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Formulation And Release Characteristics Of A Bilayer Matrix Tablet Containing Pioglitazone Hydrochloride As Immediate Release Component And Metformin Hydrochloride As Sustained Release Component .

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ABSTRACT:
Diabetes mellitus (DM) is a common diseases that often coexist. The most common cause of death in the diabetic patient is heart disease. In the present investigation we combine Pioglitazone HCl and Metformin for better patient compliance. IR layer of Pioglitazone, was formulated using cross Povidone and Micro translucent cellulose (MCC) as it was fixed to 150 mg.and SR layer was formulated using polymers Poly ethylene oxide (PEO-303) and MCC as it was fixed to 800 mg.to the tablet formulation and dissolution medium of (IR) and (SR) enhanced the release of drugs from both layers. Kinetic studies of optimized IR layer and SR layer showed good linearity with regression coefficient respectively. The details F8 and F13 were reasonable to support the medication discharge for a time of 12hrs, followed first request energy displayed Higuchi's model and Krosmeyer-Peppas dramatic coefficient Thus can presume that figured Bilayered tablets of Pioglitazone HCl and Metformin HCl were grown effectively with IR layer containing Crospovidone and SR layer including PEO-303 and CARBOPOL 971P as polymers by Direct Compression procedure

KEY WORDS: *Pioglitazone, Metformin HCL Bilayered tablets , Crospovidone, carbopol*

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I. INTRODUCTION

As not many medications are emerging from innovative work and as of now existing medications are experiencing the issue of obstruction because of their unreasonable use and complexities engaged with showcasing new medication elements have expanded, and additionally the longing to keep a close consistent or uniform blood drug levels, just as upgraded clinical viability of the medication for its expected utilize made a few medications more powerful by slight modification in the medication conveyance. With attending acknowledgment of the helpful benefits of Sustained medication conveyance and Controlled medication conveyance, more prominent consideration has been centered around improvement of Sustained delivery drug conveyance frameworks and Controlled medication conveyance frameworks.

Controlled Release Drug Delivery frameworks are the measurements structures intended to convey the medication at a foreordained rate, locally or fundamentally, for a predefined timeframe.Supported Release Drug Delivery frameworks are those that give prescription throughout a drawn out timeframe. Supported delivery drug conveyance frameworks can be characterized as any measurement structure that delays the restorative action of the medication by consistently delivering medicine throughout a lengthy timeframe. Without any appropriate clinical proof of this remedial impact it tends to be characterized as any measurements frames that give prolongation of the medication levels in the blood. The significant benefit of this class is that, notwithstanding the comfort of diminished recurrence organization, it gives levels that are without the pinnacle and valley impact .

By giving smooth plasma level of medication throughout longer timeframe, maintained - discharge drug conveyance innovation can limit incidental effects, further develop viability and by empowering once day by day dosing-boost patient consistence.

II. MATERIALS AND METHOD

Preparation of Bilayer Tablets:

In this present investigation Bilayered tablets of Pioglitazone HCl and Metformin HCl were formulated by Direct Compression Technique and Wet Granulation Technique. 1 Direct Compression Technique:

Sustained release layer of Metformin HCl was prepared by dry granulation technique. Metformin HCl, Poly ethylene oxide (PEO-303) and MCC were passed through sieve no # 40. All the above were mixed in geometric proportion in a poly bag for 15 minutes. Talc and magnesium stearate were passed through sieve no # 60. Sifting was performed and the lubricated material was passed through the poly bag and mixed for 2 minutes. Compositions of different trial formulations for the IR layer were given in table 6.5.2. The final weight of the SR layer was fixed to 800 mg.

5.10.2. 2 Wet Granulation Technique:

6.5 Granules of Sustained release layer was formulated by uniformly mixing required amount of Metformin HCl with measured quantities of polymer and diluent as specified in the formulation table 6.5.3 using 1:1 ratio of ethanol and water as diluting fluid. Now the wet damp mass was passed through sieve no #20 and the granules were dried in hot air oven at 50^{o}C. Talc and magnesium stearate were added and mixed thoroughly before compression of granules. The final weight of the SR layer was fixed to 800 mg

6.6 Formulation tables:

Table – 6.5.1 Composition for IR layer of Bilayered tablet

S.No	Ingredients (mg/tab)	Formulations		
		F1	F2	F3
1	Pioglitazone HCl	15	15	15
2	Cross povidone	2.5	5	7.5
3	Lactose	74.5	72	69.5
4	MCC	50	50	50
5	Aerosil	3	3	3
6	Mg stearate	3	3	3
7	Sunset yellow	2	2	2
Total Weight		150	150	150

Table – 6.5.2 Composition for SR layer of Bilayered Tablets prepared by Direct Compression technique

S.No.	Ingredients (mg/tab)	Formulations					
		F4	F5	F6	F7	F8	F9
1	Metformin HCl	500	500	500	500	500	500
2	PEO-303	50	100	150	200	250	296
3	MCC	246	196	146	96	46	-
4	Mg stearate	2	2	2	2	2	2
5	Talc	2	2	2	2	2	2
Total Weight		800	800	800	800	800	800

Table – 6.5.3 Composition for SR layer of Bilayered Tablets prepared by Wet Granulation technique

S.No.	Ingredients (mg/tab)	Formulations				
		F10	F11	F12	F13	F14
1	Metformin HCl	500	500	500	500	500
3	Carbopol 971P	50	75	100	150	200
4	cmm	246	221	196	146	96
5	Mg stearate	2	2	2	2	2
6	Talc	2	2	2	2	2
7	Diluting fluid (ethanol and water1:1)	qs	qs	qs	qs	qs

Total Weight	800	800	800	800	800

- Bulk Density:

The powder blend of all formulations was evaluated separately inorder to determine their bulk densities. Powder blend was weighed (M) and later the weighed powder blend was transferred in to the measuring cylinder and volume occupied was noted (V_b).

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

V_b is known as the Bulk volume and Bulk density is expressed in terms of g/ml.

Tapped density

Powder blend was transferred into the measuring cylinder and subjected for 100 tappings. The obtained volume was noted as the tapped volume. Tapped density is expressed as g/ml and tapped density is given by the formula;

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

- Carr's index

Carr's Index is one more measure to know the flow properties. It is indicated by the letter (I) and expressed in terms of percentage

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

- Hausner's ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material.
Hausner's ratio was calculated by using the formula;

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

- Angle of repose

Angle of repose is the maximum angle possible between the surface of the pile of granules and the horizontal plane. This is one of the measures for flow properties. Powder blend was allowed to flow through the funnel attached to a stand and later height and radius of the heap of the powder blend formed was noted. Based on the height and radius obtained Angle of repose was calculated using the formula;

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

Table No. 2: Evaluation (Pre-compression) parameters of all formulation (F1-F12)

Formulation	Bulk density	Tapped density	Angle of repose	Compressibility index	Hausner's ratio
F1	0.598	0.643	21.5	16.3	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

POST COMPRESSION STUDIES

1. Weight Variation

Twenty tablets were weighed collectively and individually. Average weight was calculated and based on the obtained weights % weight variation was calculated using the formula,

$$\% \text{ Weight Variation} = \frac{\text{Average weight} - \text{Individual weight}}{\text{Average weight}} \times 100$$

.

2. Hardness test

Hardness of the tablet was tested by placing the tablet longitudinally in between the two plungers of the Monsanto tablet hardness tester and the obtained hardness was mentioned in terms of kg/sq.cm.

Limits for Hardness are 4-6kg/sq.cm.

3. Thickness

The Thickness of tablet was measured by Vernier caliper & the Furosemide tablet of thickness were found in between the 2.30±0.45 to 2.70±0.05.

4. Friability test

The friability of the tablets was determined by Roche Friabilator in which the tablets were subjected to the combined effect of abrasions and shock in a plastic chamber revolving at 25rpm and dropping the tablets at a height of 6 inches in each revolution.

Pre weighed sample of tablets were placed in the friabilator and allowed to rotate for 100 revolutions. Later the tablets were dedusted and the tablets were reweighed. Percent friability is given by the formula;

$$\%F = (1-W/W_0) \times 100$$

Where, W_0 is the weight of the tablets before the test

W is the weight of the tablets after the test

Limits for friability are %friability should not be more than 1%.

5. Content uniformity

Twenty tablets were crushed and powder equivalent to weight of one tablet was dissolved in phosphate buffer 6.8. Then suitable dilutions were made and absorbance at 276 nm wavelength was taken by using a UV visible spectrophotometer. The content uniformity of Furosemide were found to be 95.23±1.09 to 99.36±0.48.

6. Disintegration time

Fast Disintegrating tablets apply the tests observe the tablets within the time limit all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely repeat the test on 12 additional tablets, not less than 16 of the total of 18 tablets tested disintegrate completely. The Furosemide tablets were found in between the 14 sec. to 46 sec.

In-vitro drug release studies:

. **Post Compressional Parameters Bilayered Tablets of Pioglitazone HCl and Metformin HCl by Direct Compression technique**

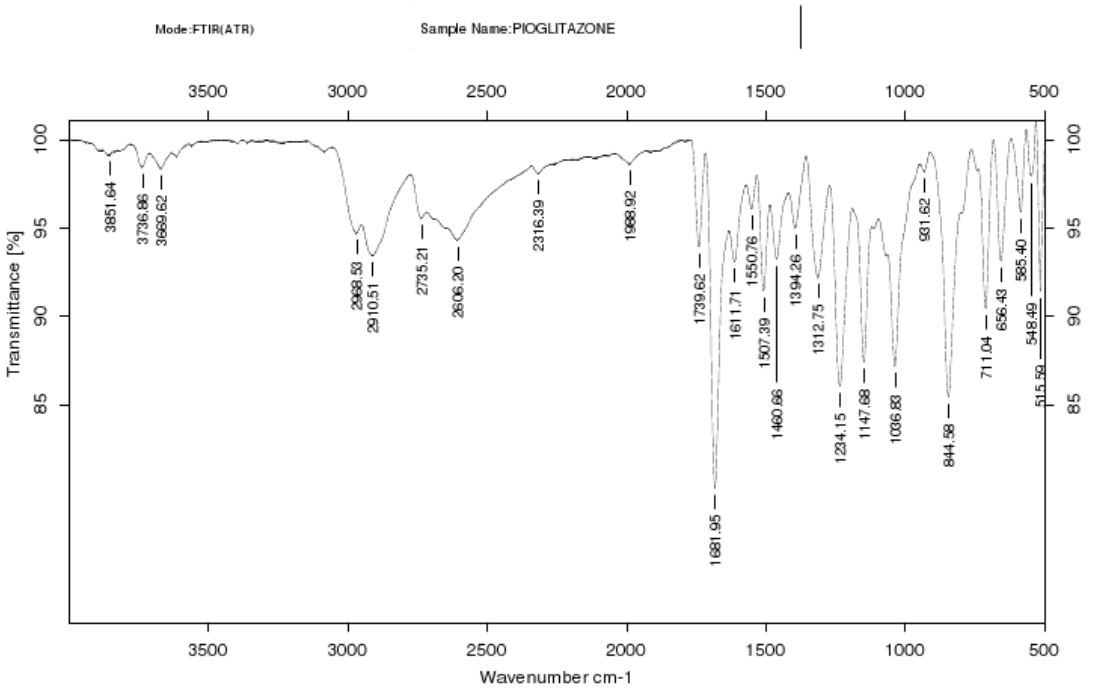
Formulation code	Average Weight (±SD)	Thickness (mm)	Hardness kg/cm^2	Friability (%)	Drug Content (%)	
					Pioglitazone HCl	Metformin HCl
F4	950.4±0.55	8.47±0.01	7.30±0.04	0.23±0.05	98.75±0.73	99.40±0.77
F5	948.6±1.34	8.48±0.03	7.34±0.42	0.21±0.06	98.26±1.08	98.89±1.73
F6	947.6±0.89	8.52±0.03	7.21±0.23	0.2±0.05	98.50±1.05	100.20±0.45
F7	948.6±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	7.11±0.30	0.19±0.03	99.03±0.89	99.62±0.86
F9	949.4±0.48	8.50±0.03	7.28±0.24	0.20±0.08	99.2±0.56	99.64±0.52

2 Post Compressional Parameters of Pioglitazone HCl and Metformin HCl by Wet Granulation technique

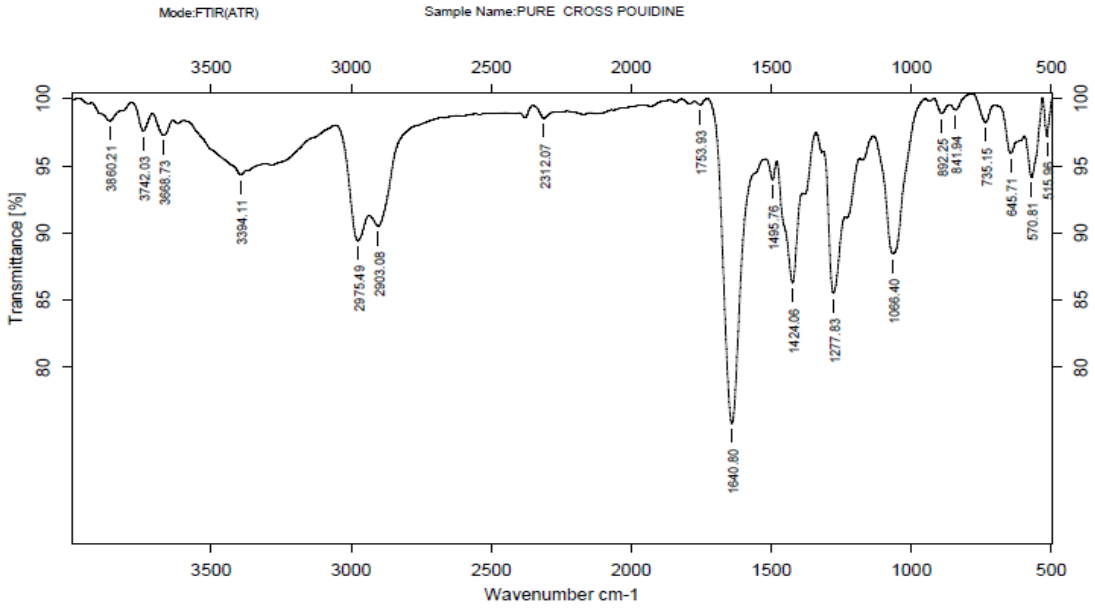
Formulation code	Average Weight (±SD)	Thickness (mm)	Hardness kg/cm^2	Friability (%)	Drug content (%)	
					Pioglitazone HCl	Metformin HCl
F10	950.4±0.35	8.14±0.05	7.28±0.11	0.22±0.04	99.75±0.43	99.10±0.37
F11	949.6±0.98	8.09±0.02	7.30±0.41	0.21±0.02	99.26±1.18	99.37±1.03
F12	950.6±0.46	8.19±0.02	7.21±0.43	0.23±0.04	98.90±1.01	99.28±0.75
F10	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

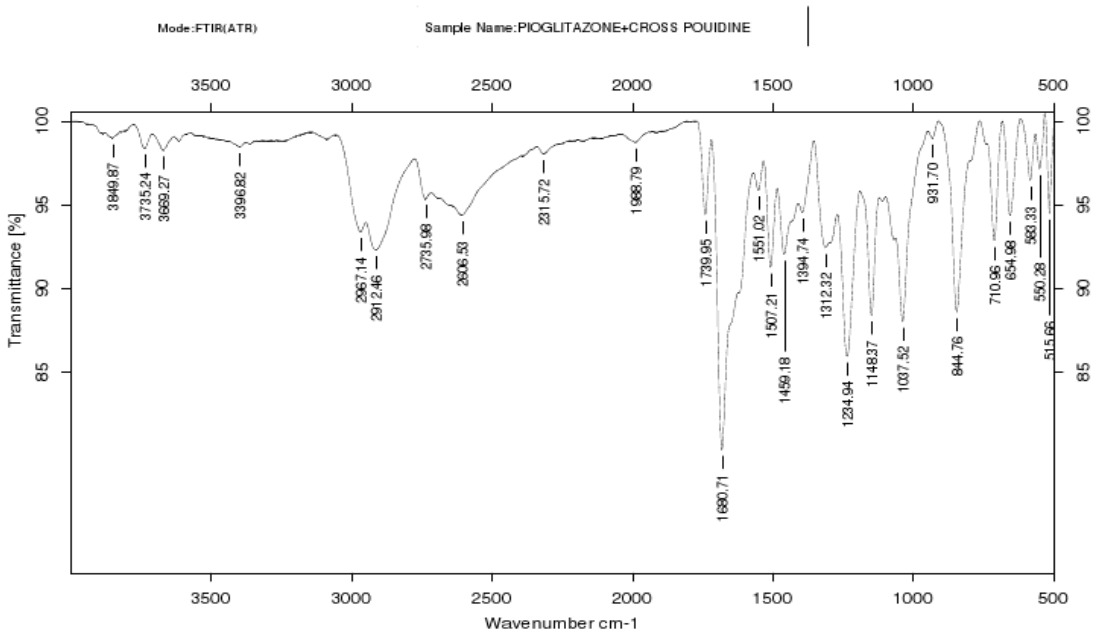
FTIR RESULT



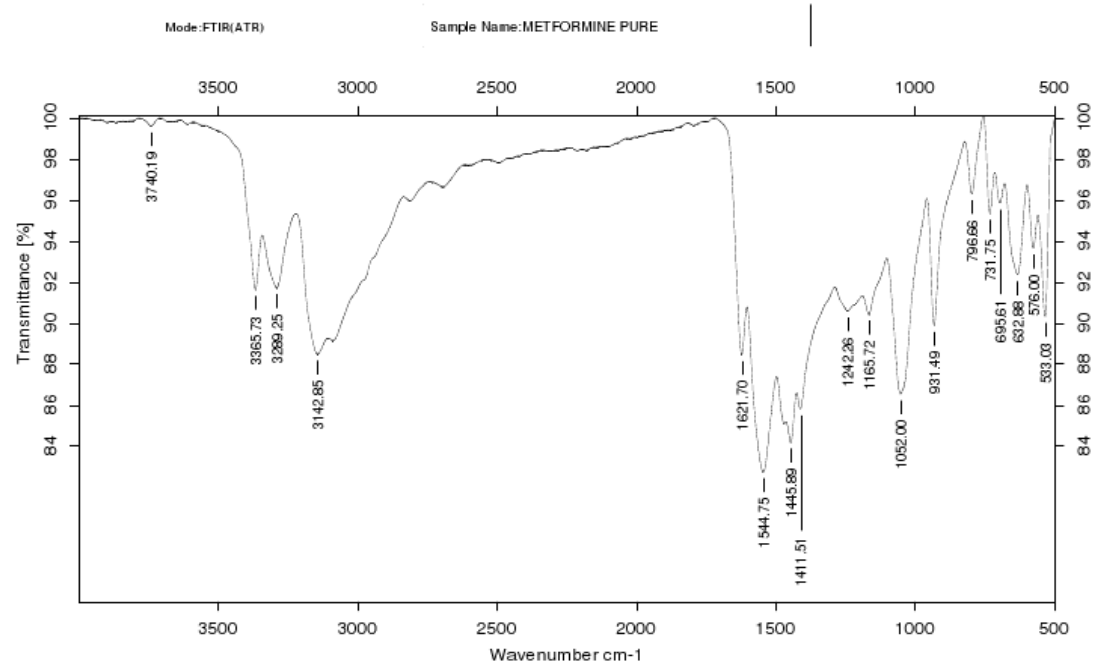
FT-IR Spectrum of pure Pioglitazone HCl



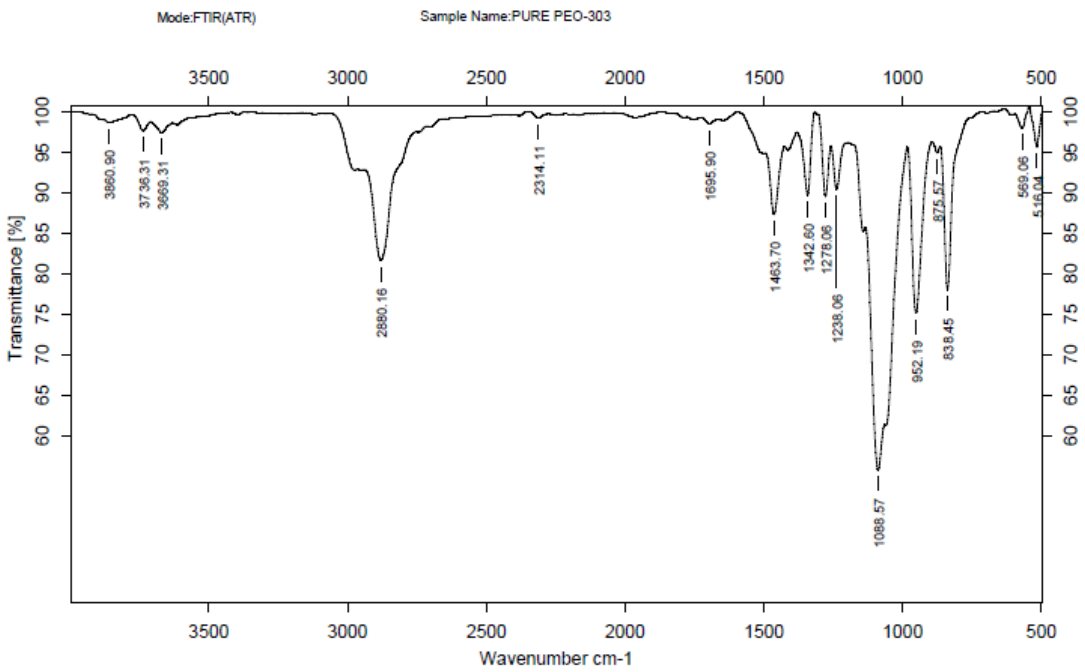
FT-IR Spectrum of pure Crospovidone



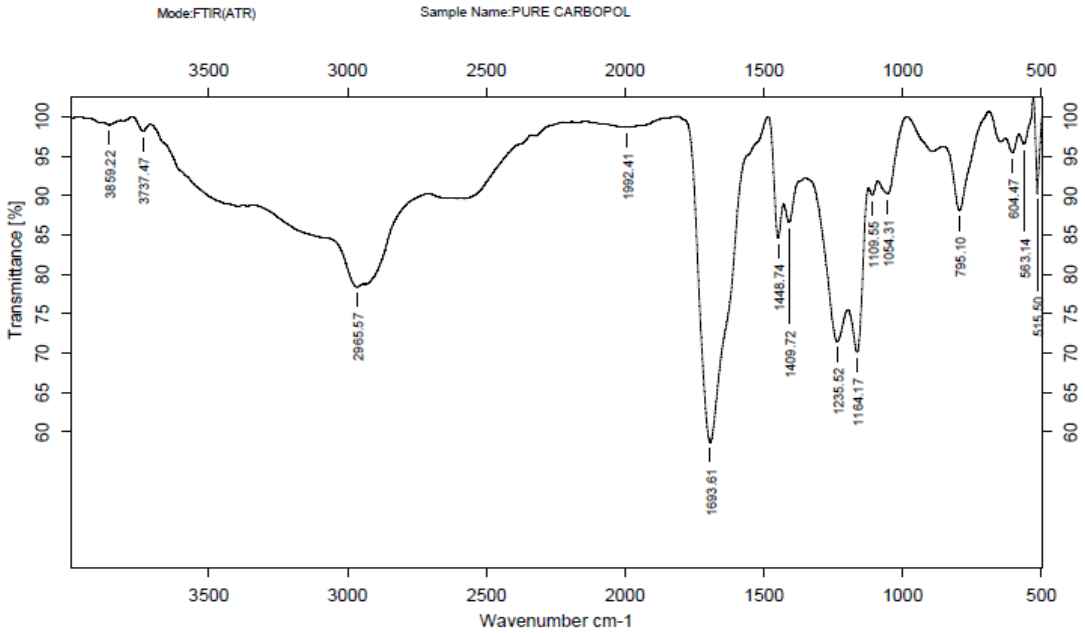
FT-IR Spectrum of prepared formulation



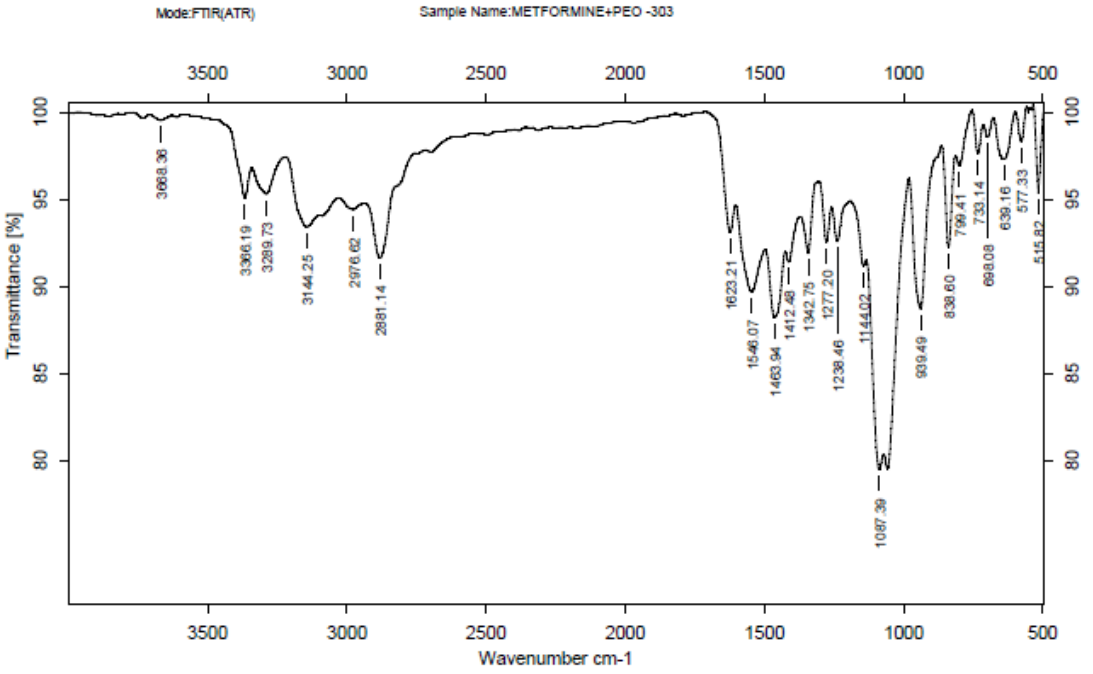
FT-IR Spectrum of pure Metformin HCl



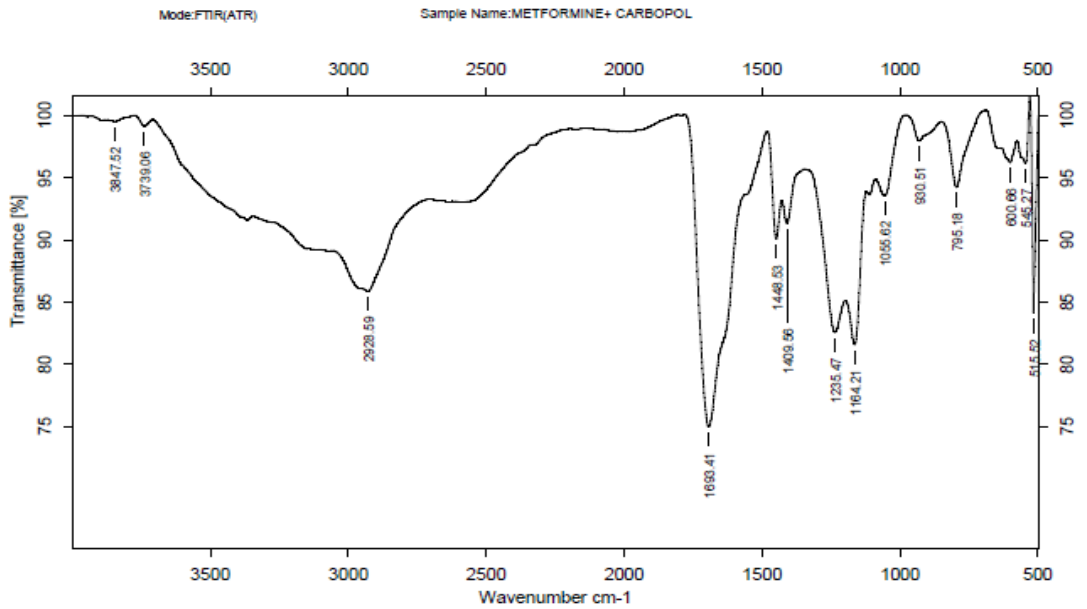
FT-IR Spectrum of pure PEO-303



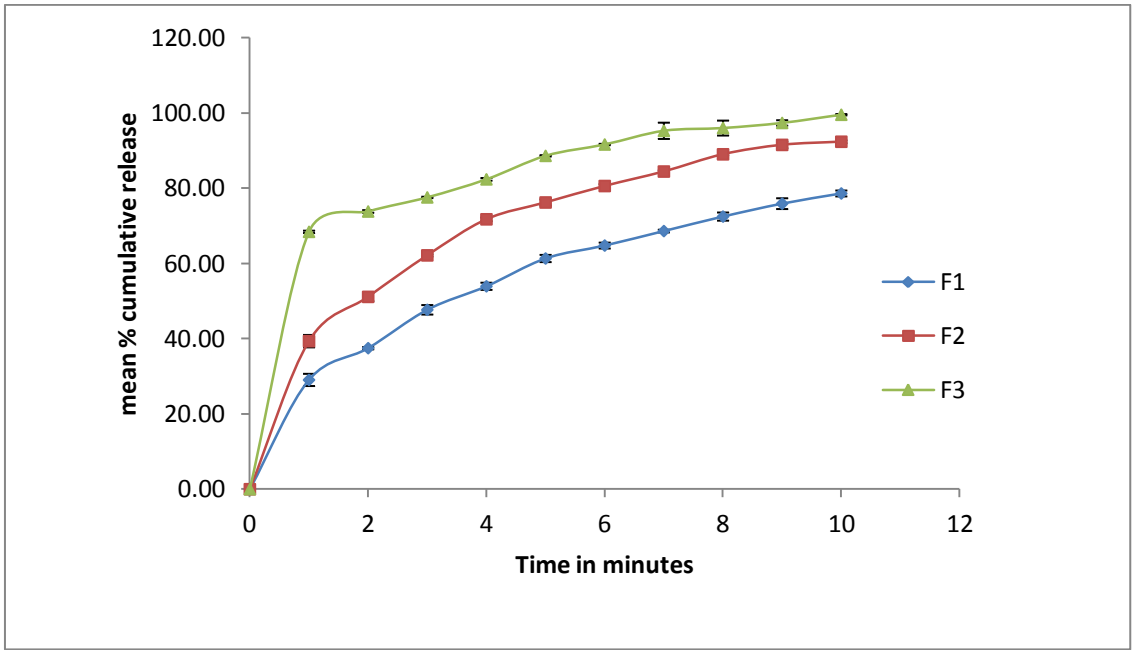
FT-IR Spectrum of pure CARBOPOL 971P



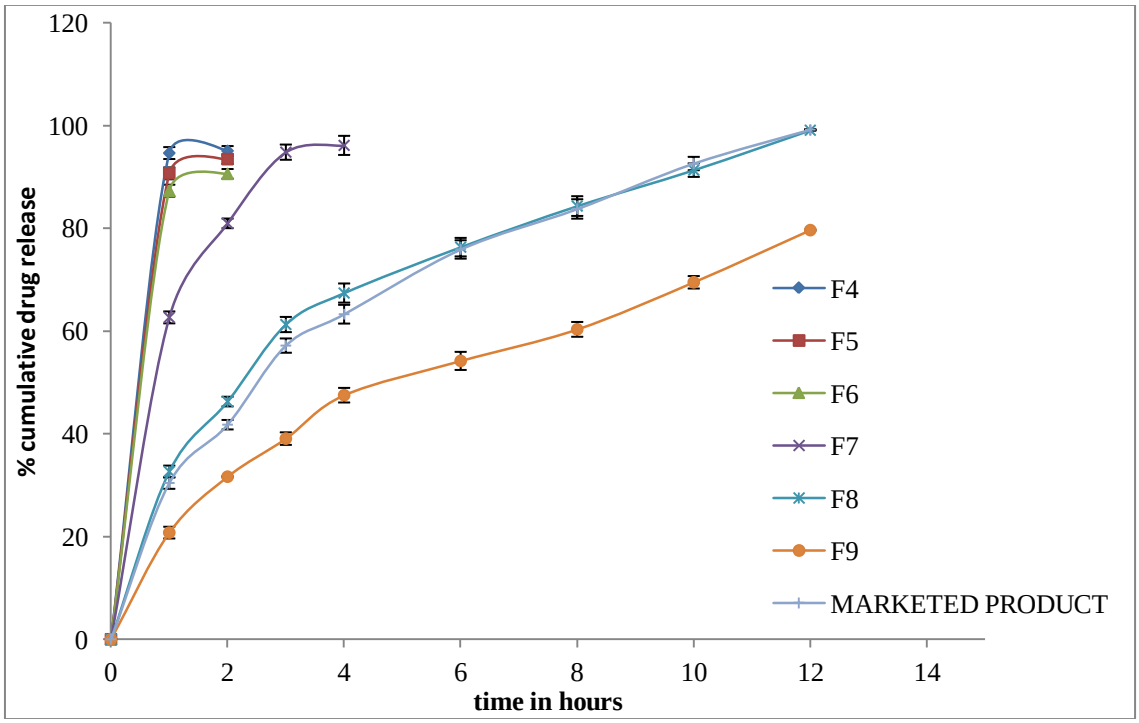
7 FT-IR Spectrum of formulation prepared with PEO-303



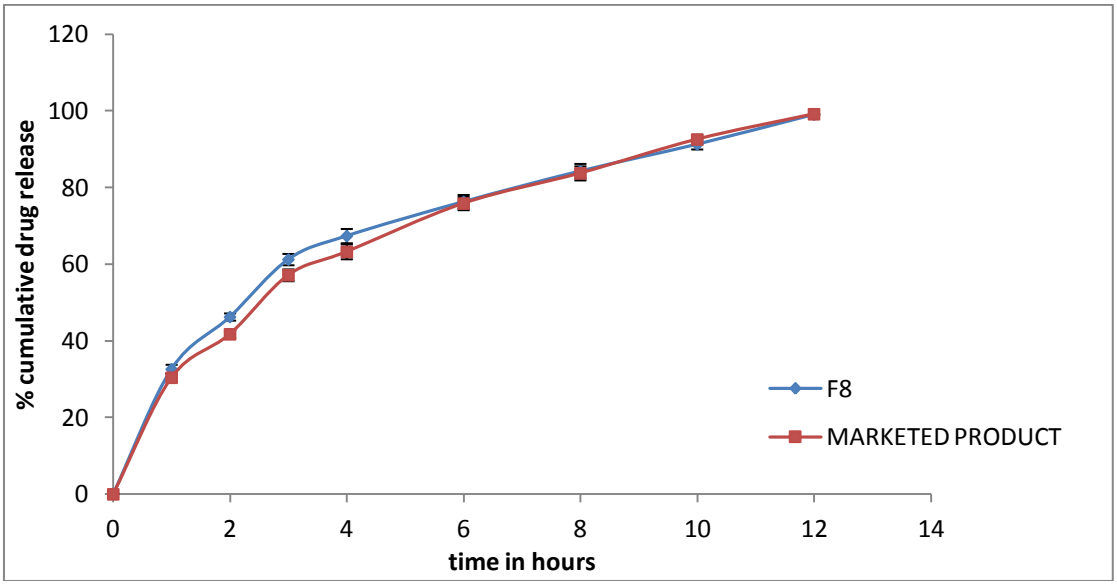
FT-IR Spectrum of formulation prepared with CARBOPOL 971P



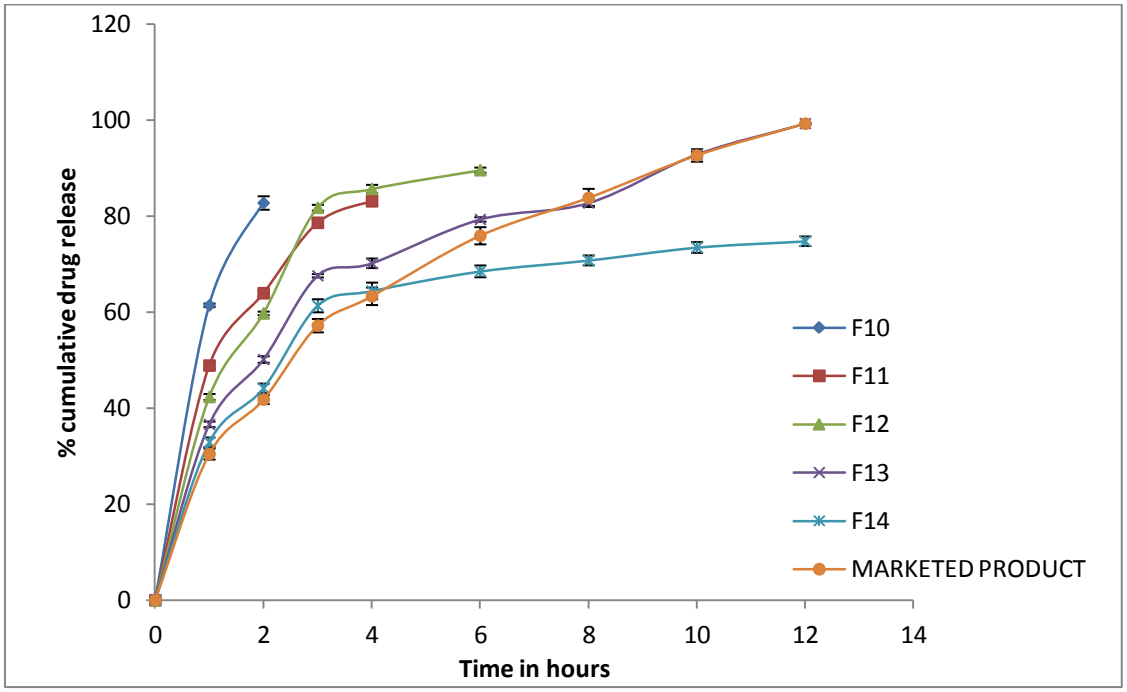
Cumulative Percent Drug Release profiles for IR layer formulations



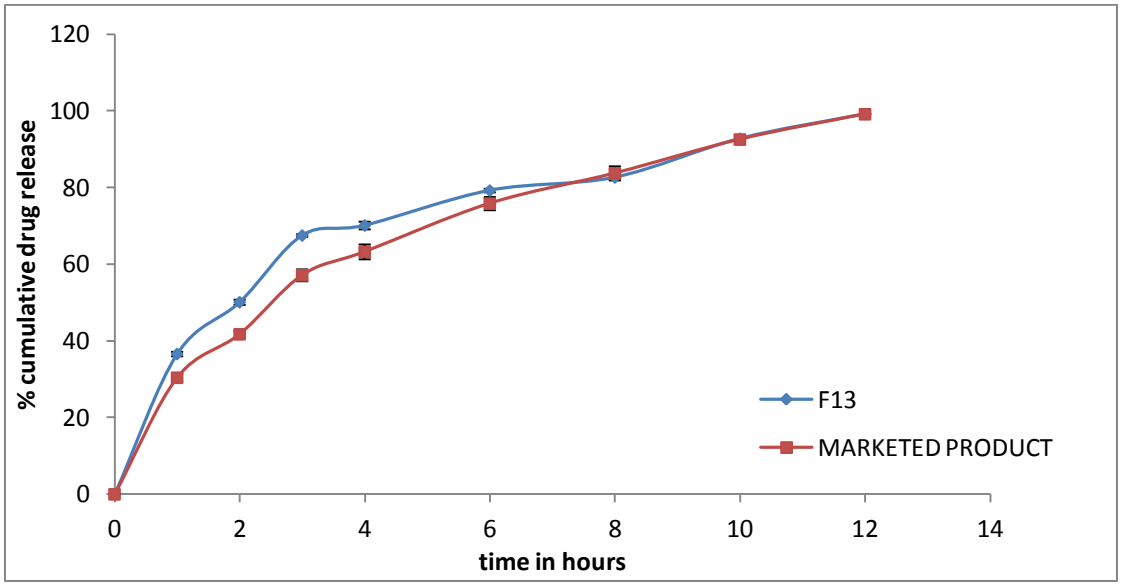
Cumulative Percent Drug Release profiles for Bilayered Tablets Formulated by Direct Compression technique



3 Comparision of Percent Drug Release profiles for F8 and Marketed formulation



Cumulative Percent Drug Release profiles for Bilayered Tablets Formulated by Wet Granulation technique



Comparision of Percent Drug Release profiles for F13 and Marketed formulation

III. CONCLUSION

Pioglitazone HCl and Metformin HCL and the excepients selected for this investigation were compatible and it was confirmed by FT-IR studies. postcompressional and Postcompressional parameters were found to be within the satisfactory limits and hence suitable to formulate Bilayered tablets. The order of cumulative % drug release from IR layer formulations was found to be F3>F2>F1. The IR layer formulation ie; F3 was optimized because it released the maximum amount of the drug.The results of *in-vitro* drug release profile of Bilayered tablets depicts that increase in polymer concentration, increases the retardation of drug release from the SR layer of a Bilayered tablet.The desired drug release rate obtained for F8 and F13 was found to be near to that of the theoretical desired drug release rate.The desired drug release rate obtained for F8 and F13 was found to be near to that of the drug release rate of Marketed formulation.The formulations F8 and F13 were suitable to sustain the drug release for a period of 12hrs, followed first order kinetics exhibited Higuchi's model and Krosmeyer-Peppas exponential coefficient 'n' < 0.5 indicates that the release was governed by Fickian diffusion.Hence can conclude that formulated Bilayered tablets of Pioglitazone HCl and Metformin HCl were developed successfully with IR layer comprising of Crospovidone and SR layer comprising of PEO-303 and CARBOPOL 971P as polymers by Direct Compression technique and Wet Granulation technique. From the above results it can be concluded that by using PEO-303 and CARBOPOL 971P we can successfully formulate Bilayer tablets of Pioglitazone HCl and Metformin HCl which showed sustained drug release up to 12hours.

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