

Formulation, Evaluation and Characterization of Solid Dispersions of Pioglitazone Hydrochloride

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ABSTRACT

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Pioglitazone HCl is a BCS class-II (poorly water soluble) drug and its absorption is dissolution rate limited. The solubility and the dissolution rate of the drug was enhanced by using the solid dispersion technique. Solid dispersions were prepared using PVP K30, PVP K12, PEG-6000, HPMC 5cps as the hydrophilic carriers. The solid dispersions were characterized by using DSC (Differential scanning calorimetry), XRD (X-ray diffractometry) and FTIR (Fourier transform infrared spectroscopy). Solid dispersions were formulated in to tablets. The solid dispersion tablets enhanced the dissolution rate of the poorly soluble drug. The XRD studies demonstrated the remarkable reduction in the crystallinity of the drug in the solid dispersion. The faster dissolution rate of the drug from the solid dispersion is attributed to a marked reduction in the crystallinity of the drug. The DSC studies revealed the absence of the drug-polymer interaction.

INTRODUCTION

The therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. A large majority of the new chemical entities (NCE) and many existing drug molecules are poorly soluble, thereby limiting their potential uses and increasing the difficulty of formulating bioavailable drug products. Solubility and dissolution rate are important parameters to achieve the desired concentration of drug in the systemic circulation, so that the required pharmacological response will be elicited. Currently only 8% of new drug candidates have both high solubility and permeability. There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are: particle size reduction: micronization, nanosuspension; modification of the crystal habit: polymorphs, pseudopolymorphs; drug dispersion in carriers: eutectic mixtures, solid dispersions, solid solutions; complexation: use of complexing agents; solubilization by surfactants: microemulsions, self microemulsifying drug delivery systems. Although salt formation, particle size reduction, etc. have commonly been used to increase the dissolution rate of the hydrophobic drugs, there are practical limitations with these techniques. The desired bioavailability enhancement may not always be achieved. Therefore, formulation approaches are being explored to enhance the bioavailability of poorly water-soluble drugs. One such

formulation approach that has been shown to significantly enhance the dissolution rate and absorption of hydrophobic drugs is to formulate or prepare the solid dispersion.

Chiou and Riegelman¹ defined the term solid dispersion as “a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures”. The term solid dispersion²⁻⁴ refers to the dispersion of one or more active ingredient in an inert carrier or matrix at the solid state prepared by melting (fusion), solvent, or the melting-solvent method. Once the solid dispersion⁵⁻⁷ is exposed to aqueous media, the hydrophilic carrier^{8,9} dissolves spontaneously and the drug is released as very fine, colloidal particles. Because of the greatly enhanced surface area obtained in this way, the dissolution rate^{10,11} and the bioavailability of poorly water-soluble drugs are expected to be high.

Pioglitazone hydrochloride¹² belongs to the class of thiazolidinediones, is used to decrease the insulin resistance. The drug is practically water insoluble and its absorption is dissolution rate limited. It is an antidiabetic agent to manage a certain type of diabetes like NIDDM (non-insulin-dependent diabetes mellitus, sugar diabetes) called type 2 diabetes. It improves glycemic control while reducing circulating insulin levels. The drug acts as an agonist at peroxisome proliferator activated receptors (PPAR) in target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR-gamma receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In this way, pioglitazone enhances tissue sensitivity to insulin. The drug is used for the treatment of type 2 diabetes in monotherapy and in combination with

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sulfonylurea, metformin, or insulin. The main aim of this study was to enhance the solubility of a poorly soluble drug, Pioglitazone hydrochloride, using solid dispersion technology and thereby improve its dissolution characteristics. The solid dispersions were prepared using various hydrophilic carriers: PVP K 30, PVP K12, PEG 6000, HPMC E5 cps. The solid dispersions were characterized by FTIR, DSC and XRD techniques. The solid dispersions were compressed into tablets. These tablets are evaluated for the quality control parameters and the dissolution rate.

MATERIALS AND METHODS

The pioglitazone HCl, PVP K30, PVP K12, PEG 6000, HPMC 5 cps, croscarmellose sodium, lactose monohydrate and magnesium stearate were supplied by the Hetero Drugs Ltd., Hyderabad. All other chemicals used were of analytical grade.

Preformulation studies

Preformulation testing is an investigation of the physical and chemical properties of a drug substance. The overall objective of preformulation testing is to generate information useful in developing the formulation which is stable and bioavailable. Further, the use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product. For any drug substance to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug like physical appearance, solubility, bulk density, tapped density and the compressibility index.

Determination of bulk density and tapped density

It refers to a measurement to describe the packing of particles and also used to determine the amount of drug that occupies the volume in grams/ml before tapping and after tapping. An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the bulk volume (V_b) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 500 taps and after that, the tapped volume (V_t) was measured and the operation was continued till the two consecutive readings were equal. The bulk density and the tapped density were calculated using the following formula: Bulk Density = (Weight of the sample / Bulk volume). Tapped Density = (Weight of the sample / Tapped volume).

Carr's Index

Carr's index (compressibility index) value of the sample was computed according to the following equation: Carr index (%) = $[(\text{Tapped density} - \text{Bulk Density}) / \text{Tapped Density}] \times 100$.

Hausner's Ratio

Hausner's ratio of the sample was determined by using the equation: Hausner's Ratio = Tapped density / Bulk Density.

Estimation of Pioglitazone hydrochloride

The 100 mg of Pioglitazone hydrochloride was dissolved in 10 ml of methanol and the volume was adjusted up to 100 ml with 0.1N hydrochloric acid (1000 µg/ml) (Stock solution). The above solution was diluted with 0.1 N HCl to obtain the series of dilutions containing 5, 10, 15, 20, 25, 30, 35 and 40 µg/ml of Pioglitazone hydrochloride. The absorbance of the above solutions was measured on a Shimadzu UV-Visible Spectrophotometer at 269 nm. The calibration curve was plotted and it was used for the estimation of Pioglitazone hydrochloride.

Preparation of solid dispersion by solvent evaporation method

Solvent evaporation method was used for the preparation of solid dispersion of drug with PVP and HPMC as the hydrophilic polymers (table 1). In this method water was used as the solvent. Respective amount of carrier was dissolved in required amount of water taken in a glass beaker to get a clear polymer solution. The weighed amount of the drug was added to this solution carefully with constant stirring and dispersed to get the uniform mass. The wet mass was dried in an oven at 50°C. The mass obtained is further pulverized and sifted through the 40 mesh sieve.

Preparation of solid dispersion by melting method

Melting method was used for the preparation of solid dispersion of drug with PEG 6000 as the hydrophilic polymer (table 1). Respective amounts of carriers were melted in a glass beaker and the drug was added to it and dispersed. Then the mass was allowed to cool till solidification. Then it was pulverized and sifted through the 40 mesh sieve.

Solubility studies

Solubility studies were performed as described by Higuchi and Connors¹³. Excess amount of pure Pioglitazone hydrochloride and the solid dispersions were added to 20 ml

Table 1: Composition of Solid dispersions of Pioglitazone hydrochloride (Drug: polymer ratios)

| | |
|-----------------|-------|
| DRUG:PVP K-30 | 1:0.5 |
| | 1:1 |
| DRUG:PVP K-12 | 1:1 |
| DRUG:PEG 6000 | 1:0.5 |
| | 1:1 |
| DRUG:HPMC 5 CPS | 1:1 |
| | 1:1.5 |
| | 1:2 |

of different buffers or distilled water taken in a stoppered conical flask and the mixture was shaken for 24 hrs on a rotary flask shaker. After, the equilibrium was attained, the 2 ml aliquots were withdrawn at 1 hr intervals and filtered through the millipore membrane filter (0.45 μ). The filtrate was analysed spectrophotometrically at 269 nm. Shaking was continued until three consecutive readings were the same. Results are indicated in table 2 and 3.

FORMULATION DEVELOPMENT:

Based on preformulation data, the various excipients were selected and the composition of the tablet formulations is shown in the table 4. All the tablet formulations were prepared by the direct compression method.

In F1: Here the tablets showed very high value for disintegration time and the drug release was also very slow and the desired dissolution profile was not achieved.

In F2: To increase the dissolution rate, the polymer concentration was decreased. But the disintegration time remained high. The dissolution rate was improved but the desired dissolution profile was not achieved.

In F3: To improve the dissolution rate, the polymer grade was changed from PVP K-30 to PVP K-12. But the disintegration time was still very high and the desired dissolution profile was not achieved. To decrease the disintegration time, the superdisintegrant concentration was increased, but the disintegration time was not decreased.

In F4: Polyethylene Glycol(PEG 6000) was used in this trial. The desired dissolution rate was not achieved.

In F5: To improve the drug release, polyethylene glycol concentration was decreased. But the release rate was quite less.

In F6: In this trial Hydroxypropyl methyl cellulose was used in equal ratio with the drug, the desired dissolution rate was achieved. The drug release was slightly faster when compared to the marketed brand(innovator).

In F7 and F8: To get the drug release profile similar to that of the innovator, the polymer concentrations of HPMC were increased in these trials. In F7, the desired drug release was achieved but the dissolution rate is slightly lower than the innovator. In case of F8, the dissolution rate was decreased.

In F9: Finally the trial 6 was confirmed and repeated once again for reproducibility.

Table 2: Solubility studies on Pioglitazone hydrochloride

| Solvent | mg/20 ml | mg/ml |
|-----------------------|----------|--------|
| 0.1 N HCL, pH 1.2 | 129.7 | 6.50.3 |
| M KCL Buffer, pH | 2.03.4 | 0.17 |
| Mcllavaine buffer, pH | 2.52.1 | 0.104 |
| Water | 1.0 | 0.05 |

Table 3: Solubility studies on solid dispersion(Drug:HPMC, 1:1)

| Solvent | mg/20 ml | mg/ml |
|---------------------------|----------|----------|
| 0.1 N HCL, pH 1.2 | 298.4 | 14.910.3 |
| M KCL Buffer, pH 2.0 | 11.6 | 1.16 |
| Mcllavaine buffer, pH 2.5 | 13.9 | 0.694 |
| Water | 3.1 | 0.156 |

EVALUATION OF TABLETS:

The prepared tablets were evaluated for general appearance, thickness, hardness, weight variation, friability and drug content. The results are indicated in table 5.

Weight variation test:

This is an important in-process quality control test to be checked frequently. Corrections were made during the compression of tablets. Any variation in the weight of tablet leads to either under medication or overdose. So, every tablet in each batch should have uniformity of weight. The 20

Table 4: Composition of tablet formulations

| Trials | Drug :Polymer ratio | Ingredients(mg/tablet) | | | |
|--------|---|------------------------|---------------------|-----------------------|--------------------|
| | | Solid dispersion | Lactose monohydrate | Croscarmellose sodium | Magnesium stearate |
| F1 | D:PVP K-30(1:1) | 30 | 61.9 | 4.0 | 1.0 |
| F2 | D:PVP K-30(1:0.5) | 22.5 | 70.2 | 4.0 | 1.0 |
| F3 | D:PVP K-12(1:1) | 30 | 61.9 | 4.0 | 1.0 |
| F4 | D:PEG 6000(1:1) | 30 | 61.9 | 4.0 | 1.0 |
| F5 | D:PEG 6000(1:0.5) | 22.5 | 70.2 | 4.0 | 1.0 |
| F6 | D:HPMC 5CPS(1:1) | 30 | 61.9 | 4.0 | 1.0 |
| F7 | D:HPMC 5CPS(1:1.5) | 37.5 | 53.7 | 4.0 | 1.0 |
| F8 | D:HPMC 5CPS(1:2) | 45 | 45.4 | 4.0 | 1.0 |
| F9 | D:HPMC 5CPS(1:1) Reproducibility batch | 30 | 61.9 | 4.0 | 1.0 |

Table 5: Evaluation of quality control parameters of tablets

| S. No. | Physical parameter | F 1 | F 2 | F 3 | F 4 | F 5 | F 6 | F 7 | F 8 | F 9 |
|--------|----------------------------------|-------|----------------|----------------|----------------|---------------|---------------|--------------|---------------|---------------|
| 1 | Weight variation(%)n=20 | 0.3 | 0.2 | 0.2 | 0.4 | 0.4 | 0.4 | 0.4 | 0.3 | 0.4 |
| 2 | Hardness(Kg/cm ²)n=5 | 4.5 | 4.3 | 4.5 | 4.3 | 4.6 | 4.8 | 4. | 4.3 | 4.3 |
| 3 | Thickness(mm)n=5 | 3.35 | 3.33 | 3.35 | 3.34 | 3.33 | 3.32 | 3.35 | 3.35 | 3.35 |
| 4 | Friability(%)n=10 | 0.09 | 0.093 | 0.12 | 0.24 | 0.25 | 0.31 | 0.29 | 0.27 | 0.30 |
| 5 | Disintegration time,n=6 | 20min | 17min 35sec | 16min 18sec | 12min 45sec | 8min 30sec | 2min 10sec | 3min 5sec | 4min 10sec | 2min 11sec |

tablets were weighed collectively and individually. Average weight was calculated from the total weight of all the tablets. The individual weights were compared with the average weight. The percentage weight variation is required to be within the permissible limits.

Thickness:

The thickness of the tablets was calculated by using the vernier callipers.

Hardness test :

Hardness (diametral crushing strength) is the force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The hardness was tested using hardness tester. The average of the five determinations was determined and reported.

Friability test :

Friability is the loss of weight of the tablet in the container/package, due to removal of fine particles from the surface. Roche friabilator was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets with in the chamber of the friabilator. After, 100 rotations (i.e. in 4 minutes), the tablets were taken out from the friabilator and the intact tablets were again weighed collectively. Permitted friability limit is 1.0%. The percent friability was determined using the following formula

$$(W_1 - W_2)/W_1 \times 100 ,$$

where, W_1 = weight of the tablets before test, W_2 = weight of the tablets after the test.

Disintegration time:

Disintegration time of the tablet was observed with the help of disintegration test apparatus consisting of a basket rack assembly with 1000 ml beaker ,a thermostatic arrangement for heating the beaker between 35^oC to 39^o C, and a device for raising and lowering the basket in the immersion fluid at a constant rate between 29 and 32 cycles per min. The test is

provided to check whether the tablets disintegrate with in the prescribed time when placed in a liquid medium at the experimental conditions presented above.

Drug content:

The 20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 15mg of pioglitazone HCl was transferred in to a 100 ml volumetric flask, the drug was dissolved in 10 ml of methanol and the volume was adjusted to 100ml with 0.1N HCl. The sample was filtered to remove the insoluble excipients. Further, 10ml of the above solution(filtrate) was diluted to 100 ml with 0.1N HCl and the absorbance of the resulting solution was observed spectrophotometrically (shimadzu)at 269 nm.

Dissolution study:

The dissolution behaviour of the pure drug, the solid dispersions and the prepared tablets was evaluated using the following parameters: pH 2.0 buffer,900 ml was used at 37 ± 0.5°C.The USP apparatus II ,paddle method was used at 75 rpm. At definite time intervals, the 5 ml of the dissolution fluid was withdrawn; filtered and subjected for analysis. The 5ml of the fluid was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed spectrophotometrically at 269nm.Each experiment was carried out in triplicate.The results are indicated in table 6 and fig.1-5.

Similarity factor (f₂ analysis):

$$f_2 = 50. \log \{ [1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2]^{-0.5} . 100 \}$$

Where ' R_t ' and ' T_t ' are the cumulative percentage drug dissolved at each of the selected n time point of the reference and the test product respectively. Where as factor f_2 is inversely proportional to the averaged squared difference between the two profiles, with emphasis on the larger difference among all the time points.

Stability Study

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at both normal and exaggerated temperature conditions(as per the ICH guidelines) with the necessary

extrapolations to ensure the product will, over its designed shelf life, provide medication for the absorption at the same rate as when originally formulated. The tablet formulation F9 was stored at 40°C/75%RH for two months. The drug content and the dissolution rate were evaluated at the end of the first month and the second month.

Characterization of Solid dispersion:

The solid-state properties of drug in the solid dispersion was investigated using differential scanning calorimetry (DSC), X-Ray diffractometry (XRD) and Fourier Transform Infrared Spectroscopy (FTIR), since this would influence the *in vitro* and *in vivo* dissolution characteristics.

A. Differential Scanning Calorimetry (DSC)

The DSC measurements (fig.6-9) were carried out on a Mettler Toledo DSC 821 model. The accurately weighed sample was placed in an aluminum pan. An empty aluminum pan was used as the reference. The experiment was carried out in nitrogen atmosphere at scanning rate of 10°C/min., in the range :30°C–300°C.

B. X-ray diffractometry (XRD)

The XRD patterns (fig.10) of all the samples were recorded using Bruker X-Ray diffractometer with the tube anode Cu over the interval, 3-50°/2θ. The generator tension (voltage) and the generator current was kept at 40 kV and 30 mA respectively with the scanning speed of 2°/min.

C. Fourier Transform Infra Red Spectroscopy (FTIR)

The FTIR study was undertaken to assess the drug-polymer interaction. FTIR spectra (fig.11-13) of Pioglitazone hydrochloride, physical mixture and the solid dispersion were recorded on a Bruker FTIR spectrophotometer. The KBr pellet method was employed. Each spectrum was recorded in the region 400-4000 cm⁻¹ at spectral resolution of 2 cm⁻¹.

RESULTS AND DISCUSSION

The present study was undertaken to formulate Pioglitazone hydrochloride solid dispersion tablets. The study involves preformulation studies of the drug, formulation development and evaluation of the formulated tablets.

Preformulation studies

The drug appeared as white to off white crystalline powder, it is poorly water soluble (0.05 mg/ml), the bulk density and the tapped density of the pure drug (pioglitazone HCl) was found to be 0.526 g/ml and 0.746 g/ml respectively. The compressibility index and the Hausner's ratio of the pure drug was found to be 29.4% and 1.35 respectively.

Preparation of solid dispersions

The solid dispersions were prepared using PVP K30, PVP

K12 and HPMC 5 cps as the hydrophilic carriers by the solvent method. The drug-PEG 6000 solid dispersions were prepared by the melting method. All the prepared batches of solid dispersions were found to be non-hygroscopic, free flowing powders. All the prepared solid dispersions exhibited uniformity of drug content. The drug content of the solid dispersions was found in the range: 97% to 103%.

Solubility studies

The aqueous solubility of Pioglitazone hydrochloride was found to be 0.05 mg/ml, and the drug release was found to be only 23.5% during the *in vitro* dissolution study in pH 2.0 buffer, suggesting a strong need to enhance the solubility and the dissolution rate of Pioglitazone hydrochloride. Therefore, the solid dispersion technique (using PEG 6000, PVP K30, PVP K12, HPMC 5 cps as the hydrophilic polymers) was employed for improving the solubility and the dissolution rate of Pioglitazone hydrochloride. The improvement in solubility was observed with the solid dispersions (SD). The results are indicated in table 2 and 3. The results of the solubility are in accordance with the well established formation of soluble complexes between the water soluble polymeric carriers and the poorly water soluble drugs¹⁴.

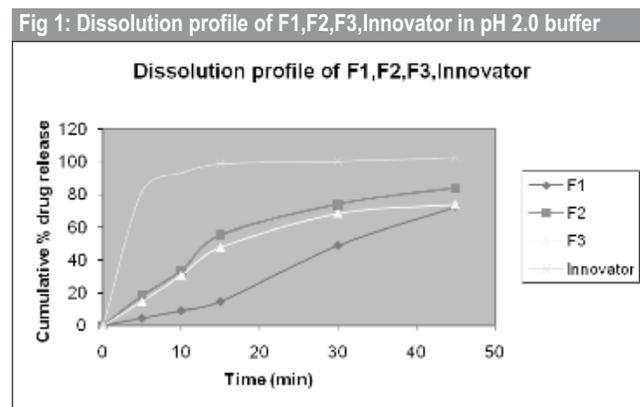
Formulation studies

The composition of the prepared tablets is indicated in table 4. The tablet formulations (F1-F9) exhibited uniform drug content. The drug content of all the tablet formulations was found in the range :98% to 103%. All the formulated tablets fulfilled the compendial limits of weight variation, hardness, friability and the disintegration time (table 5).

Dissolution studies

Formulation 1,2,3:

The *in-vitro* drug release profile of tablets from the batch (F1, F2, F3) prepared with different ratios of PVP was carried in pH 2.0 buffer for 45 min. and the plot of the cumulative % drug released versus time (min) was plotted and depicted in Fig.1.



Formulation 4,5:

The in-vitro drug release profile of tablets from batch F4,F5 prepared with different ratios of PEG 6000 were conducted in pH 2.0 buffer for 45 min. and the plot of cumulative % drug released versus time (min) was plotted and depicted in Fig2.

Formulation 6,7,8:

The in-vitro drug release profile of tablets from batch F6,F7,F8 prepared with different ratios of HPMC were conducted in pH 2.0 buffer for 45 min. and the plot of the cumulative % drug released versus time (min) was plotted and depicted in Fig 3.

Formulation 9:

The in-vitro drug release profile of tablets from batch F9 which is the reproducibility batch of F6 prepared with HPMC as the carrier (drug and polymer ratio of 1:1) was carried in pH 2.0 buffer for 45 min., and the plot of the cumulative % drug released versus time (min.) was plotted and depicted in Fig.4 and the results were found to be reproducible.

From the dissolution profiles and the dissolution parameters, it is clear that among all the prepared formulations, the batch F6 showed the maximum dissolution. The results of the dissolution studies are indicated in table 6 and fig.1-5. The dissolution parameters of the different tablet formulations: the % drug dissolved in 10 min., T_{50} (time taken for 50% of the drug release), T_{75} (time taken for the 75% of drug release), T_{90} (time taken for 90% of the drug release) are indicated in table 6. Based on the dissolution parameters, it is evident that the tablet formulation F6 demonstrated the best dissolution rate. The f_2 value (similarity factor) of the batch F6 was calculated and it was found to be 77%, which is greater than 50%. So the test and reference (innovator brand) profiles are similar. The results of the dissolution study indicate an improvement of dissolution rate of pioglitazone HCl in the solid dispersion tablets. The rate of dissolution increases as the concentration of the hydrophilic polymeric carriers increases in the solid dispersions. The improvement in the

Fig. 2: Dissolution profile of F4,F5,Innovator in pH 2.0 buffer

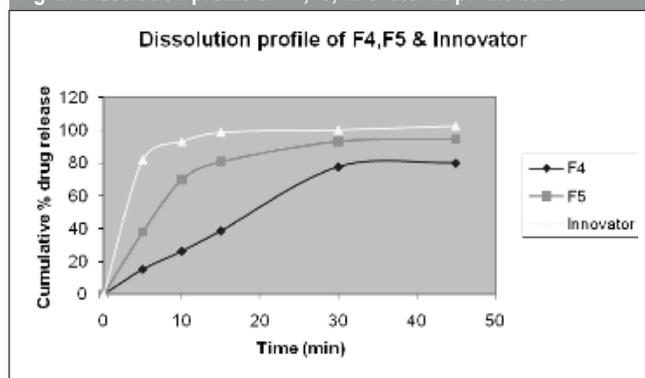


Fig. 3: Dissolution profile of F6,F7,F8,Innovator in pH 2.0 buffer:

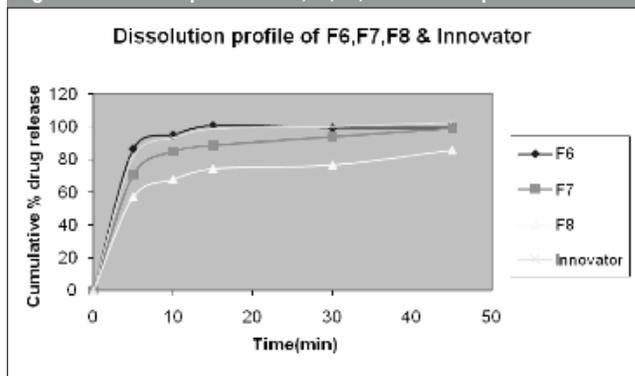


Fig. 4: Dissolution profile of reproducibility batch(F9)

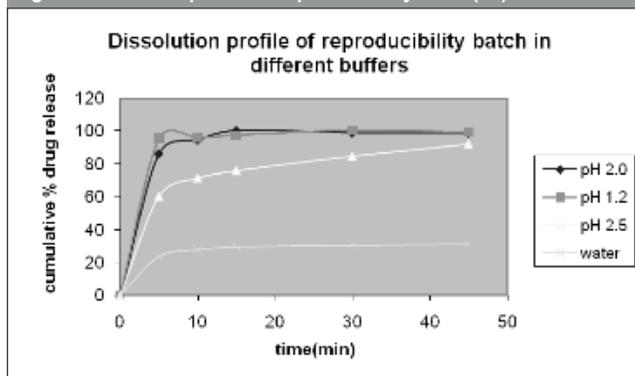
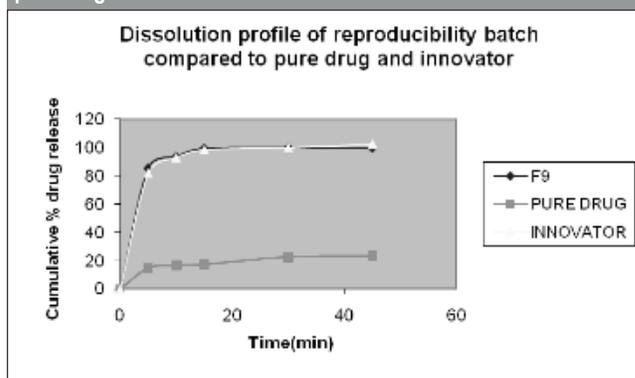


Fig. 5: Dissolution profile of reproducibility batch(F9) compared to pure drug and innovator



dissolution rate is possibly caused by several factors. Such factors are :the strong hydrophilic property of the polymeric carriers, which improves the water penetration and the wettability of the hydrophobic drug; the optimal dispersion of the drug in the hydrophilic polymeric carrier; the absence of crystals (amorphous dispersions)corresponds to lower energy required for dissolution ;the molecular dispersion of drug on the polymeric carrier improves the hydrophilic characteristics of the hydrophobic drug¹⁵. Also, the decrease in the particle size and the improvement in the dispersibility of the hydrophobic drug particles can improve also the dissolution rate of the drug¹⁶.

Stability studies:

The formulation F9 was stored at 40 °C /75%RH for two months. After 1 month and 2 months period of stability studies, the drug content and the dissolution rate were evaluated. At the end of the first month and the second month, the drug content and the dissolution rate of the batch F9 are within the limits. As the drug content and the dissolution rate are within the limits, the formulation F9, passes the stability test.

Characterization of Solid Dispersions of Pioglitazone hydrochloride prepared with Hydroxypropyl methyl cellulose 5 cps:

Differential Scanning Calorimetry(DSC)

The fig.6-9, shows the thermal behaviour of the pure pioglitazone HCl, Hydroxypropyl methyl cellulose and their corresponding binary systems. Pure drug exhibited a sharp endothermic peak at 197°C, indicating the melting point of the crystalline pioglitazone HCl(Fig.6). The DSC thermogram of Hydroxy propyl methyl cellulose exhibited broad endothermic peak at 60°C attributed to the evaporation of absorbed water (Fig.7). The drug-HPMC physical mixture displayed (Fig.8) endothermic peak of the drug at 194°C.

However, the peak was progressively reduced in the area and appeared with decreased intensity. In solid dispersion system, the endotherm of the drug was shifted towards lower temperature 185°C and the peak was gradually reduced in area(Fig. 9). The lower melting point (temperature) of the drug in the solid dispersion was because of the melting point depression. As the intensity of the endotherm was markedly decreased in the drug-HPMC solid dispersion, the faster dissolution rate of the drug from the solid dispersion is attributed to the reduction in the crystallinity of the drug. Crystallization inhibition is attributed to the entrapment

Fig. 6: DSC thermogram of Pioglitazone hydrochloride

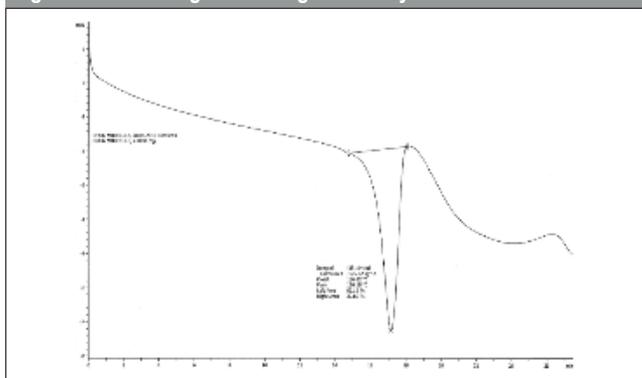


Fig. 7: DSC thermogram of Hydroxypropyl methyl cellulose

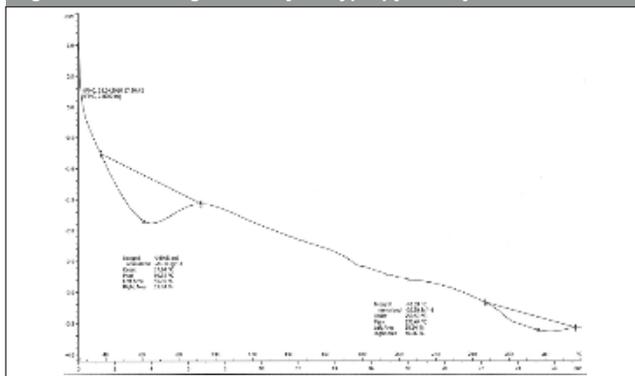


Fig. 8: DSC thermogram of physical mixture of Pioglitazone hydrochloride and Hydroxypropyl methyl cellulose

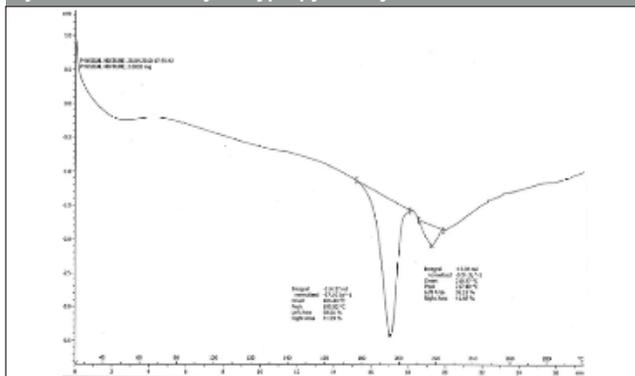


Fig. 9: DSC thermogram of Solid dispersion of Pioglitazone hydrochloride and HPMC

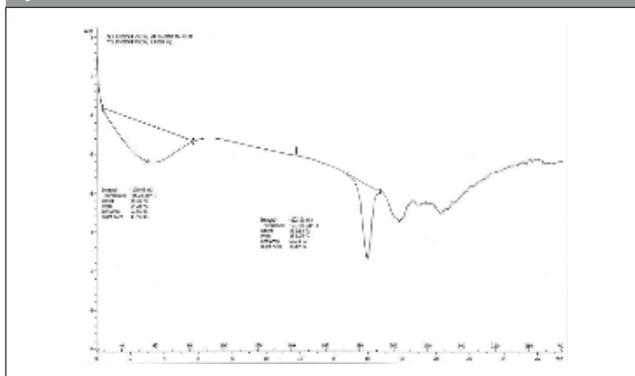
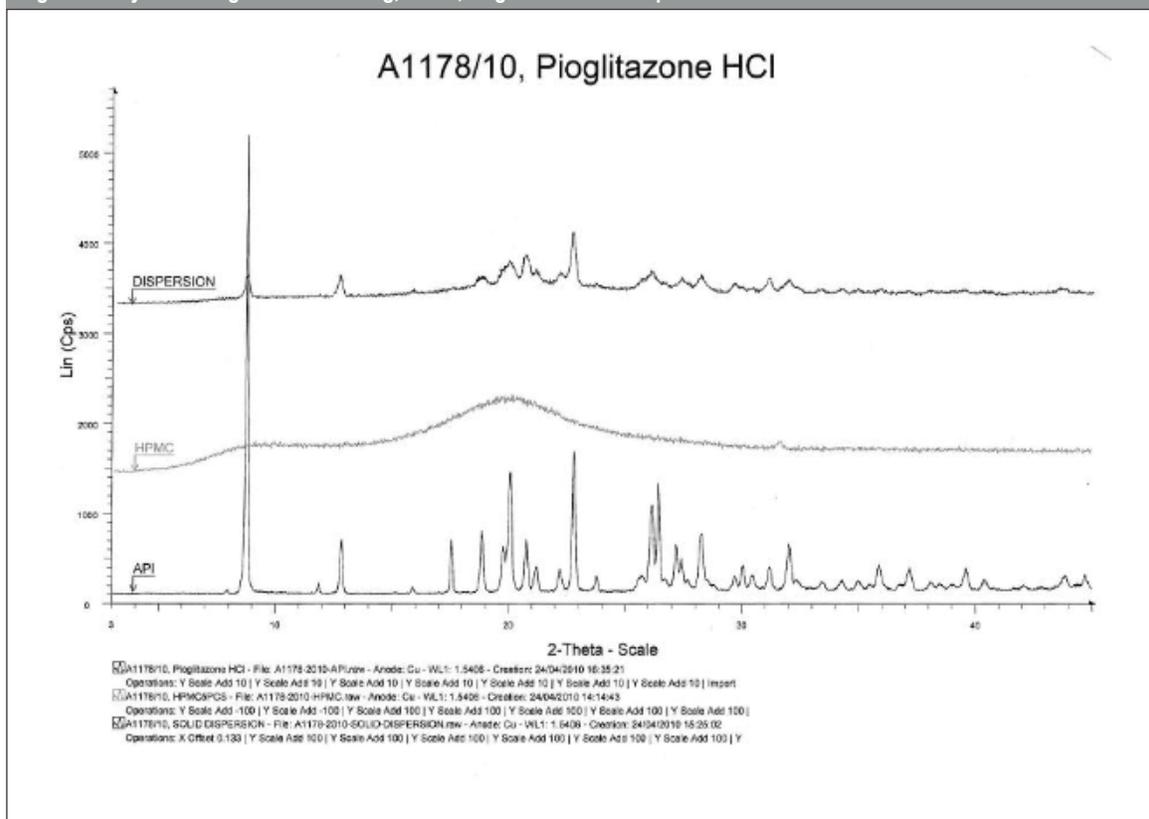


Table 6: Dissolution parameters of Pioglitazone hydrochloride tablets

| Formulations | Dissolution parameters | | | |
|-----------------|----------------------------|-----------------------|-----------------------|-----------------------|
| | % Drug dissolved in 10 min | T ₅₀ (min) | T ₇₅ (min) | T ₉₀ (min) |
| F1 | 9.11 | 31 | - | - |
| F2 | 33.51 | 4 | 31 | - |
| F3 | 30.69 | 17 | - | - |
| F4 | 26.25 | 20 | 28 | - |
| F5 | 69.56 | 7 | 13 | 25 |
| F6 | 94.5 | 3 | 4 | 7 |
| F7 | 84.79 | 4 | 7 | 23 |
| F8 | 67.62 | 4.5 | 15 | - |
| Innovator brand | 90.16 | 4 | 6 | 10 |

Fig. 10: X Ray Diffractograms of the drug, HPMC, drug-HPMC solid dispersion.



of drug molecules in the polymer matrix during the solvent evaporation¹⁷. Numerous studies have shown that polymers like HPMC, PVP used in the solid dispersions can inhibit the crystallization of drugs resulting in an amorphous form of the drug in the solid dispersions^{18,19}.

X-ray diffractometry (XRD)

The X-ray diffraction pattern (Fig 10) of pioglitazone HCl exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of the drug. The solid dispersion system displayed less intense and highly diffused peaks as compared to the pioglitazone HCl. The XRD studies revealed the reduction in the crystalline nature of the drug in the solid dispersion. The enhancement in the dissolution rate of the drug from the drug-HPMC solid dispersion is ascribed to the marked reduction in the crystallinity of the drug. The microcrystals are formed as a consequence of evaporation of solvent during the preparation of solid dispersions by the solvent evaporation technique. Evaporation of solvent increases the viscosity very rapidly leading to a decrease in drug mobility preventing re-crystallization. When the solvent is evaporated completely drug molecules are frozen in the polymer. A crystal lattice is not formed, but the drug molecules are of randomly dispersed order over only a few molecular dimensions²⁰.

Fourier transform infrared spectroscopy (FTIR)

The fig. 11-13 displays the FTIR spectra of pioglitazone HCl, physical mixture of drug-HPMC and the drug-HPMC solid dispersion respectively. The FTIR spectrum of pure pioglitazone HCl (Fig. 11) demonstrated the FTIR peaks at 3084 cm^{-1} (aromatic C-H stretching), 2966 cm^{-1} (aliphatic C-H stretching asymmetric), 1743 cm^{-1} (amide C=O stretching), 1610 cm^{-1} (C=C), 1460 cm^{-1} (ring C-N stretching), 1243 cm^{-1} (C-S stretching), 1038 cm^{-1} (aliphatic C-O-C) and 850 cm^{-1} (para disubstituted aromatic ring). No significant alterations in the FTIR peaks of the pure drug were detected in the drug-HPMC physical mixture (Fig. 12). However, some of the peaks of the pioglitazone HCl were slightly shifted and found to be attenuated. The solid dispersion of pioglitazone-HPMC (Fig. 13) did not show any new peaks and it is evident from spectra that the drug peaks are also present in the solid dispersion spectra. The shift in the peaks associated with the C=O group of the drug indicates some sort of solid state interactions between the drug and the polymer in the solid dispersion and the physical mixture. The interactions are due to the intermolecular hydrogen bonding between the drug and the polymer²⁰. An intermolecular hydrogen bond was expected to occur between the C=O group of the drug and one of the hydrogen atoms of HPMC^{21,22}. The FTIR data suggest

Fig. 11: FTIR spectrum of Pioglitazone hydrochloride

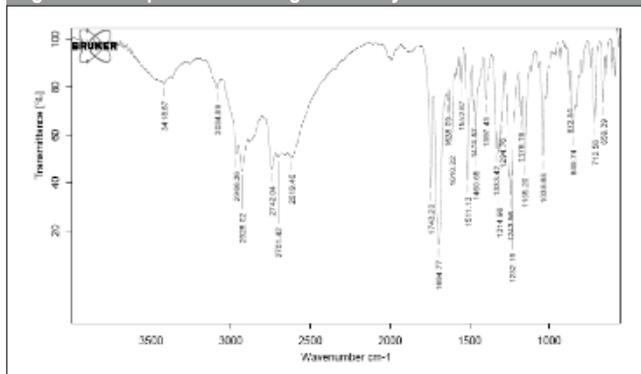


Fig. 12: FTIR spectrum of physical mixture of Pioglitazone hydrochloride and Hydroxypropyl methyl cellulose

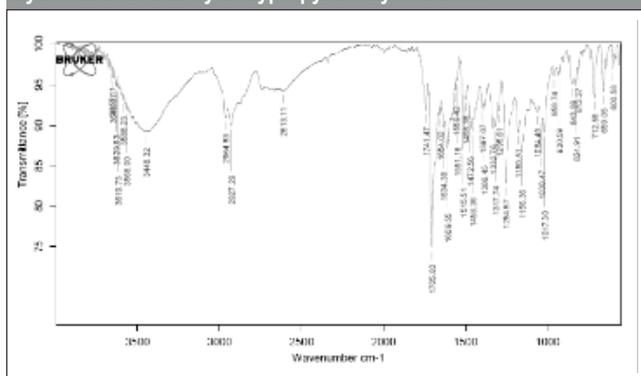
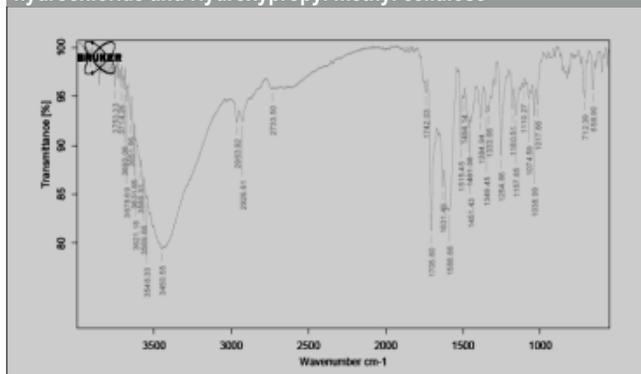


Fig. 13: FTIR spectrum of Solid dispersion of Pioglitazone hydrochloride and Hydroxypropyl methyl cellulose



the formation of intermolecular hydrogen bonding between the drug and the HPMC.

CONCLUSION

In this study solid dispersions of Pioglitazone hydrochloride were prepared using Polyvinyl pyrrolidone K-30 and K-12, Polyethylene glycol 6000 and Hydroxypropyl methyl cellulose 5 cps as the hydrophilic polymers. The solid dispersions were compressed in to tablets. The tablet formulation, F6 which has the drug- polymer ratio of 1:1 was found to be the best of all the trials showing drug release

matching the innovator product. The best formulation F6 was repeated again for reproducibility, and all the tests were done for conformation. For the reproducibility batch the release profile was observed in different dissolution media of different pH values. From the results it is concluded that the solubility and the dissolution rate of the drug was enhanced.

The DSC showed the depression of the melting point of Pioglitazone HCl from 197^oC to 185^oC in the solid dispersion. The X-Ray diffraction patterns of solid dispersion displayed less intense and highly diffused peaks compared to the pure Pioglitazone HCl. It indicates the reduction in the crystallinity of Pioglitazone HCl in the solid dispersion. The reduction in the crystallinity of the drug contributes to the increase in the solubility of poorly soluble drug and also, enhances the dissolution rate of Pioglitazone hydrochloride. From these results, it is concluded that the solubility and the dissolution rate of the drug can be increased by formulating the solid dispersions with Hydroxypropyl methyl cellulose (5 cps) as the hydrophilic polymer.

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REFERENCES

1. Chiou WL, Riegelman S. Pharmaceutical application of solid dispersion system. *J. Pharm. Sci.* 1971;60:1281-302.
2. Goldberg A, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures III - experimental evaluation of griseofulvin- succinic acid solid solution. *J. Pharm. Sci.* 1966;55:487-92.
3. Narang A., Shrivastava A. Melt extrusion solid dispersion technique. *Drug Dev. Ind. Pharm.* 2002; 26:111-5.
4. Varma MM, Pandit JK. Dissolution, solubility, XRD and DSC studies on flurbiprofen-nicotinamide solid dispersions. *Drug Dev Ind Pharm.* 2005;31:417-23.
5. Choudhary D, Kumar S, Gupta GD. Enhancement of solubility and dissolution of glipizide by solid dispersion (kneading) technique. *Int. J Pharm.* 2009;3:245-51.
6. Alazar N, Ghebremeskel, Lodaya M, Vemvarapu C. Use of Surfactants as Plasticizers in Preparing Solid Dispersions of Poorly Soluble API: Stability Testing of Selected Solid Dispersions. *Pharm. Res.* 2006;23:1928-36.
7. Okonogi S, Puttipatkhachorn S. Dissolution Improvement of High Drug-loaded Solid Dispersion. *AAPS PharmSciTech.* 2006; 7:148-53.
8. Van den Mooter G, Sandrien Janssens, Nagels S. Formulation and characterization of ternary solid dispersions made up of Itriconazole and two excipients, TPGS 1000 and PVPVA 64, that were selected based on super saturation screening study, *Eur J Pharm Biopharm.* 2008;69:158-66.

9. Van den Mooter G. Mechanism of increased dissolution of diazepam and temazepam from polyethylene glycol 6000 solid dispersions. *Int J Pharm.*2002;249:45-58.
10. Shawn A, Mitchell ,Reynolds TD, Dasbach. TP. A compaction process to enhance dissolution of poorly water-soluble drugs using hydroxypropyl methylcellulose. *Int. J Pharm.*2003;250:3-11.
11. Sang-Chul S, Kim J. Physicochemical characterization of solid dispersion of furosemide with TPGS. *Int. J Pharm.*2003;251:79-84 .
12. Tripathi K.D. Antidiabetic drugs, in: *Essentials of Medical Pharmacology*, 5th (Ed), Jaypee Brothers Ltd., New Delhi. 2003 ,pp.345-52.
13. Higuchi T, Connors KA. Phase solubility techniques. In: C.N. Reilley (Ed). *Advances in Analytical Chemistry and Instrumentation*. New York, Wiley Interscience, 1965, vol 4, pp. 117.
14. Costa P, Loba JMS. Modelling and composition of dissolution profiles. *Eur. J Pharm. Sci.*2001;13:123-33.
15. Karavas E, Ktisis G, Xenakis A, Georgarakis E. Miscibility behaviour and formation mechanism of stabilized felodipine-polyvinylpyrrolidone amorphous solid dispersions. *Drug Dev. Ind. Pharm.*2005;31:473-89.
16. Ford JL. The current status of solid dispersions. *Pharm. Acta Helv.*1986;61:69-88.
17. Bettinetti GP, Mura P, Giordano F, Setti M. Thermal behaviour and physicochemical properties of naproxen in mixtures with polyvinylpyrrolidone. *Thermochim. Acta.* 1991;199:165-71.
18. Yamashita K, Nakate T, Okimoto K, Ohike A, Tokunaga Y, Ibuki R. Establishment of new preparation method for solid dispersion formulation of tacrolimus. *Int. J Pharm.*2003;267:79-91.
19. Tantishaiyakul V, Kaewnopparat N, Ingkatawornwong S. Properties of solid dispersions of piroxicam in polyvinylpyrrolidone. *Int. J Pharm.*1999;18:143-61.
20. Van den Mooter G, Augustijns P, Bleton N, Kinget R. Physicochemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30. *Int. J Pharm.*1998;164:67-80.
21. Roni MA, Islam MS, Kibria G, Sadat SMA, Rony MR, Rahman MH, Jalil R. Effects of Poloxamer and HPMC on the dissolution of clonazepam-polyethylene glycol solid dispersions and tablets. *Ind. J. Pharm. Edu. Res.*2011;45:139-44.
22. Rao M, Mandage Y, Khole I, Munjapara G. Characterization of solid dispersions of simvastatin with PVP K30 and Poloxamer 188. *Ind. J. Pharm. Edu. Res.*2011;45:145-52.
