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DEVELOPMENT AND IN VITRO EVALUATION OF OPTIMIZED BILAYER TABLETS OF GLIPIZIDE AND METFORMIN HYDROCHLORIDE FOR BIPHASIC DRUG DELIVERY IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

The bilayer tablet has been prepared in the present study comprising of two drugs glipizide and metformin to obtain immediate and sustained release of the drugs for better optimization of the treatment protocol of type 2 diabetes mellitus patients. Various quantity of cross povidone was used as super disintegrants for formulation of layer of immediate release glipizide and Carbopol 971P was used with wet granulation technique for formulation of sustained release (SR) layer of metformin hydrochloride. FT-IR analysis was performed to assess the compatibility of drugs with excipients, and it was noted that there was no chemical interaction between the two. Prior to compression, various characteristics like flowability and compressibility of blend were analyzed.

The in vitro drug release study of the formulations showed that the drug is released quickly from the IR component, with F3 releasing 99.69% of the drug after 10 minutes. For the SR formulations, the F8 and F13 formulations (PEO 303 and Carbopol 971P, respectively) sustained drug release for up to 12 hrs with cumulative percentage drug released 99.06% and 99.21%, respectively. The drug release rate kinetic analysis revealed that IR tablets exhibited

first order kinetic model while bilayer tablets fit well with Higuchi and Korsmeyer–Peppas model.

Thus, the optimized bilayer tablets can provide both an immediate release and a sustained release of the drugs in a single dosage form, which is a potential dosage form for treating type 2 diabetes mellitus.

Keywords: Bilayer Tablet, Immediate Release, Sustain Release, Controlled Drug Delivery System, Metformin, Glipizide, Type 2 Diabetes Mellitus

1. INTRODUCTION

Metabolic disease which requires lifelong treatment with medications to maintain proper regulation of glucose, is the Type 2 diabetes mellitus (T2DM). Overusing single medications is often preferred because they can address more than one physiological component of the disease and enhance patient adherence with using multiple medications. Glipizide belongs to the sulfonylurea group of medications and it causes an immediate decrease in blood sugar by stimulating the release of insulin from the pancreas, metformin decreases the production of glucose from the liver and increases the sensitivity of the body to insulin **[1]**.

The bilayer formulation is a reasonable way of incorporating drugs with various needs for delivery into one single unit dose. The approach makes drug delivery quick, hence, the fast onset of pharmacological activity and at the same time, sustained drug delivery is also included, which results in sustained drug action. Thus, the dosing amount is minimized and compliance enhanced. Gel formation upon hydration has been widely used to achieve sustained drug delivery of hydrophilic drugs by using hydrophilic carriers, such as PEO 303 and Carbopol 971P.

In this study, the development of bilayer tablets consisting of immediate release glipizide and sustained release metformin by means of direct compression and wet granulation techniques was **[2]**. The formulated tablets were optimized and tested for physical, chemical properties, in vitro dissolution profile, release kinetics and similarity with commercial preparation with the aim of enhancing the efficacy of the therapy for T2DM.

2. MATERIALS AND METHODS

2.1 Materials

Glipizide and metformin hydrochloride were selected as API for making bilayer tablets. (Drug Dev Ind Pharm. The other ingredients used for bilayer tablet preparation were PEO 303, Carbopol 971P, cross povidone, microcrystalline cellulose (MCC), talc, magnesium stearate and Thickening agent. All chemical reagents,

solvents and chemicals used in this study were of analytical grade.

The drug release from each layer (immediate-release and sustained-release) of the bilayer tablet was investigated in vitro, and the dissolution data were fitted to kinetic models to identify the drug release mechanism. The dissolution profiles were obtained by kinetic analysis which included plotting zero order (cumulative dissolved amount per unit time vs. time), first order (log cumulative drug remaining per unit time vs. time), Higuchi (cumulative drug release vs. square root of time) and Korsmeyer-Peppas (log cumulative drug release vs. log time). Plots were used to determine the correlation coefficient (r^2) values which were instrumental in determining the best kinetic models of release. Graphs for zero-order and first-order release profiles were used to analyze the concentration-independent and -dependent release profiles, whereas Higuchi and Korsmeyer-Peppas plots were used to understand diffusion-controlled release mechanisms.

2.2 Preparation of Bilayer Tablets

Bilayer tablets were prepared with direct compression and wet granulation technique comprising immediate release (IR) of Glipizide and sustained release (SR) of Metformin HCl.Formulation of Immediate Release Layer (Glipizide) Dry granulation method was used to prepare the IR layer **[3, 4]**. The ingredients glipizide, cross povidone, and MCC were sieved through sieve No. 40. The lake with sunset yellow was sieved to get uniform particle size with sieve No. 200. The ingredients listed above were mixed together in a 15-minute period using a geometric mixing procedure in a polybag. The fumed silica powder and magnesium stearate which had been sieved through sieve No. 60 were added to the mixture and then mixed for another 2 minutes. This led to the formation of a lubricated mixture of weight 150 mg.

2.2.1 Formulation of Sustained Release Layer (Metformin HCl)

2.2.1.1 Direct Compression Method:

Each of the ingredients, metformin hydrochloride, PEO 303 and MCC, was screened through sieve No. 40 and was then mixed for 15 minutes to ensure even mixing. After a further mixing time of 2 minutes to ensure lubrication, the other ingredients (talc and magnesium stearate) that had already been sieved with sieve No. 60 were added to the mixed. The SR layer weighed a total of 800 mg **[5]**.

2.2.1.2 Wet Granulation Method:

The selected polymer and diluent were mixed with metformin hydrochloride by the proposed formulation technique. (Drug Dev Ind Pharm. A solvent, hydroalcoholic liquid (ethanol:water at 1:1) was used. The wet mass thus obtained was sieved through sieve No. 20 and dried in an air dried oven at

50 °C. The dried granules were then coated with talc and magnesium stearate and the compaction was initiated. The weight of the sustained release (SR) layer was kept constant at 800 mg.

2.2.1.3 Compression of Bilayer Tablets:

The compression of sustained-release formulation containing Metformin 800 mg was performed using a gentle compression using a one punch tablet compression machine (Cad Mach Machinery Co. Pvt. Ltd., India) with 12 mm diameter flat punch. The immediate release formulation containing Glipizide with a dose of 150mg was then applied on top of the sustained release formulation to achieve a hardness of 6-7kg/cm² **[6]**.

3 Evaluation of bilayered tablets:

3.1 The pre compression evaluation

Bulk Density:

The amount of mass of powder blend and the volume of the powder blend in a graduated cylinder was measured to determine the bulk density.

$$D_b = \frac{\text{Mass of the powder blend (M)}}{\text{Vol. occupied by powder blend } (V_b)}$$

Tapped Density:

The powder was tapped 100 times with a measuring cylinder and tapped density was measured.

$$D_t = \frac{\text{Mass of the powder blend (M)}}{\text{Tapped volume (Vt)}}$$

Angle of Repose:

The angle of repose was obtained from the fixed funnel method and the height and radius of the powder heap were used to calculate the angle.

$$\tan(\theta) = \frac{\text{Height of the heap (h)}}{\text{Radius of the heap(r)}}$$

Carr's Index:

Bulk and tapped density were used to calculate the percent compressibility.

$$I = \frac{\text{Tapped density - bulk density} \times 100}{\text{Tapped density}}$$

Hausner's Ratio:

The ratio of tapped density to bulk density was determined as Hausner's ratio.

$$\text{The ratio of Hausner} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

3.2 Post Compression Evaluation

Weight Variation:

Total of 20 tablets were weighed individually and in bulk and percentage weight variation was calculated as per pharmacopeial requirement **[7]**

Hardness:

Hardness of the tablets was determined by Monsanto hardness tester and reported in kg/cm².

Friability:

The friability was determined by Roche at 25 rpm for 100 revolutions. Tablets with a friability of less than 1% were deemed acceptable.

Drug Content Estimation:

10 mg of Glipizide and Metformin were dissolved separately in methanol and distilled water, respectively, to obtain an equivalent amount of powder. These were then filtered and suitably buffered at pH 1.2 for Glipizide and pH 6.8 for Metformin and

were then studied using UV-visible spectrophotometry at 269 nm and 232 nm respectively **[8]**.

In Vitro Dissolution Studies:

The dissolutions were carried out in triplicate with the use of USP type II dissolution apparatus (Paddle method), with 900 mL medium kept at 37 ± 0.5 °C and speed of 100 rpm. The tablets were then exposed to pH 1.2 buffer solution for 2 hours, then changed into pH 6.8 phosphate buffer solution for 10 hours **[9]**.

Drug Release Kinetics:

To determine the drug release mechanism from the sustained release layer, the dissolution data were modeled using zero order, first order **[9]**.

Similarity Factor (f_2)

Similarity factor (f_2) was determined to compare the dissolution profile of optimized formulations with the marketed reference formulation. Similarities were suggested by an f_2 value of between 50 and 100.

Drug–Excipient Compatibility Studies

FT IR spectroscopy was used for the compatibility studies of pure drugs, polymers and formulations. All the characteristic peaks of Glipizide and Metformin HCl were present in the formulations and there was no interaction between the drug and excipients **[6]**.

3.3 RESULTS AND DISCUSSION

3.3.1 Pre-formulation Studies

The FT-IR spectroscopy technique was used to investigate the drug–excipient interactions in IR and SR layers of the bilayer tablet formulations **[10]**. The FT-IR spectra of the glipizide and metformin showed typical peaks corresponding to their functional groups, which were kept in the FT-IR spectra of the prepared tablets.

The FT-IR spectrum of the formulation containing PEO-303 as polymer did not show any significant changes, disappearance or appearance of new peaks, indicating no drug-polymer interaction, and hence, metformin was chemically stable in the polymer-based matrix **(See Fig 1-4)** Likewise, the formulation with the polymer of Carbopol 971P did not show any chemical modification of metformin hydrochloride and all the peaks of the drug remained unchanged.

Moreover, the presence of cross povidone as the super disintegrant in the formulation did not cause any change in the chemical structure of glipizide, as seen from the FT-IR spectrum of this formulation with the super disintegrant, where the peaks of glipizide were maintained with no modification. There were no indications of the appearance of additional peaks or peak broadening, which would indicate chemical changes of the drug due to drug-excitement interactions. **[11]**. Overall, the drug did not change after being incorporated into the excipient.

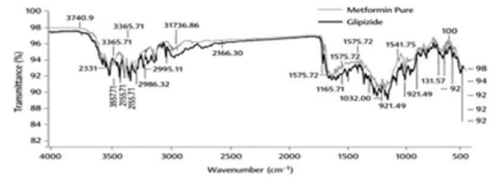


Fig1 IR Spectrum for Metformin and Glipizide

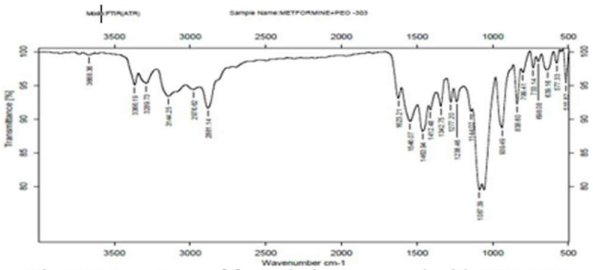


Fig 2 IR Spectrum of formulation prepared with PEO-303

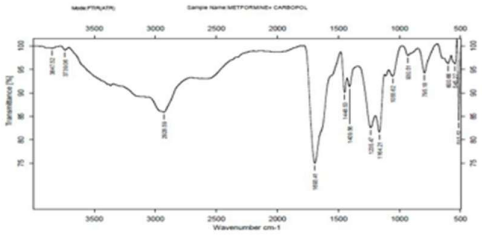


Fig-3 IR Spectrum of formulation prepared with CARBOPOL 971P

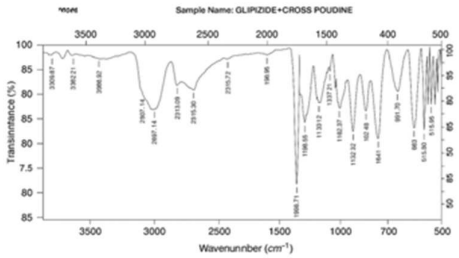


Fig 4 IR Spectrum of formulation prepared with CROSS POVIDONE

3.3.1.2 Micromeritic Properties

The properties of powder blends for the IR (F1–F3) and SR layers (F4–F14) are presented in **Table 1**. The IR formulations exhibited an angle of repose of 21.0° to 22.5° and compressibility index value of 15.97% to 16.36% and Hausner's ratio of 1.16–1.23, which are good flow properties. Likewise, SR formulations with PEO 303 and Carbopol 971P had acceptable flow properties such as angle of repose less than 25°, compressibility index less than 18% and Hausner's ratio less than 1.25. A slight decrease in flow was noted with higher concentration of polymer, but all the blends could be compressed into tablets **[4]**.

Table 1: Micromeritic properties for both IR and SR layers

Formulation code	Micromeritic properties				
	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (°)	Compressibility index (%)	Hausner's ratio
F1	0.598	0.643	21.5	16.36	1.16
F2	0.659	0.732	21	15.97	1.23
F3	0.688	0.768	22.5	16.08	1.19
F4	0.576	0.654	21.5	16.07	1.18
F5	0.532	0.612	23	15.90	1.17
F6	0.569	0.636	21	15.50	1.19
F7	0.592	0.664	22.5	16.67	1.21
F8	0.657	0.743	22	16.07	1.16
F9	0.689	0.776	24	17.63	1.14
F10	0.546	0.624	22.5	16.09	1.19
F11	0.572	0.642	22	16.76	1.16
F12	0.587	0.676	21.5	16.50	1.21
F13	0.643	0.714	21	15.97	1.18
F14	0.623	0.703	21.5	16.50	1.17

3.3.2 Post Compressional Parameters:

The post compression evaluation results **(Table 2, 3)** indicate that all the bilayer tablet formulations met the pharmacopeial standards. The weight variation was within acceptable limits and it was concluded that the die filling was uniform. The thickness of the tablet (8.09–8.52 mm) and hardness (7.11–7.34 kg/cm²) remained similar in all the formulations. The friabilities were less than 0.25%, indicating good mechanical integrity. The percentage of drug content was in the range of 97–101% for both drugs which is an indication of uniform drug distribution. Higuchi, T. (1963). Mechanism of sustained-action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. Tablet formulations of glipizide and metformin were prepared by direct compression method.

Table 2: Post compression parameters bilayer tablets of glipizide and metformin by direct compression

Formulation code	Average Weight (±SD)	Thickness (mm)	Hardness kg/cm^2	Friability (%)	Drug Content (%)	
					Pioglitazone HCl	Metformin
F4	950.4±0.55	8.47±0.01	7.30±0.04	0.23±0.05	98.75±0.73	99.40±0.77
F5	948.6±1.34	8.48±0.03	7.34±0.42	0.21±0.06	98.26±1.08	98.89±1.73
F6	947.6±0.89	8.52±0.03	7.21±0.23	0.2±0.05	98.50±1.05	100.20±0.45
F7	948.8±0.84	8.52±0.02	7.11±0.17	0.17±0.04	97.09±0.73	99.39±0.73
F8	950.4±0.52	8.51±0.02	7.17±0.30	0.19±0.03	99.03±0.89	99.62±0.86
F9	949.6±0.48	8.50±0.03	7.28±0.24	0.20±0.08	99.24±0.56	99.64±0.52

Table 3: Post compression parameters bilayer tablets of glipizide and metformin by wet granulation technique

Formulation code	Average Weight (±SD)	Thickness (mm)	Hardness kg/cm^2	Friability (%)	Drug content (%)	
					Pioglitazone HCl	Metformin
F10	950.4±0.35	8.14±0.05	7.28±0.11	0.22±0.04	99.75±0.43	99.10±0.37
F11	949.6±0.98	8.09±0.02	7.30±0.41	0.21±0.02	99.26±1.18	99.37±1.03
F12	950.6±0.46	8.19±0.02	7.21±0.43	0.23±0.04	98.90±1.01	99.28±0.75
F13	951.8±0.78	8.19±0.03	7.19±0.15	0.19±0.03	99.09±0.23	99.09±0.33
F14	950.6±0.41	8.10±0.05	7.14±0.20	0.17±0.04	98.03±0.59	98.72±0.46

Fast drug delivery was observed in the IR formulae **(see Fig 5)**. Formula F1 had a drug delivery rate of 78.65% in 10 minutes, F2 delivered 92.40% while F3 delivered 99.69%. This increase in drug delivery rate in formula F3 was due to the increased amount of cross povidone that led to fast disintegration of the tablet **[10]**.

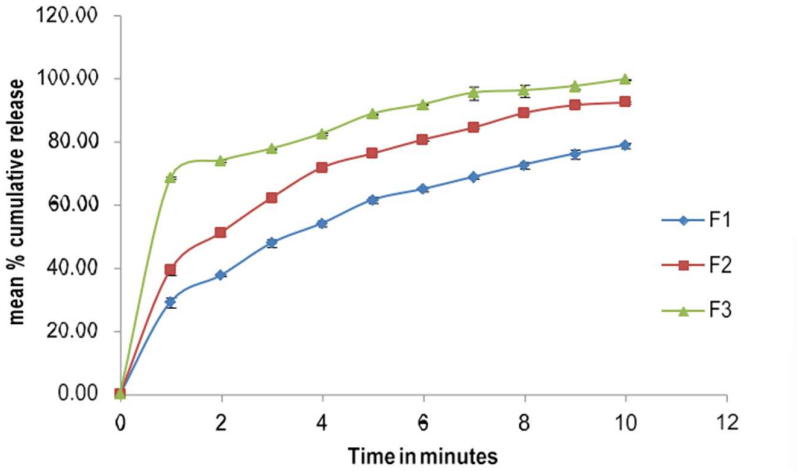


Fig 5: Shows the cumulative % drug release profile for the IR layer formulations

3.3.2.1 Sustained Release Layer – Direct Compression

The release profile of the drugs used was found to be concentration dependent in SR preparations containing PEO 303 (F4-F9). Formulation F4 showed the highest drug release (>95%) in 2 hours, which indicated that the drug release was not sustained enough. F8 and F9 were found to have a slow and sustained drug release pattern till 12 hours, out of which F8 had maximum (99.06%) drug release till 12 hours.

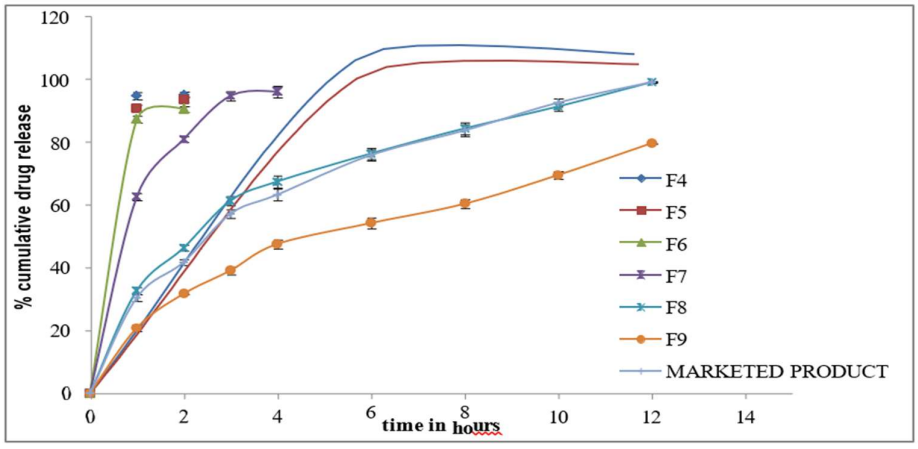


Fig 6: Cumulative % drug release profiles of the bilayer tablets prepared by direct compression method

Wet granulation is used to produce sustained release tablets. Sustained release tablets can be prepared by wet granulation. The formulations with Carbopol 971P as the SR polymers (F10-F14) showed better control of drug release particularly with the increase in the concentration of the polymer. The formulation F10 showed rapid drug release while F13 and F14 showed controlled release of the drug for 12 hours **(See Fig 7)**. The formulation F13 showed 99.21% drug release in 12 hours **(Table 4, 5)**.

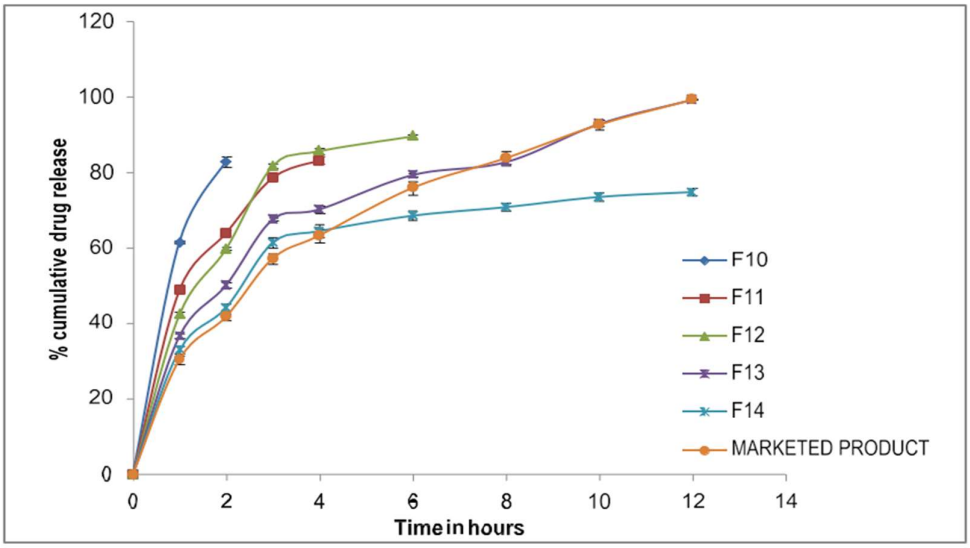


Fig 7: Cumulative % drug release profiles of bilayer tablets prepared by wet granulation method

3.4 Drug Release Kinetics:

Table 4: *In-vitro* Drug Release Kinetics for IR layer formulations

Formulation code	Correlation coefficient		K(hr.$^{-1}$)
	Zero order (mol. L^{-1}.min^{-1})	First order (min^{-1})	
F1	0.875	0.981	0.142
F2	0.812	0.990	0.248
F3	0.600	0.916	0.432

Describe the method of comparing two polymers. Discuss the comparative evaluation of two polymers **(Table 5, 6)**. Both PEO 303 and Carbopol 971P were found to be effective in controlling the release of the drugs in a dose dependent manner, however. The release control and matrix strength of PEO 303 were slightly better when it was wet granulated using Carbopol 971P than when it was dry compacted **(See Fig 9, 10)**.

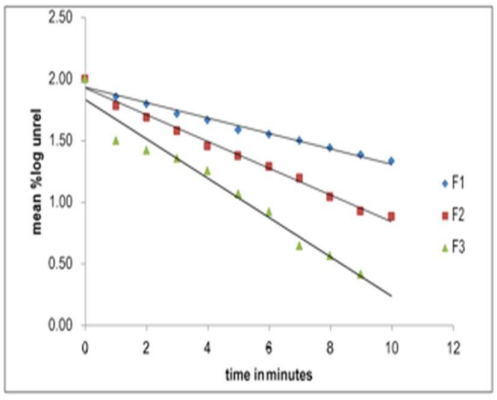


Fig 8: First order kinetics

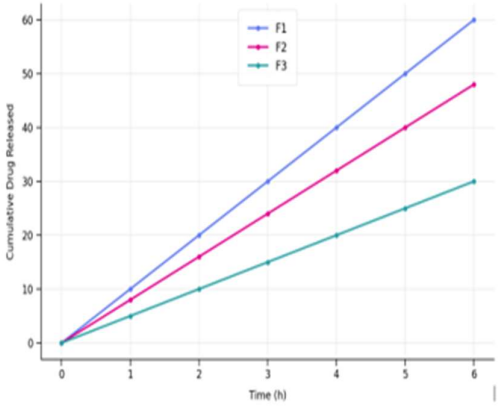


Fig 9: Zero order kinetics

Table 5: *In-vitro* Drug Release Kinetics for Bilayer Tablets Formulated by Wet Granulation technique

Formulation Code	Zero order		First order		Higuchi		Peppas	
	K Value mol. $L^{-1}.h^{1}$)	r^2 value	K value (h^{-1})	r^2 value	K value	r^2 value	n value	r^2 value
F4	28.03	0.311	0.888	0.321	0.245	0.159	0.001	0.159
F5	31.27	0.405	1.179	0.567	13.40	0.546	0.075	0.665
F6	35.86	0.592	1.440	0.915	32.13	0.961	0.176	0.983
F7	4.90	0.464	0.227	0.646	16.12	0.743	0.199	0.896
F8	7.10	0.855	0.237	0.990	27.36	0.979	0.466	0.990
F9	5.69	0.911	0.115	0.917	22.92	0.983	0.589	0.991

Table 6*: In-vitro* Drug Release Kinetics for Bilayer Tablets Formulated by Wet Granulation technique

Formulation Code	Zero order		First order		Higuchi[7]		Peppas	
	K value (mol. $L1.h^{1}$)	r^2 value	K value (h^{-1})	r^2 value	K value	r^2 value	n value	r^2 value
F10	37.35	0.896	0.829	0.991	57.25	0.997	0.482	0.998
F11	18.57	0.859	0.430	0.979	40.20	0.988	0.454	0.994
F12	14.07	0.820	0.393	0.948	37.95	0.952	0.469	0.983
F13	7.010	0.830	0.313	0.891	26.71	0.968	0.430	0.985
F14	5.251	0.716	0.108	0.836	20.09	0.892	0.408	0.952

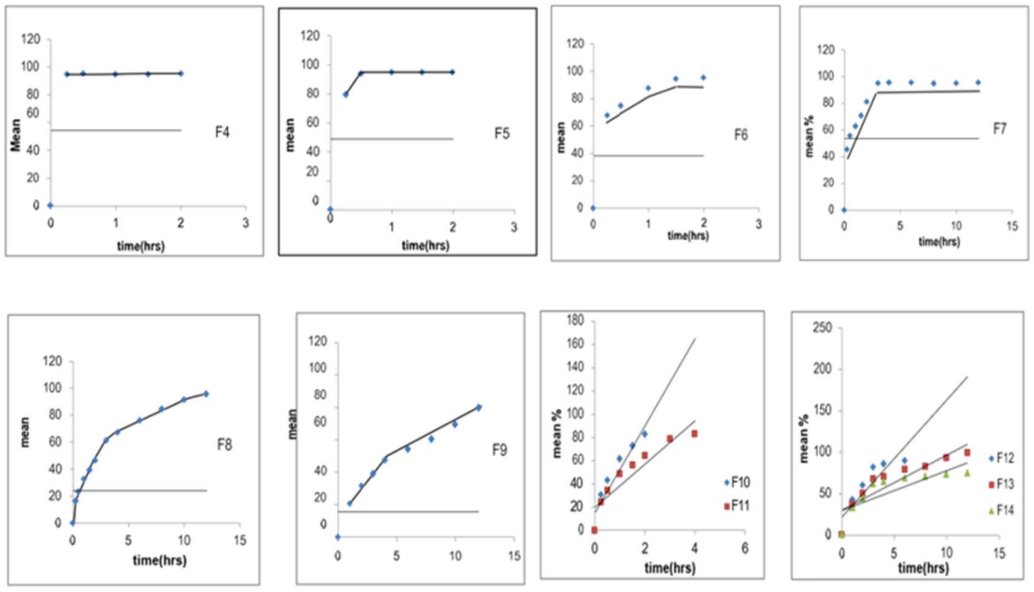


Fig 10: Drug release kinetics for sustain release layer (Zero order plots)

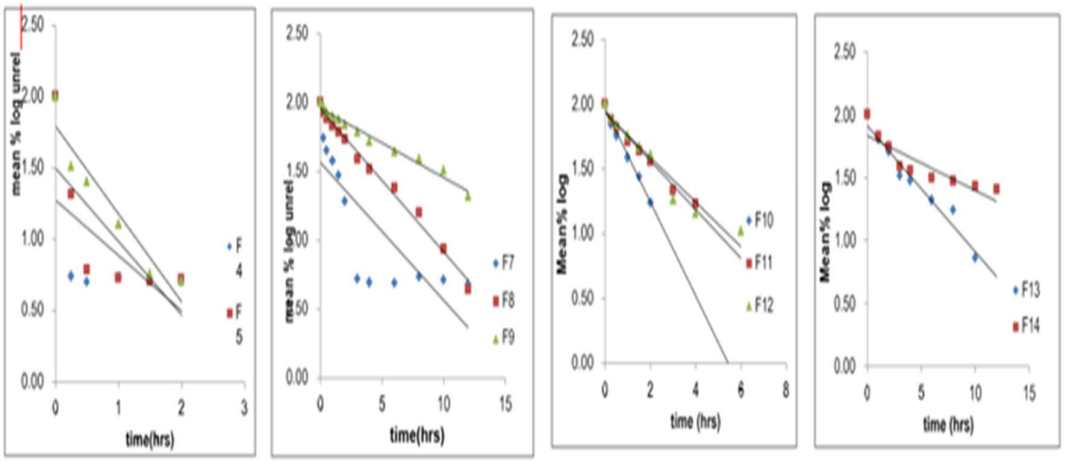


Fig 11: Drug release kinetics for sustain release layer (First order plots)

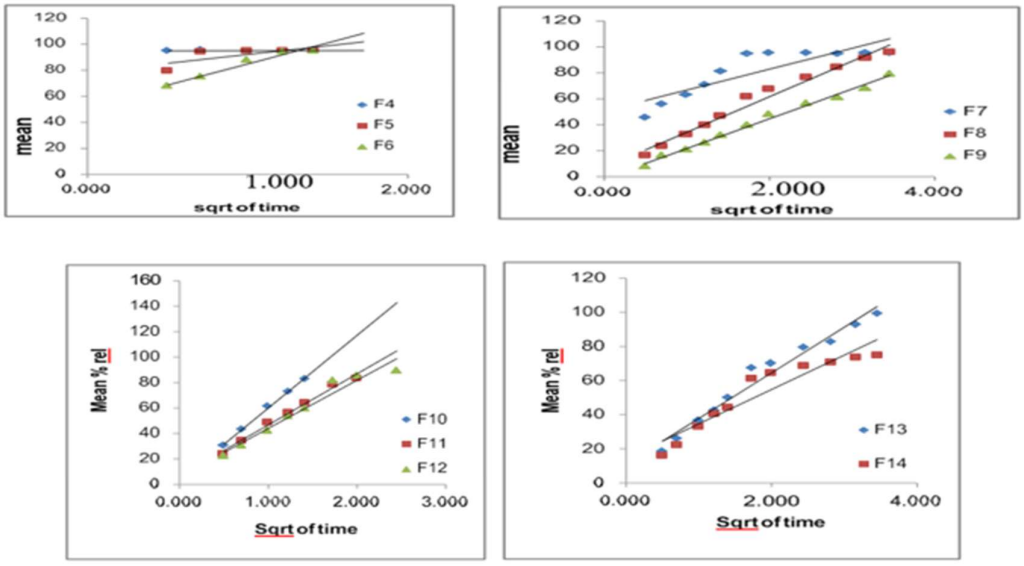


Fig 12: Drug release kinetics for sustain release layer (Higuchi's plots)

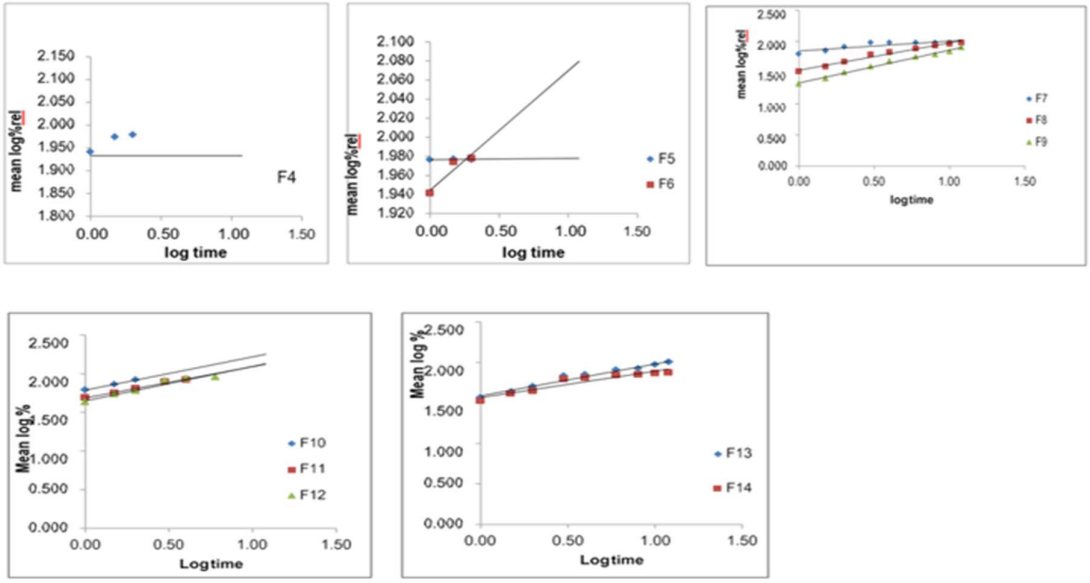


Fig 13: Drug release kinetics for sustain release layer (Peppas plots)

3.5 Comparative Evaluation of Polymers

However, both PEO 303 and Carbopol 971P could effectively control the release of the drugs in a dose-dependent manner. Wet granulation of Carbopol 971P provided slightly improved release control and matrix strength than dry compaction of PEO 303 **(See Fig 11, 12)**.

3.6 Optimized Formulation

Based on the micromeritic properties, post compression behavior and dissolution studies it was seen that F3 was an optimized formulation of IR layer **(See Fig 5)**. For the SR layer **(See Fig 7)**, optimized formulations F8 (PEO 303, direct compression) and F13 (Carbopol 971P, wet

granulation) were chosen. The bilayer tablets of glipizide and metformin were successfully prepared **[6]**. Formulation and evaluation of bilayer tablets of metformin hydrochloride and glipizide.

4. CONCLUSION:

The present research study has successfully validated preparation and characterization of bilayer tablet of Glipizide (IR) and Metformin (SR) with the aim of achieving a biphasic drug release pattern for the treatment of Type 2 Diabetes Mellitus patients. The selected excipients and polymers namely cross povidone (IR layer) and either PEO 303 or Carbopol 971P (SR layer) were found to be compatible with the drugs, as there was no drug-excipient interaction observed by FT-IR spectroscopy. The pre compression analysis of powders revealed satisfactory bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio values of the powders indicating good powder flowability and compressibility suitable for compaction in tablet form. Moreover, it was found that all the bilayer formulations had uniformity of weight variation, good hardness, non-friability and uniform drug content within the Pharmacopoeia limits after compression. In vitro dissolution study revealed that IR formulation with higher concentration of cross povidone had faster dissolution of Glipizide (F3) compared to other IR formulation (F1, F2, F4, F5). There was polymer dependent and concentration dependent drug dissolution with sustained release formulations. Direct compression formulations F8 having PEO 303 were the best sustained-release formulations releasing Metformin for up to 12 h. Wet granulations using Carbopol 971P like F13 had excellent sustained-release profile up to 12 hrs.The results of the drug release kinetic studies showed that the immediate release layer had first order drug release while the sustained release layer had Higuchi and Korsmeyer-Peppas model kinetics, which indicated a diffusion controlled process. The bilayer formulations developed were able to deliver the desired release profile and may offer advantages in terms of treatment efficacy and compliance in the area of type 2 diabetes mellitus fixed-dose combination therapy**[9]**

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