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Original Research Article

Solubility Enhancement of Pioglitazone by Solid Dispersion Method

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Abstract:
The major challenge with conventional dosage forms of Pioglitazone is poor aqueous solubility. Through this study are to improve its aqueous solubility by preparing its solid dispersion by fusion method using various carriers that will improve its absorption and subsequent bioavailability. The solid dispersions of Pioglitazone were prepared using PEG-4000, PEG-6000 and PVP K30 as carrier, using fusion method. Solid dispersions of Pioglitazone were prepared using PEG-4000, PEG-6000 and PVP K30 as carrier, using fusion method and total 9 formulation (F1-F9) were prepared. Tablets were prepared (TF5) from the optimum formulation (F5). The prepared tablets (TF5) were subjected to evaluation for parameters like shape and size, weight variation, hardness, friability, disintegration time, drug content etc. The solid dispersion (F5) as well as the tablet (TF5) showed greater rate and extent of dissolution as compared to pure drug.
Keywords: bioavailability, dissolution rate, PEG, PVP K30, solid dispersion, Pioglitazone

Introduction

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. [(1)] Solid Dispersions technique exhibit great potential toward solubility enhancement via dispersion of drugs in inert carriers or matrix at solid state. Melting and solvent evaporation methods are the two major processes of preparing solid dispersions.[(2)]

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and bioavailability. There are practical limitations for these techniques. The salt formation is not feasible for compounds that are neutral, weakly

acidic or weakly basic.[3] The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and co solvents leads to liquid formulations that are usually undesirable from the view points of patient acceptability and commercialization. [4,5]

Pioglitazone is an oral hypoglycaemic drug, used for the treatment of type 2 diabetes. Pioglitazone decreases fasting and postprandial plasma glucose levels by improving the sensitivity of hepatic and peripheral (muscle) tissue to insulin. The major challenge with conventional dosage forms is poor aqueous solubility of Pioglitazone.[6] The main objectives of this study is to improve its aqueous solubility by preparing its solid dispersion by fusion method using various carriers, that will improve its absorption and subsequent bioavailability.

MATERIAL AND METHODS

Materials

Pioglitazone was obtained from Micro Labs Ltd., Bengaluru, PVP K30, PEG-6000 and PEG-4000 was obtained from Loba Chemicals Pvt. Ltd. Rest of the chemicals were of research grade.

Methodology

Physicochemical Characterization of Drug (Preformulation Studies)

Physical Appearance

The physical form and color of the drug Pioglitazone was observed visually.

Melting Point

The melting point determination of the drug (Pioglitazone) was done by using the melting point apparatus. A small amount of pure drug (Pioglitazone) was taken in a capillary tube and it was kept in the melting point apparatus. The reading of melting point was taken in triplicate and noted.

Calibration Curve of Pioglitazone using UV-Visible Spectroscopy:

Scanning of Pioglitazone in Distilled water and Acid buffer pH 1.2

50 mg of drug (Pioglitazone) was dissolved in Distilled water and Acid buffer pH 1.2 in two 100 ml volumetric flasks, and volume was made to 100 ml with distilled water. 2 ml of this stock solution was further diluted to 50 ml to get concentration of 20 µg/ml. This solution was scanned in UV-spectrophotometer and characteristic peak (λmax) was observed.

Calibration curve of Pioglitazone in Distilled water and Acid buffer pH 1.2

50 mg of Pioglitazone was dissolved in in Distilled water and Acid buffer pH 1.2 in two 100 ml volumetric flasks. This gave the concentration of 500 µg/ml (stock solution). 1, 2, 3, 4, 5 and 6 ml of this stock solution was further diluted to 100 ml to get different concentrations of 5, 10, 15, 20, 25 and 30 µg/ml. Absorbances were measured at the respective λmax. The process was performed in triplicate. The standard curve was obtained by plotting concentration (µg/ml) on X-axis and absorbance on Y-axis.

Solubility determination

An excess of the drug was added to conical flasks containing each of 20 ml of distilled water and acid buffer pH 1.2 respectively. Then conical flasks were shaken manually for some time. After that these conical flasks were kept on a rotary shaker for 24 hours. After 24 hours of shaking, these solutions were filtered using a 0.45µ size filter. Then absorbance of the filtered liquid was taken by using a UV-Visible spectrophotometer at respective λmax. Concentration of dissolved drug was calculated using the standard curve, which is equal to solubility of drug in respective solvent. [6]

Drug-Excipient Compatibility Study (FTIR)

The compatibility studies provide the suitability of the drug's combination with excipients in the fabrication of the dosage form. The compatibility study is carried out to establish that the drug has not undergone any change(s) after it has been subjected to various processing steps during the formulation.

The drug-excipient compatibility study was done by using an FTIR spectrophotometer. The FTIR spectrum of pure drug were recorded. Then, after preparing the formulation (solid dispersion), IR spectrum of selected formulations and physical mixture of ingredients corresponding to those formulations were also recorded. The range of scanning was 4000 cm^{-1}

- 400 cm^{-1}. The characteristic peaks of Pioglitazone were compared in these spectra. [7]

Formulation of Solid dispersion containing Pioglitazone

The solid dispersions of Pioglitazone were prepared using PEG-4000, PEG-6000 and PVP K30

Method of preparation:

Pioglitazone and carrier(s) were weighed and taken into a china dish. It was heated gradually with constant stirring until it melts. Then, it was cooled to normal temperature with constant gentle stirring. The resulting solid dispersion was stored in desiccator for two days. Finally, it was triturated in mortar and passed through sieve no. 45. Solid dispersions of different compositions were prepared using this method.

Table 1: Formulation of Solid dispersion containing Pioglitazone

Formulation Code	Solid Dispersions	Drug: Carrier Ratio
F1	Pioglitazone - PEG 4000	1:1
F2	Pioglitazone - PEG 4000	1:3
F3	Pioglitazone - PEG 4000	1:5
F4	Pioglitazone - PEG 6000	1:1
F5	Pioglitazone - PEG 6000	1:3
F6	Pioglitazone - PEG 6000	1:5
F7	Pioglitazone – PVP K30	1:1
F8	Pioglitazone – PVP K30	1:3
F9	Pioglitazone – PVP K30	1:5

Evaluation of Solid dispersion containing Pioglitazone

The prepared solid dispersions containing Pioglitazone were evaluated for the solubility. An excess of the solid dispersion containing Pioglitazone were added to conical flasks containing each of 20 ml of distilled water and acid buffer pH 1.2 respectively. Then conical flasks were shaken manually for some time. After that these conical flasks were kept on a rotary shaker for 24 hours. After 24 hours of shaking, these solutions were filtered using a 0.45µ size filter. Then absorbance of the filtered liquid was taken by using a UV-Visible spectrophotometer at respective λmax. Concentration of dissolved drug was calculated using the standard curve, which is equal to solubility of drug (in prepared solid dispersion) in respective solvent. [8]

Preparation of tablet from optimized solid dispersion

Tablets from the optimized solid dispersion of Pioglitazone were prepared by direct compression method. Solid dispersion and excipients were mixed properly. Lubricant (talc) and glidant (magnesium stearate) were mixed to this prepared powder mixture. The powder mixture was passed through sieve no. 60 and this powder blend was used to prepare tablet by direct compression using tablet punching machine.

Table 2: Formulation of tablet from optimized solid dispersion

Ingredients	Amount
Solid dispersion (mg)	equivalent to 30 mg Pioglitazone
Lactose, spray dried (mg)	70 mg
Starch (mg)	5 mg
Sodium starch glycolate (mg)	2 mg
Magnesium stearate (mg)	2 mg
Talc (mg)	3 mg

Evaluation of Prepared Tablet from Optimized Solid Dispersion

After formulation of tablets, they are evaluated for various parameters. Prepared tablets were evaluated for following parameters:

Shape and Size

Diameter and thickness of prepared tablets were determined using Vernier callipers. Three tablets were taken and average was calculated.

Weight variation

This test is performed to check the uniformity of weight of the prepared tablets, as drug content is directly related to the weight of tablet. In this process, 20 tablets were weighed individually. The average weight of one tablet was calculated by taking average mean. As per IP, not more than two tablets deviate by more than the limit prescribed and none tablet deviate by more than twice of the limit prescribed in individual monograph.

Hardness

Hardness of tablets is the amount of force needed to split them. Monsanto's hardness tester, Pfizer's hardness tester, and others are used to determine the tablet hardness. Hardness is measured in kilogram or pounds.

Both Monsanto and Pfizer hardness tester were used to determine the hardness of the formulated tablets. The hardness was calculated as kg/cm^2. Three tablets were taken and average was calculated. [10]

Friability

The friability of the tablet is determined using the friability test apparatus. Friability is used to determine the amount to which tablets break during physical stress situations such as packaging, handling, transportation, and so on. The % weight reduction is estimated by comparing the pre- and post-operative weight of 20 tablets.

The Roche friabilator was used to measure friability of the formulated tablets. Weight of 20 tablets was measured and placed in the friabilator chamber. The friabilator was rotated at speed of 25 rpm for 4 min. After completion of 100 revolutions, the tablets were weighted again and % weight loss is calculated, which corresponds to friability.

$$\%\ Friability = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100$$

Disintegration time

Disintegration time of prepared tablets was determined using the disintegration test apparatus. One tablet was kept in each tube of the disintegration test apparatus. Distilled water and Acid buffer pH 1.2 were used to determine disintegration time at 37°C. The time taken to disintegrate all six tablets was noted as disintegration time. [11]

Drug content

The drug content was calculated by triturating ten tablets in a mortar with pestle to get fine powder. Powder equivalent to weight of one tablet was taken and was dissolved in distilled water. Measure the absorbance of diluted sample (if required) of drug at respective λmax using UV-Visible Spectrophotometer. The drug

content was calculated by using standard calibration curve.

Dissolution Test

Dissolution testing measures the extent and rate of solution formation from a dosage form. The dissolution of a drug is important for its bioavailability and therapeutic effectiveness. Dissolution of pure drug, selected solid dispersion (F5) and prepared tablets (TF5) was determined in Acid buffer pH 1.2 using paddle apparatus, 50 RPM at 37^0C.

Accelerated Stability Studies

Short term accelerated stability studies of the selected formulation (F5) were carried out at 40^0C/75%RH (ICH guidelines) over a period of 3 months. The formulation were wrapped with aluminium foil, and stored in humidity controlled oven for 3 months. Samples were analysed for residual drug contents at time interval of 15 days. [(11)]

RESULTS AND DISCUSSION

Physicochemical Characterization of Drug (Preformulation Studies):

Physical Appearance

The physical form and color of the drug Pioglitazone was observed visually as white solid powder.

Melting Point

The melting point determination of the drug (Pioglitazone) was done by using the melting point apparatus. The melting point of Pioglitazone was found to be 192^0 C - 194^0C, which is same as documented (193^0 - 194^0C)

Calibration Curve of Pioglitazone using UV-Visible Spectroscopy:

(A). Calibration curve of Pioglitazone in Distilled water and acid buffer pH 1.2

50 mg of Pioglitazone was dissolved in distilled water and acid buffer pH 1.2 and volume was made up to 100 ml by same solvent. This gave the concentration of 500 µg/ml (stock solution). 1, 2, 3, 4, 5 and 6 ml of this stock solution was further diluted to 100 ml to get different concentrations of 5, 10, 15, 20, 25 and 30 µg/ml. Absorbances were measured at 269 nm and . The process was performed in triplicate. The standard curve was obtained by plotting concentration (µg/ml) on X-axis and absorbance on Y-axis.

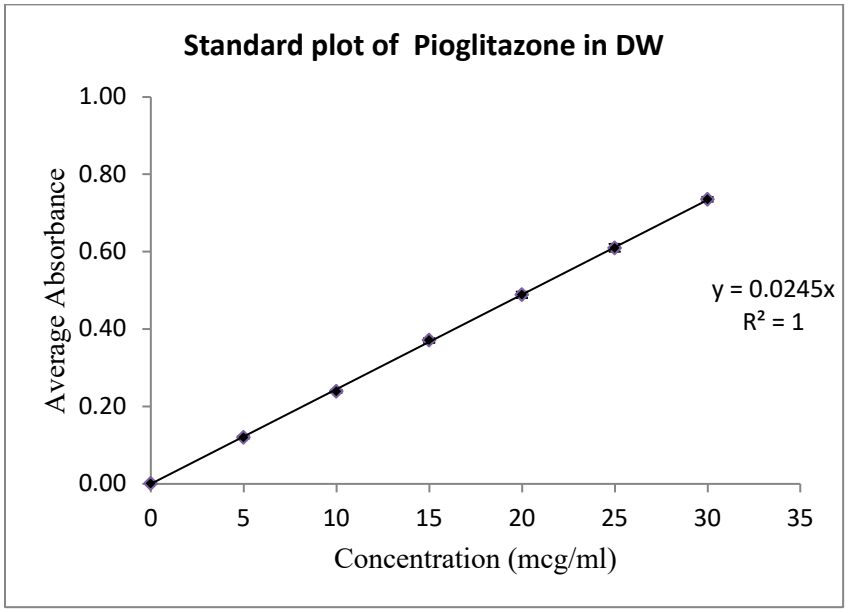

Figure 1: Calibration curve of Pioglitazone in distilled water; n=3

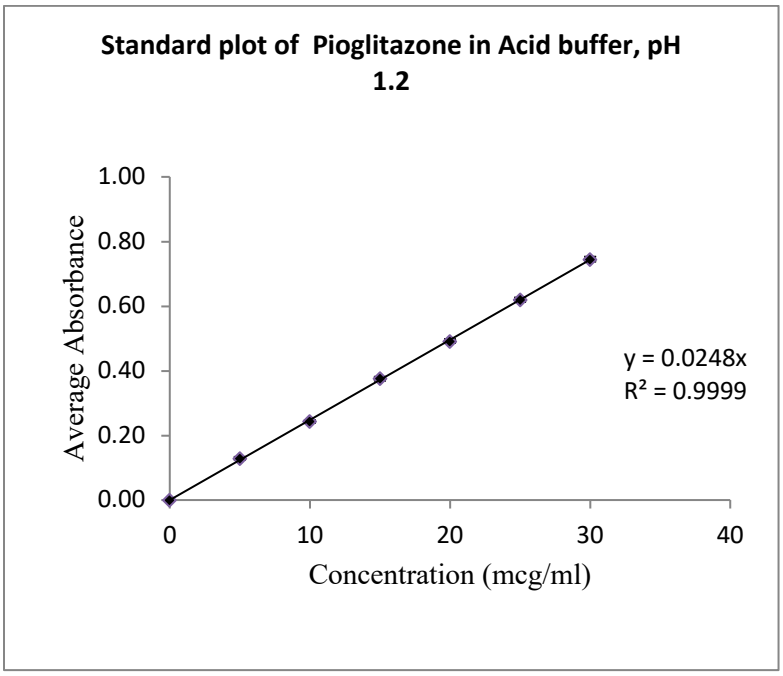

Figure 2: Calibration curve of Pioglitazone in Acid buffer pH 1.2; n=3

7.1.4 Solubility determination

Solubility of Pioglitazone was determined to be 0.005mg/ml and 0.007mg/ml in distilled water and Acid buffer pH 1.2 respectively. The values indicate hydrophobic nature of the Pioglitazone.

7.1.5 Drug-Excipient Compatibility Study (FTIR)

The drug-excipient compatibility study was done by using an FTIR spectrophotometer. The FTIR spectrum of pure drug were recorded. Then, after preparing the formulation (solid dispersion), IR spectrum of selected formulation (F5) and physical mixture of ingredients corresponding to that formulation (F5) were also recorded. The range of scanning was 4000 cm^{-1} - 400 cm^{-1}. The characteristic peaks of Pioglitazone were compared in these spectra.

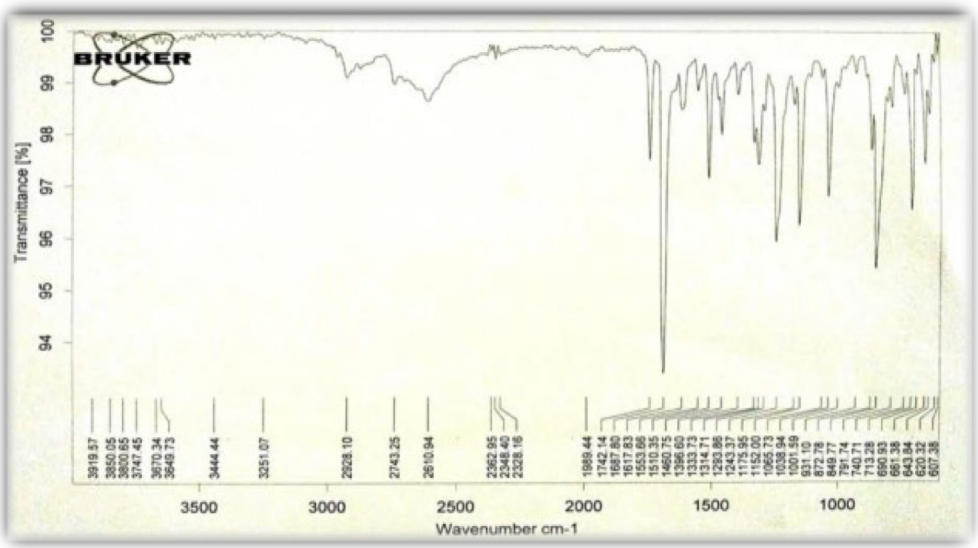

Figure 3: FTIR spectrum of Pioglitazone

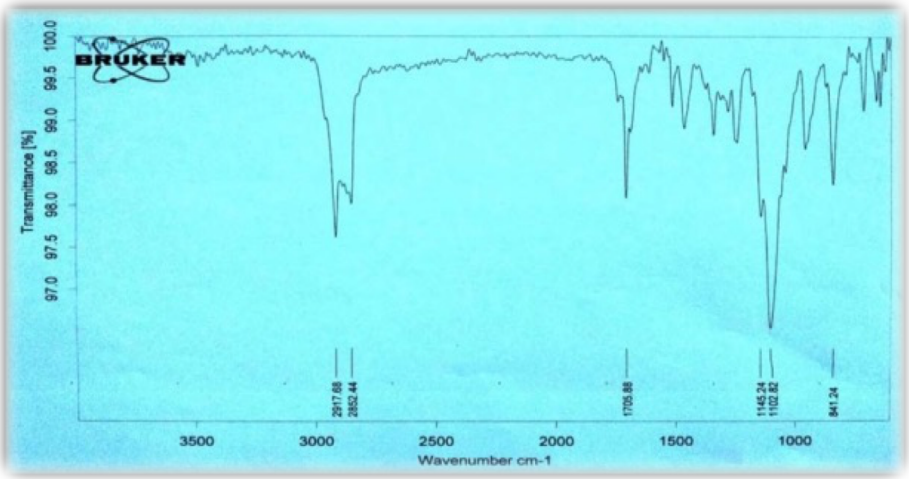

Figure 4: FTIR spectrum of Physical mixture corresponding to F5

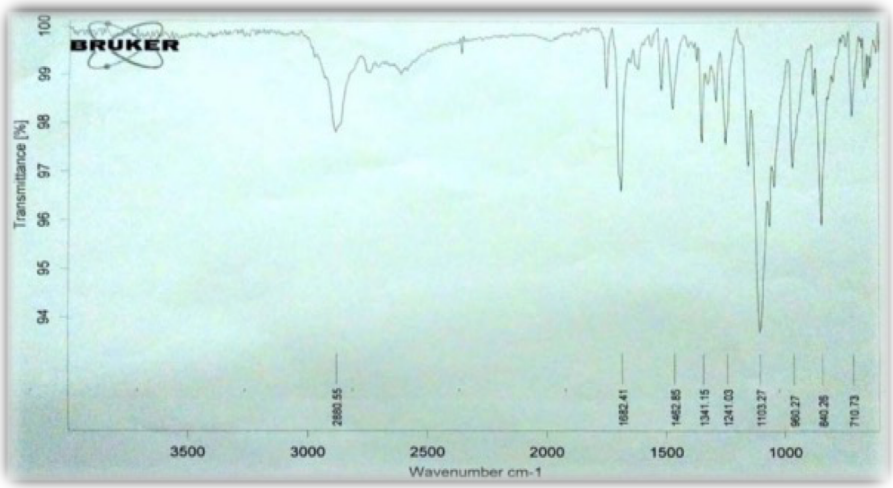

Figure 5: FTIR spectrum of Formulation F5

The peaks of drug are shown in the table. The peaks observed, match with the peaks mentioned in the literature which confirms the identification of drug with its functional groups. The FTIR spectra of pure drug (Pioglitazone) showed all the characteristic peaks, which confirm the identification of drug.

FTIR spectra of the selected formulation (F5) and physical mixture corresponding to the selected formulation (F5) were also recorded. The spectra showed that all the characteristic peaks were intact. It showed that no interaction occurred between the drug and excipients during formulation. Therefore the method can be used to prepare solid dispersion using the fusion method.

Formulation of Solid dispersion containing Pioglitazone

The solid dispersions of Pioglitazone were prepared using PEG-4000, PEG-6000 and PVP K30 as carrier, using fusion method.

Materials:

1. Pioglitazone (drug)
2. Polyethylene glycol-4000/ PEG 4000 (carrier)
3. Polyethylene glycol-6000/ PEG 6000 (carrier)
4. Polyvinyl pyrrolidone K30/ PVP K30 (carrier)

Method of preparation:

Pioglitazone and carrier(s) were weighed and taken into a china dish. It was heated gradually with constant stirring until it melts. Then, it was

cooled to normal temperature with constant gentle stirring. The resulting solid dispersion was stored in desiccator for two days. Finally, it was triturated in mortar and passed through sieve no. 45. Solid dispersions of different compositions were prepared using this method.

Evaluation of Solid dispersion containing Pioglitazone

The prepared solid dispersions containing Pioglitazone were evaluated for the solubility of Pioglitazone.

An excess of the solid dispersion containing Pioglitazone were added to conical flasks containing each of 20 ml of distilled water and acid buffer pH 1.2 respectively. Then, conical flasks were shaken manually for some time. After that, these conical flasks were kept on a rotary shaker for 24 hours. After 24 hours of shaking, these solutions were filtered using a 0.45µ size filter. Then absorbance of the filtered liquid (solution) was taken by using a UV-Visible spectrophotometer at respective λmax. Concentration of dissolved drug was calculated using the standard curve, which is equal to solubility of drug (in prepared solid dispersion) in respective solvent.

Table 3: Solubility of Pioglitazone and Solid dispersions in various solvents

Formulation Code	Solubility (mg/ml)	
	Distilled water	Acid buffer pH 1.2
Pure drug	0.005 mg/ml	0.007 mg/ml
F1	0.180 mg/ml	0.195 mg/ml
F2	0.205 mg/ml	0.220 mg/ml
F3	0.170 mg/ml	0.195 mg/ml
F4	0.250 mg/ml	0.260 mg/ml
F5	**0.285 mg/ml**	**0.310 mg/ml**
F6	0.195 mg/ml	0.210 mg/ml
F7	0.140 mg/ml	0.160 mg/ml
F8	0.225 mg/ml	0.230 mg/ml
F9	0.240 mg/ml	0.245 mg/ml

From the solubility of pure drug (Pioglitazone) and various formulations, it may be observed that the solubility of the drug increased sigficantly. All the formulations (F1 - F9) showed increased solubility of Pioglitazone. Formulation F5 showed maximum solubility and was used for further tableting.

Preparation of tablet from optimized solid dispersion

Tablets from the optimized solid dispersion of Pioglitazone (F5) were prepared by direct compression method (TF5). Solid dispersion and excipients were mixed properly. Lubricant (talc) and glidant (magnesium stearate) were mixed to this prepared powder mixture. The powder mixture was passed through sieve no. 60 and this powder blend was used to prepare tablet by direct compression using tablet punching machine.

Evaluation of Prepared Tablet from Optimized Solid Dispersion

After formulation of tablets (TF5), they are evaluated for various parameters. Prepared tablets were evaluated for various parameters. Results are as below:

Shape and Size

Diameter and thickness of prepared tablets were determined using Vernier callipers. Three tablets were taken and average was calculated. The tablet formed was round and have optimum diameter and thickness.

Weight variation

This test is performed to check the uniformity of weight of the prepared tablets, as drug content is directly related to the weight of tablet. In this process, 20 tablets were weighed individually. The average weight of one tablet was calculated by taking average mean. As per IP, not more

than two tablets deviate by more than the limit prescribed and none tablet deviate by more than twice of the limit prescribed in individual monograph. None of the tablet deviated by the limit prescribed. Therefore, the prepared tablets pass the test for weight variation.

Hardness

The hardness was calculated as kg/cm^2. Three tablets were taken and average was calculated. The average hardness of prepared tablets was found to be 3.5 kg. It is also optimum for a tablet.

Friability

The friability of the tablet is determined using the friability test apparatus. Friability is used to determine the amount to which tablets break during physical stress situations such as packaging, handling, transportation, and so on. The % weight reduction is estimated by comparing the pre-

The friability of the prepared tablets was found to be 0.15%, which is less than the specified limit (< 1%). Therefore, the prepared tablets pass the friability test.

Disintegration time

The time taken to disintegrate all six tablets was noted as disintegration time. Disintegration time for the prepared tablet was found to be 11 minute, 30 second and 13 minute, 15 second in distilled water and acid buffer pH 1.2 respectively. It is also within the specified limit for uncoated tablets. Therefore, the prepared tablets pass the test for disintegration time.

Drug content

Average drug content in prepared tablets was found to be 95.5%. It is also meeting the requirement.

Dissolution Test

Dissolution of pure drug, selected solid dispersion (F5) and prepared tablets (TF5) was determined in Acid buffer pH 1.2 using paddle apparatus, 50 RPM at 37^{0}C.

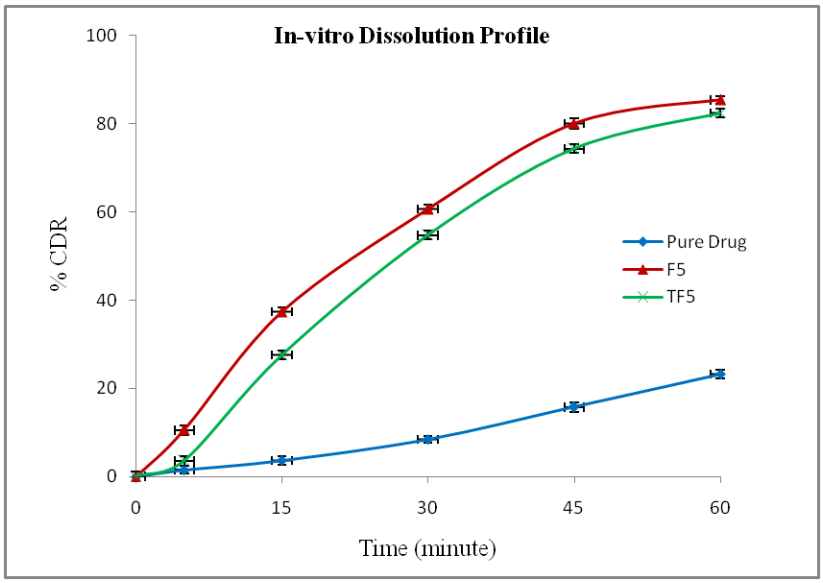

Figure 5: Dissolution profile of pure drug, F5 and TF5

In dissolution study, it is observed that dissolution of pure drug is very slow. This may be attributed to the very low solubility of drug. The prepared solid dispersion (F5) showed greater rate and extent of dissolution as compared to pure drug. Similarly, the prepared tablet (TF5) also exhibited better dissolution profile than pure drug.

Therefore, the solid dispersion method can be used to improve solubility and dissolution profile of Pioglitazone.

Accelerated Stability Studies

Short term accelerated stability studies of the selected formulation (F5) were carried out at 40^0C/75%RH (ICH guidelines) over a period of 3 months. The formulation were wrapped with aluminium foil, and stored in humidity controlled oven for 3 months. Samples were analysed for residual drug contents at time interval of 15 days. Average of 3 films was taken for this purpose.

Table-4: Drug content of selected formulation (F5) at accelerated conditions (AST)

Duration (Days)	% Drug content remaining (Mean±S.D.*)
0	98.70±1.25
15	98.50±1.32
30	98.10±1.84
40	98.00±1.84
60	97.80±1.64
75	97.70±1.95
90	97.60±1.94

* Standard deviation, n=3

The formulation showed good stability at accelerated conditions. When content of Pioglitazone were analysed at various time interval, it was found to be more than 97.60% after 3 month.

Therefore, it may be concluded that the prepared solid dispersion showed good stability during AST study.

Summary & Conclusion

Pioglitazone is an oral hypoglycaemic drug, used for the treatment of type 2 diabetes. Pioglitazone decreases fasting and postprandial plasma glucose levels by improving the sensitivity of hepatic and peripheral (muscle) tissue to insulin.

The major challenge with conventional dosage forms is poor aqueous solubility of Pioglitazone. The main objectives of this study was to improve aqueous solubility of Pioglitazone by preparing its solid dispersion by fusion method using various carriers, that will improve its absorption and subsequent bioavailability.

Preformulation studies of drug were performed which included Physical appearance, determination of Melting point which confirmed the identity of the drug. Scanning of Pioglitazone was done in distilled water and acid buffer pH 1.2 and peak (λmax) was observed at 269 nm and 270 nm respectively using UV-spectrophotometer. Subsequently, calibration curve of Pioglitazone was prepared in distilled water and acid buffer pH 1.2. Linearity was observed with R^2 values more than 0.999. Solubility of pure drug was also determined in distilled water and acid buffer pH 1.2, which was 0.005 mg/ml and 0.007 mg/ml respectively and is very less. Drug- excipient compatibility study was performed using FTIR. The FTIR spectrum of pure drug was recorded. Then, after preparing the formulation (solid dispersion), IR spectrum of selected formulation (F5) and physical mixture of ingredients corresponding to that formulation (F5) were also recorded. The range of scanning was 4000 cm^{-1} - 400 cm^{-1}. The characteristic peaks of Pioglitazone were compared in these spectra. The spectra showed that all the characteristic peaks were intact. It showed that no interaction occurred between the drug and excipients during formulation.

After preformulation studies, solid dispersions of Pioglitazone were prepared using PEG-4000, PEG-6000 and PVP K30 as carrier, using fusion method. Total 9 formulation (F1-F9) were prepared.

All the prepared solid dispersions (F1-F9) containing Pioglitazone were evaluated for the solubility of Pioglitazone. solubility were determined in distilled water and acid buffer pH 1.2. Solubility of Pioglitazone were found to be between 0.180 - 0.310 mg/ml in various formulations. It was observed that solubility was increased in all the solid dispersions. Formulation F5 showed maximum solubility in both the solvents i.e. distilled water and acid buffer pH 1.2. Therefore, formulation F5 was considered as best/ optimum formulation of solid dispersion as it exhibited maximum solubility.

Finally, tablets were prepared (TF5) using the optimum formulation (F5). The prepared tablets (TF5) were evaluated for various parameters i.e. shape and size, weight variation, hardness, friability, disintegration time, drug content etc. The prepared tablet passed all the tests.

Dissolution profile of pure drug, optimum formulation/ solid dispersion (F5) and tablet prepared from optimum formulation (TF5) were evaluated. In dissolution study, it was observed that dissolution of pure drug was very slow and less. This may be attributed to the very low solubility of Pioglitazone. The solid dispersion (F5) as well as the tablet (TF5) showed greater rate and extent of dissolution as compared to pure drug.

Short term accelerated stability studies of the selected formulation (F5) were carried out at 40^0C/75%RH over a period of 3 months. The formulation showed good stability at accelerated conditions. When content of Pioglitazone were analysed at various time interval, it was found to be more than 97.60% after 3 month. Therefore, it was concluded that the prepared solid dispersion showed good stability during AST study.

Finally, it can be concluded that solid dispersion of Pioglitazone may be prepared to improve its solubility and dissolution. This will lead to better absorption and hence improved bioavailability of the drug (Pioglitazone).

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