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Research Article

FORMULATION AND EVALUATION OF BILAYER TABLET 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, sodium starch glycolate, cross carmellose sodium as polymers and Metformin hydrochloride for sustained release using HPMC K4M, HPMCK15M 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 show zero order release and diffusion and erosion was the dominant mechanism of drug release. The combination of HPMC K4M and HPMC K15M had significant effect on the release of Metformin HCl matrix tablets. 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, Matrix tablets.

Introduction

Type 2 diabetes mellitus is a heterogeneous disorder characterized by multiple defects in the pancreatic β-cell, liver, and peripheral tissues such as skeletal muscle and adipose tissue. Combination therapy has various advantages over monotherapy such as problem of dose-dependent side effects is minimized. A low dose combination of two different agent reduces the dose related risk, the addition of agent may counteract some deleterious effects of the other, using low

dosage of two different agents minimize the clinical and metabolic effects that occur with maximal dose of individual component of the combined tablet. The major therapeutic goals in subjects with type 2 diabetes are to optimize blood glucose control. Multiple dosing regimens together, along with large doses, dose dependent absorption, and poor bioavailability of Metformin HCI are not preferred since it leads to patient noncompliance, potential side effects and danger of overdosing. It is therefore imperative to shift from multiple dosing to once –a –day or twice –a –day dosing regimens.

Metformin is an oral anti –hyperglycemic agent, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50 – 60% with relatively short plasma half - life of 1.5 - 4.5 h.

The pioglitazone, act by binding and activating the peroxisome proliferation -activated receptor -γ (PPAR-γ) and, do not stimulate insulin release or because hypoglycemia. These agents can reduce, mean HbA1c both as monotherapy and in combination. In combination with metformin , it improved glycemic control, insulin sensitivity and beta-cell function. Pioglitazone has an oral bioavailability of 83 % and peak plasma concentrations of pioglitazone are achieved in 2–2.5 hours. Elimination half of Pioglitazone is 3 to 7 hrs.

The Main Objectives

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 of Bilayered tablets.
4. To study the release kinetics and transport mechanism of drug from the formulations.

Materials and Methods

Preparation of Immediate Release Layer of Pioglitazone HCl(F1 –F6*).* Immediate release layer of pioglitazone HCl was prepared by direct compression method. Pioglitazone HCl, sodium starch glycolate, cross carmellose sodium crospovidone, Microcrystalline cellulose were accurately weighed and passed through sieve number 40. All the above ingredients as shown in Table were mixed in a polybag. Talc and magnesium stearate were added after passing through sieve number 40 and mixed properly.

Preparation of Controlled Release Layer of Metformin HCl: Metformin HCl granules containing HPMC K4M, HPMC K15M, and combination of HPMC K4M and HPMC K15M were prepared by wet granulation

technique by adding PVP K 30 dissolved in iso propyl alcohol as a granulating fluid . Required quantities of metformin HCl, HPMC, and Micro crystalline cellulose were passed through sieve number 40 and were mixed thoroughly and a sufficient volume of granulating fluid was added slowly. After enough cohesiveness was obtained, the mass was passed through sieve number 12. The obtained granules were dried at 50^0C in hot air oven till a constant weight was obtained (until dry). The dried granules were then passed through sieve number 40. Talc and magnesium stearate were added after passing through sieve number 40 and mixed properly.

Compression of bilayer tablets

Final bilayer tablets were compressed as one layer only for Metformin Hcl and second layer for Pioglitazone Hcl using 16mm punch. The tablet was compressed as a bilayer tablet using both Metformin Hcl granules and Pioglitazone Hcl powder. In t his Metformin Hcl granules was introduced into the die cavity and a slight precompression was made so tbat the layer was uniformly distributed after that pioglitazone Hcl granules was added and a final compression was made.

Pre formulation studies

a) Drug and excipient compatibility studies

The drug, polymer, drug – polymer interactions were studied by FTIR spectrometer. The characteristics peaks were recorded.

b) Angle of repose : The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height (h) of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder . The powder was allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan \theta = h/r$

Therefore, $\theta = \tan h/r$

Where, θ = angle of repose,

h= height of the pile,

r = radius of the pile base

c) Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 10 ml measuring cylinder . After the initial volume was observed , the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5cm at 2 sec intervals . The tapping was continued until no further change in volume was noted .Bulk density is calculated by using formula :

Weight of the powder Bulk density (pb) = Bulk volume of the powder

Weight of the powder Tapped density (p,) = Tapped volume of the powder

d) Carr's index

It helps in measuring the force required to break the friction between the p articles and the hopper. It is expressed in % and given by

Carr's Index (%) = [(TBD - LBD) x 100] / TBD

Where,

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

Evaluation

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,

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

Specifications of weight variation.

Average weight of tablet	% deviation
80 mg or less	10
More than 60mg but less than 250 mg	7.5
250 mg or more	5

Hardness: 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 5-6 kg/sq.cm.

Friability:

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 degusted and the tablets were reweighed.

Percent friability is given by the formula;

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

Where, W0 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%.

Estimation of Drug Content

Equivalent to 10 mg 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 267 nm and 233 nm respectively.

***In-vitro* dissolution studies.**

In vitro dissolution studies was conducted using USP dissolution apparatus - II at 37 ± 0.5^0C temperature and at 50 rpm and the volume of dissolution media is 900 ml. 0.1 N hydrochloric acid was used as dissolution medium for the first two hours and

6.8 pH phosphate buffer for the remaining time. Samples of 5 ml were withdrawn at predetermined time intervals and replaced with 5 ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, wherever necessary, and were analyzed for the pioglitazone HCl for the first two hours at 267 nm and for metformin HCl for the remaining time at 233 nm by using a double beam UV

spectrophotometer.

Result

Hardness, Thickness, Friability and all other parameters were found to be within the acceptable limits as per IP. From the dissolution profile of immediate release layer formulation containing pioglitazone sodium starch glycolate and pioglitazone-cross povidone requires 30minutes to drug release. But the formulation pioglitazone with cross carmellose sodium (15mg ,12mg) shows drug release within 10 minutes.

From the controlled release layer of metformin with Hpmc K4M the drug is released within 2hrs., from the formulation containing metformin and hpmc k15m the drug is released 80 % upto 12 hrs. The drug Metformin and combination of hpmc k4m and hpmc k15m (500mg, 80mg, 40mg respectively) shows 75% of drug release. But the formulation containing the drug Metformin and combination of hpmc k4m and hpmc k15m (500mg , 40mg, 80mg respectively) shows 95 % drug release upto 12hrs.

It was found that controlled (metformin) optimized formulation followed zero order and peppas release. Immediate release layer (pioglitazone) followed first order release.

It describes the systems where the controlled drug release rate is independent of its concentration of the dissolved substance and the systems where the immediate drug release rate is dependent of its concentration of the dissolved substance

Peppas R^2 value 0.996, n value 0.7864 indicates anomalous non fickian diffusion. Anomalous non fickian diffusion refers to the combination of both diffusion and erosion of the polymeric chain.

Conclusion

Pioglitazone HCl and Metformin HCl and the excipients selected for this investigation were compatible and it was confirmed by FT-IR studies.

Precompressional and Postcompressional parameters were found to be within the satisfactory limits and hence suitable to formulate Bilayered tablets.

The immediate release layer formulation i.e.; P4 was optimized because it released the maximum amount of the drug.

The results of *in-vitro* drug release profile of Bilayered tablets depicts that combination of polymer concentration, increases the retardation of drug release from the sustained release layer of a Bilayered tablet.

The formulations P4 were suitable to immediate drug release within 10 minutes and M5 were suitable for sustain the drug release for a period of 12hrs . Immediate release layer followed first order release , Controlled release layer followed zero order and peppas release.

Hence can conclude that formulated Bilayered tablets of Pioglitazone HCl and Metformin HCl were developed successfully with immediate release layer comprising of cross carmellose sodium, and sustained release layer comprising of combination of hpmc k4m and k15m by direct compression technique and wet granulation technique. Based on the above studies the sustained release bilayer matrix tablets of Pioglitazone HCl and Metformin HCl could be suitable for sustaining the drug release over a prolonged period. The formulations prepared were found to be linear in releasing the drug for a prolonged period of time i.e. 12 hours. Then these formulations can be further subjected to pharmacodynamic and pharmacokinetic studies in a suitable animal model. Hence the above found formulations may be suitable for once a day administration.

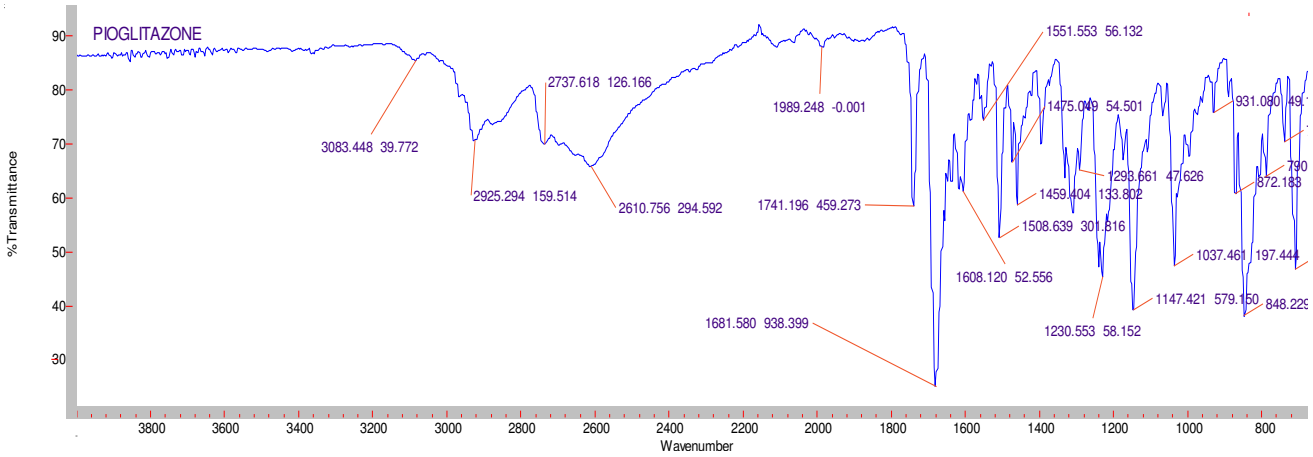

Fig-1: IR Spectra of Immediate release layer (pioglitazone).

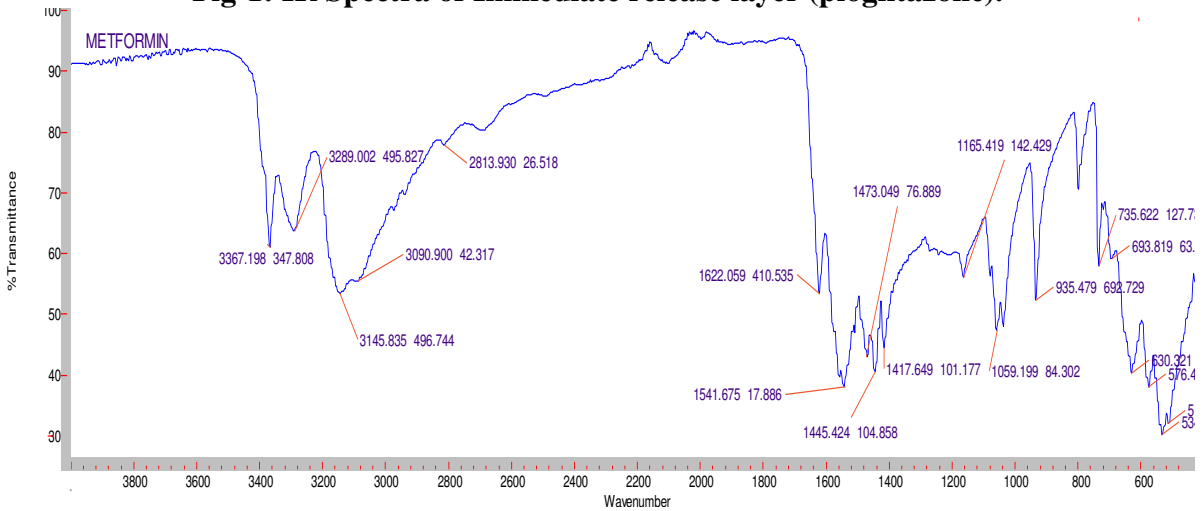

Fig-2: IR Spectra of controlled release layer (metformin).

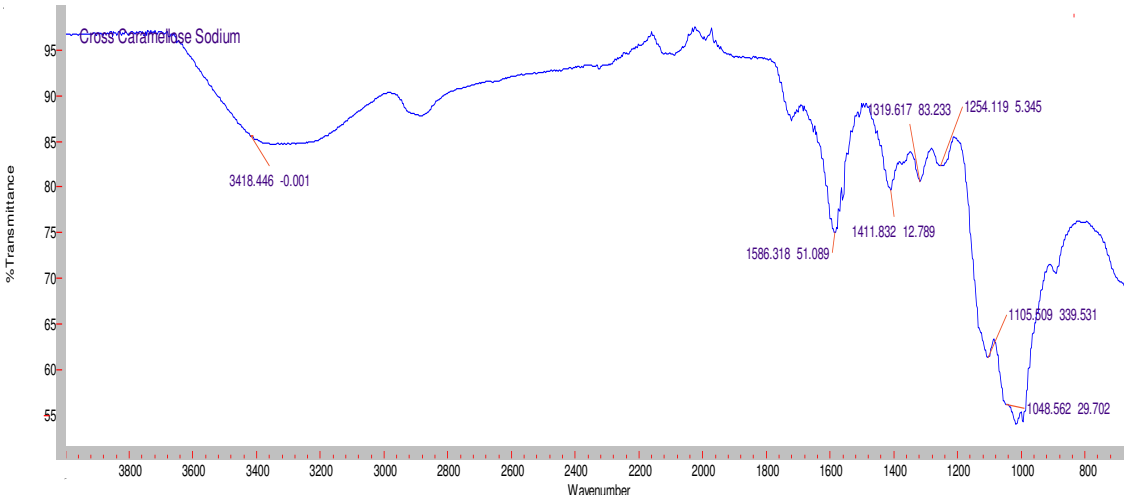

Fig-3: IR Spectra of cross carmellose sodium.

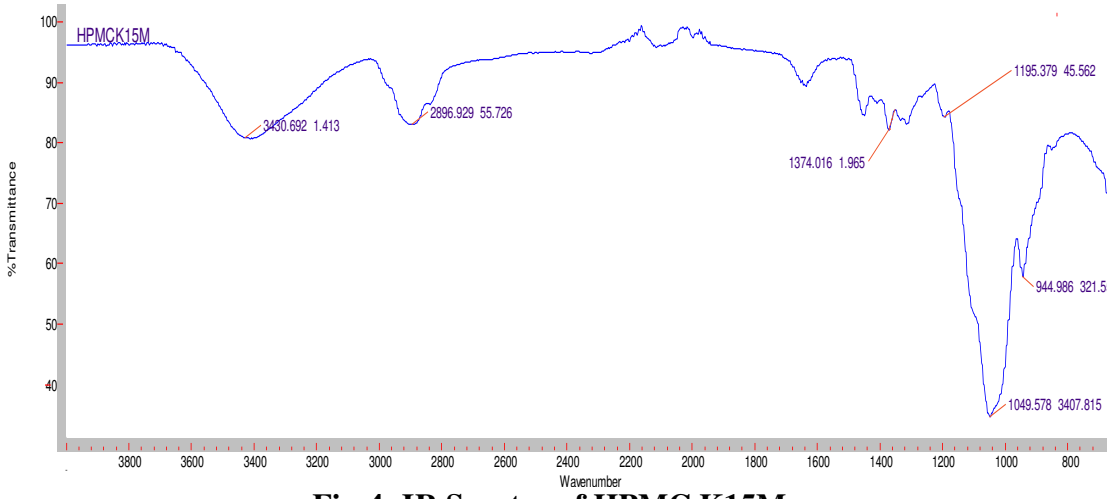

Fig-4: IR Spectra of HPMC K15M.

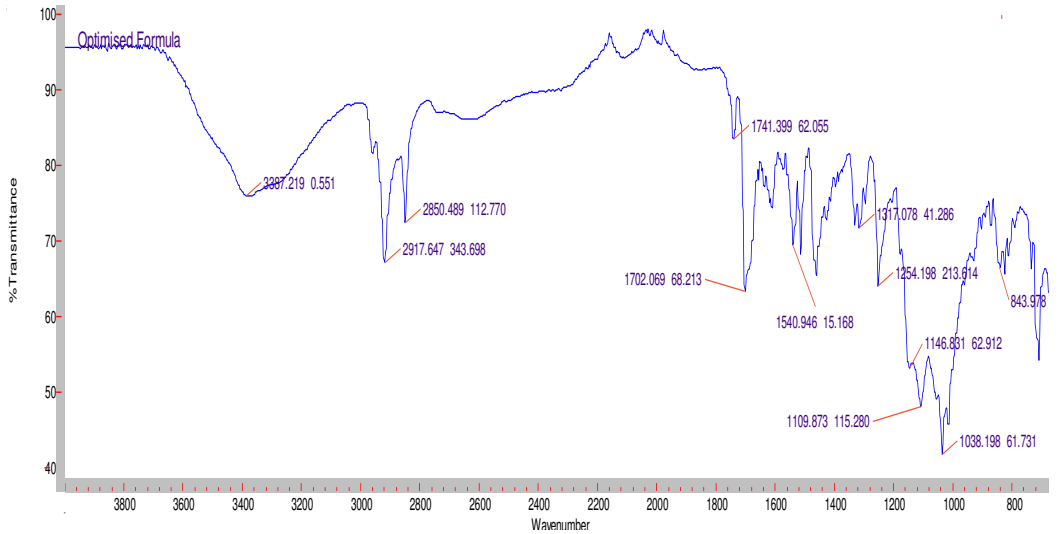

Fig-5: IR Spectra of Optimized formula.

Table-1: Composition of Immediate release layer.

Formulation Code Composition (mg)	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**
Pioglitazone	15	15	15	15	15	15
SSG	6	12	---	---	---	---
CCS	---	---	6	12	---	---
CP	---	---	---	---	6	12
MCC	95	89	95	89	95	89
Mg.stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2

Table-2: Composition of Controlled release layer.

Formulation Code Composition (mg)	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**
Metformin	500	500	500	500	500	500
HPMC K4M	80	120	---	---	40	80
HPMC K15M	---	---	80	120	80	40
PVP K30	30	30	30	30	30	30
IPA	q.s	q.s	q.s	q.s	q.s	q.s
MCC	200	160	200	160	160	160
Mg.stearate	10	10	10	10	10	10
Talc	10	10	10	10	10	10

Table-3: Precompression parameters of controlled release layer and optimized immediate release layer.

Formulation batch code	M1	M2	M3	M4	M5	M6	P4
Angle of Repose ± S.D	27.30±1.04	29.02±1.02	28.20±1.40	30.81±1.09	29.52±1.23	28.57±1.12	28.69±1.342
Bulk Density (g/ml)	0.282±0.007	0.289±0.012	0.296±0.014	0.287±0.012	0.311±0.08	0.313±0.006	0.384±0.012
Tapped Density (g/ml)	0.342±0.007	0.357±0.006	0.367±0.015	0.345±0.011	0.394±0.056	0.397±0.005	0.416±0.005
Carr's Index (%)	18.01±1.83	19.14±0.04	19.09±0.08	10.85±0.04	16.11±0.04	20.94±0.04	7.68±0.55
Hausner's Ratio	1.22±1.04	1.23±1.02	1.23±1.40	1.20±1.09	1.20±1.23	1.260±1.23	1.083±1.34

Table-4: Evaluation of Tablets.

FORMULATION	Hardness	Friability	Thickness	Drug content (Metformin)	Drug content (pioglitazone)
F1	5.16±0.28	0.44	6.52	92.25±0.09	98.25±1.16
F2	5.25±0.05	0.35	6.61	96.69±0.98	99.01±1.10
F3	5.36±0.28	0.37	6.82	95.15±1.92	98.97±1.23
F4	5.61±0.28	0.40	6.67	92.34±1.52	99.19±0.90
F5	5.33±0.28	0.37	6.67	93.58±1.52	98.26±0.78
F6	5.36±0.57	0.42	6.85	95.52±1.41	98.78±0.86

Table-5: *In-vitro* dissolution studies of immediate release layers.

Time(min)	P1	P2	P3	P4	P5	P6
1	18.26	23.55	7.67	15.19	7.95	24.66
2	31.07	48.06	20.74	31.91	14.36	44.16
3	46.39	63.10	32.74	58.93	20.49	55.86
5	57.53	74.80	43.33	79.26	27.17	63.94
10	79.82	89.29	55.03	98.99	37.76	81.49
15	90.12	93.19	60.88		40.26	84.27
30	99.32	98.48	70.35		48.34	94.30
45			82.32		55.30	98.82
50					56.98	

Table-6: *In-vitro* dissolution studies of controlled release layers.

TIME(0.5 HOURS)	M1	M2	M3	M4	M5	M6
0.5	69	69.79	17.41	6.73	20.6	20.8
1	79.62	79.90	36.19	12.86	34.13	37.27
2	80.28	70.70	52.74	19.36	59.08	47.60
3			66.39	26.03	74.69	63.43
4			74.69	33.38	84.05	68.45
6			84.1	47.50	89.27	89.3
8			80.9	61.11	93.36	66.53
10			79.87	74.31	92.64	76.2
12			81.04	84.26	94.26	77.33

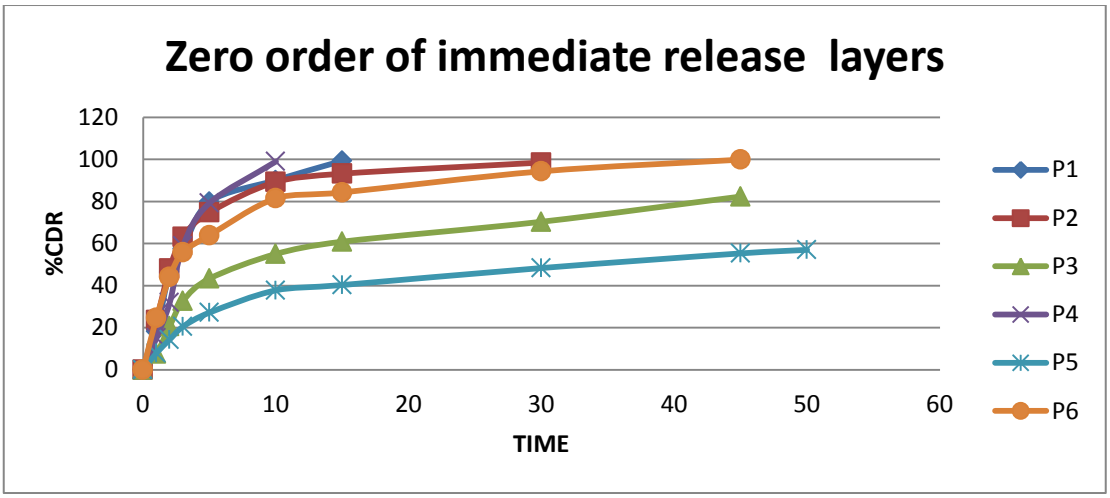

Fig-6: Comparative Zero order plots of immediate release layers of Pioglitazone.

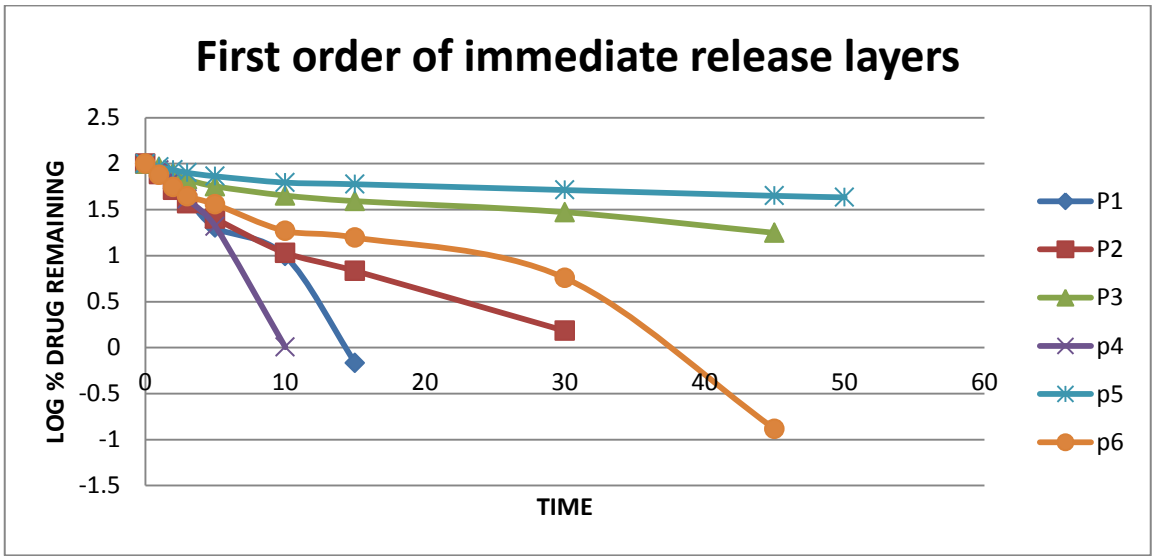

Fig-7: Comparative First order plots of immediate release layers of Pioglitazone.

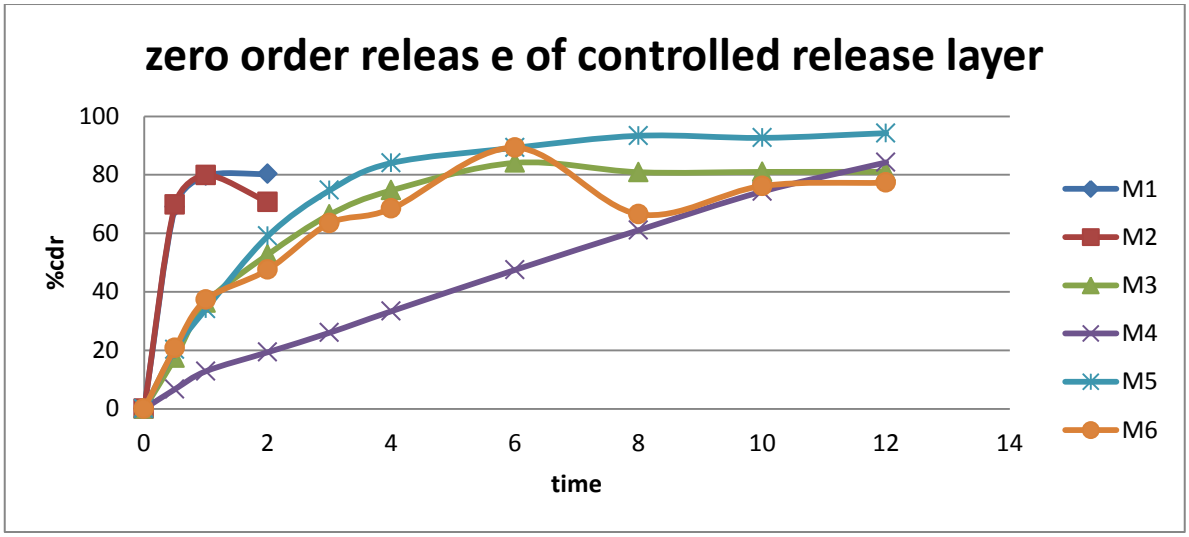

Fig-8: Comparative zero order plots of extended release layers of Metformin.

Table-7: Kinetic values obtained from *In vitro* release data for controlled release layer.

Formulation code	Zero order R^2 value	First order R^2 value	higuchi R^2 value	Korsemeyer peppas	
				R^2 value	n value
M1	0.569	0.664	0.847	0.790	0.1092
M2	0.446	0.402	0.749	0.007	0.0093
M3	0.642	0.733	0.859	0.861	0.4538
M4	0.994	0.969	0.956	0.996	0.7864
M5	0.689	0.896	0.890	0.897	0.4773
M6	0.0.604	0.543	0.818	0.855	0.3925

Table-8: Kinetic values obtained from *In vitro* release data for immediate release layer.

Formulation code	Zero order	First order
P1	0.761	0.960
P2	0.564	0.948
P3	0.748	0.917
P4	0.871	0.970
P5	0.802	0.883
P6	0.610	0.936

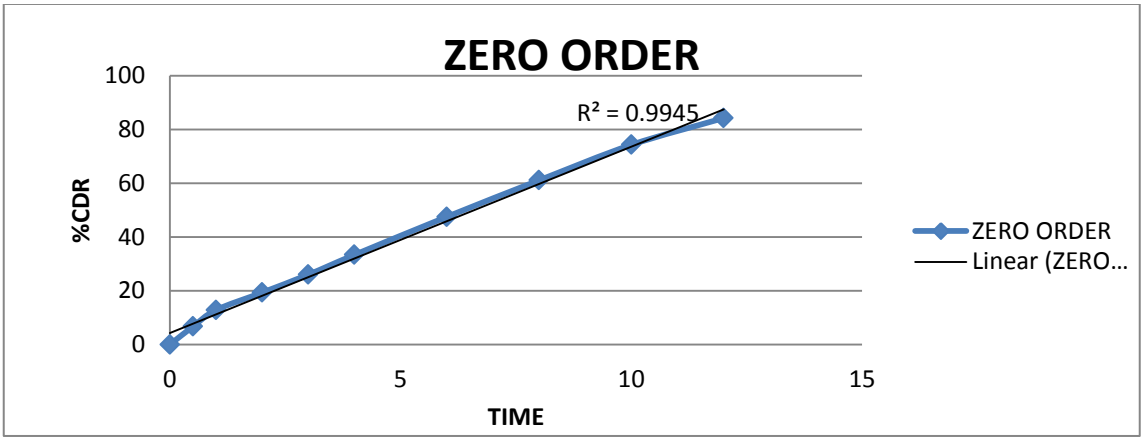

Fig-9: Zero order kinetic studies of M4.

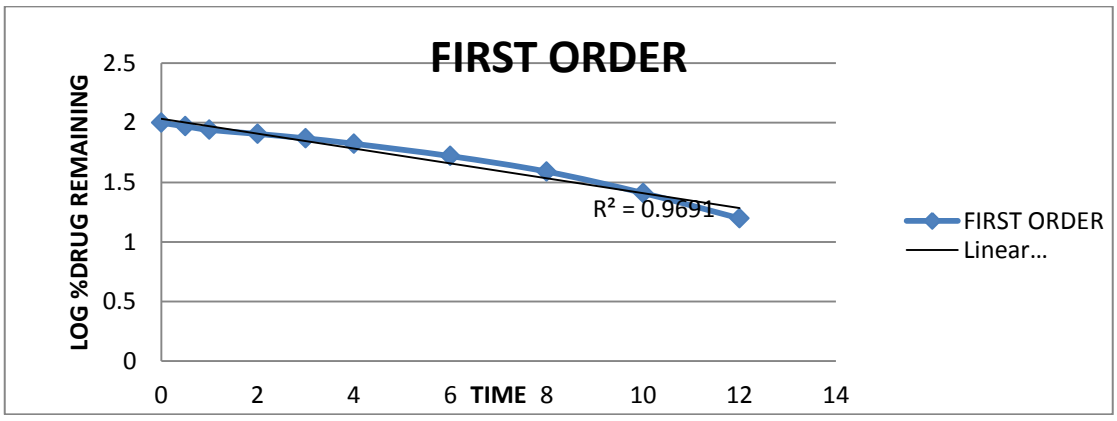

Fig-10: First order kinetic studies of M4.

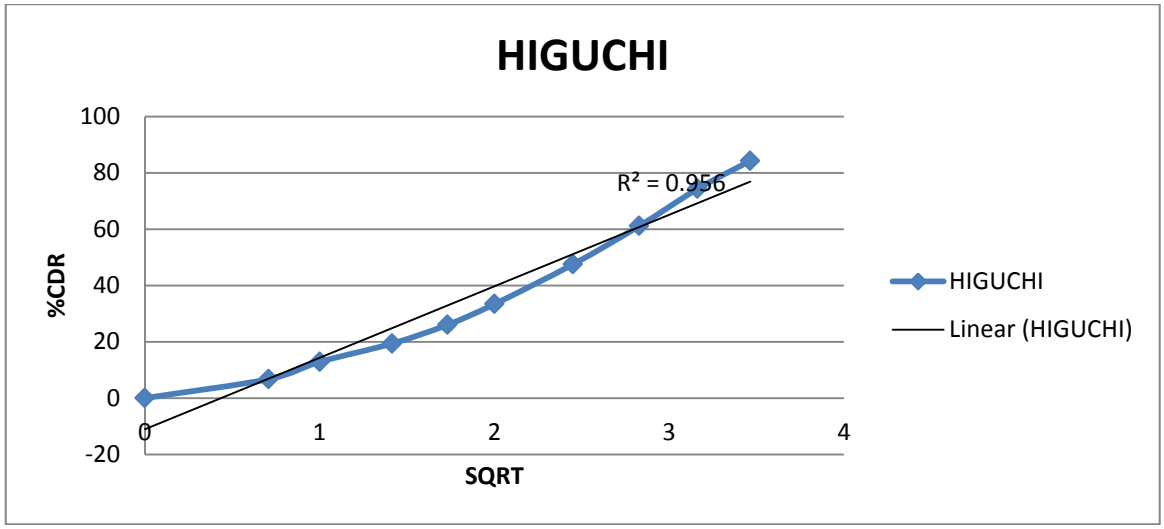

Fig-11: Higuchi Equation of M4.

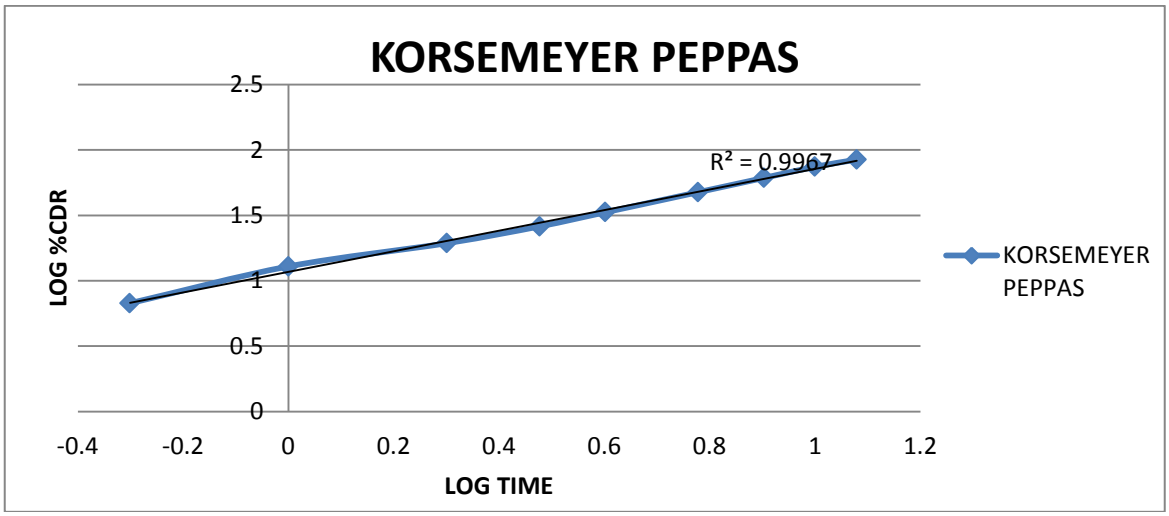

Fig-12: Korsemeyer peppas of M4.

Table-9: Stability studies of optimized formulation of Losartan potassium SR tablet.

Characteristic	Initials	1 Month	2 Month	3 Month
Hardness (kg/cm^2)*	5.33±0.28	5.15±0.22	4.9±0.10	4.9±0.48
Friability	0.37	0.35	0.36	0.35
In vitro drug release at 12^{th} hour*(%)*	84.26±1.08	84.14±0.65	83.23±0.77	82.00±0.77

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