CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1000995

Available online at: http://www.iajps.com *Research Article*

DEVELOPMENT AND EVALUATION OF METFORMIN HCL LOADED EUDRAGIT®RSPO AND EUDRAGIT®RLPO AND GLIMEPIRIDE BILAYER TABLETS

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Abstract:
The present study was carried out for developing the formulation of Bilayer tablets of Glimepiride, Metformin HCl. Immediate Release (IR) layer was compressed as direct compression method and Sustained Release (SR) layer blends were compressed by wet granulation method. IR and SR layers were evaluated for pre and post compression studies and all studies were found to be within limits. From dissolution data of Glimepiride Immediate release layer, IR5 formulation was shown maximum drug release at 60 min i.e., 96.4%. Hence IR5was concluded as optimised formulation for IR layer. Sustained layer consists the drug Metformin HCl From the dissolution data of bilayer tablets of Anti Diabetic drugs F4 (IR5&SR4) has shown optimum drug release,SR4 contains Eudragit RL100 Polymer.SR4 formulation was shown best drug release(95.57%)within 24 hours. Finally SR4 formulation was optimised formulation and follows Higuchi release kinetics.

Key Words: *Glimepiride, Metformin HCl, Bilayer tablets, direct compression, wet granulation, Ethyl Cellulose, Eudragit RL100, PVP K30.*

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Please cite this article in press as T.Mallika et al, ***Development and Evaluation of Metformin Hcl Loaded Eudragit®Rspo and Eudragit®RLPO and Glimepiride Bilayer Tablets,*** *Indo Am. J. P. Sci, 2017; 4(09).*

INTRODUCTION:

Historically, oral drug administration has been the predominant route for drug delivery. A major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs, therefore properties of drugs and the way in which they are delivered must be optimised [1-4].

In the last decade, interest in developing a combination of two or more active ingredients in a single dosage form has been increased in pharmaceutical industry, promoting patient convenience and compliance. Bilayer tablet is suitable for sequential release of two or more 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 [5-7].

MATERIALS AND METHODS:

Metformin HCl and Glimepiride were obtained at Matrix Labs, Hyderabad, India. Ethyl cellulose, Kollidon, Explotab, Eudragit RL_{100}, PVP K_{30}, and other ingredients were procured from Merck Specialities Private Ltd, Mumbai, India.

Formulation Development of Bilayer Tablets:

Immediate layer was prepared by direct compression and Sustained layer was compressed by direct compression technique. The compositions of different formulations of IR and SR tablets are given in the following tables. Drug and all other ingredients were individually passed through sieve no#60.All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. The tablets were prepared by using direct compression method.

Analytical method development:

a) Preparation of calibration curve for Metformin HCl and Glimepiride:

10 mg of Metformin HCl/Glimepiride pure drug was dissolved in 10ml of methanol (primary stock solution).From primary stock solution, 1ml of solution was taken and make up with 10ml of 0.1N HCl (100*u*g/ml) from this secondary stock solution 0.5, 1, 1.5, 2, and 2.5 ml was taken and diluted up to 10 ml with 0.1 N HCl to obtain 5, 10, 15, 20 and 25*u*g/ml concentration. The absorbance of the above dilutions was measured at respective wavelength by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking concentration on X-axis and absorbance on Y-axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient(R^2) which determined by least square linear regression analysis. The same procedure was repeated for taking 6.8 phosphate buffers as blank.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany (Alpha T).The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000cm^{-1} to 550cm^{-1}.

Table 1: Formulation composition for immediate release tablets

Ingredients(mg)	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8	IR9
Glimepiride	5	5	5	5	5	5	5	5	5
Kollidon	5	6.25	7.5	-	-	-	-	-	-
Explotab	-	-	-	5	6.25	7.5	-	-	-
Ac-di-sol	-	-	-	-	-	-	5	6.25	7.5
Mg.Stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
TOTAL TABLET WEIGHT	100	100	100	100	100	100	100	100	100

All the quantities were taken in **mg.**

Table 2: Formulation composition for Bilayer tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
IMMEDIATE LAYER	IR5	IR5	IR5	IR5	IR5	IR5	IR5	IR5	IR5
SUSTAINED LATER	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8	SR9
Metformin HCl	500	500	500	500	500	500	500	500	500
Ethyl cellulose	50	75	100	-	-	-	-	-	-
Eudragit RL 100	-	-	-	50	75	100	-	-	-
Eudragit RS 100	-	-	-	-	-	-	50	75	100
PVP K30	5	5	5	5	5	5	5	5	5
Sunset yellow colour	2	2	2	2	2	2	2	2	2
Mg. Stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight of SR layer	700	700	700	700	700	700	700	700	700

Preformulation parameters

Angle of repose:

The angle of repose was calculated using the following formula:

Tan θ = h / r Tan θ = Angle of repose

h = Height of the cone, r = Radius of the cone base

Table 3: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density

Tap = Tapped Density

Table 4: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
21 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Evaluation of post compression parameters for prepared tablets

***In vitro* drug release studies**

Dissolution study for immediate layer optimisation:

900ml of 0.1N HCl was placed in vessel and the USP apparatus-II (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of 37^0c+_0.5^0c.Tablet was placed in the vessel and the vessel was covered ,the apparatus was operated for 1 hour and then the medium 0.1N HCl was taken and process was continued at 50rpm.At definite time intervals 5ml of the medium was withdrawn, filtered and again 5ml fresh medium was replaced. Suitable dilutions were done with recepter fluid and analysed by spetrophotometrically at respective wavelength using UV-spectrophotometer.

Dissolution study for Bilayer Tablets:

The dissolution study of Bilayer tablets was performed over a 12hr period using USP type II (paddle) Dissolution testing apparatus (Lab India). 900ml of 0.1N HCl was used as dissolution medium agitated at 50 rpm, at 37 ± 0.5^0c. 5ml of samples were withdrawn at 5, 10, 15 and 20 min to estimate the release of immediate release of Glimepiride and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12, 16, 20, 24 hrs for estimating Sustained release of Metformin HCL. The samples were analysed at respective wavelength in UV spectrophotometer by keeping the 0.1N HCl for 2 hrs and after 2 hrs maintain 6.8 Phosphate buffer.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyse the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics: To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = K_0 t$$

Where, 'F' is the drug release at time't', and 'K_0' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$Log\ (100\text{-}F) = k_t$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k_{t1/2}$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer-Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t / M_\infty = Kt^n$$

Where, M_t / M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case II transport), n=1; and for super case II transport, n > 1. In this model, a plot of log (M_t / M_∞) versus log (time) is linear.

RESULTS AND DISCUSSIONS:

a. **Glimepiride standard graph in 0.1N HCl (at 260nm)**

The graph of Glimepiride was plotted as per the procedure in the experimental method and the graph showed good linearity with R^2 of 0.999, which indicates that it obey Beer-Lamberts law.

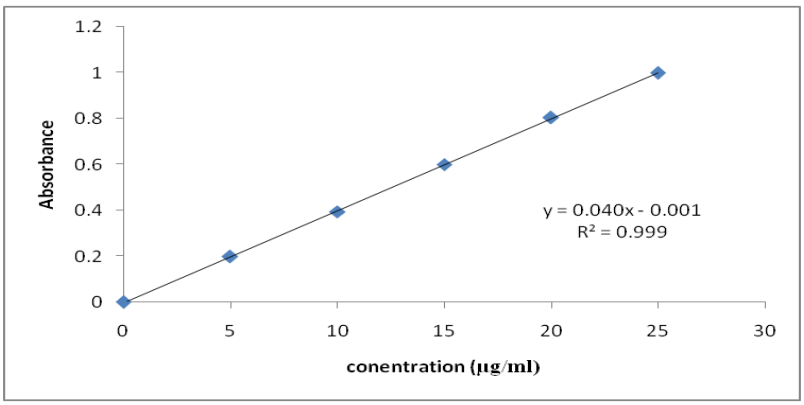


Fig 1: Standard graph of Glimepiride in 0.1N HCl (260 nm)

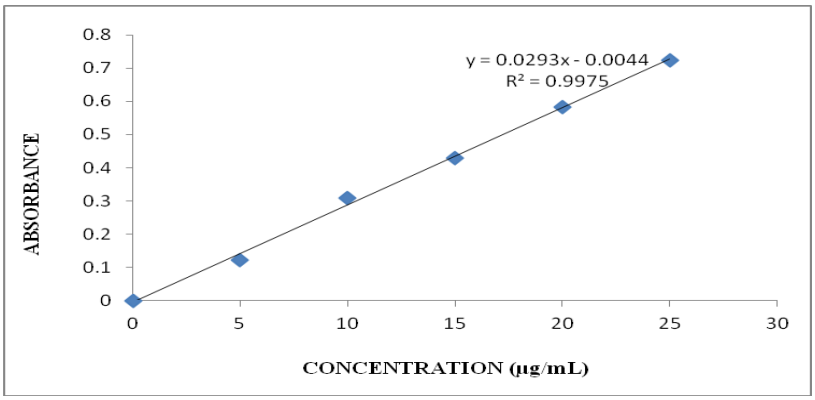


Fig 2: Standard graph of Metformin in 0.1N HCl (272 nm)

b. Drug-Excipient compatibility studies

Fourier Transform-Infrared Spectroscopy:

Fourier transform infrared (FTIR) spectra of the drugs and the optimised formulation were recored. The FT-IR spectra of pure Glimepiride drug, Metformin drug, optimised formulation shown in below figures respectively.

There was no disappearance of any characteristics peak in the FT-IR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the drug polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

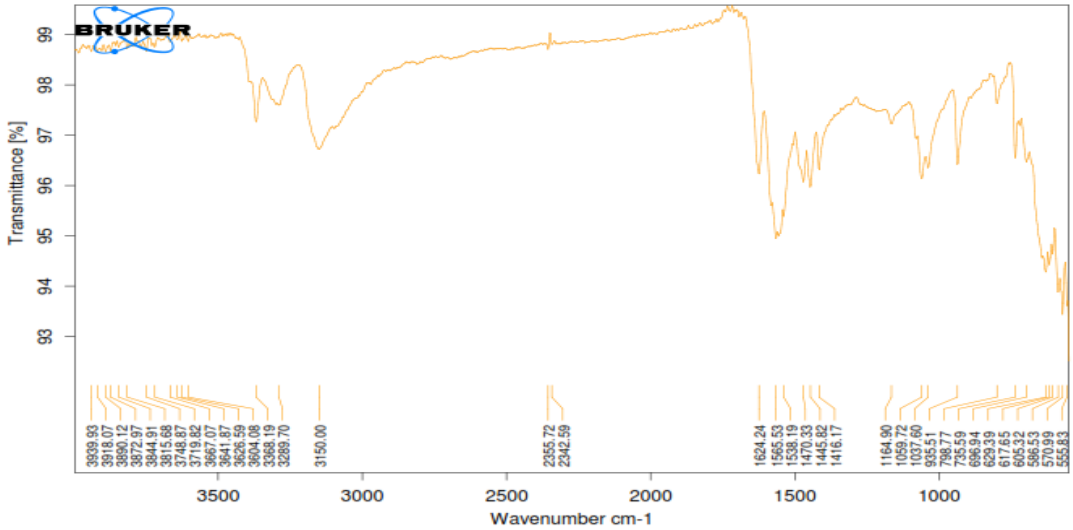


Fig 3: FT-TR Spectrum of Metformin.

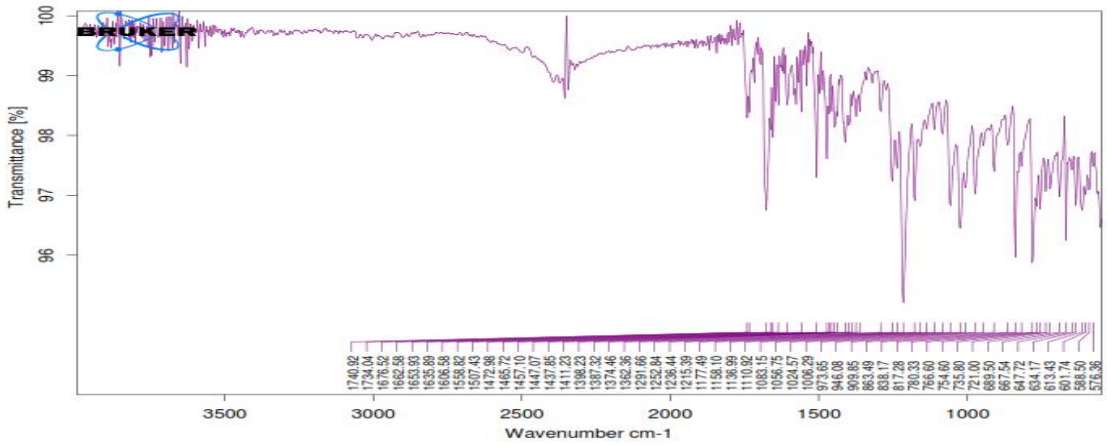


Fig 4: FTIR Spectrum of Glimepiride.

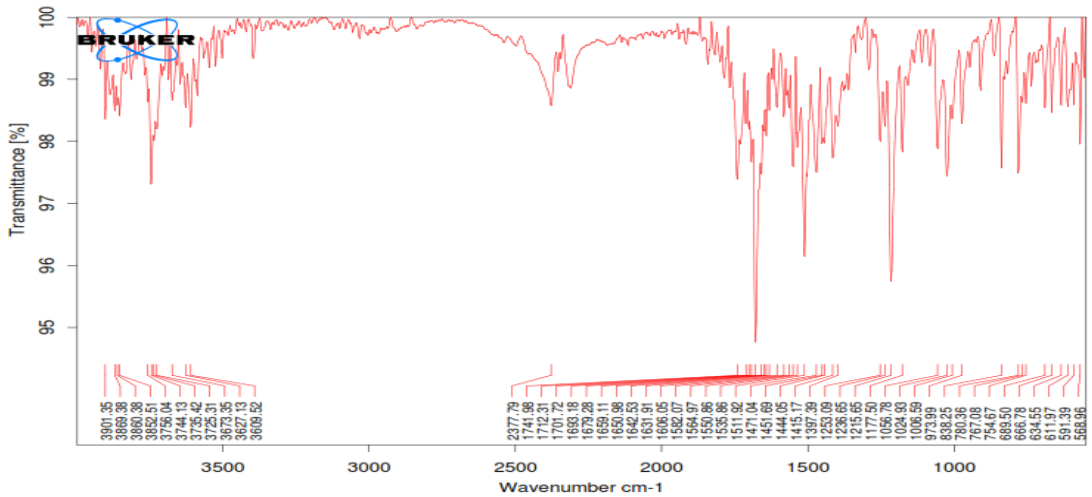


Fig 5: FT-IR Spectrum of Optimised formulation.

3. Preformulation parameters of powder blend for immediate layer:

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all formulations was found to be in the range of 0.49 to 0.56(gm/mL) showing that the powder has good flow properties. The tapped density of all formulations was found to be in the range of 0.57 to 0.68 showing that the powder has good flow properties. The compressibility index of all formulations was found to be below 18 which show that the powder has good flow properties. All the formulations has shown the Hausners ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Table 5: Pre-formulation parameters of blend for sustained layer

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
IR1	26.01	0.49	0.57	14.03	1.16
IR2	24.8	0.56	0.65	13.84	1.16
IR3	22.74	0.57	0.68	16.17	1.21
IR4	25.33	0.54	0.64	15.62	1.18
IR5	26.24	0.55	0.67	17.91	1.21
IR6	26.12	0.56	0.66	15.15	1.17
IR7	25.12	0.59	0.67	11.86	1.11
IR8	26.8	0.48	0.54	12.5	1.12
IR9	23.74	0.56	0.66	17.85	1.17

Table 6: Preformulation parameters of powder blend for Sustained layer:

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
SR1	27.67	0.429	0.546	23.93	1.272
SR2	24.19	0.547	0.624	12.33	1.140
SR3	24.70	0.462	0.591	21.82	1.279
SR4	24.70	0.519	0.683	13.46	1.315
SR5	22.67	0.395	0.475	20.25	1.202
SR6	21.12	0.409	0.531	22.97	1.298
SR7	23.98	0.549	0.626	12.30	1.140
SR8	25.73	0.60	0.69	13.04	1.28
SR9	27.51	0.63	0.74	14.86	1.17

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all formulations was found to be in the range of 0.49 to 0.59(gm/mL) showing that the powder has good flow properties. The tapped density of all formulations was found to be in the range of 0.57 to 0.66 showing that the powder has good flow properties. The compressibility index of all formulations was found to be below 18 which show that the powder has good flow properties. All the formulations has shown the Hausners ratio ranging between 0 to 1.2 indicating the powder has good flow properties

4. Quality control parameters for tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets.

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Table 7: *In vitro* quality control parameters for IR tablets

Formulation codes	Average Weight (mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	*In Vitro* Disintegration Time (sec)
IR1	95.5	4.5	0.52	3.5	99.76	32.14
IR2	102.4	4.0	0.54	3.3	97.45	23.19
IR3	97.6	4.4	0.51	3.1	98.34	14.52
IR4	99.6	4.5	0.55	3.4	99.87	32.13
IR5	102.4	4.4	0.56	3.2	99.14	25.27
IR6	100.7	4.2	0.45	3.4	97.56	16.35
IR 7	98.95	4.2	0.45	3.1	98.3	35.14
IR 8	99.15	4.7	0.54	3.2	99.3	26.21
IR 9	100.26	4.2	0.55	3.3	98.2	15.30

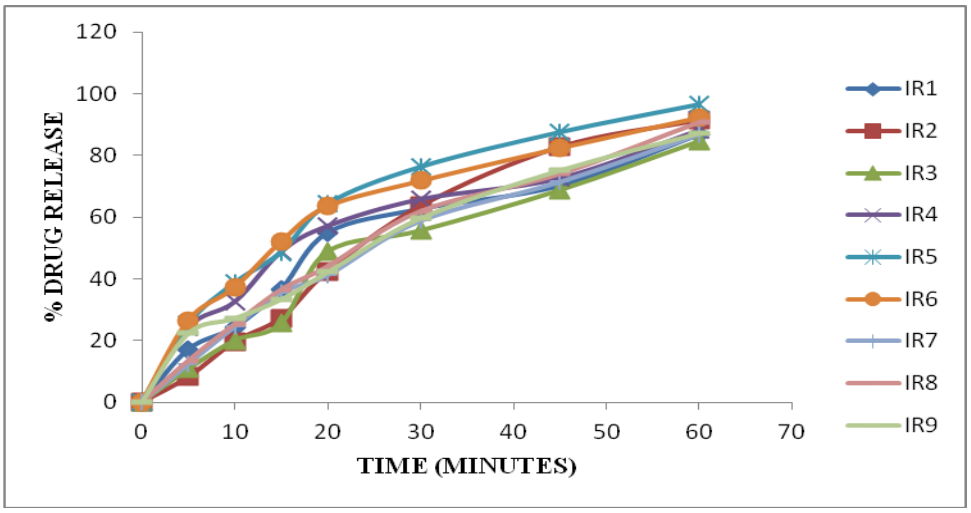
Table 8: *In- vitro* quality control parameters for Bi layer tablets

Formulation code	Average Weight (mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	798.4	5.1	0.61	5.3	98.42
F2	799.2	5.2	0.58	5.2	99.65
F3	501.3	5.5	0.45	5.4	99.12
F4	796.3	5.1	0.61	5.3	98.42
F5	798.6	5.3	0.59	5.5	99.65
F6	802.4	5.5	0.65	5.4	99.12
F7	800.6	5.3	0.62	5.6	98.16
F8	801.2	5.2	0.59	5.4	98.11
F9	802.8	5.9	0.34	5.2	99.45

Table 9: Dissolution data of Immediate release layer by using Different Superdisintegrants

TIME (Min)	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8	IR9
0	0	0	0	0	0	0	0	0	0
5	17.11	8.23	10.79	24.3	25.3	26.56	12.34	13.51	22.32
10	24.3	19.65	20.08	32.56	38.7	37.3	24.56	25.37	27.18
15	36.66	27.32	25.72	48.8	48.6	52.21	35.63	36.54	33.37
20	54.9	42.38	48.86	57.1	64.2	63.57	41.23	44.07	42.16
30	62.57	63.54	55.73	65.78	76.2	71.83	58.84	61.95	59.7
45	70.1	82.69	68.87	72.6	87.4	82.49	71.46	74.03	75.24
60	86.64	91.36	84.72	88.2	96.4	92.35	86.88	90.77	87.31

Fig 6: Dissolution data of Immediate release layer by using different superdisintegrants.



From the dissolution data of Glimepiride immediate release layer, IR5 formulation was shown maximum drug release at 60 min. i.e., 96.4%. Hence IR5 was concluded as optimized formulation for IR layer.

Table 10: Dissolution data of Bilayer Tablets using Different polymer

Time(Min/ hr)	SR 1	SR 2	SR 3	SR 4	SR 5	SR 6	SR 7	SR 8	SR 9
0	0	0	0	0	0	0	0	0	0
30 (0.5hr)	16.31	17.51	39.10	15.18	4.8	7.03	5.8	8.6	9.41
60 (1 hr)	26.70	30.69	50.77	30.74	8.7	9.19	12.3	11.1	13.75
120 (2 hr)	39.26	39.66	62.87	45.83	15.7	15.42	17.8	24.7	22.14
180 (3 hr)	42.77	47.86	74.10	49.6	19.8	25.71	22.8	30.5	26.43
240 (4 hr)	49.67	57.64	80.15	59.62	23.8	33.86	31.8	36.4	38.18
300 (5 hr)	52.54	63.92	85.76	61.03	31.7	43.90	39.3	45.2	42.27
360 (6 hr)	55.72	76.13	90.30	65.63	36.8	46.61	46.9	58.7	48.54
420 (7 hr)	63.86	80.67	94.41	70.39	43.2	49.55	51.8	64.4	53.78
480 (8 hr)	77.70	91.92	95.05	77.91	49.6	51.74	65.3	67.3	55.68
540 (9 hr)	82.53	93.85	95.92	81.93	58.6	53.17	76.6	71.8	67.35
600 (10 hr)	88.16	96.32	96.35	84.68	68.8	55.35	89.3	76.5	73.62
660 (11 hr)	95.71	97.59	100	90.71	81.6	62.14	95.21	83.4	76.43
720 (12 hr)	97.38	100	100	94.11	89.8	67.95	100	90.8	78.84
1440 (24 hr)	100	100	100	95.57	92.36	70.34	100	94.36	83.28

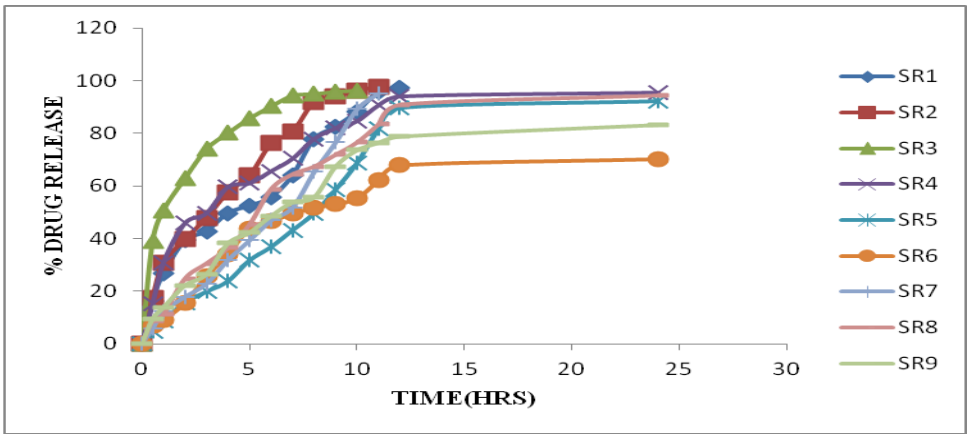


Fig 7: Dissolution data of Bilayer Tablets using SR1-SR9

From the above dissolution data of Metformin Sustained release Layer, SR4 formulation was shown maximum drug release at 24 hours. i.e., 95.57%. Hence SR4 was concluded as optimised formulation for Sustained layer. F4 Bilayer tablet Formulation consist IR5 and SR4 Formulation, which is considered as optimized formulation because it retards the drug release up to 24 hours and the highest drug release.

Release kinetics:

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Metformin release from Sustained Layer. The data was fitted into various kinetic models such as Zero, First order kinetics; Higuchi and Korsmeyer peppas mechanisms and the results were shown in below table 11.

Table 11: Invitro release kinetics data of Metformin Hcl from sustained layer

Cumulative (%) Release Q	Time (T)	Root (T)	Log (%) Release	Log (T)	Log (%) Remain	Release Rate (Cumulative % Release/T)	1/Cum% Release	Peppas Log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2				100	4.642	4.642	0
15.18	0.5	0.707	1.181	-0.301	1.928	30.36	0.0659	-0.819	84.82	4.642	4.394	0.248
30.74	1	1	1.488	0	1.84	30.74	0.0325	-0.512	69.26	4.642	4.107	0.535
45.83	2	1.414	1.661	0.301	1.734	22.915	0.0218	-0.339	54.17	4.642	3.784	0.858
49.6	3	1.732	1.695	0.477	1.702	16.533	0.0202	-0.305	50.4	4.642	3.694	0.948
59.62	4	2	1.775	0.602	1.606	14.905	0.0168	-0.225	40.38	4.642	3.431	1.211
61.03	5	2.236	1.786	0.699	1.591	12.206	0.0164	-0.214	38.97	4.642	3.39	1.251
65.63	6	2.449	1.817	0.778	1.536	10.938	0.0152	-0.183	34.37	4.642	3.251	1.39
70.39	7	2.646	1.848	0.845	1.471	10.056	0.0142	-0.152	29.61	4.642	3.094	1.548
77.91	8	2.828	1.892	0.903	1.344	9.739	0.0128	-0.108	22.09	4.642	2.806	1.836
81.93	9	3	1.913	0.954	1.257	9.103	0.0122	-0.087	18.07	4.642	2.624	2.017
84.68	10	3.162	1.928	1	1.185	8.468	0.0118	-0.072	15.32	4.642	2.484	2.158
90.71	11	3.317	1.958	1.041	0.968	8.246	0.011	-0.042	9.29	4.642	2.102	2.539
94.11	12	3.464	1.974	1.079	0.77	7.843	0.0106	-0.026	5.89	4.642	1.806	2.836
95.57	24	4.899	1.98	1.38	0.646	3.982	0.0105	-0.02	4.43	4.642	1.642	2.999

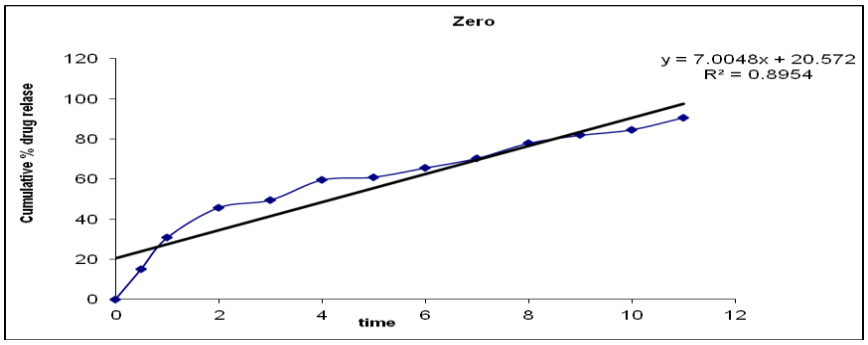


Fig 8: Zero order release kinetics graph

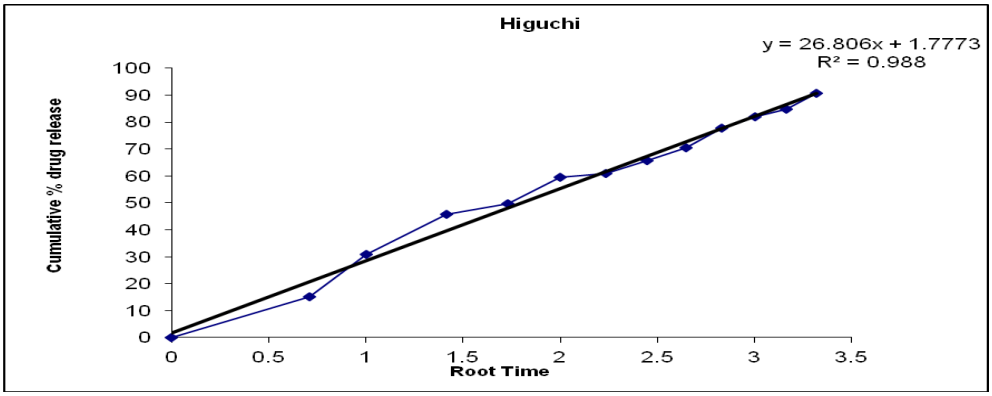


Fig 9: Higuchi release kinetics graph

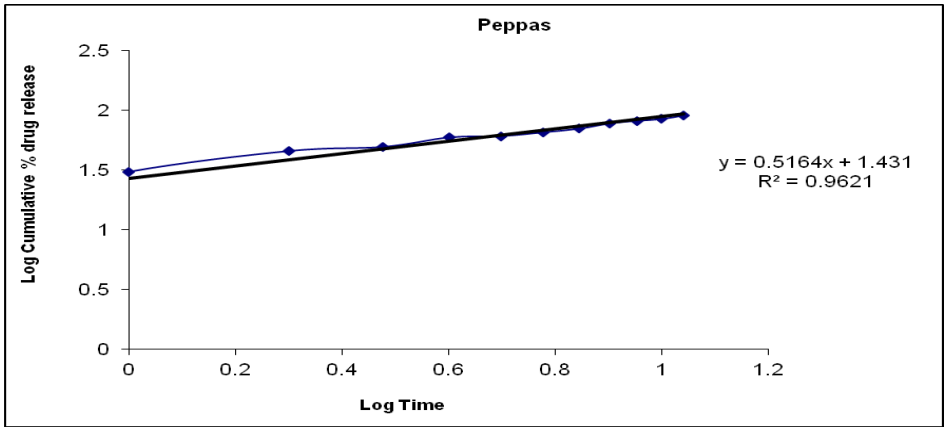


Fig 10: Peppas release kinetics graph

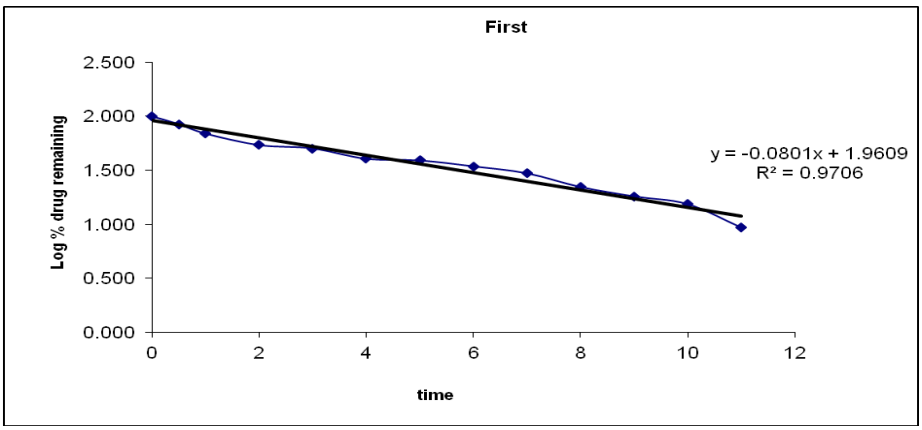


Fig 11: First order release kinetics graph

From the above graphs it was evident that the formulation SR4 was followed Higuchi release kinetics.

CONCLUSION:

The present study was carried out for bilayer tablets of Metformin HCl and Glimepiride Among all the formulations, F1-F9 were developed by using optimised immediate release layer (IR5) with combination of sustained release formulation blend powder. IR layer formulations were developed using super disintegrants From dissolution study IR5 formulation was shown maximum drug release at 60min i.e.,96.4%.SR4 formulation was best formulation, the drug release was 95.57%up to desired time period 24hrs. F4 bilayer tablet formulation is considered as optimised one as it follows Higuchi release kinetics.

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