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FORMULATION AND EVALUATION OF BILAYER TABLETS OF METFORMIN HCL AND PIOGLITAZONE HCL

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ABSTRACT

The aim of present study was to design the concept of bilayered tablets containing Pioglitazone hydrochloride for immediate release using cross Povidone as super disintegrant and Metformin hydrochloride for sustained release using EUDRAGIT ESPO as matrix forming polymer. The tablets were evaluated for physicochemical properties. All the values are found to be satisfactory. In vitro release studies were carried out as per USP in pH 1.2 and phosphate buffer pH 6.8 using the USP apparatus II. The release kinetics of Metformin hydrochloride was evaluated using the regression coefficient analysis. The formulated tablets (F5) shows first order release and diffusion was the dominant mechanism of drug release. The polymer EUDRAGIT ESPO had significant effect on the release of Metformin HCl matrix tablets (F5).Thus formulated bilayer tablets proved immediate release of Pioglitazone and Metformin HCl as sustained release over a period of 12 hours. The stability studies and FT-IR studies were also indicating the absence of strong interactions between the components and suggesting drug-excipient compatibility in all the formulations examined.

KEYWORDS: Bilayered tablets, Sustained release, Metformin HCl, Pioglitazone HCl, Eudragit ESPO, Croscarmalose sodium, Sodium Starch glycollate.

INTRODUCTION

In order to achieve sustained therapeutic action oral SRDDS will release the drug at a slow rate and thus during the initial stages of medication, the plasma drug concentration generally stays below the minimum effective concentration and as a result the patient does not get any therapeutic benefit. Bilayered SR tablets are a solution to above problem. These preparations provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific period of time. The major advantage of this category is that, in addition to the convenience of reduced frequency administration, it provides levels that are devoid of the peak and valley effect.

They contain two layers formulated with the same drug or two different drugs. The first layer is a fast releasing layer consists a loading dose of the drug while the second layer is a sustaining later layer containing maintained dose of drug. Loading dose layer: provides initial burst release that takes the drug concentration above MEC. Maintenance dose layer: provides slow sustained release that maintains the drug concentration above the MEC for the remaining period.

The aim of this investigation is to Design and Develop Bilayered oral sustained matrix tablets of Pioglitazone hydrochloride and Metformin hydrochloride. The concept of Bilayered tablet technology is utilized for stabilization of two incompatible drugs, taste masking of drugs, delivering two drugs having synergistic effects or to deliver a drug for biphasic drug release profile and for the purpose of extension of patents. A Bilayered tablet comprises of two layers among which the first layer is immediate release layer for sudden onset of action and the second layer is Sustained release layer to maintain the steady state concentrations of drug in the blood.

The main objectives are

1. To formulate and evaluate the Bilayered tablets of Pioglitazone HCl and Metformin HCl.
2. To carry out the drug - excepient compatibility studies by IR spectral analysis.
3. To carry out the Precompressional parameters for the powder blend of IR layer of Bilayered tablets.
4. To carry out the Precompressional and Postcompressional parameters for Bilayered tablets.
5. To study the release kinetics and transport mechanism of drug from the formulations.

6. To study the comparative release profiles of tablets formulated with marketed formulation using the similarity factor.

MATERIALS

Metformine HCl, Pioglitazone was purchased from the yarrow chemicals, Mumbai and other excipients hydroxy propyl methyl cellulose, Eudragit RSPO, hydroxy propyl cellulose, lactose, iron oxide red, cros carmellose sodium, micro crystalline cellulose, starch 1500, magnesium sterate were purchased from alkem pvt.ltd, Mumbai.

METHDOLOGY

Formulation of the sustained release layer

The granules for the sustained release layer of Metformin hydrochloride was prepared by *wet granulation technique*. The sustained release layer is fabricated as a matrix system comprising a combination of hydrophilic (HPMC K 100M) and hydrophobic polymer (Eudragit RSPO). The average weight of the sustained release layer was set as 900mg.

Preliminary trial batches

A total of 5 preliminary trial batches were formulated with various levels of polymers and with certain modifications in the granulation process, so as to achieve the desired sustained release profile as per pharmacopoeial specifications. Table No.: elaborates the formula for various preliminary batches. Numerical values in the table represent the quantities of each ingredient per tablet in mg.

P_1, P_2 & P_3: In these batches the proportion of HPMC K 100M and Eudragit RSPO were altered as specified in the table no: 3 and the drug release from the prepared tablets were studied by dissolution process as per IP 2010. The compositions of the preliminary batches were tabulated in table no.1.

Optimization of Sustain release layer

On the basis of the preliminary trial batches, the trial with desired sustained release profile was selected. The selected batch was subjected to optimization process to detect the robustness of the formula and to study the effect of the two polymers – Eudragit RSPO and HPMC K 100M on the drug release profile. The compositions of the 9 optimization batches are tabulated in table no.2.

Formulation of the immediate release layer

The immediate release layer of Pioglitazone hydrochloride was prepared by *Wet granulation technique*, the layer is set to an average weight of 200mg. The granules of the immediate release trial batches were compressed in a punch, inorder to analyze the drug release and assay. Based on the results obtained a large scale batch was taken and this was used for the Bilayer tablet compression. The formula was shown in the table.No.3

Compression of the bilayer tablets

The optimum formulation (**F_5**) of the sustained release layer of Metformin Hydrochloride was chosen by a Face-centered Central composite design. The trial L_1 of the immediate release layer of Pioglitazone Hydrochloride met the Dissolution specifications as per IP 2010. Hence the batches F_5 and L_1were selected as the two layers for the final Bilayer tablets. The bilayer tablets were compressed in a 27 -station rotary compression machine using 19.5 x 9.5 mm punches. The sustained release layer formed as the bottom layer with the immediate release layer on top. The bilayer tablets were evaluated for Hardness, Thickness, Friability, Drug content and Drug release.

Evaluation of post-compression parameters

Hardness

Tablets require a certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packaging, and shipping. Tablet hardness has been defined as, the force required to break a tablet in a diametric compression test. Tablet hardness of all the formulations was measured using a Monsanto hardness tester and the results were in limits. These results were reported in table no.11.

Thickness

Tablet thickness is an important parameter to be controlled to facilitate packaging. Tablet thickness, at constant compressive load, varies with changes in die fill, with particle size distribution and packing of the particle mix being compressed; whereas at constant die fill, thickness varies with variations in compressive load. Tablet thickness must be controlled within a ±5% variation of a standard value. Any variation within a particular lot should not be apparent to the unaided eye of the consumer. Thickness of all the formulations was measured using a digital vernier calliper. These results were reported in table no.11

Friability

Twenty tablets were weighed accurately and placed in the friabilator and was operated for 100 revolutions or 4 minutes. The tablets were then dedusted and weighed. The weight loss of 0.5 to 1% is considered as acceptable limits for conventional uncoated tablets. The weight loss was calculated using the formula,

Friability, F (%) = (Weight loss/Initial weight)*100

The friability of the all the formulations was determined as per the above procedure.
These results were reported in table no.11

Disintegration test

Tablet disintegration study was performed for immediate release tablets of Pioglitazone Hcl and for the immediate release portion of the final bilayer tablets. Disintegration time was determined using USP tablet disintegration tester in distilled water at 37^{o}C±2˚C. These results were reported in table no. 11

Assay

Equivalent to 10mg each of Pioglitazone HCl and Metformin HCl was accurately weighed from powdered bilayered tablets and it was dissolved in methanol and distilled water respectively to form a clear solution. Later it was made up to volume with methanol and distilled water respectively. One ml of the sample was withdrawn, suitably diluted with pH 1.2 buffers and pH 6.8 phosphate buffers respectively and analyzed spectrophotometrically at 269nm and 232nm respectively. These results were reported in table no.11

***In vitro* dissolution study**

An *in vitro* drug release study from the prepared bilayered tablets, in triplicate , was determined using the USP eight station Dissolution Rate Test Apparatus(model QAE 016 and NRE 002, M/S Campbell Electronics) employing a paddle stirrer . With 900 ml of pH of 1.2 and followed by phosphate buffer pH 6.8 was used as dissolution media and maintained at 37±0.5oC at a rotational speed of 100 rpm, for 2 hrs and 10 hrs respectively. Then the dissolution samples were analyzed in UV-VIS double beam spectrophotometer, while keeping the dissolution media as a blank at 232nm. These results were reported in table no.14

Study of kinetics of drug release

To study the kinetics of drug release from the sustained release matrix, the in vitro dissolution study data of the optimized batch (F_5) was fitted into various kinetic models as described below. The best fitting model was selected on the basis of correlation coefficient (r^2) obtained for each of the graphs described. The results are tabulated in a Table.No.9.

Stability studies

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutics and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and to establish a retest for the drug substance or a shelf life for the drug product and recommended storage conditions. The ICH guideline recommends the following storage conditions for stability studies. The results were tabulated in the table.No.15&16

Compatability Studies

Physical compatibility studies were assured by FT-IR studies. The crude drug sample, drug-polymer mixtures and the complete formula of the final formulation were chosen for the study. The FT-IR spectras of the above samples were studied after a period of 30 days from preparation of the mixtures, to facilitate prompt detection of incompatibility. The spectras were obtained by preparing Potassium bromide pellets under dry condition by using pellet press. The spectra of the crude drug sample and that of the drug-excipient mixtures were compared to check the incompatibility problems, if any. The FT-IR spectras of optimized formulation was shown in the fig.No.5

Table No.1: Formulation of trail batches of sustain release layer

S.No.	Ingredient	P_1	P_2	P_3	P_4	P_5
1.	Metformin Hydrochloride	500	500	500	500	500
2.	Eudragit RSPO	90	135	180	150	180
3.	Microcrystalline Cellulose	100	120	30	40	60
4.	Methylene Chloride	q.s.	q.s.	q.s.	q.s.	q.s.
5.	HPMC K 100 M CR Premium	200	135	180	200	150
6.	Magnesium stearate	10	10	10	10	10

*All ingredients are in mg.

Table No.2: Formulation desgin of sustain rlease layer

S.No.	Ingredients	Qty/Tablet (mg)								
		F_1	F_2	F_3	F_4	F_5^*	F_6	F_7	F_8	F_9
1.	Metformin HCl	500	500	500	500	500	500	500	500	500
2.	MCC	156	111	66	111	66	21	66	21	---
3.	Eudragit RSPO	117	117	117	162	162	162	207	207	207
4.	Dichloromethane	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
5.	HPMC K 100 M	117	162	207	117	162	207	117	162	207
6.	Magnesium Stearate	10	10	10	10	10	10	10	10	10

*F_5 is chosen as centre point and five replicate batches were studied.

Table.No.3: Formula for Immediate release layer

S.No.	Ingredients	Qty/Tab (mg)
1.	Pioglitazone Hydrochloride	16.53
2.	Lactose Monohydrate	157.87
3.	Starch 1500	10.00
4.	Hydroxypropyl Cellulose	6.00
5.	Croscarmellose Sodium (M)	4.00
6.	Water	q.s.
7.	Croscarmellose Sodium (L)	4.00
8.	Iron oxide red	0.60
9.	Magnesium Stearate	1.00

Table No.4: Post comprssional parameters of Trail batches

S.No.	Formulation Code	Hardness* (kg/cm^2)	Thickness* (mm)	Friability* (%)	Assay# (%)
1.	P_1	7±0.34	5.6±0.015	0.136±0.007	100.154±0.404
2.	P_2	7±0.32	5.48±0.021	0.142±0.003	99.952±0.526
3.	P_3	8±0.26	5.636±0.018	0.138±0.002	100.62±0.42
4.	P_4	7±0.31	5.6±0.012	0.099±0.006	101.23±0..261
5.	P_5	7±0.28	5.693±0.012	0.126±0.008	100.34±0.513

* Mean ± SD (n=6); # Mean ± SD (n=3)

Table No.5: Post Compressional parameters of Optimized batchs

S.No.	Formulation Code	Hardness* (kg/cm^2)	Thickness* (mm)	Friability* (%)	Assay# (%)
1.	F_1	6±0.391	5.48±0.021	0.23±0.003	98.456±0.43
2.	F_2	7.5±0.418	5.588±0.014	0.16±0.002	99.672±0.39
3.	F_3	7±0.324	5.64±0.018	0.191±0.005	99.954±0.31
4.	F_4	9.5±0.447	5.49±0.012	0.13±0.0009	100.76±0.408
5.	F_5	8±0.351	5.53±0.026	0.142±0.007	100.04±0.52
6.	F_6	11±0.408	5.51±0.029	0.098±0.021	101.23±0.265
7.	F_7	8.5±0.276	5.51±0.023	0.156±0.006	99.327±0.612
8.	F_8	9.08±0.584	5.521±0.027	0.163±0.008	98.986±0.217
9.	F_9	11±0.324	5.62±0.009	0.112±0.01	100.12±0.192

***In Vitro* dissolution study**

Table No.6: Dissolution study of preliminary batches of Metformin Hydrochloride

S.No.	Formulation Code	% Drug release*		
		1st hour	3rd hour	10th hour
1.	P_1	55.66±0.29	77.19±0.474	100.257±0.57
2.	P_2	52.28±0.34	83.80±0.52	99.96±0.51
3.	P_3	40.90±0.23	68.59±0.463	98.48±0.28
4.	P_4	32.13±0.19	62.18±0.396	100.33±0.42
5.	P_5	36.31±0.52	64.05±0.28	99.12±0.64

* Mean ± SD (n=6)

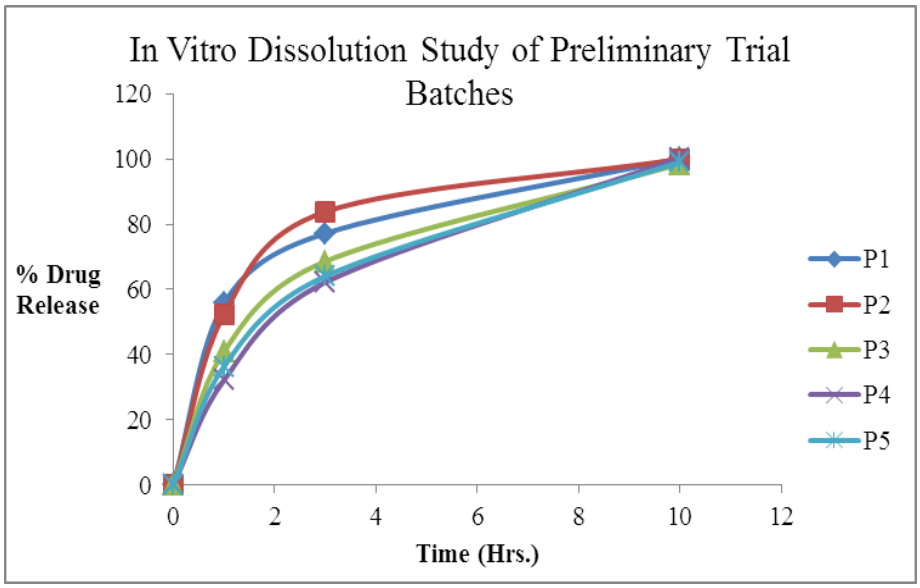

Fig.No.1: *In vitro* diddolution studies of preliminary trail bstches

Table No.7: Dissolution study of Metformin Hydrochloride

S.No.	Formulation Code	% Drug release*		
		1st hour	3rd hour	10th hour
1.	F_1	59.01±0.61	79.47±0.509	101.63±0.407
2.	F_2	47.42±0.32	72.24±0.302	98.58±0.23
3.	F_3	43.55±0.41	67.78±0.281	95.97±0.509
4.	F_4	42.71±0.27	67.54±0.59	99.65±0.43
5.	F_5	29.98±0.59	58.98±0.467	94.59±0.57
6.	F_6	24.54±0.36	53.42±0.254	89.97±0.381
7.	F_7	40.58±0.48	65.41±0.532	97.92±0.491
8.	F_8	26.27±0.28	55.51±0.461	91.02±0.308
9.	F_9	19.67±0.12	48.45±0.35	84.23±0.26

*** Mean ± SD (n=6)**

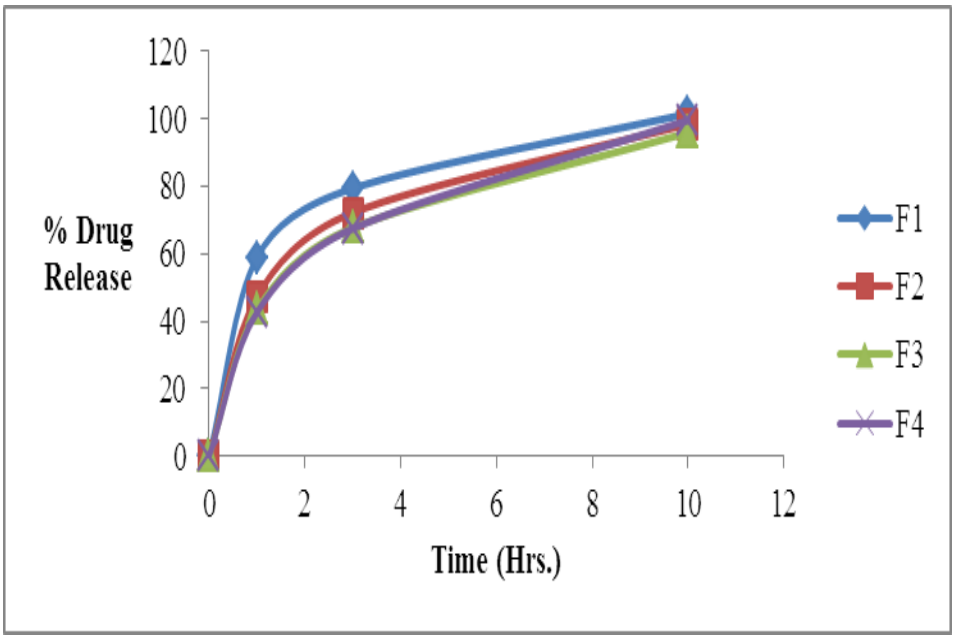

Fig.No.2: *In Vitro* drug release profile of Optizd batches from F1-F4

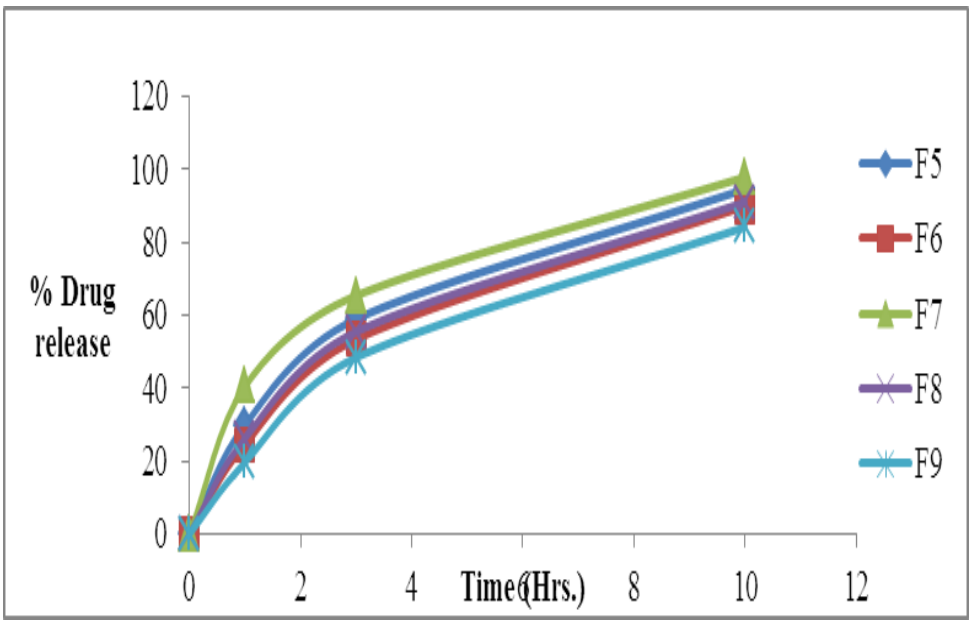

Fig.No.3: *In Vitro* drug release profile of Optizd batches from F5-F9

Comparative Dissolution Profile Study

Table No.8: Comparative dissolution profile of F5 with marketed product

Dissolution time points	Formulation F_5*	Glucophage XR*
1st hour	35.2	28.86
3rd hour	60.07	58.69
10th hour	96.6	93.75

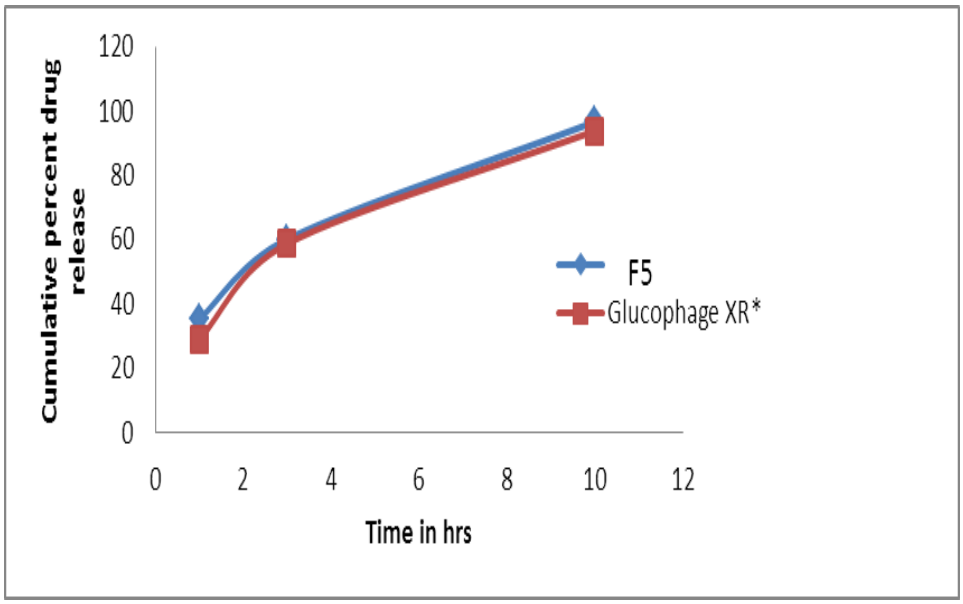

Fig.No.7.18 : Comparitive dissoution profile of F_5 with marjeted product.

a. *In Vitro* Release Kinetics

Table No.9: Release Kinetics of Optimized formula

Release kinetics	R^2	Diffusional exponent 'n'
Zero order	0.8565	-
First order	0.9974	-
Higuchi	0.9924	-
Korsmeyer-peppas	0.9964	0.4377
Hixson-crowell cube root plot	0.9865	-

Immediate release layer of Pioglitazone Hydrochloride

Physical parameters & Assay

Table No.7.11: Post Compressional Parameters of immediate release layer

S.No.	Parameters	Observed Values
1.	Hardness* (kg/cm^2)	3 ± 0.07
2.	Thickness* (mm)	1.25 ± 0.32
3.	Friability* (%)	0.093 ± 0.0002
5.	Disintegration time*	99 secs ± 0.02
6.	Assay (%)#	100.06 ± 0.34

*** Mean ± SD (n=6); # Mean ± SD (n=3)**

***In Vitro* Dissolution study**

Table No.12: Dissolution study of Pioglitazone Hydrochloride

S.No.	Parameter - %Drug Release	Observed values*
1.	15 mins	100.12 ± 0.23

* Mean ± SD (n=6)

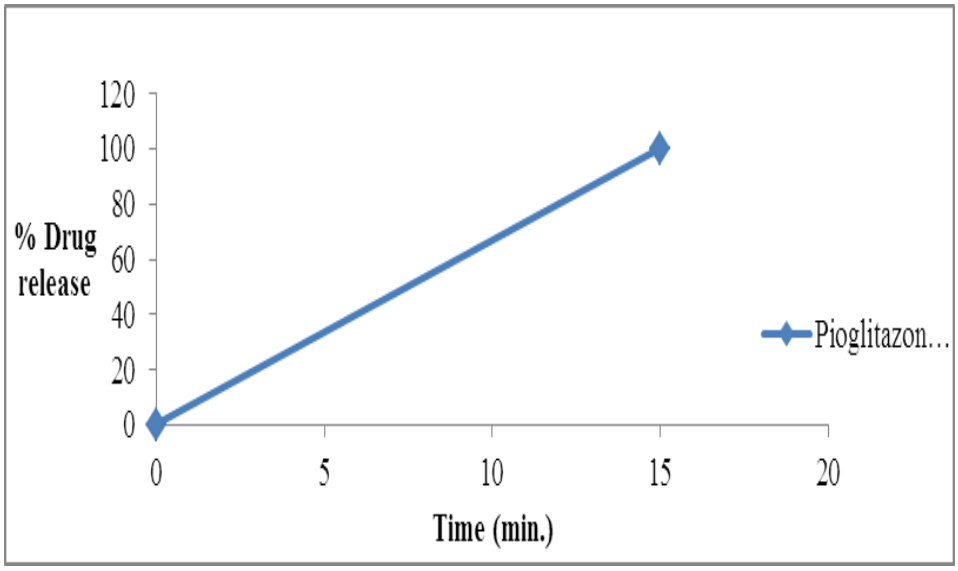

Fig.No.4: *In Vitro* drug Relase study of Immediate release layer

Evaluation of Bilayer Tablets

Table No.13: Evaluation parameters of bilayer tablet

S.No.	Parameters	Observed Values
1.	Hardness* (kg/cm^2)	9 ± 0.51
2.	Thickness* (mm)	6.841 ± 0.034
3.	Friability* (%)	0.12 ± 0.002
4.	Disintegration time* (IR layer)	1 min 12 sec ± 0.05
5.	Assay (%) # Metformin Hcl Pioglitazone Hcl	99.89 ± 0.406 100.2 ± 0.23

* Mean ± SD (n=6); # Mean ± SD (n=3)

Table No.14: Dissolution study of Metformin Hydrochloride from the bilayer tablets

S.No.	% Drug release*		
	1st hour	3rd hour	10th hour
1.	36.64±0.54	60.32±0.23	97.75±0.356

* Mean ± SD (n=6)

Table No.15: Dissolution study of Pioglitazone Hydrochloride from the bilayer tablets

S.No.	Parameter - %Drug Release	Observed values*
1.	15 mins	99.456% ± 0.34

* Mean ± SD (n=6)

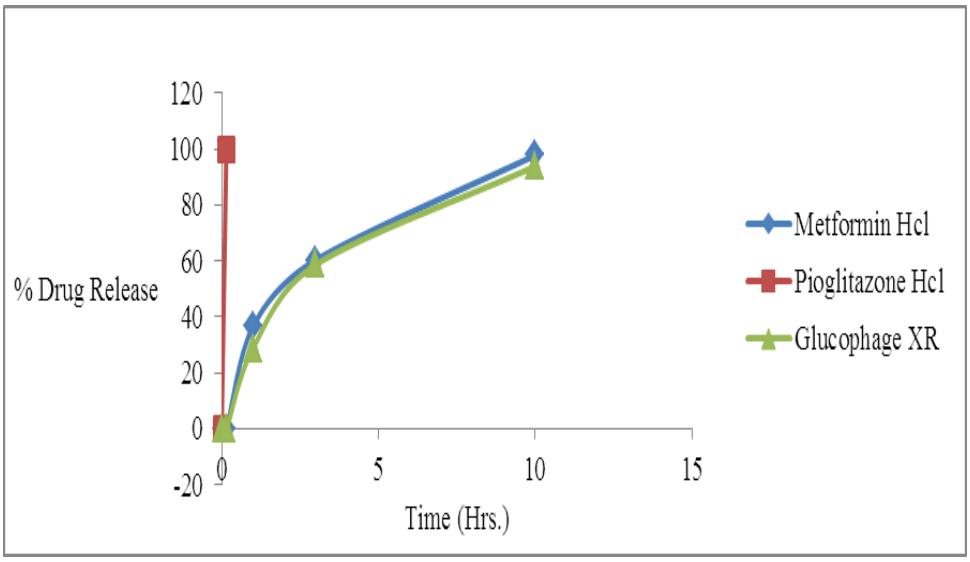

Fig.No.5: *In vitro* Dissolution study of the final bilayer tablet

Table No.15: Stability Studies of Bilayered tablet

Parameters	Storage condition 40˚C ± 2˚C / 75% RH ± 5% RH			
	Initial	1st month	2nd month	3rd month
Description	*	*	*	*
Average weight (mg)	1100.8	1099.1	1100.9	1100.6
Hardness (kg/cm^2)	9	8.5	10	9
Thickness (mm)	6.87	6.83	6.85	6.81
Friability (%)	0.12	0.12	0.16	0.09
Disintegration time (IR layer)	1 min 10 sec	1 min 30 sec	1 min 16 sec	1 min 40 sec
Assay (%)				
Metformin Hydrochloride	99.89	100.31	98.992	99.723
Pioglitazone Hydrochloride	100.2	100.09	99.76	99.954

Table No.16:– *in vitro* dissolution study of Bilayered tablet during storage conditions

Dissolution Time points (Hr)	Storage condition 40˚C ± 2˚C / 75% RH ± 5% RH			
	Initial	1st month	2nd month	3rd month
IMMEDIATE RELEASE LAYER				
0.15	99.456±0.34	100.06±0.25	99.67±0.16	99.75±0.24
SUSTAINED RELEASE LAYER				
1	36.64±0.54	32.32±0.32	34.92±0.47	35.08±0.26
3	60.32±0.23	59.67±0.31	60.98±0.23	60.16±0.307
10	97.75±0.356	96.45±0.27	96.01±0.36	95.98±0.601

Compatibility studies

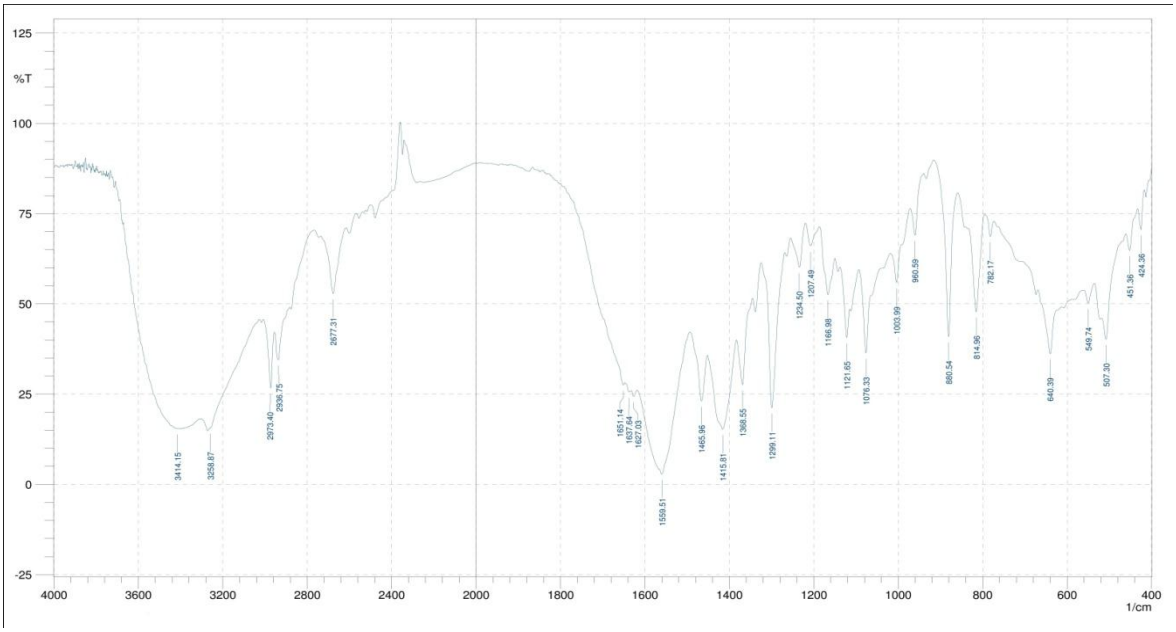

Fig.No.5: FTIR of optimized formula of bilayer tablets

CONCLUSION

The present study intended to develop a dual release bilayered tablet formulation fabricating a sustained release layer of Metformin Hydrochloride and an immediate release layer of Pioglitazone Hydrochloride.

The sustained release layer was fabricated using a combination of Hydrophilic-Hydrophobic matrix system. The polymers HPMC K100M CR premium and Eudragit RSPO were used as the matrix retardants. The rough estimate of the amount of polymers required to retard the drug release as per IP specifications was determined by the Preliminary trial batches P_1 to P_5. It was found that a drug release profile within the limits of IP specification could be obtained when the two polymers were employed at a level of 20% each per tablet weight. Further the ratio of the two polymers was fine tuned so as to achieve an optimum release profile that matches with that of the innovator.

The optimum formulation was then was then selected by Desirability approach by using the IP limits for drug release as the constraints. The results showed that optimum drug release profile could be obtained when Eudragit RSPO and HPPMC K100M were added at 17.84 and 18.35% respectively. A formulation F_5 comprising the polymers at these levels was taken as a large scale batch and the in vitro release study was performed. The experimental values of drug release were in accordance with the predicted values. Also, a comparative dissolution

profile study of F_5 was performed against Glucophage XR. The results was concluded that the two products were similar in terms of *in vitro* sustained release profile.

The data of in vitro dissolution study of F_5 was fitted into various kinetic models to analyze the kinetics of drug release. The results showed that the drug release form the matrix of F_5 follows first order kinetics, Higuchi model and KoresmeyerPeppas model. The 'n' value obtained was 0.4377, hence the drug release is by Fickian diffusion.

The immediate release layer of Pioglitazone Hydrochloride was formulated by using superdisintegrants like Croscarmellose Sodium and Starch 1500. The formula L_1released almost 100% of the drug within 15 minutes time point in 0.1N HCL as dissolution medium. Hence this batch was selected for bilayer compression.

The formulation F_5 and L_1 were selected as the sustained release and immediate release layers respectively for compression into the final bilayer tablets. The compressed bilayer tablets were evaluated for physical parameters, Assay and Dissolution studies. There were no significant changes in release profiles of the two layers after being compressed as a bilayer tablet.

The bilayer tablets were finally subjected to Accelerated stability studies as per ICH guidelines. The results of stability studies showed that there were no significant change in the physical parameters of the tablets, assay and in the Dissolution profiles until the end of 3 months form initial values. Hence the formulation is considered stable and the data can be employed for prediction of shelflif of the product.

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