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Research Article

Preparation and Evaluation of Pioglitazone Tablet by Solid Dispersion Technique

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Abstract:
Pioglitazone is an oral hypoglycemic drug, used for the treatment of type 2 diabetes. The main objectives of this study were 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. The prepared tablets (TF1-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. 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).
Key words: Hypoglycemic drug, solubility, fusion method, bioavailability.

Introduction

The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration, compactness and easy manufacturing. [1]
The term ‘solubility’ is defined as maximum amount of solute that can be dissolved in a given amount of solvent. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. [2]

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.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. [3]

Pioglitazone

Its chemical formula is $C_{19}H_{21}ClN_2O_3S$. It is a thiazolidinedione used adjunctively with diet and exercise to normalize glycemic levels in adults with type 2 diabetes mellitus. It is a Antidiabetic drug.Pioglitazone is a selective agonist at peroxisome proliferator-activated receptor-gamma (PPARγ) in target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ increases the transcription of insulin-responsive genes involved in the control of glucose and lipid production, transport, and utilization.Through this mechanism, pioglitazone both enhances tissue sensitivity to insulin and reduces the hepatic production of glucose (i.e. gluconeogenesis) - insulin resistance associated with type 2 diabetes mellitus is therefore improved without an increase in insulin secretion by pancreatic beta cells. [4, 5]

Material and Methods

Pioglitazone, PVP K30, PEG-6000, Poloxamer, Tween-80, Potassium dihydrogen orthophosphate, Methanol, Sodium hydroxide, Lactose, spray dried, Starch, Sodium starch glycolate, Magnesium stearate and Talc were used.

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 - Poloxamer	1:1
F2	Pioglitazone - Poloxamer	1:3
F3	Pioglitazone - Poloxamer	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 prepared tablets from optimized Solid Dispersion

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

Shape and Size [6]

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 [7]

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 hardness tester were used to determine the hardness of the formulated tablets. The hardness was calculated as kg/cm2. Three tablets were taken and average was calculated.

Friability [8]

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.

Drug content [9]

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 [10]

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 370C.

Accelerated Stability Studies [11]

Short term accelerated stability studies of the selected formulation (F5) were carried out at400C/75%RH (ICH guidelines) over a period of 3 months. The formulation were wrapped with aluminium foil, and stored in humidity controlled oven for 6 months. Samples were analyzed for residual drug contents at time interval of 30 days.

Results and discussion:

Table 2: Evaluation parameters: shape, diameter, thickness, average weight, friability, drug content

Formulation	Shape	Diameter	Thickness	Average weight (mg)(Mean±S.D.*)
TF1	Round	7 mm	3 mm	201.20 ±0.20
TF2	Round	7 mm	3 mm	203.20±0.30
TF3	Round	7 mm	3 mm	199.30±0.10
TF4	Round	7 mm	3 mm	201.20±0.20
TF5	Round	7 mm	3 mm	200.10±0.30

All the tablets prepared were round in shape. Diameter was found to be range in 7.0 mm and range thickness were found to be 3.0 mm for all the formulations. A tablet is designed to contain a specific amount of drug. When the average mass of the tablet is 200 mg the Pharmacopoeial limit for percentage deviation is ± 7.5%. The percentage deviation from average tablet weight for all the tablet was found to be within the specified limits and hence all formulations complied with the test for weight variation according to the Pharmacopoeial specifications.

Table 3: Evaluation parameters: friability, drug content and average hardness

Formulation	Friability (%)	Drug content (%w/w)	Average hardness (kg/cm^2)(Mean±S.D.*)
TF1	0.51±0.30	98.64±0.16	4.1±0.4
TF2	0.45±0.20	98.17±0.11	3.9±0.3
TF3	0.42±0.20	98.88±0.23	3.8±0.4
TF4	0.30±0.10	99.09±0.12	3.7±0.5
TF5	0.21±0.10	99.85±0.14	3.5±0.2

The hardness of tablets was found to be in the range of 4.1±0.4kg/cm2 to 3.5±0.2kg/cm^2. The friability of the prepared tablets was found to be0.51±0.30 0.21±0.10%, which is less than the specified limit (< 1%). Therefore, the prepared tablets pass the friability test. The % drug content of prepared tablets was found to be 98.17±0.11 to 99.85±0.14 %, which is within the prescribed limits. Therefore, the prepared matrix tablets pass the test for drug content (content uniformity).

Disintegration Time

Table 4: Disintegration time of prepared tablets

Formulation	Disintegration time	
	Distilled water	Acid buffer pH 1.2
TF1	11 minute, 30 second	13 minute, 15 second
TF2	11 minute, 10 second	13 minute, 05 second
TF3	10 minute, 40 second	12 minute, 35 second
TF4	10 minute, 20 second	11 minute, 30 second
TF5	9 minute, 30 second	10 minute, 10 second

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 for TF1 formulation. TF5 have disintegration time 9 minute, 30 second in water and 10 minute, 10 second in acid buffer pH 1.2. It is also within the specified limit for uncoated tablets. Therefore, the prepared tablets pass the test for disintegration time.

Dissolution Test

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.

Table 5: Dissolution profile of pure drug (Pioglitazone), F5 and TF5

S.No.	Time (Minute)	% Cumulative Drug Released (Mean±S.D.*)		
		Pure drug (Pioglitazone)	Solid dispersion (F5)	Tablet(TF5)
1.	0	0.00±0.00	0.00±0.00	0.00±0.00
2.	05	1.51±0.05	10.52±0.04	3.50±0.06
3.	15	3.66±0.05	37.31±0.07	27.64±0.04
4.	30	8.44±0.04	60.60±0.05	54.76±0.04
5.	45	15.77±0.04	80.13±0.06	74.34±0.05
6.	60	23.29±0.06	85.40±0.05	82.50±0.05

* Standard deviation, n=3

Accelerated Stability Studies

Table 6: Drug content of selected formulation (F5) at accelerated conditions (AST)

Duration (Month)	% Drug content remaining(Mean±S.D.*)
0	99.85±0.14
1	99.50±1.22
2	99.10±1.87
3	98.00±1.78
4	97.80±1.66
5	97.70±1.91
6	97.60±1.94

* Standard deviation, n=3

The formulation showed good stability at accelerated conditions. When content of Pioglitazone was analysed at various time interval, it was found to be more than 97.60±1.94 % after 6 month.

Conclusion

In the present research tablets of Pioglitazonewere prepared from Solid Dispersion method. Various types of evaluation parameters were evaluated and result of all the parameters were with in limit.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 at40^0C/75%RH over a period of 6months.The formulation showed good stability at accelerated conditions.It was 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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