Development and Evaluation of Dual Release Tablet of Metformin and Pioglitazone for the Treatment of Diabetes Mellitus

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Abstract

The objective of present work is to develop and characterize dual release tablet formulation containing Metformin in extended release matrix form and Pioglitazone in immediate release form for the treatment of Diabetes mellitus. Different formulations containing Metformin HCl were manufactured using 3^2 factorial designs. Influences of hydrophobic carrier, hydrophilic polymer on drug release were studied. Immediate release layer of Pioglitazone was optimized using different disintegrants. All formulations were evaluated for percentage drug release and analyzed according to various release kinetic models. Optimization results indicated that release rate of Metformin is directly proportional to the levels of stearic acid (SA) and poly-ethylene-oxide (PEO). Kinetic analysis showed that formulation M6 was good releasing with f2 value of 81.08 and follows Higuchi and Peppas model with correlation coefficient value 0.9780 and 0.9910 respectively. Similarly, optimization study indicated that release of Pioglitazone is dependent on the level and type of disintegrant, formulation P5 shown highest f2 value of 84.08. Results confirmed that dual-release inlay-tablet formulation containing extended release of Metformin HCl and immediate release of Pioglitazone HCl could be developed for the treatment of Diabetes mellitus.

Introduction

The major therapeutic goals in subjects with type 2 diabetes are to optimize blood glucose control, induce weight loss, and normalize lipid disturbances and elevated blood pressure [1]. Thiazolidinediones such as Pioglitazone HCI is a new class of compounds to improve insulin sensitivity in type 2 diabetes [2]. It is soluble in 0.1 N HCl and practically insoluble in water and has practically insoluble to sparingly soluble in different pH buffers [3,4].

Biguanide, in particular Metformin HCI, increases the sensitivity to insulin in peripheral tissues of the hosts. Metformin HCl is also involved in inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. The plasma half-life of Metformin HCl is 1.5-4.9 hours.

Metformin HCI and Pioglitazone HCI have differing mode of peripheral action, which leads to synergy of drug action and better control of diabetic state [2]. The combination formulation of drugs with dual release mechanism (one extended release and one immediate release) for the treatment various diseases and disorders are available in market either in multilayer tablets or coated tablets. Both these formulations have certain disadvantages from industrial manufacturing point of view like layers separation during handling and transportation, mixing of multiple layers during compression on the machine turret, addition of overages, unnecessary exposure heat, solvent and mechanical stress during coating [5]. To overcome these disadvantages an alternative approach has been made in this study to prepare an oral tablet formulation showing dual release pattern of two drugs (one extended release and one immediate release).

Melt granulation method can be used for granulating water sensitive material and producing SR granulation. This technique fulfills today's pharmaceutical industry need because of its simplicity, continuous and efficient process and also due to many advantages over conventional methods of granulations such as wet and dry granulation [6,7].

Adopted factorial design software for the optimization procedure is facilitated by construction of a mathematical equation that describes the experimental results as a function of the factor levels by Design-Expert®. A polynomial equation can be constructed in the case of a factorial design where the coefficients in the equation are related to effects and interactions of the factors by Design-Expert®. Hence present study was aimed towards the design and *in vitro* evaluation of extended release formulation of Metformin HCl with combination of hydrophilic pH independent polymer and hydrophobic melting carrier.

Materials and Methods

Materials

Metformin HCl and Pioglitazone HCl were used as model drug obtained as gift sample from USV Ltd, Mumbai and Biocon Ltd, Bangalore respectively. Polyethylene oxide (Polyox) was obtained from Colorcon India; other excipients were obtained from Signet Chemicals, India. Other materials and solvents used were of analytical grade.

Methods

Preparation and optimization of extended release layer of Metformin HCl: The extended release layer of Metformin HCl was optimized using 3^2 factorial designs. In the present study content

of PEO (WSR 303) and content of SA were selected as independent variables. The diffusion exponent (n) and percentage drug release at 1 hour (Q_1), 2 hour (Q_2), 4 hour (Q_4), 8 hour (Q_8), 10 hour (Q_{10}) and 12 hour (Q_{12}) were selected as dependent variables [8,9]. The experimental designs with corresponding formulations are outlined in Table 1.

All granulation batches were prepared by using hot melt granulation technique. Metformin HCl was sifted through 20 mesh and heated in oven at 75°C by spreading on metal tray. Stearic acid was melted in SS vessel at 75°C. The melt granulation was carried out by transferring hot Metformin HCl in high shear mixer granulator and slowly adding melted stearic acid. Granulation speed was 100 rpm for impeller and 1500 rpm for chopper and time was 5 minutes for each batch. The drug-SA granules were mixed with PEO (sieved through 20 mesh) and microcrystalline cellulose (sieved through 30 mesh) followed by mixing with colloidal silicon dioxide (sieved through 40 mesh) and magnesium stearate (sieved through 40 mesh). Then obtained blends were compressed into tablet with 19 × 9.7 mm oblong shaped punches using eight stations compression machine (Cadmach, India).

Preparation and optimization of immediate release tablet of Pioglitazone HCl: The tablets were prepared by dry blending of ingredients followed by direct compression using composition outlined in Table 2. All ingredients except for magnesium stearate and colloidal silicon dioxide were sieved through 40 mesh and manually blended for 5 minutes. Colloidal silicon dioxide (sieved through 40 mesh) was added next and blended for 3 minutes. Finally magnesium stearate (sieved through 40 mesh) was added and mixed for additional 2 minutes. Then obtained blend was compressed into tablet with 7.0 mm round shaped punches using eight stations compression machine.

Preparation and evaluation of dual release tablet: Dual release inlay tablets were prepared by using optimized composition of Metformin HCl extended release layer (M6) and immediate release tablet of Pioglitazone (P5). First extended release blend of Metformin HCl was introduced into the die cavity and immediate release tablet of Pioglitazone HCl was placed over it and final compression was made using 19 × 9.7 mm oblong shaped punches of 8 station compression machine.

Evaluation of tablets: Prepared tablets were evaluated for thickness, weight variation, assay, hardness, friability and *in vitro* drug release studies.

Thickness: The thickness of 10 tablets from each batch was measured by using digital Vernier caliper and standard deviations were calculated.

Weight variation: 20 tablets from each batch were weighed individually using analytical balance and standard deviations were calculated.

Hardness: The hardness of 10 tablets from each batch was measured by using physical hardness tester and standard deviations were calculated.

Friability: The percentage friability of ten tablets was measured using a friabilator (Electrolab, India). Tablets were rotated at 25 rpm for 4 minutes or up to 100 revolutions. The tablets were then dedusted and the loss in weight caused by fracture or abrasion was recorded.

% Friability={(initial weight-final weight)/(initial weight)} × 100

Disintegration: Disintegration time for pioglizaone tablets was determined using USP disintegration apparatus. The volume of water was 900 ml and temp was 37 ± 0.2°C. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was recorded.

Evaluation of *in vitro* release: The *in vitro* drug release was performed using USP type I (basket) apparatus using 900 ml of 0.1N HCl for one hour followed by 900 ml phosphate buffer pH 6.8 for further eleven hours at the rotations of 100 rpm at 37 ± 5°C. After one hour in 0.1 N HCl carefully transferred the dosage form (by lifting the shaft with baskets) to the vessels containing phosphate buffer pH 6.8 which has been previously warmed to 37 ± 5°C. The samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.45 μm membrane filter, suitably diluted and analyzed at 233 nm for Metformin HCl and 270 nm for Pioglitazone HCl by UV-spectrophotometer. The content of drug and cumulative percentage drug release was calculated using calibration curve. Also the *in vitro* drug release study was conducted for marketed product.

Analysis of drug release kinetics: To analyze the *in vitro* release data various kinetic models like zero order rate (eqn. 1), first order (eqn. 2), Higuchi (eqn. 3) and Hixson-Crowell cube root law (eqn. 4) were used [10].

$$C=k_o t \qquad (1)$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$LogC=LogC_0 \, kt/2.303 \qquad (2)$$

Where, C_0 is the initial concentration of drug and K is first order constant.

$$Q=Kt^{1/2} \qquad (3)$$

Where, K is the constant reflecting the design variables of the system.

$$Q_0^{1/3}-Q_t^{1/3}=K_{HC} \, t \qquad (4)$$

Where, Q_t-the amount of drug released in time t;

Q_0: Initial amount of the drug in tablet and

Factorial design 3^2		PEO		
		ρ1	ρ2	ρ3
SA	α1	M1	M2	M3
	α2	M4	M5	M6
	α3	M7	M8	M9

Polyethylene oxide (PEO) concentration: ρ1-10%, ρ2-20%, ρ3-30%
Stearic acid (SA) concentration: α1-4%, α2-8%, α3-12%
Each formulation contains: Metformin HCl-500mg, Microcrystalline cellulose-quantity sufficient to 900 mg, Aerosil – 0.55%, Magnesium stearate – 0.55%

Table 1: Formulation of Metformin HCl matrix tablet as per 3^2 factorial design [8,9].

Formulations	P1	P2	P3	P4	P5	P6
Pioglitazone HCl	15	15	15	15	15	15
Avicel PH 102	128.5	125.5	122.5	128.5	125.5	122.5
Copovidone	3	3	3	3	3	3
Sodium starch glycollate	1.5	4.5	7.5	0	0	0
Crospovidone	0	0	0	1.5	4.5	7.5
Red iron oxide	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
Tablet weight (mg)	150.0	150.0	150.0	150.0	150.0	150.0

Table 2: Formulation of immediate release tablet of Pioglitazone HCl.

K_{HC}: The rate constant for Hixson-Crowell rate equation.

Mechanism of drug release: A simple relationship which described drug release from a polymeric system is described in (eqn. 5). To find out the mechanism of drug release data was fitted in Korsmeyer-Peppas model [10].

$$Mt/M_{\infty} = Kt^n \qquad (5)$$

Where, M_t/M_{∞}: Fraction of drug released at time t;

K: The rate constant and n is the release exponent.

The n value is used to characterize different release mechanisms. For cylinder shape matrices diffusion exponent of 0.45 represents fickain diffusion, $0.45 < n < 0.89$ represents anomalous (non-fickian) diffusion, 0.89 represents case-II transport and $n > 0.89$ indicates super case-II transport.

Similarity assessment between formulations: Similarity factor ($f2$) was used to compare the difference of dissolution profile after regular intervals. According to FDA guidelines, $f2$-values between 50 and 100 ensure similarity of two sets of dissolution data.

$$f_2 = 50 \, log \left\{ \left[1 + 1/n \sum_{t=1}^{n} \left(R_t - T_t \right)^2 \right]^{-0.5} \times 100 \right\} \qquad (6)$$

Where R_t and T_t represent dissolution values of the reference and test products, respectively.

Statistical analysis: The statistical evaluation of dependent variables was performed by analysis of variance (ANOVA) using Microsoft Office Excel 2003. The confidence limit was set at 95%. Mean ± SD for tablet thickness, weight and hardness of tablets was calculated by using Microsoft Office Excel 2003.

Results

Table 3 indicates the results of physicochemical tests such as weight variation, friability, hardness and thickness performed on the Metformin tablet formulations. The data show that hardness ranged from 66 to 80 N while thickness ranged from 5.10-5.41 mm. The hardness and thickness of tablets produced by increasing PEO and SA was statistically significant ($p < 0.05$). The friability for all the batches was below the pharmacopoeia limit and assay values in the range 98.20%-100.10%.

Table 4 indicates the results of physicochemical tests performed on the Pioglitazone tablet formulations. The data show that hardness ranged from 74 to 82 N while thickness ranged from 3.56-3.66 mm. The hardness and thickness observed for tablets produced by different disintegrate concentration was statistically significant ($p < 0.05$). The friability for all the batches was in the range 0.18%-0.34% and assay values in the range 98.20%-102.20%.

Table 5 indicates the results of physicochemical tests performed on the dual release tablet formulation. The data show that average hardness of 85 N while thickness of 5.99 mm. The friability was 0.21%. Assay value of 99.82 and 98.95% for Metformin and Pioglitazone respectively.

Formulation code	Average weight (mg)[a] n=20	Thickness (mm)[a] n=10	Hardness (N)[a] n=10	Friability (%) n=10	Assay (%) n=20
M1	902 ± 4.04	5.30 ± 0.02	80 ± 4.06	0.21	99.92
M2	901 ± 3.97	5.23 ± 0.02	78 ± 4.45	0.25	99.96
M3	900 ± 3.76	5.20 ± 0.01	74 ± 3.91	0.31	100.10
M4	899 ± 4.51	5.25 ± 0.02	75 ±2.83	0.28	100.02
M5	900 ± 4.37	5.24 ± 0.01	74 ± 3.95	0.26	99.97
M6	900 ± 4.66	5.20 ± 0.03	76 ± 2.07	0.19	99.95
M7	901 ± 3.72	5.23 ± 0.02	79 ± 2.62	0.21	98.20
M8	904 ± 4.73	5.22 ± 0.01	75 ± 4.14	0.23	99.20
M9	898 ± 5.00	5.10 ± 0.03	70 ± 4.58	0.28	97.85

[a]Mean ± SD

Table 3: Physicochemical evaluation of extended release Metformin HCl tablets.

Formulation code	Average weight (mg)[a] n=20	Thickness (mm)[a] n=10	Hardness (N)[a] n=10	Friability (%) n=10	DT (Sec)	Assay (%) n=20
P1	150 ± 2.96	3.56 ± 0.05	74 ± 3.10	0.25	75	99.20
P2	151 ± 2.19	3.61 ± 0.04	76 ± 4.47	0.16	67	97.75
P3	148 ± 2.32	3.63 ± 0.02	77 ± 4.92	0.34	55	98.25
P4	152 ± 3.27	3.64 ± 0.03	78 ± 4.49	0.22	55	98.28
P5	150 ± 2.68	3.65 ± 0.04	80 ± 4.50	0.17	42	103.10
P6	148 ± 2.51	3.67 ± 0.05	79 ± 4.64	0.29	38	99.95

[a]Mean ± SD; DT: Disintegration Time

Table 4: Physicochemical evaluation of immediate release Pioglitazone HCl tablets.

Formulation code	Average weight (mg)[a] n=20	Thickness (mm)[a] n=10	Hardness (N)[a] n=10	Friability (%) n=10	DT (sec)[#]	Assay (%) n=20
DR	1052 ± 4.91	5.99 ± 0.02	85 ± 4.18	0.21	68	99.82* 98.95[#]

[a]Mean ± SD, *-for Metformin, [#]-for Pioglitzone

Table 5: Physicochemical evaluation of dual release tablets.

Evaluation of *in vitro* release

The *in vitro* drug release studies were carried out in biphasic media (i.e. 0.1 N HCl followed by pH 6.8 phosphate buffer) for all test formulations along with a marketed product and results are shown in Figures 1-3.

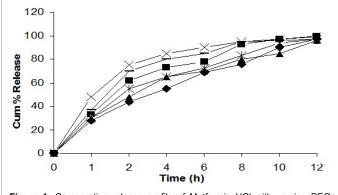It is evident that in case of extended release layer, drug release rate

Figure 1: Comparative release profile of Metformin HCl with varying PEO content.
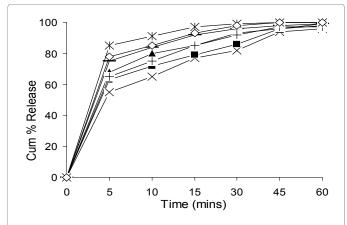

Figure 2: Comparative release profile of Pioglitazone HCl (P1=X; P2=■; P3=▲; P4=+, P5=▬, P6=ж); with marketed product (MP=◊).
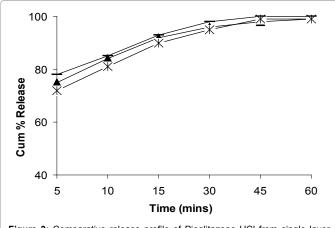

Figure 3: Comparative release profile of Pioglitazone HCl from single layer immediate release tablet and dual release tablet (P5=▲, DR=ж) with marketed product (MP=▬).

was decreased as the concentration of polyethylene oxide (PEO) and stearic acid (SA) increased. The release profile of M6 formulation is similar with marketed product and having f2 value (similarity factor) of 81.08. The results of dissolution data from dissolution profiles fitted to various drug release kinetic equations of zero order, first order, Higuchi, Hixson-Crowell and Korsemeyer Peppas having r, n and k. Higuchi and Peppas model found to be best fitted for formulation M6 with higher correlation coefficient value 0.9780 and 0.9910 respectively the values of n was found to be 0.4967. Also it is evident that in case of immediate release Pioglitazone layer, drug release is dependent on the type and particle size of disintegrant. The release profile of P5 formulation is similar with marketed product and having f2 value (similarity factor) of 84.08.

Discussion

Metformin HCl has a relatively shorter half-life of 2-6 h and bioavailability of about 50%-60% for 500 mg immediate release tablet hence it can be a good candidate for extended release formulation. In the present study an attempt was made to control the delivery of Metformin HCl by using combination of hydrophilic (PEO) and hydrophobic (SA) release retarding excipients. Furthermore effect of different disintegrant was studied on immediate release layer of Pioglitazone HCl [11].

It can be seen from physicochemical properties of the tablet, that the weight variation obtained for all formulations were well in the range of official limit. The friability of all the formulations was found to be less than 1.0%, which shows the durability of the prepared tablets; resistance to loss of weight indicates the tablet's ability to withstand abrasion in handling, packaging, and shipment. These data suggest that the use of combination of polyethylene oxide and stearic acid can produce physically stable formulation which also justified the selection of polymers for present study. The hardness of the tablet produced by melt granulation technique was varied in the range of 70-80 N (Table 3) and was found to be dependent on the level of PEO and which was statistically significant ($p<0.05$). The drug content study proved that all the formulations had better uniformity and the amount between the formulations did not vary more than 3% (Table 3).

In case of Pioglitazone tablet showed the disintegration time of less than 1.5 minutes and the drug content study proved that all the formulations had better uniformity between and amount between formulations varies from 97.75-103.10% (Table 4). The hardness and thickness observed for tablets produced by different disintegrant concentration was statistically significant ($p<0.05$).

In vitro dissolution studies showed decrease in release rate of Metformin HCl with increase in the concentration of polyethylene oxide (PEO) and stearic acid (SA). The results of this study are consistent with the previous findings in a previous report, which showed effect of PEO concentration on drug release [12,13]. In contact with an aqueous medium, poly (ethylene oxide) hydrates and gels superficially, the polyether chains of PEO forming strong hydrogen bonds with water. Drug release from poly (ethylene oxide) matrices is controlled by polymer swelling and erosion, or drug diffusion through the gel, or by both processes [14]. Higuchi and Peppas model found to be best fitted for formulation M6 with higher correlation coefficient value 0.9780 and 0.9910 respectively the values of n was found to be 0.4967 indicating anomalous transport and diffusion mechanism with erosion.

The f2 value (similarity factor) of 84.08 was found for formulation P5 of piglitazone layer indicated equivalence of in vitro release profile.

Inlay tablet prepared by using optimized composition of Metformin HCl and Pioglitazone HCl showed acceptable physicochemical properties as like mono drug tablet. *In vitro* release profile of inlay tablets has f2 value (similarity factor) of 81.92 for Metformin HCl and 82.53 for Pioglitazone HCl with its mono layer tablet.

Conclusion

In conclusion, a dual release tablet containing an extended release Metformin HCl and immediate release Pioglitazone was successfully developed for the treatment of Diabetes mellitus using hot melt granulation method and combination of PEO and SA for extended release layer.

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