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Research Article

Formulation and Evaluation of Bilayer tablet of Lisinopril and Gliclazide for Diabetic Hypertension

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Abstract

Bilayer tablet technology offers an effective approach for the management of chronic diseases requiring combination therapy. The present study focuses on the formulation and evaluation of bilayer tablets containing Lisinopril and Gliclazide for the treatment of hypertension associated with type 2 diabetes mellitus. The objective of the study was to develop a formulation providing immediate release of Lisinopril for rapid antihypertensive action and sustained release of Gliclazide for prolonged glycemic control. Bilayer tablets were prepared by direct compression method using different concentrations of superdisintegrants and matrix forming polymers such as Hydroxypropyl Methylcellulose (HPMC), Hydroxypropyl Cellulose (HPC), Hydroxyethyl Cellulose (HEC) and Ethyl Cellulose (EC). Precompression parameters including angle of repose, bulk density, Carr's index and Hausner ratio were found within acceptable pharmacopeial limits, indicating good flowability and compressibility of powder blends. Postcompression evaluation showed satisfactory hardness (3.40–3.83 kg/cm^2), friability below 1%, uniform thickness and acceptable drug content. The optimized immediate release formulation CC8 showed 96.65% drug release of Lisinopril within 30 min, whereas sustained release formulations prolonged the release of Gliclazide for more than 8 h following zero-order kinetics with super case-II transport mechanism. The optimized bilayer tablet formulation BCC8F14 exhibited satisfactory physicochemical properties and desired bimodal drug release profile. Stability studies revealed no significant changes under accelerated conditions. The developed bilayer tablet formulation may improve therapeutic efficacy, patient compliance and effective management of diabetic hypertension.

Keywords: Bilayer tablet, Lisinopril, Gliclazide, Immediate release, Sustained release, Diabetic, Hypertension.

INTRODUCTION

Hypertension and diabetes mellitus are among the most prevalent chronic metabolic disorders affecting the global population. The coexistence of hypertension and type 2 diabetes mellitus significantly increases the risk of cardiovascular diseases, nephropathy, retinopathy and cerebrovascular complications. Patients suffering from both disorders require long-term multidrug therapy, which may reduce patient compliance and therapeutic effectiveness. Therefore, development of combination dosage forms has gained considerable attention for improving therapeutic efficacy and patient adherence.[1,2] Lisinopril is a long-acting angiotensin converting enzyme (ACE) inhibitor commonly prescribed for the treatment of hypertension, congestive heart failure and diabetic nephropathy. It acts by inhibiting the conversion of angiotensin I into angiotensin II, thereby reducing peripheral vascular resistance and blood pressure. Lisinopril also exhibits renal protective activity in diabetic patients and decreases the progression of cardiovascular complications associated with hypertension.[3] The drug possesses good oral bioavailability and is widely used in maintenance therapy for chronic hypertensive conditions.

Gliclazide is a second-generation sulfonylurea antidiabetic drug indicated for the treatment of type 2 diabetes mellitus. It stimulates insulin secretion from pancreatic β-cells and effectively controls blood glucose level. Compared to other sulfonylureas, gliclazide shows lower incidence of hypoglycemia and provides antioxidant as well as hemovascular protective effects.[4] Due to its short biological half-life, gliclazide requires repeated administration to maintain therapeutic plasma concentration.

Bilayer tablet technology is an advanced drug delivery system designed to incorporate two compatible or incompatible drugs in a single dosage form with

different release patterns. Bilayer tablets provide several advantages including reduced dosing frequency, improved patient compliance, prevention of chemical incompatibility, ease of administration and enhanced therapeutic response. One layer may provide immediate release of drug for rapid onset of action, whereas the second layer may provide sustained or controlled release for prolonged therapeutic effect.[5,6] Bilayer tablet formulation has emerged as an effective approach for the management of chronic diseases such as hypertension and diabetes where combination therapy is essential. This dosage form can maintain steady plasma drug concentration for prolonged duration and minimize fluctuations associated with conventional dosage forms. In addition, bilayer tablets reduce pill burden and improve medication adherence in geriatric and chronic patients.[7]

The formulation of bilayer tablets requires careful selection of excipients, polymers and compression parameters to achieve acceptable hardness, friability, layer adhesion, weight variation and drug release characteristics. Major challenges associated with bilayer tablets include layer separation, insufficient mechanical strength, cross contamination and inaccurate weight control during compression. Proper optimization of formulation variables is therefore necessary to obtain stable and effective bilayer tablets.[8,9]

Several researchers have developed bilayer tablet formulations containing antihypertensive and antidiabetic drugs for improved therapeutic effectiveness. Combination therapy using bilayer tablets has demonstrated better patient compliance and enhanced disease management compared with conventional multiple dosage regimens. The incorporation of lisinopril and gliclazide into a bilayer tablet may provide simultaneous management of hypertension and diabetes mellitus in patients suffering from both disorders.[10]

Hence, the present study was aimed to formulate and evaluate bilayer tablets of lisinopril and gliclazide using suitable pharmaceutical excipients and polymers. The prepared bilayer tablets were evaluated for pre-compression parameters such as bulk density, tapped density, Carr's index, Hausner ratio and angle of repose as well as post-compression parameters including hardness, thickness, friability, weight variation, drug content uniformity and in-vitro dissolution studies to assess the quality, stability and effectiveness of the developed formulation.

MATERIALS AND METHODS

Materials

Lisinopril and Gliclazide were used as active pharmaceutical ingredients for the preparation of bilayer tablets. Hydroxypropyl methylcellulose (HPMC), Hydroxypropyl cellulose (HPC), Ethyl cellulose (EC), lactose anhydrous, microcrystalline cellulose (MCC), croscarmellose sodium, magnesium stearate, talc and colloidal silicon dioxide were used as polymers and excipients. All chemicals and reagents used during the study were of analytical grade and were obtained from local pharmaceutical suppliers and laboratory sources.

Methodology

1. Estimation of Lisinopril
2. Determination of λmax of Lisinopril

Accurately weighed quantity of Lisinopril was dissolved in 0.1 N HCl solution to prepare standard stock solution. Suitable dilutions were prepared using the same solvent. The prepared solution was scanned in the UV region of 200–400 nm using UV-Visible spectrophotometer against 0.1 N HCl as blank. The wavelength showing maximum absorbance was considered as λmax of Lisinopril.

Preparation of Standard Stock Solution of Lisinopril

Accurately weighed 10 mg of Lisinopril was transferred into 100 ml volumetric flask and dissolved in small quantity of 0.1 N HCl. The volume was adjusted up to 100 ml with the same solvent to obtain stock solution having concentration of 100 µg/ml.

Preparation of Calibration Curve of Lisinopril

From the prepared stock solution, aliquots were withdrawn and diluted suitably with 0.1 N HCl to obtain concentrations ranging from 2–12 µg/ml. The absorbance of resulting solutions was measured at determined λmax using UV-Visible spectrophotometer. Calibration curve of concentration versus absorbance was plotted.

Estimation of Gliclazide

Determination of λmax of Gliclazide

Accurately weighed quantity of Gliclazide was dissolved in phosphate buffer pH 6.8 and scanned between 200–400 nm using UV-Visible spectrophotometer. The wavelength corresponding to maximum absorbance was recorded as λmax of Gliclazide.

Preparation of Standard Stock Solution of Gliclazide

Accurately weighed 10 mg of Gliclazide was transferred into 100 ml volumetric flask and dissolved in phosphate buffer pH 6.8. Final volume was adjusted up to 100 ml with same buffer solution to obtain concentration of 100 µg/ml.

Preparation of Calibration Curve of Gliclazide

Aliquots were withdrawn from standard stock solution and diluted with phosphate buffer pH 6.8 to obtain concentration range of 2–12 µg/ml. The absorbance of prepared solutions was measured at λmax using UV-Visible spectrophotometer and calibration curve was prepared.

Drug-Polymer Compatibility Study

Drug-polymer compatibility study was carried out by Fourier Transform Infrared Spectroscopy (FTIR). FTIR spectra of pure drugs, polymers and optimized formulation were recorded using FTIR spectrophotometer within the range of 4000–400 cm^{-1}. The spectra were analyzed to detect possible interaction

between drug and excipients by comparing characteristic peaks of pure drug and formulation.

Preparation of Immediate Release Layer (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.

Preparation of Sustained Release Layer (Gliclazide)

Sustained release tablet layer was prepared by direct compression method according to the formula given in table. All the ingredients including drug were weighed accurately and passed through 60 mesh 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.

Formulation of Bilayer Tablets

Bilayer tablets of Lisinopril and Gliclazide were prepared by direct compression method. The formulation consisted of immediate release layer containing Lisinopril and sustained release layer containing Gliclazide.

All ingredients were accurately weighed according to formulation design. The materials were passed through sieve no. 60 separately to ensure uniform particle size distribution. Drug and excipients were blended thoroughly using mortar and pestle to obtain uniform powder mixture. Talc and magnesium stearate were added at final stage as glidant and lubricant respectively.

Initially, sustained release layer containing Gliclazide was introduced into die cavity and lightly compressed. Subsequently, immediate release layer containing Lisinopril was added over the first layer and final compression was carried out using tablet punching machine to obtain bilayer tablets of uniform thickness and hardnes

Table 1: Composition of lisinopril fast releasing layer.

Ingredients	SSG4	SSG6	SSG8	CC4	CC6	CC8	CP4	CP6	CP8
Lisinopril	10	10	10	10	10	10	10	10	10
Sodium starch glycolate	4	6	8	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	4	6	8	-	-	-
Crospovidone	-	-	-	-	-	-	4	6	8
MC	18	18	18	18	18	18	18	18	18
Magnesium Stearate	02	02	02	02	02	02	02	02	02
Colloidal silicon dioxide	01	01	01	01	01	01	01	01	01
Total	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

*All quantities in mg per tablet, F=formulation codes

Table 2: Composition of gliclazide sustained release layer

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12	F-13	F-14	F-15	F-16
Gliclazide	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
HPMC	120	-	-	-	30	90	30	90	30	90	-	-	-	-	-	-
EC	-	120	-	-	90	30	-	-	-	-	90	30	90	30	-	-
HPC	-	-	120	-	-	-	90	30	-	-	30	90	-	-	90	30
HEC	-	-	-	120	-	-	-	-	90	30	-	-	30	90	30	90
Lactose anhydrous	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
MCC	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
Talc	01	01	01	01	01	01	01	01	01	01	01	01	01	01	01	01
Magnesium Stearate	01	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Total	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Table 3: Formulation of bilayer tablet of gliclazide and lisinopril.

Ingredients	BCC8F4	BCC8F12	BCC8F14	BCC8F16
Gliclazide	40	40	40	40
EC	-	30	30	-
HPC	-	90	-	30
HEC	120	-	90	90
Lactose anhydrous	20	20	20	20
MCC	18	18	18	18
Talc	1	1	1	1
Magnesium stearate	1	1	1	1
Lisinopril	10	10	10	10
Croscarmellose sodium	8	8	8	8
MCC	18	18	18	18
Magnesium stearate	2	2	2	2
Colloidal silicon dioxide	1	1	1	1
Total	**300**	**300**	**300**	**300**

Evaluation of Powder Blend (Pre-Compression Parameters)

Angle of Repose

Angle of repose was determined by fixed funnel method. The powder blend was allowed to flow through funnel and height and radius of formed heap were measured.

$$\tan \theta = h/r$$

Where,

θ = Angle of repose

h = Height of pile

r = Radius of pile

Bulk Density

Bulk density was determined by pouring powder into a graduated cylinder and noting the initial volume. It was calculated using formula:

$$\text{Bulk Density} = \text{Mass} / \text{Bulk Volume}$$

Tapped Density

Tapped density was determined by tapping the cylinder until constant volume was obtained.

$$\text{Tapped Density} = \text{Mass} / \text{Tapped Volume}$$

Hausner Ratio

Hausner ratio was calculated to evaluate flow property of powder blend.

Hausner ratio was calculated as:

$$\text{Hausner Ratio} = \text{Tapped Density} / \text{Bulk Density}$$

Compressibility Index

The compressibility index of the powder blend was determined using bulk density and tapped density values.

Carr's index was calculated using bulk and tapped density values:

$$\text{Carr's Index} = [(\text{Tapped Density} - \text{Bulk Density}) / \text{Tapped Density}] \times 100$$

Preparation and Evaluation of Immediate Release Layer

An immediate-release layer containing Lisinopril was prepared using croscarmellose sodium as a superdisintegrant. All ingredients were blended uniformly and compressed. The prepared layer was evaluated for flow properties and compression characteristics.

Preparation and Evaluation of Sustained Release Layer

A sustained-release layer containing Gliclazide was prepared using different concentrations of HPMC, HPC, and EC polymers. The prepared powder blend was evaluated for angle of repose, bulk density, tapped density, Hausner ratio and compressibility index prior to compression.

Preparation of bilayer tablet of lisinopril and gliclazide





Optimized batch of lisinopril (CC8) and gliclazide (F-4,F-12,F-14 & F-16) 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. Prepared bilayer tablet are shown below.

EVALUATION OF BILAYER TABLETS

Thickness

Thickness of prepared bilayer tablets was measured using Vernier caliper and average values were recorded.

Hardness

Hardness of tablets was determined using Monsanto hardness tester and expressed in kg/cm^2.

Friability

Friability test was performed using Roche friabilator operated at 25 rpm for 4 min.

The difference in the weight is noted and expressed . It should be perfectly below 1.0%.

$$\% \text{ Friability} = [(W1-W2)/W1] \times 100$$

Where,

W1= weight of tablets before test,

W2 = weight of tablets after test.

Twenty tablets were weighed individually and average weight was calculated. The deviation in individual tablet weight from average weight was determined.

Drug Content Uniformity

Ten tablets were powdered and quantity equivalent to required dose was dissolved in suitable solvent. The solution was filtered, diluted appropriately and analyzed spectrophotometrically at respective λmax values.

In-vitro Dissolution Study

In-vitro dissolution study of bilayer tablets was performed using USP dissolution apparatus type II (Paddle method). Dissolution medium consisting of phosphate buffer pH 6.8 was maintained at 37 ± 0.5°C with paddle speed of 50 rpm. Samples were withdrawn at predetermined time intervals and replaced with equal quantity of fresh dissolution medium to maintain sink condition. The samples were filtered and analyzed using UV-Visible spectrophotometer at respective λmax values of Lisinopril and Gliclazide.

RESULT AND DISCUSSION

Bilayer Tablet Formulation

Bilayer tablets of Lisinopril and Gliclazide were successfully prepared by direct compression technique to provide immediate release of Lisinopril and sustained release of Gliclazide for effective management of diabetic hypertension and improvement of patient compliance.

Calibration Curve and Drug Estimation

The calibration curves of Lisinopril and Gliclazide showed good linearity within the selected concentration range with correlation coefficient value greater than 0.999, indicating compliance with Beer-Lambert's law and suitability of the analytical method for drug estimation.

FTIR Compatibility Study

FTIR studies confirmed compatibility between drugs and excipients. The characteristic peaks of both drugs were retained without significant shifting or disappearance of peaks, indicating absence of chemical interaction between drugs and selected polymers and superdisintegrants.

Precompression Parameters

The precompression parameters of powder blends such as angle of repose, bulk density, tapped density, Carr's index and Hausner ratio were found within acceptable pharmacopeial limits. The angle of repose values for immediate release and sustained release blends indicated excellent flow property, while Carr's index and Hausner ratio confirmed good compressibility suitable for direct compression method.

Evaluation of Immediate Release Layer

The immediate release layer of Lisinopril prepared using sodium starch glycolate, crospovidone and croscarmellose sodium showed satisfactory hardness, thickness, friability, weight variation and drug content uniformity. The hardness was found in the range of 3.40–3.83 kg/cm^2 and friability was below 1%, indicating satisfactory mechanical strength and handling properties of tablets. Drug content uniformity was found above 94%, indicating uniform distribution of drug within the formulation.

Disintegration Study

The in-vitro disintegration time of all fast dissolving formulations was less than 1 min. Increase in concentration of superdisintegrants decreased the disintegration time due to rapid water uptake and swelling property of polymers. Among all formulations, croscarmellose sodium showed faster disintegration compared with crospovidone and sodium starch glycolate.

Dissolution Study of Immediate Release Layer

The in-vitro dissolution study showed rapid release of Lisinopril from all formulations. The formulation containing croscarmellose sodium exhibited maximum drug release of 96.65% within 30 min due to rapid swelling and enhanced water uptake capacity. The drug release pattern followed the order: croscarmellose sodium > crospovidone > sodium starch glycolate. Based on disintegration and dissolution studies, formulation CC8 was selected as optimized immediate release layer.

Evaluation of Sustained Release Layer

The sustained release layer of Gliclazide prepared using HPMC, HPC, EC and HEC polymers showed satisfactory physical characteristics with acceptable hardness, thickness, friability and drug content uniformity above 95.81%, indicating uniformity and good mechanical strength of tablets.

Dissolution Study of Sustained Release Layer

The sustained release formulations prolonged the release of Gliclazide up to and beyond 8 h. Formulations containing HPMC and EC sustained drug release up to 8 h, whereas HPC and HEC extended the release for more than 8 h due to formation of swellable polymeric matrix. Drug release kinetics followed zero-order release pattern with super case-II transport mechanism, indicating diffusion-controlled drug release from polymer matrix system. Based on dissolution profile, formulations F4, F12, F14 and F16 were selected for bilayer tablet preparation.

Optimized Bilayer Tablet

The optimized bilayer tablet formulation BCC8F14 prepared using optimized immediate release layer CC8 and sustained release layer F14 showed satisfactory physical characteristics, rapid release of Lisinopril and prolonged release of Gliclazide with desired bimodal release profile. The optimized formulation demonstrated acceptable mechanical strength, rapid disintegration of immediate release layer and sustained drug release behavior, indicating its suitability for effective management of diabetic hypertension.

Table 4: Calibration curve of lisinopril in 0.1 N HCl solution.

Concentration (mcg/ml)	Absorbance* (mean± SD)
0.00	0.00± 0.000
10.00	0.211± 0.005
20.00	0.410± 0.003
30.00	0.600± 0.001
40.00	0.802± 0.005
50.00	0.998± 0.003

*Average of three determinations

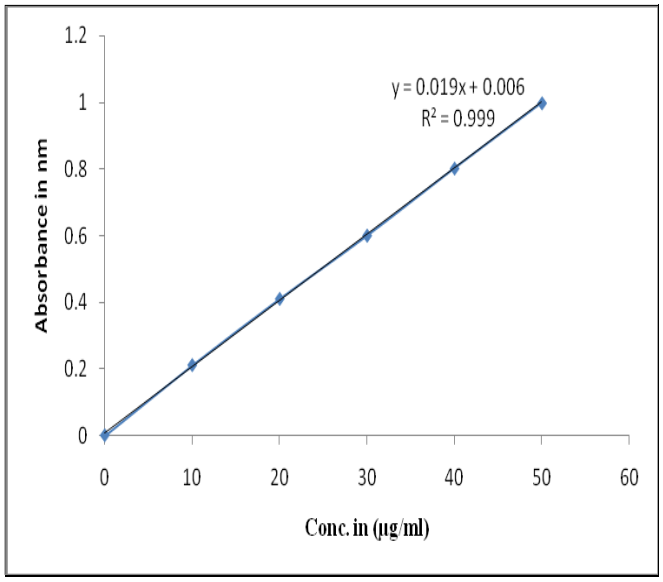


Figure 1: Calibration curve of lisinopril in 0.1 N HCl solution

Table 5: Calibration curve of gliclazide in 0.1 N HCl solution.

Concentration (mcg/ml)	Absorbance* (mean±SD)
0.00	0.00± 0.000
2.00	0.111± 0.005
4.00	0.222± 0.002
6.00	0.325± 0.003
8.00	0.436± 0.005
10.00	0.544± 0.004

*Average of three determinations

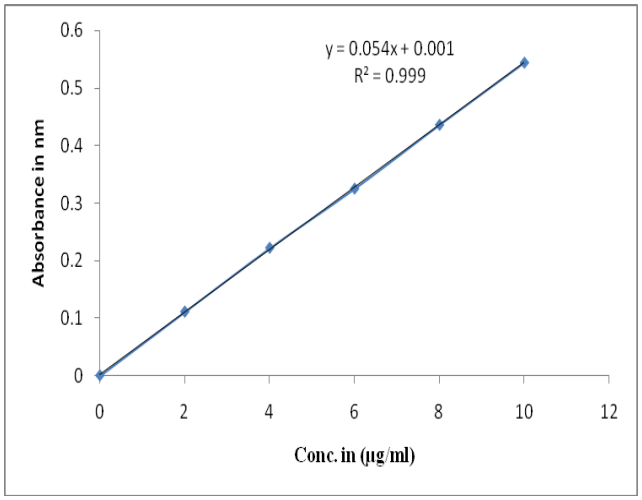


Figure 2: Calibration curve of gliclazide in 0.1 N HCl solution.

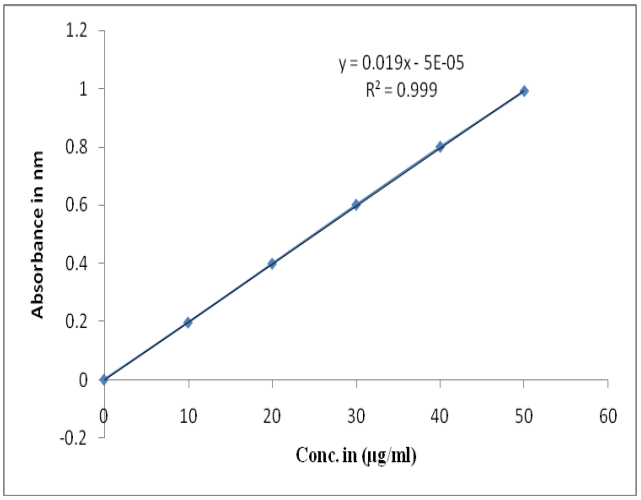


Figure 3: Calibration curve of gliclazide in pH 6.8 phosphate buffer solution.

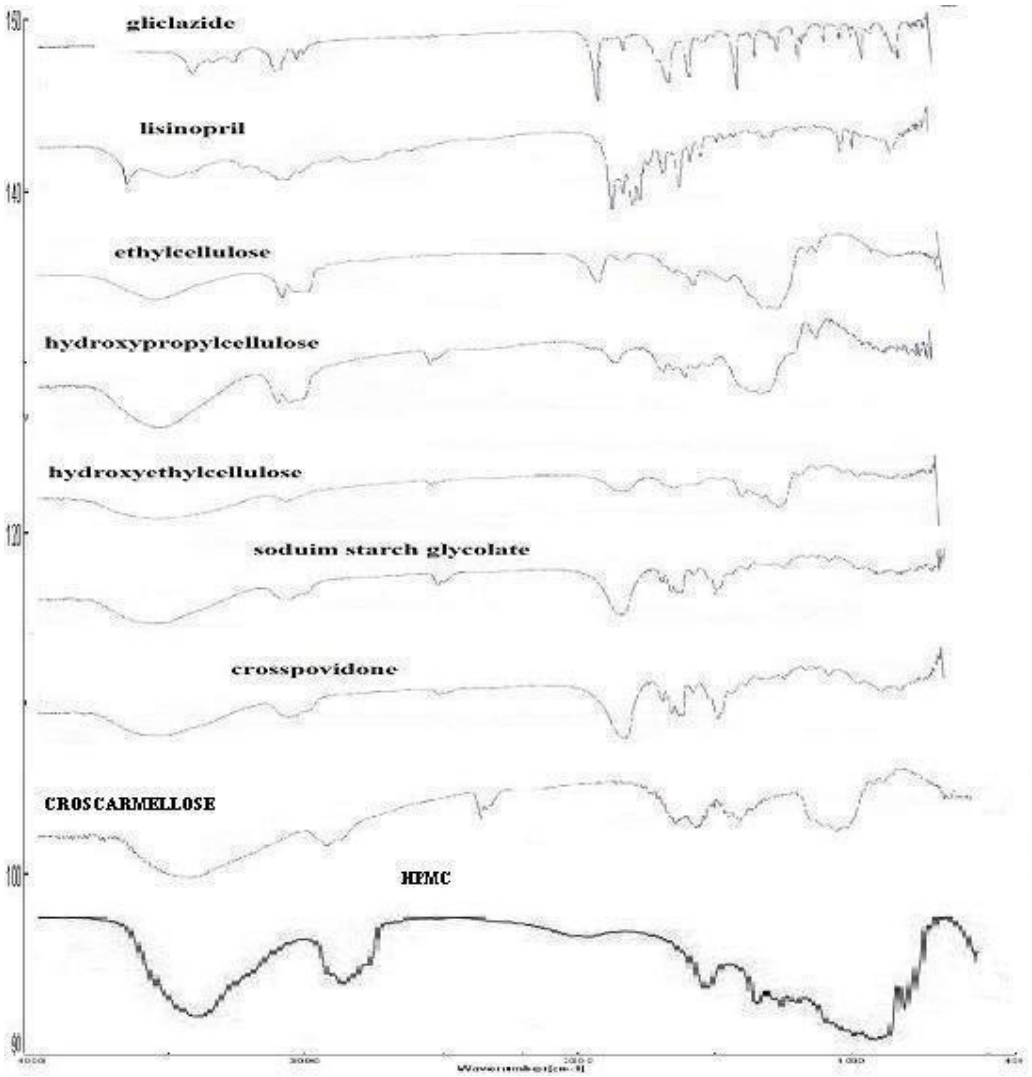
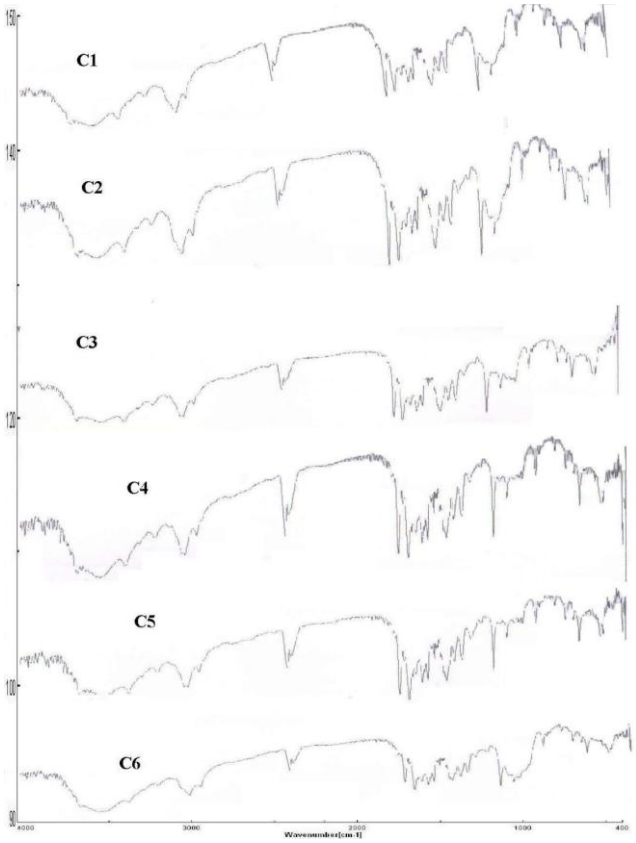


Figure 4: FTIR spectra of gliclazide, lisinopril, ethylcellulose, hydroxyl- propylcellulose, hydroxyethylcellulose, sodium starch glycolate, crospovidone and croscarmellose sodium.



C1: HEC+EC+CC+gliclazide+lisinopril.

C2: HEC+EC+CP+gliclazide+lisinopril.

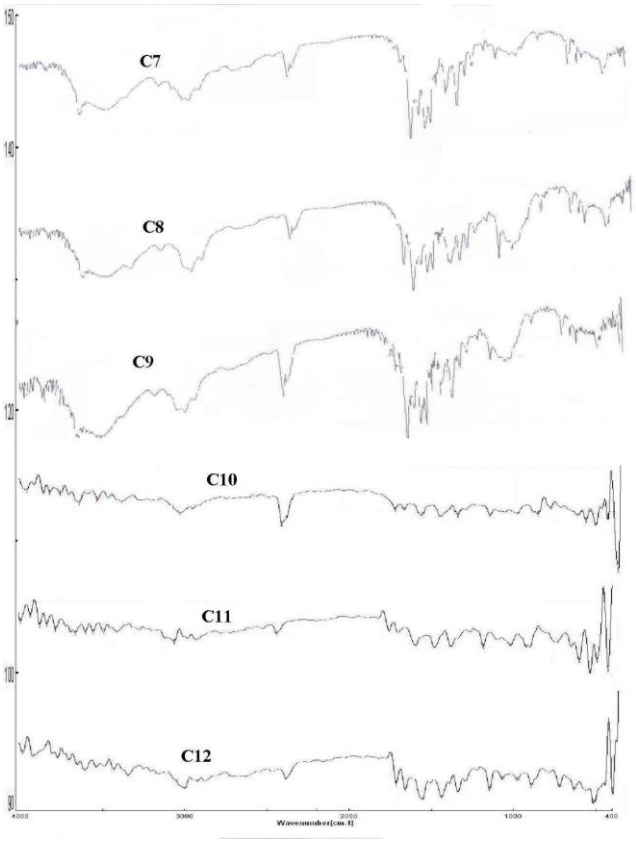
C3: HEC+EC+SSG+gliclazide+lisinopril.

C4: HEC+HPC+CC+ gliclazide+lisinopril.

C5: HEC+HPC+CP+ gliclazide+lisinopril.

C6: HEC+HPC+SSG+ gliclazide+lisinopril.

Figure 5: FTIR spectra of combination of different polymer, superdisintegrants and drugs.



C7:HEC+EC+CC+gliclazide+lisinopril

C8:HEC+EC+CP+ gliclazide+lisinopril.

C9:HEC+EC+SSG+gliclazide+lisinopril.

C10:HPMC+EC+CC+ gliclazide+lisinopril.

C11:HPMC+HPC+CC+ gliclazide+lisinopril.

C12: HPMC+HEC+CC+ gliclazide+lisinopril.

Figure 6: FTIR spectra of combination of different polymer, superdisintegrants and drug

Table 6: Precompression parameters for lisinopril fast dissolving layer.

Batch code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (IC)	Hausner ratio (HR)	Angle of repose (θ)
SSG4	0.27 ± 0.05	0.31 ± 0.01	14.81 ± 0.10	1.15 ± 0.02	24.61 ± 0.05
SSG6	0.26 ± 0.05	0.28 ± 0.05	7.14 ± 0.10	1.08 ± 0.04	22.05 ± 0.05
SSG8	0.28 ± 0.05	0.31 ± 0.01	9.67 ± 0.05	1.10 ± 0.07	26.00 ± 0.05
CP4	0.26 ± 0.07	0.30 ± 0.07	13.33 ± 0.05	1.15 ± 0.05	25.49 ± 0.05
CP6	0.25 ± 0.01	0.29 ± 0.01	13.79± 0.01	1.16 ± 0.01	21.66 ± 0.01
CP8	0.25 ± 0.01	0.28 ± 0.07	10.71 ± 0.10	1.12 ± 0.01	26.26 ± 0.01
CC4	0.27 ± 0.07	0.30 ± 0.05	10.00 ± 0.10	.11 ± 0.07	22.12 ± 0.05
CC6	0.27 ± 0.07	0.29 ± 0.01	6.89 ± 0.05	1.07 ± 0.07	23.11 ± 0.01
CC8	0.27 ± 0.01	0.31 ± 0.01	12.90 ± 0.05	1.14 ± 0.02	21.96 ± 0.05

Each value represents as mean±SD of three determinants.

Table 7: Precompression parameters for gliclazide sustained release layer

Batch code	Bulk density (gm/cm³)	Tapped density (gm/cm³)	Carr's index (IC)	Hausner ratio (HR)	Angle of repose (θ)
F-1	0.380 ± 0.05	0.440 ± 0.03	13.55 ± 0.10	1.15 ± 0.02	24.20 ± 0.01
F-2	0.381 ± 0.04	0.443 ± 0.05	14.03 ± 0.11	1.16 ± 0.04	26.76 ± 0.05
F-3	0.378 ± 0.05	0.449 ± 0.05	15.78 ± 0.05	1.18 ± 0.06	21.36 ± 0.05
F-4	0.362 ± 0.02	0.446 ± 0.04	18.96 ± 0.06	1.23 ± 0.03	27.67 ± 0.01
F-5	0.375 ± 0.04	0.454 ± 0.05	17.40 ± 0.09	1.21 ± 0.07	29.08 ± 0.00
F-6	0.430 ± 0.01	0.508 ± 0.01	15.35 ± 0.07	1.18 ± 0.02	21.96 ± 0.01
F-7	0.436 ± 0.07	0.496 ± 0.07	12.10 ± 0.05	1.14 ± 0.05	25.09 ± 0.05
F-8	0.409 ± 0.01	0.486 ± 0.02	15.90± 0.09	1.18 ± 0.08	28.36 ± 0.00
F-9	0.420 ± 0.05	0.476 ± 0.03	11.76 ± 0.10	1.13 ± 0.04	27.26 ± 0.05
F-10	0.465 ± 0.04	0.516 ± 0.04	9.88 ± 0.11	1.11 ± 0.08	29.24 ± 0.01
F-11	0.332 ± 0.07	0.374 ± 0.03	11.22 ± 0.11	1.12 ± 0.03	24.85 ± 0.10
F-12	0.450 ± 0.05	0.500 ± 0.06	9.80 ± 0.09	1.10 ± 0.07	26.11 ± 0.05
F-13	0.426 ± 0.07	0.466 ± 0.07	8.58 ± 0.05	1.09 ± 0.05	25.49 ± 0.00
F-14	0.409 ± 0.01	0.466 ± 0.02	12.23± 0.09	1.13 ± 0.08	28.36 ± 0.10
F-15	0.425 ± 0.04	0.500 ± 0.04	15.00 ± 0.11	1.17 ± 0.08	23.24 ± 0.01
F-16	0.406 ± 0.07	0.474 ± 0.03	14.34 ± 0.11	1.16 ± 0.03	21.85 ± 0.05

Each value represents as mean±SD of three determinants.

Table 8: Evaluation parameters of lisinopril fast dissolving layer.

Batch code	Hardness Kg/cm²	Thickness (cm)	% Friability	Weight Variation (mg)	Drug content	*In- vitro* disintegration time(sec)
SSG4	3.46 ± 0.05	2.24 ± 0.05	0.43 ± 0.05	100 ± 0.02	96.65 ± 0.90	52.33 ± 2.51
SSG6	3.40 ± 0.00	2.30 ± 0.00	0.33 ± 0.05	100 ± 0.05	98.21 ± 0.90	46.66 ± 1.52
SSG8	3.43 ± 0.05	2.23 ± 0.04	0.40 ± 0.01	101 ± 0.01	96.23 ± 0.54	40.66 ± 1.15
CP4	3.50 ± 0.00	2.17 ± 0.04	0.53 ± 0.05	100 ± 0.02	95.08 ± 1.27	38.66 ± 1.15
CP6	3.56 ± 0.05	2.24 ± 0.05	0.56 ± 0.05	100 ± 0.02	96.13 ± 0.36	35.33 ± 1.15
CP8	3.53 ± 0.11	2.19 ± 0.03	0.50 ± 0.05	100 ± 0.01	97.28 ± 1.26	31.66 ± 1.00
CC4	3.76 ± 0.05	2.27 ± 0.04	0.16 ± 0.05	100 ± 0.57	95.08 ± 1.80	31.00 ± 2.88
CC6	3.70 ± 0.00	2.24 ± 0.05	0.20 ± 0.00	100 ± 0.57	94.56 ± 0.90	27.66 ± 2.51
CC8	3.83 ± 0.05	2.23 ± 0.04	0.20 ± 0.00	100 ± 0.02	96.65 ± 0.90	22.66 ± 2.51

Each value represents as mean±SD of three determinants.

Table 9: *In vitro* release data of lisinopril from fast dissolving layer.

Time in mins	In vitro release								
	SSG4	SSG6	SSG8	CP4	CP6	CP8	CC4	CC6	CC8
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10	51.24	69.97	74.93	60.06	76.59	84.3	71.08	82.1	89.81
20	64.46	82.1	84.85	73.28	86.51	94.22	81	90.91	95.87
30	79.89	89.81	91.46	84.85	91.46	96.97	90.91	94.22	99.73
40	90.91	92.57	94.22	90.91	95.87	99.73	96.42	99.18	
50	94.22	95.87	98.63	95.32	99.18		99.42		
60	96.42	97.53		98.63					
70	99.18								

Each value represents as mean±SD of three determinan

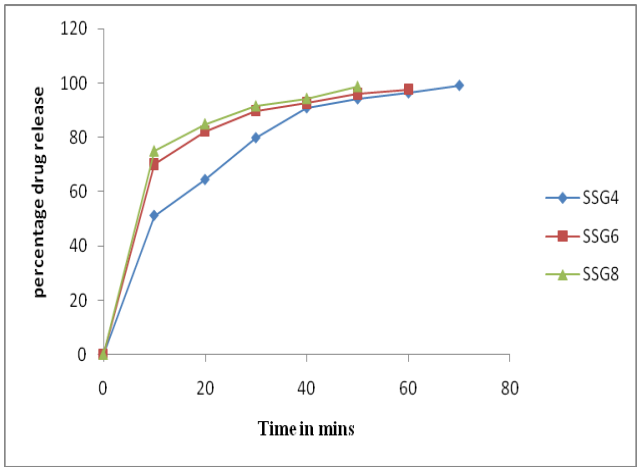


Figure 7: *In vitro* release of lisinopril from fast dissolving layer containing sodium starch glycolate.

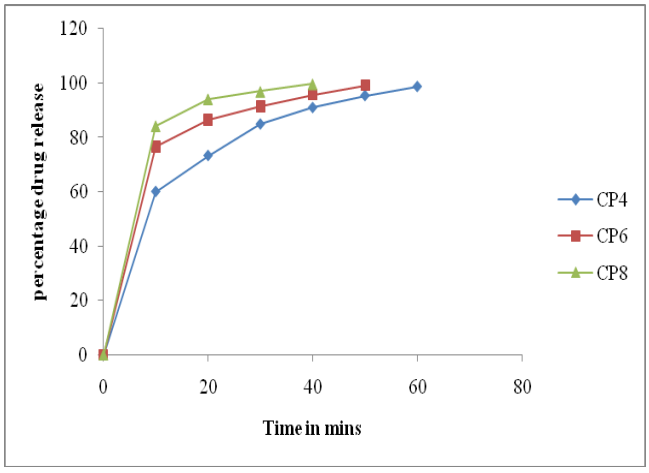


Figure 8: *In vitro* release of lisinopril from fast dissolving layer containing crospovidone.

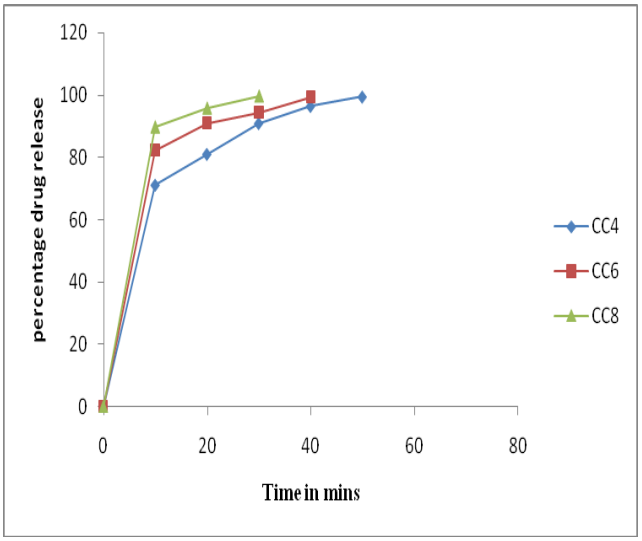


Figure 9: *In vitro* release of lisinopril fast dissolving layer containing croscarmellose sodium.

Table 10: Evaluation parameters of gliclazide sustained release layer.

Batch code	Hardness Kg/cm²	Thickness(cm)	Weight Variation (mg)	% Friability	Drug content(%)
F-1	5.53 ± 0.05	4.12 ± 0.02	200 ± 0.02	0.53 ± 0.05	96.65 ± 0.90
F-2	5.96 ± 0.01	4.21 ± 0.02	200 ± 0.05	0.50 ± 0.00	98.21 ± 0.90
F-3	5.60 ± 0.01	4.01 ± 0.02	201 ± 0.01	0.76 ± 0.05	96.23 ± 0.54
F-4	5.00 ± 0.05	3.86 ± 0.02	200 ± 0.02	0.43 ± 0.05	95.08 ± 1.27
F-5	5.26 ± 0.05	4.81 ± 0.01	202 ± 0.01	0.83 ± 0.05	97.28 ± 1.26
F-6	5.36 ± 0.05	4.71 ± 0.02	200 ± 0.57	0.63 ± 0.05	95.08 ± 1.80
F-7	5.53 ± 0.05	4.26 ± 0.01	200 ± 0.02	0.76 ± 0.05	96.65 ± 0.90
F-8	5.63 ± 0.05	4.33 ± 0.02	201 ± 0.02	0.23 ± 0.05	95.81 ± 0.90
F-9	5.06 ± 0.05	4.73 ± 0.02	202 ± 0.02	0.26 ± 0.05	97.07 ± 1.26
F-10	5.36 ± 0.01	4.68 ± 0.02	200 ± 0.10	0.33 ± 0.05	95.29 ± 1.62
F-11	5.73 ± 0.05	4.16 ± 0.02	200 ± 0.57	0.43 ± 0.05	97.27 ± 2.53
F-12	5.93 ± 0.05	4.03 ± 0.02	199 ± 0.02	0.73 ± 0.05	96.65 ± 1.80
F-13	5.60 ± 0.05	4.63 ± 0.05	200 ± 0.05	0.23 ± 0.05	98.94 ± 0.17
F-14	5.23 ± 0.05	4.61 ± 0.02	202 ± 0.05	0.17 ± 0.05	97.59 ± 0.36
F-15	5.43 ± 0.05	4.03 ± 0.05	200 ± 0.02	0.63 ± 0.05	94.97 ± 1.08
F-16	5.23 ± 0.01	4.05 ± 0.08	200 ± 0.10	0.50 ± 0.00	97.59 ± 0.36

Each value represents as mean±SD of three determinants.

Table 11: *In vitro release* of gliclazide sustained release layer.

Time In Hrs	*In vitro release*															
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12	F-13	F-14	F-15	F-16
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.25	5.06	1.66	0.76	0.66	0.99	2.16	0.09	2.07	0.91	4.56	1.60	0.09	1.32	0.33	2.07	0.58
0.5	9.05	3.15	2.53	1.66	3.55	3.48	2.74	6.06	3.07	9.88	2.96	4.15	3.32	1.66	3.57	2.07
0.75	13.88	5.81	5.07	2.99	6.64	4.98	6.97	10.71	6.89	13.04	4.65	7.31	7.06	3.73	5.23	5.23
1	18.27	9.72	7.70	4.07	9.22	7.27	10.05	14.12	10.21	17.11	5.92	10.25	10.05	7.47	8.72	6.85
1.5	24.09	13.88	13.88	6.72	14.72	10.75	14.75	20.6	15.45	22.51	7.61	16.53	16.03	13.12	15.12	11.84
2	29.07	27.93	26.32	12.46	18.95	22.93	19.19	27.00	21.6	27.33	9.81	21.07	26.00	21.32	20.1	16.84
3	42.15	42.06	35.54	21.24	28.01	36.73	30.13	39.01	32.07	38.00	27.16	33.00	34.14	28.94	29.45	25.89
4	56.36	52.05	47.05	35.04	39.10	52.47	41.05	48.07	43.16	49.00	48.66	43.08	45.00	37.15	41.47	34.00
5	66.01	63.14	60.00	50.95	51.20	66.86	53.32	60.00	52.05	60.17	55.52	52.47	54.76	45.7	50.86	45.87
6	76.00	73.12	71.09	60.00	63.14	76.09	65.00	71.01	61.27	70.08	70.25	61.78	62.97	53.57	59.24	56.36
7	85.14	82.01	81.42	69.74	74.14	82.1	75.07	82.1	70.08	77.02	76.16	70.25	74.05	61.02	71.26	63.93
8	94.11	92.25	87.34	76.59	83.11	88.53	84.97	91.07	79.05	87.53	86.33	80.4	82.11	69.15	79.56	71.6

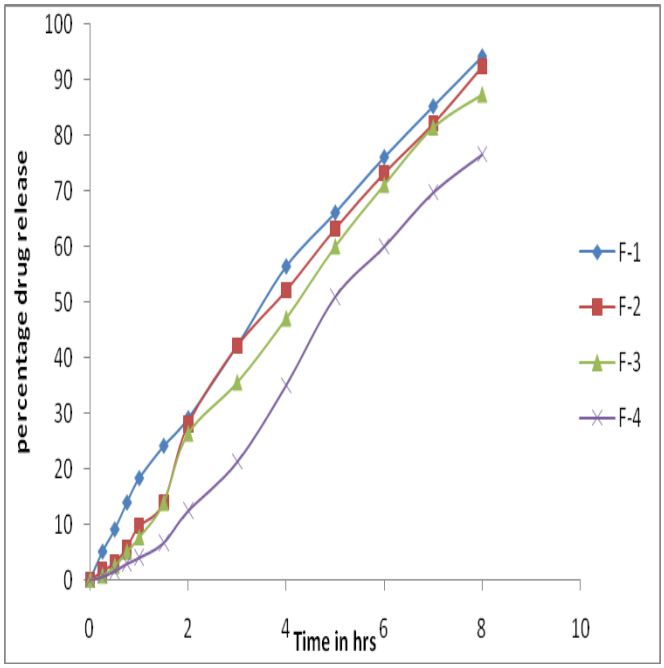


Figure 10: *In vitro* release of gliclazide from sustained release layer F-1, F-2, F-3 and F-4.

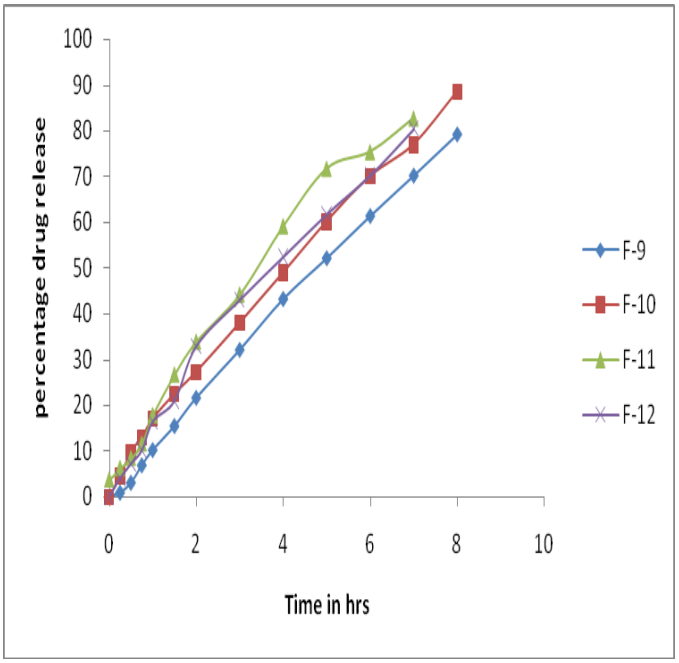


Figure 12: *In vitro* release gliclazide from sustained release layer F-9, F-10, F-11 and F-12.

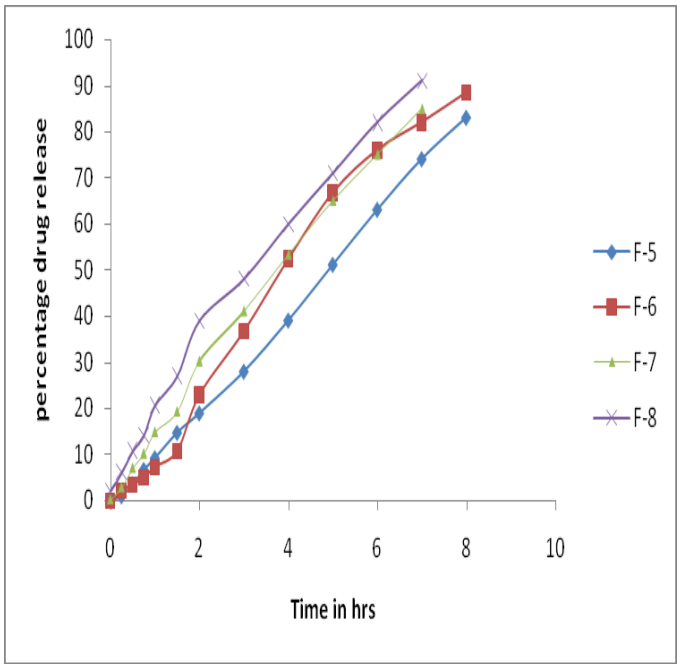


Figure 11: *In vitro* release of gliclazide from sustained release layer F-5, F-6, F-7 and F-8

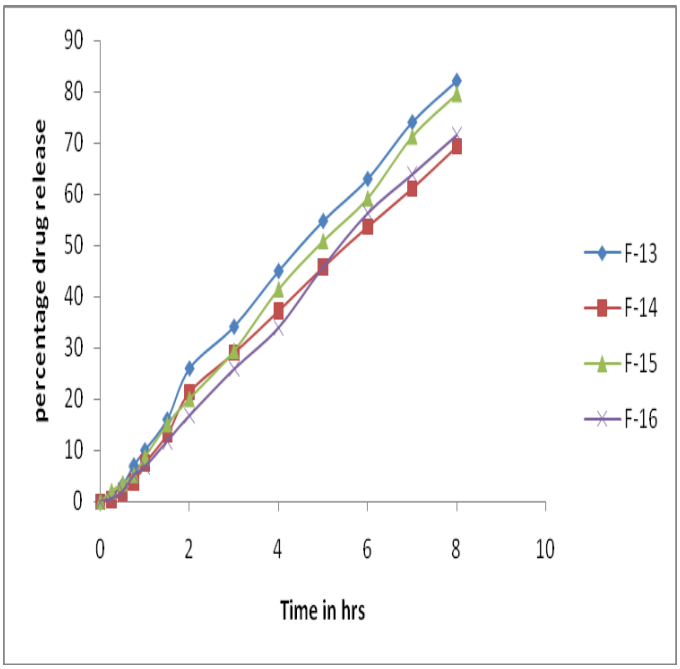


Figure 13: *In vitro* release gliclazide from sustained release layer F-13, F-14, F-15 and F-16

Table 12: 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	Erosion	Baker-Lonsdale
	'r'	'r'	'r'	'r'	n	'r'	'r'	'r'
F-1	0.9961	-0.9641	0.983	0.9992	0.84	0.9904	-0.9905	0.9993
F-2	0.9948	-0.9694	0.9717	0.9937	1.209	0.9912	-0.9912	0.9981
F-3	0.9966	-0.9816	0.9681	0.9912	1.35	0.9938	-0.9938	0.9983
F-4	0.9939	-0.979	0.9423	0.9985	1.425	0.9869	-0.9896	0.9917
F-5	0.9993	-0.9724	0.9603	0.9931	1.199	0.9871	-0.9871	0.9958
F-6	0.9919	-0.9869	0.9634	0.9918	1.191	0.9947	-0.9947	0.9958
F-7	0.9995	-0.9724	0.9632	0.9320	1.59	0.9882	-0.9882	0.9969
F-8	0.9985	-0.9663	0.9768	0.9924	1.024	0.9886	-0.9886	0.9985
F-9	0.9986	-0.9883	0.9730	0.9879	1.214	0.9964	-0.9964	0.9996
F-10	0.9973	-0.9749	0.9816	0.9984	0.82	0.9915	-0.9915	0.9985
F-11	0.9957	-0.9879	0.9734	0.9979	0.945	0.995	-0.995	0.9974
F-12	0.9987	-0.9856	0.9734	0.9159	1.526	0.9953	-0.9953	0.9994
F-13	0.9974	-0.9856	0.9744	0.9921	1.662	0.994	-0.9954	0.999
F-14	0.9968	-0.9948	0.9725	0.9773	1.44	0.9982	-0.9982	0.9987
F-15	0.9994	-0.982	0.9666	0.9974	1.098	0.9927	-0.9927	0.9983
F-16	0.9991	-0.9882	0.962	0.9902	1.32	0.9945	-0.9945	0.9987

Table 13: Evaluation parameters of bilayer tablet of lisinopril and gliclazide.

Batch code	Hardness Kg/cm²	Thickness (cm)	% Friability	Weight Variation (mg)	*In- vitro* disintegration time(sec)
BCC8F4	5.80 ± 0.20	5.17 ± 0.01	0.60 ± 0.09	300 ± 0.05	22.66 ± 2.51
BCC8F12	6.30 ± 0.17	5.39 ± 0.01	0.50 ± 0.00	300 ± 0.05	22.66 ± 2.51
BCCF14	5.86 ± 0.11	5.24 ± 0.00	0.71 ± 0.09	301 ± 0.05	20.33 ± 1.15
BCCF16	5.93 ± 0.11	5.22 ± 0.01	0.83 ± 0.00	300 ± 0.05	22.33 ± 1.15

Each value represents as mean±SD of three determinants

CONCLUSION

The present study successfully demonstrated the formulation and evaluation of bilayer tablets of Lisinopril and Gliclazide for effective management of diabetic hypertension. The prepared bilayer tablets showed satisfactory precompression and post compression characteristics within acceptable pharmacopeial limits. FTIR studies confirmed compatibility between drugs and excipients without significant interaction.

The immediate release layer of Lisinopril showed rapid disintegration and faster drug release, while the sustained release layer of Gliclazide provided prolonged drug release for more than 8 h. Among all formulations, bilayer tablet formulation BCC8F14 was selected as optimized batch based on satisfactory tablet properties and desired drug release profile. The developed bilayer tablet may serve as a promising approach for improving patient compliance and therapeutic effectiveness in the management of hypertension associated with diabetes mellitus.

Future Scope

The developed bilayer tablet of Lisinopril and Gliclazide showed promising immediate and sustained drug release characteristics for effective management of diabetic hypertension. Further studies can be carried out to evaluate long-term stability, large scale manufacturing feasibility and pharmacokinetic

performance of the optimized formulation. In vivo studies and clinical evaluation may also be performed to establish therapeutic efficacy, safety and patient compliance of the developed bilayer tablet system.

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Consent Statement: Not applicable.

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Ethics approval: Not Applicable.

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