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Original Article

# SOLUBILITY AND DISSOLUTION ENHANCEMENT OF PIOGLITAZONE USING SOLID DISPERSION TECHNIQUE

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**ABSTRACT**

**Objective:** To design the study to improve the solubility and hence enhance the dissolution of hydrophobic drug Pioglitazone in order to increase its bioavailability.

**Methods:** Solid dispersion of Pioglitazone using carriers Poloxomer 188 and HPβCD was formulated in different ratios by microwave induced fusion method. In particular, the Microwave technology has been considered in order to prepare an enhanced release dosage form for poorly water soluble drug Pioglitazone. Statistical Analysis: Their physicochemical characteristics and solubility were compared to the corresponding dispersions and marketed drug. Drug and polymer were further characterized by FTIR.

**Results:** The results of FTIR revealed that no chemical interaction between the drug and the polymer exist.

**Conclusion:** All the formulations showed a marked increase in drug release with the increase in the concentration of Poloxomer 188 and HPβCD.

**Keywords:** Pioglitazone, Solid dispersion, Microwave Irradiation Method, Poorly water soluble drugs.


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## INTRODUCTION [1-3]

The enhancement of the solubility of poorly water soluble drugs is one of the major current challenges to pharmaceutical sciences. Oral bioavailability of a drug depends on its solubility and dissolution rate, which is the rate determining step for the onset of therapeutic activity. Several techniques have been developed over the years to enhance the dissolution of the drug such as micronization, solubilization, salt formation, complexation with polymers, change in physical form, use of prodrugs, drug derivatization, alteration of pH, the addition of surfactants etc.

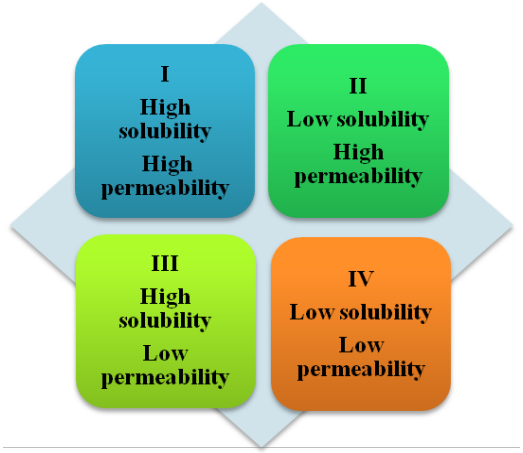



**Fig. 1: Biopharmaceutical classification system (BCS)**

If formulated as a solid dispersion the dissolution rate and the solubility of the active compound are often significantly increased. Contributing factors are particle size reduction, improved wetting and an enhancement of the solubility of the active compound in the solution that is formed, as the carrier dissolves. Also the carrier can have influence on the crystallization kinetics in the supersaturated solution that is formed during the process of dissolution. Several water soluble carriers such as Sodium Starch Glycolate, Microcrystalline Cellulose, Magnesium Stearate, Talc, Lactose, Poloxamer 188 etc. are used as carriers for solid dispersions. Pioglitazone is an oral rapid and short acting anti diabetic drug from the Thiazolidinedione class. It is classified as second generation Thiazolidinedione, which means that it undergoes enter hepatic circulation. As per BP, Pioglitazone is practically insoluble in water because of its poor solubility (classified as BCS class II drug).

Hence, there is a neefor development of novel solid dispersion to improve the solubility of Pioglitazone and their inI High solubility High permeability II Low solubility High permeability III High solubility Low permeability IV Low solubility Low permeability vitro characterization. The present study is an attempt to overcome the poor aqueous solubility of Pioglitazone by using solid dispersion solvent evaporation/spray drying/melt or any appropriate suitable method.

### Preparative method of solid dispersion

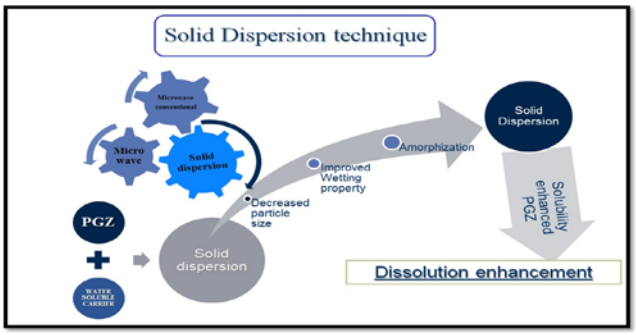
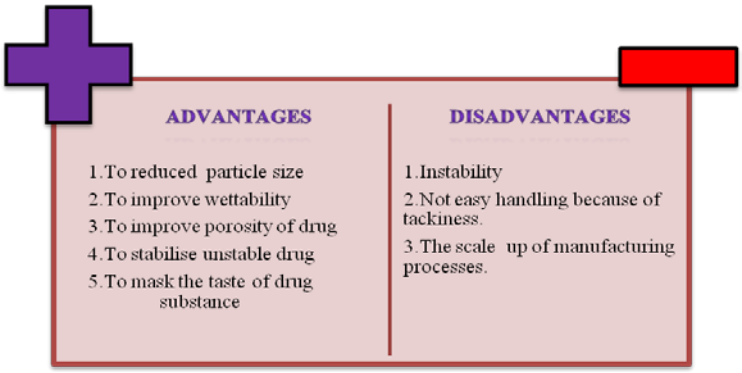



**Fig. 2: Solid dispersion technique.**

**Advantage and disadvantage**




**Preparation of solid dispersions by microwave asssisted method [9]**

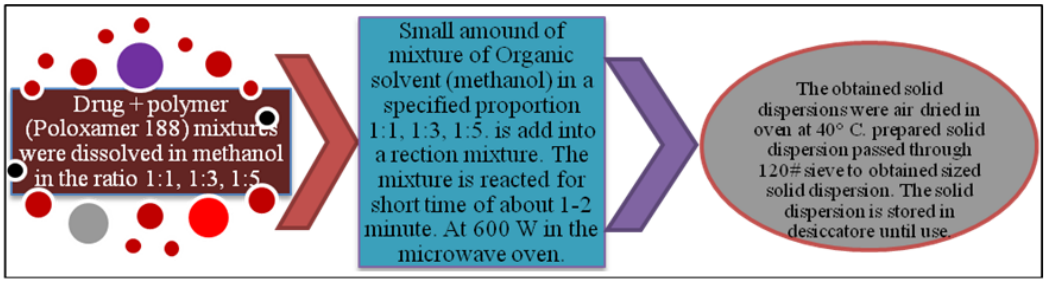



**Fig. 3: Solid dispersions by microwave asssisted method**

## MATERIALS AND METHODS

### Material

Pioglitazone was obtained as a gift sample from Cipla pharmacutical Ltd, Verna Goa. Poloxomer 188 and HPβCD were purchased from Glenmark Pharmaceuticals, Sinnar, Nashik. All other chemicals used were of pharmaceutical grade. Method Solid dispersions were prepared by Microwave irradiation induced fusion method in three different ratios. Pioglitazone with Poloxomer 188 and HPβCD was weighed according to different weighed ratio, as shown in table 1 and 2.

### Microwave induced fusion method [9]

Solid dispersion with different ratios of Pioglitazone with Poloxomer 188 and HPβCD was prepared using the microwave induced fusion method. Firstly, Pioglitazone with Poloxomer 188 and HPβCD was weighted in ratios of 1:1,1:3 and 1:5 W/W followed by gentle mixing for 5 min using a mortar and pestle. A fixed amount of these mixtures were subjected to microwave for 5 min, 6 min and 7 min at a constant chosen power of 700W in a microwave instrument. Only one beaker at a time was placed inside the microwave. The samples were exposed in the microwave for a predetermined time interval. The beaker was Drug+polymer (Poloxamer 188) mixtures were dissolved in methanol in the ratio 1:1, 1:3, 1:5. Small amound of a mixture of Organic solvent (methanol) in a specified proportion 1:1, 1:3, 1:5. Is add into a reaction mixture.

The mixture is reacted for short time of about 1-2 minute. At 600 W in the microwave oven. The obtained solid dispersions were air dried in an oven at 40 ° C. prepared solid dispersion passed through 120# sieve to obtained sized solid dispersion. The solid dispersion is stored in desiccatore until use. Then placed at room temperature for solidification. Solid dispersions were collected and stored in the desiccators for 24 hr and then the product was pulverized using a mortar and pestle. The pulverized powders were passed through an 80# sieve.

**Mechanism of microwave heat**

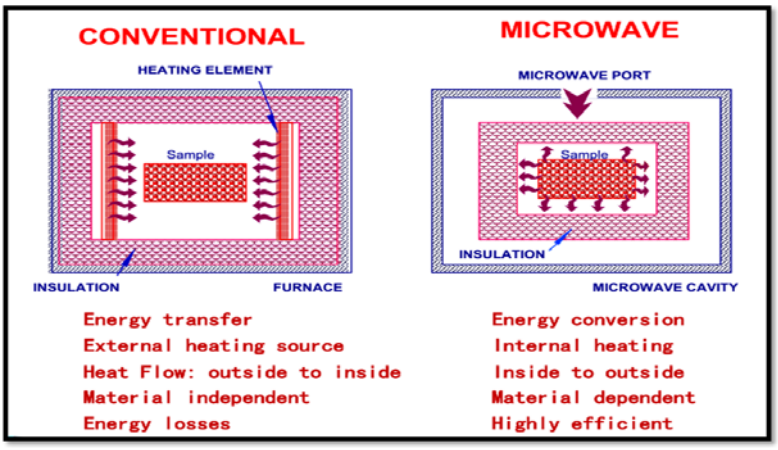



**Fig. 4: Mechanism of microwave heat**

**Binary solid dispersion: {MW}**

**Table 1: Formula for the preparation of pioglitazone solid dispersion with poloxamer 188**

| S. No. | Composition | Ratio (w/w) |
|---|---|---|
| | Drug: polymers | |
| 1 | Pioglitazone: Poloxamer 188 | 1:1 |
| 2 | Pioglitazone: Poloxamer 188 | 1:3 |
| 3 | Pioglitazone: Poloxamer 188 | 1:5 |

**Table 2: Formula for the preparation of pioglitazone solid dispersion with HPβCD**

| S. No. | Composition | Ratio (w/w) |
|---|---|---|
| | Drug: polymers | |
| 1 | Pioglitazone: HPβCD | 1:1 |
| 2 | Pioglitazone: HPβCD | 1:3 |
| 3 | Pioglitazone: HPβCD | 1:5 |

**Tertiary solid dispersion {MW}**

**Table 3: Formula for the preparation of pioglitazone solid dispersion with poloxamer188: HPβCD**

| S. No. | Composition | Ratio (w/w) |
|---|---|---|
| | Drug: Polymers | |
| 1 | Pioglitazone: Poloxamer 188: HPβCD | 1:1 |
| 2 | Pioglitazone: Poloxamer 188: HPβCD | 1:3 |
| 3 | Pioglitazone: Poloxamer 188: HPβCD | 1:5 |

**Physical mixture**

**Table 4: Formula for the preparation of pioglitazone solid dispersion with poloxamer 188**

| S. No. | Composition | Ratio (w/w) |
|---|---|---|
| | Drug: polymers | |
| 1 | Pioglitazone: Poloxamer 188 | 1:1 |
| 2 | Pioglitazone: Poloxamer 188 | 1:3 |
| 3 | Pioglitazone: Poloxamer 188 | 1:5 |

**Melting point determination of pioglitazone [42]**

Melting point of Pioglitazone was determined melting point apparatus.

**Solubility studies [11, 12, 18]**

Solubility studies were performed according to the method described by Higuchi and Connors. The saturation solubility of drug and SDs with Poloxomer 188 and HPβCD respectively, (1:1, 1:3 and 1:5 w/w) in water was determined by adding an excess of drug and SDs to 50 ml distilled water in conical flask and were rotated in a orbital shaking incubator for 72 hr. at 370C±0.50C. The saturated solutions were filtered through a 0.45 µm membrane filter, suitably diluted with water and analyzed by Jasco V-630 UV spectrophotometer at 269 nm.

***In vitro* dissolution studies [9]**

Dissolution studies on Pioglitazone (Plain drug), as well as the Solid dispersions, were performed using the USP tablet dissolution test apparatus II with Samples equivalent to 15 mg of Pioglitazone was hold in Muslin cloth and then added to 900 ml of phosphate buffer pH 7.4 at 37±0.5 ° C and stirred at 50 rpm. 5 ml aliquots were withdrawn at time interval of 5, 15, 30, 45, 60 min and filtered through Whatman's (No. 41) filter paper. An equal volume of fresh dissolution medium was replaced to maintain the volume of dissolution medium. The filtered samples were analyzed spectrophotometrically at 269 nm. Cumulative percentage of the labeled amount of drug released was calculated.

**Fourier transform infrared spectroscopy (FTIR)**

The KBr discs of Pioglitazone, Poloxomer 188 and HPβCD and finalized solid dispersions were prepared using electrically operated KBr Press Model SHIMADZU FTIR-5300 Fourier transform spectrophotometer was used to record IR spectra of the prepared discs, to confirm any interaction of Pioglitazone with other excipients of dispersion.

**RESULTS**

**Melting point**

The melting point of pioglitazone was found to be 187–192 °C

**Solubility**

Practically insoluble in water; very slightly soluble in methanol and 0.1N HCL; practically insoluble in ethanol (95 per cent). Solutions of Pioglitazone was prepared in methanol and scanned between 200-400 nm using UV spectrophotometer showed a peak at wavelength 269.0 nm. However, keeping in mind the probable concentrations likely to be encountered while carrying out *In vitro* release studies and considering the predicted theoretical λmax involved, the working λmax was decided as 269.0 nm.

**Table 5: Standard calibration curve data of pioglitazone in methanol at 269 nm**

| S. No. | Concentration (ppm) | Absorbance at 249 nm |
|---|---|---|
| 1. | 2 | 0.126 |
| 2. | 4 | 0.245 |
| 3. | 6 | 0.356 |
| 4. | 8 | 0.416 |
| 5. | 10 | 0.483 |
| 6. | 12 | 0.568 |
| 7. | 14 | 0.672 |
| 8. | 16 | 0.915 |

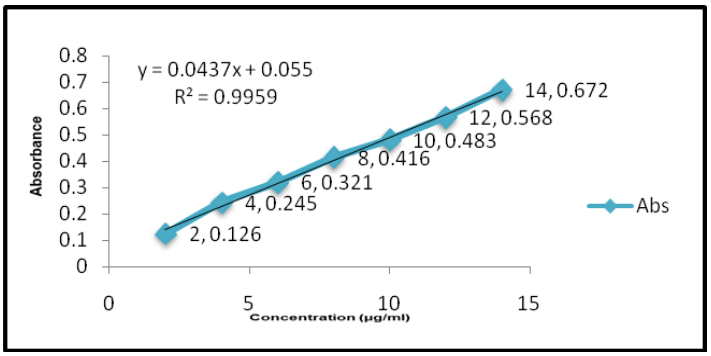



**Fig. 5: Calibration curve of PGZ in methanol at 269.0 nm**

**Table 6: Result of phase solubility study**

| S. No. | Formulation code | Drug | Polymer | Ratio | Solubility (mg/ml)±SD |
|---|---|---|---|---|---|
| 1. | Drug | PGZ | ----- | ----- | 0.045 |
| 2. | SD1 | PGZ | PLX 188 | 1:1 | 51.69±0.014 |
| 3. | SD2 | PGZ | PLX 188 | 1:3 | 27.30±0.003 |
| 4. | SD3 | PGZ | PLX 188 | 1:5 | 22.57±0.008 |
| 5 | SD1 | PGZ | HPßCD | 1:1 | 20.51±0.006 |
| 6 | SD2 | PGZ | HPßCD | 1:3 | 17.03±0.011 |
| 7. | SD3 | PGZ | HPßCD | 1:5 | 13.82±0.006 |
| 8. | SD1 | PGZ | PLX 188+HPßCD | 1:1:1 | 19.44±0.008 |
| 9. | SD2 | PGZ | PLX 188+HPßCD | 1:3:1.5 | 22.75±0.0089 |
| 10. | SD3 | PGZ | PLX 188+HPßCD | 1:5:2.5 | 11.5±0.0057 |
| 11. | SD4 | PGZ | PLX 188+HPßCD | 1:2:3 | 18.46±0.01 |
| 12. | PM1 | PGZ | PLX 188 | 1:1 | 42.44±0.0088 |
| 13. | PM2 | PGZ | PLX 188 | 1:3 | 43.64±0.011 |
| 14. | PM3 | PGZ | PLX 188 | 1:5 | 41.05±0.008 |

**Percentage yield**

The production yield of solid dispersion prepared by Microwave assisted method was found to be 80 %.

Any loss in yield can be attributed to the product remaining adhered to the walls of the mortar which could not be retrieved the results of Percentage Yield are shown in (table 24).

**Table 7: Result of percentage yield**

| S. No. | Drug | Polymer | Ratio | Percentage yield |
|---|---|---|---|---|
| 1. | PGZ | PLX 188 | 1:1 | 80 % |
| 2. | PGZ | PLX 188 | 1:3 | 85 % |
| 3. | PGZ | PLX 188 | 1:5 | 76.6% |

**Dissolution study of solid dispersion with pure drug**

**Table 8: Dissolution study of pure drug and PGZ solid dispersion**

| Time (min) | (%) drug release±SD | |
|---|---|---|
| | Marketed drug | PGZ solid dispersion |
| 05 | 28.05±0.012 | 28.25±0.088 |
| 15 | 52.75±0.015 | 54.54±0.017 |
| 30 | 64.06±0.014 | 64.84±0.084 |
| 45 | 86.68±0.008 | 88.01±0.0115 |
| 60 | 94.23±0.014 | 98.60±0.115 |

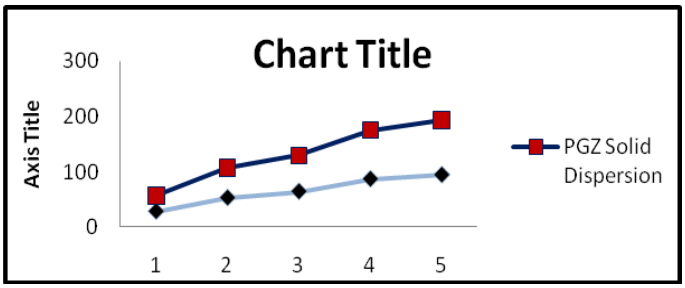



**Fig. 6: Dissolution profiles of marketed drug and PGZ solid dispersion**

**FT-IR spectroscopic studies**

FTIR was performed on Pioglitazone, Poloxomer 188 and HPβCD, a solid dispersion of Pioglitazone with all carriers as per fig. 6, table 7 and fig. 7, table 8 resp. The IR spectra of solid dispersion showed all the principal IR absorption peak of Pioglitazone 3251 cm-1, 2928 cm-1, 1687 cm-1, 1314 cm-1, 1243 cm-1, and 849 cm-1. FTIR of a solid dispersion of drug and all carriers shows that all the peaks of drug and carrier as it is and the drug is present in free form. This indicates that there is no interaction in between Pioglitazone and the entire carrier employed in solid dispersion.

The obtained spectrum was compared with the spectrum that was in literature to confirm the authenticity of the given sample. These results suggested that there was no interaction between Pioglitazone and Poloxomer 188 and HPβCD.

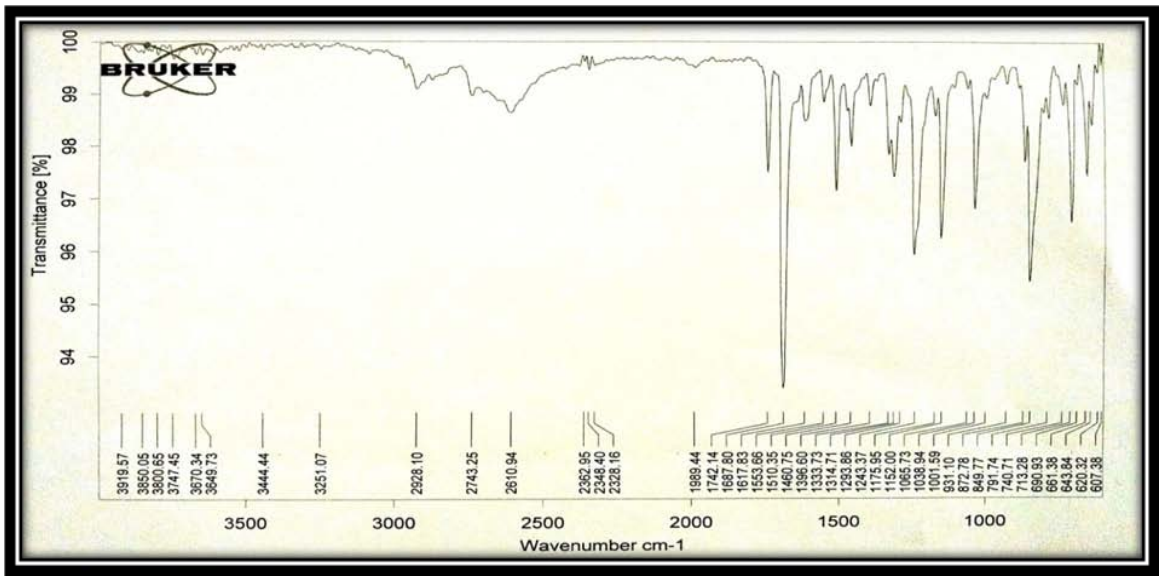



**Fig. 7: FT-IR spectrum of pioglitazone**

**Table 9: Functional groups with frequencies present in FTIR spectrum of PGZ**

| S. No. | Functional group | Standard frequency (cm-1) | Observed IR frequency (cm-1) |
|---|---|---|---|
| 1. | C-O fingerprint region (Aliphatic) | 600-1400 | 849 |
| 2. | C-S Stretching | 1136-1347 | 1243 |
| 3. | C-N Stretching | 1080-1360 | 1314 |
| 4. | C=O Streching (Amide) | 1670-1820 | 1687 |
| 6. | C-H Stretching (Aromatic) | 3000-3100 | 2928 |
| 7. | N-H Stretching (Amide) | 3310-3140 | 3251 |

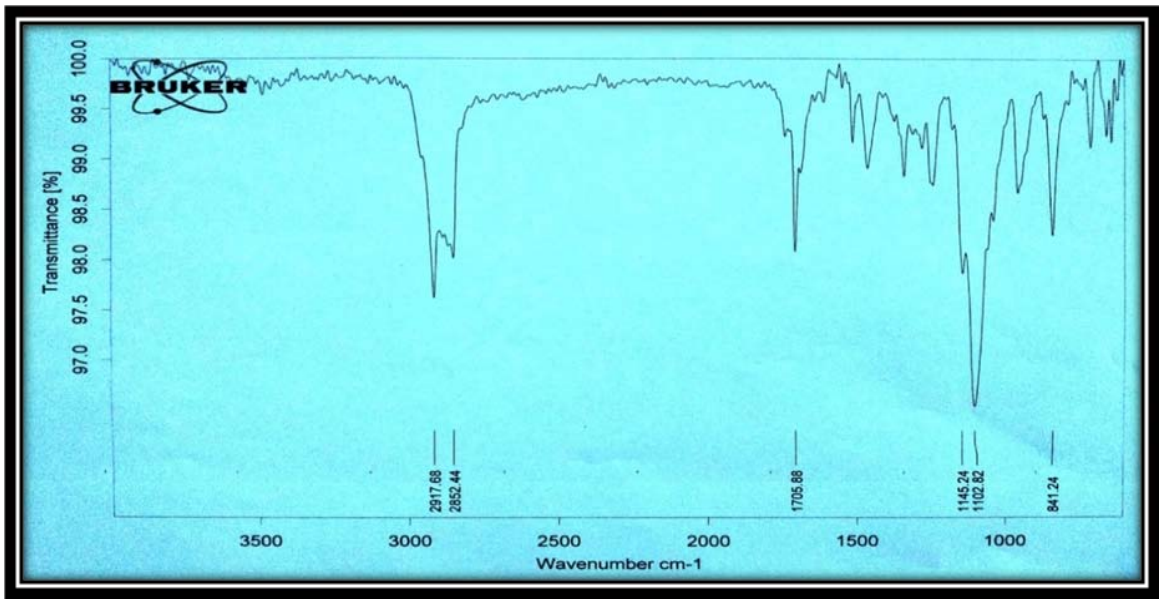



**Fig. 8: FT-IR spectrum of PGZ+POLOXAMER 188 (PM)**

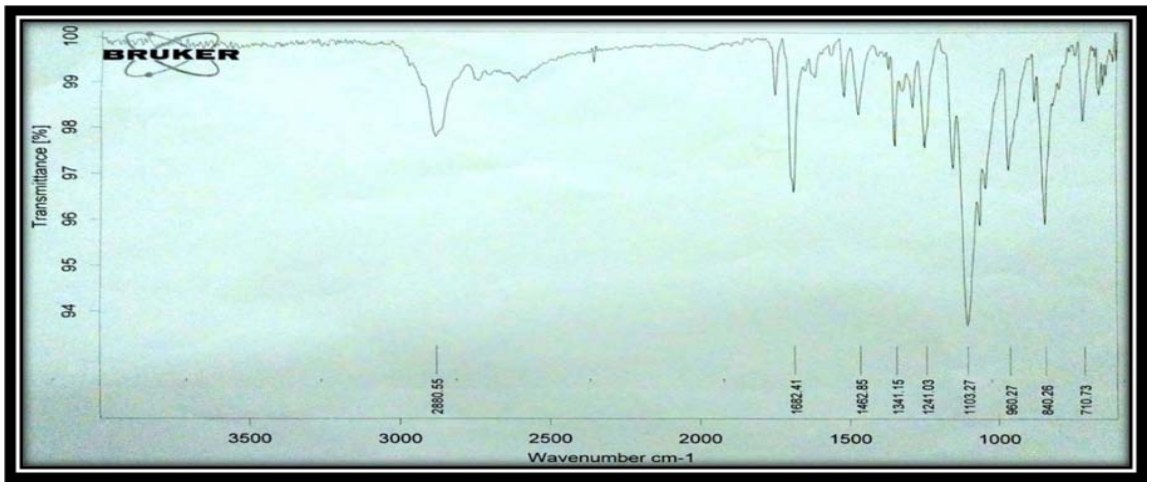



**Fig. 9: FTIR spectra of pioglitazone+poloxamer 188SD (MW)**

**Powder X-Ray diffraction**

The SD was studied for prediction of crystallinity. The PXRD Pattern of PGZ is shown in fig. 21. Based on the diffractogram it can be suggested that PGZ is present in its amorphous form since it exhibits several well-defined peaks at a diffractogram angle of 2θ. The strong peak at 2θ of 22.762 was a highly intense peak with 100% intensity indicating the presence of amorphous PGZ.

PGZ: PLX 188(MW) fig. 22, XRD diffraction pattern revealed that the functional peak of PGZ was of low intensity and showing a characteristic peak of PLX 188 in the solid dispersion at 2θ of 22.520 indicating the presence of PGZ in the crystalline state within the PLX 188.

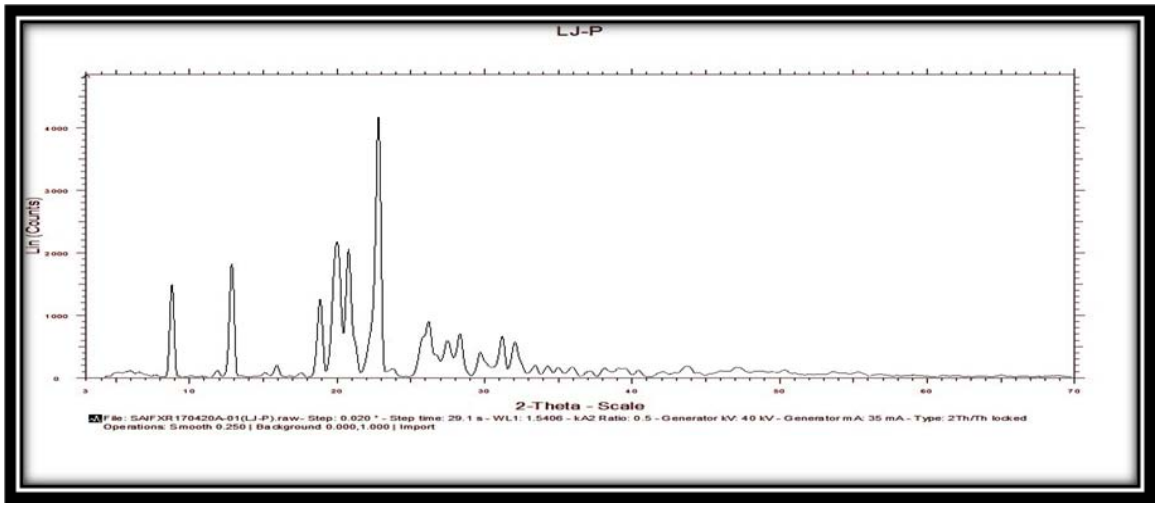



**Fig. 10: PXR-diffractogram of PGZ**

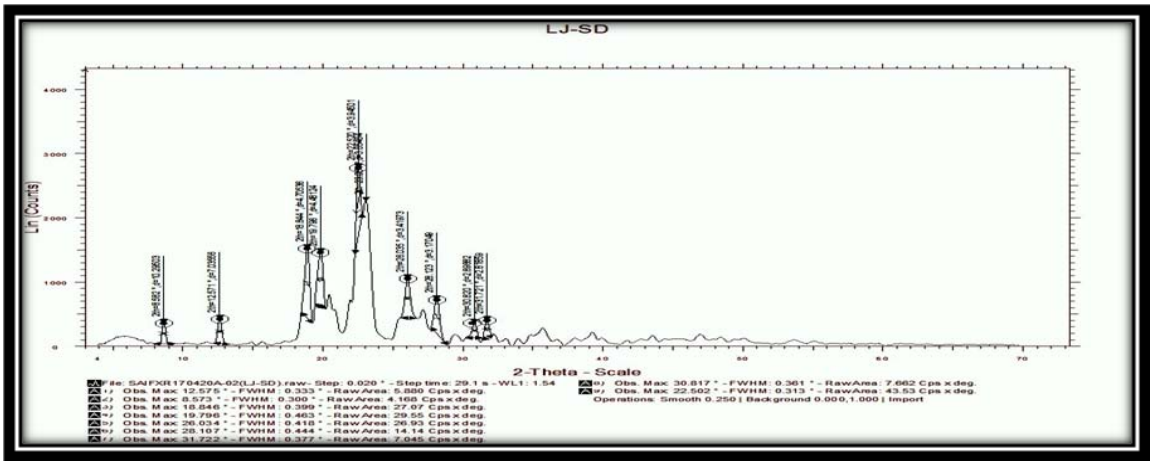



**Fig. 11: PXR-diffractogram of PGZ: PLX 188(MW)**

**Differential scanning calorimetry**

The amorphous form of drug in spite of having high solubility is high energy unstable form of the drug which tends to re-crystallize owing to thermodynamic driving force leading to product failure. One approach employed to prevent or slow the transformation from amorphous to the crystalline state is the addition of compatible polymers. Polymers are thought to improve the stability of amorphous solids to crystallization by increasing the glass transition temperature (Tg) of the resultant SD, resulting in a decrease in mobility of the drug molecules, and through the formation of drug-polymer specific interactions which act to disrupt self-assembly. Drug-polymer specific interactions are thought to be of particular importance and needed to be analyzed by using Differential Scanning Calorimetry.

Differential scanning calorimetry studies were carried out in order to evaluate the ability of the polymer to stabilize amorphous form of the drug in SD. DSC thermograph of PGZ is shown in fig. 23 which shows melting endotherm at 197.790 c i.e. melting point and the amorphous state of the drug.

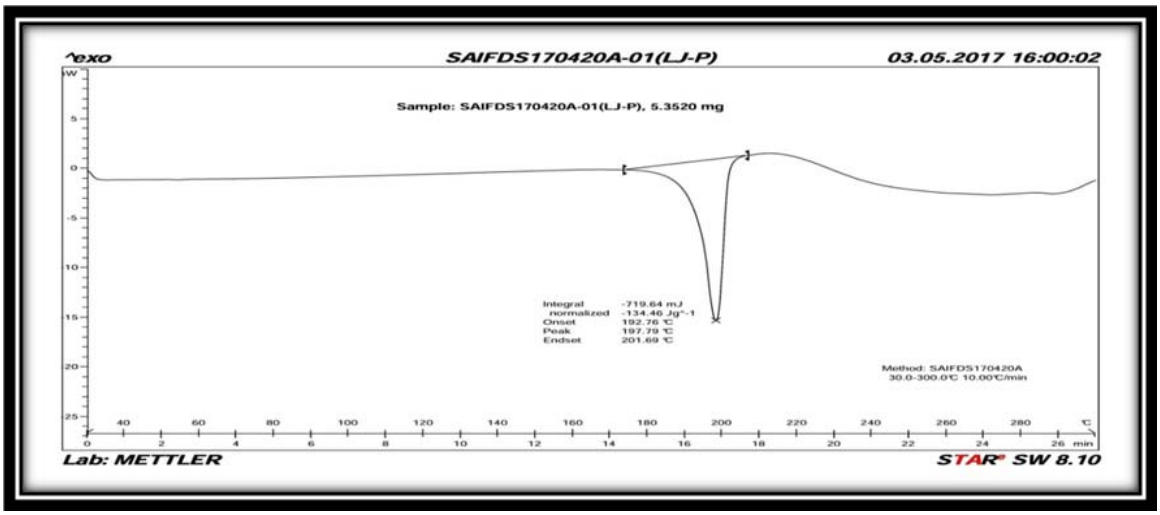



**Fig. 12: DSC thermograph of PGZ**

DSC thermograph of PGZ: PLX 188 (MW) is shown in fig. 24 indicating the formation of stable crystalline SD investigated by a decline in melting endotherm of PLX 188 from 50.830 c to 60.780 c and increase in melting endotherm of PGZ from 189.710 c to 202.620 c.

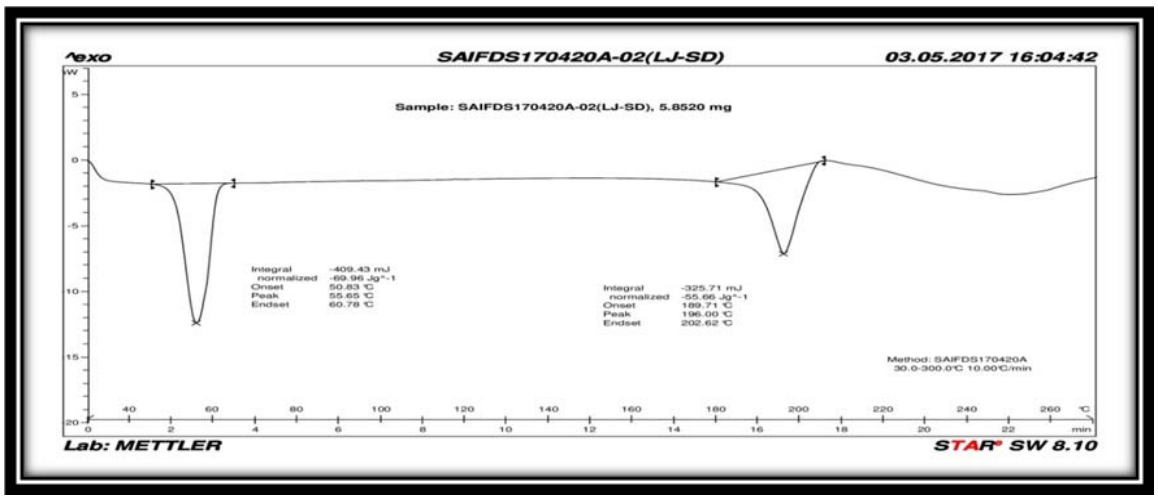



**Fig. 13: DSC thermograph of PGZ: PLX 188(MW)**

**DISCUSSION**

There is an enhancement of the solubility rate if Pioglitazone by solid dispersion with Poloxamer 188 prepared by Microwave irradiation method. The binary system found to be better solubility enhancement (11.46 fold) as compared to a ternary system and Physical Mixture. It was found that in the binary system there is 11.46 fold increasing solubility in from the FT-IR, DSC, PXRD characterization it can be concluded that the Pioglitazone has been converted into an amorphous form in solid dispersion and which is mainly responsible for solubility and dissolution enhancement.

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**CONFLICT OF INTERESTS**

Declare none

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