ORIGINAL ARTICLE

In vitro-in vivo evaluation of fast-dissolving tablets containing solid dispersion of pioglitazone hydrochloride

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ABSTRACT

Investigation of *in vitro/in vivo* behavior of fast-dissolving tablets containing solid dispersions of pioglitazone hydrochloride (PIO) is the focus of the present research work. The effect of various hydrophilic polymers on the aqueous solubility of PIO was studied. Poly vinyl pyrrolidine K 30 (PVPK 30) carrier was selected and solid dispersions were prepared by various methods. Evaluation of solid dispersion for percentage yield, drug content, solubility, and Fourier Transform Infrared-indicated kneading method was most appropriate. Furthermore, the dissolution studies exhibited an enhancement in drug dissolution. One-way ANOVA of *in vitro* data suggested that there was significant ($P \leq 0.05$) difference in dissolution profile of PIO solid dispersion when compared with pure drug and commercial product. Infrared spectroscopy, differential scanning calorimetry, and powder X-ray diffraction performed on solid dispersion indicated lack of physicochemical interaction between the drug and the carrier. The selected formulation is compressed into fast-dissolving tablets which were further evaluated for tablet properties and *in vitro* drug release. *In vivo* studies of pure drug, selected formulation, and marketed product were carried out in male Wistar rats and pharmacokinetic parameters were calculated using Kinetica software 2000. The best formulation has shown T_{max} of 1 hour which was highly significant ($P < 0.01$) when compared with pure drug and marketed formulation. Therefore, the solid dispersions prepared by kneading method using PVPK 30 as hydrophilic carrier can be successfully used for improvement of dissolution of PIO and resulted in faster onset of action as indicated by *in vivo* studies.

Key words: Dissolution profile, hydrophilic carriers, kneading method, solubility, solid dispersions

INTRODUCTION

Pioglitazone, 5-[4-[2-(5-Ethyl-2-pyridinyl) ethoxy] benzyl] thiazolidine-2,4-dione, is a thiazolidinedione derivative with insulin-sensitizing effect that acts as agonist of the peroxisome proliferator-activated receptor subtype gamma in type II diabetes. Pioglitazone hydrochloride (PIO) has biological half-life of 4 to 7 hours with excellent oral bioavailability (83%).[1,2] Although at steady state, the maximum plasma drug concentrations (C_{max}) were reported as 0.7 (for 15 mg/day dose) and 1.2 mg/l (for 30 mg/day dose), the T_{max} were reported to be 4.8 and 3.7 hours, respectively. This delayed T_{max} may be due to the poor aqueous solubility of PIO (solubility of 0.015 mg/ ml) and may result in the delayed onset of action because of subtherapeutic plasma drug levels; may also lead to therapeutic failure.[3]

Solid dispersions[4,5] refer to a system in which hydrophobic drug is dispersed in hydrophilic matrix, in order to improve its dissolution properties and bioavailability. In solid dispersion, a drug can exist in an amorphous or

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crystalline form in hydrophilic polymeric carriers[6,7] such as polyethylene glycols (PEG), poly vinyl pyrrolidine K 30 (PVPK 30), urea, etc. which results in improved solubility and dissolution rates.

Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of noncompliance and ineffective therapy.[8] Fast-dissolving tablets also called orodispersible tablets are gaining prominence as new drug-delivery systems. These dosage forms dissolve or disintegrate in the oral cavity within three minutes[9] without the need of water or chewing. Fast-dissolving tablets of loratadine, piroxicam, famotidine, clonazepam, etc. are commercially available.[10]

The objective of the present research work was to formulate solid dispersions of PIO; various hydrophilic carriers were evaluated to determine their effect on solubility of PIO; different methods were then evaluated to select the best method of preparation of solid dispersions. Furthermore, the solid dispersions were formulated into fast-dissolving tablets and effect of formulation on the T_{max} of PIO was studied.

MATERIALS AND METHODS

Materials

PIO was a gift sample from Aurobindo Pharma, (Hyderabad, India). PEG 4000, PEG 6000, PEG 20,000 (PEG 20 K), and PVP K30 were provided by Dr. Reddy's Laboratories Ltd (Hyderabad, India). Urea, citric acid, and mannitol were procured from Himedia, New Delhi. All other reagents and solvents used were of analytical grade.

Methods

Solubility studies of pure pioglitazone in distilled water and buffers

Solubility studies were carried out by Higuchi and Connors method.[11] An excess amount of pioglitazone was added to distilled water, pH 1.2 and pH 7.4 buffers, respectively, in different screw-capped bottles. The bottles were placed in holder and shaken at room temperature (26 ± 2°C) in water bath shaker for 24 hours. The samples were filtered through membrane filter (0.22 μm). The filtrate was diluted suitably and analyzed using UV spectrophotometer (Shimadzu Pharmaspec-1700 UV- visible spectrophotometer) at 270 nm.

Screening of appropriate carrier for pioglitazone solid dispersion

The physical mixtures (PMs) of pure drug and different water-soluble polymers viz., mannitol, citric acid, urea, PEG 4000, PEG 6000, PEG 20 K, and PVP K30 in the ratio 1 : 1 were subjected for solubility studies, in distilled water by the method described above. Based on the results obtained, PEG 20 K and PVP K30 were chosen as carriers for solid dispersion.

Preparation of solid dispersions

Solid dispersions were prepared by three different methods viz., kneading, hot-melt, and microwave method. The drug to carrier ratio is shown in Table 1.

Kneading method

The drug and carrier were gently mixed to get uniform mixture.[12] Water : methanol in the ratio of 1 : 1 was added in small quantity to make a paste. The paste was allowed to stand for 45 minutes and dried in hot air oven at 40 ± 2°C. The product obtained was pulverized and passed through mesh (#) 85.

Hot-melt method

The carrier was melted in a china dish and the drug was dispersed in it to get molten mixture which was constantly stirred. The dispersion was cooled.[13] The product obtained was dried at room temperature and was passed through mesh (#) 85.

Microwave method

Initially, the drug and carrier were gently mixed to get uniform mixture. Fixed amount of this mixture was subjected to microwave at the power of 800-1500 W in a domestic microwave oven (Samsung M1739N) at a precise place for optimized duration of 2 minutes.[14] The products were kept at room temperature, pulverized, and passed through mesh (#) 85. The various positions viz., corner, center, and off center inside the oven were optimized by keeping the time constant at 2 minutes.

The prepared formulations were evaluated for % yield, drug content, solubility analysis, and Fourier Transform Infrared (FTIR) studies in order to select the appropriate method of preparation. Based on the above studies, the formulation F4, F10, and F16 were selected for further studies.

Evaluation of Solid Dispersions

Percentage yield

Yield was calculated with respect to dry product. Based on the practical yield (P.Y) obtained and the calculated theoretical yield (T.Y), % yield was calculated by using the following formula:

$$\%\text{Yield} = \frac{\text{P.Y} \times 100}{\text{T.Y}}$$

Drug content

Solid dispersion equivalent to 15 mg of PIO was taken and dissolved in 100-ml volumetric flask in 0.2M HCl. Absorbance was measured at 270 nm in triplicate.

Solubility Studies of Solid Dispersions

An excess[11] of pure PIO and prepared solid dispersions were added to screw-capped bottles containing distilled

Table 1: Effect of the method and drug to polymer ratio on % yield, drug content, and solubility of solid dispersions

Formulation codes	Method of preparation	Drug : PEG	Drug: PVPK 30	% Yield	% Drug content	Solubility (mg/ml)
PIO	Pure drug	-	-	-	-	0.013 ± 0.002
F1	Kneading	1:0.5	-	91.56 ± 0.005	96.56 ± 0.001	0.356 ± 0.035
F2	Kneading	1:1	-	89.59 ± 0.001	95.16 ± 0.021	0.332 ± 0.001
F3	Kneading	1:1.5	-	92.86 ± 0.004	97.18 ± 0.008	0.407 ± 0.001
F4	Kneading	-	1:0.5	94.17 ± 0.008	98.15 ± 0.006	0.386 ± 0.003
F5	Kneading	-	1:1	89.16 ± 0.002	98.10 ± 0.003	0.357 ± 0.000
F6	Kneading	-	1:1.5	94.38 ± 0.005	98.78 ± 0.001	0.348 ± 0.003
F7	Hot melt	1:0.5	-	78.15 ± 0.002	85.13 ± 0.001	0.286 ± 0.002
F8	Hot melt	1:1	-	72.90 ± 0.002	70.18 ± 0.002	0.243 ± 0.008
F9	Hot melt	1:1.5	-	81.86 ± 0.002	41.56 ± 0.002	0.325 ± 0.001
F10	Hot melt	-	1:0.5	84.41 ± 0.002	78.63 ± 0.002	0.231 ± 0.005
F11	Hot melt	-	1:1	86.39 ± 0.003	73.46 ± 0.003	0.206 ± 0.002
F12	Hot melt	-	1:1.5	81.33 ± 0.003	51.89 ± 0.001	0.279 ± 0.001
F13	Microwave	1:0.5	-	89.10 ± 0.004	93.20 ± 0.003	0.303 ± 0.002
F14	Microwave	1:1	-	90.36 ± 0.005	94.56 ± 0.004	0.379 ± 0.001
F15	Microwave	1:1.5	-	89.20 ± 0.002	91.25 ± 0.002	0.377 ± 0.001
F16	Microwave	-	1:0.5	81.75 ± 0.002	93.26 ± 0.001	0.365 ± 0.002
F17	Microwave	-	1:1	80.25 ± 0.001	92.81 ± 0.001	0.362 ± 0.002
F18	Microwave	-	1:1.5	80.08 ± 0.001	91.31 ± 0.003	0.392 ± 0.002

Mean ± SD, n = 6 PEG - polyethylene glycols; PVPK - Poly vinyl pyrrolidine K

water. Bottles were shaken mechanically at 26 ± 2°C for 24 hours and aliquots were withdrawn, filtered (0.22 μm), and assayed for drug content at 270 nm spectrophotometrically.

Fourier Transform Infrared Spectroscopy

FTIR spectra were recorded by potassium bromide (KBr) disc method using Shimazdu FTIR-8700 spectrophotometer (Tokyo, Japan). The scanning range was 400 to 4 000/cm and the resolution was 4/cm.

Powder X-ray Diffractometry

Powder X-ray diffraction (PXRD) patterns for pure PIO, PM, and selected formulations were recorded on a Rigaku Geigerflex diffractometer using Ni-filtered, CuKα radiation, a voltage of 40 kV, and a 25-mA current.

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) analysis was performed using Perkin-Elmer series 7 DSC on 2 to 8 mg samples (Sartorius BP 210 S Germany) of pure PIO, PM, and selected formulations. Samples were heated in an open aluminum pan at a rate of 10°C/min in a 0 to 250°C temperature range under a nitrogen flow of 40 ml/min as purging gas.

In vitro Release Studies

The *in vitro* dissolution for the selected solid dispersions (equivalent to 15 mg of PIO) was carried out by using USP type II apparatus (Paddle method). The dissolution medium used was distilled water (900 ml), maintained at 37 ± 0.5°C with rotational speed of 75 rpm. At an interval of 15 minutes, samples were withdrawn and filtered through filter paper (0.22 μm) and were analyzed spectrophotometrically at 270 nm after appropriate dilutions, against a similarly treated blank.

Similarly, the pure drug (15 mg) and PM were subjected for *in vitro* drug release studies and the release profile was compared with selected formulations.

Mathematical Analysis of *in vitro* Data

The data obtained from *in vitro* release studies were analyzed by curve fitting method to various models viz., Zero, First order kinetics, Higuchi and Korsmeyer-Peppas model, using PCP disso v2.08 software. Dissolution efficiency (DE)[15,16] is the area under the dissolution curve up to a certain time 't' expressed as percentage of area of the rectangle described by 100% dissolution in the same time [Table 2].

Mean dissolution time (MDT) was calculated by using the equation[17]

MDT= (n / n +1). k- 1/ n

Where, n = release exponent and k = release rate constant.

The dissolution data of pure PIO, PM, selected formulations, and Marketed formulation (MF) were further statistically analyzed by one way ANOVA technique (Graphpad Instat

software; demo version) where $P \leq 0.05$ considered being significant.

Preparation of Pioglitazone Hydrochloride Tablets

The solid dispersion having the maximum solubility and dissolution rate was selected for preparation of fast-dissolving tablets prepared according to the formula [Table 3]. Formulation F4, the solid dispersion prepared by kneading method, was selected and 15 mg PIO equivalent was incorporated into each tablet. All the ingredients were passed through mesh # 80, mixed thoroughly to get uniform mixture and compressed on a ten station tablet punching machine (Cadmach, India) equipped with flat-faced 6-mm punches. The tablet weight was adjusted to ~100 mg.

Evaluation of the Prepared Tablets

The tablet thickness was determined by using Vernier caliper, while the tablet hardness and friability was determined using Monsanto tablet hardness tester and friabilator (Roche), respectively. The disintegration time was measured by using tablet disintegrator (Electrolab, India). Wetting time was determined by well-reported method. A tissue paper was folded double and placed in a Petri dish (internal diameter 10 cm) containing 10 ml of Amaranth solution. The tablet was carefully placed on the surface of tissue paper. The time required for the tablet to get colored completely pink was noted as wetting time.

In vitro Release Studies of Pioglitazone Tablets

The release rate of fast-dissolving tablets containing pure PIO (T1), solid dispersion of PIO (T4), and MF (containing equivalent of 15 mg of PIO) ($n = 6$) was determined using USP type II apparatus (Paddle method). The dissolution test was performed using 900 ml of simulated gastric fluid, at 37 ± 0.5°C and 75 rpm. At an interval of 15 minutes, samples were withdrawn and filtered through filter paper (0.22 μm). The samples were analyzed spectrophotometrically at 270 nm against similarly treated blank.

In order to evaluate the similarity between the best formulation and MF, the *in vitro* dissolution profiles of both were compared. Similarity factor ($f2$) was calculated[18] by using the following formula:

$$f2 = 50 \times \log \{[1+(1/n) \sum_{j=1} (Rj - Tj)^2]^{-0.5} \times 100 \}$$

In vivo Studies

The bioavailability studies for tablets with pure PIO (T1), solid dispersion of PIO (T4), and MF (Pioglit^R) were carried out using male Wistar rats (200-250 g). The animals were

Table 2: Curve fitting of selected solid dispersions along with dissolution efficiency of pioglitazone hydrochloride

Mathematical models		Pure PIO	Physical mixture (PM)	F4	F16
Zero-order model	R_1	0.9985	0.9766	0.8637	0.8801
First-order model	R_2	0.9944	0.9933	0.9566	0.9893
Higuchi-matrix model	R_3	0.9385	0.9685	0.9659	0.9710
Korsmeyer-peppas model	R_4	0.9973	0.9594	0.9553	0.9509
Hixson crowell model	R_5	0.9963	0.9893	0.9686	0.9900
Best fit model		Zero order	First-order	Hixson Crowell	Hixson Crowell
Korsmeyer-Peppas constant	N	1.2613	1.3180	0.5177	0.5971
	K	0.0439	0.0649	8.2539	5.6155
% DE	15 min	0.67	0.71	13.97	11.17
	30 min	1.36	2.06	27.62	23.07
	180 min	13.97	27.22	80.40	76.24
MDT	180 min	94.46	76.25	37.02	42.48

PIO - pioglitazone hydrochloride; MDT - Mean dissolution time; DE - Dissolution efficiency

Table 3: Composition of fast dissolving tablets of pioglitazone hydrochloride

Ingredient*	T1	T2	T3	T4	T5	T6	T7	T8
Pure PIO	15.00	-	-	-	-	-	-	-
Solid dispersion equivalent to 15 mg PIO	-	22.50	22.50	22.50	22.50	22.50	22.50	22.50
Sodium starch glycolate	5.00	5.00	5.72	6.70	8.00	4.28	3.30	2.00
Pharmaburst®	5.00	5.00	4.28	3.30	2.00	5.72	6.70	8.00
Aspartame	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
Talc	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Magnesium stearate	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Microcrystalline cellulose (q.s)	100	100	100	100	100	100	100	100

*All the ingredients were represented as % w/w

maintained in a clean room at a temperature between 20 – 25°C with 12-hour light and dark cycles and controlled relative humidity. The animals were fasted for 12 hours prior to commencement of the study as well as during the study and had access to water *ad libitum*. The institutional animal ethical clearance (vide letter no. AACP/IAEC/P-46/2007) was obtained before conducting the studies. They were divided into four groups (six in each group); group I served as a control group whereas other three groups were treated with tablet formulation containing pure drug PIO (T1), MF, and tablet formulation containing solid dispersion of PIO (T4), respectively. Tablets with a dose of 10 mg/kg body weight of rats were administered by dispersing in distilled water through oral feeding pipe.[19]

Blood samples were collected through the lateral tail vein[20] of rats at 0, 5, 10, 15, 20, 30, 40, 50, and 60 minutes followed by 3, 8, 12, and 24 hours after administration. The blood samples were centrifuged at 10 000 rpm for 10 minutes. After centrifugation, plasma was transferred into clean, fresh Eppendorf tubes and frozen at −20ºC until assayed. The plasma concentration of drug was determined by High Performance Liquid Chromatography (HPLC)[21] (Shimadzu LC 10 AT VP pumps; SPD-10 A detector), using Merck C-18 (250 mm × 4.6 mm, 5 µm) column and 0.05M potassium dihydrogen phosphate and methanol (35:65) as mobile phase at 258 nm.

The results obtained were analyzed for various non-compartmental pharmacokinetic parameters using Kinetica 2000 software. Furthermore, the pharmacokinetic data were analyzed statistically[22] by one way ANOVA followed by Dunett Post Hoc test for multiple comparison using graph pad prism (demo version).

In vitro-in vivo correlation

In Biopharmaceutical Classification System (BCS) of drugs, PIO was placed in Class II drug, i.e., drugs having high permeability and low solubility. Level A correlation is the highest category of correlation and represents a point-to-point relationship between *in vitro* dissolution rate and *in vivo* input rate of the drug from the dosage form.[22,23] *In vitro-in vivo* correlation of tablets with solid dispersion of PIO (T4) was investigated by plotting the percent drug dissolved (Fr) *vs* percent drug absorbed (Fa). Percent dissolved values were taken from *in vitro* release data and percent absorbed was determined by the Wagner-Nelson[24] method using the following equation:

$$F_a = [(C_t + k_e AUC_{0-t} / k_e AUC_{0-\alpha})] \times 100$$

Where, F_a is the fraction of drug absorbed, C_t is the drug plasma concentration at time t, k_e is the overall elimination rate constant, AUC_{0-t}, and $AUC_{0-\alpha}$ are areas under the curve between time zero and time *t* and between time zero and infinity, respectively.

Stability Studies

Stability studies[25] were performed with T1 and T4 as per ICH guidelines for 6 months at 40°C ± 2°C / 75% RH ± 5%. Samples were withdrawn at regular intervals and evaluated for change in *in vitro* drug release pattern, hardness, and disintegration time.

RESULTS

Solubility Studies of Pure Pioglitazone Hydrochloride

The solubility of pure PIO in water, pH 1.2 and pH 7.4, was found to be 0.013 ± 0.002 mg/ml, 0.020 ± 0.002 mg/ml, and 0.018 ± 0.001 mg/ml, respectively.

Screening of Carriers

Figure 1 illustrates that citric acid, urea, PEG 20 K, and PVP K30 enhances the solubility of pure PIO significantly. The solid dispersions of citric acid and urea were unstable; therefore, PEG 20 K and PVP K30 were selected as carrier for preparation of solid dispersions of PIO.

Preparation and Evaluation of Solid Dispersions

Solid dispersions were prepared by three different methods viz., Kneading method, hot-melt method, and microwave method using PEG 20 K and PVP K 30. The solid dispersions obtained by kneading method were free flowing in nature, whereas the solid dispersions prepared by hot-melt method and microwave method were sticky in nature. Percentage yield and percentage drug content of solid dispersion are presented in Table 1. The maximum percentage yield (89.16 ± 0.002% to 94.38 ± 0.005%) and drug content (>98%) was observed in case of kneading method. The drug content was significantly decreased in hot-melt method (51.89 ± 0.001 to 78.63 ± 0.002%). Pure PIO spectra showed sharp characteristic peaks at 3406.9 due to N-H stretching, 2927.7, 2633.4, and 2361.7 due to Aliphatic C-H stretching. All the above characteristic peaks appear in the spectra of PM and the solid dispersion formulations (F_4 and F_{16} prepared by kneading and microwave technique) indicating no interaction between the drug and carrier.

The FTIR of F_{10} (data not shown) has showed absence of the characteristic peaks indicating the possible degradation of drug. Solubility studies of solid dispersion prepared by kneading method and microwave method showed significant increase in the solubility of PIO. From the above results, we concluded that hot-melt method was not suitable for preparing solid dispersion of PIO. Solid dispersions with PVP K30 prepared by both kneading (F_4) and microwave (F_{16}) method showed enhanced solubility of 0.386 ± 0.003 mg/ml and 0.365 ± 0.002 mg/ml, respectively. FTIR spectra of PIO, PM, and its solid dispersions F_4 and F_{16} are presented in Figure 2.

Differential Scanning Calorimetry

The thermal curves of PIO and of selected SDs along with

PM are shown in Figure 3. The thermal curve of pure PIO exhibited an initial flat profile followed by a sharp endothermic effect, with a T_{peak} at 200.3°C indicative of its anhydrous crystalline state. The DSC profile of PVP K30 was typical of amorphous substances, showing a large dehydration band in the 50°-100°C temperature range. The thermal curve of the PM was practically the sum of those of pure components, showing endothermic effect due to polymer dehydration followed by sharp endothermic peak at 200°C corresponding to the melting point of the drug. There was disappearance of the peak in the solid dispersion formulation indicating the change in crystalline nature of PIO in solid dispersion.

Powder X-ray Diffractometry

In PXRD, sharper diffraction peaks indicate more crystalline material. The sharp, intense representative peaks of pure PIO, notably at (2θ) 9, 13, 17.5, 19, 20, and 23 were observed. This series of sharp and intense diffraction peaks indicated the crystalline state of pure PIO. The powdered PVP K30 was amorphous in nature as there were few peaks with very weak intensities. The diffraction pattern of the PM was simply the superimposition of those of the pure components. In case of solid dispersions (F_4 and F_{16}), there was reduction in the intensities of the drug peaks indicating the formation of amorphous compound [Figure 4].

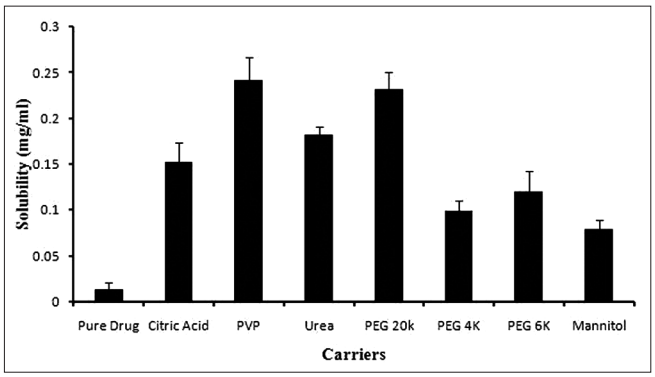

Figure 1: Effect of carriers on the solubility of pure pioglitazone hydrochloride

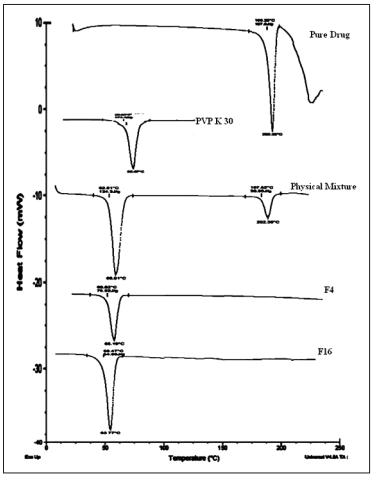

Figure 3: DSC curves for pure drug, PVP K 30, physical mixture, and solid dispersions of Pioglitazone hydrochloride (F4 and F16)

Dissolution Rate Studies

The dissolution profiles of pure PIO, solid dispersions along with PM in simulated gastric fluid, are shown in Figure 5. PIO has shown release of 48.56 ± 2.01% after 4 hours reflecting its low solubility. The dissolution from the PM showed improved drug release profile of 62.25 ± 2.79%, whereas in the solid dispersions, 101.1 ± 1.38% and 93.25 ± 2.08% for F_4 and F_{16} formulations, respectively, were observed. The DE was calculated and is summarized in Table 2.

Mathematical Analysis of *in vitro* Data

The release data of pure drug (PIO), PM, and selected solid dispersions (F_4 and F_{16}) were examined according to the

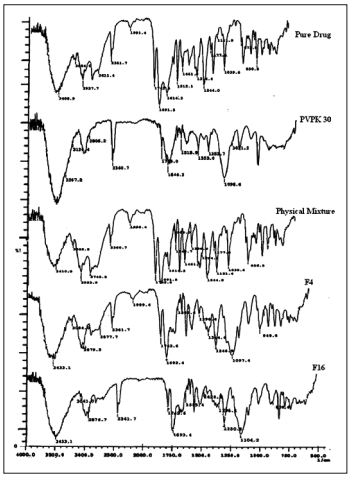

Figure 2: FTIR spectra of pure drug, PVP K 30, physical mixture, and solid dispersions of Pioglitazone hydrochloride (F4 and F16)

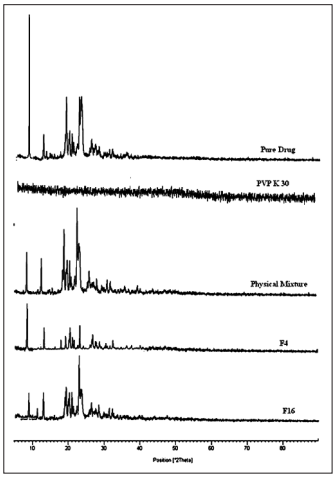

Figure 4: PXRD pattern of pure pioglitazone hydrochloride, PVP K 30, physical mixture (PM), and selected solid dispersion formulations, i.e., F4 and F16

Zero-order, First-order, and Higuchi's, Hixson Crowell, and Korsmeyer-Peppas model using PCP Disso v2.08 software. It was observed that the Hixson Crowell was most suitable mathematical model for describing experimental data for solid dispersions [Table 2].

Preparation and Evaluation Pioglitazone Hydrochloride Tablets

Based on the DE and drug release profile, the solid dispersion F_4 was selected for the formulation of fast-dissolving tablets. The fast-dissolving tablets of PIO were prepared by direct compression [Table 3]. The average weight of the prepared tablets was in range of 97.56 and 102.81 mg and thickness was found to be 2.45 ± 0.01 mm to 2.47 ± 0.05 mm. The hardness of prepared tablets was between 3.1 to 3.3 kg/cm^2. The friability of all the formulations was less than 1% indicating the ability of tablet to withstand abrasion in handling packaging and shipment. The wetting time of formulations, water absorption ratio, and weight variation are indicated in Table 4. The disintegration time of the tablets containing solid dispersion varied from 40 ± 2.0 to 90 ± 3.0 seconds. The *in vitro* drug release from tablet containing solid dispersion of PIO (T4) was 93.52 ± 3.05% and drug release of tablet containing pure PIO (T1) showed drug release of 42.12 ± 2.14%, whereas MFs released 45.23 ± 1.0% of drug within 60 minutes [Table 4]. The similarity factor f2 method can be used to compare two dissolution profiles. Similarity factor analysis between the prepared tablet containing solid dispersion of PIO (T4) and the marketed tablet (Pioglit[a]) for the release of PIO showed an f2 factor <50 which confirms that the release of PIO from the prepared tablets was not similar to that of the marketed tablet. The release profile is shown in Figure 6.

Table 4: Evaluation of fast-dissolving tablets

Properties	T1	T2	T3	T4	T5	T6	T7	T8	Marketed formulation
Thickness (mm)	2.45 ± 0.01	2.47 ± 0.05	2.44 ± 0.01	2.45 ± 0.02	2.46 ± 0.01	2.45 ± 0.01	2.44 ± 0.02	2.43 ± 0.01	1.89 ± 0.39
Hardness (kg/cm^2)	3.1 ± 0.2	3.2 ± 0.3	3.1 ± 0.1	3.2 ± 0.2	3.3 ± 0.1	3.2 ± 0.2	3.1 ± 0.3	3.2 ± 0.1	3.5 ± 0.41
Friability (%)	0.20 ± 0.03	0.20 ± 0.050	0.22 ± 0.031	0.21 ± 0.020	0.21 ± 0.001	0.18 ± 0.021	0.17 ± 0.01	0.18 ± 0.01	0.10 ± 0.005
Weight variation (%)	1.63 ± 0.24	2.03 ± 0.32	1.81 ± 0.12	1.89 ± 0.20	2.09 ± 0.41	1.55 ± 0.13	1.68 ± 0.24	2.11 ± 0.51	1.85 ± 0.81
Wetting time (sec)	>160	11 ± 3.0	12 ± 1.0	10 ± 4.0	20 ± 5.0	40 ± 3.0	45 ± 4.0	50 ± 2.0	>240
Water absorption ratio	341.56 ± 2.06	125.26 ± 1.36	167.25 ± 2.36	175.52 ± 3.56	184.36 ± 3.27	102.55 ± 5.21	118.24 ± 2.65	116.58 ± 4.85	501 ± 1.16
Disintegration time (sec)	>240	40 ±2.0	38 ± 3.2	30 ± 1.0	48 ± 5.0	50 ± 4.0	72 ± 2.0	90 ± 3.0	>600
% Drug release (60 min)	42.12 ± 2.14	86.61 ± 1.85	84.41 ± 2.08	93.52 ± 3.05	83.56 ± 1.25	78.95 ± 2.55	75.99 ± 3.11	71.81 ± 2.68	45.23 ± 1.33

Mean ± SD, $n = 6$

In Vivo Studies

The plasma drug level curve for the formulation T1 containing PIO, T4 containing solid dispersion of PIO, and marketed product is shown in Figure 7. The various pharmacokinetic parameters were calculated using Kinetica 2000 software, and results are shown in Table 5.

In vitro-in vivo Correlation

An *in vitro-in vivo* correlation was carried out using the Wagner-Nelson method.[23] Fraction of drug dissolved (Fr) when plotted against fraction of drug absorbed (Fa) gives a good linear regression y = 1.013x + 2.426 [Figure 8]. The correlation coefficient *R* of 0.993 indicates a good correlation.

Stability Studies

Stability studies was performed on T1 and T4 as per ICH guidelines for 6 months at 40°C ± 2°C/75% RH ± 5% using. Studies indicated no significant changes in *in vitro* drug release pattern, hardness, and disintegration time ($P < 0.05$).

DISCUSSION

PIO is poorly soluble in water with poor dissolution profile

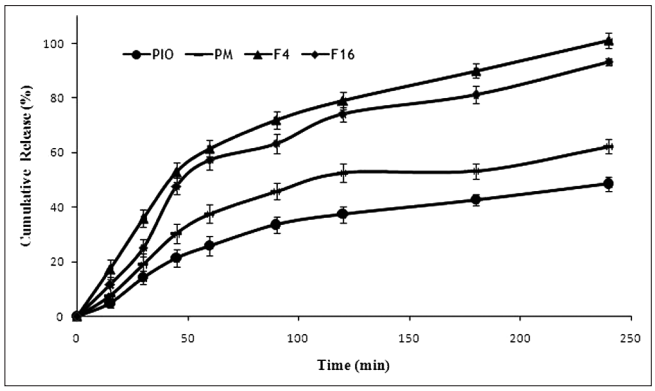

Figure 5: Drug release profile of pioglitazone hydrochloride, physical mixture, and solid dispersion formulations, i.e., F4 and F16

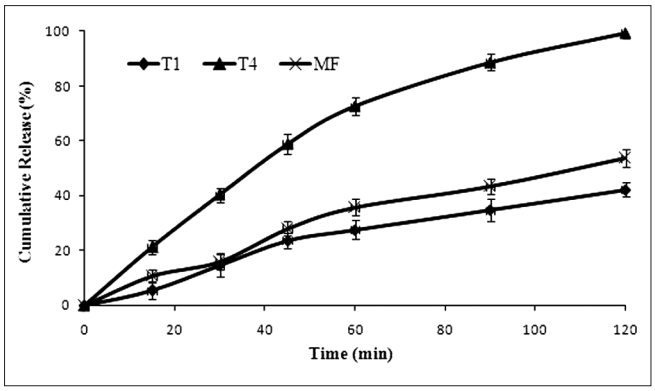

Figure 6: Comparison of drug release profile of fast-dissolving tablets (T1 and T4) with marketed formulation (MF)

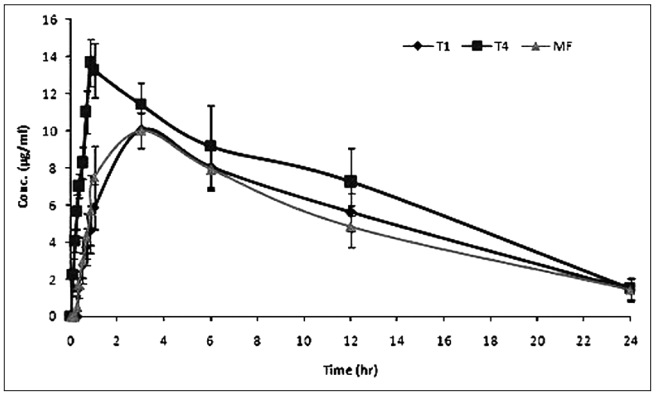

Figure 7: Plasma drug level curve for tablet containing pure Pioglitazone hydrochloride (T1), solid dispersion (T4), and marketed formulation (MF) in Wistar rat

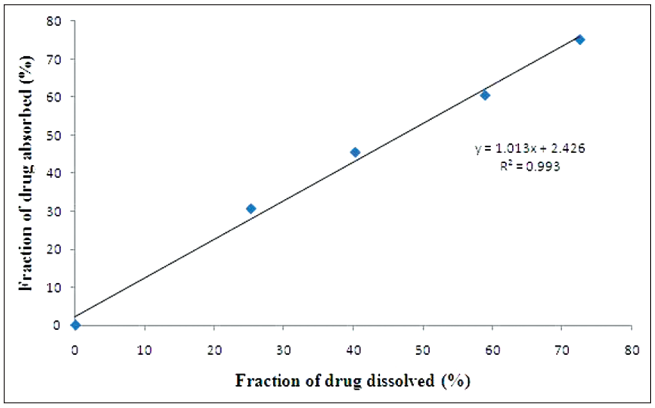

Figure 8: *In vitro-in vivo* correlation of fast dissolving tablets of PIO

Table 5: Pharmacokinetics of fast-dissolving tablets of pioglitazone hydrochloride

Pharmacokinetic parameter	T1	T4	Marketed formulation
Peak plasma concentration C_{max} (µg/ml)	10.04 ± 0.97	13.69 ± 1.31	10.00 ± 0.96
Time to reach peak plasma concentration t max (hr)	3 ± 0.00	0.833 ± 0.00**	3 ± 0.00^{ns}
Elimination half life $t_{1/2}$ (hr)	6.44 ± 1.04	5.90 ± 0.74	6.67 ± 0.107
Elimination rate constant Ke (hr^{-1})	0.110 ± 0.016	0.119 ± 0.014	0.098 ± 0.022
Area under the curve AUC $_{(Total)}$ (µg/ml*hr)	140.81 ± 23.42 ^{ns}	177.90 ± 29.78 ^{ns}	138.61 ± 26.46 ^{ns}
AUMC (µg /ml*hr)	1655.48 ± 451.27	1780.81 ± 503.38	1611.18 ± 523.57
MRT (hr)	11.59 ± 1.35	10.29 ± 1.16	11.27 ± 1.47

Mean ± SD, $n = 6$; Statistics: One Way ANOVA followed by Dunnett post hoc test. T1 *vs* T4---- ** ($P < 0.01$), T1 *vs* MF---^{ns} ($P > 0.05$)

and belongs to class II of BCS. The solubility studies in buffers have shown increased solubility when compared with distilled water.

Screening of Carriers

Preliminary solubility analysis was carried out to screen the most appropriate carriers where in mannitol, citric acid, urea, PEG 4000, PEG 6000, PEG 20 K, and PVP K30 were used. Solubility in citric acid, urea, and PEG 20000 and PVP K 30 was found to be maximum when compared with other carriers [Figure 1]. Thus, these carriers were selected for the preparation of the solid dispersion. In preliminary studies, it was found that solid dispersions of citric acid and urea were not stable. Therefore, PEG 20 K and PVPK 30 were selected as carriers for preparation of solid dispersion.

Preparation and Evaluation of Solid Dispersions

Solid dispersions were prepared by kneading, hot-melt, and microwave method, with chosen carriers in three different drugs to carrier ratio as shown in Table 1. There was no significant effect on solubility observed when the carrier concentration was increased. It was observed that the solubility of PIO was augmented as the concentration

of hydrophilic polymer increased from 1: 0.5, below this ratio there was no significant increase in the solubility indicating concentration-independent solubility of PIO above a particular ratio.

The hot-melt method resulted in solid dispersion with low drug content of 41.56 ± 0.002 to 85.13 ± 0.001%. This may be due to degradation of drug in molten carrier. This was further supported by FTIR studies which indicated that there was no characteristic peak of PIO in the solid dispersion prepared by hot melt method [Data not shown].

From the above results, we concluded that hot-melt method was not suitable for preparing solid dispersion of PIO. Moreover, the physical observation of solid dispersion prepared by both kneading and microwave method indicated that solid dispersions of PEG 20 K are sticky in nature, while the PVP K30 formulations were free flowing in nature; therefore, it was concluded that PVP K30 was the most suitable polymeric carrier. Solid dispersions with PVP K30 prepared by both kneading (F_4) and microwave (F_{16}) method showed an increase of 30 fold in the solubility of PIO [Table 1].

Fourier Transform Infrared Spectroscopy

The IR spectrum of pure PIO revealed the presence of a peak at 3 084/cm due to N-H stretching while peaks at 2 927 and 2 740/cm corresponds to CH stretching. Strong absorption peaks was observed at 1 742 and 1 691/cm that are assigned to drug carbonyl stretching vibration (C = O). A peak at 1 614/cm indicates the aromatic ring and a peak at 1 244/cm is due to C-O-Ar group. All these characteristic peaks appeared in the spectra of PM and solid dispersions indicating no interaction of drug with hydrophilic carrier.

Differential Scanning Calorimetry

The DSC curve of PIO profiles a sharp endothermic peak (T peak = 200.3°C) corresponding to its melting, indicating its crystalline nature. In contrast, a broad dehydration band over the temperature range 50 to 100°C shown by PVP K30 was typical of amorphous hydrated substance.[26] The characteristic endothermic peak, corresponding to drug melting, was shifted or disappeared in both PMs as well as solid dispersions (F4 and F16) revealing amorphorization of the drug.[27] The data depict that there was no interaction between the components of binary system.

X-ray Powder Diffractometry

All the principal peaks from pure pioglitazone were present in their PM and solid dispersion with lower intensity. The positions of diffraction peaks of pure PIO is present with very low intensity indicating decreased crystallinity which may contribute to enhanced dissolution of drug. No new peaks could be observed, suggesting the absence of interaction between the drug and the carrier.

Dissolution Rate Studies

Dissolution profiles of PIO, PM, and solid dispersions, i.e., F_4 and F_{16} are presented in Figure 5. The DE at 15 minutes (DE 15), 30 minutes (DE 30), and 180 minutes (DE 180) for PIO, PM, and selected solid dispersions are presented in Table 2. The values given in Table 3 indicate that F_4 (DE180 = 80.40%) shows maximum enhancement in dissolution rate. However, F_{16} also produces comparable results in terms of DE (DE180 = 76.24%). PM also improves dissolution rate to a significant extent as compared with pure drug alone. The order of efficiencies of products based on DE values was F4 >F16 > PM >PIO.

MDT value was in the range of 37.02 ± 2.5 to 94.46 ± 1.89 minutes. MDT is used to characterize drug release rate from a dosage form. It was observed that in case of solid dispersions, i.e., F_4 and F_{16}, the value was much lesser (37.02 ± 2.50 minutes and 42.48 ± 1.52 minutes) when compared with pure drug and MF (94.46 ± 1.89 minutes and 90.70 ± 2.09 minutes), indicating fast dissolution of drug carrier system of solid dispersions. The unpaired one tail **t**-test has showed very significant difference in MDT of pure drug and solid dispersion formulations ($P < 0.001$).

The curve fitting of dissolution profile of F_4 and F_{16} showed Hixson Crowell model as best fit model with n value of 0.5177 and 0.5971, respectively, indicating anomalous (non-Fickian) diffusion ($0.45 < n < 0.89$).[28,29]

The similarity factor (f2) was calculated for dissolution profile between F_4 (kneading method) *vs* F_{16} (microwave method). It was found that the value of f2 was 66.79 indicating similarity between two dissolution profiles. Furthermore, the dissolution profiles of formulation F_4 *vs* MF was subjected for similarity profile that indicated dissimilar profile as the f2 value is 12.26. This enhancement of dissolution of PIO from solid dispersion may be due to several factors. Presence of amorphous nature, increased wettability and dispersibility, and particle size reduction are the important factors for dissolution rate enhancement. Enhanced dissolution in case of PM can be attributed to higher wettability and dispersibility. During dissolution studies, the solid dispersion settled down immediately while the pure drug was floating on surface of the medium for a long time. Moreover, other factors such as absence of aggregation and/or re-agglomeration phenomenon during dissolution and particle size reduction could be attributed to the better dissolution profile.[30,31]

Preparation of Pioglitazone Tablets

Based on the *in vitro* release profile and DE, the solid dispersion F_4 was selected for formulation of fast-dissolving tablets. The fast-dissolving tablets of PIO was prepared by direct compression technique [Table 3]. Various superdisintegrants including Sodium starch glycolate (SSG), crosspovidone, croscarmellose, and Pharmaburst®

were screened alone and in combination (results not shown). Finally, SSG and Pharmaburst were chosen and overall superdisintegrant concentration was optimized between 5-10%. The average weight of the prepared tablets was in range of 97.56 and 102.81 mg and thickness was found to be 2.45 ± 0.01 mm to 2.47 ± 0.05 mm. The hardness of prepared tablets was between 3.1 to 3.3 kg/cm^2. The friability of all the formulations was less than 1%, indicating the ability of tablet to withstand abrasion in handling, packaging, and shipment. The wetting time of formulations, water absorption ratio, and weight variation is indicated in Table 4.

It was observed that the wetting time, water absorption ratio, and disintegration time for tablet formulation containing PIO (T1) and MF was significantly different from the tablet formulations containing solid dispersion of PIO (T2-T8) as shown in Table 4. This rapid disintegration of tablets was due to the presence of the pores resulting in faster penetration of medium leading to swelling and wicking of superdisintegrants, creating hydrodynamic pressure inside the tablets for quick and complete disintegration of the tablet.[32,33]

The tablet (T4) containing superdisintegrants in the ratio of 1 : 0.5 (SSG and Pharmaburst) disintegrated faster than tablets prepared with other ratios (1 : 0.25, 1 : 0.75, and 1 : 1). The *in vitro* drug release from tablet containing solid dispersion of PIO (T4) was 93.52 ± 3.05% and drug release of tablet containing pure PIO (T1) showed drug release of 42.12 ± 2.14%, whereas MFs released 45.23 ± 1.0% of drug within 60 minutes [Table 4].

The *in vitro* release profile of T1, T4, and MF was statistically analyzed by one way ANOVA which indicated a significant difference ($P \leq 0.05$) in dissolution rate profile of formulation T4 when compared with T1 and MF. The drug release profiles of T1, T4, and MF are shown in Figure 6.

In vivo Studies

The bioavailability studies for tablets containing pure drug (T1), solid dispersion (T4), and MF were carried out using Wistar rats [Figure 7]. The various pharmacokinetic parameters were calculated using Kinetica 2000 software; results are shown in Table 5.

Pharmacokinetic profile of T1, T4, and MF was compared by one way ANOVA followed by Dunnett Post Hoc multiple comparison test. Though there was no significant difference in C_{max} (10.04 ± 0.97 μg/ml, 13.69 ± 1.31 μg/ml, and 10.00 ± 0.96 μg/ml) of the formulations, a significant difference ($P < 0.01$) in T_{max} values (3.0 hours for T1 and MF and 0.833 hour for T4) was observed. The decrease in T_{max} values indicates faster absorption of the drug from T4 formulation. This would be particularly beneficial when pioglitazone tablets are administered at bed time after food.

In vitro-in vivo Correlation

Level A correlation gives direct relationship between *in vivo* data such that measurement of *in vitro* dissolution rate alone is sufficient to determine the biopharmaceutical rate of the dosage form. *In vitro* data when superimposed on to the *in vivo* data have shown good correlation coefficient (R = 0.993) as shown in Figure 8.

Stability Studies

The stability studies indicated that there was no significant change observed for *in vitro* dissolution studies after three months. Fast-dissolving tablets (T4) were found to be stable for the period of six months at 40°C ± 2°C/75% RH ± 5%.

CONCLUSION

The study showed that the dissolution rate of PIO was enhanced to a greater extent by solid dispersion technique using kneading method and microwave technique. The kneading method was much simpler and industrially feasible and thus can be adopted in order to enhance the dissolution profile of PIO. PVP K30 showed most prominent results indicating the usage of this carrier for solid dispersion of PIO. Furthermore, the fast-dissolving tablets of PIO were successfully prepared by using SSG and Pharmaburst as superdisintegrants. The *in vivo* studies clearly indicated that solid dispersion approach can be adopted for formulation of PIO tablets in order to achieve a faster onset of action.

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