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FORMULATION DESIGN, PREPARATION AND *IN VITRO* CHARACTERIZATION OF PIOGLITAZONE HCL SOLID DISPERSION

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ABSTRACT

Pioglitazone hydrochloride is a novel antidiabetic drug in thiazolidinediones group and it improves insulin sensitivity in insulin resistant patients. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. The present study is an attempt to enhance the dissolution rate of pioglitazone HCl by solid dispersion technique. The solid dispersions were prepared by physical mixture method using drug and carriers (β-cyclodextrin and PEG 6000) in the ratios of 1:1, 1:2 and 1:3 respectively. The drug carrier interaction study was carried out by Fourier Transform Infrared Spectroscopy (FTIR). The prepared solid dispersions were characterized for percentage yield, bulk density, tapped density, Carr's Index, Hausner's ratio, angle of repose, drug content, drug dissolution and stability study. The FTIR study suggesting no interaction between drug and carrier of solid dispersion. The physical mixture technique was found to be efficient method to obtained good yield solid dispersions with good flow properties. The drug content was found in the ranges of 75.6±0.34 to 86.2±0.19 %. Dissolution study revealed that there is marked enhancement in the dissolution rate of pioglitazone from all the solid dispersions when compared to pure pioglitazone itself. From the *in vitro* drug release profile, it can be seen that formulation F6 (1:3 ratio of drug: PEG 6000) shows higher dissolution rate compared with other formulations. All pioglitazone solid dispersions were found to be stable in various storage temperatures. All data are found to be significant by applying one way ANOVA at 5% level of significance ($p < 0.05$).

INTRODUCTION:

Oral bioavailability of drugs depends on its dissolution rate, therefore major problems associated with these drugs was its very low aqueous solubility, which results into poor bioavailability after oral administration. Many methods are available to improve dissolution rate, solubility characteristics, including salt formation, micronization, and addition of solvent or surface active agents[1]. Solid dispersions prepared by physical mixture method, which is most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs[2,3]. Several water soluble carriers such as mannitol, urea, lactose, citric acid, polyvinyl pyrrolidone, β-cyclodextrin and polyethylene glycols are used as carriers for enhancement of aqueous solubilty[4-6].

Pioglitazone hydrochloride is a thiazolidinedione antidiabetic agent that decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output[7]. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma[8]. The solid dispersions of pioglitazone solve the problems like gastro-intestinal disturbances, headache, dizziness, fatigue and insomnia[9]. Pioglitazone is practically insoluble in water; this prompted us to investigate the possibility of improving the solubility of drug by preparing solid dispersion of pioglitazone prepared by physical mixture techniques with water-soluble carriers β-cyclodextrin and PEG 6000.

MATERIALS AND METHOD:

Pioglitazone HCl was obtained as gift sample from Cipla Ltd., Baddi, Himachal Pradesh, India. β-cyclodextrin and PEG 6000 were procured from Loba Chemie Pvt. Ltd., Banglore, India. All other chemicals and reagents used were of analytical grade and procured from authorized dealer.

Preparation of solid dispersion by physical mixture

The physical mixtures were prepared using pioglitazone HCl as drug, β-cyclodextrin (F1, F2 and F3) and PEG 6000 as carriers in the ratios of 1:1, 1:2 and 1:3 (F4, F5 and F6) respectively[3]. The pure drug of pioglitazone HCl was considered as formulation F0. The required quantity of carrier was weighed in electronic digital balance (Sartorius Electronic balance, BT-2245, Calcutta, West Bangle, India), taken in a mortar and it was mixed with weighed quantity of drug with geometric dilution method. The mixture was then continuously mixed in a Pneumatic mixer (Rolex Pvt. Ltd., Calcutta, West Bangle, India) to form a homogeneous physical mixture. The physical mixture was dried properly using Hot air oven (Rolex Pvt. Ltd., Calcutta, West Bangle, India) at 45°C for 1 h. The dried mixture was passed through sieve no 80 and stored in a desiccator for further study.

Characterization of pioglitazone HCl solid dispersions

Fourier transforms Infrared radiation (FT-IR) studies

The FT-IR (Shimadzu IR spectrophotometer, model 840, Japan) was used for these IR analyses in the frequency range between 4000 and 600 cm^{-1} and at 1 cm^{-1} resolution[10]. The samples of pure drug pioglitazone, β-cyclodextrin, PEG 6000, physical mixtures of drug and carriers were prepared separately by palletization technique in KBr using IR press. The IR peaks of pure pioglitazone were analyzed and were compared with the peaks obtained from FTIR spectra of solid dispersions.

Percentage yield

The yield was calculated as the weight of the solid dispersion obtained from each batch divided by total weight of drug and carrier incorporated multiplied by 100. The percentage yields of each formulation were replicated three times[11].

Flow properties

Flowability of solid dispersions was investigated by determining angle of repose, bulk density, tapped density, Carr's index and Hausner ratio[12,13]. The angle of repose was determined by fixed funnel method. The physical mixtures were tapped using bulk density apparatus (Excel Enterprises, Kolkata, West Bangle, India) for 100 taps in a cylinder and the change in volume were measured. Carr's index and Hausner ratio were calculated by the formula: Carr's index (%) = $[(D_f - D_0)/D_f] \times 100$ and Hausner ratio = D_f / D_0, Where, D_f is tapped density; D_0 is poured density. All the experimental units were studied in triplicate (n=3).

Drug content

Solid dispersion of each formulation equivalent to 25 mg of pioglitazone HCl was accurately weighed and it was dissolved in methanol. The solution was filtered through Whatmann filter paper no 1. The filtrate solution was suitably diluted with 0.1N HCl. Then the amount of drug present in solution was analyzed by using UV-Visible spectrophotometer (Shimadzu UV spectrophotometer, model 1700, Japan) at λ_{max} 269 nm[14]. All the experimental units were studied in triplicate (n=3).

In vitro drug release study

The release profile of an entrapped drug predicts how a delivery system might function and gives valuable insight into its *in vivo* behavior. *In vitro* release profile for each solid dispersions as well as pure drug was performed using USP XXII type 2 dissolution apparatus (IP/ BP/ USP 8 paddle Digital Test Apparatus, Scientific Engineering Corporation Ltd., New Delhi, India)[14]. Sample equivalent to 30 mg of pioglitazone was added to 900 ml 0.1N HCl at (37±0.5)ºC and stirred at 50 rpm. An aliquot sample (5 ml) was withdrawn at an interval of 15 min with replacement of fresh medium and each drug solution was analyzed for

pioglitazone content by UV-Visible spectrophotometer at 269 nm. The same method was adopted for each formulation of solid dispersion. All the experimental units were studied in triplicate (n=3).

Accelerated stability study

Stability studies were performed according to ICH guidelines[15]. The formulations were stored in hot air oven at (37±2, 45±2 and 60±2) °C for a period of 12 weeks. The samples were analyzed for drug content every two weeks by UV-Visible spectrophotometer at 269 nm.

Statistical analysis

Each value is expressed as mean ± standard deviation (n = 6). For determining the statistical significance, standard error mean and one way analysis of variance (ANOVA) at 5 % level significance was employed. P values < 0.05 were considered significant[16].

RESULTS AND DISCUSSION:

The physical mixtures were found to be efficient methods to obtained good yield solid dispersions. The interaction between the drug and carriers often leads to identifiable changes in the FTIR profile of solid systems. FTIR spectra at 45 scans and a resolution of 1 cm-1 were recorded in KBr pellets for pure drug (Fig 1A), polymer (β-cyclodextrine) (Fig 1B), physical mixture of drug β-cyclodextrine (Fig 1C), polymer (PEG 6000) (Fig 1D) and physical mixture of drug PEG 6000 (Fig 1E) as represented in Fig 1. The spectrum of solid dispersion formulation was equivalent to the addition spectrum of polymers and drug indicating no interaction occurring in the solid dispersion of drug and polymers. The yields of all the formulations were good and satisfactory as shown in Table 1. The yields varied from 98.89±0.02 to 99.82±0.09 %, suggesting that the processing parameters did not affect the yield from the solid dispersions prepared by both methods. The bulk density, tapped density, angle of repose, Hausner's ratio and Carr's index values of the prepared solid dispersion are represented in Table 2. The bulk density was found in the ranges of 0.78±0.22 to 0.92±0.18 g/cc. The solid dispersion of all formulations had Hausner's ratio of 1.237 or less indicating good flowability. The Carr's index was found between 15.625 to 19.192 indicating good flowability. The good flowability of the solid dispersion was also evidenced with angle of repose within range of 25.7±0.44 to 29.8±0.26°, which is below 30° indicating good flowability. Relatively high drug content was observed for each formulation as presented in Table 2. The drug content was found in the ranges of 75.6±0.34 to 86.2±0.19 %. The maximum drug content was obtained with formulation F1 with drug β-cyclodextrin ratio is 1:1. The *in vitro* drug releases of acquired solid dispersions were shown in Table 2 and Fig 2. Cumulative percent drug released after 60 min was 91.1±1.25, 94.5±1.32, 87.7±1.02, 87.8±1.02, 85.5±1.12 and 97.6±1.10 % for F1, F2, F3, F4, F5 and F6 respectively, where as pure drug pioglitazone was releasing only 21.8±0.96 % in 60 min. *In vitro* release studies reveal that there is marked enhancement in the dissolution rate of pioglitazone from all the solid dispersions when compared to pure pioglitazone itself. From the *in vitro* drug release profile, it can be seen that formulation F6 (1:3 ratio of drug: PEG 6000) shows higher

dissolution rate compared with other formulations. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier. The accelerated stability studies were performed according to ICH guidelines for 12 weeks and the results were found to be stable in varying temperature as shown in Table 3. Data are found to be statistically significant (*F value* < *F crit*) by testing through one way ANOVA at 5 % level of significance ($p < 0.05$ that is $p = 0.029471$).

CONCLUSION:

The study concluded that the solid dispersion prepared by physical mixture method (F6, 1:3 ratio of drug: PEG 6000) shows higher dissolution rate compared with other formulations and pure drug. The study shows that the dissolution rate of pioglitazone can be enhanced to a great extent by solid dispersion technique. It is, however, suggested that further research on large scale be carried out by using other hydrophilic carrier.

TABLE 1. FORMULATION DESIGN OF PIOGLITAZONE SOLID DISPERSIONS WITH PEG 6000.

Sl. No.	Formulation code	Drug: carrier	Drug (g)	Carrier (g)	Yield (%) (X±S.D.)
1	F1	1:1	1.5	1.5	99.52±0.12
2	F2	1:2	1	2	99.82±0.09
3	F3	1:3	0.75	2.25	98.89±0.02
4	F4	1:1	1.5	1.5	99.12±0.11
5	F5	1:2	1	2	99.02±0.10
6	F6	1:3	0.75	2.25	99.23±0.08

Each value is expressed as mean ± standard deviation (n = 3). F1-F3 contains β-cyclodextrin and F4-F6 contains PEG 6000. Standard error of mean < 0.069.

TABLE 2. FLOW PROPERTIES, DRUG CONTENT AND IN VITRO DRUG RELEASE STUDY OF VARIOUS PIOGLITAZONE HCL SOLID DISPERSIONS.

Parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Bulk density (g/cc) (X±S.D.)	0.78±0.22	0.80±0.31	0.81±0.14	0.92±0.18	0.80±0.27	0.81±0.16
Tapped density (g/cc) (X±S.D.)	0.94±0.21	0.98±0.31	0.96±0.23	1.11±0.19	0.99±0.33	0.99±0.25
Carr's Index (%)	17.021	18.367	15.625	17.117	19.192	18.182
Hausner's ratio	1.205	1.225	1.185	1.206	1.237	1.222
Angle of repose (°) (X±S.D.)	25.7±0.44	26.8±0.39	29.8±0.26	27.5±0.31	28.8±0.37	27.4±0.17
Flow comment	Good	Good	Good	Good	Good	Good
Drug content (%) (X±S.D.)	86.2±0.19	82.3±0.21	77.2±0.28	83.6±0.24	80.3±0.28	75.6±0.34
Cumulative % drug release (X±S.D.)	91.1±1.25	94.5±1.32	87.7±1.02	87.8±1.02	85.5±1.12	97.6±1.10

ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	70.32667	5	14.06533	0.207918	0.029471	4.387374
Within Groups	405.89	6	67.64833			
Total	476.2167	11				

Each value is expressed as mean ± standard deviation (n = 3). F1-F3 contains β-cyclodextrin and F4-F6 contains PEG 6000. Standard error of mean < 0.762. Data are found to be significant (*F value* < *F crit*) by testing through one way ANOVA at 5 % level of significance ($p < 0.05$ that is $p = 0.029471$)

TABLE 3. STABILITY STUDY OF VARIOUS PIOGLITAZONE HCL SOLID DISPERSIONS AS PER ICH GUIDELINES.

Formulation code	Storage Temp. (°C)	Potency of formulation (%)						
		Period of studies in week						
		1st day	2nd	4th	6th	8th	10th	12th
F1	99.97	99.81	99.74	99.55	98.43	98.39	98.32	99.97
	99.69	99.57	99.52	99.46	99.29	99.09	99.03	99.69
	99.33	99.28	99.04	98.89	98.77	98.41	98.28	99.33
F2	99.56	99.31	99.12	99.08	98.97	98.81	98.63	99.56
	99.26	99.11	99.04	98.96	98.81	98.69	98.44	99.26
	99.14	99.08	98.84	98.55	98.12	98.03	97.97	99.14
F3	99.26	99.11	98.92	98.85	98.70	98.44	98.32	99.26
	98.96	99.77	98.56	98.36	98.12	98.02	97.85	98.96
	98.66	98.42	98.39	98.16	98.01	97.88	97.62	98.66
F4	99.53	99.32	99.10	99.07	98.87	98.80	98.61	99.53
	99.22	99.10	99.04	98.94	98.81	98.67	98.41	99.22
	99.16	99.03	98.74	98.53	98.11	98.00	97.92	99.16
F5	99.94	99.80	99.72	99.54	98.41	98.36	98.31	99.94
	99.68	99.55	99.50	99.48	99.25	99.06	99.00	99.68
	99.32	99.26	99.00	98.88	98.74	98.43	98.29	99.32
F6	99.10	99.05	98.42	98.83	98.64	98.60	98.41	99.10
	98.92	98.75	98.56	98.40	98.34	98.26	98.02	98.92
	98.46	98.24	98.10	98.03	97.84	97.66	97.43	98.46

Potency has been expressed in terms of percentage drug content for period of 12 weeks.

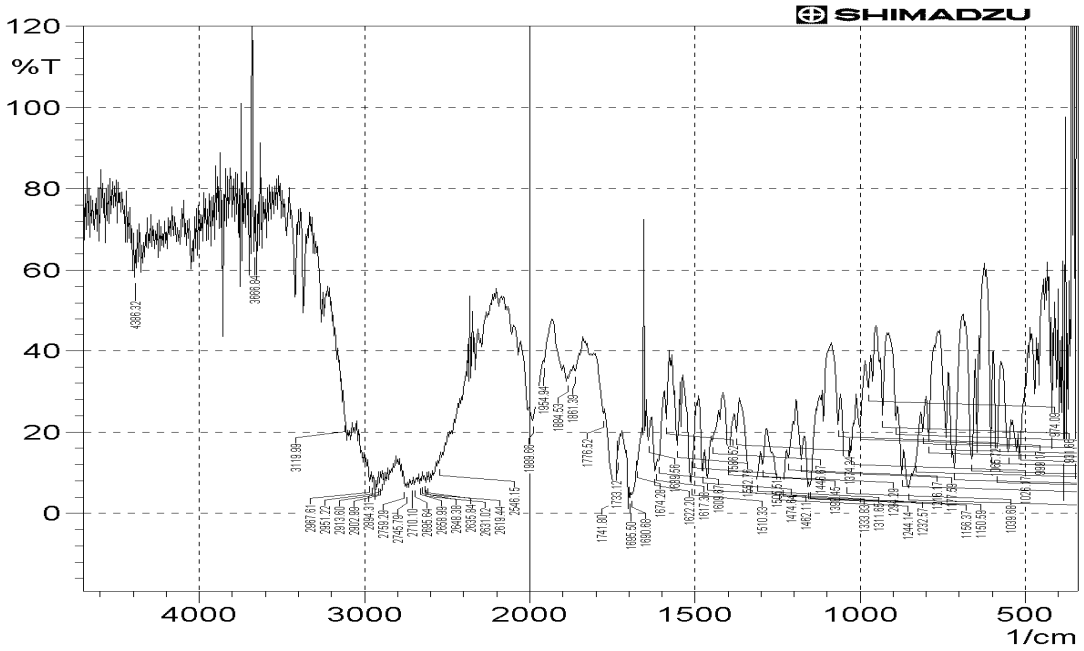

Fig 1A. FTIR spectra of pure drug pioglitazone HCl in the frequency range between 4000 and 600 cm^{-1} and at 1 cm^{-1} resolution.

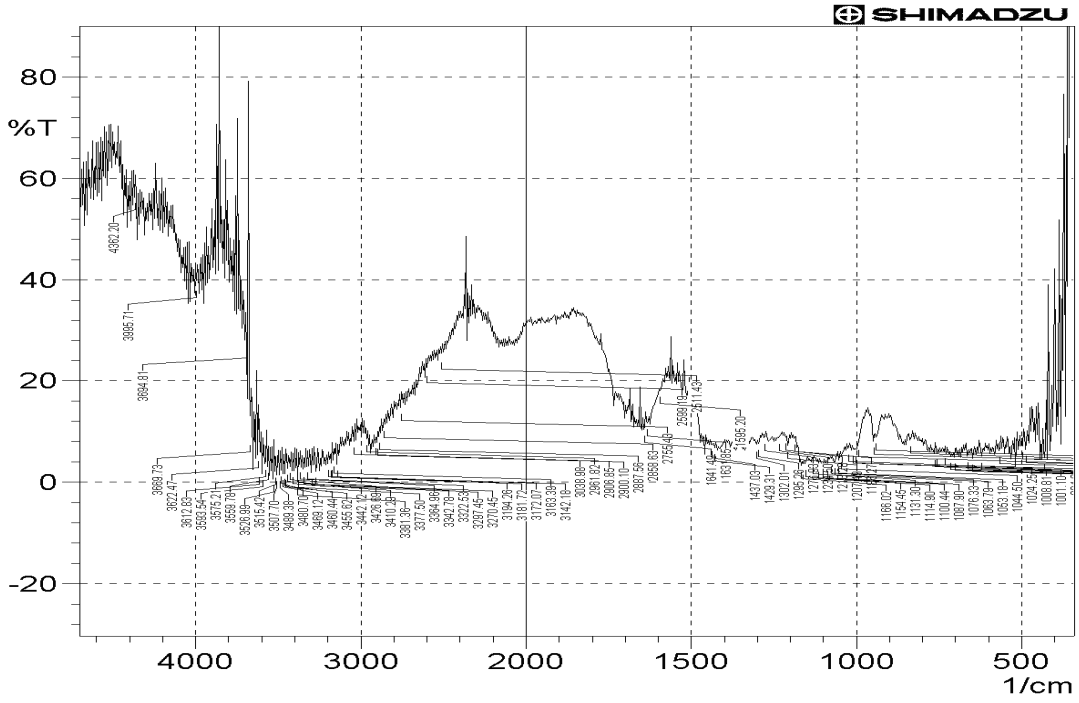

Fig 1B. FTIR spectra of carrier β-cyclodextrine in the frequency range between 4000 and 600 cm^{-1} and at 1 cm^{-1} resolution.

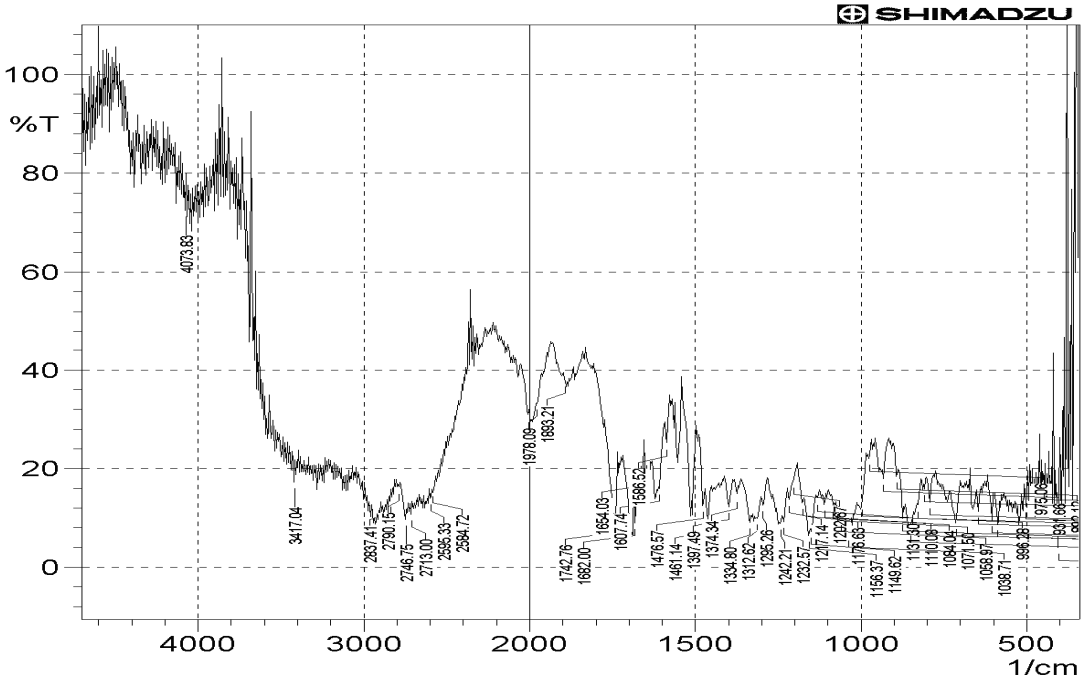

Fig 1C. FTIR spectra of pioglitazone β-cyclodextrine physical mixture in the frequency range between 4000 and 600 cm^{-1} and at 1 cm^{-1} resolution.

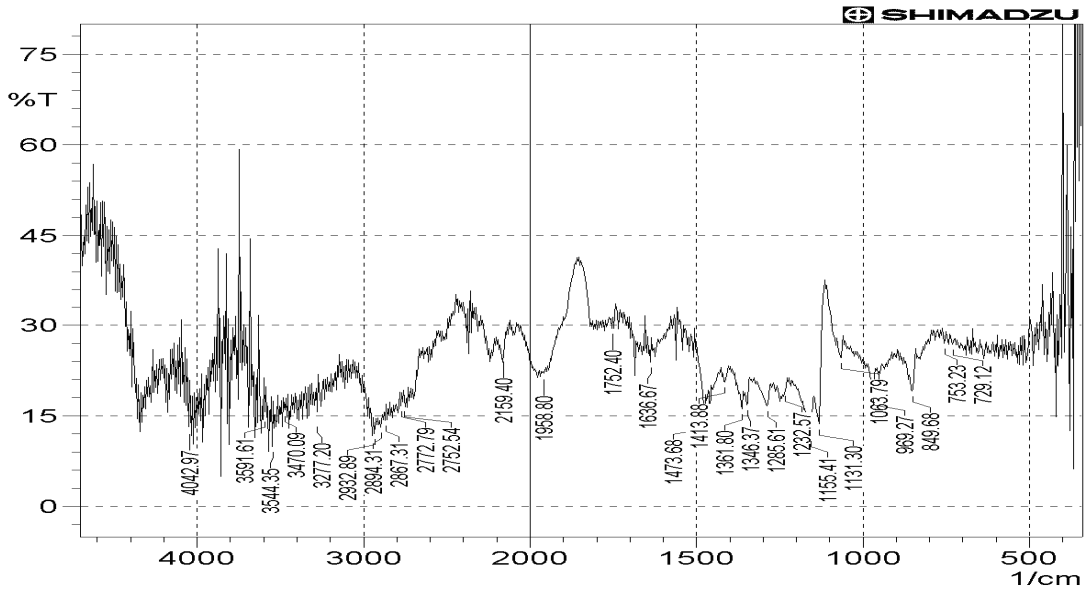

Fig 1D. FTIR spectra of carrier PEG 6000 in the frequency range between 4000 and 600 cm^{-1} and at 1 cm^{-1} resolution.

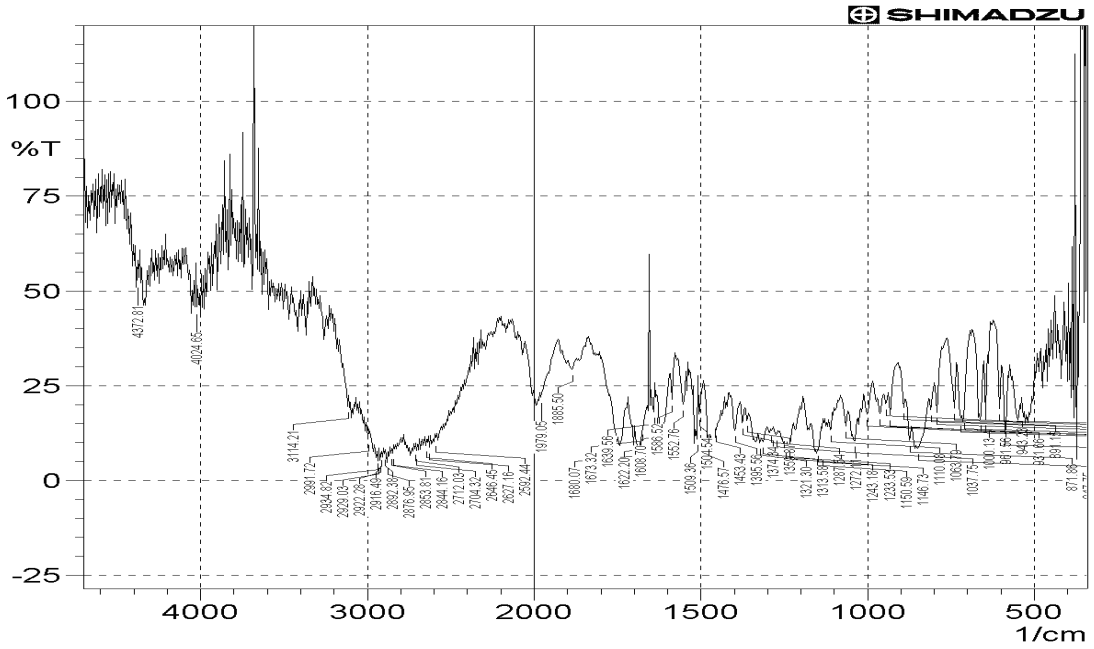

Fig 1E. FTIR spectra of pioglitazone peg 6000 solid dispersion in the frequency range between 4000 and 600 cm^{-1} and at 1 cm^{-1} resolution.

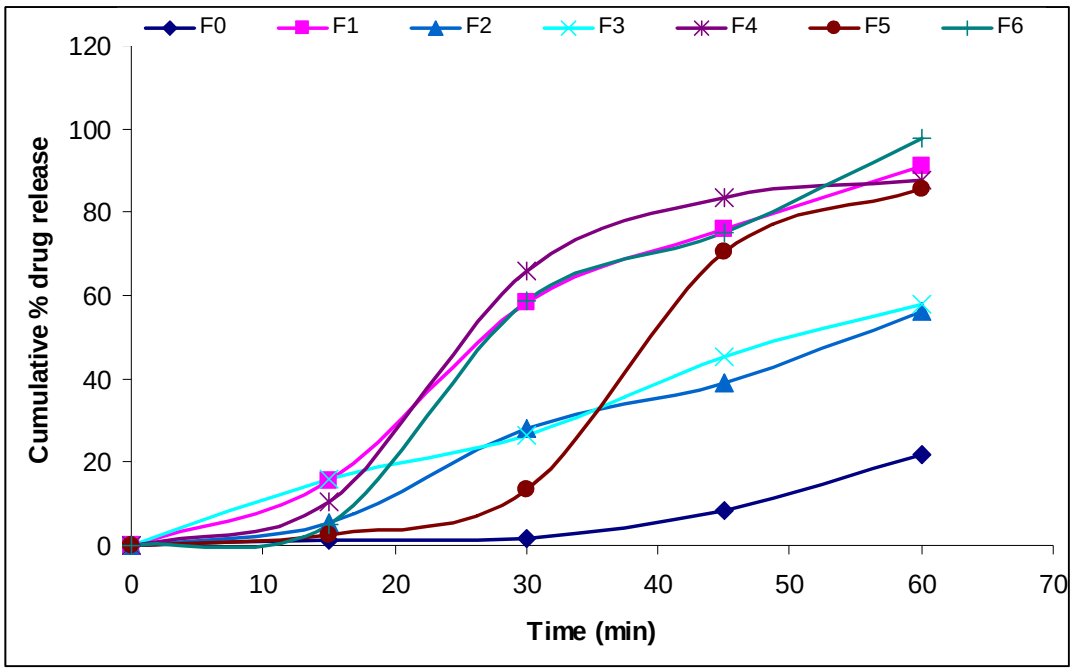

Fig 2. *In vitro* drug release profile of pioglitazone solid dispersions in 0.1N HCl.

F0 – Pioglitazone HCl pure drug.

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