro* disintegration time of lisinopril layer was performed using Electrolab disintegrating apparatus

using 0.1N HCl maintained at 37±0.5ºC as the immersion fluid. For drug content uniformity of gliclazide layer, the tablets were assayed using methanol as the extracting solvent at 226 nm.

***In vitro* dissolution studies of lisinopril:** Dissolution rate was studied by using USP type-II apparatus at 50 rpm using 900ml of 0.1 N HCl solutions as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5°C, aliquot of 5 ml of dissolution medium was withdrawn at every 10 min interval. The absorbance of solution was measured by UV spectrophotometric method at 258 nm and concentration of the drug was determined. The volume of the dissolution medium was adjusted to 900 ml at every sampling time by replacing 5 ml with same dissolution medium.

***In vitro* dissolution studies of gliclazide:** The *in vitro* release of drug from gliclazide layer was carried out for 8 hours using paddle type tablet dissolution apparatus USP XXIII containing 900 ml of dissolution medium maintained at 37±0.5ºC and speed of agitation at 50 rpm. For the first 2 hours, 0.1N HCl buffer solution was used as dissolution medium and then the dissolution medium was changed by replacing with pH 6.8 phosphate buffer solution for further 6 hours. At prefixed time interval, 5 ml of solution was withdrawn and analyzed spectrophotometrically at 226 nm after suitable dilution. The volume of the dissolution medium was adjusted to 900 ml at every sampling time by replacing 5 ml with same dissolution medium.

Analysis of release data[8]: The released data obtained were fitted into various mathematical models like zero order, first order, Higuchi, Korsmeyer-Peppas, and Hixon-Crowell. Regressional analysis was performed by using INSTAT Software on the *in vitro* release data to best fit into various kinetic models according to the regression coefficient 'r'.

Preparation of bilayer tablet of lisinopril and gliclazide:
Optimized batch of lisinopril (L-6) and gliclazide (G-5) layers were selected for preparation of bilayer tablet. The quantity of powder blend for the sustained release layer was compressed lightly at 10 station Rimek tablet press using 8mm round concave punches. Over this compressed layer, required quantity of powder blend for fast release layer was placed and compressed with the hardness in the range of 5-7 $kgcm^2$ to form a bilayer matrix tablet

Evaluation:
Standard physical test such as hardness, thickness, friability, weight variation and *In vitro* disintegration time for bilayer tablets was performed using same method as describe above.

***In vivo* animals study of bilayer tablet using Wistar rats[9]:**
Experimental animals: Male wistar strains rats (159-250gms) were used for the studies. The experiment was conducted according to protocol approved by the institutional animal ethics committee (IAEC Reg No.346/CPCSEA). All the animals were housed in polypropylene cages lined with husk under 12/12 hr light/dark cycle at 22 ± 2 °C and 45-55% relative humidity. The animals were feed with standard pellets diet supplied by Lipton India Ltd and allow to free access of tap water *ad libitum*. After randomization into various groups, the animals were acclimatized for a period of 7 days.

Antihyperglycemic effects of bilayer tablet (BL):
In this study overnight fasted male wistar rats were made diabetic by single intraperitoneal injection of streptozotacin (90mg/kg dissolved in mM citrate buffer pH 4.5). After one week of streptozotacin injection animals exhibits blood glucose levels greater than 135mg/dL were included in the study. The blood sample were collected from tail vein of rats at different time intervals to detect blood glucose level after 2, 4, 8 and 24 hr after administration of formulation gliclazide (0.72mg/kg) and gliclazide+lisinopril (0.72mg/kg+0.9mg/kg) for group III and group IV resp. whereas group I and group II serves as normal control and diabetic negative contol. Statistical analysis: All the results are expressed as Mean±SEM one way ANNOVA following dunnets test by using INSTAT graph pad USA for statistical analysis between groups. The test is consider to be significant when $P<0.05$

RESULTS AND DISCUSSION

The precompression parameters for lisinopril fast dissolving layer and gliclazide sustained release layer are tabulated in Table-1. The bulk density was found in range of 0.26 to 0.42 gm/cm^3 which indicated good packing characteristics. The Carr's compressibility index was found to be below 15% which suggested good compressibility

of blend. The values of hausner ratio where found in the range of 1.07 to 1.23 suggested good flowability of powder blend. The angle of repose of all the blend was within range of 21.66 to 28.36^{o} indicated excellent flow property of powder blend.

The lisinopril fast dissolving layer and gliclazide sustained release layer was evaluated for hardness, thickness, friability, weight variation, drug content uniformity and *in vitro* disintegration time as represented in table-4. The hardness was in the range of 3.40 to 5.96 kg/cm^2 respectively which was within the acceptable range of pharmacopeial specification. The thickness was from 2.23 to 4.63 cm suggested uniformity in thickness of both the layer. The friability was less than 1% indicated good handling of both the layer. The weight variation results suggested uniformity in weight of both layers. The content uniformity was in range of 97.59 to 98.94% indicated uniform dispersion of lisinopril and gliclazide in two the layer. The *in vitro* disintegration time for the layer containing sodium starch glycolate was 40.66 to 52.33 sec, and the layer containing croscarmellose sodium showed 22.66 to 31.66 sec. As the concentration of superdisintegrants was increased there was decreased in the disintegration time, which was due to the fact that higher level of disintegrants probably made the large pores with continuous network of skeleton providing enough pressure within matrix for faster disintegration[10]. Hence the disintegration time for all the prepared layer was less than 1 minutes indicated that the prepared layer was fast dissolving.

The *in vitro* release data of lisinopril is tabulated in table-5. The *in vitro* release of lisinopril was plotted as percent drug release versus time as depicted in fig-2. The *in vitro* release of lisinopril was rapid from all the layers. The layer prepared by using sodium starch glycolate showed 98.63 to 94.22% within 50 mins which was due to enormous swelling followed by rapid disintegration. The rapid *in vitro* release of lisinopril in the range 99.73 to 90.91% in 30 mins from the layer containing croscarmellose sodium which was attributed to fact that highest water uptake with strong swelling of this disintegrants[11]. As the concentration of superdisintegrants increased in all the formulated layers, the release was more and rapid which was due to rapid disintegration in shortest time. Hence based on the disintegration time and *in vitro* release study L-6 layer was selected as fast dissolving layer of lisinopril for further preparation of bilayer tablet. The *in vitro* release data of gliclazide from sustained layer is tabulated in table-6 and illustrated in fig-3 the *in vitro* release of gliclazide was fast in 0.1N HCl due to the swelling of polymer matrix used in the preparation of sustained release layer. About 30% drug was released in initial first two hours. Then *in vitro* release was sustained in pH 6.8 phosphate buffer due to the hydrophobic ethyl cellulose polymer which is strong retarder. A maximum of 95.25% from HEC, 87.34% from HPC and 76.59% from EC polymer matrix of sustained release layer was released within 8hrs. In the present work HPC and HEC were used as hydrophilic polymer whereas EC was used as hydrophobic polymer as a matrix in the preparation of sustained release layer. The *in vitro* release followed the rank order according to polymer matrix as HEC> HPC>EC. The highest release was observed with HEC which is commonly used hydrophilic matrix, gets swelled and dissolved in aqueous media forming viscous gel thereby rapidly releasing the drug[12]. Combination of HPC with EC significantly prolonged the release as compared to HPC and EC alone. The combination of HEC with EC extended the release more than 8 hours as shown in formulation G-5 which was attributed to fact that the hydroxyethylcellulose enormously get swells along with EC to form a highly viscous gel network and incorporation of ethylcellulose decreased the penetration of solvent molecules leading to decrease diffusion of the drug from the gel matrix. The overall results of *in vitro* release study suggested that the rate of drug release from the matrix tablet was found to be decrease with the increase in polymer ratio, because an increase in polymer concentration caused an increased in viscosity of gel (by making it more resistant to drug diffusion and erosion) as well as the formation of a gel layer with a longer diffusion path, which ultimately reduced the drug release rate.

The *in vitro* release data from sustained release layer was subjected to zero order, first order, Higuchi, Korsmeyer-Peppas and Hixon-Crowell, in order to establish drug release mechanism and kinetics of drug released from sustained release layer. The goodness of best fit was evaluated by regressional analysis of the said models. The correlation coefficient r^2 according to all the models is mentioned in table-7. The kinetics of *in vitro* release from the formulation G-5 obeyed zero order with the high regression r^2 value of 0.9974 for the part curve which shows sustained release after 2 hrs primarily and the remaining part curve for initial 2hrs obeyed first order which showed less r^2 value due to initial burst effect. As the polymers used were matrix hence Higuchi model was applied which showed good linearity with high regression 0.9725 suggested that the release mechanism was diffusion controlled. Hixon-Crowell cube root model showed high r value of 0.9982 to 0.9871 suggested that the geometrical shape of tablet diminished proportionality due to erosion of hydrophilic gel layer. In order to define a model which will represent the data fit for release kinetic and mechanism, the *in vitro* release data was subjected to Korsmeyer-Peppas

model which shows good linearity with high r^2 value of 0.9985 to 0.9902. All formulation showed value of 'n' higher than 1 in the range of 1.09 to 1.42 indicated the release probably by super case II transport mechanism due to the large increase in osmotic pressure driving force[13]. Hence from overall study of gliclazide sustained release layer G-5 were selected for the preparation of bilayer tablet.

The bilayer tablets were evaluated for different physical parameter. The hardness of bilayer tablet was found in the range of 5.86 ± 0.11 kg/cm^2 which was more as compare to individual layer because of double compression. The thickness of the bilayer tablet was in the range of 5.24 ± 0.00 cm which was increased as compare to individual layer because of increase in amount of excipients. The friability was 0.71 ± 0.09% for bilayer tablet which was less than 1 indicating good handeling of tablet. The weight variation study showed low standard deviation uniformity in weight of the tablets 300 ± 0.05mg. The *in vitro* disintegration time was 20.33 ± 1.15 sec for the tablets suggested rapid disintegration of only lisinopril layer whereas the gliclazide layer was not disintegrated but swells.

The selected bilayer tablet (BL) and plain gliclazide tablet was evaluated for *in vivo* antidiabetic activity in Wistar albino rats. The results are shown in table-9 & fig-4. The bilayer tablet of lisinopril and gliclazide (BL) showed significant (P<0.05) reduction in blood glucose level after 2, 4, 8, and 24 hours, whereas the plain gliclazide tablet also shows significant (P<0.05) reduction in blood glucose level after 2, 4, 8, and 24 hours. The reduction in blood glucose level was maintained upto 24 hours constantly using bilayer tablet which may be due to lisinopril potentiate the effect of giclazide[14] and also due to sustained release of gliclazide, whereas plain gliclazide showed fluctuation in maintaining blood glucose level upto 24 hours because it was a conventional tablet containing alone gliclazide.

Table 1: Precompression parameters for lisinopril and gliclazide layer

Batch code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (I_C)	Hausner ratio (H_R)	Angle of repose (θ)
L-1	0.27±0.05	0.31±0.01	9.67±0.05	1.15±0.02	24.61±0.05
L-2	0.26±0.05	0.28±0.05	7.14±0.10	1.08±0.04	22.05±0.05
L-3	0.28±0.05	0.31±0.01	9.67±0.05	1.10±0.07	26.00±0.05
L-4	0.27±0.07	0.30±0.05	10.00±0.10	1.11±0.07	22.12±0.05
L-5	0.27±0.07	0.29±0.01	6.89±0.05	1.07±0.07	23.11±0.01
L-6	0.27±0.01	0.31±0.01	12.90±0.05	1.14±0.02	21.96±0.05
G-1	0.381 ± 0.04	0.443 ± 0.05	14.03 ± 0.11	1.16 ± 0.04	26.76 ± 0.05
G-2	0.378 ± 0.05	0.449 ± 0.05	15.78 ± 0.05	1.18 ± 0.06	21.36 ± 0.05
G-3	0.362 ± 0.02	0.446 ± 0.04	18.96 ± 0.06	1.23 ± 0.03	27.67 ± 0.01
G-4	0.426 ± 0.07	0.466 ± 0.07	8.58 ± 0.05	1.09 ± 0.05	25.49 ± 0.00
G-5	0.409 ± 0.01	0.466 ± 0.02	12.23± 0.09	1.13 ± 0.08	28.36 ± 0.10
G-6	0.425 ± 0.04	0.500 ± 0.04	15.00 ± 0.11	1.17 ± 0.08	23.24 ± 0.01
G-7	0.406 ± 0.07	0.474 ± 0.03	14.34 ± 0.11	1.16 ± 0.03	21.85 ± 0.05

Table 2: Composition of lisinopril fast dissolving layer

Ingredients	L-1	L-2	L-3	L-4	L-5	L-6
Lisinopril	10	10	10	10	10	10
Sodium starch glycolate	4	6	8	-	-	-
Croscarmellose sodium	-	-	-	4	6	8
MCC	83	81	79	83	81	79
Magnesium Stearate	02	02	02	02	02	02
Colloidal silicon dioxide	01	01	01	01	01	01
Total	100	100	100	100	100	100

Table 3: Composition of gliclazide sustained release layer.

Ingredients	G-1	G-2	G-3	G-4	G-5	G-6	G-7
Gliclazide	40	40	40	40	40	40	40
HEC	80	-	-	60	20	-	-
HPC	-	80	-	-	-	60	20
EC	-	-	80	20	60	20	60
Lactose anhydrous	60	60	60	60	60	60	60
MCC	16	16	16	16	16	16	16
Talc	02	02	02	02	02	02	02
Magnesium Stearate	02	02	02	02	02	02	02
Total	200	200	200	200	200	200	200

Table 4: Physical evaluation parameter for lisinopril and gliclazide layers

Batch code	Hardness Kg/cm3	Thickness (cm)	% Friability	Weight Variation (mg)	Drug content	*In- vitro* disintegration time(sec)
L-1	3.46±0.05	2.24±0.05	0.43±0.05	100±0.02	96.65±0.90	52.33±2.51
L-2	3.40±0.00	2.30±0.00	0.33±0.05	100±0.05	98.21±0.90	46.66±1.52
L-3	3.43±0.05	2.23±0.04	0.40±0.01	100±0.01	96.23±0.54	40.66±1.15
L-4	3.76±0.05	2.27±0.04	0.16±0.05	100±0.57	95.08±1.80	31.00±2.88
L-5	3.70±0.00	2.24±0.05	0.20±0.00	100±0.57	94.56±0.90	27.66±2.51
L-6	3.83±0.05	2.23±0.04	0.20±0.00	100±0.02	96.65±0.90	22.66±2.51
G-1	5.96±0.01	4.21±0.02	0.50±0.00	200±0.05	98.21±0.90	--
G-2	5.60±0.01	4.01±0.20	0.76±0.05	200±0.10	96.23±0.54	--
G-3	5.00±0.05	3.96±0.02	0.43±0.05	200±0.02	95.81±0.90	--
G-4	5.60±0.05	4.63±0.05	0.23±0.05	200±0.02	98.94±0.17	--
G-5	5.23±0.05	4.61±0.02	0.17±0.05	200±0.10	97.59±0.36	--
G-6	5.43±0.05	4.03±0.05	0.63±0.05	200±0.10	94.97±0.90	--
G-7	5.23±0.05	4.05±0.08	0.50±0.00	200±0.10	97.59±0.36	--

Table 5: *In vitro* cumulative drug release profile of lisinopril from fast dissolving layer

Time in mins	L-1	L-2	L-3	L-4	L-5	L-6
0	0.00	0.00	0.00	0.00	0.00	0.00
10	51.24±0.16	69.97±0.04	74.93±0.05	71.08±0.30	82.10±0.05	89.81±0.30
20	64.46±0.48	82.10±0.24	84.85±0.05	81.00±0.90	90.91±0.05	95.87±0.30
30	79.89±0.08	89.91±0.24	91.46±0.01	90.91±0.90	94.22±0.05	99.73±0.10
40	90.91±0.16	92.57±0.72	94.22±0.50	96.42±0.30	99.18±0.01	
50	94.22±0.48	95.87±0.04	98.63±0.50	99.42±0.90		
60	96.42±0.48	97.53±0.32				
70	99.18±0.16					

Table 6: *In vitro* cumulative drug release profile of gliclazide from sustained release layer

Time in hrs	G-1	G-2	G-3	G-4	G-5	G-6	G-7
0	0	0	0	0	0	0	0
0.5	30.81±0.10	28.07±0.90	27.99±0.10	29.06±0.40	30.73±0.90	28.23±0.90	29.23±0.90
1	36.72±0.10	35.70±0.90	33.07±0.90	36.05±0.40	36.47±0.90	34.72±0.50	33.85±0.90
2	49.93±0.90	48.32±0.90	45.46±0.90	46.01±0.40	45.32±0.90	46.1±0.40	34.84±0.90
3	60.06±0.90	58.54±0.90	51.24±0.90	52.14±0.10	51.94±0.90	49.45±0.10	43.89±0.90
4	73.05±0.90	67.05±0.90	60.40±0.40	59.91±0.10	55.05±0.90	56.47±0.10	50.34±0.10
5	80.14±0.90	75.09±0.10	65.95±0.10	67.76±0.10	58.71±0.10	60.86±0.10	56.87±0.10
6	86.12±0.40	81.09±0.10	72.00±0.10	74.97±0.10	61.57±0.10	68.24±0.40	63.36±0.10
7	90.01±0.40	84.42±0.10	74.74±0.90	79.05±0.10	64.02±0.10	72.26±0.40	67.93±0.10
8	95.25±0.10	87.34±0.10	76.59±0.10	83.11±0.10	67.15±0.10	79.56±0.40	71.60±0.40

Table 7: Regression analysis and correlation coefficient 'r' values of the *in vitro* release data according to various release kinetic model

Batch code	**Zero order**	**First order**	**Higuchi**	**Korsmeyer-Peppas**		**Hixon-Crowell**
	'r'	**'r'**	**'r'**	**'r'**	**N**	**'r'**
G-1	0.9477	-0.9694	0.9717	0.9937	1.209	0.9912
G-2	0.9966	-0.9816	0.9681	0.9912	1.350	0.9938
G-3	0.9993	-0.9724	0.9603	0.9931	1.199	0.9871
G-4	0.9968	-0.9856	0.9744	0.9921	1.422	0.9940
G-5	0.9974	-0.9948	0.9725	0.9773	1.240	0.9982
G-6	0.9994	-0.9820	0.9666	0.9974	1.098	0.9927
G-7	0.9991	-0.9882	0.9620	0.9902	1.320	0.9945

Table 8: Formulation of bilayer tablet of gliclazide and Lisinopril

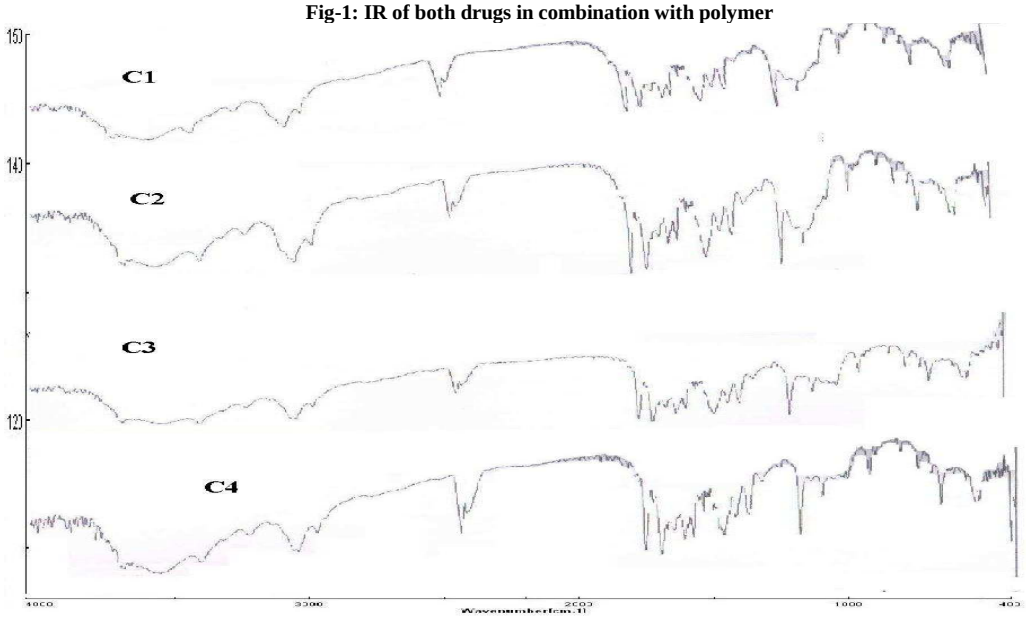
Ingredients	BL
Gliclazide	40
HEC	20
EC	60
Lactose anhydrous	60
MCC	16
Talc	02
Magnesium stearate	02
Lisinopril	10
Croscarmellose sodium	8
MCC	79
Magnesium stearate	2
Colloidal silicon dioxide	1
Total	300

Table 9: *In vivo* antidiabetic activity of bilayer tablet

Group	Blood Glucose level in mg/dL					
	Body weight(gms)	0 hr	2hr	4hr	8hr	24hr
Normal control	230	92	68	64	66	113
	270	93	122	103	113	83
	220	81	192	91	90	118
values in SEM ± Mean		88.66±3.84	127.33 ±35.89	86.00±11.53***	89.66±13.5***	104.67±10.92*
Negative control	250	345	239	334	225	172
	230	202	210	215	231	499
	210	364	355	315	252	532
values in SEM ± Mean		302.67±51.12	301.33±45.90	288.00±36.91	236.00±3.18	401.00±114.9
Gliclazide plain tabet	200	170	120	111	99	104
	300	142	80	84	88	79
	230	166	109	105	71	121
values in SEM ± Mean		159.33±8.74	103.33±5.45**	100.66±18.78***	86.33±6.93***	101.66±10.73*
Bilayer tablet	170	139	105	97	106	105
	170	137	81	68	55	50
	170	135	75	63	60	58
values in SEM ± Mean		136.33±1.76	86.66±5.92**	76.33±12.60***	73.33±6.69***	71.00±8.78*

** indicates P<0.05, ** indicates P<0.01, ***indicates P<0.001, 'ns' indicates P<0.05*

Fig-1: IR of both drugs in combination with polymer



C1 → HEC+EC+CC+gliclazide+lisinopril, C2 → HEC+EC+SSG+gliclazide+lisinopril, C3 → HEC+HPC+CC+ gliclazide+lisinopril, C4 → HEC+HPC+SSG+ gliclazide+lisinopril

Fig-2: *In vitro* release profile of lisinopril fast dissolving layer

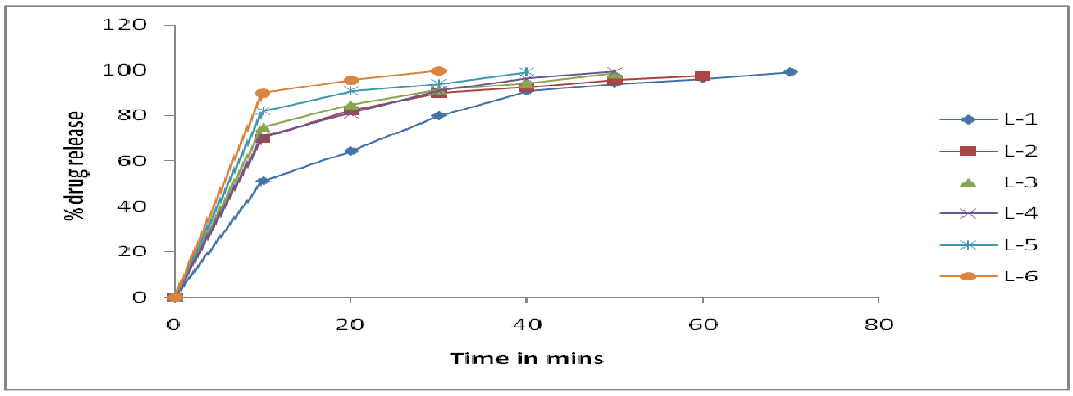


Fig-3: *In vitro* release profile of gliclazide sustained layer

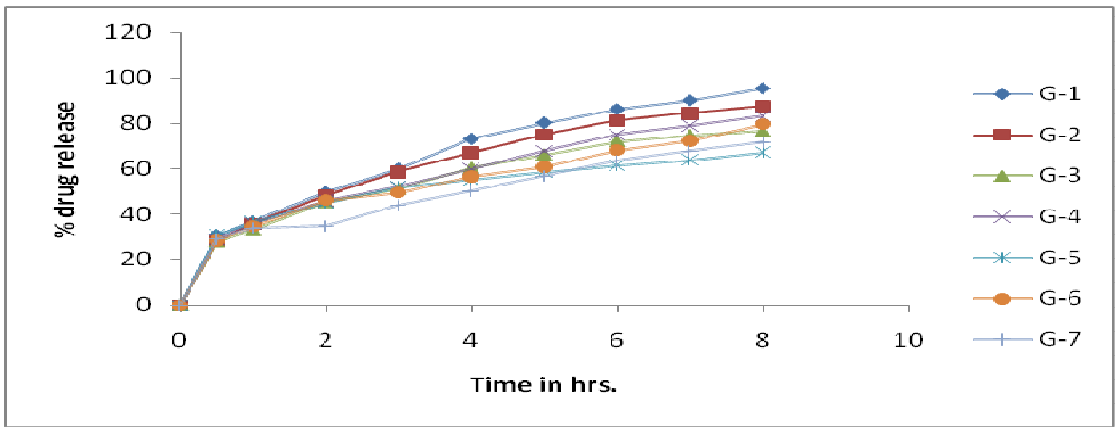
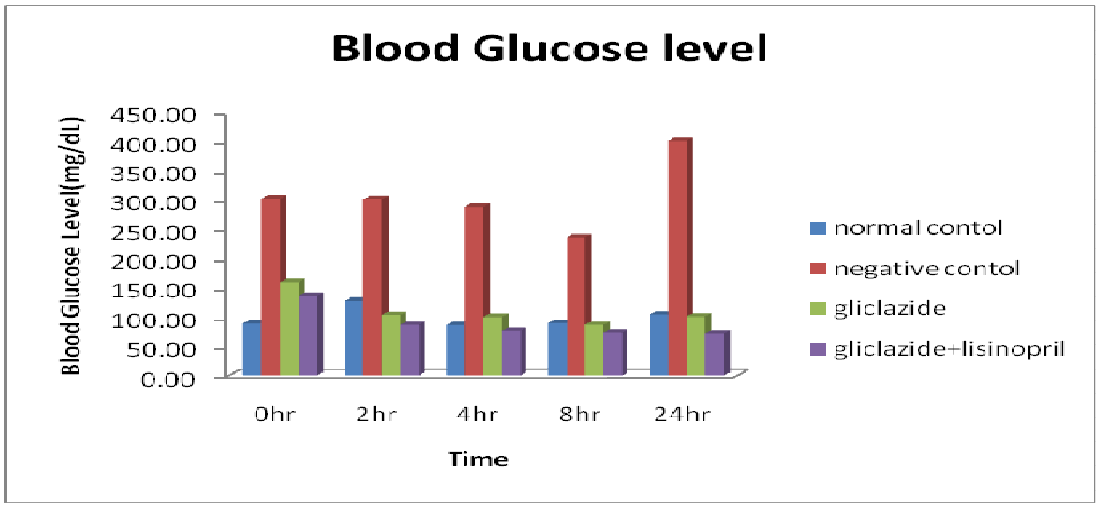


Fig 4: *In vivo* antidiabetic activity of bilayer tablets



CONCLUSION

Bilayer tablets were prepared by double compression of optimized lisinopril fast dissolving layer (L-6) along with gliclazide sustained release layers (G-5). The physical parameter of bilayer tablets were within the acceptable range of good mechanical and handeling properties and the *in vitro* disintegration time was less than 1 min for fast

dissolving layer**.** The *in vivo* antidiabetic activity using bilayer tablet suggested that lisinopril potentiate hypoglycemic effects of gliclazide and the blood glucose level was constantly maintained upto 24 h. Hence bilayer tablets of lisinopril and gliclazide as fast and sustained release combination could be used to improve patient compliance towards the effective management of diabetes along with diabetic hypertension and nephropathy.

Acknowledgement
The Author is thankful to Ipca Laboratries Pvt Ltd, Dehradun and Astro Pharmaceuticals Pvt Ltd Daman for providing lisinopril and gliclazide as a gift sample respectively

REFERENCES

[1] Gunsel W C. Compression-coated and layer tablet. In: Lieberman A H, (Ed). Pharmaceutical dosage forms: tablets. New York: Decker; **1989**:274-84
[2] Cooper M A, Jerums G, Chattington P D. *Saudi J Kidney Dis Transplant* **1999**; 10(3):325-32
[3] Samuel Dagogo J. Complication of diabetes mellitus-Metab III. Deckker Intlectuall Properties.**2010**; **7**: 5-15.
[4] Sweetman SC (Eds). In Martindale: The complete drug reference. Great Britain, Pharmaceutical press PhP.**2002**; 3: 322,921.
[5] Tripathi, K D. Essentials of Medical Pharmacology. Jaypee Brothers Medical Publishers Pvt. Ltd New Delhi, India.**2004**; 33: 246-50
[6] Subrahmanyam CVS. A textbook of Physical Pharmaceutics. Vallabh prakashan Delhi.**2000**: 214-29
[7] Lachman L, Lieberman H A, Kanig J L. The theory and practice of industrial pharmacy. Varghese Publishing House Mumbai.**1987**;3: 297-299
[8] Costa P, Lobo JM. *Eur J Pharm Sci*.**2001**; 13: 123-33.
[9] Mazumdar P M, Farswan M, Parcha V. *Nat. Prod. Rad*.**2009**; 8(5):478-482.
[10] Shenoy V, Agrawal S, Pandy S. *Ind J Pharm Sci*.2003; **2**:197-200.
[11] Rowe RC, Sheskey PJ, Owen SC. Handbook of Pharmaceutical Excipients. 5th edition. **2006**: 206,663
[12] Tiwari SB, Murthy KT, Pai RV, Mehta PR, Chowdary PB. *AAPSPharmSciTech*.**2003**; 4(3):1-6.
[13] Brazil CS, Peppas NA. *Polymer*.**1999**; 40:3383-98