INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

ISSN:2320-2831

IJPAR |Vol.5 | Issue 4 | Oct - Dec -2016
Journal Home page: www.ijpar.com

Research article *Open Access*

Formulation, invitro evaluation & stability studies of the bilayered tablets of combination-glipizide (I.P) & pioglitazone (I.P)

Romana Siddiqua*, Dr.Syed Abdul Azeez Basha

Deccan School of Pharmacy, Darussalam, Hyderabad.

***Corresponding Author: Romana Siddiqua**
Email: romana.siddiqui7@gmail.com

ABSTRACT

The objective of present investigation was to formulate and evaluate bilayered tablets containing Pioglitazone (I.R) & Glipizide (S.R).The Bilayered tablets prepared by direct compression method. The sustained release layer is prepared by wet granulation method using synthetic and natural polymers like HPMC K4M, Ethylcellulose, and Guargum& Xantham gum. The immediate release layer is prepared by direct compression method using superdisintegrants like Crosscamellose sodium; Crosspovidone & Sodium starch glycolate (SSG). The physicochemical evaluation results for the powdered blend of all trials pass the official limits in Bulk density, Tapped density, Compressibility index, Hausner ratio, and Angle of repose. The formulated tablets were evaluated for thickness, weight variation test, hardness test, friability test and drug content. The prepared tablets exhibited satisfactory physico-chemical characteristics. The formulation (F6) having immediate release layer of Pioglitazone showed 100.8%drug release within 60min & the formulation (F4) having sustained release layer of Glipizide showed 100.1% drug release within 12 hours. The drug release from the tablets was sufficiently sustained. The kinetic modeling of in vitro dissolution profiles revealed diffusion release mechanism. The stability studies revealed no significant changes in physical and chemical properties for the optimized formulation.

Keywords: Sustained Release, Immediate Release, Bilayered tablets, Glipizide, Pioglitazone.

INTRODUCTION

Bilayered tablets

Bi-layer tablet is a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles [1]. Bi-layer tablet is suitable for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is for immediate release as loading dose and second layer is maintenance dose. So use of bi-layer tablets is a very different aspect for anti-hypertensive, diabetic, anti-inflammatory and analgesic drugs where combination therapy is often used.

A solid dosage form is drug delivery system that includes tablets, capsules, sachets and pills as well as a bulk or unit-dose powders and granules [2]. Among the various dosage forms oral solid dosage forms have greater importance and occupy a prime role in the pharmaceutical market.

AIM AND OBJECTIVE OF PRESENT STUDY

Aim

To study & evaluate physico-chemical properties, drug-excipient compatibility and to design formulation of bilayered tablets of Glipizide and Pioglitazone & to carry invitro dissolution and stability studies.

Objectives

1. To optimize the concentration of Polymer for sustaining Glipizide.
2. To select the suitable filler to produce the bulkiness and desired weight.
3. To select the dissolution media, by performing solubility studies.
4. To perform the drug – excipient compatibility studies as per ICH guideline

METHODOLOGY

Formulation of Immediate release layer

The immediate release tablets containing 7.5mg Pioglitazone were prepared with a total tablet weight of 250mg. The immediate release granules were prepared by blending the drug with different super disintegrants (Sodium starch glycolate, Croscarmellose sodium, Crosspovidone) at different concentrations and along with other excipients [3].The granules so obtained were used to obtain immediate release layer of drug in bilayer tablets. For preliminary studies to optimize the IR formulations, a weighed quantity of above lubricated drug mixture blend was fed manually into the die and directly compressed using 12 mm flat faced punch of 10 station Cadmach compression machine to get IR tablets [4]. Seven formulation batches were made in order to achieve desired disintegration time and drug release. Formulation compositions of different immediate release batches are given in the Table1

Table1: Composition formula for Pioglitazone immediate release layer (F1-F7)

S.NO	FORMULATION (mg)	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)
1	PIOGLITAZONE	7.5	7.5	7.5	7.5	7.5	7.5	7.5
2	SODIUM STARCH GLYCOLATE	--	5%	--	--	--	5%	--
3	CROSS CARMELLOSE SODIUM	5%	--	--	--	--	--	--
4	CROSS POVIDONE	--	--	5%	7.5%	10.5%	12.5%	12.5%
5	POLY VINYL PYRROLIDONE	5%	5%	5%	5%	5%	5%	5%
6	MG STEARATE	2%	2%	2%	2%	2%	2%	2%
7	DICALCIUM PHOSPHATE	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
	TOTAL WEIGHT	250	250	250	250	250	250	250

Formulation of Sustained Release Tablet

Glipizide and all other ingredients were individually passed through sieve 60.All the ingredients were mixed thoroughly by triturating up to 15min.The powder mixture was lubricated with Magnesium stearate [5]. The tablets were prepared by using direct compression method according to the formulation table 2. Then the blend was compressed using 12mm round punches.

Table2: Composition formula for Glipizide as sustained release layer (F1-F7)

S.NO NO	INGREDIENTS	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)
1	**GLIPIZIDE**	5	5	5	5	5	5	5
2	**HPMC K4M**	10%	-	-	-	10%	-	-
3	**GUAR GUM**	-	10%	5%	5%	10%	-	-
4	**XANTHUM GUM**	-	-	10%	-	-	-	10%
5	**ETHYLCELLULOSE**	-	-	-	10%	5%	5%	5%
6	**STARCH**	5%	5%	5%	5%	5%	5%	5%
7	**MG STEARATE**	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
8	**TALC**	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
9	**MICROCRYSTALLINE CELLULOSE**	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
	TOTAL TABLET WEIGHT	250	250	250	250	250	250	250

RESULTS AND DISCUSSION

Preformulation studies

Solubility

Pioglitazone: Soluble in water (<1 mg/ml), DMF, methanol, ethanol (4 mg/ml), and DMSO (79 mg/ml).

Glipizide: Soluble in water (partly), chloroform, DMF, DMSO (48 mg/ml), and methanol.

Melting point

Pioglitazone: 192-195° C
Glipizide: 200-203° C

Evaluation of pioglitazone (I.R) tablets

Pre-compression parameters of pioglitazone (I.R)

Tablet No -3 Pre Compression Parameters for Pioglitazone (I.R) Tablets

Formulations	Angle of Repose (θ)	Loose Bulk	Tapped Bulk	%Compressibility
		Density (g/ml)	Density (g/ml)	
F1	24.8	0.3	0.36	16.67
F2	28.5	0.29	0.34	14.71
F3	26.4	0.37	0.45	17.78
F4	27.3	0.34	0.43	20.93
F5	25.2	0.45	0.52	13.46
F6	27.5	0.42	0.48	12.50
F7	25.7	0.34	0.43	20.93

From the above pre-compression parameters it was clear evidence that granules has excellent flow properties. The bulk density and tapped density for all formulation (F1 – F7) varied from 0.29 - 0.37 gm/cm3 and 0.29 - 0.37 gm/cm3 respectively. The results of carr's consolidate index or % compressibility index and hausner's ratio for the entire formulation (F1 – F7) blend range from 12.50- 20.93 and 1.21-1.28 respectively, shows fair flow properties.

Post compression parameters

Tablet No -4Post Compression Parameters for Pioglitazone (I.R) Tablets

Formulation	Average weight (mg)	Hardness Kg/cm^2	Thickness (mm)	Friability (%)	Disintegration Time	Drug content (%)
F1	252	4.20	3.10	0.18	45 sec	95.8
F2	255	4.00	3.28	0.20	40 sec	98.6
F3	248	4.10	3.20	0.17	45 sec	96.8
F4	247	4.10	3.22	0.16	35 sec	96.8
F5	249	4.20	3.12	0.21	40 sec	98.0
F6	253	4.20	3.11	0.22	40 sec	99.9
F7	253	4.10	3.24	0.18	35 sec	98.4

The thickness of the tablets was found to be in the range of 3.10-3.28mm. Hardness was found to be in between 4.0-4.2 Kg/cm2.Friability below 1% was an indication of good mechanical resistance of tablets. All the formulations showed more than 95% of drug content indicating content uniformity in the prepared batches. It proved that all batches were found to be within the limits.

Invitro dissolution studies of pioglitazone (I.R) tablets

In-vitro Dissolution studies

Dissolution is carried out in USP apparatus type-2 apparatus at 50rpm in 900ml dissolution media (0.1 N HCl) for 60 minutes. At the end of 20 minutes almost total amount of the drug is released (i.e 100.8%), from the formulation F6.

Table 5: Comparative In vitro dissolution study of immediate release tablet of Pioglitazone (F1-F7)

Time in mins	F1 (% drug release)	F2 (% drug release)	F3 (% drug release)	F4 (% drug release)	F5 (% drug release)	F6 (% drug release)	F7 (% drug release)
5	6.4	7.2	17.1	20.1	26.8	20.6	30.2
10	14.1	12.4	30.2	31.8	50.4	45.4	49.2
15	24.8	28.1	50.9	50.6	85.7	70.1	71.8
30	38.9	33.4	63.8	76.5	100.6	86.4	99.7
45	50.6	40.6	71.5	93.2	-	93.8	-
60	93.8	96.7	90.1		-	100.8-	-

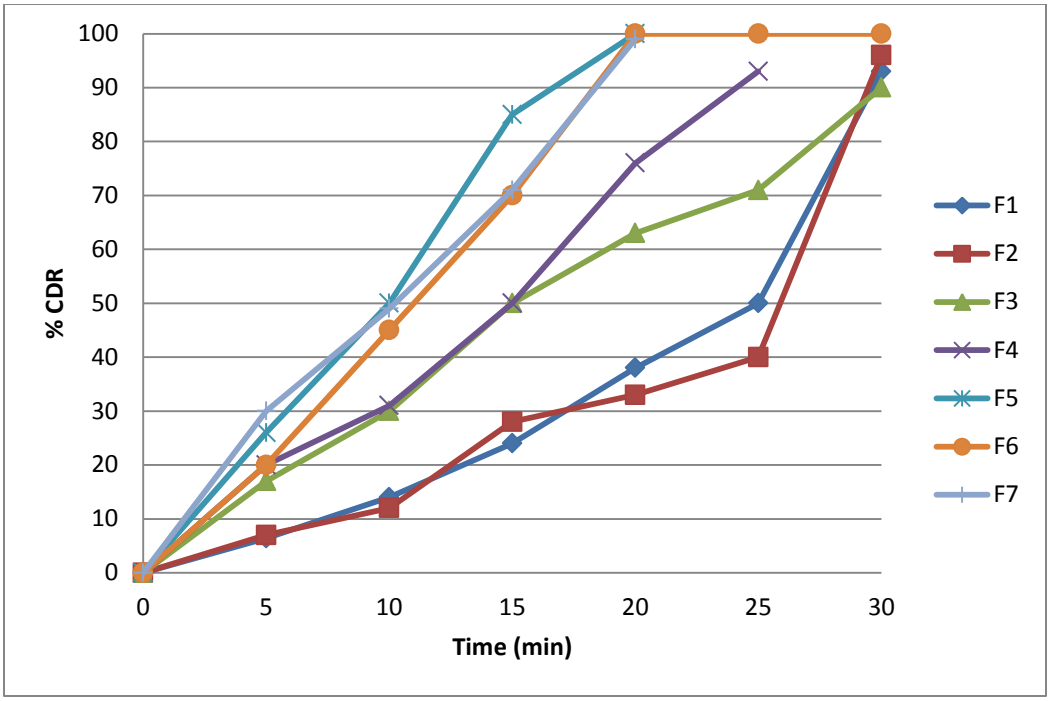

Figure 1: Dissolution Graph of immediate release tablet of Pioglitazone

Evaluation of glipizide (S.R) tablets

Pre-compression parameters of glipizide (S.R)

Table no.6 Pre-Compression Parameters of Glipizide (S.R)

Formulations	Angle of Repose (θ)	Loose Bulk Density (g/ml)	Tapped bulk density (g/ml)	%Compressibility
F1	25.34	0.31	0.37	16.22
F2	26.78	0.35	0.41	14.63
F3	26.43	0.33	0.39	15.38
F4	28.49	0.29	0.35	17.14
F5	29.31	0.36	0.43	16.28
F6	30.05	0.37	0.46	19.57
F7	26.43	0.30	0.37	18.92

From the above pre-compression parameters it was clear evidence that a granule has excellent flow properties. The bulk density and tapped density for all formulation (F1 – F7) varied from 0.29 - 0.37 gm/cm3 and 0.35 - 0.46 gm/cm3 respectively. The results of carr's consolidate index or % compressibility index and hausner's ratio for the entire formulation (F1 – F7) blend range from 14.63- 18.92 and 1.10-1.25 respectively, shows fair flow properties.

Post-compression parameters of glipizide (S.R)

Table no.7 Post-Compression Parameters of Glipizide (S.R)

Formulations	Weight variation	*Hardness*	Thickness (mm)	Friability (%)	Drug content
F1	251	4.8	3.41	0.12	99.0
F2	249	5.6	3.40	0.13	99.4
F3	254	5.9	3.41	0.09	98.6
F4	252	5.7	3.42	0.10	100.1
F5	249	5.5	3.43	0.12	99.4
F6	251	5.9	3.46	0.09	99.5
F7	251	5.8	3.41	0.10	98.1

The thickness of the tablets was found to be in the range of 3.40-3.46mm. Hardness was found to be in between 4.8-5.9 Kg/cm.Friability below 1% was an indication of good mechanical resistance of tablets. All the formulations showed more than 95% of drug content indicating content uniformity in the prepared batches. It proved that all batches were found to be within the limits

Invitro dissolution studies of glipizide (S.R) tablets

In-vitro Dissolution studies

Dissolution is carried out in USP apparatus type-2 apparatus at 50rpm in 900ml dissolution media [6] (pH 6.8phosphate buffer) for 12 hrs. At the end of 12 hrs almost total amount of the drug is released (i.e 100.1%), from the formulation F4.

Table 7: Comparative In vitro dissolution study of sustained release tablet of Glipizide (F1-F7)

Time(hrs)	F1 (% drug release)	F2 (% drug release)	F3 (% drug release)	F4 (% drug release)	F5 (% drug release)	F6 (% drug release)	F7 (% drug release)
0.5	13.2	17.8	15.8	18.9	20.1	10.1	12.4
1	21.4	26.4	27.3	24.8	29.1	18.2	20.1
2	38.6	40.8	41.9	38.3	40.2	30.6	28.7
3	51.7	60.2	54.2	50.1	53.8	41.8	42.9
4	78.8	79.1	70.4	68.7	66.2	50.2	53.4
6	99.8	98.6	82.8	73.2	85.8	64.9	70.1
8	-	-	99.5	86.4	99.8	76.3	83.1
10	-	-	-	96.5	-	88.5	99.8
12	-	-	-	100.1	-	99.6	-

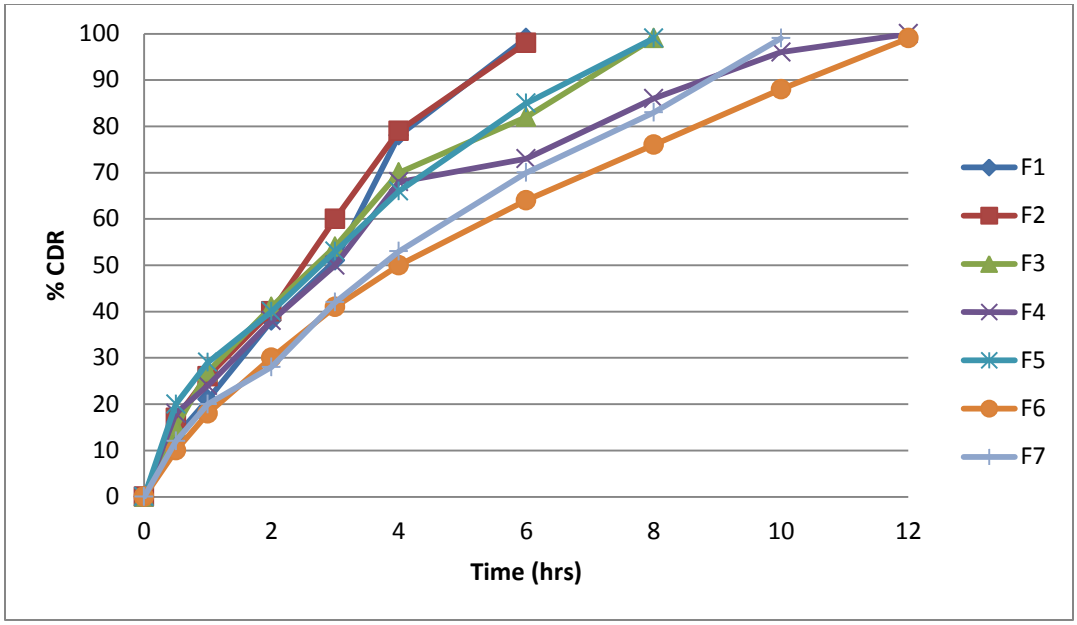

Figure 2: Dissolution Graph of sustained release tablet of Glipizide

RELEASE KINETICS

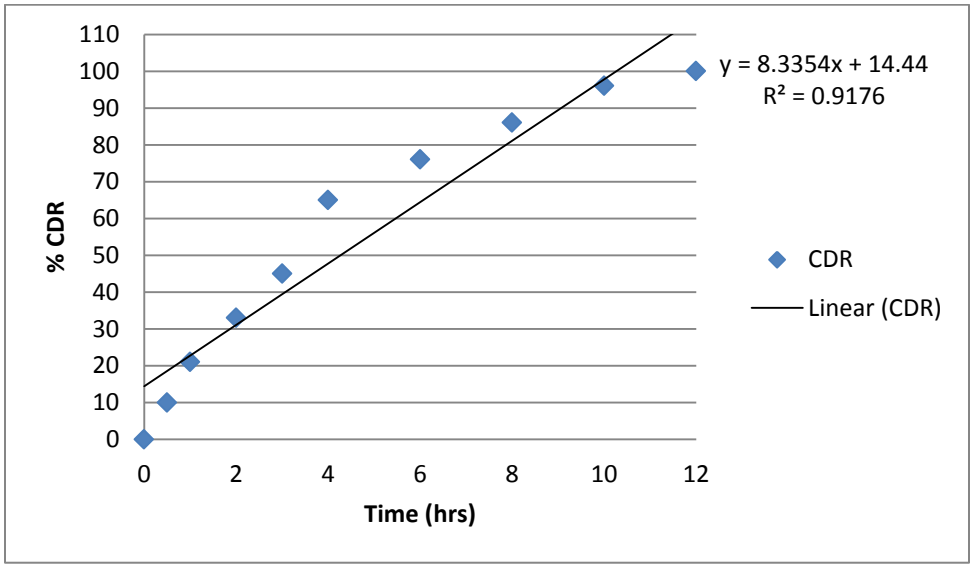

Figure 3: Zero order plot for the F4 optimized formulation

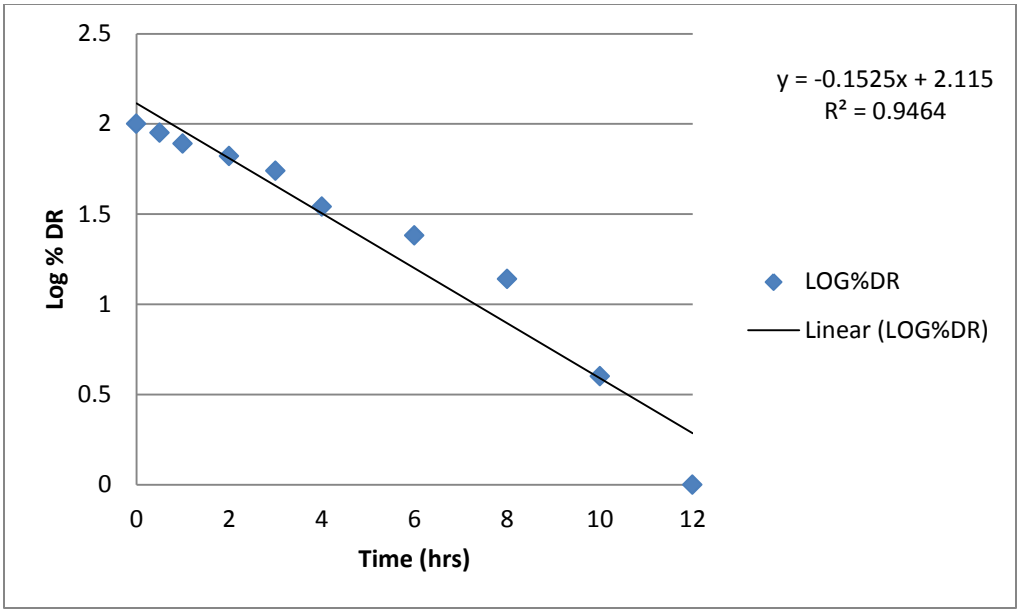

Figure 4: First order plot for the F4 optimized formulation

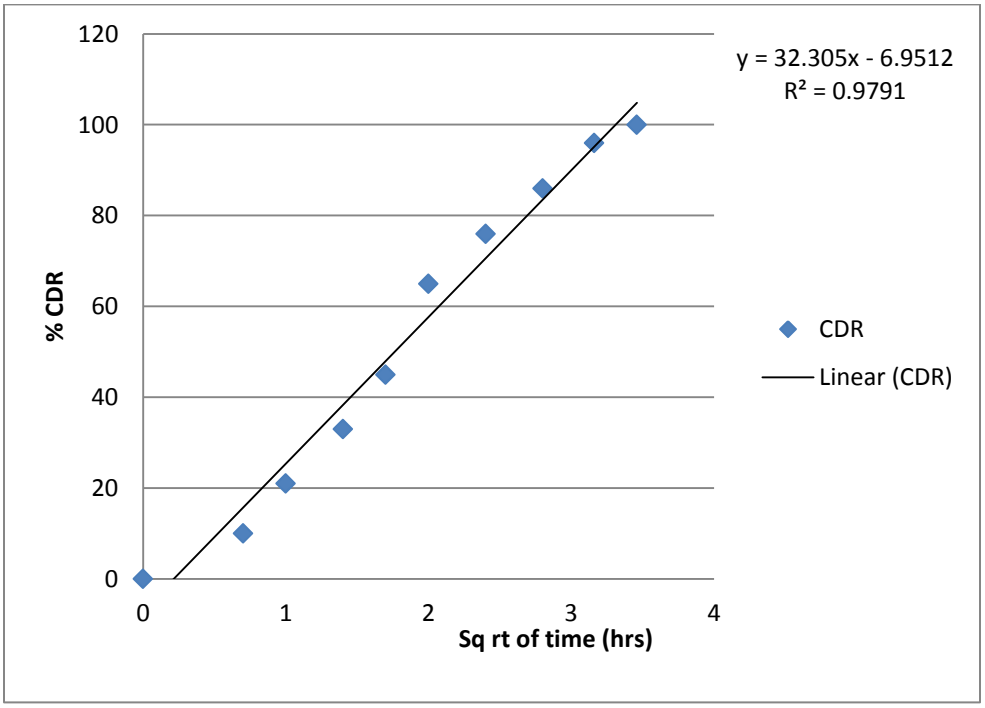

Figure 5: Higuchi plot for the F4 optimized formulation

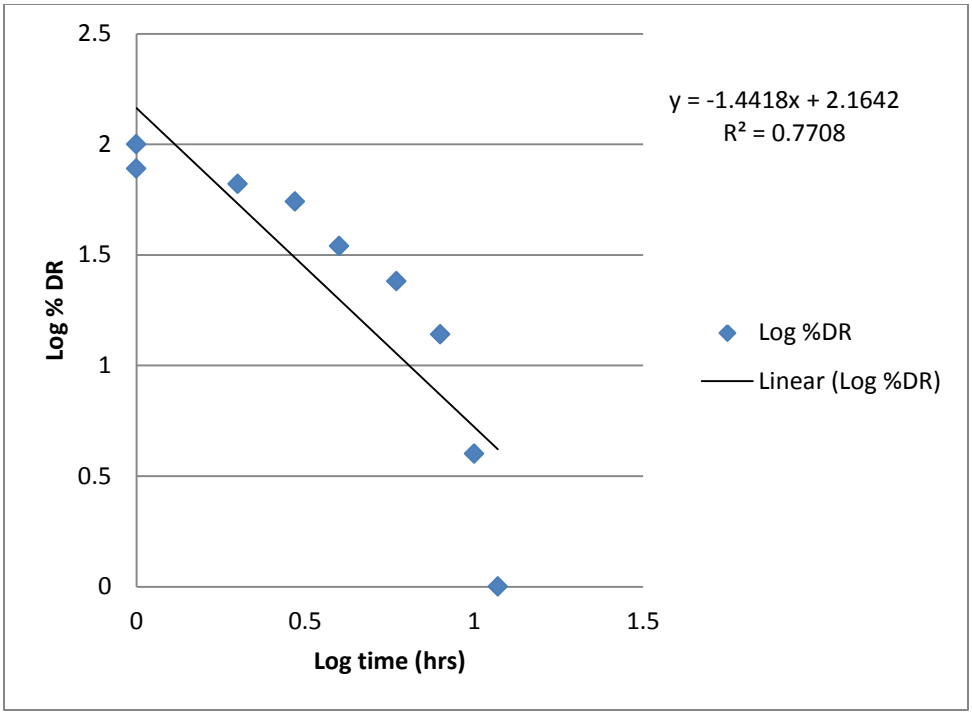

Figure 6: Korsmeyer-Peppas plot for the F4 optimized formulation

KINETIC RELEASE MODELS

Release kinetics for F4 formulation for sustained release layer

Table no.8 Release kinetics for F4 formulation for sustained release layer

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	8.335	0.152	32.30	1.441
R 2	0.917	0.946	0.979	0.770

Discussion for in-vitro release of Glipizide

From the table, it was confirmed that the F1, F2, F5, F6, of SR layer does not fulfill the sustained release theory. And also from the table, it was also confirmed that the formulation made with Guar gum (F2,F3&F5) F4 showed highest percent of drug release compared to the formulations made with GUAR GUM (F2 to F5).

Bilayered tablet punch

After the batch was optimized in both Pioglitazone as immediate release layer (F6) and Glipizide as Sustained release layer (F4).The optimized batch in both was compressed by using same ingredients.

Dissolution study (bilayered tablets)

Dissolution profile of bilayered tablet of combination Pioglitazone (I.R) & Glipizide (S.R)

Table no.9 Dissolution study of Bilayered Tablets

S.No	Sampling time	Percentage drug released (%)	
		Pioglitazone	Glipizide
1	15mins	80.8	3.8
2	30 mins	99.5	8.0
5	1hr	--	29.6
6	2hr	--	33.9
7	3hr	--	42.7
8	4hr	--	55.8
9	5hr	--	65.8
10	6hr	--	77.0
11	8hr	--	89.8
12	12hr	--	98.9

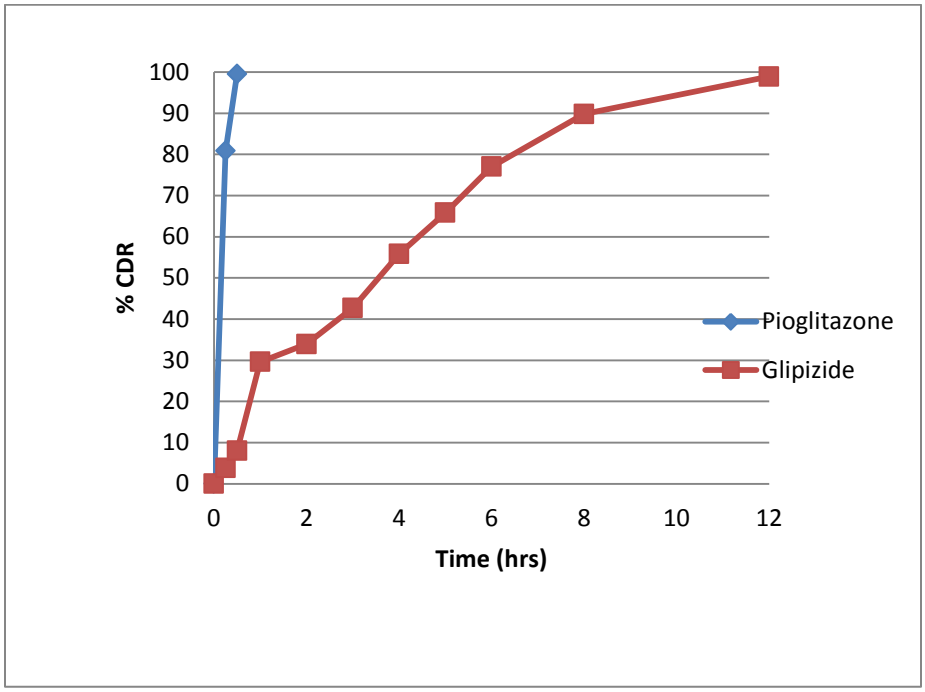

Figure 7: Dissolution graph of Pioglitazone and Glipizide

Stability data of optimized bilayered formulation

Table no.10 Stability Data of Optimized Bilayered Formulation

S.No	Time points (hrs)	Initial	Cumulative % Drug Release (mean SD) (n=3)	
			25C/60%RH	40C/75%RH

			1st Month	3rd Month	1stMonth	3rdMonth
1	**15mins**	**80.8**	79.184	78.376	77.568	76.356
2	**30 mins**	**99.5**	97.51	96.515	95.52	94.0275
3	**1hr**	**29.6**	29.008	28.712	28.416	27.972
4	**2hr**	**33.9**	33.222	32.883	32.544	32.0355
5	**3hr**	**42.7**	41.846	41.419	40.992	40.3515
6	**4hr**	**55.8**	54.684	54.126	53.568	52.731
7	**5hr**	**65.8**	64.484	63.826	63.168	62.181
8	**6hr**	**77.0**	75.46	74.69	73.92	72.765
9	**8hr**	**89.8**	88.004	87.106	86.208	84.861
10	**12hr**	**98.9**	96.922	95.933	94.944	93.4605
11	**Assay**	**99.9**	98.5	98.4	99.6	99.4

DISCUSSION

The release profile of formulations F_1, F_2, F_3, F_4 F_5,F_6 and F_7 comprising various polymers like crospovidone ,croscarmellose and sodium starch glycolate with equal concentrations. Formulations F_1, F_2, F_3 ,F_4 F_5,F_6 and F_7 exhibits release rates of 20.6%,45%,470.1%,86.4%,93.8%,100.8%various time intervals as shown in the table. Among all of these 7 formulations F_6 contains **Crosspovidone** shows maximum drug release at the end of 30 mins. Hence it was optimized and decided to develop further formulations.

CONCLUSION

- The Bilayered tablets containing Glipizide SR and Pioglitazone IR were successfully prepared by direct compression method.
- Various formulations were prepared and evaluated with an aim of presenting Glipizide as sustained release and Pioglitazone as immediate release for improving the patient's compliance.
- The physiochemical evaluation results for the granules of all trials pass the official limits in angle of repose, compressibility index.
- The prepared blend for IR layer tablets and SR layer tablets were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability.
- The optimized formulation F6 in IR formulations contains the average thickness of 3.11mm, average hardness of 4.20 kg/cm^2, average weight of 253mg, friability of 0.22%.
- The optimized formulation F4 in SR formulations contains the average thickness of 3.42mm, average hardness of 5.7kg/cm^2, friability of 0.10%.
- The F4 formulation which releases the Glipizide in sustained manner in 1st hour it releases 24.8% but the remaining drug release was sustained up to 12 hours and Pioglitazone immediate release F6 formulation showed 100.8% drug release with in 30 min.
- With the data of kinetic analysis, F4 formulation showed best linearity in First order plot indicating that the release of drug is dependent upon concentration and the mechanism from matrix tablet follows Non Fickian diffusion.
- The dissolution study was carried out for optimized bilayer tablet and it correlates with the drug release of individual release layer formulations.
- Stability studies conducted as per ICH guidelines for optimized bilayered formulation at 25^{O} C/60%RH and 40 ^{o}C/75% RH for 90 days. There was no significant change in the physical property and percent of drug release was within the limits during the stability period.

REFERENCES

[1]. C. Gopinath, V. Hima Bindu*,M. Nischala, "An Overview On Bilayered Tablet Technology" . Journal of Global Trends in Pharmaceutical Sciences. 4(2), 2013, 1077-1085.

[2]. Melissa Archer, Gary Oderda,Kelsey Rihards, Scott Turpin, "Sulfonylurea Agents & Combination Products Drug Class Review", International Journal Of Pharmaceutical And Chemical Sciences. 2013.

[3]. Ananda B,Michael D,Jensen, Frances M,Debabrata M,Joyer, Rizza RA, "Effects of pioglitazone versus glipizide on body fat distribution, body water content, and hemodynamics in type 2 diabetes", International Journal of Pharmacy and Pharmaceutical Sciences. 29(3), 2006, 510

[4]. Nirav Patel, Jinal Patel, Moin Modasiya . "Formulation and In Vitro Evaluation of Glipizide as Floating Drug Delivery System, Journal of drug release and therapeutics", International Journal of Pharmaceutical Sciences. 2(2), 2012, 67-73.

[5]. Singh Amit Kumar, Arora Vandana, "Formulation and In Vitro Evaluation of Glipizide as Floating Drug Delivery System with natural polymer", International Journal of Pharmacol. 2012, 24-28.

[6]. Patil Narayan Venkatrao, Dr. S. AppalaRaju, "Formulation & Evaluation of Gastro-retentive Drug Delivery System of Glipizide", Journal of pharmacy research. 3(3), 2015, 1-10.

[7]. Jayvadan K. Patel, Rakesh P. Patel, Avani F Amin & Madhabhai M. Patel, "Formulation and evaluation of mucoadhesive glipizide microspheres", International Journal of Pharmaceutical Education and Research .6(1), 2005, E49–E55.

[8]. Patel, Dhaval Patel , Ramesh Parmar , Chirag Patel ,Tejas Serasiya, S.D. Sanja, "Development And Invitro Evaluation Of Fast Dissolving Tablets of Glipizide". 1(1), 2009.

[9]. Dinesh R. Rathod, Manjusha N. Dole, Sanjay D. Sawant, "Spectrophotometric Determination Of Glipizide In Bulk And Tablet Dosage Form By Absorption Maxima, First Order Derivative Spectroscopy And Area Under The Curve".5(3), 2012.

[10]. Eni Williams, Omudhome Ogbru, Jay W Marks, glipizide, Glipizide XL, Glucotrol, Glucotrol XL, International Journal Of Pharmaceutical And Chemical Sciences. 15, 2016

[11]. M. Rangapriya, V. Manigandan, R. Natarajan & K. Mohankumar,"Formulation and Evaluation of Floating Tablets of Pioglitazone Hydrochloride", International Journal Of Pharmaceutical And Chemical Sciences. 1(3), 2012.