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Formulation and Evaluation of the Bi-Layered Sustained Release Matrix Tablets of Metformin Hcl Sr and Pioglitazone

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Abstract: The purpose of this research work was to establish Metformin HCL SR 1000 mg and Pioglitazone HCL 15 mg in the form of bi-layered sustained release matrix tablets. The tablets were prepared using sodium carboxymethylcellulose(SCMC) and Hydroxypropyl Methyl cellulose (HPMC K4M & HPMC 15cps) as bio-adhesive polymers and Cross Carmellose Sodium to act as an impermeable backing layer. Tablets were evaluated by different parameters such as thickness, hardness, friability, weight variation, *in-vitro* dissolution studies, content of active ingredient, stability studies and IR studies. The physico-chemical property of the finished product complies with the In-house Specifications of Micro Labs Limited. *In vitro* release from the formulation was studied as per the USP XXIII dissolution procedure. The formulations gave an immediate release effect followed by sustained release for 8 h which indicates bimodal release of Metformin HCL from the matrix tablets. The data obtained were fitted into Higuchi's models. Analysis of n values of Korsmeyer equation indicated that the drug release involved both diffusional and dissolutional mechanisms. The stability studies of the formulated product also comply with ICH guidelines in the initial two months of study and further studies is in progress. The present study concluded that bi-layer tablets of Pioglitazone HCl and Metformin HCl can be a good way to extent metabolism and to improve the bioavailability of Pioglitazone HCl and Metformin HCl.

Key words: Bilayered tablet · Pioglitazone HCl · Metformin HCl · Sustained release

INTRODUCTION

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. Combination therapy of biguanides along with the sulfonylureas is important for the adequate control of blood glucose level [1]. It is reported that Metformin is the only drug among biguanides, which, very rarely, causes lactic acidosis & is given in combination with sulfonylureas [2]. But such a high dose of Metformin, in combination can not be given as a conventional dosage form, due to it's poor bioavailability, owing to an increased dosing frequency, thereby reducing patient acceptability [3]. Pioglitazone is a potent and highly selective agonist for the peroxisome proliferator-activated receptor gamma (PPARγ). PPARγ - receptor are found in tissues, which are target sites of insulin action e.g. adipose tissue, skeletal muscle and the liver. Activation of the PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism [4].

Hence to reduce frequency of administration and to improve patient compliance, bilayer tablet formulation having an immediate disintegration layer (of pioglitazone) and another of a sustained release layer (of Metformin) 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 [5]. The pharmacokinetic advantage relies on the fact that drug release from fast releasing granules leads to a sudden rise in the blood concentration. However, the blood level is

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maintained at steady state as the drug is released from the sustaining granules. Among the different polymers, Hydroxypropyl Methyl cellulose (HPMC K4M and HPMC 15cps) and Sodium carboxy methyl cellulose have been used successfully to obtain appropriate sustained release matrix formulations of different materials [6]. The present study aimed at formulating bilayered tablets of Metformin HCL SR and Pioglitazone HCL with a fast release layer using Cross Carmellose Sodium.

MATERIALS AND METHODS

Pioglitazone hydrochloride (99.96% purity), Metformin hydrochloride (99.96% purity), HPMC K4M, HPMC 15cps, Sodium carboxy methyl cellulose, Low substituted hydroxy propyl cellulose, Cross Carmellose Sodium, Lactose DCL-15, Talc, Magnesium Stearate, Quinoline Yellow lake, Anhydrous dibasic calcium phosphate and Povidone were collected from Micro labs, Hosur, India. All other reagents and chemicals used were of analytical reagent grade.

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

Preformulation

Drug-Excipients Compatibility Studies: Preformulation which is the testing, was the first step in the rational development of dosage form. Is an investigation of physical and chemical properties of individual drug substances alone and after combining with the excipients. Metformin HCL and Pioglitazone HCL were taken individually in a glass vial, both Metformin HCL along with various excipients and Pioglitazone HCL with various excipient in different ratios i.e., 1:1 and 1:10 were also taken in glass vial. All the above mixtures of drug substances were kept at various accelerated condition (30°C/65%RH and 40°C/75%RH) in stability chamber (Newtronic walkin Humidity chamber, India). It was carried out for one month in open and closed glass vials. At the time interval of 2 weeks (till 4th week), the samples were withdrawn and checked out for any changes in physical character like color. Finally the mixture with no color change was selected for formulation [7].

Preparation of Bilayer Formulation

Preparation of Immediate Release Layer of Pioglitazone HCL: Immediate release layer of Pioglitazone HCL (P1 to P3) were prepared by dry granulation technique as per the composition Table 1. Pioglitazone HCL, HPC-LH11, Lactose DCL 15, Cross Carmellose Sodium were passed through Sieve no# 40. The Quinoline Yellow Lake was passed through Sieve Number #200. 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 mixed for 2 minutes. Table 1 represents the preparation of immediate release layer of *Pioglitazone hydrochloride.*

Preparation of Sustained Release Layer of Metformin HCL: The dose of Metformin HCL for sustain release was fixed as 1000mg. The Metformin HCL(M1 to M3) sustain release layer was prepared by wet granulation technique with various excipients as per the formula given in Table 2. The drug and additives were as through sieve no. # 40 and the mixture were mixed thoroughly in a poly bag for 30 minutes for uniform mixing. Using povidone solution as binder the above mixture was granulated. The coherent mass was passed through sieve no.# 14 an Fluid Bed dried. The resultant dried granules were passed through milling 1.5 mm screen and sift through sieve no #20 and finally lubricated with the lubricants. Table 2 represents the preparation of sustained release layer of Metformin hydrochloride.

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

Preparation of Bilayer Formulation: Final bilayer tablets were compressed as one layer only for Metformin HCl (M3) and second layer for Pioglitazone HCL(P3) using 19.8x8.7 mm oblong shape punch in 27 station tablet compression machine (Cadmach, India). The tablet was compressed as a bilayer tablet using both Metformin HCl and Pioglitazone HCl granules. In this, Metformin HCl granules were introduced first into the die cavity and a slight pre compression was made so that the layer was uniformly distributed after that Pioglitazone HCl granules were added and a final compression was made.

Table 1: Preparation of Immediate release layer of Pioglitazone hydrochloride

S. No.	Ingredient	Category	(P1) Quantity/ Tablet (in mg)	(P2) Quantity/ Tablet (in mg)	(P3) Quantity/ Tablet (in mg)
1	Pioglitazone hydrochloride	Active ingredient	16.614	16.614	16.614
2.	Low substituted hydroxyl propyl cellulose	Binder	5.250	2.500	8.000
3.	Cross Carmellose Sodium	Super Disintegrant	5.250	8.000	2.500
4.	Lactose DCL-15	Diluent	103.886	103.886	103.886
5	Talc	Glidant	0.800	0.800	0.800
6.	Magnesium Stearate	Lubricant	1.800	1.800	1.800
7.	Quinoline Yellow lake	Colouring agent	1.400	1.400	1.400
	Average weight of tablet		135mg/tablet	135mg/tablet	135mg/tablet

Table 2: Preparation of sustained release layer of Metformin hydrochloride

S. No.	Ingredient	Category	(M1) Quantity/Tablet (in mg)	(M2) Quantity/Tablet (in mg)	(M3) Quantity/Tablet (in mg)
1.	Metformin hydrochloride	Active ingredient	1002.708	1002.708	1002.708
2.	HPMC K4M	Polymer	90.000	95.000	100.000
3.	HPMC 15cps	Polymer	10.000	12.500	15.000
4.	Sodium carboxy methyl cellulose	Binder	30.000	30.000	30.000
5.	Anhydrous dibasic calcium phosphate	Diluent	47.000	39.792	47.292
6.	Povidone	Binder	12.000	12.000	12.000
7.	Purified water	Solvent	Q.S	Q.S	Q.S
8.	Aerosil	Gildant	15.000	15.000	10.000
9.	Talc	Gildant	10.000	10.000	4.000
10.	Magnesium stearate	Lubricant	13.000	13,000	9.000
	Average Weight of tablets		1230mg/tablet	1230mg/tablet	1230mg/tablet

Physical Tests for the Bilayer Tablets: Standard physical tests for the bilayer matrix tablets were performed and average values were calculated [8]. 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 Monsanto 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 Friabilator, 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 Uniformity

Chromatographic Conditions:

Apparatus : High Performance Liquid Chromatograph
Column : C- 18; 250x 4.6mm; 5µ
Wave length : 225nm
Flow rate : 1.0ml/min
Injection volume : 20 µl

Filtered and degassed mixture of Buffer and Acetonitrile (600:400) was used as mobile phase. Buffer was prepared by dissolving 3.9 g of sodium dihydrogenphosphae in 1 litre of water adjusted to pH 6.0 using diluted sodium hydroxide solutions. 80 % Acetonitrile was used as diluent.

Solution 1: 0.0439 g of Pioglitazone hydrochloride working standard was weighed accurately and transferred in to a 50 ml volumetric flask, then 30 ml of diluent was added, the flask was shaken and sonicated for 15minutes, finally the volume was made up to the mark with diluent.

Standard Preparation: 0.2672 gm of Metformin hydrochloride working standard was weighed accurately and transferred in to a 100 ml volumetric flask, then diluent was added, the flask was shaken and sonicated for 15minutes, then 5ml of solution–1 was added and mixed well. Finally the volume was made up to the mark with diluent. From this solution 10ml was diluted to 25 ml with diluent. The solution was filtered through 0.45 µM membrane filter. The filtrate was collected after discarding the first few ml of the filtrate.

Sample Preparation: Twenty tablets were finely powdered and an amount equivalent to 1.3987g of

the powdered tablets was accurately weighed and transferred to a 50 ml volumetric flask then diluent solution was added, the flask was shaken and sonicated for 15 minutes, Finally, the volume was made up to the mark with diluent. From this solution 5ml was pipetted out and diluted with diluent in to a 100ml volumetric flask. The second solution was filtered through 0.45 µM membrane filter. The filtrate was collected after discarding the first few ml of the filtrate. 10ml of filtrate was diluted with diluent into a 25ml volumetric flask. The solution was filtered through 0.45 µM membrane filter. The filtrate was collected after discarding the first few ml of the filtrate.

20µl of filtered portion of the blank, sample preparation and standard preparation was separately injected. The chromatogram was recorded and measured the responses for the major peaks. The content of Metformin HCl and Pioglitazone HCl per tablet in mg was calculated.

***In vitro* Dissolution:** Release of metformin hydrochloride was determined using a Dissolution Apparatus II of IP (Basket) at 100 rpm. The dissolution was studied using 900 mL 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 (Auroco Pvt Ltd, Thailand) and replaced by an equal volume of dissolution medium. Samples were suitably diluted and analyzed for metformin hydrochloride content using chromatogram. The percentage of metformin HCl release was calculated.

Release of Pioglitazone hydrochloride was determined using a Dissolution Apparatus Type I of IP (Paddle) at 100 rpm. The dissolution was studied using 900 mL of 0.1 M Hydrochloric acid. The temperature was maintained at 37 ± 0.5°C. The sample (5 mL) was withdrawn at different time intervals, i.e., 5, 10, 15, 20, 25, 30, 35, 40 and 45 minutes, filtered through Whatman filter paper (Auroco Pvt Ltd, Thailand) 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. The solutions were analyzed by using same procedure of assay of drug content.

Characterization of the Release Profile: The experimental results of the release studies were fitted according to the exponential equation.

Zero Order Release Equation:

$$Q = K_0 t \quad (1)$$

Higuchi's Square Root of Time Equation:

$$Q = K_H t^{1/2} \quad (2)$$

Korse-Meyer Peppas Equation:

$$F = (M_t/M) = K_m t^n \quad (3)$$

Whereas, Q= Amount of drug release at time t, M_t= drug release at time t, M= total amount of drug in dosage form, F= fraction of drug release at time t, K_0= zero order release rate constant, K_H= 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 0.55 indicate Fickian diffusion, between 0.45 and 0.89 indicate anomalous transport and 0.89 indicate case-II transport.

Stability Studies: As the *in vitro* release of formulation F3 was found to be desirable than other formulation it was chosen for stability studies. The tablets were Al/PVC packed and kept for 60 days at 30°C and 65% RH, 40°C and 75% RH in a stability chamber (New tronic walk in humidity chamber, India). The tablets were evaluated for physical properties, invitro drug release and assay at the different time intervals i.e., 1 and 2 months.

FT-IR Study: Infrared spectrum was taken (FT-IR, Spectrum RX 1, Perkin Elmer Ltd, Swizerland) by scanning the sample in potassium bromide discs. The samples of pure drug andgranules containing different polymers were scanned individually.

RESULTS AND DISCUSSION

The preformulation studies of both Metformin HCL SR and Pioglitazone HCL were evaluated for various physical properties individually and the values were present in the Tables 3 and 4 From Table 3 and Table 4 observations, the flow was poor for the drug Metformin HCL, as the flow was good for the drug Pioglitazone HCL. Both the drugs were required to be granulated. In drug excipients compatibility studies, the samples which were kept at various accelerated condition, were withdrawn

Table. 3: Preformulation Studies of Metformin HCL

S. No.	Experiment	Properties	Observation
1.	Physico-chemical properties	Bulk density	0.56 g/cm ^{3}
		Tap density	0.39 g/cm^3
		Hausner ratio	1.35
		Angle of repose	48.3°
		Compressibility Index	28.8 %

Tab. 4: Preformulation Studies of Pioglitazone HCL

S. No.	Experiment	Properties	Observation
1.	Physico-chemical properties	Bulk density	0.37 g/cm^3
		Tap density	0.23 g/cm^3
		Hausner ratio	1.01
		Angle of repose	25.2°
		Compressibility Index	5.9 %

Tab.5: Evaluation of granules of all formulation

S. No.	Formulation	Bulk density g/cm^3	Tap density g/cm^3	Hausner ratio	Compressibility Index (%)	Angle of repose(°)	Moisture content (%)
1	M 1	0.35	0.27	1.07	6.9	28.9	0.80
2	M2	0.33	0.28	1.05	6.5	27.1	0.96
3	M3	0.33	0.27	1.05	6.7	28.0	0.81
4	P1	0.28	0.25	1.01	5.9	26.9	1.08
5	P2	0.28	0.25	1.01	6.0	27.0	1.04
6	P3	0.29	0.26	1.01	6.0	26.9	1.00

M – Metformin HCL Formulation, P – Pioglitazone HCL Formulation

and carried out physical characteristics evaluation like color change at different intervals. From the results of compatablity studies, we observed that there was no incompatability in drugs alone or with excipients. According to above evaluation studies, drugs formulation were granulated and investigated for various physical properties individually and the values were present in the Table 5.

From the results which present in Table 6, the values of bulk densities for the granules of various formulations indicate good packing character. The compressibility index (CI) for all the formulations was found to be below 15%, indicating desirable flow properties. The flow properties of granules were further analyzed by determining the angle of repose for all granules; ranges were less than 30°. The hausner ratio for all the granules formulated was less than 2 %. The moisture content was less than 2 %.

By *in vitro* release study, M3 and P3 were considered to be optimized one. The drug release rate in SR decreases as the concentration of HPMC K4M and HPMC 15cps polymers increases. Thus the concentration of the polymers HPMC K4M and HPMC 15cps was the predominant controlling factor. Good dissolution profile of M3 might be due to high amount of dibasic calcium phosphate (anhydrous) instead of using combination of diluents. Figures 1 and 2 expressed the dissolution studies of Metformin Hydrochloride and Pioglitazone Hydrochloride respectively.

All the batches of tablets were manufactured under similar conditions to avoid processing variables. Mass of the bilayer tablets was 1364 ± 4.16 mg, hardness was 13± 0.76 kg cm–2 and thickness was 7.3 ± 0.1 mm. The percentage friability of all the formulations was 0.5 ± 0.3%. Values of the hardness test and percent friability indicate good handling properties of the prepared bilayer tablets. The drug content uniformity in the bilayer matrix tablets was 103.8 ± 0.32% for Metformin hydrochloride and 98.88± 0.38% for Pioglitazone hydrochloride.

Stability Study: No significant changes were observed in the physical appearance, color, hardness and dissolution studies of the SR, drug content and IR of bilayer tablet of the optimized batch. The dissolution rate was analyzed statistically and no statistically significant difference in % CDR was found after 1 and 2 month with the control (zero month).

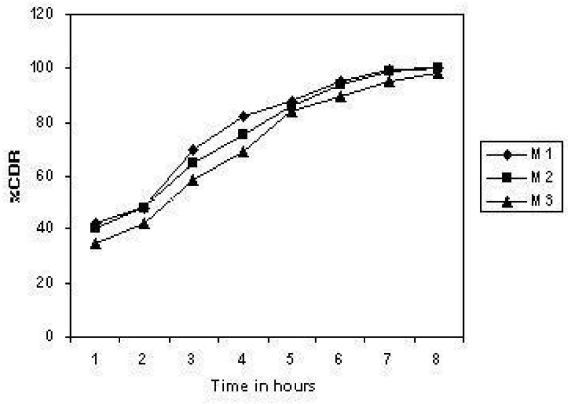

Fig. 1: Dissolution studies of Metformin Hydrochloride

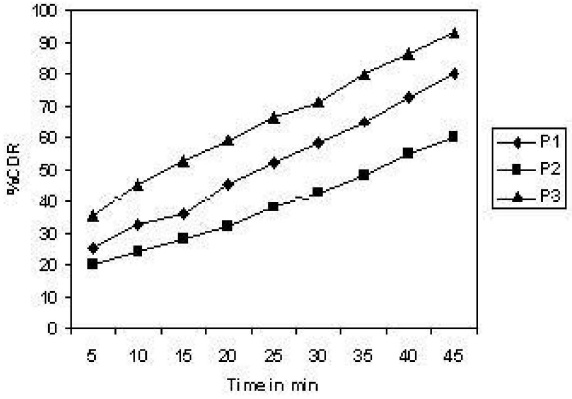

Fig. 2: Dissolution studies of pioglitazone Hydrochloride

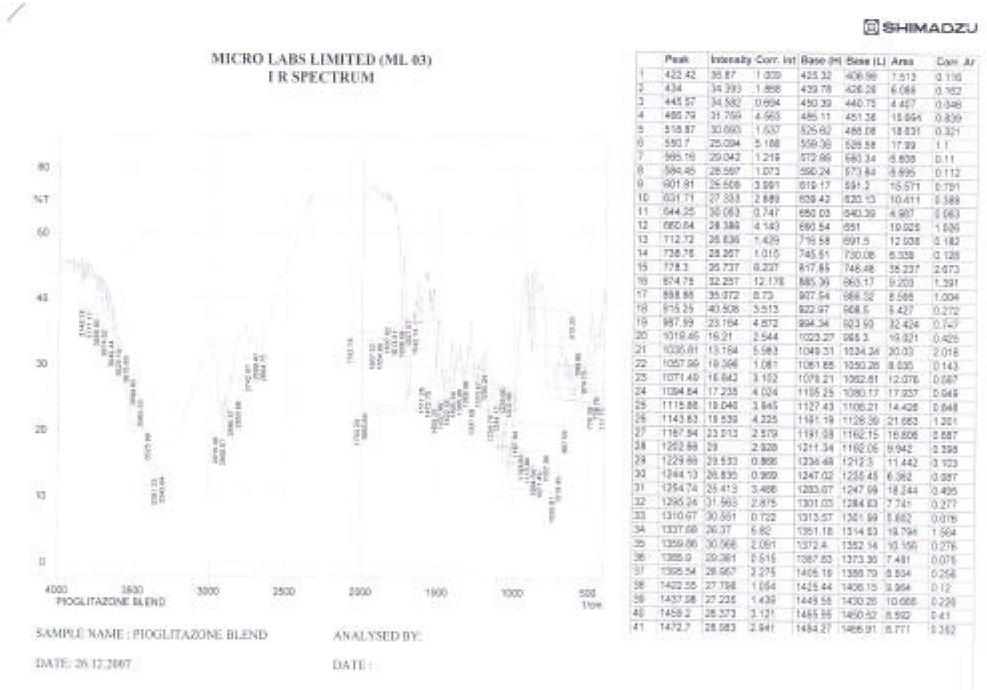

Fig. 3: FTIR spectrum of bilayer tablet

IR Study: The FT-IR spectrum of bilayer tablet metformin hydrochloride and Pioglitazone hydrochloride was shown in Fig. 3. The wavenumbers of individual drug were compared with F3 (combination of M3 and P3) formulated product IR spectrum. The results revealed that there was no disturbance in the principle peaks of pure drugs Metformin and Pioglitazone. This further confirms the integrity of pure drug and compatibility of them with excipients.

In conclusion the present research was carried out to develop a bilayer tablet of metformin hydrochloride and Pioglitazone hydrochloride using super disintegrant Cross Carmellose Sodium for the fast release layer and HPMC K4M, HPMC 15cps and Sodium carboxy methyl cellulose for the sustaining layer. Bilayer tablets showed an immediate release effect to provide the loading dose of the drug, followed by sustained release for 8 h, indicating a promising potential of the metformin hydrochloride and Pioglitazone hydrochloride bilayer tablet as an alternative to the conventional dosage form.

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