FORMULATION AND EVALUATION OF ANTIDIABETIC BILAYER TABLET OF GLIMEPIRIDE AND PIOGLITAZONE HCL

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Abstract: *The aim of present study was to develop and submit antidiabetic bilayer tablet of sustain release Glimepiride and Immediate release Pioglitazone HCl. The drug procurement was completed from the gift sample from various companies. Sustained release of Glimepiride developed by using polymer like HPMC K4M and HPMC K100M. Super disintegrants such as Crospovidone and Kyron T-314 are used to prepare the immediate release layer. The drug excipient compatibility study was done with help of FTIR and there was no chemical interaction found in the study. The powder blend was evaluated for the various aspects such as the angle of repose, bulk density, tapped density, Hausner's ratio, Carr's index. The results were satisfied and showed the good result hence the conclusion that we can go for the tablet manufacturing. The tablets were manufactured with help of the direct compression method. The prepared tablets were evaluated for different tests and found in limit of uniformity of weight, hardness, thickness, diameter, and friability. Tablets from each batch studied for the drug content and was found within range of 96-99%, disintegration test was performed, the time was found 62-85sec. The In vitro dissolution was performed by using USP Type II apparatus. The release data further indicated that HPMC K100M can give the sustained release with maximum drug release up to 12 hrs. Which shows minimize the burden of dosing. Immediate Release layer IR6 containing Kyron T314 shows maximum drug release about 98.10 % up to 40 min. than other formulations. HPMC K100M polymer controlled the release of Glimepiride up to 12 hr. intended for once daily administration. The release data of In vitro study indicates that formulation follows zero order, Higuchi equation and diffusion takes place via non-fickian transport. The optimized tablets were studied for the stability study for period of 3 months. Formulation F3 found to be stable at accelerated stability as per the ICH guidelines for a period of 3 months.*

Keywords: *Type 2 diabetes, Bilayer Tablet, Glimepiride, Pioglitazone HCl, HPMC K100 M, HPMC K4M, Kyron T 314, Crospovidone.*

INTRODUCTION

Oral route is one of the most popular routes of drug delivery due to its ease of dministration, patient compliance, least sterility constraints and flexible design of dosage form. The oral route of administration is the most preferred route due to its many advantages like ease of administration, accurate dosage, self-medication, pain avoidance, versatility and patient compliance. Tablets and capsules are

the most popular dosage forms. Ideally a drug to provide desired therapeutic action should arrive rapidly at the site of action in optimum concentration, remain there for the desire time, be excluded from other site[1,2]. The fact that absorption rate of drug into the body can be decreased by reduction of the rate of release of the drug from the dosage form is one of the most recent and interesting result of pharmaceutical research, but one important condition including stroke, Parkinson's disease, neurological disorders, AIDS etc. Dual release Tablets is a unit compressed Tablets dosage for intended for oral Application. It contains two layers in which one layer having conventional or immediate release part of single or multiple actives; another layer is sustained or controlled release part of single or multiple actives. They are also called as Bilayer Tablets, multi-layer Matrix Tablets. A bilayer Tablets is a type of multiple compressed Tablets. Tablets are composed of two layers of granulation compressed together. Monograms and other distinctive marking may be compressed in the surface of the bilayer Tablets. Coloring the separate layer provide many possibilities for unique Tablets identity. There are some applications like Bilayer Tablets are mainly used in the combination therapy. Bilayer Tablets are used to deliver the loading dose and sustained dose of the same or different drugs. Bilayer Tablets are used to deliver the two different drugs having different release. They are used as an extension of a conventional technology Potential use of single entity feed granules. Patient compliance is enhanced leading to improved drug regimen efficacy. Patient convenience is improved because fewer daily doses are required compared to traditional drug delivery system. Maintain physical and chemical stability. Retain potency and ensure dose accuracy [3-4].

Pioglitazone HCl is Thiazolidinedione (TZD) class of drug with hypoglycemic, antihyperglycemic and antidiabetic action. Chemically Pioglitazone is (RS)-5-(4-[2-(5-ethylpyridin-2-yl) ethoxy] benzyl) thiazolidine-2, 4-dione. Pioglitazone is used for the treatment of diabetes mellitus type 2 (previously known as non-insulin-dependent diabetes mellitus, NIDDM) in monotherapy and in combination with a sulfonylurea, Metformin. Pioglitazone has also been used to treat non-alcoholic fatty liver. Pioglitazone has also been found to reduce the risk of conversion from prediabetes to diabetes mellitus type 2 by 72%. It has short biological half-life of 3-5 hrs. [5,6]. Glimepiride acts at ATPase-dependent potassium channels in β cells of the pancreas to stimulate insulin release. using glycemic and hyperglycemic clamp studies it has been shown to improve both first- and second-phase insulin secretion.15 Glimepiride binds to 65-kD proteins on β cells. In healthy volunteers, a linear relationship was shown between serum Glimepiride concentrations and insulin release during Euglycaemia and a nearly linear relationship under Hyperglycemic conditions [7,8].

MATERIAL AND METHOD

The API's and excipients were obtained as gift sample from various companies. The Pioglitazone obtained from Brundavan Chemicals, Hydrabad. Glimepiride obtain from the Surya chemicals, Mumbai. The Signet Excipients Pvt. Ltd. Mumbai provided various excipients of pharmacopeial grades such as Lactose, Magnesium Sterate, Talc. Nb Entrepreneurs, Nagapur Provide Avicel Ph 101 Ip. Superdisintegrant Such As Kyron T-314 Supplied By Corel Pharma Chem, Ahmedabad. Crospovidone Given By Prachin Chemical, Ahmedabad.

All ingredients were collected and weighed accurately. Sifted API's and polymers through sieve no. 60# and then mixed with remaining excipients. Sifted talc and magnesium stearate separately, through sieve no. 60#. Pre-blending of all ingredients (except lubricant magnesium stearate) in blended for 15 minutes. Blend then again blended for 5-6 min then added magnesium stearate blended 5 min. Lubricated powder was compressed by rotary machine. Compressed tablets were examined as per official standards and unofficial tests. Prior to the compression the drug and polymers were evaluated for several tests.

EXPERIMENTAL WORK

Determination of Absorption Maxima of drugs

Confirmation of Pioglitazone HCl through UV spectral analysis:

The stock solution of, prepared by about 10 mg of Pioglitazone HCl was accurately weighed and dissolved in 100 ml of methanol to obtain a concentration 100 µg/ml. From stock solution different aliquots were taken in series of 0.2, 0.4, 0.6, 0.8, 10 ml in 10 ml volumetric flask and diluted with methanol to obtain a series of concentration. The solutions were scanned in spectrophotometer in UV range 200 - 400 nm. The absorption maxima of Pioglitazone were found to be 268 nm. The standard curve was plotted and values of slope, intercept and coefficient of correlation were calculated. The standard curve was plotted and values of slope, intercept and coefficient of correlation were calculated.[9]

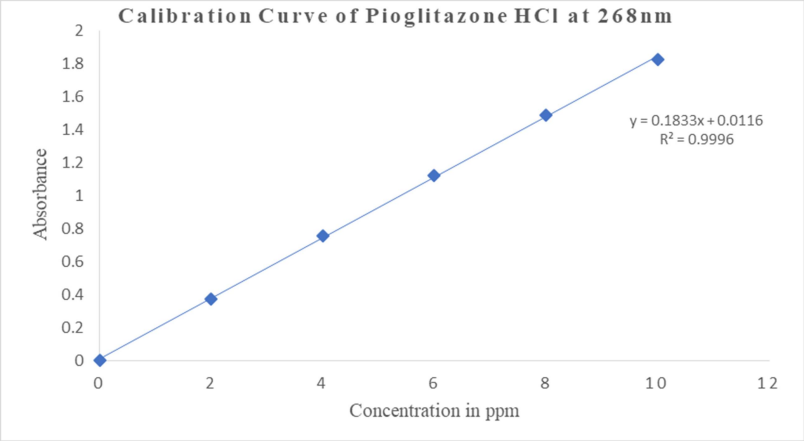

Fig 1: Calibration curve of Pioglitazone HCl in methanol.

Estimation of Glimepiride

Preparation of calibration curve of Glimepiride in Methanol: -

The stock solution of, prepared by about 10 mg of Glimepiride was accurately weighed and dissolved in 100 ml of methanol to obtain a concentration 100 µg/ml. From stock solution different aliquots were taken in series of 0.2, 0.4, 0.6, 0.8, 10 ml in 10 ml volumetric flask and diluted with methanol to obtain a series of concentration. The solutions were scanned in spectrophotometer in UV range 200 - 400 nm. The absorption maxima of Glimepiride were found to be 228 nm. The standard curve was plotted and values of slope, intercept and coefficient of correlation were calculated.[10]

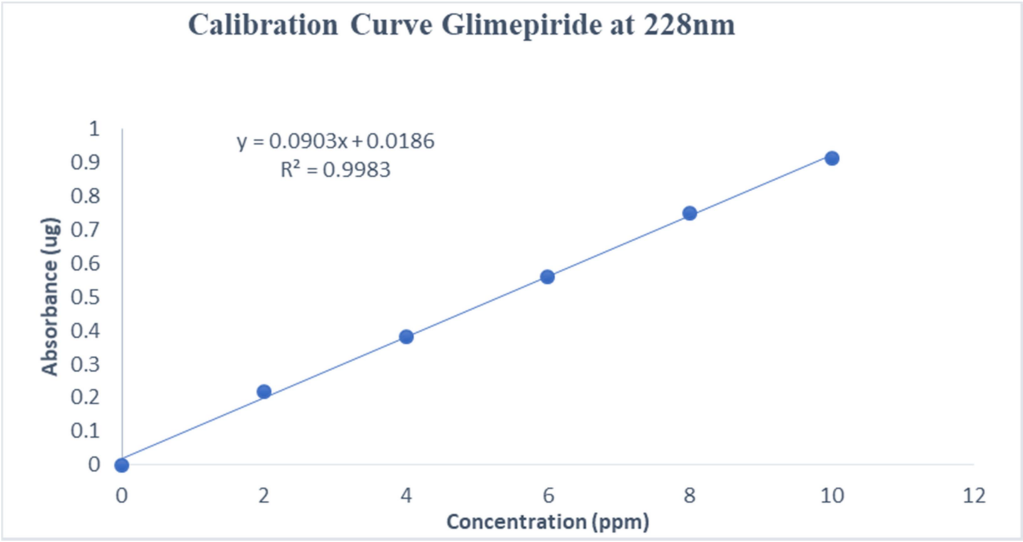

Fig 2: Calibration curve of Glimepiride in Methanol

Ftir Spectroscopy

The active pharmaceutical ingredient was identified by FTIR analysis of the sample obtained from sources. The sampling technique was mixing the API with the KBr and forming of the pellet which was then analyzed in 400-4000 wave number range by the FTIR Spectrophotometer.

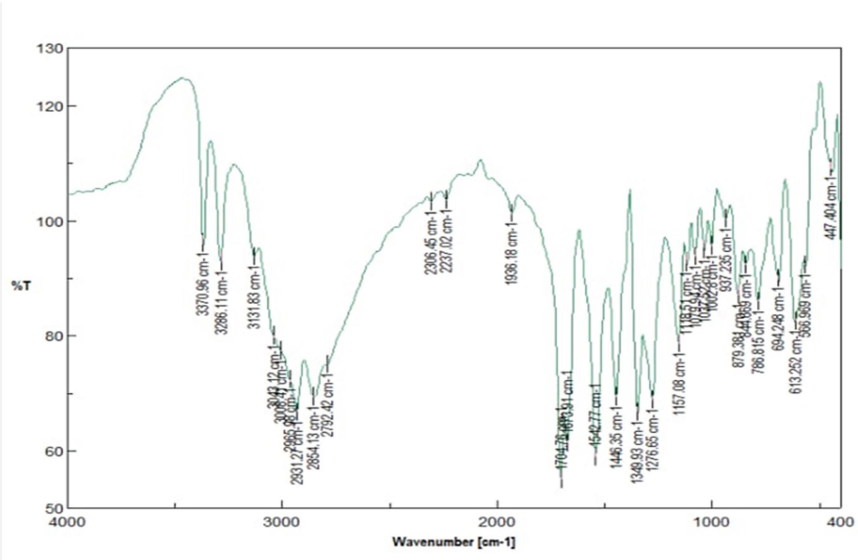

Fig 3: FT-IR of pure Glimepiride

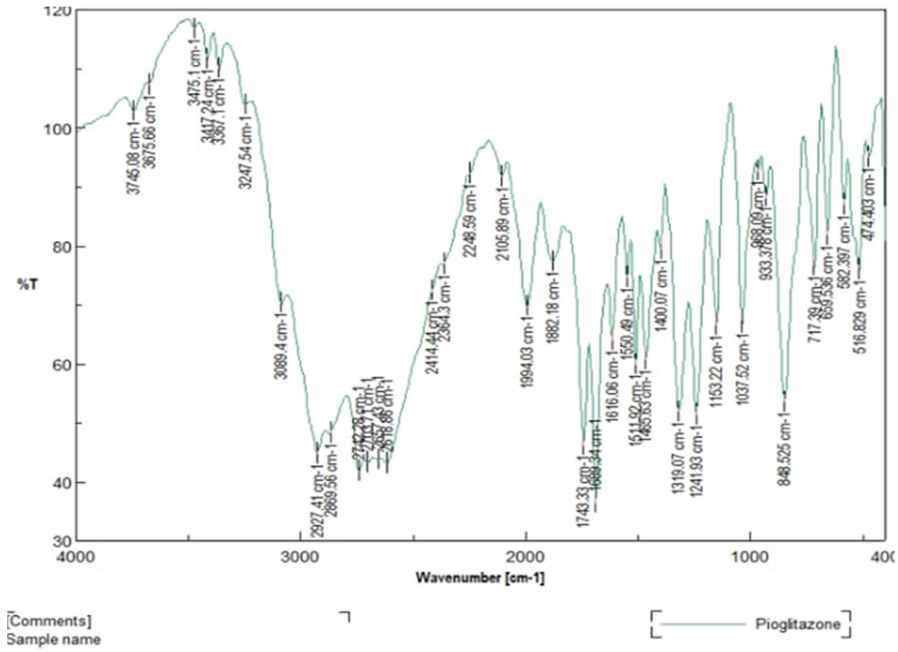

Fig 4: FT-IR of pure Pioglitazone HCl

Drug excipient Compatibility study

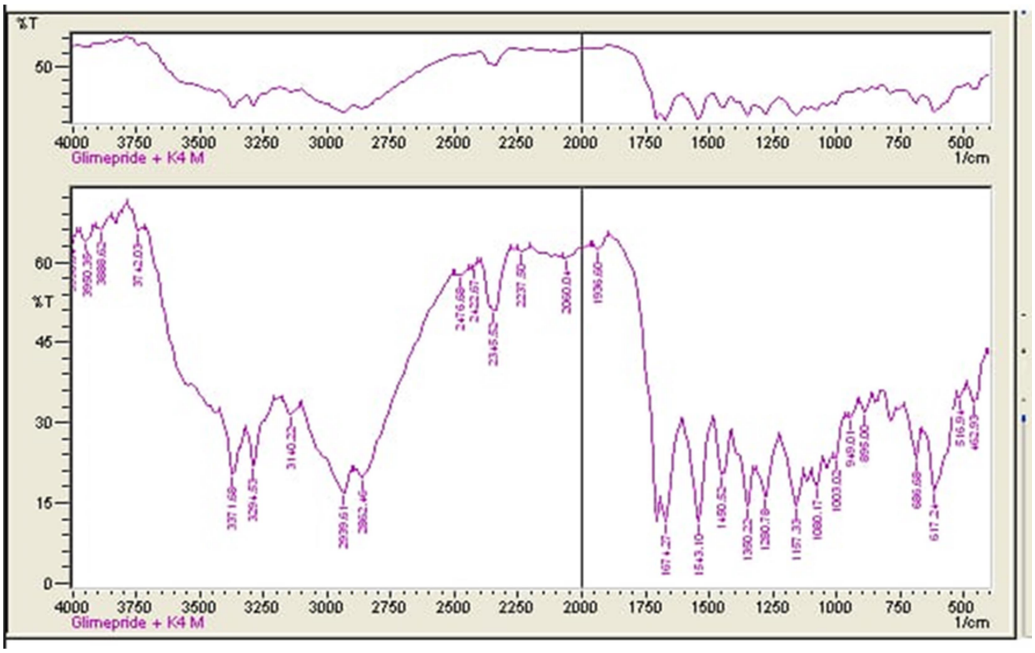

Fig 5: FTIR of Physical Mixture of Glimepiride + HPMC K4M

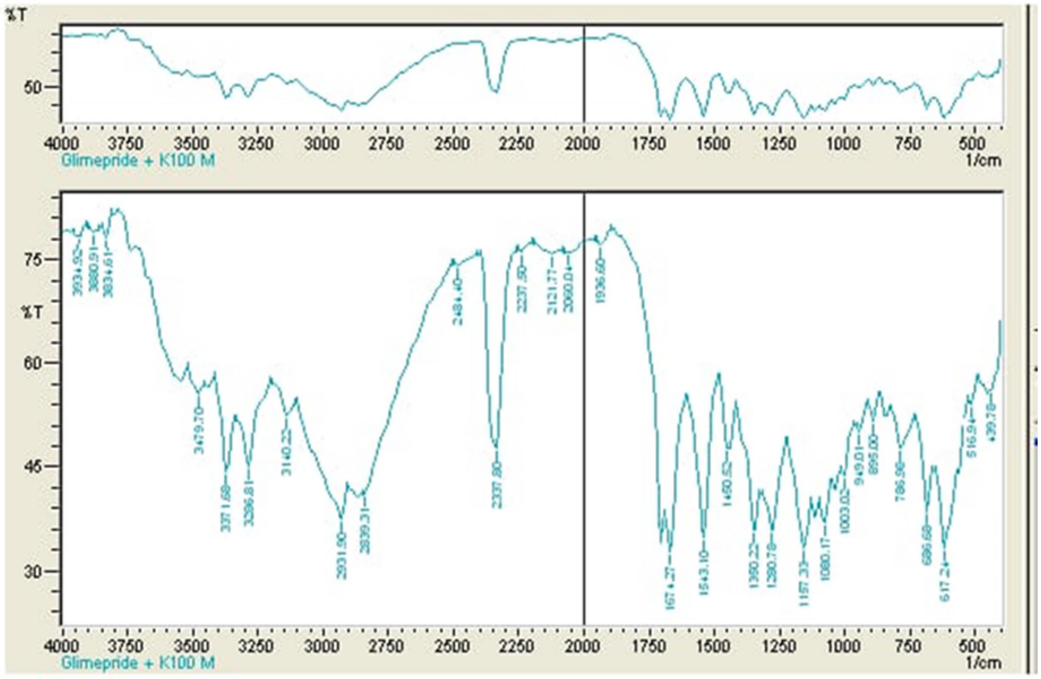

Fig 6: FT-IR of Physical Mixture of Glimepiride + HPMC K100M

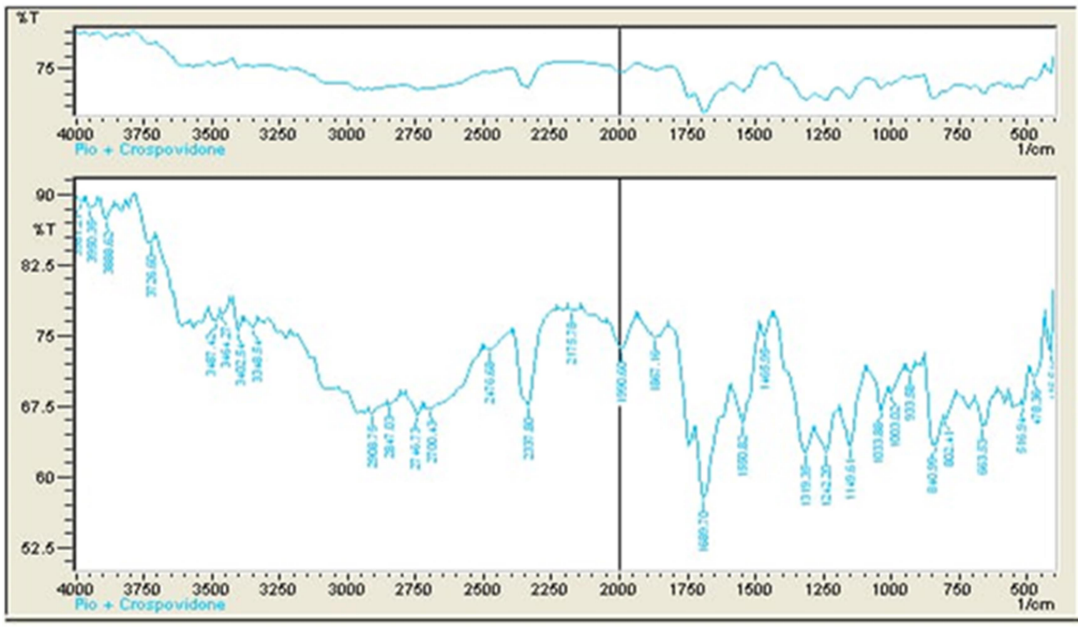

Fig 7: FT-IR of Physical Mixture of Pioglitazone HCl + Crospovidone

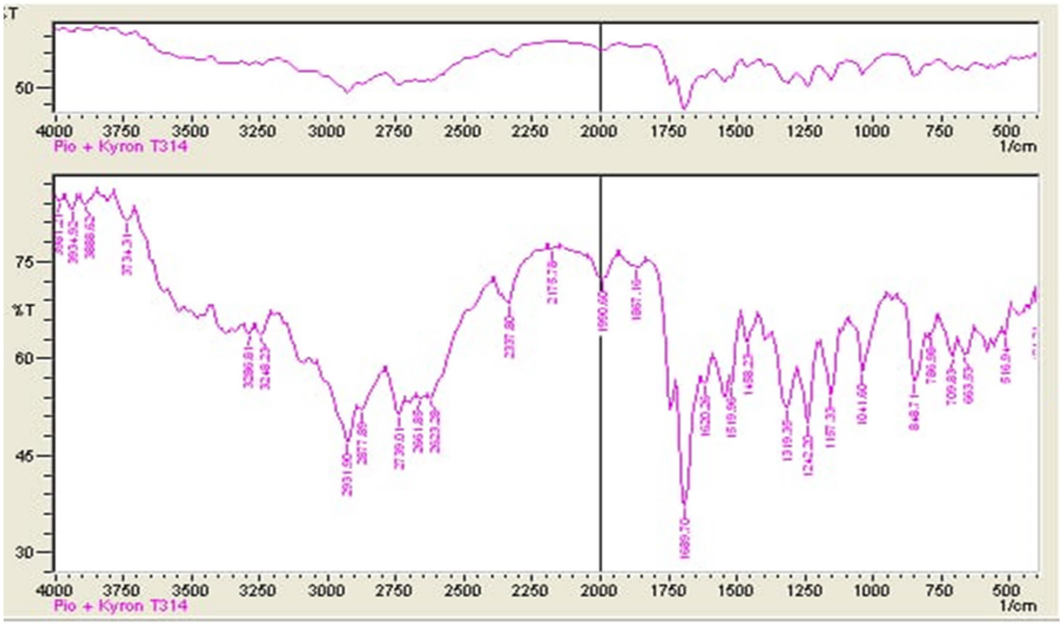

Fig 8: FT-IR of Physical Mixture of Pioglitazone HCl + Kyron T314

Preparation of tablet

Immediate Release Layer

The immediate layer was prepared by mixing the ingredients in the proper proportion. The following steps were followed during the preparation of the direct compression layer. Sifting of API (Pioglitazone HCI) and Excipients is the first step in the formulation. All ingredients were weighed accurately and sieved. Dry mix: Pioglitazone, microcrystalline cellulose, KYRON T-314 and lactose were mixed together. The mixing was done till the through mixing was confirmed. The lubricant (Mag Stearate) was

shifted and transferred to the mixture to aid the flow property. Compression: the mixture was compressed into the tablet using the low force compression

Preparation of Sustained Layer

All the ingredients including active drug (Glimepiride) were weighed properly, sieved and mixed thoroughly. Individually every tablet was prepared by direct compression method with a pressure of 5 ton by hand compression machine**.**

Table 1: bilayer tablet formulation table

Formulation	F1	F2	F3	F4	F5	F6
Sustained release layer (mg)	**SR1**	**SR2**	**SR3**	**SR4**	**SR5**	SR6
Glimepiride	8	8	8	8	8	8
HPMC K4M	38	45	52	-	-	-
HPMC K100M	-	-	-	38	45	52
MCC (Avicel 101)	100	93	86	100	93	86
Magnesium stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Total	**150**	**150**	**150**	**150**	**150**	150
Immediate release layer (mg)	**IR1**	**IR2**	**IR3**	**IR4**	**IR5**	IR6
Pioglitazone	30	30	30	30	30	30
Crospovidone	4	6	8	-	-	-
Kyron T-314	-	-	-	1	2	3
Avicel 101	62	60	58	65	64	65
Magnesium stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Total	**100**	**100**	**100**	**100**	**100**	100
Overall Total	250	250	250	250	250	250

Evaluation [11,12,13]

The prepared bilayer tablets from each optimized formulation batches were tested against the official standard evaluation parameters to ensure the proper manufacturing and release rate of the dosages of the drug. Following evaluation parameters were performed:

Size, shape and thickness

The size and shape of the tablets can be dimensionally described, monitored and controlled. The thickness of the tablets is the only dimensional variable related to the process of tableting. At a constant compressive load, tablet thickness varies with the change in the die fill, with particle size distribution and packing of the particle mix being compressed, and with the tablets weight, while with the constant die fill, thickness varies with the variations in compressive load. The tablet thickness should be maintained well within a ± 5% variation of the standard value.

Weight variation

Weigh individually 20 tablets selected at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the table and none deviates by more than twice that percentage

Friability

This test is applicable to compressed tablets and is intended to determine the physical strength of tablets and is measured by Roche Friabilator. For tablets with an average weight of 0.65 g or less take a sample of whole tablets corresponding to about 6.5 g and for tablets with an average weight of more than 0.65 g

take a sample of 10 whole tablets. The tablets were de-dust carefully and weighed accurately. The tablets were place in the drum and the drum was rotated 100 times. The tablets were removed after 100 revolutions, any loose dust was removed from them and weighed accurately again. The test is run only once unless the results are difficult to interpret or if the weight loss is greater than the targeted value, in which case, the test is repeated twice and the mean of the three tests is determined. A maximum loss of weight (from a single test or from the mean of the three tests) not greater than 1.0 % is acceptable for most tablets. If obviously cracked, chipped or broken tablets are present in the sample after tumbling, the sample fails the test15.

Hardness

Hardness is the measure of the strength of the tablet to withstand the mechanical shock of manufacturing, packaging and transportation. Hardness is sometimes also referred to as tablet crushing strength. The hardness of the tablets is estimated by Pfizer hardness tester or Erweka tester.

Drug content

10 tablets are taken randomly and weighed. The average weight is calculated and the tablets are then crushed in the mortar. The weight equivalent to the label claim is weighted accurately and is dissolved in 100 ml of the solvent being used for the dissolution study. The solution thus prepared is analyzed spectro-photometrically and the concentration is determined.

In vitro drug release

In vitro dissolution studies of bilayer tablets were studied using USP dissolution test apparatus-II employing a paddle stirrer. 900 ml of 0.1N HCl (pH 1.2) was used as a dissolution medium for first two hours and then was replaced with Phosphate Buffer solution (pH 6.8) for specified time of 10hrs. The temperature of the dissolution medium is maintained to 37 ± 0.5ºC. One tablet from each batch was used in each test. 5 ml of the sample of dissolution medium was withdrawn by means of pipette at known intervals of time and the sample was filtered using the Whatman filter paper. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The sample is analyzed, for drug release and release kinetics, spectrophotometrically using UV-visible spectrophotometer (Shimadzu-1800) after suitable dilutions. The for immediate release layer its analyses for 228nm λ_{max} range and for sustain its aliases for 268nm λ_{max}. [14]

Stability testing of formulated bilayer tablet of optimized batch

The formulated bilayer tablets were kept at different storage conditions. The test samples were kept at was kept at 25°C±2°C, 60% RH and at 40°C±2°C, 75% RH according to ICH guidelines. The Hardness, friability, drug content of the tablets was determined initially and then at the interval of 15 days and one month. The hardness, friability and drug content of the optimized formulation after 30 days were reported in table

RESULT AND DISCUSSION

Compatibility study

Spectra of the pure drug, excipient and physical mixture of drug and excipient were recorded in between 400-4000 wavenumber (cm^{-1}). The FTIR spectral analysis showed that there is no appearance or disappearance of any characteristic peaks of pure drug Glimepiride and Pioglitazone HCl and in the physical mixture which confirms the absence of chemical interaction between drug and polymers.

Evaluation of the powder bled

The angle of repose was found to be ranging from 21°30'+0.04 to 26° 16'40.02 for the granules of all the formulations. Compressibility index was found to be ranging from 11.92 0.07 to 14.77±0.04 % for the granules of all the formulations. The results of Hausner's ratio were found to be lesser than 1.25 which

indicates better flow properties. The results of angle of repose (<30) indicates good flow properties of the powder. This was further supported by lower compressibility index values. Generally, compressibility values up to 15% results in good to excellent flow properties.

Table 2: Evaluation of prepared tablet blends for pre compression study of Immediate release

Formulations	Angle of Repose(θ˚)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hauser's Ratio (HR)	Carr's Compressibility Index (%)
F1	29.03±0.14	0.285±0.06	0.324±0.04	1.13±023	12±0.14
F2	27.74±0.35	0.292±0.02	0.33±0.04	1.14±0.31	12.31±0.25
F3	27.11±0.17	0.30±0.06	0.375±0.05	1.17±0.45	14.77±0.17
F4	28.36±0.28	0.290 ±0.06	0.315±0.01	1.07±0.41	7.3±0.85
F5	27.74±0.84	0.307±0.9	0.333±0.09	1.08±0.32	7.8±0.35
F6	28.81±0.24	0.307±0.01	0.342±0.09	1.11±0.12	10.23±0.36

Layer

Formulations	Angle of Repose(θ˚)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hauser's Ratio (HR)	Carr's Compressibility Index (%)
F1	27.69±0.35	0.457±0.05	0.5±0.02	1.09±0.5	8±0.19
F2	27.74±0.54	0.465±0.01	0.509±0.04	1.096±0.87	8.64±0.84
F3	28.19±0.45	0.473±0.05	0.529±0.06	1.12±0.54	10.59±0.33
F4	27.744±0.65	0.465±0.02	0.509±0.04	1.09±0.51	8.64±0.14
F5	27.203±0.78	0.473±0.09	0.519±0.08	1.09±032	8.88±0.48
F6	27.699±0.25	0.482±0.08	0.540±0.04	1.12±0.47	10.74±0.37

Table 3: Evaluation of prepared tablet blends for pre compression study of sustaine release Layer

Post Compression Study Of Bilayer Tablet

Table 4: Evaluation of prepared tablet blends for post compression study of Bilayer tablet

Formulations	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Dug content (%)		Disintegration time(sec)
					IR	**SR**	
F1	249.3±1.25	3.6±0.14	3.1±	0.47±0.02	98.40±1.3	97.53±0.30	84±5
F2	251±0.94	3.4±0.21	3.6±0.14	0.439±0.03	96.36±0.27	97.6±1.8	75±1
F3	248.9±0.59	3.4±0.36	3.5±0.24	0.396±0.01	97.86±1.39	97.73±0.30	71±3
F4	249.7±0.95	3.3±0.29	3.4±0.16	0.83±0.09	97.54±0.61	97.70±0.63	72±4
F5	251.2±0.74	3.4±0.18	3.7±0.36	0.51±0.08	96.79±0.14	97.5±1.3	69±4
F6	250.8±0.65	3.5±0.41	3.5±0.25	0.516±0.04	98.51±0.09	99.26±0.19	62±2

Dissolution Study

Table 5: In Vitro Drug Release Profile of Formulations of Sustained Released Tablet

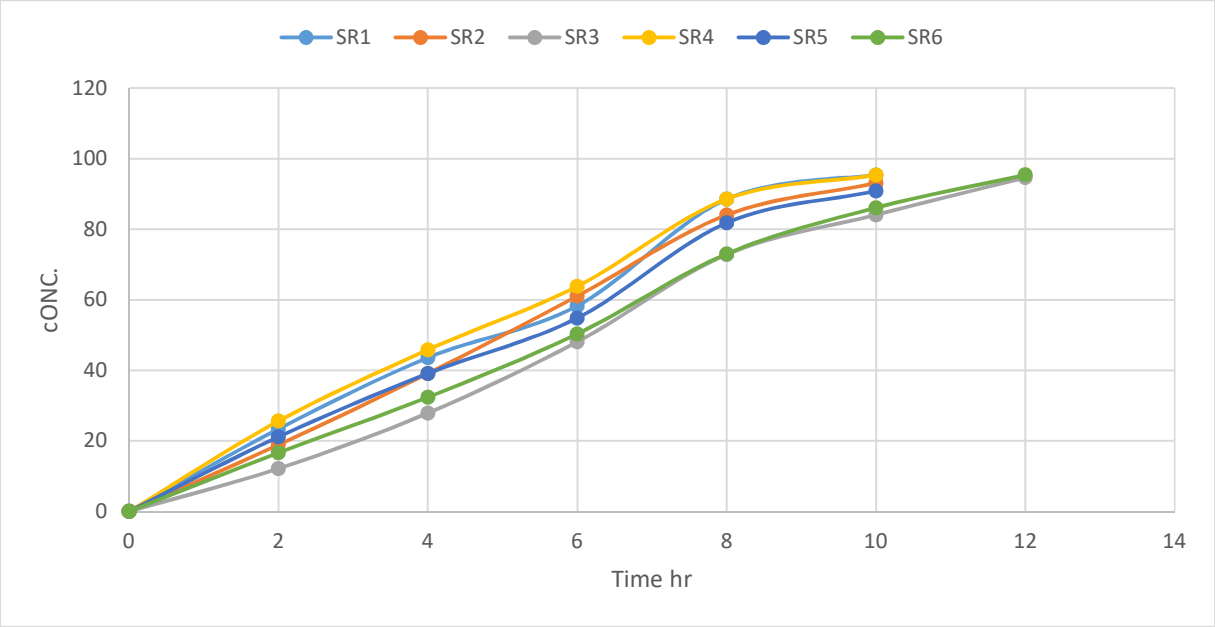

Fig 9: cumulative drug release in sustained release Glimepiride

The effect of polymer concentration on drug release could be clearly seen from the variation of dissolution profiles. It was found that drug release from SR3 composed of HPMC K4M in high concentration was 12 hrs. And also shows significantly higher drug release rate than other formulations. Formulation SR6 containing 52 mg of HPMC K100M of Cumulative drug release which comparatively greater than other formulation batches so SR6 was selected for further formulation of bilayer tablet of Glimepiride

In Vitro Drug Release Study for Immediate release Tablet of Pioglitazone HCl

Table 6: Immediate release layer dissolution profile

Time in hour	% Cumulative drug release					
	IR1	**IR2**	**IR3**	**IR4**	**IR5**	**IR6**
0	0.000	0.000	0.000	0.000	0.000	0.000
5	10.378±0.14	12.178±0.75	14.141±0.37	12.669±0.62	15.941±0.49	20.195±0.75
10	15.952±0.25	21.353±0.49	24.628±0.62	23.399±0.51	31.420±0.43	34.778±0.86
15	33.394±0.25	37.656±0.51	41.589±0.62	35.696±0.38	39.717±0.86	42.343±0.86
20	40.303±0.25	44.733±0.65	49.815±0.62	46.370±0.62	53.913±0.38	59.896±0.38
25	54.827±0.25	58.608±0.75	63.205±0.49	57.874±0.99	62.071±0.51	70.352±0.25
30	68.059±0.14	71.762±0.79	75.218±0.28	71.436±0.62	74.411±0.86	80.574±0.29
35	85.231±0.25	89.102±0.43	86.836±0.86	81.250±43	85.046±0.71	88.516±0.14
40	89.416±0.25	92.146±0.43	96.013±71	91.484±0.62	94.139±0.99	99.249±0.62

Time in hour	% Cumulative drug release					
	SR1	**SR2**	**SR3**	**SR4**	**SR5**	**SR6**
0	0.000	0.000	0.000	0.000	0.000	0.000
2	23.36±0.35	21.50±0.65	12.90±0.65	23.36±2.24	18.88±0.58	16.64±2.24
4	43.57±0.47	39.45±0.65	29.36±0.65	43.67±2.25	39.16±0.54	32.42±2.24
6	63.79±0.65	55.26±0.78	50.24±1.8	64.09±2.27	66.28±0.58	50.54±2.27
8	88.52±0.56	82.15±1.14	74.28±0.59	89.85±2.24	84.58±0.55	73.23±2.26
10	97.58±0.97	94.57±0.78	84.45±0.65	96.32±0.98	94.01±0.64	87.09±0.47
12	---	--	97.99±1.71	-------	-----	96.53±2.68

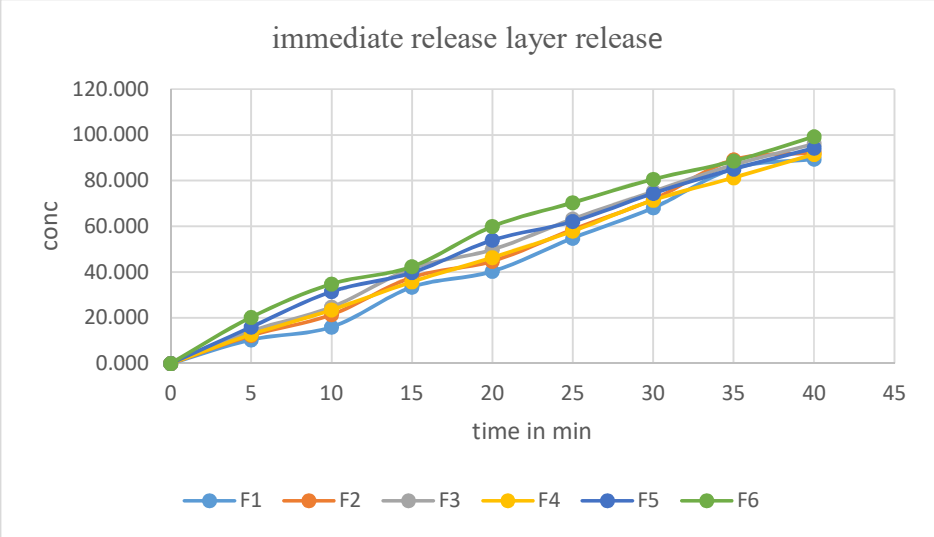

Fig 10: cumulative drug release immediate Pioglitazone HCl

The effect of Super-disintegrants concentration on drug release could be clearly seen from the variation of dissolution profiles. It was found that drug release from IR6 composed of Kyon T314 in high concentration was 98.10% drug release after 40 min. and also shows significantly higher drug release rate than other formulations. Formulation IR6 containing 3 mg of Kyron T314 of Cumulative drug release which comparatively greater than other formulation batches so IR6 was selected for further formulation of bilayer tablet of Pioglitazone HCl.

Stability Studies of Bilayer Tablet

Stability study for the developed formulation F3 were carried out as per ICH guideline by storing at 40°C/75% RH for the two months. The formulation F3 was selected on the basis of their cumulative percentage drug release in the dissolution test. In the comparative study for immediate release F6 was the optimized match and F6 in sustain release containing HPMC K 100M optimized**.**

Table 10: Comparative % drug release of immediate release layer F6 Batch

Time in Minutes	% Cumulative drug release	
	IR6 Initial	IR6 after three Months
0	0.000	0.000
5	20.35±0.54	16.92±0.52
10	35.84±0.45	28.14±0.34
15	42.26±0.54	40.61±0.57
20	58.50±0.45	53.33±0.36
25	70.10±0.81	65.26±0.46
30	80.98±0.46	73.52±082
35	89.17±0.48	83.08±0.55
40	98.10±0.74	96.59±0.74

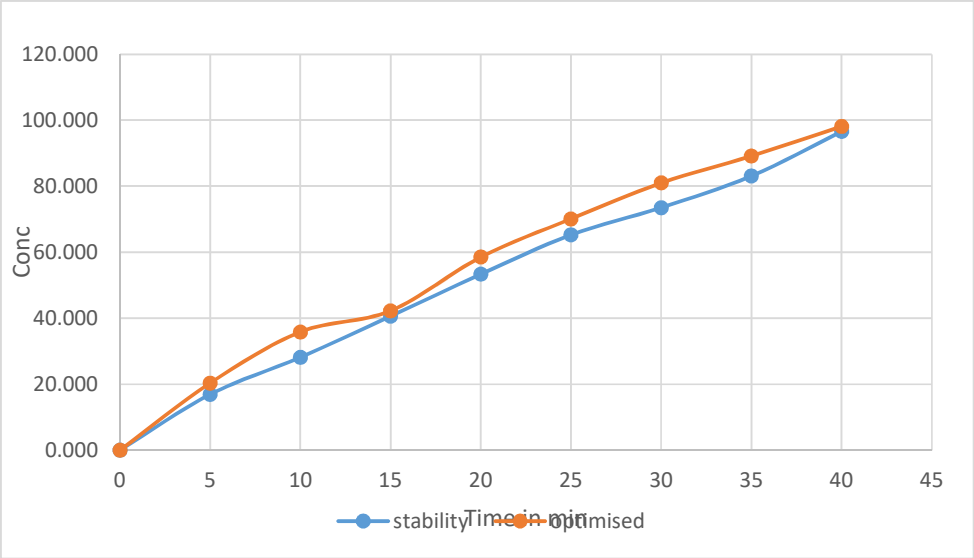

Fig 10: Comparative drug % release of SR6 batch

Table 11: % cumulative drug release of stability study of SR6

Time Hr.	% Cumulative drug release	
	SR1	**After 3 months**
0	0	0
2	12.16±0.19	10.29±0.34
4	27.86±0.16	25.84±0.22
6	48.07±0.2	44.18±0.56
8	72.78±0.16	70.83±0.34
10	84.07±0.28	82.64±0.72
12	97.61±0.37	95.81±0.45

The stability study graphical representation

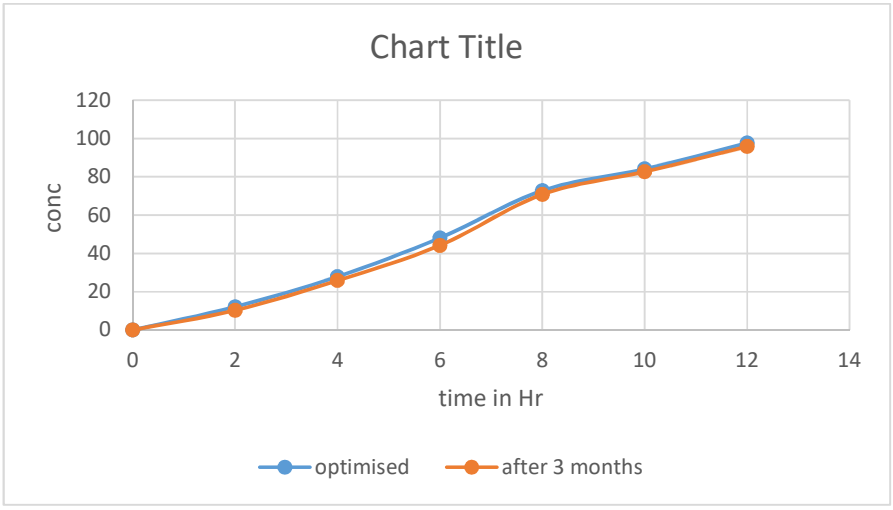

Fig 11: Comparative drug release of sustained release IR 6 batch

CONCLUSION

Sustained release of Glimepiride developed by using polymer like HPMC K4M and HPMC K100M and incorporation of superdisintegrants like Crospovidone and Kyron T314 in immediate release layer. The release data further indicated that HPMC K100M can give the sustained release with maximum drug release up to 12 hrs. Which shows minimize the burden of dosing. Immediate Release layer IR6 containing Kyron T314 shows maximum drug release about 98.10 % up to 40 min. than other formulations. HPMC K100M polymer controlled the release of Glimepiride up to 12 hrs intended for once daily administration. The release data of in vitro study indicates that formulation follows zero order, Higuchi equation and diffusion takes place via non-fickian transport. Formulation F3 found to be stable at accelerated stability as per the ICH guidelines for a period of 3 months

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