ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 6, Suppl 3, 2013

ISSN - 0974-2441

Research Article

FORMULATION AND EVALUATION OF BILAYERMATRIX TABLET OF PIOGLITAZONE HCL METFORMIN HCL USP 15MG&500MG

KOTTA KRANTHI KUMAR*[1], M. NARASIMHA REDDY[2], R.NAGA KISHORE[3]

Department of Pharmaceutics, S.K.U College of Pharmaceutical sciences S.K.University[*1, 2] Anantapur, Sri Lakshmivenkateseara pharmacy college[3] produttur. E-mail: kranthikumarkotta@gmail.com

Received: 29 May 2013, Revised and Accepted: 26 June 2013

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 poly ethylene oxide (PEO-303) 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 Polyethylene oxide (PEO- 303) 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, Matrix tablets, PEO-303.

INTRODUCTION [1-4]

Bilayered Tablets[1]

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.

Drug release from Bilayered tablet

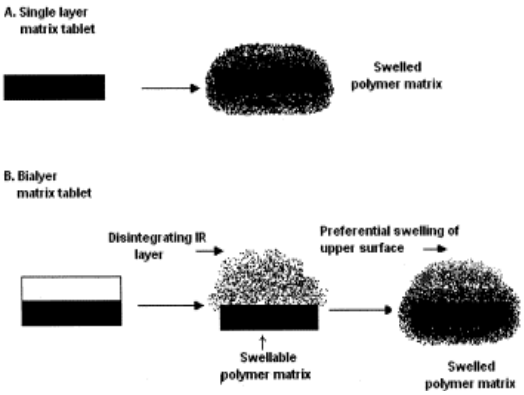


Fig. No: 1

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 [5]

Materials Used

Table No: 1

S.No	Ingredients	Supplier
1	Pioglitazone HCl	Darwin Pvt ltd. Vijayawada.
2	Metformin HCl	Darwin pvt ltd. Vijayawada.
3	Polyethylene oxide (PEO303)	Colorcon Asia pvt. Ltd
4	Carbopol 971P	HiMedia Pharmaceuticals Pvt Ltd Mumbai
5	Microcrystalline Cellulose	SD Fine chemicals Mumbai
6	Spray Dried Lactose	SD Fine chemicals Mumbai
7	Crospovidone	SD Fine chemicals Mumbai
8	Aerosil	SD Fine chemicals Mumbai
9	Magnesium Stearate	SD Fine chemicals Mumbai
10	Talc	SD Fine chemicals Mumbai

Instruments Used

Table No: 2

S. NO	Name of the Instrument	Instrument Model And Manufacturer
1	Digital balance	Essae –teraoku Ltd
2	Tablet dissolution test apparatus,USP	Labindia, Disso 2000
3	UV-Visible Spectrophotometer	Elico Ltd., SL 150, Hyderabad
4	Compression machine	Cadmach Machinery , Kolkata
5	Roche Friabilator	Campbell Electronics
6	Monsanto Hardness Tester	Shreeji Chemicals , Mumbai
7	Disintegration apparatus	Thermonic Campbell electronics, Mumbai
8	pH meter	Elico Li 120

EXERIMENTAL SESSION[6-15]

PREFORMULATION STUDIES

DRUG EXCIPIENT COMPATABILITY STUDIES:

The drug-polymer and polymer-polymer interactions were studied by FTIR spectrometer. The characteristic peaks were recorded.

Compatibility studies of Pioglitazone Hcl with different excipients for one month.

Table No: 3

Ingredients	Ratio	Initial Colour	After one week 40 °C/ 75%RH	After two Weeks 40 °C / 75%RH	After three weeks 40 °C / 75%RH	After four weeks 40 °C / 75%RH
Pioglitazone hcl + Crospovidone	1:1	Cream or white	Cream or white	Cream or white	Cream or white	Cream or white
Pioglitazone hcl+lactose	1:1	White powder	White Powder	White powder	White powder	White Powder
Pioglitazone hcl+MCC	1:1	White powder	White powder	White Powder	White powder	White powder
Pioglitazone hcl+Aerosil	1:1	White powder	White powder	White Powder	White powder	White powder
Pioglitazone hcl +Magnesiumstearate	1:1	White powder	White powder	White powder	White powder	White powder
Pioglitazone hcl+Sunset yellow	1:1	White powder	White powder	White powder	White powder	White powder

Compatibility studies of Metformin hcl with different excipients for one month.

Table No: 4

Ingredients	Ratio	Initial Colour	After one week 40 oC/ 75%RH	After two Weeks 40 oC/ 75%RH	After three weeks 40 oC/ 75%RH	After four weeks 40 oC/ 75%RH
Metformin Hcl+PEO-303	1:1	Cream or white	Cream or white	Cream or white	Cream or white	Cream or white
Metformin Hcl +Carbopol 971P	1:1	White powder	White Powder	White powder	White powder	White Powder
Metformin Hcl+Crospovidone	1:1	White powder	White powder	White Powder	White powder	White powder
Metformin Hcl +MCC	1:1	White powder	White powder	White Powder	White powder	White powder
Metformin Hcl + Magnesium stearate	1:1	White powder	White powder	White powder	White powder	White powder
Metformin Hcl +Talc	1:1	White powder	White powder	White powder	White powder	White Powder

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.

Formulation of Immediate Release layer

Immediate release layer of Pioglitazone HCl was prepared by dry granulation technique. Pioglitazone, cross Povidone and Micro crystalline cellulose (MCC) were passed through sieve no # 40. The Sunset yellow lake was passed through sieve no #200. All the above were mixed in geometric proportion in a poly bag for 15 minutes. Aerosil 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 6.5.1. The final weight of the IR layer was fixed to 150 mg.

Composition for IR layer of Bilayered tablets

Table No.5

S.No	Ingredients (mg/tab)	Formulations				
		IR1	IR2	IR3	IR4	IR5
1	Pioglitazone HCl	15	15	15	15	15
2	Cross Povidone	2.5	5	7.5	-	-
3	Croscarmellose sodium	-	-	-	2.5	5
4	Lactose	74.5	72	69.5	74.5	72
5	MCC	50	50	50	50	50
6	Aerosil	3	3	3	3	3
7	Mg stearate	3	3	3	3	3
3	Sunset yellow	2	2	2	2	2
	Total Weight (mg)	**150**	**150**	**150**	**150**	**150**

Formulation of Sustained Release layer[16-19]

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 9. The final weight of the SR layer was fixed to 800 mg. Composition for SR layer of Bilayered Tablets prepared by direct compression technique.

Table No: 6

S.No	Ingredients	Formulations					
	(mg/tab)	F1	F2	F3	F4	F5	F6
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 (mg)		800	800	800	800	800	800

2. Wet Granulation Technique

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 50oC. 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

Composition for SR layer of Bilayered tablets prepared by wet granulation technique

Table No: 7

S.No	Ingredients	Formulations				
	(mg/tab)	F6	F7	F8	F9	F10
1	Metformin HCl	500	500	500	500	500
2	Carbopol 971P	50	75	100	150	200
3	MCC	246	221	196	146	96
4	Mg stearate	2	2	2	2	2
5	Talc	2	2	2	2	2
Total Weight (mg)		800	800	800	800	800

3 Compressions of Bilayer Tablets

The extended release blend of Metformin HCl (800 mg) was compressed lightly using single punch tablet machine (Cad mach machinery Co Pvt.Ltd, India) equipped with 12mm circular, flat and plain punches. Over this compressed layer, the immediate release layer of Pioglitazone HCl (150mg) was placed and compressed to obtain hardness in the range of 6-7kg/cm2 to form a bilayered matrix tablet.

EVALAUTION OF BILAYER TABLETS[20-26]

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

Table No: 8

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

These results were reported in table no.11.

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 4-6kg/sq.cm.

These results were reported in table no.11.

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;

$$\%F = (1 - W/W0) \times 100$$

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%.
All the results were reported in table no.11.

Estimation of Drug Content

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 Studies**

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-1213,14.

RESULTS

Compatibility studies of Pioglitazone Hcl with different excipients for one month.

Table no: 9

Ingredients	Ratio	Initial Colour	After one week 40 °C/ 75%RH	After two Weeks 40 °C / 75%RH	After three weeks 40 °C / 75%RH	After four weeks 40 °C / 75%RH
Pioglitazone hcl + Crospovidone	1:1	Cream or white	NCC	NCC	NCC	NCC
Pioglitazone hcl +lactose	1:1	White powder	NCC	NCC	NCC	NCC
Pioglitazone hcl +MCC	1:1	White powder	NCC	NCC	NCC	NCC
Pioglitazone hcl +Aerosil	1:1	White powder	NCC	NCC	NCC	NCC
Pioglitazone hcl + Magnesiumstearate	1:1	White powder	NCC	NCC	NCC	NCC
Pioglitazone hcl +Sunset yellow	1:1	White powder	NCC	NCC	NCC	NCC

Compatibility studies of Metformin hcl with different excipients for one month.

Table no: 10

Ingredients	Ratio	Initial Colour	After one week 40 oC/ 75%RH	After two Weeks 40 oC/ 75%RH	After three weeks 40 oC/ 75%RH	After four weeks 40 oC/ 75%RH
Metformin Hcl+ PEO-303	1:1	Cream or white	NCC	NCC	NCC	NCC
Metformin Hcl +Carbopol 971P	1:1	White powder	NCC	NCC	NCC	NCC
Metformin Hcl +Crospovidone	1:1	White powder	NCC	NCC	NCC	NCC
Metformin Hcl + MCC	1:1	White powder	NCC	NCC	NCC	NCC
Metformin Hcl + Magnesium stearate	1:1	White powder	NCC	NCC	NCC	NCC
Metformin Hcl +Talc	1:1	White powder	NCC	NCC	NCC	NCC

NCC-No colour change

The overall observation of infrared study suggested that formulation development of drugs in combination with excipients, functionalities of drugs was unreacted and hence contribution of drugs along with excipients can be formulated safely.

POST COMPRESSIONAL PARAMETERS

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

Table No:11

Formula-tion code	Average Weight (±SD)	Thickness (mm)	Hardness kg/cm2	Friability (%)	Drug Content (%)	
					Pioglitazone HCl	Metformin HCl
IR1	151.7±0.87	1.33±0.34	3.5±0.35	0.12±0.02	98.50±1.05	-
IR2	149.5±1.05	1.38±0.12	3.4±0.25	0.27±0.01	99.03±0.89	-
IR3	150.2±0.45	1.35±0.34	3.4±0.74	0.14±0.03	98.50±1.05	-
IR4	151.2±0.78	1.32±0.51	3.6±0.32	0.23±0.06	99.20±0.71	-
IR5	149.8±0.55	1.35±0.24	3.4±0.54	0.14±0.09	98.50±0.85	-
F1	950.4±0.55	8.47±0.01	7.30±0.04	0.23±0.05	98.75±0.73	99.40S±0.77
F2	948.6±1.34	8.48±0.03	7.34±0.42	0.21±0.06	98.26±1.08	98.89±1.73
F3	947.6±0.89	8.52±0.03	7.21±0.23	0.2±0.05	98.50±1.05	100.20±0.45
F4	948.8±0.84	8.52±0.02	7.11±0.17	0.17±0.04	97.09±0.73	99.39±0.73
F5	950.4±0.52	8.51±0.02	7.17±0.30	0.19±0.03	99.03±0.89	99.62±0.86
F6	949.6±0.48	8.50±0.03S	7.28±0.24	0.20±0.08	99.24±0.56	99.64±0.52

Post compression parameters of Pioglitazone HCl and Metformin HCl by Wet Granulation technique

Table No: 12

Formula-tion code	Average Weight (±SD)	Thickness (mm)	Hardness kg/cm2	Friability (%)	Drug Content (%)	
					Pioglitazone HCl	Metformin HCl
F7	950.4±0.35	8.14±0.05	7.28±0.11	0.22±0.04	99.75±0.43	99.10±0.37
F8	949.6±0.98	8.09±0.02	7.30±0.41	0.21±0.02	99.26±1.18	99.37±1.03
F9	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
F11	950.6±0.41	8.10±0.05	7.14±0.20	0.17±0.04	98.03±0.59	98.72±0.46

Cumulative percent drug Release

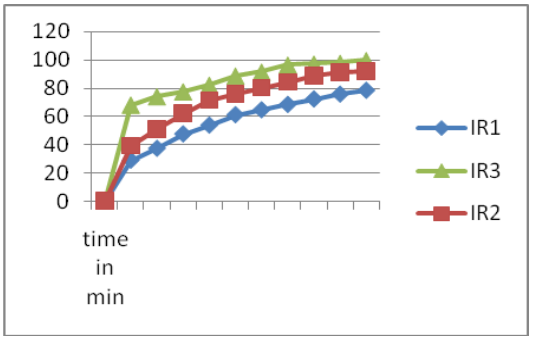
Cumulative percent drug release data for IR layer formulations

Table No:13

Time In minutes	Cumulative % drug release				
	IR1	IR2	IR3	IR4	IR5
0	0	0	0	0	0
1	29.06	39.38	68.13	25.06	36.38
2	37.50	51.15	74.06	34.50	48.15
3	47.71	62.19	77.50	46.71	60.19
4	53.96	71.77	82.19	51.96	69.77
5	61.35	76.25	88.75	60.35	74.25
6	64.79	80.63	91.56	63.79	79.63
7	68.65	84.48	96.56	65.65	82.48
8	72.50	89.06	97.19	70.50	86.06
9	75.94	91.56	97.81	73.94	89.56
10	78.65	92.40	99.69	76.65	91.40

Cumulative percent drug release Profiles for IR layer formulations

Fig No: 2



Based on the results, the cumulative % drug released for IR1, IR2, IR3, IR4andIR5 formulations were found to be 78.65, 92.40, 99.69, 76.65 and 91.40respectively. The results depict that, the maximum amount of drug was released from the formulation IR3 when compared to other formulations IR1, IR2, IR4 and IR5. This is due to the more concentration of superdisintegrants in the formulation. Hence, formulation IR3 was confirmed as an optimized immediate release layer.

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

Table No:14

Time In minutes	Cumulative % drug release		
	F5	F6	Innovator
0	0	0	0
1	32.64	20.76	33.64
2	46.26	31.64	46.16
3	61.25	39.05	60.95
4	67.38	47.5	66.98
6	76.31	54.17	75.91
8	84.3	60.31	84.32
10	91.3	69.47	91.37
12	99.06	79.62	99.46

COMPARETIVE DRUG RELEASE PROFILE OF TRIAL BATCHES

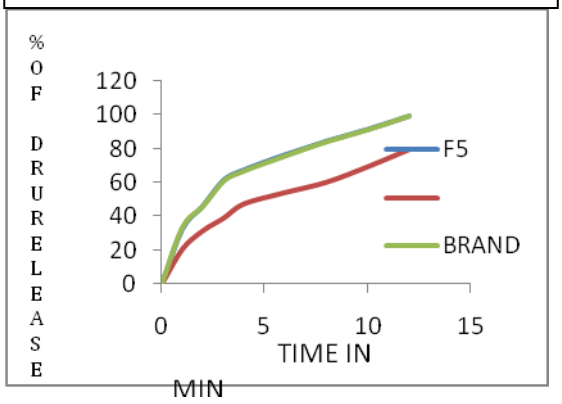


Fig No: 3

Comparison of Percent Drug Release profiles for F5 and Marketed formulation

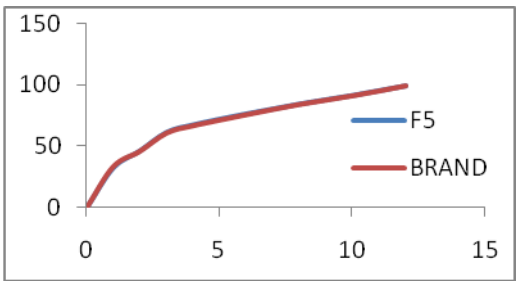


Fig No: 4

All the formulations (F1 to F4) showed the sudden release of Metformin HCl in the initial hours, which is due to faster dissolution of the highly water soluble drug from the superficial layers of matrix and its diffusion out of the matrix which leads to the entry of dissolution media through the pores. F5 showed sustained drug release up to 12 hours which is nearly identical to the release profile of marketed formulation. F6 showed a release over 12 hours, due to increase in the concentration of PEO-303 in the formulation, resulted in a decreased drug release rate. A sufficient polymer concentration in the hydrophilic matrix system is required to form a uniform gel barrier around the tablet upon hydration. This barrier is expected to prevent the drug from immediate release into the dissolution medium. If the polymer concentration is low, a complete gel layer may not form resulting in a significant amount of drug being released too quickly in the worst case, tablet disintegration. F1 to F4 failed to sustain the drug release due to in sufficient polymer concentration in the matrix system. It can be seen that polymer concentration of less than 30% are insufficient to produce adequate extended release of Metformin HCl. Similar results were reported by Dow for HPMC ER matrices. The *in vitro* dissolution study also shows that an increased PEO level in the formulation resulted in a decreased drug release rate (F9).

A further increase in PEO concentration from 30% to 60% resulted in a slower drug release profile. This effect of slower Metformin HCl release for higher polymer level is due to the longer period of time required to reach the polymer chain disentanglement concentration at the tablet surface, which in turn equates to greater resistance of the matrix to surface erosion.To ascertain the mechanism of drug release, *in-vitro* release data were fitted into various release kinetic models such as First order, zero order, Higuchi, and Peppas. The first order plots obtained were linear when compared with the zero order plots. Hence the order of release for formulations followed first order kinetics. From the above results F8 formulation was best among other formulations and the release was governed by Fickian diffusion.

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

Table No: 15

Time In minutes	Cumulative % drug release		
	F10	F11	Innovator
0	0	0	0
1	36.6	32.88	36.3
2	50.1	44.1	50.5
3	67.53	61.29	66.53
4	70.14	64.38	71.14
6	79.26	68.45	78.26
8	82.68	70.73	83.68
10	92.78	73.42	91.78
12	99.21	74.72	98.91

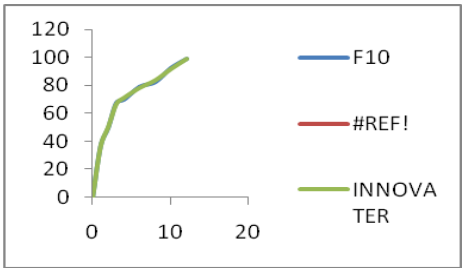


Fig N0: 5

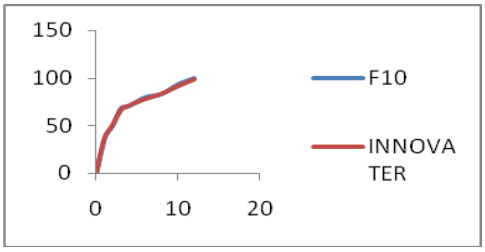


Fig no: 6

Comparison of Percent Drug Release profiles for F10 and Marketed formulation

The Cumulative % drug release for F7, F8, F9, F10 and F11 was 82.68±1.40, 83.04±0.93, 89.51±0.54, 99.21±0.05 and 74.72±1.00. All the formulations (F7 to F9) showed the sudden release of Metformin HCl in the initial hours, which is due to faster dissolution of the highly water soluble drug from the superficial layers of matrix and its diffusion out of the matrix which leads to the entry of dissolution media through the pores. F10 showed sustained drug release up to 12 hours which is nearly identical to the release profile of marketed formulation. F11 showed a release over 12 hours, due to increase in the concentration of Carbopol 971P in the formulation, resulted in a decreased drug release rate.

A sufficient polymer concentration in the hydrophilic matrix system is required to form a uniform gel barrier around the tablet upon hydration. This barrier is expected to prevent the drug from immediate release into the dissolution medium. If the polymer concentration is low, a complete gel layer may not form resulting in a significant amount of drug being released too quickly in the worst case, tablet disintegration. F7 to F9 failed to sustain the drug release due to insufficient polymer concentration in the matrix system. It can be seen that polymer concentration of less than 18% are insufficient to produce adequate extended release of Metformin HCl.

The *in vitro* dissolution study also shows that an increased Carbopol level in the formulation resulted in a decreased drug release rate (F11). A further increase in Carbopol concentration above 18% resulted in a slower drug release profile. This effect of slower Metformin HCl release for higher polymer level is due to the longer period of time required to reach the polymer chain disentanglement concentration at the tablet surface, which in turn equates to greater resistance of the matrix to surface erosion.

To ascertain the mechanism of drug release, *in-vitro* release data were fitted into various kinetic models such as First order, zero order, Higuchi, and Peppas. The first order plots obtained were linear when compared with the zero order plots. Hence the order of release for formulations followed first order kinetics. From the above results F10 formulation was best among other formulations and the release was governed by Fickian diffusion.

The similarity factor (f2) was also calculated in order to compare optimized formulation (F5 and F10) with that of the reference formulations. Compression of the profiles indicated that the formulations (F5and F10) had a profile similar to the reference formulation (f2 = 51.41and 51.21) respectively. So these two formulations were comparable with the marketed formulation.

SUMMARY AND CONCLUSION

In the present investigation, Sustained release Bilayered tablets of Pioglitazone HCl and Metformin HCl were formulated by Direct Compression technique and Wet Granulation technique. Bilayered tablets comprise of IR for sudden onset of action formulated with Crospovidone and SR layer formulated with Polyethylene oxide (PEO-303) and Carbopol 971 P inorder to sustain the drug release. Drug-excepient compatibility were studied by FT-IR spectral analysis, the results revealed that there were no interactions between drug and excepients in this investigation for the development of the Bilayered tablet formulation. The Precompressional parameters for IR, SR layer formulations ie; Angle of repose, Bulk density, Tapped density, Compressibility index, Hausner's ratio were studied and found to be in satisfactory limits indicating that the Physical mixtures of the formulations are suitable to formulate the Bilayered tablets. Postcompressional parameters for Bilayered tablets ie; Weight variation, Hardness, Friability, Drug content, were evaluated and the results obtained were satisfactory.

The *in-vitro* drug dissolution studies were carried out for the formulations in pH 1.2 and pH 6.8 phosphate buffer for 2hrs and 10hrs respectively and based on the *in-vitro* drug release profile IR layer formulation (IR3) was optimized for the further development of Bilayered tablets. The formulation F5 comprising of PEO-303 and the formulation F10 comprising of CARBOPOL 971P sustained the drug release for a period of 12 hrs. Dissolution profile of formulations F5 and F10 were compared with the dissolution profile of marketed formulation and Similarity factor for the formulations F5 and F10 was found to be 51.41 and 51.21 respectively.

The similarity factor (f2) was also calculated in order to compare optimized formulation (F5 and F110) with that of the reference formulations. Compression of the profiles indicated that the formulations (F5and F10) had a profile similar to the reference formulation (f2 = 51.41and 51.21) respectively. So these two formulations were comparable with the marketed formulation.

The conclusions drawn from the results include

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 order of cumulative % drug release from IR layer formulations was found to be IR3>IR2>IR5>IR1>IR4.

The IR layer formulation ie; IR3 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 F5 and F10 was found to be near to that of the theoretical desired drug release rate.

The desired drug release rate obtained for F5 and F10 was found to be near to that of the drug release rate of Marketed formulation.

The formulations F5 and F10 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.

Based on the above studies the sustained release bilayer matrix tablets of Pioglitazone HCl and Metformin HCl with polymers such as PEO-303 and CARBOPOL 971P 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.

REFERENCE

1. Lechman, L., Liberman, H.A., Kanig, J.L.,In., The Theory and Practice of Pharmacy, 3rd Ed., Varghese Publishing House,Bombay, 1987, p 430-453.
2. Notari, R., Biopharmaceutics and Clinical Pharmacokinetics, An Introduction, 3rd Ed., Marcel Dekker Inc. New York, 1980, p152-54.
3. Dr P.K. Sahoo.Pharmaceutical technology,Delhi Institute of Pharmaceutical Sciences and research. New Delhi:Page no 1-3.
4. Remington,"The Science and Practicen of pharmacy", 20th Edition, Volume I, Pg.No.903-913.
5. Raymand C Rowe, Paul J Sheskey, Paul J Weller, "Handbook of Pharmaceutical Excipients", 4th edition, publish by Pharmaceutical Press, 297-300.
6. Brahmankar D.M. and Jaiswa S.B.in"Biopharmaceutics and Pharmacokinetics", "A Treatise," Vallabh Prakashan, 1st Edition, 1995, Pg.No.347- 3
7. Raymand C Rowe, Paul J Sheskey, Paul J Weller, "Handbook of Pharmaceutical Excipients", 4th edition, publish by Pharmaceutical Press, 297-300.
8. Mr. ashish a pahade, dr. mrs. v.m.jadhav and dr. mr. v.j.kadam, "Formulation and development of a bilayer sustained released tablets of isosorbide mononitrate" international journal of pharma and bio sciencesvol.1/issue-4/oct-dec.2010.
9. Chinam niranjan patra, Arethi bharani kumar, Hemant kumar pandit, Satya prakash singh Meduri vimala devi, "Design and evaluation of sustained release bilayer tablets of propranolol hydrochloride", Acta Pharm., 2007; 479–489.
10. Chitra karthikeyini.S, Jayaprakash.S, Abirami.A, Mohamed Halith.S, "Formulation and Evaluation of Aceclofenac sodium Bilayer sustained release tablets", International Journal of ChemTech Research, Oct-Dec 2009; vol-1, No.4, 1381-1385.
11. Madhusudan Rao Yamsani et; al, "Factors Influencing the Design and Performance of Oral Sustained/Controlled Release Dosage Forms", International Journal of Pharmaceutical Sciences and Nanotechnology, vol-2, Issue-3, October- December 2009; 583-593.
12. Patel D, Patel A, Solanki T. Formulation and evaluation of bilayer tablet by using melt granulation technique for treatment of diabetes mellitus. J Pharm Bioallied Sci. 2012 Mar;4(Suppl 1):S37-9. doi: 10.4103/0975-7406.94135.
13. Mandal U, Gowda V, Ghosh A, Selvan S, Solomon S, Pal TK. Formulation and optimization of sustained release matrix tablet of metformin HCl 500 mg using response surface methodology. Yakugaku Zasshi. 2007 Aug;127(8):1281-90.
14. Shahi, SaAdhaana; Shivanikar, Shantanu; Zadbuke et al Formulation and evaluation of Bilayer Tablet of Metformin Hcl and Pioglitozone Hcl International Journal of Pharmacy & Pharmaceutical Sciences;Dec2012 Supplement 5, Vol. 4, p380.
15. Patra CN, Kumar AB, Pandit HK, Singh SP, Devi MV. "Design and evaluation of sustained release bilayer tablets of propranolol hydrochloride" Acta Pharm. 2007 Dec; 57(4):479-89.
16. Divya.A,K.kavitha,M.Rupesh kumar,Dakshayani S,Jagadesh Singh SD "Bilayer tablet technology:An overview"Journal of applied pharmaceutical science 2011.
17. Nirmal J, Saisivam S, Peddanna C, Muralidharan S, Godwinkumar S, Nagarajan M "Bilayer tablets of atorvastatin calcium and nicotinic acid: formulation and evaluation". Chem Pharm Bull (Tokyo). 2008 Oct;56(10):1455-8.
18. Kumar VB,Prasad G,Ganesh B,Swathi C,Rashmi A,Reddy AG.Development and evaluation of Guafenesin bilayer tablet,Int.J.Pharm.Sci.NanoTech.2010;3(3):1122-1128.
19. Rao NGR,Yadav A,Kulkarni U.Formulation and evaluation of zero order release glipizide bilayer matrix tablet using natural and synthetic polymers.2010;2(1):34-42.
20. Kartheikeyini CS,Jayaprakash S,Abirami A,Halith MS, Formulation and evaluation of Aceclofenac sodium bilayer tablets.Int.J.ChemTech.Res.2009;1(4):1381-1385.
21. Shirwaikar AA,Shrinatha A, sustained release bilayer tablet Of diltiazem Hcl us Insoluble matrix system. Int.J.Pharm.Sci.2004;6(4):433-437.
22. Prasanthi NL,Manikiran SS,Rao NR, Fomulation and evaluate bilayer tablet of propranolol Hcl by using natural gums. Asian J.Pharma.Clin.Res.2010;3(2):104-105.
23. Nagaraju R,Kaza R. Fomulation and evaluate bilayer sustained release tablets of Salbutamol and Theophylline International journal of pharmaceutical sciences and nanotechnology 2009;vol.2.
24. Sale V.V,P.K. Choudhari, A.M.Avachat,S.M.Sheikh,'Development and characterization of bilayer controlled release tablet of Tramadol Hcl 'In AAPS-000667,2008.
25. 25.N.G.Raghavendra rao,Ashok yadav,et al.Formulation and evaluation of zero order release glipizide bilayered matrix tablets using natural and synthetic polymers.International journal of current pharmaceutical research 2010;2(1):pp 34-42.
26. Mandal U, Pal TK. "Formulation and in vitro studies of a fixed-dose combination of a bilayer matrix tablet containing metformin HCl as sustained release and glipizide as immediate release". Drug Dev Ind Pharm. 2008 Mar; 34(3):305-13.