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Research Article

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

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ABSRACT

The present study was to establish Bi-layer tablets containing Metformin HCl as sustained release and Pioglitazone HCl as immediate release layer. Sustained layer were prepared by wet granulation method using different viscosity grade of HPMC (HPMC K4M & HPMC K100M) as polymers and immediate release layer were prepared by direct compression method using superdisintegrants such as sodium starch glycolate and crosscarmellose sodium. The tablets were evaluated for physicochemical properties. All the values were found to be within limit. In vitro release studies were carried out by USP type-2 paddle apparatus. The result showed that combinations of polymers namely HPMC K100M and HPMC K4M in sustained layer can control the release of drug. The *in vitro* release profiles of drug from sustained release layer could be best expressed by Higuchi's equation as the plots showed high linearity (R^2 >0.988) and diffusion was the dominant mechanism of drug release. The formulations (P6M7) having immediate release layer produces immediate effect within 54 second followed by sustained release (97.35%) at 8 hrs and it comparable with innovator. The present study concluded that Bilayer tablets of Pioglitazone HCl and Metformin HCl as an alternative to the conventional dosage form.

Keywords: Bilayer tablets, Metformin HCl, Pioglitazone HCl, Sustained Release, Higuchi equation.

INTRODUCTION

Diabetes is one of the major causes of death and disability in the world. World Health Organization estimate for the number of people with diabetes worldwide, in 2000, is 171 million, which is likely to be at least 366 million by 2030 (Ritu et al., 2009). Non-insulin-dependent (Type 2) diabetes mellitus is a heterogeneous disorder characterized by an underlying insufficiency of insulin. This insufficiency results from defective insulin utilization and can be corrected by administration of one or more of the currently available oral hypoglycemic agents (Howida et al., 2010).

Combination therapy have various advantages over monotherapy such as problem of dose-dependent side effects is minimized, a low-dose combination of two different agents reduces the dose-related risk, the addition of one 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 dosage of individual component of the combined tablet (Jitendra et al., 2009).

Metformin is an oral biguanidine first-line choice of drug. Metformin has an oral bioavailability of 50–60% under fasting conditions, and is absorbed slowly. The average elimination half-life in plasma is 6.2 hours. Peak plasma concentrations (C_{max}) are reached within 4 to 8 hours with extended-release formulations (Rachel et al., 2006).

Pioglitazone is orally administered insulin sensitizing thizolidinedione agent and highly selective agonist for the peroxisome proliferator-activated receptor gamma (PPAR γ). PPAR γ- receptor are found in tissues, which are target sites of insulin action e.g. adipose tissue, skeletal muscle and the liver. Activation of the PPAR γ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism. 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. (John Waugh.et al.,2006).

The evidence shows that a fixed-dose formulation of Pioglitazone and Metformin offers an effective option for the management of patients with type 2 diabetes when monotherapy fails in the achievement of the recommended standards of care (Giuseppe et al., 2007) . Such a combination is superior than another in terms of glycaemic control as well as an improvement in the cardiovascular outcome of patients with type 2 diabetes, according to the PROactive (PROspective pioglitazone Clinical Trial In macroVascular Events) study and the UKPDS (UK Prospective Diabetes study) and also improvement in triglyceride levels (John Waugh et al., 2006).

Hence to reduce frequency of administration and to improve patient compliance, bilayer tablet formulation having an immediate releasing layer (Pioglitazone HCl) and a sustained release layer (Metformin HCl) was attempted. The multilayered tablet concept has been long utilized to develop sustained release formulations. Such a tablet has a fast releasing layer and may contain bi- or triple layers to sustain the drug release. The pharmacokinetic advantage relies on the fact that drug release from fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer. Thus, the developed single tablet will be sufficient instead of two to three tablets of both drugs per day, and it will also increase patient compliance and therapeutic efficacy (Ramesh et al., 2010).

The present study was aimed to formulate sustained release bilayer tablets of Metformin HCl and Pioglitazone HCl. Metformin HCl as a sustained release layer were prepared by using different viscosity grade of HPMC such as (HPMCK100M & HPMC K4M) and Pioglitazone as immediate release layer were prepared by using super superdisintegrants such as sodium starch glycolate and crosscarmellose sodium.

MATERIALS AND METHODS

Materials

Pioglitazone hydrochloride (99.96% purity), Metformin hydrochloride (99.96% purity), HPMC K100M, HPMC K4M, Sodium Starch Glycolate, Crosscarmellose Sodium, Microcrystalline cellulose, Lactose, PVP K-30, Isopropyl alcohol, Magnesium stearate, Talcum, Ferric iron oxide red were collected from Lincoln Pharmaceuticals ltd, Ahmedabad, India. All others reagents and chemicals used were of analytical reagent grade.

Development of bilayer tablet of Metformin HCl and Pioglitazone HCl was carried in two different stages. Blends of Sustained release layer of Metformin HCl and immediate release layer of Pioglitazone HCl were separately prepared. After optimization of individual layer, the bilayer tablet was prepared using optimized formulas.

Methodology

Preparation of Bilayered tablets

Blends of immediate release layer of pioglitazone HCl

Immediate release layer of Pioglitazone HCl (P1 to P3) were prepared by direct compression technique as per the composition Table 1. Pioglitazone and other excipient sifted through sieve no 40 # and thoroughly mixed in a blender approximately for 5 min. The color iron oxide red was passed through the sieve number # 100 and add above mixer. Above mixer was lubricated for 2 min with Magnesium Stearate which was already passed through sieve 60. For Batches P1 to P3, crosscarmellose sodium and P4 to P6, sodium starch glycolate were used as superdidintegrants.

Granulation of sustained release layer of metformin HCl

The dose of Metformin HCl for sustained release was fixed as 500 mg. Metformin HCl (M1 to M7) as sustained release layer was prepared by wet granulation technique with various excipients as per the formula given in Table 2. Metformin HCl, Microcrystalline cellulose, Lactose, HPMC K100M and HPMC K4M were sifted through Seive no. # 40. Then the above sifted materials were mixed in Rapid Mixer Granulator for 5 min (RPM of Impeller- 150). PVP K-30 was dissolved in mixture of IPA .Then above mixture with binder PVP K-30 solution was granulated at Impeller RPM 150 and kneading for 2 min (Impeller RPM 150 and chopper RPM 1500). The granules were dried in tray dryer at 65°C (LOD 1.5 to2.5 % w/w). The granules were passed through mesh no.# 20 in oscillating granulator. Finally mixture was lubricated with talc and magnesium stearate for 2 min in Cage blender. In Batch M1 to M2, HPMC K4M was used as a polymer and Batch M3 to M4, HPMC K100M was used as a Polymer and Batch M5 to M7,combination of HPMC K100M and HPMC K4M was used as a polymer.

Characterization of granules

Prior to compression, blends of two layer were evaluated for their characteristic parameters, such as density, bulk density, tapped density, compressibility index and Hausner Ratio. Carr's index was calculated from the bulk and tapped densities using a digital tap density apparatus (Electrolab Ltd, india).

Preparation of Bilayer formulation

Final Bi-layer tablets were compressed by as one layer only for Metformin HCl and second layer for Pioglitazone HCl using 19 X 9 mm D Tooling oblong shape punch in 27 station tablet compression machin (Cadmech, India). The tablet was compressed as a B-ilayer tablet using both Metformin HCl granules and Pioglitazone HCl blend. In this Metformin HCl granules were introduced first into the die cavity and a slight pre compression was made so that layer was uniformly distributed after that Pioglitazone HCl blend were added and final compression was made.

Physico chemical properties of bilayer tablets

Standard physical tests for the sustained release bilayer tablets were performed and average values were calculated. Mass variation was determined by weighing 20 tablets individually, the average mass was calculated and the percent variation of each tablet was calculated. Hardness was determined by taking 6 tablets from each formulation using a Mansanto hardness tester (Electrolab Pvt. Ltd, India) and the average of pressure (kg cm $^{-2}$) applied for crushing the tablet was determined. Friability was determined by first weighing 20 tablets after dusting and placing them in a Roche Friabilitor, which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of the tablets was recorded and the percent friability was calculated. Thickness was determined by digital vernier caliper. It is expressed in mm.

Drug content

Twenty tablets were weighed and finely powdered. The powder equivalent to 500 mg of Metformin HCl and 30 mg of Pioglitazone HCl were transferred to a 100 ml volumetric flask. Add about 50 ml of diluents and sonicate to dissolve. Make volume up to the mark with diluents and mix. Dilute 1.0 ml of this solution to 100.0 ml with diluents and mix. Acetronitrile was used as diluents. The total amount of drug within the tablets was analyzed by modified HPLC method (Ramesh et al., 2010).

In vitro dissolution studies

Chromatographic conditions

Apparatus : High Performance Liquid Chromatography

Column : 150 mm x 4.6 mm, 5µm, C_{18}, ODS

Flow Rate : 1.0 ml/min

Temp : 25^0 C

Injected Volume : 10 µl

Detector : 225 nm

Retention time : About 4.5 min Metformin and 8.6 min Pioglitazone

Buffer preparation: Buffer was prepared by dissolving 3.9 g of sodium dihydrogenphosphate in 1 litre of water adjusted to pH 6.0 using diluted sodium hydroxide solutions.

Diluent: Acetonitrile was used as diluents

Mobile phase **:** Filtered and degassed mixture of Buffer and Acetonitrile (600:400).

Release of Pioglitazone hydrochloride was determined using a dissolution Apparatus type II at 100 rpm. The dissolution was studied using 900ml of 0.1 N Hydrochloric acid. The temperature was maintained at 37 **±** 0.5°C. The sample (5 ml) was withdrawn at different time intervals, i.e., 5, 15, 30, 45, minutes, filtered through Whatman filter paper and replaced by an equal volume of dissolution medium. Samples were suitably diluted and analyzed for Pioglitazone hydrochloride content using chromatogram. The percentage of Pioglitazone hydrochloride release was calculated.

Release of Metformin hydrochloride was determined using a dissolution Apparatus type II at 100 rpm. The dissolution was studied using 900ml of Phosphate Buffer pH 6.8. The temperature was maintained at 37 **±** 0.5°C. The sample (5 ml) was withdrawn at different time intervals, i.e., 1, 2, 3, 4, 5, 6, 7 and 8 hours, filtered through Whatman filter paper and replaced by an equal volume of dissolution medium. Samples were suitably diluted and analyzed for Metformin hydrochloride content using chromatogram (Ramesh et al., 2010).

Characterization of the Release Profile:

The experimental results of the release studies were fitted according to the exponential equation.

Zero order Release Equation:

$Q = K_0t$

First Order Release Equation

$\text{Log } C = \log C_0 - Kt / 2.303$

Higuchi's Square Root of Time Equation:

$Q = Kt^{1/2}$

Korse-Meyer Peppas Equation:

$M_t / M_\alpha = K_m t^n$

Whereas, Q = Amount of drug release at time t, C = Amount of drug remained at time't', C_0 = Initial amount of drug, K = First – order rate constant (hr^{-1}). M_t = drug release at time t, M_α = total amount of drug in dosage form, F = fraction of drug release at time t, K_0 = zero order release rate constant, K = Higuchi square root of time release rate constant, K_m = constant depend on geometry of dosage form, n = diffusion exponent indicating the mechanism of drug release where for cylinder value of n is <0.5 indicate Fickian diffusion, between 0.5 and 1.0 indicate Non-Fickian and > 1.0 indicate case-II transport.

FT-IR study

Infrared spectrum was taken (FT-IR, spectrum RXI, Perkin Elmer Ltd, Switzerland) by scanning the sample in Potassium bromide discs. The samples of pure drug and formulated tablets were scanned individually.

RESULTS AND DISCUSSION:

The FTIR studies proved chemical and physical compatibility of drug with excipients.

Tablet characteristics

Tablets of all formulations were subjected to various physico–chemical evaluation parameters such as thickness, hardness, friability, and drug content. The results of these studies were also found to be within limits and were uniform givin in Table 5.

In vitro Drug Release Study

Figure 2 show comparative percentage drug release of Pioglitazone HCl formulations (P1 to P6). The percentage *in vitro* drug release from formulations P1 to P6 ranged from 89.33 ± 1.25% to 98.30 **±** 0.11% is given in table 3. Complete Pioglitazone release occurred within 45 minutes, from the P6 formulation and it showed comparable drug release with innovator . It may be due to sodium starch glycolate as superdisintegrant in immediate release formulations. Hence P6 formulation is consider for IR layer.

Figure 3 show cummulative percentage drug release of Metformin HCl formulations (M1 to M7). The *in vitro* drug release from formulations M1 to M7 is given in table 4 . Complete release of Metformin occurred from the bilayer tablets within 8 hours. The drug release rate in sustained layer decrease as the viscosity of HPMC increases. Thus the concentration of the HPMC K100M (8.82%) and HPMC K4M (4.70%) was the predominant factor. Good dissolution profile of M7 might be due combination of HPMC K100M and HPMC K4M and it showed comparable drug release with innovator.

The result suggested that for highly water soluble drug like Metformin HCl, it is desirable to use combination of different viscosity grade of HPMC such as (HPMC K100M and HPMC K4M) for sustained release layer and incorporation of superdisintegrants such as SSG and CCS in immediate release layer. The release data further indicated that combination of HPMC K100M (8.82%) and HPMC K4M (4.70%) can give the sutained release effect followed by the initially burst release effect due to the superdisintegrant SSG (5%) in immediate release layer.

Kinetic modeling of drug release

The kinetics parameters for Metformin HCl release are shown in table 6. The *in vitro* release profiles of drug from sustained release layer could be best expressed by Higuchi's equation as the plots showed high linearity (R^2 >0.988). Release of the drug from the sustained release tablets containing hydrophilic polymers generally involves factors of diffusion. To confirm the diffusion mechanism, the data was fitted into korsmeyer's equation, with slope (n) values ranging from 0.405 to 0.468. This result suggests that, the release of drug follows Fickian transport and it indicates the deliver of drug from the tablet through diffusion dominated mechanism.

Table 1: Preparation of immediate release layer of Pioglitazone hydrochloride

Sr No	Ingredients	P1	P2	P3	P4	P5	P6
	Qty(mg)/tab						
1	Pioglitazone HCl	30	30	30	30	30	30
2	MCC	159.8	157.2	155.2	159.2	157.2	155.2
3	CCS	6	8	10	-	-	-
4	SSG	-	-	-	6	8	10
5	Mg Stearate	2	2.5	2.5	2.5	2.5	2.5
6	Talcum	2	2	2	2	2	2
7	Iron oxide red	0.3	0.3	0.3	0.3	0.3	0.3
	Total weight	200	200	200	200	200	200

Table 2: Preparation of sustained release layer of Metformin hydrochloride

Sr No.	Ingredients	M1	M2	M3	M4	M5	M6	M7
	Qty(mg)/tab							
1	Metformin HCl	500	500	500	500	500	500	500
2	HPMC K4M	100	125	-	-	40	40	40
3	HPMC K100M	-	-	100	125	85	70	60
4	MCC	128	98	123	98	98	113	123
5	Lactose	72	72	72	72	72	72	72
6	PVP K 30	30	30	30	30	30	30	30
7	Isopropyl Alcohol	q.s	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
8	Magnesium Stearate	10	15	15	15	15	15	15
9	Talcum	10	10	10	10	10	10	10
	Total weight	850	850	850	850	850	850	850

Table 3: Comparative *In-Vitro* Drug Release Profile of Pioglitazone HCl IR Layer at pH 1.2

Time (min)	Innovator	P1	P2	P3	P4	P5	P6
0	0	0	0	0	0	0	0
5	58.84	46.56	49.31	52.78	53.49	56.48	59.32
15	79.41	67.24	70.9	73.74	75.7	76.56	81.63
30	94.6	80.71	85.83	90.57	90.43	92.63	94.34
45	97.76	89.33	93.63	95.34	94.76	96.64	98.3
F2 value		57.96	66.2	76.6	79.22	89.56	97.84

Table 4: Comparative In-Vitro Drug Release Profile of Metformin HCl SR Layer(M1 TO M7) at pH 6.8

Time (hrs)	Innovator	M1	M2	M3	M4	M5	M6	M7
0	0	0	0	0	0	0	0	0
1	41.79	46.56	44.37	43.51	42.54	38.7	40.55	40.85
2	54.31	69.19	61.52	59.55	57.41	48.51	49.82	53.56
3	62.49	79.25	75.27	71.26	68.57	60.38	63.26	62.56
4	73.51	93.24	87.65	78.46	76.55	67.36	71.55	74.65
5	79.63	98.46	92.35	84.62	82.41	72.48	76.83	79.17
6	86.26		97.83	91.58	89.42	77.08	80.33	86.85
7	91.93			97.5	94.43	85.24	88.51	92.19
8	97.14				98.95	91.43	94.42	96.63
F2 value		48.97	54.92	69.61	77.73	67.8	79.24	97.35

Table 5: Post compression parameter of Bilayer tablets

code	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Weight variation (mg)	DT (IR layer) (second)	Drug content (%)	
						Pioglitazone	Metformin
P1M1	6.85±0.07	19.47±0.12	0.05±0.004	1051 ±0.81	94± 0.81	97.46 ±0.37	98.14 ± 0.37
P2M2	6.59±0.13	19.43±0.33	0.07±0.001	1053.33 ±1.24	89 ± 0.94	98.26 ±0.09	99.14 ± 0.28
P3M3	6.73±0.06	19.4±0.16	0.05±0.004	1049.33 ±2.05	74 ± 1.6	98.6 ± 0.27	100.07 ± .28
P4M4	6.8±0.08	19.43±0.33	0.04±0.001	1053.67 ±1.24	66 ± 1.63	98.98 ± 0.5	99.3 ± 0.19
P5M5	6.77±0.04	19.27±0.2	0.05±0.002	1050±2.44	62 ± 0.94	99.27 ±0.27	99.53 ± 0.17
P6M6	6.73±0.12	19.07±0.12	0.04±0.08	1051±0.81	54 ± 1.41	99.46 ±0.26	98.97 ± 0.06
P6M7	6.77±0.04	19.07±0.17	0.04±0.08	1051.33±0.4	54 ± 1.41	99.46 ±0.26	99.65 ± 0.25

Table 6: The Regression co-efficient values for different formulations

Formulation code	Zero order (R^2)	First order (R^2)	Higuchi's plot	Peppa's plot		Mechanism of Drug Release
				(R^2)	(n)	
M1	0.879	0.942	0.985	0.988	0.468	Fickian diffusion
M2	0.861	0.965	0.991	0.990	0.45	Fickian diffusion
M3	0.849	0.939	0.989	0.997	0.408	Fickian diffusion
M4	0.848	0.899	0.989	0.998	0.405	Fickian diffusion
M5	0.871	0.966	0.992	0.993	0.412	Fickian diffusion
M6	0.864	0.957	0.992	0.99	0.411	Fickian diffusion
M7	0.869	0.961	0.996	0.996	0.422	Fickian diffusion
Innovator	0.868	0.943	0.993	0.997	0.41	Fickian diffusion

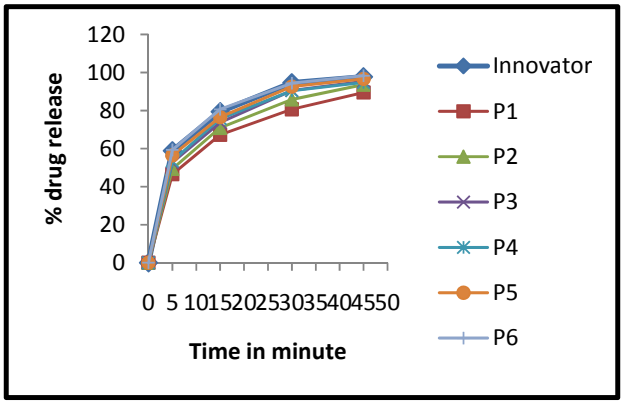

Fig. 1: Comparative dissolution profile of P1 to P6 batches with innovator release profile at pH 1.2

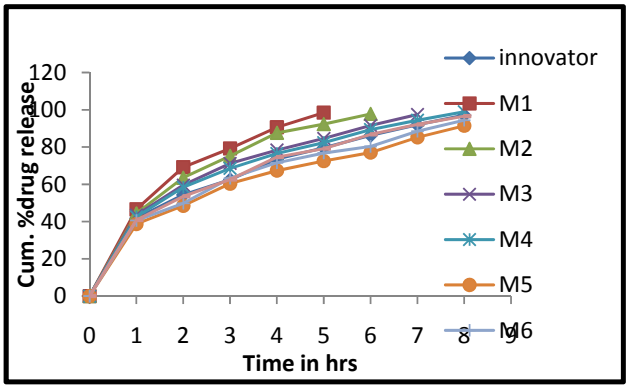

Fig. 2: Cummulative In-Vitro Drug Release Profile of Metformin HCl SR Layer (M1 TO M7) at pH 6.8

CONCLUSION

The present research work was carried out to develop a Bi-layer tablet of Metformin hydrochloride as sustained release layer was prepared by HPMC K100M and HPMC K4M and Pioglitazone hydrochloride as immediate release layer was prepared by using superdisintegrants such as sodium starch glycolate and crosscarmellose in order to match release profile with the innovator product. The result demonstrated that initially burst release was due to sodium starch glycolate as superdisintegrant in immediate release formulation and followed by sustained release due to combination of polymers such as HPMC K100M (8.82%) and HPMC K4M (4.70%) in sustained release formulation. Hence it concluded that Bi-layer tablets showed an immediate release effect to provide the loading dose of the drug, followed by sustained release for 8 hrs, indicating a promising potential of the Metformin HCl and Pioglitazone HCl Bi-layer tablet as an alternative to the conventional dosage form.

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