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FORMULATION AND EVALUATION OF SUSTAINED RELEASE BILAYER TABLETS OF METFORMIN HCL AND GLIMEPIRIDE

Ch.Anil Kumar[1*], J.Sreekanth [2], N.Raghunandhan[3]

[1]University College of Pharmaceutical Sciences, Satavahana University, Karimnagar
[2]General Manager, MSN Pharmaceuticals, Hyderabad, A.P, India
[3]Principal, Balaji Institute of Pharmaceutical Sciences, Narsampet, Warangal
*Corresponding Author Email: chanil123@gmail.com

ABSTRACT

The present study was to establish Bi-layer tablets of Metformin HCl and Glimepiride HCl of which Metformin HCl as sustained release and Glimepiride as immediate release layer. Sustained layer were prepared by wet granulation method using Eudragit's as polymers, immediate release layer were prepared by direct compression method using super disintegrants such as cross carmellose sodium and sodium starch glycollate. The tablets were evaluated for Bulk density, Tapped density, Compressibility index, Hausner ratio, and Angle of repose. All the values were found within limits of standard. In vitro release studies were carried out by USP type 2 paddle apparatus. The results showed that Eudragit's in sustained layer can control the release of drug. The in vitro release profile of drug from sustained release layer could be expressed by higuchi's equation as pilot show high linearity R^2=0.9911and diffusion was the dominant mechanism of drug release. The formulation (F13) having immediate release layer produces immediate effect 94.53 ± 0.30 within 45 minutes followed by sustained release effect 95.77 ± 0.37 up to 8 hours. The present study concluded that Bilayer tablets of Glimepiride and Metformin HCl can be a better alternative to conventional dosage form for providing sustained drug delivery.

KEY WORDS

Bilayer tablet, glimepiride, Metformin HCl, Sustained Release, Higuchi equation.

INTRODUCTION

Diabetes mellitus, often simply referred to as diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin or because cells do not respond to the insulin that is produced **[1]**. Diabetes is one of the major cause of death and disability in the world. World Health Organization estimate for the number of people with diabetes worldwide, in 2000, is 171 million, which is likely to be at least 366 million by 2030. Non-insulin dependent (Type 2) diabetes mellitus is a heterogeneous disorder characterized by an underlying insufficiency of insulin. This insufficiency results from defective insulin utilization and can be corrected by administration of one or more of the currently available oral hypoglycemic agents **[2]**. Combination therapy have various advantages over monotherapy such as problem of dose-dependent side effects is minimized, a low dose combination of two different agents reduces the dose-related risk, the addition of one agent may counteract some deleterious effects of the other, using low dosage of two different agents minimize the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet **[3]**. Metformin is an oral biguanidine first-line choice of drug. Metformin has an oral bioavailability of 50–60% under fasting conditions, and is absorbed slowly. The average elimination half-life in plasma is 6.2hours. Peak plasma

concentrations (C_{max}) are reached within 4 to 8 hours with extended-release formulations.[4, 5] Glimepiride is orally administered sulfonyl urea agent and highly selective agonist for the sulfonyl urea receptor (SUR) are found in pancrease, which are target sites of insulin secretion. Activation of the SUR receptors activates the secretion of insulin involved in the control of glucose and lipid metabolism. Glimepiride has an oral bioavailability of 85% and peak plasma concentrations of glimepiride are achieved in 3–3.5 hours. Elimination half of glimepiride is 4 to 7 hrs. **[4, 5]**

METHODS AND MATERIALS

Metformin HCl and glimepiride HCl were gift samples obtained from Abhilasha Pharma, Ankleshwar and Cadila Healthcare Limited, Ahmedabad respectively. MCC was purchased from FMC Biopolymer, India; Red Iron Oxide- Roha dye Chem., Mumbai Colorants; PVP K 30- Cadila Healthcare, Ahmedabad; Magnesium stearate, CCS- Astron Research Limited, Ahmedabad; Eudragits- Cadila Healthcare, Ahmedabad; Talc– Merck Specialties Private Limited, Mumbai. All the chemicals and reagents were of high quality analytical grade.

Method of Preparation of Granular blend [10]

Blend preparation of immediate release layer of Glimepiride

The dose of glimepiride HCl for immediate release was fixed as 15 mg. immediate release layer of glimepiride HCl (**G1-G13**) were prepared by direct compression technique as per the composition **Table 1**. Glimepiride and other excipients were passed through sieve no. 40 # and thoroughly mixed in a blender approximately for 5 min, the color iron oxide reds was passed through the sieve No. 100 # and add to above mixer. The whole blend was lubricated for 2 min with Magnesium Stearate which was already passed through sieve no. 60 #. For Batches PM1-PM14, Crosscarmellose sodium and sodium starch glycollate was used as super disintegrants.

Granule preparation of sustained release layer of metformin HCl

The dose of Metformin HCl for sustained release was fixed as 500mg. The sustained release layer of Metformin HCl (**F1-F13**) was prepared by wet granulation technique with various excipients as per the formula given in Table 2, Metformin HCl, Microcrystalline cellulose, Lactose, Eudragit L100 and Eudragit RSPO were sifted through Sieve no. 40#. Then the above sifted materials were mixed in mortar and pestle for 5 min. PVP K-30 was dissolved in mixture of IPA. Then above mixture with binder PVP K-30 solution was granulated and kneading for 2 min. The granules were dried in tray dryer at 65°C.The granules were passed through mesh no. 20# in oscillating granulator. Finally mixture was lubricated with talc and magnesium stearate for 2 min.

Table 1: Composition of immediate release layer of Glimepiride Hydrochloride

FORMULATION	G1	G2	G3	G4	G5	G6	G7	G8	G9	G10	G11	G12	G13
Glimepiride	1	1	1	1	1	1	1	1	1	1	1	1	1
SSG	-----	-----	-----			2	4	6	8	10	7.6	8.4	8.8
CCS	2	4	6	8	10	-----	-----	-----	-----	-----	-----	-----	-----
AvicelpH101	-----	-----	18	18	18	-----	-----	18	18	18	18	18	18
Lactose MH-NF	134.7	132.7	113.7	111.7	110	134.7	132.7	114	111.7	110	112.1	111	110.9
Povidone K30	10	10	10	10	10	10	10	10	10	10	10	10	10
Polysorbate 80	1	1		------	------	1	1	-----	-----	-----	-----	-----	-----
Mg.Sterate	1	1	1	1	1	1	1	1	1	1	1	1	1
Iron oxide red	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Total wt	150	150	150	150	150	150	150	150	150	150	150	150	150

Table 2: Composition of sustained release layer of Metformin hydrochloride

Code	METFORMIN HCL SUSTAINED RELEASE LAYER												
	G1	G2	G3	G4	G5	G6	G7	G8	G9	G10	G11	G12	G 13
Met	500	500	500	500	500	500	500	500	500	500	500	500	500
E-L100	200	250	300	-----	-----	------	100	150	200	205	210	205	205
E-RSPO	-----	-----	-----	200	250	300	200	150	100	100	100	95	90
PVP	17	17	17	17	17	17	17	17	17	17	17	17	17
MCC	125	75	25	125	75	25	25	25	25	20	15	25	30
Talc	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3
Mg.Sterate	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3
IPA	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
T wt	850	850	850	850	850	850	850	850	850	850	850	850	850

Compression method [15]

Final bilayer tablets were compressed by as one layer only for Metformin HCl and second layer for glimepiride HCl using 12 mm punch in rotary tablet compression machine. The tablet was compressed as bilayer tablets using both Metformin HCl granules and glimepiride HCl blend. In this Metformin HCl granules were introduced first into the die cavity and slight pre compression was made so the layer was uniformity distributed after that glimepiride HCl blends were added and final compression was made.

Evaluation

All the formulations were evaluated for Weight variation test, Hardness, Thickness, Friability and drug content [16, 17, 18]

Determination of In vitro dissolution studies [19]

Release of glimepiride hydrochloride was determined using a USP dissolution Apparatus type II at 100 rpm. The dissolution was studied using 900ml of 0.1 N Hydrochloricacid. The temperature was maintained at 37 ± 0.5°C. The sample (5 ml) was withdrawn at different time intervals, i.e., 5, 15, 30, and 45 minutes, filtered through Whatman filter paper and replaced with an equal volume of fresh dissolution medium. Samples were suitably diluted and analyzed for glimepiride hydrochloride content using Shimadzu 1700 UV-Visible spectrophotometer. The percentage of glimepiride hydrochloride release was calculated. Release of Metformin hydrochloride was determined using a USP dissolution Apparatus type II at 100 rpm. The dissolution was studied using 900ml of Phosphate Buffer pH 6.8. The temperature was maintained at 37 ± 0.5°C. The sample (5 ml) was withdrawn at different time intervals, i.e., 1, 2, 3, 4, 6 and 8 hours, filtered through Whatman filter paper and replaced with an equal volume of fresh dissolution medium. Samples were suitably diluted and analyzed for Metformin hydrochloride content using Shimadzu 1700 UV-Visible spectrophotometer.

RESULTS AND DISCUSSION

Table 3: Physico-mechanical properties of Metformin HCl granular blend and Pre-compression properties of formulation:

POWDER BLEND	BULK DENSITY (gr/cm3)	TAPPED DENSITY (gr/cm3)	ANGLE OF REPOSE (°)	COMPRESSIBILITY INDEX (%)	HEUSNER'S RATIO
G1	0.434	0.533	23°.34'	18.57	1.228
G2	0.437	0.536	23°.62'	18.47	1.226
G3	0.439	0.538	23°.83'	18.4	1.225
G4	0.442	0.544	20°.41'	18.75	1.23
G5	0.446	0.548	20°.73'	18.61	1.228
G6	0.449	0.547	20°.96'	17.91	1.218
G7	0.451	0.553	21°.33'	18.44	1.226
G8	0.453	0.556	22°.96'	18.52	1.227
G9	0.454	0.559	21°.96'	18.78	1.231
G10	0.454	0.55	20°.18'	17.45	1.231
G11	0.442	0.524	21°33'	15.64	1.211
G12	0.432	0.502	21°.92'	13.94	1.162
G13	0.436	0.5	19°.14'	12.8	1.146

Table 4: Physico-mechanical properties of Glimepiride HCl granular blend

POWDER BLEND	BULK DENSITY (gr/cm^3)	TAPPED DENSITY (gr/cm^3)	ANGLE OF REPOSE (°)	COMPRESSIBILITY INDEX (%)	HEUSNER'S RATIO
F1	0.44	0.49	37°.99'	10.2	1.11
F2	0.48	0.55	33°.34'	12.72	1.14
F3	0.49	0.58	28°.52'	10.34	1.18
F4	0.54	0.58	24°.05'	15.51	1.07
F5	0.52	0.58	20°.07'	10.34	1.11
F6	0.48	0.56	33°.34'	14.28	1.16
F7	0.48	0.57	28°.52'	15.78	1.18
F8	0.49	0.55	26°.11'	10.9	1.12
F9	0.48	0.55	22°.96'	12.72	1.08
F10	0.48	0.54	21°.55'	11.11	1.12
F11	0.47	0.53	22°.28'	11.32	1.12
F12	0.48	0.55	20°.18'	12.72	1.14
F13	0.52	0.58	19°.65'	10.34	1.11

Table 5: Physico-chemical properties of finished dosage forms containing Glimepiride and metformin

FORMULATION CODE	THICKNESS (mm)	WEIGHT VARIATION (mg)	HARDNESS (Kg/cm2)	FRIABILITY (%)	DRUG CONTENT	
					GLIMEPIRIDE HCL	METFORMIN HCL
GF1	6.89±0.6	1001±0.61	7.2±0.11	0.048	100.69	99.13
GF2	6.72±0.7	1003±0.34	7.3±0.21	0.043	101.65	99.25
GF3	6.98±0.4	998±0.62	7.4±0.22	0.052	100.32	99.36
GF4	6.92±0.7	1001±0.67	7.3±0.14	0.034	100.21	99.47
GF5	6.91±0.6	999±0.71	7.4±0.26	0.053	100.25	99.58
GF6	6.93±0.8	999±0.25	7.3±0.13	0.065	100.57	99.69
GF7	6.97±0.7	1001±0.56	7.4±0.16	0.032	100.32	99.32
GF8	6.95±0.5	999±0.42	7.4±0.14	0.052	100.19	99.53
GF9	6.93±0.4	1000±0.55	7.2±0.26	0.044	100.28	99.75
GF10	6.88±0.6	1005±0.32	7..2±0.24	0.048	100.73	99.07
GF11	6.91±0.6	1004±0.62	7.2±0.24	0.048	99.31	100.21
GF12	6.94±0.6	1002±0.45	7.1±0.24	0.048	99.52	100.32
GF13	6.89±0.3	1001±0.33	7.2±0.24	0.048	99.63	101.56

All the values mentioned in Mean ± S.D (N=3)

Kinetics of drug release:

Data obtained from dissolution studies was fitted to various kinetic equations. Parameters of the mathematical models and descriptive statistics of regression for the dissolution data of all formulations are given in **Table 6**.

Fig1: In-Vitro Dissolution of Glimepiride in 0.1 N HCl

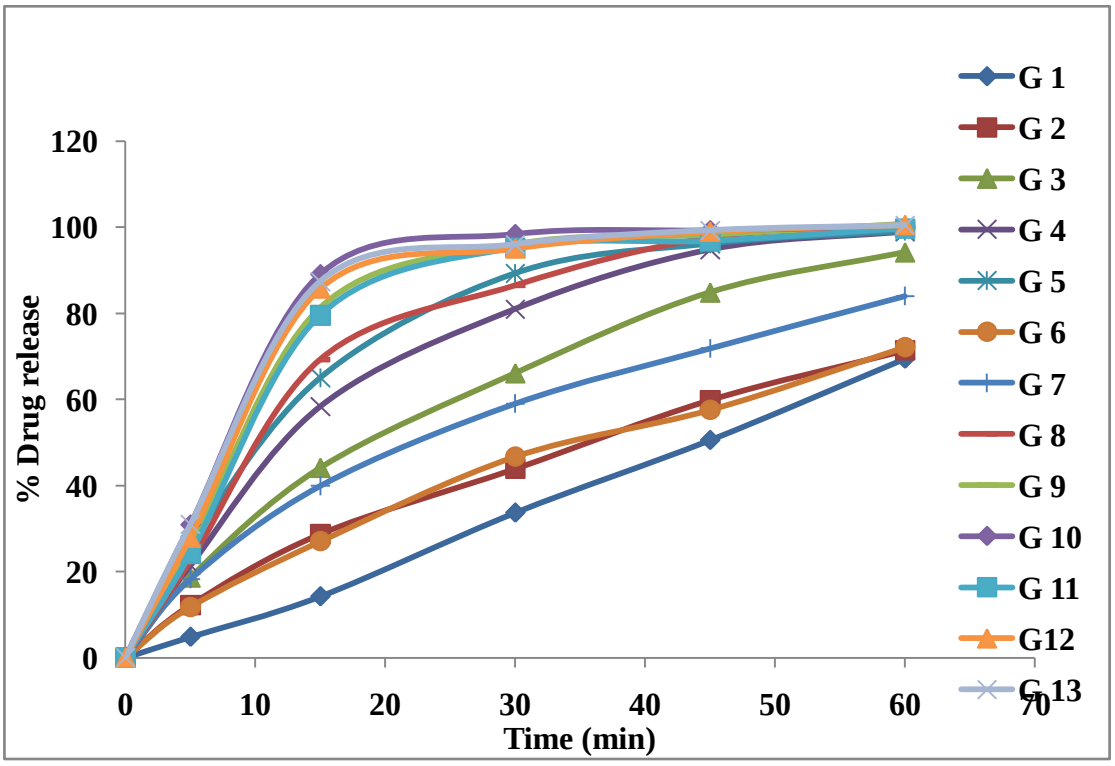
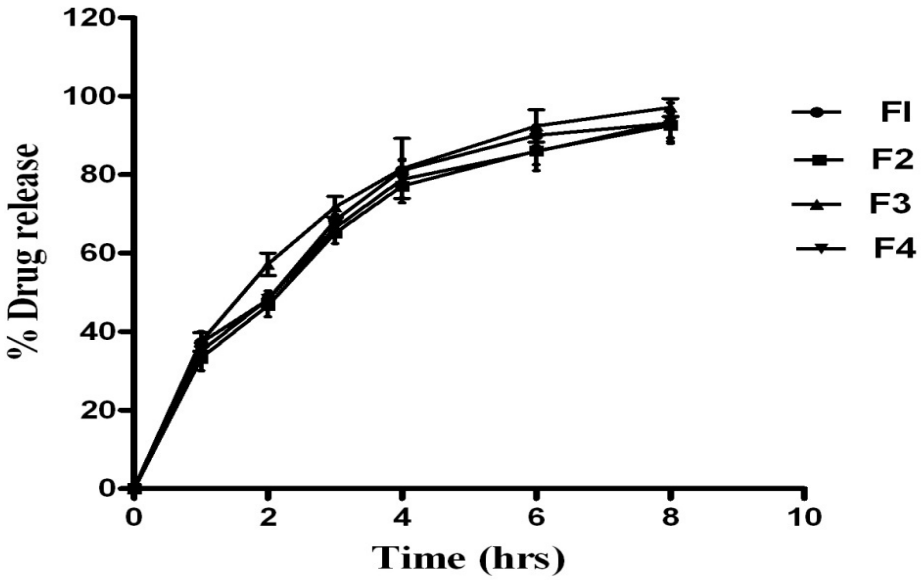
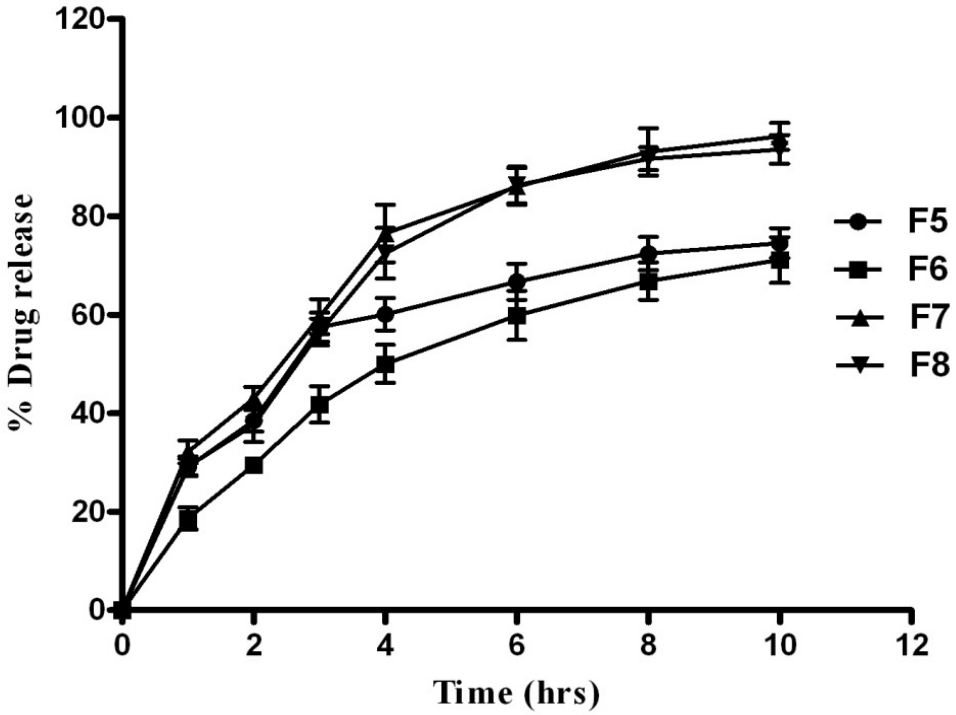


Fig2: In-Vitro Dissolution of metformin in 6.8 pH buffer





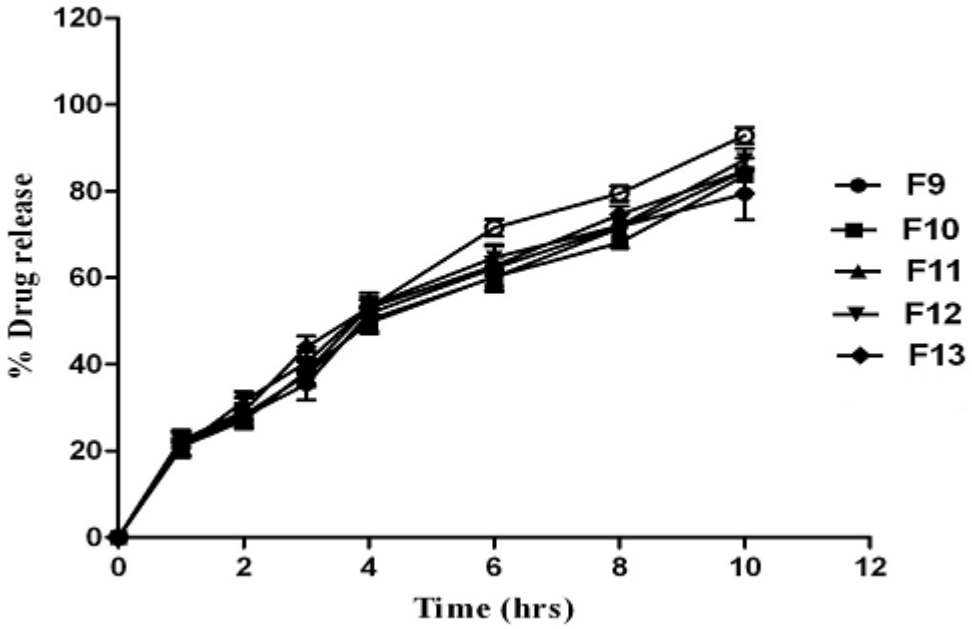


Table 6: Release kinetics of Metformin Hcl from sustained release layer

	Zero order		First order		Higuchi		Hixon-crowell		Korsmeyer-peppas		
	r^2	k	r^2	k	r^2	k	r^2	k	n	r^2	K
F1	0.785	14.98	0.962	-0.387	0.982	36.25	0.945	-0.087	0.479	0.972	37.67
F2	0.822	14.52	0.977	-0.340	0.986	34.99	0.959	-0.081	0.516	0.976	34.34
F3	0.764	15.58	0.970	-0.461	0.983	37.78	0.964	-0.097	0.466	0.976	40.18
F4	0.805	14.68	0.964	-0.358	0.985	35.45	0.954	-0.084	0.492	0.978	36.08
F5	0.656	9.748	0.878	-0.166	0.965	26.66	0.828	-0.045	0.420	0.963	30.93
F6	0.863	8.725	0.965	-0.138	0.988	23.32	0.940	-0.039	0.592	0.983	19.99
F7	0.797	12.73	0.962	-0.348	0.982	33.12	0.962	-0.075	0.508	0.975	32.87
F8	0.832	11.94	0.977	-0.301	0.981	32.09	0.960	-0.069	0.556	0.970	29.22
F9	0.914	9.278	0.974	-0.162	0.980	24.52	0.969	-0.044	0.590	0.973	20.72
F10	0.937	9.308	0.975	-0.168	0.984	24.58	0.982	-0.049	0.618	0.987	19.69
F11	0.842	9.438	0.987	-0.171	0.987	24.82	0.990	-0.045	0.615	0.991	20.09
F12	0.927	9.807	0.979	-0.168	0.988	25.89	0.984	-0.048	0.622	0.993	20.84
F13	0.918	9.762	0.992	-0.180	0.991	25.84	0.987	- 0.047	0.599	0.990	21.65

DISCUSSION

The purpose of the present study was to formulate and evaluate sustained release bilayer tablet of Metformin HCl and glimepiride HCl. The sustained release layer was prepared by wet granulation method using polymers like Eudragit L100 and RSPO and immediate release layer was prepared by direct compression method using disintegrant like CCS and SSG. From the melting point determination it has been found that melting point of Metformin HCl was found in the range of 222°C-224°C and glimepiride HCl was in the range of 188°C-191°C.

λ_{max} was determined for both drugs, glimepiride HCl in 0.1 N HCl and for Metformin HCl in phosphate buffer pH 6.8. It was found to be 270 nm for glimepiride HCl and 233 nm for metformin HCl, which was exactly similar to the earlier reported λmax. Then after Calibration curve was determine for Glimepiride

in 0.1 N HCl at λ_{max} 270 nm and for Metformin HCl in pH 6.8 at λmax 233. Results were reported in tables respectively. This shows the linearity in the range of 4- 20 µg/ml for glimepiride HCl and for 4-20 for Metformin HCl. Preformulation studies for powder blend of glimepiride HCl ready for compression and Granular bland of Metformin HCl ready for compression was carried out to determine Bulk density, Tapped density, Carr's index, Hausner's ratio and angle of repose, results are shown in tables. From the values of bulk densities of various formulations indicated good packing character. The compressibility index for all the formulations was found to be below 10%, indicating desirable flow properties. The flow properties of granules were further analyzed by determining the angle of repose for all formulations; ranges were less than 31°. The hausner's ratio for all the granules formulated was less than 2%. The total nine batches has been prepared to obtained the similar release profiles of the both drug as compare with marketed product used in the present study. Each prepared batch was then subjected to post formulation evaluation like hardness, thickness, weight variation, friability and drug content and results were reported in the Table 5 & 6. Each of the prepared batches was then subjected to In vitro drug release study. In the glimepiride HCl IR layer, batch G1 shows less release profile due to low concentration of disintegrant. As the concentration increases in combination the G12 and G13 show better release profile. In the Metformin HCl SR layer, batch F1 shows fast release profile due to low concentration of polymer. As the concentration increases in the batches F2 to F7, show sustained release profile, the batch F13 was optimized batch. Figure 1 and 2 expressed the dissolution studies of glimepiride HCl and Metformin HCl respectively.

CONCLUSION

The aim of dissertation entitled "Formulation and evaluation of sustained release Bilayered tablets of Metformin Hcl and Glimepiride" was to formulate a stable, safe and convenience dosage form. The preformulation studies proved that there was no interaction between drug and excipients. Various post compression parameter were checked and found satisfactory result. HPMC is one of the most widely used hydrophilic polymer having GRAS regulatory status and easily available in all the grades. It is also having pH independent profile. CCS and SSG (super disintegrant) was used in the immediate release part to give immediately release effect. Initially, loading dose was needed so glimepiride Hcl was used as immediately release part which give release within 45 minute while then Metformin HCl give result for rest of the time period 8hours. Sustained Release part and immediately release part was first prepared individually then bilayer tablet was prepared using rotary compression machine. All batches were subjected to post formulation studies and finally in vitro release studies were determined. It can be concluded that by considering the concentration of disintegrants (CCS and SSG) for immediate release part and the concentration of polymer (ERL100 and ERSPO) for sustained release part, we successfully developed bilayer tablet.

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***Corresponding Author:**
CH. ANIL KUMAR*
University College of Pharmaceutical Sciences,
Satavahana University,
Karimnagar