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Fast dissolving tablet of pioglitazone with super disintegrants.

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Abstract The aim of this study was to optimize and formulate fast disintegrating tablets (FDTs) of Pioglitazone using different superdisintegrants by using method i.e. direct compression method. The tablets are formulated using three superdisintegrants viz., Emcosoy, crospovidone and Croscarmellose sodium in different concentrations. Post-compression parameters and in-vitro dissolution studies were carried out. Formulation PTZN6 was compare with two different marketed formulations of different brands. Compression indicated that the prepared formulation PTZN6 containing 5 % crospovidone and 4 % Emcosoy showed 99.31 ± 0.61 % drug release in 20 min whereas marketed formulation MKT1 and MKT2 showed 85.65 ± 0.50 % and 80.78 ±0.41 % drug release within 20 min which was less than formulation PTZN6

Key words: superdisintegrants, tablet, fast disintegration.

INTRODUCTION

Due to its self-administration, compactness, and ease of manufacturing, the tablet is currently the most common dosage form. Tablets that dissolve in the mouth are also known as orally disintegrating tablets, fast disintegrating tablets, rapid disintegrating tablets, porous tablets, quick melt tablets, and rapid melt tablets1. Numerous pharmaceutical studies have been carried out in recent decades with the goal of creating novel dosage forms. late development in original medication conveyance framework (NDDS) plan to upgrade wellbeing and viability of medication atoms by forming religious community dose structure for organization

and to accomplish better understanding consistence. Among the many changes made to make administration easier: The most popular product is a tablet that dissolves quickly.2 Presentable drug packaging is today's fundamental requirement. The dosage form is a method of drug delivery used to administer drugs to living organisms. The oral route of administration is widely accepted for up to 60% of the total dosage. In the late 1970s, the first fast-dissolving drug delivery systems were developed as an alternative to conventional dosage forms for pediatric and geriatric patients. These tablets are made to dissolve and dissolve quickly in saliva, typically in less than 60 seconds. Some drugs may have a higher bioavailability because of their absorption in the oral cavity and the pre-gastric absorption of drug-containing saliva that passes down into the stomach; additionally, the amount of drug that is subjected to first pass metabolism is lower than for standard tablets.

The formulation of the fast-dissolving tablet can be accomplished in a number of traditional ways, such as by direct compression. Tablet molding, mass extrusion, freeze drying, spray drying, adding super-disintegrants, and sublimation are all methods. The addition of superdisintegrants, such as crospovidone, microcrystalline cellulose, carboxy methylcellulose, modified corn starch, polacriyil potassium, and others, is a fundamental method that is crucial to the development of fast-dissolving tablets. in concentrations of 1 to 15 percent w/w. Pioglitazone is a diabetic drug (thazolidine dione-type, also known as "glitazone") that is used in conjunction with a proper diet and exercise program to control high blood sugar in patients with type2 diabetes.4,5 Drugs that are poorly water soluble (class 2) have a slower rate of absorption, high permeability, and low bioavailability due to less dissolution. Therefore, it is necessary to improve the dissolution rate of such drugs, which may lead to It works by lowering blood sugar and restoring your body's normal response to insulin.

Nuclear receptor peroxisone proliferator-activated receptor gamma (PPAR-gamma) is selectively inhibited by pioziltazone. As a result, it was hypothesized that the fast-dissolving tablet of Pioglitazone will provide better therapeutic action for the treatment of diabetic disease and enhanced patient compliance, particularly for pediatric and geriatric patients. This is because it modifies the transcription of the insulin-sensitive genes that are involved in the control of glucose and lipid metabolism in the lipidic, muscular, and liver.7 As a result, our research aims to develop and evaluate Pioglitazone tablets that dissolve quickly to speed up the course of action and improve patient compliance. The novel approach to resolving a variety of issues, such as dysphagia, is the development of an appropriate dosage form that is desirable for pediatric and geriatric patients. In today's world, designing appropriate dosage forms that are user-friendly and convenient for patients is becoming

increasingly important. The development of an appropriate dosage form that is to be desirable for pediatrics and geriatric patients is the novel approach in order to resolve the various problems such as dysphagia.8, 9These fast-dissolving tablets are developed for several symptoms ranging from migraine (rapid onset of action is important) to mental illness for which patient compliance is important for treating chronic conditions such as depression and schizophrenia. Fast dissolving drug delivery systems are novel drug delivery techniques that focus on designing the dosage form that offers immediate release, enhanced.[10]

Desired criteria for Fast dissolving tablets:

- There is no requirement of water for oral administration as the tablets disintegrates in mouth within seconds.
- Tablet must be highly porous.
- The active compound has to be soluble, stable and easily permeate the mucosal barrier with rapid disintegration.
- They should leave minimal or no residue in mouth after administration.
- They should be harder and less friable.
- They should have pleased mouth feel.
- They should withstand to humidity and temperature.
- They should be able to absorb water rapidly for the fast de aggregation of the matrix.
- They should have acceptable taste masking property.[11]

Advantages of fast dissolving tablets:

- Improved patient's compliance
- No water needed
- No chewing needed
- Improved stability
- Suitable for controlled as well as fast release actives
- Cost effective[12,13]

Disadvantages of fast dissolving tablets:

- The tablet may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
- Careful handling is required due to its insufficient mechanic
- Sometimes grittiness may retain in the mouth if not properly formulated.
- FDTs kept in dry place because of their hygroscopic nature.[14,15]

Technique for preparing Fast Dissolving Tablets:

Many techniques have been reported for the formulation dissolve tablets or Mouth dissolving tablets.

1. Freeze drying / Lyophilization
2. Tablet Moulding
3. Direct compression

4. Sublimation
5. Mass extrudation

Freeze - Drying or Lyophilization

The removal of water from a product after it has been frozen is known as freeze drying. An amorphous, porous structure that can dissolve quickly is produced by this method. This section describes a typical procedure for producing ODT with this method. A carrier/polymer solution is used to dissolve or disperse the active drug. The mixture is poured into the walls of the preformed blister packs by weight. In order to freeze the drug solution or dispersion, the blister pack trays are passed through a liquid nitrogen freezing tunnel. The freeze-drying of the frozen blister packs is then continued in refrigerator cabinets. Using a blister-sealing machine, the aluminum foil backing is applied following the freeze-drying process. The blister is then shipped in its final form. The freeze-drying method has demonstrated increased bioavailability and improved absorption. The significant drawbacks of Lyophilization procedure are that it is costly and tedious; Traditional packaging is unsuitable for these products due to their fragility and poor stability under stress.[16]

Tablet Molding

To ensure that the tablets dissolve completely and quickly, they should be made using ingredients that dissolve in water. The embellishment interaction is of two kinds: heat and solvent methods. The solvent method involves moistening the powder blend with a hydro-alcoholic solution, compressing it under low pressure to form a wet mass between the molding plates, and then air drying the solvent out. A drug, agar, and sugar suspension is made during the heat molding process and poured into the blister packaging wells. The agar is then solidified to form a jelly at room temperature before being dried in a vacuum at 30 °C. Significant benefit of this procedure is that as the scattering network is produced using water dissolvable sugars, shaped tablets deteriorate all the more quickly and offer superior taste. The molded tablets' low mechanical strength is a drawback, making them susceptible to friability during transportation and handling, leading to erosion and breakage.[17]

Direct Compression

The simplest and most cost-effective method for making tablets is direct compression. Due to the availability of improved excipients, particularly super-disintegrants and sugar-based excipients, this method can be used to prepare ODT.[18]

Spray Drying

As the processing solvent evaporates during the process, this technology produces extremely porous and fine powders. Supporting matrix, non-hydrolyzed and hydrolyzed gelatin, bulking agent Mannitol, and super-disintegrants such as sodium starch glycolate or Croscarmellose sodium were utilized in this method to create FDTs. The addition of acidic substances like citric acid or alkaline substances like sodium bicarbonate further enhanced disintegration and dissolution. Porous powder is produced using this formulation method, and the disintegration time is less than 20 seconds.[19]

Sublimation

Camphor, urea, urethane, and other volatile substances are utilized in this method. with additional excipients before being compressed into tablets. When the tablet comes into contact with saliva, the pores formed by the sublimation of volatile substances accelerate its disintegration. This method allows for the formation of tablets that are very porous and have a high mechanical strength.[20]

Mass- Extrusion

In this method, the solvent mixture of water-soluble methanol and polyethylene glycol is used to soften the active blend. The softened mass is then expelled through an extruder or syringe to form tablets by cutting them into even segments with a heated blade. Additionally, the dried cylinder can be used to coat the granules of bitter drugs, masking their taste.[21]

Important patented technologies for FDTs: [22]

Zydis Technologies

The Zydis formulation is a one-of-a-kind freeze-dried tablet in which the drug is physically entrapped or dissolves within the matrix of a carrier material that dissolves quickly. The freeze-dried structure of Zydis units does not require water to aid swallowing when they are placed in the mouth. Polymers like gelatin, dextran, or alginate are incorporated to influence the material's strength and resilience during handling. To achieve crystallinity, elegance, and hardness, saccharides like Mannitol or sorbitol are incorporated to form a glossy amorphous structure. Various gums are used to prevent the dispersed drug particles from sedimenting during the manufacturing process, and water is used to ensure the production of porous units for rapid disintegration. During the freeze-drying process or long-term storage, Zydis units are prevented from shrinking with the help

of a collapse protectant like glycerin. Blister packs are used to package Zydis products to keep the formulation dry from the environment.

Wow Tab Technology

This technology was patented by Yamanouchi. WOW implies without water. Utilizing saccharides of low and high modudability, this technology produces FDTs through conventional granulation and tableting processes. Saccharides with a low moldability include lactose, glucose, sucrose, and xylitol. Maltose, maltiol, sorbitol, and oligosaccharides are examples of high-moldability saccharides. Combinations of these low- and high-mouldable saccharides are used because the resulting tablets lack the desired properties of rapid disintegration and hardness. The active ingredient is combined with saccharides with a low moldability, such as lactose, glucose, and mannitol, granulated with saccharides with a high moludality, such as maltose, and compressed into a tablet. As a result, tablet obtain demonstrated sufficient hardness and rapid breakdown. The tablet's general manufacturing method is superior to that of Zydis, and it is suitable for both standard bottles and blister packaging. However, this technology requires the preparation of sucrose and blister packaging. Because of its hardness, the tablet exhibits rapid salvation in the mouth and provides a very pleasant taste.

Durasolv Technology

CIMA labs hold a patent on this technology. The conventional tableting equipment is used to make these tablets using this technology. Drug, lubricant, and non-direct compression fillers are used to create these tablets. Dextrose, Mannitol, Sorbitol, Lactose, and Source are examples of non-direct fillers. These fillers have the advantages of dissolving quickly and avoiding a gritty texture. The tablet breaks down in less than sixty seconds. The formulation can include a greater number of hydrophobic lubricants with this technology. To compress the tablet, a low compressive force is required. Because the direct compression method and conventional package equipment are used, the production cost is significantly lower.

Orasolv Technology

CIMA labs hold a patent on this technology. This includes producing the FDTs by compressing an effervescent disintegrating agent at low pressure. A positive organoleptic property is the sensation of fizzing caused by the evolution of carbon dioxide from the tablet. The effervescent is typically used at a concentration of 20-25% of the tablet weight. The taste-masking particle coating does not crack when subjected to compression force.

Tablets are soft and fragile because they are made with a low compression force. This led to the creation of Pak Solv, a blister package in the shape of a dome that stops the tablet from moving vertically inside the depression. Pak Solv also protects against moisture, light, and children.

Flash tab Technology

This technology is covered by a patent held by Prographarm labs. Microgranules of the taste-masked active drug are utilized in this technology. Conventional methods like coacervation, microencapsulation, and extrusion superiorization can be used to prepare these. All of these methods make use of standard tableting technology. These flavors include a disintegrating agent, a swelling agent, a masked microcrystalline active drug, and other excipients like soluble diluents, among others. are compressed into a multi-specific tablet that quickly breaks down. Carboxy methylcellulose and reticulated polyvinylpyrrolidone are examples of disintegrating substances. Carboxy methylcellulose, microcrystalline cellulose, carboxy methylated starch, and modified starch are examples of swelling agents. The physical resistance of these tablets is satisfactory. Within one minute, disintegration occurs.

4. Methodology

4.1 PREFORMULATION

It very well may be characterized as an examination of physical and compound properties of a medication substance alone or potentially when joined with excipients. The overall goal of pre-formulation testing is to provide the formulator with information that will help them create stable, safe, and bioavailable dosage forms.[50]

4.11 Drug identification

4.1.1.1Physical characterization

The medication was truly described based on variety, smell and taste. All physical parameters were recorded and compared to the existing body of knowledge.[51]

4.1.1.2Determination melting point: [52.53]

The digital melting point apparatus was used to determine Pioglitazone's melting point. The capillary tube was filled with a small quantity of the drug and placed in the melting point apparatus with one end closed. The point of melting was recorded.

4.1.2 Determination of λmax and preparation of calibration curve:

4.1.2.1 Determination of λmax in methanol:

Utilizing a UV spectrophotometer, the drug was scanned in the range of 400-200 nm to determine its absorption maxima (max) in methanol.

4.1.2.2 Preparation of stock solution:

To obtain a concentration of 1000 g/ml, 100 mg of pioglitazone, accurately weighed, was dissolved in 100 ml of methanol. To obtain concentrations of 100 g/ml, 10 ml of this solution was taken out, transferred to the volumetric flask, and the volume was increased to 100 ml. Stock solution was the name of this solution.

4.1.2.3 Preparation of calibration curve in methanol:

In methanol, serial dilutions of the stock solution with concentrations ranging from 10 to 20 g/ml were made. Absorbance was estimated at 225 nm against comparatively treated clear utilizing UV-VIS spectrophotometer.

4.1.2.4 Preparation of stock solution in phosphate buffer pH 6.8:

To obtain a concentration of 1000 g/ml, 100 mg of pioglitazone, accurately weighed, was dissolved in 100 ml of phosphate buffer pH 6.8. To obtain concentrations of 100 g/ml using phosphate buffer pH 6.8, 10 ml of this solution was taken out, transferred to the volumetric flask, and increased to 100 ml. Stock solution was the name of this solution.

4.1.2.5 Preparation of calibration curve in phosphate buffer pH 6.8:

In methanol, serial dilutions of the stock solution with concentrations ranging from 6 to 20 g/ml were made. Using a UV-VIS spectrophotometer, absorbance was measured at 268 nm against a blank that had been treated similarly.[54]

4.1.3 Determination of drug solubility:

The drug's solubility is directly related to its release from the dosage form: Therefore, Pioglitazone was tested for solubility in water, methanol, and phosphate buffer (6.8) with a small amount of drug mixed in 5 milliliters of solvent(s) to determine the amount of drug absorbed into the blood. Using a mechanical shaker, the solution was thoroughly shaken for 24 hours. Using a UV spectrophotometer, the solution was measured at 255 nm 24 hours later.[55]

4.1.4 Determination of partition coefficient of Pioglitazone:

Two immiscible phases—the aqueous phase and the oil phase—were used to calculate Pioglitazone's partition coefficient. The aqueous phase contains 10 milliliters of water, while the oil phase contains 10 milliliters of octanol. The mixture was shaken for thirty seconds. without the drug) in a funnel for separation. The mixture was shaken for three hours after the drug (10 mg) was added. To separate the two layers (the oily layer and the aqueous layer), the final mixture was kept for one hour. Test (1ml) from the fluid layer was taken and weakens s up to 10 ml with methanol examined 225nm against comparably treated clear utilizing UV spectrophotometer. A 1-milliliter sample was taken from the oil layer and kept at room temperature for 6-7 hours. The remaining solution was diluted with methanol up to 10 ml, and a UV spectrophotometer was used to compare the solute's concentration at 225 nm to that of a blank that had been treated similarly. The formula that was used to calculate the partition coefficient was as follows[56]

$$Partition\ \text{Coefficient} = \frac{concentration\ of\ drug\ in\ organic\ layer}{concentration\ of\ drug\ in\ aqueous\ layer}$$

4.1.5 Fourier transformer infrared spectroscopy (FT-IR):

FT-IR spectroscopy of unadulterated medication was done utilizing Fourier transformer infrared spectrophotometer. Dried potassium bromide (KBr) powder and the dried sample were combined. KBr press at 10000 to 15000 psi was used to prepare the samples discs. The sample disc was inserted into the sample holder and scanned at a resolution of 4 cm- from 4000 to 400 cm-1[1].[57]

4.1.6 Drug excipients compatibility study:

In this study, Pioglitazone was combined with each of the selected excipients—crospovidone, croscarmellose sodium, microcrystalline cellulose, magnesium stearate, D-mannitol, and talc—in equal amounts. KBr, drug,

and excipients were used to prepare the sample discs using a KBr press at 10000 to 15000 psi. The sample disc was scanned from 4000 to 400 cm-1 before being placed in the sample holder. at a 4 cm resolution[-1].[58]

4.1 Formulation of fast dissolving tablets of Pioglitazone

Sr.No.	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
1	Pioglitazone	30	30	30	30	30	30	30	30	30
2	Croscarmellose Sodium	4	8	12	4	8	12	4	8	12
3	Crospovidone	-	-	-	5	5	5	10	10	10
4	Microcrystalline cellulose	120	120	120	120	120	120	120	120	120
5	D- Mannitol	80	76	72	75	71	67	70	66	62
6	Magnesium Stearate	2	2	2	2	2	2	2	2	2
7	Talc	4	4	4	4	4	4	4	4	4
8	Emcosoy	2	2	2	4	8	4	8	4	

Total weight – 250 mg

4.1FORMULATION OF TABLETS

Fast dissolving tablet of Pioglitazone were formulated by direct compression method. Different superdisintegrants were used (crospovidone, Croscarmellose and Emcosoy) with different concentration.

4.2 PREPATRATION OF POWDER BLENDS BY DIRECT COMPRESSION METHODS

In the present study we approach direct compression method for the development of fast dissolving tablet. Direct compression method is most easy and suitable method approached by various formulation scientists. In this method all ingredients weighed according to their decreasing order of them in order to make a blend, all ingredients passed through sieve #40. For blending we mixed for 30 minutes by using double cone blender

(Rolex double cone blender). After blending it was analysed for the organoleptic properties and Micromeritics properties.[59]

4.3 EVALUATION OF POWDER BLENDS (PRECOMPRESSION STUDIES)

4.3.1Bulk density:

Bulk density was determined by pouring the weighed quantity of powder blend in measuring cylinder the bulk value was noted from the measuring cylinder. Bulk density was calculated using the given formulae below.[60]

$$Bulk\ density = \frac{weight\ of\ powder\ (g)}{bulk\ volume\ (ml)}$$

4.3.2 Tapped density:

Tapped density is defined as the ratio between weight of the powder (g) and tapped volume (ml). Tapped volume was obtaining by tapping the measuring cylinder 100 times containing known amount of powder blend. Tapped density was calculated using the following formulae.[60]

$$Tapped\ density = \frac{weight\ of\ powder}{Tapped\ volume\ of\ powder}$$

4.3.3 Hausner's ratio: Hausner's ratio is the ratio between tapped density and bulk density. hausner's ratio was calculated by using the following formulae.[61]

$$Hausner's\ ratio = \frac{Tapped\ desity}{bulk\ density}$$

4.4.4 Carr's compressibility index:

It is the simplest way of determination of the free a flow of the powder. The Carr's compressibility index was measured by the formula.[61]

$$Carr's\ Index = \frac{Bulk\ density}{Tapped\ density} \times 100$$

4.4.5 Angle of repose (θ):

Angle of repose was determining by funnel method. In this method accurately weighed of powder blend was poured over the funnel which was adjusted at a fixed height. The heap was vertically formed at certain height .now, the radius and height of the heap was measured .angle of repose was calculating using the formula.[61]

$$\tan\theta = \frac{height\ of\ the\ piles\ (h)}{radius of\ the\ piles\ (r)}$$

Where θ is angle, h is height of cone and r is the radius of the base cone.

4.4 COMPRESSION OF TABLET BY DIRECT COMPRESSION METHOD: To the above powder blends finely a magnesium stearate and talc were added and mixed thoroughly .this powders blendes of different formulations were now compressed using 8mm punch 10 station rotator tablet compression machine to produced tablets weighing 250mg each.[62, 92].

4.5 EVALUATION OF FAST DISSOLVING TABLETS (POST COMPRESSION STUDIES):

The prepared tablets were evaluated for post compression studies which are as follows:

4.5.1 General appearance:

General appearance of a tablet, its visual identity and overall elegance is essential for patient acceptance. The tablet's size, shape, colour, presence or absences of an odour, legibility of any identifying marking were studied as the general appearance characteristic.

4.5.2 Hardness:

The hardness of tablets was measured by Monsanto hardness tester, the tablet was held between the moving jaw and the screw knob was moved upward until the tablet breaks and the force required to break the tablet was noted.[63]

4.5.3Thickness:

Twenty tablets were taken and their thickness was measured using digital vernier caliper. The thickness was measured by placing tablets between two arms of the vernier caliper.[64]

4.5.4 Friability:

Friability is the loss of tablet mass in the container due to removal of fine particles from the surface during transpiration or handling.USP tablet fraibilator (EF-2, electro lab, Mumbai) was employed for the determination of tablet friability. Pre—weighted tablets, (20 tablets) were placed in the fraibilator. Fraibilator consist of a plastic chamber that revolves at 25 rpm, dropping tablets at a distance of 6 inches with each revolution. The fraibilator was rotated for 4mint.at the end of test, tablets were dusted and re-weighed.the loss in tablet weight was measured and friability was calculated using following formula.[65]

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

4.5.5 Weight variation:

Randomly 20 tablets were selected from each formulation and weighed individually. Average weight was calculated and comparison was made between individual weight and average weight of tablets. Percent weight variation was calculated by using the formula given below: [66]

$$\%weight\ variation = \frac{Average\ weight\ of\ tablets - Individual\ weight\ of\ tablets}{Average\ weight\ of\ tablets} \times 100$$

4.5.6 Determination of drug content:

10 tablets of Pioglitazone from each batch were crush and the mass equivalent to one tablet was taken.ina 100ml volumetric flask, mass equivalent to one tablet was taken and volume was made to mark with phosphate buffer (pH6.8). The flask was shaken for 24h using a water bath shaker incubator. The solution was filter and filtrated analyzed at 225nm after suitable dilutions using UV –visible spectrophotometer.[51]

4.5.7 Water absorption ratio:

For the determination of water absorption ratio, firstly weighed the tablets from each formulation before placing them into the petri plate containing 2 ml of amaranth dye and 10 ml of simulated saliva. Tablets were carefully removed from petri dish and weigh the wetted tablet. The water absorption ratio was calculated using the formula: $R = \frac{Wa-Wb}{Wa} \times 100$

Where, R is water absorption ratio, Wb is weight of tablet before water absorption, and Wa is weight of tablet after water absorption. [54, 90.]

4.5.8 *In-vitro* disintegration studies:

In-vitro disintegration studies were performed using a USP disintegration apparatus, using 900 ml of distilled water as dissolution media at 37 ± 0.5 °C. Six tablets were selected from each formulation for disintegration test which were placed in the disintegration tubes. The time required for the tablets to disintegrate completely was noted down without leaving any residues in the tubes.[51]

4.5.9 *In-vitro* dissolution studies:

The study was carried out using USP dissolution test apparatus 2 (DS 8000 Labindia, Mumbai, India) at 50rpm in 900ml of phosphate buffer (pH 6.8) as a dissolution media. The temperature was maintained at 37 ± 0.5˚C. The samples were withdrawn, filtered and analysed spectrophotometrically using UV spectrophotometer (3000^{+}, labindia, Mumbai) at 225nm. An equal amount of fresh dissolution medium, pre-warmed at 37±0.5˚C, was added that each sampling to maintain the sink condition throughout the study. Dissolution study was performed in triplicate for each batch.[51, 89.]

5.RESULTS AND DISCUSSION

5.1 Physical characteristics of Pioglitazone

PTZN drug was white colored crystalline powder which is studied according to Indian pharmacopoeia.

5.1.1 Melting point

The melting point of the drug was found to be 189.50 ± 1.52 ˚C. The melting points of the drug were as reported in literature and thus indicate purity of drug sample.

5.1.2 Absorption maxima (λ_{max}) and calibration curve

5.1.2.1 λ_{max} of Pioglitazone in methanol

The λ_{max} of 20µg/ml PTZN in methanol was observed at 225 nm. (Figure 5.1)

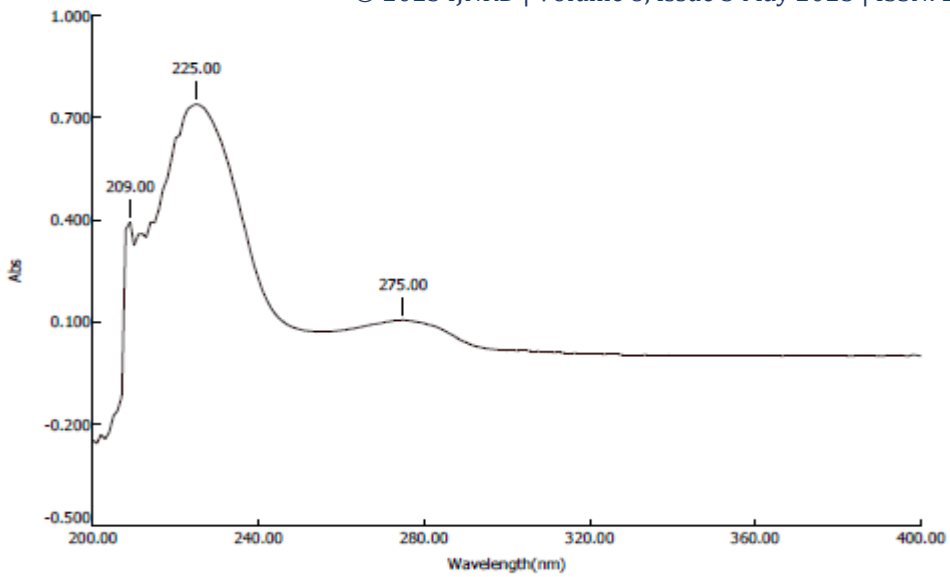

Figure 5.1 UV scan spectrum of Pioglitazone in methanol

Calibration curve of Pioglitazone in methanol

The calibration curve of PTZN was prepared in the concentration range 4-32 µg/ml in methanol. The absorbance values are tabulated in table 5.1. The PTZN was found to obey Beer-Lambert's law in the concentration range of 4-32 µg/ml (Figure 5.1) the calibration curve obtained was liner and had regression coefficient (R^2) value 0.978 will less standard deviation, indicating good linearity and reproducibility.

Table 5.1 Calibration curve data of Pioglitazone in methanol

Concentration (µg/ml)	Absorbance (nm)
0	0
4	0.067 ± 0.004
8	0.134 ± 0.003
12	0.199 ± 0.004
16	0.259 ± 0.003
20	0.394 ± 0.002
24	0.459 ± 0.002
28	0.459 ± 0.002

32	0.522 ± 0.002

Mean ± SD (n=6)

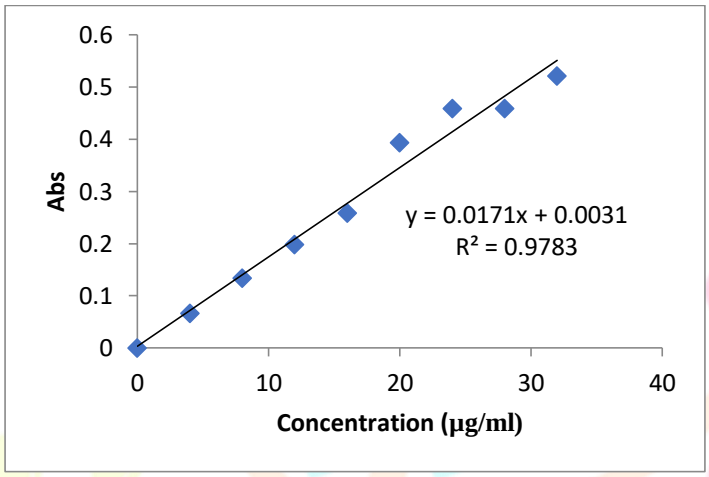

Figure 5.1 Calibration curve of Pioglitazone in methanol

5.2.1.2 λ_{max} of Pioglitazone in phosphate buffer (pH 6.8)

The λ_{max} of 20 µg/ml PTZN in phosphate buffer was observed at 268 nm.

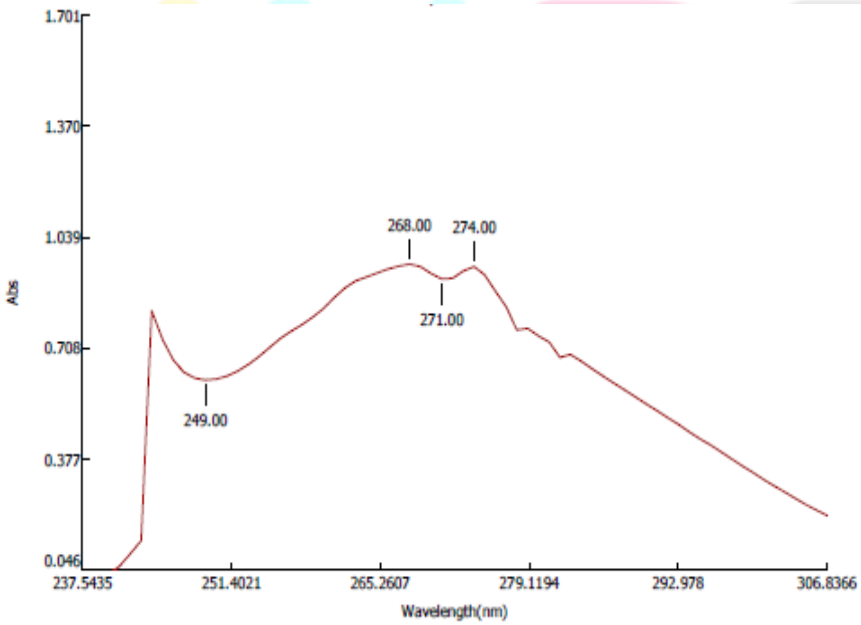

Figure 5.2 UV spectrum of pioglitazone in phosphate buffer PH 6.8

Calibration curve of Pioglitazone of phosphate buffer (pH 6.8)

The calibration curve of Pioglitazone was prepared in the concentration range 4-32µg/ml in phosphate buffer (pH 6.8). The observed absorbance values are tabulated in table 5.2 .The Pioglitazone was found to obey Beer-Lambert's law in the concentration range of 4-25µg/ml (Figure 5.2). The calibration curve obtained was a liner and had regression coefficient (R^2) value 0.999 with less standard deviation, indicating good linearity and reproducibility.

Table 5.2 Calibration curve data of Pioglitazone in phosphate buffer pH 6.8

Concentration (µg/ml)	Absorbance
4	0.118 ± 0.01
8	0.213 ± 0.01
12	0.279 ± 0.01
16	0.370 ± 0.01
20	0.473 ± 0.01
24	0.553 ± 0.01
28	0.628 ± 0.01
32	0.728 ± 0.01

Mean ± SD (n=6)

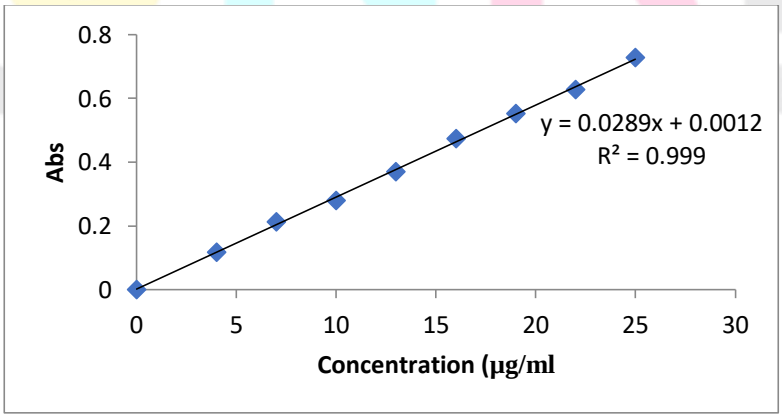

Figure 5.2 Calibration curve of Pioglitazone in phosphate buffer pH 6.8

5.1.3Solubility study of Pioglitazone Solubility study of PTZN was carried out in different solvents i.e. water, pH 6.8, and 0.1N HCL. Therefore PTZN has shown lesser solubility in water indicating hydrophobic characteristic of the drug. Solubility profile is shown in the table below:

Table 5.3 Solubility studies of Pioglitazone in different solvents

Sr. No.	Solvent used	Solubility (mg/ml)
1	Water	0.013 ± 0.002
3	Phosphate buffer pH 6.8	0.062 ± 0.138
4	0.1 N HCL	0.455 ± 0.123

Mean ±SD (n=3)

5.1.4 Partition coefficient of Pioglitazone

The partition coefficient of Pioglitazone was determined by shake flask method using aqueous phase containing 10 ml of distilled water and oil phase containing 10 ml n-octanol. The partition coefficient was found to be 2.281 ± 0.450. The high p value for PTZN further confirms their hydrophobic nature.

5.1.6 Fourier transform infrared spectroscopy (FTIR) of Pioglitazone

FTIR study was conducted for the structure characterization. FTIR spectrum of pure drug was recorded by fourier transform infrared spectroscopy using KBr press pellet method. Approximately 5 mg of pure drug was mixed with 50 mg of spectroscopic grade KBr. Prepared pellet was scanned in the IR range from 400 to 4000 cm-1. FTIR spectra of PTZN show characteristic bands are recognized to the stretching of different group vibrations: 1629.85 cm-1 stretching of amide carbonyl, 1529 cm-1 stretching of the amide band, 1435 cm-1 stretching of asymmetric methyl group. Observed peaks are shown in the Table 5.5 below and FTIR spectrum of pure drug PTZN is shown in the table 5.4 below and FTIR spectrum of pure drug PTZN is shown in the figure 5.3.

Table 5.4 Infrared spectral band in Pioglitazone

Sr. No.	Functional group	Observed peaks (cm^{-1})	Reported peaks (cm^{-1})
1	Methyl	1435.04	1435
2	Tertiary amine group	1525.69	1524
3	CH-Aromatic	3014.74	3150
4	C=O keton	1668.45	1705
5	Ortho-di substituted ring	773.46	775
6	Amide carboxyl	1629.85	1629.85

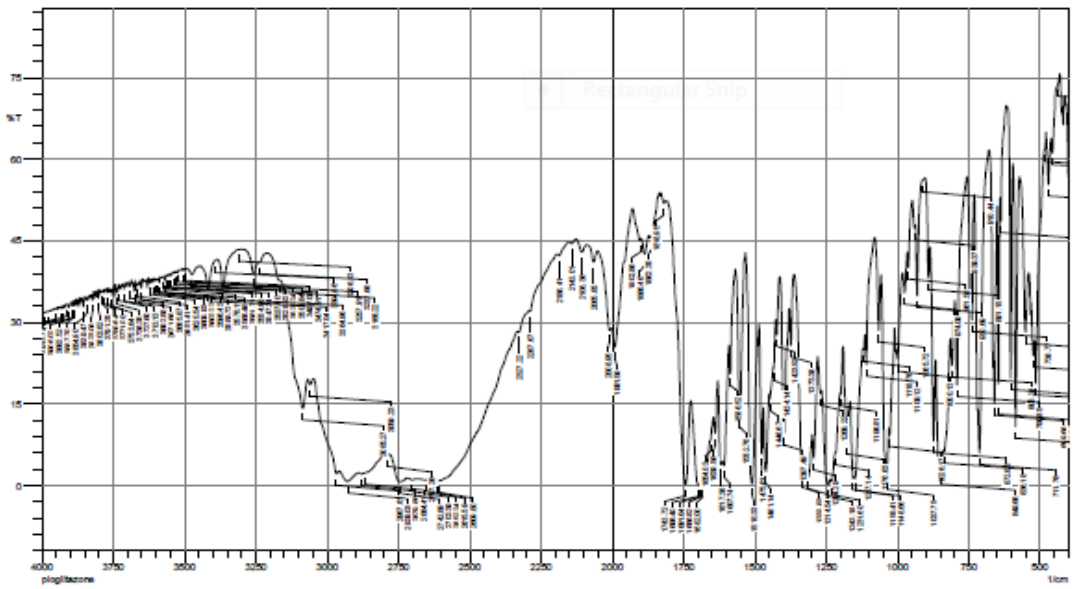

Figure 5.3 FTIR spectrum of Pioglitazone.

5.1.7 Drug excipients compatibility study by FTIR

The IR spectrum of physical mixture of pure drug and excipients were recorded by IR spectroscopy. The IR spectrum of drug and excipients did not show any significant change in the characteristic peaks of drug, which

showed that superdisintegrants and drug were compatible with each other. Interpretation data is tabulated below in the Table 5.6. The FTIR spectrum of drug and different superdisintegrants are shown in the below Figures i.e. 5.4, 5.5, 5.6, 5.7, 5.8 5.9.

FTIR spectra pure PTZN revealed the presence of a peak at 3086.82 cm^{-1} due to N-H stretching while peaks at 2927 and 2740 cm^{-1}corresponds to C-H stretching. Strong absorption peaks was observed at 1743.53 and 1689.53 cm^{-1} are assigned to drug carbonyl stretching vibration (C=O).

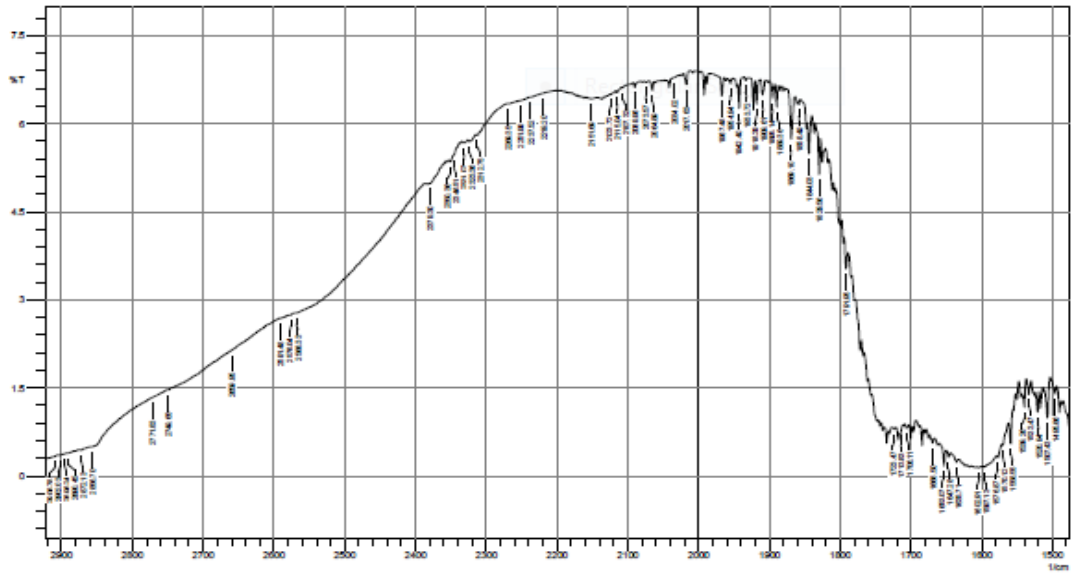

Figure 5.4 FTIR spectra of Croscarmellose Sodium with Pioglitazone.

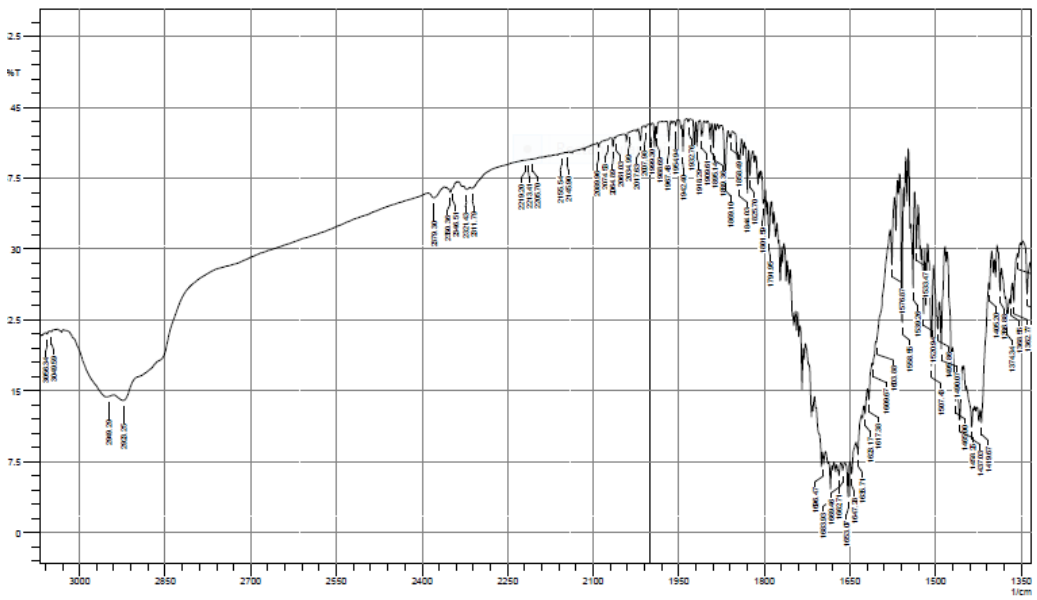

Figure 5.5 FTIR spectra of Crospovidone with Pioglitazone

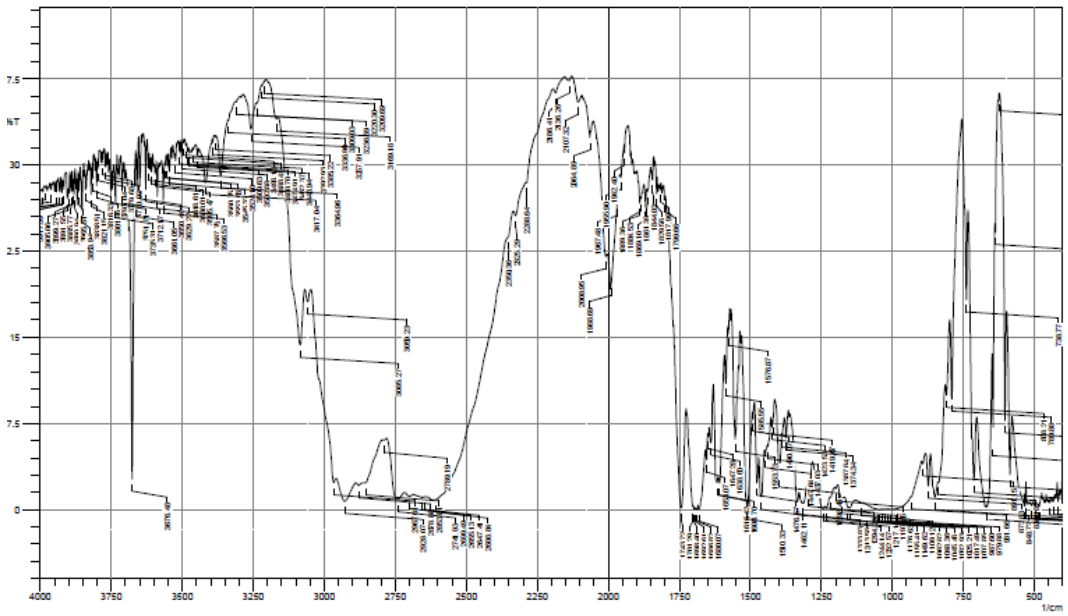

Figure 5.6 FTIR spectra of D-Mannitol with Pioglitazone

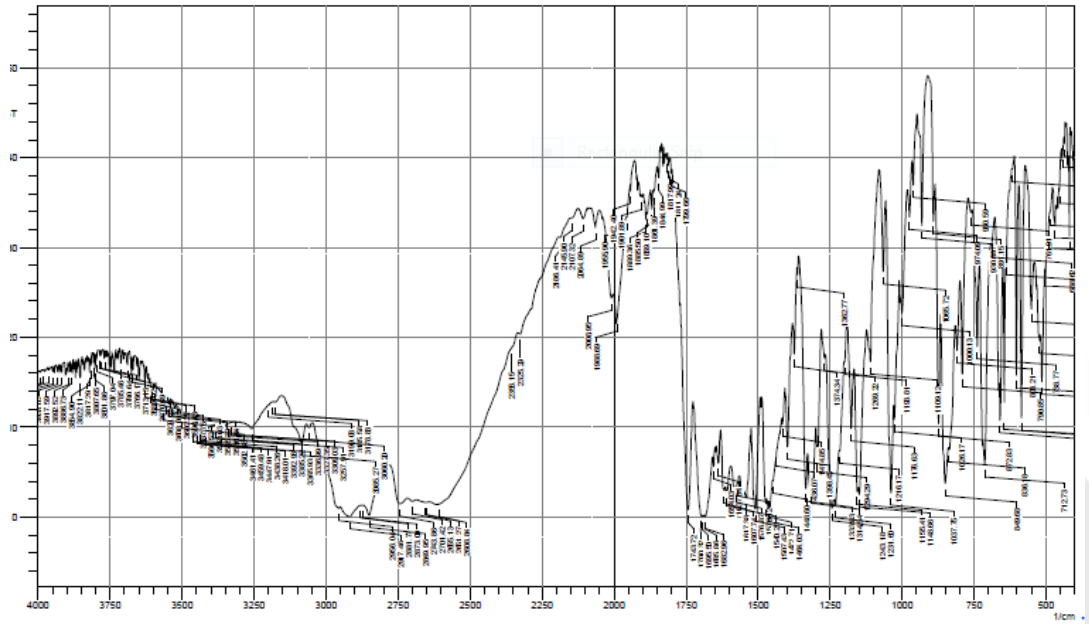

Figure 5.7 FTIR spectra of Magnesium Stearate with Pioglitazone

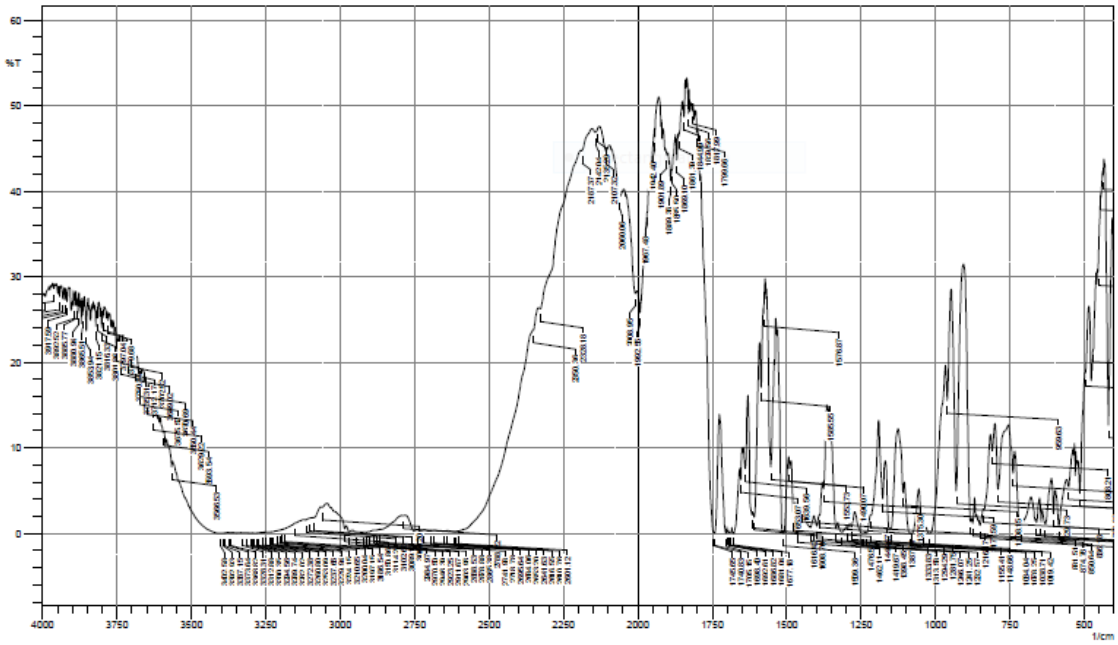

Figure5.8 FTIR spectra of Talc with Pioglitazone

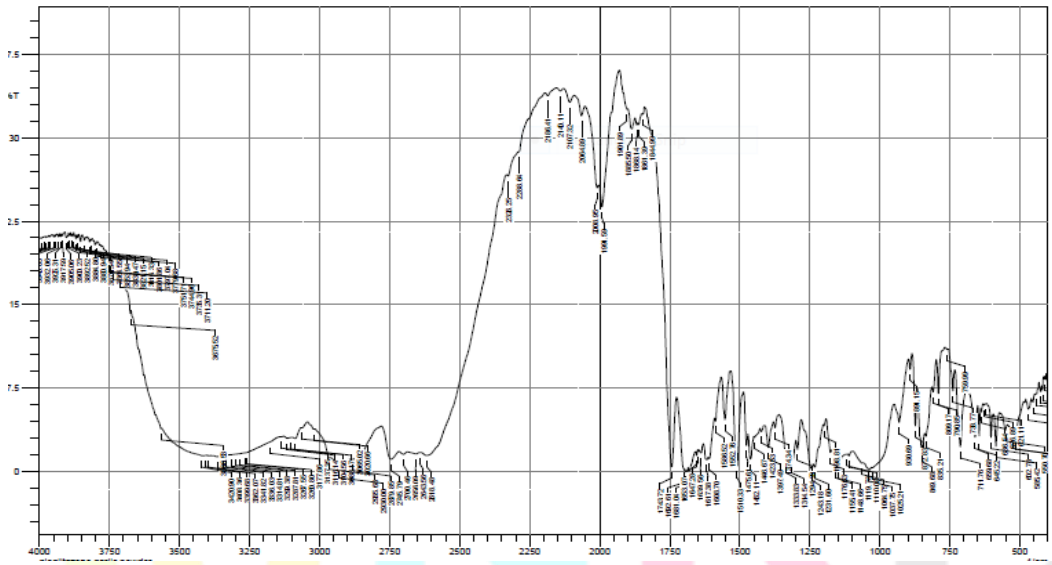

Figure 5.9 FTIR spectra of Garlic Powder with Pioglitazone.

Table 5.5 FTIR studies of Pioglitazone with superdisintegrants

IR spectra	Peak of functional group [Wave length (cm^{-1})]			
	N –H stretch	C-H stretch	C=O stretch	C-O-Ar
Standard	3086.82	2927.74	1743.53	1296.79
Spectra				

5.2	**Pioglitazone**	3086.87	2931.88	1635.98	1297.79
	Pioglitazone + CCS	3082.87	2932.91	1654.77	1298.64
	Pioglitazone + Crospovidone	3084.87	2935.76	1655.65	1295.34
	Pioglitazone + Garlic powder	3091.80	2921.88	1754.63	1290.31

EVALUATION OF POWDER BLEND

The flow properties of powders are critical for an efficient tableting operation. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. Before tablet preparation, the mixture blend of all the formulation were subjected to Precompression parameters such as angle of repose, bulk density, tapped density, hausner's ratio and carr's compressibility index.

5.2.1 Bulk density

The bulk density of all the formulations prepared by direct compression method PTZN 1to PTZN 9 was found to be in the range of 0.398 ± 0.004 g/ml to 0.392 ± 0.002 g/ml. The values are represented in Table 5.6.The bulk density of batches PTZN 1 and PTZN 9 was found to be almost similar indicating almost identical flow behavior. The powder mass of different formulation were found to be non-aggregating. The above results it indicates good flow properties.

5.2.2 Tapped density

The tapped density of the formulation PXM1 to PXM6 was observed in between the range of 0.33 ± 0.002 g/ml to 0.33 ± 0.002 g/ml. The values were shown in the Table 5.6.the difference in densities indicates very less in powder volume each after tapping and had almost same flow properties.

5.2.3 Hausner's ratio

The Hausner's ratio is an indicative of flow properties of the powder blend. Hausner's ratio (<1.25) indicates better flow properties and (>1.25) shows poor flow of powder blend. The Hausner's ratio of all the formulations PTZN1 to PTZN9 was in the range of 1.22 ± 0.019 to 1.18 ± 0.011 (Table 5.6). The above results it indicates good flow properties of powder blends.

5.2.4 Carr's compressibility index

The carr's compressibility index between 5 to 15 and 15 to 20 indicates excellent and good flow ability, respectively, while the value < 30 indicates poor flow properties. It indicated the cohesiveness of particles. The carr's compressibility index was found to be in between 15.11 ± 1.25 % to 20.25 ± 1.35% (Table 5.6).The above results it indicates good flow properties.

5.2.5 Angle of repose

The angle of repose (θ) was calculated by funnel method. It is an indicative of the flow properties of the powder. The value of angle of repose of formulations PTZN 1 to PTZN 9 prepared by direct compression were found in the range of 24.23 ± 0.57 to 24.55 ± 0.49 (Table 5.6) indicating good flow of the blend. The powder mass of the different formulation were found to be non-aggregating. The above results it indicates good flow properties.

Table 5.6 Precompression parameters of powder blend (PTZN1 to (PTZN 9).

Formulation Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner's Ratio	Carr's Index (%)	Angle of repose (θ)

PTZN 1	0.398 ± 0.004	0.33 ± 0.002	1.22 ± 0.019	15.11 ± 1.25	24.23 ± 0.57
PTZN 2	0.394 ± 0.003	0.33 ± 0.003	1.20 ± 0.011	16.80 ± 1.26	24.65 ± 1.00
PTZN 3	0.396 ± 0.004	0.33 ± 0.002	1.12 ± 0.014	17.57 ± 1.62	35.33 ± 0.41
PTZN 4	0.395 ± 0.003	0.33 ± 0.002	1.21 ± 0.024	15.70 ± 0.80	28.46 ± 0.50
PTZN 5	0.397 ± 0.003	0.33 ± 0.002	1.18 ± 0.011	16.82 ± 1.27	24.85 ± 0.84
PTZN 6	0.396 ± 0.004	0.33 ± 0.002	1.20 ± 0.018	17.84 ± 1.48	24.83 ± 0.84
PTZN 7	0.395 ± 0.003	0.33 ± 0.003	1.21 ± 0.011	17.45 ± 1.26	24.57 ± 1.80
PTZN 8	0.393 ± 0.002	0.33 ± 0.002	1.15 ± 0.010	18 .40 ± 1.22	24.59 ± 0.57
PTZN 9	0.392 ± 0.002	0.33 ± 0.002	1.18 ± 0.011	20.25 ± 1.35	24.55 ± 0.49

Mean ± SD (n=3)

Figure 5.10 Formulated tablet of Pioglitazone

5.3 EVALUATION OF FAST DISSOLVING TABLETS

The prepared tablets were subjected for the post compression evaluation.

5.3.1 General appearance

All the tablets were off white color, round in shape. The textures of tablets were smooth.

5.3.2 Hardness

The hardness of the tablets indicates the crushing tolerance, which is the force required to break a tablet in the radial direction. The hardness of the formulated tablets of formulation PTZN 1 to PTZN 9 was found to be in between 3.37 ± 0.01 kg/cm2 to 3.12 ± 0.03 kg/cm2 as shown in the Table 5.7. All the formulated tablets possess good mechanical strength with sufficient hardness. FDT has less hardness then the conventional tablets.

5.3.3 Friability

The friability of the formulations PTZN 1 to PTZN 9 is shown in the Table 5.7. It was found within the range of 0.265 ± 0.001 % to 0.131 ± 0.01 %. These values are within the acceptable limit of less than 1 % indicating the ability of tablets to withstand abrasion in handling packaging and shipment (Table 5.7).

5.3.4 Thickness

The thicknesses of tablets of formulation PXM1 to PXM9 were found to be in the range of 3.546 ± 0.069 to 3.391 ± 0.040 mm. The prepared batches of the FDT were not varying and they having minor deviation. The thickness of the tablet was as shown below (Table 5.7).

5.3.5 Weight variation

The weight variation was carried out by weighing the 20 tablets of each formulation and average weight was calculated. Individual tablets weights were also determined accurately and the weight variation is calculated. The results were within the limit as per the IP (Table 5.7).

5.3.6 Drug content

The percent drug content of formulation PTZN 1 to PTZN 9 was found to be in the range of 99.55 ± 0.218 % to 101.1 ± 0.3. All the values are tabulated in the Table 5.7. The values obtained were within the acceptance

criteria as per Indian Pharmacopoeia Table 5.7. Post compression parameters of prepared fast dissolving tablets.

Table 5.7 Post compression parameters of prepared fast dissolving tablets

Formulation Code	Hardness kg/cm^2	Friability (%)	Thickness (mm)	weight variation	Drug content (%)
PTZN 1	3.37 ± 0.01	0.265 ±.001	3.546 ± 0.069	220 ± 20	99.55 ± 0.218
PTZN 2	3.37 ± 0.14	0 ± 0.01	3.569 ± 0.068	240 ± 10	98.66 ± 0,284
PTZN 3	3.05 ± 0.06	0.140 ± 0.08	3.464 ± 0.053	250 ± 10	97.5 ± 0.278
PTZN 4	3.11 ± 0.02	0.134 ± 0.04	3.552 ± 0.045	230 ± 10	102.33 ± 0.333
PTZN 5	3.32 ± 0.12	0.134 ± 0.04	3.425 ± 0.034	220 ± 10	101.8 ± 0.4
PTZN 6	3.13 ± 0.06	0.270 ± 0.03	3.457 ± 0.038	240 ± 10	101.233 ± 0.153
PTZN 7	3.33 ± 0.09	0.134 ± 0.07	3.376 ± 0.053	230 ± 10	99.951 ± o.131
PTZN 8	3.32 ± 0.08	0.134 ± 0.05	3.390 ± 0.047	250 ± 10	99.483 ± 0.123
PTZN 9	3.12 ± 0.03	0.131 ± 0.01	3.391 ± 0.040	230 ± 10	101.1 ± 0.3

Mean ± SD (n=3)

5.3.7 Water absorption ratio

The water absorption ratio was used to determine the amount of water absorbed by tablet. The water absorption ratio of formulations PTZN1 to PTZN9 was found to be in the range 40.81 ± 0.83 to 20.07 ± 0.54 %. It was found that formulation PTZN6 showed 98 % water absorption ratio containing crospovidone and Emcosoy or formulated by direct compression method (Table 5.8).

5.3.8 *In-vitro* disintegration time

The *in-vitro* disintegration time is the time taken by the tablet to undergo complete disintegration when comes in contact with dissolution media. Disintegration of the tablet affected by hardness and concentration and nature of the superdisintegrants added. Upon disintegration tablets breaks down in small fragments. All the formulations which were formulated by direct compression method showed disintegration time between the ranges of 29.22 ± 1.63 to 13.28 ± 0.35 seconds. On the basis of best disintegration time among F6 formulation i.e. (12.41 ± 0.43 second) is the best formulation.

Table 5.8 Post compression parameters of prepared fast dissolving tablets

Formulation Code	Disintegration time (sec)	% Water Absorption Ratio
PTZN 1	29.22 ± 1.63	40.81 ±0.83
PTZN 2	26.18 ± 1.24	51.22 ±0.29
PTZN 3	21.24 ± 0.14	38.10 ± 0.35
PTZN 4	18.13 ± 1.23	26.22 ± 0.43
PTZN 5	16.24 ± 1.45	22.60 ± 0.15
PTZN 6	12.41 ± 0.43	18.44 ± 0.11
PTZN 7	16.49 ± 0.65	24.12 ± 0.41
PTZN 8	14.19 ± 1.22	30 .67 ± 0.63
PTZN 9	13.28 ± 0.35	20.07 ± 0.54

Mean ± SD (n=3)

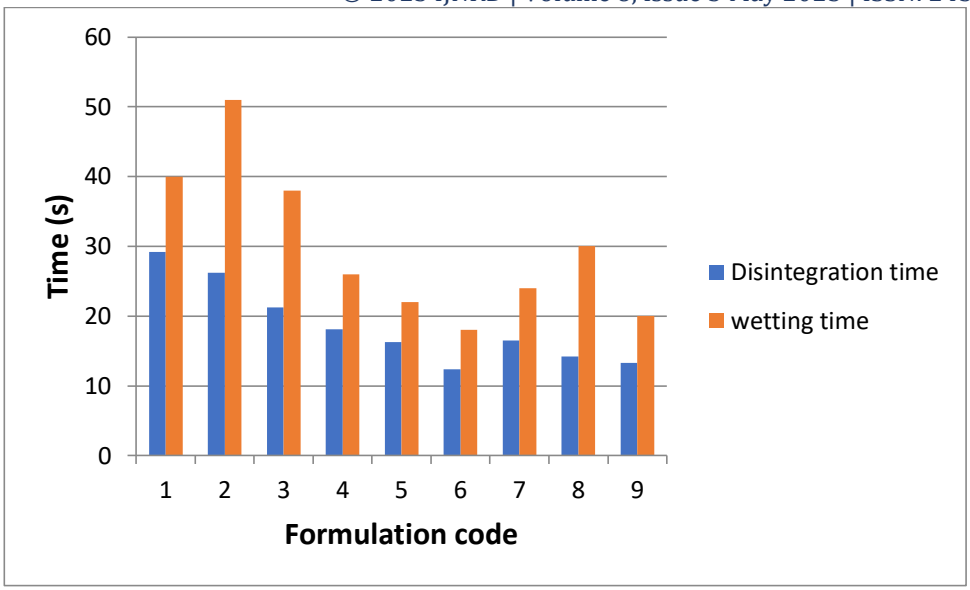

Figure 5.10 Relationship between disintegration time and wetting time of different fast dissolving tablets (formulation PTZN1-PTZN9)

5.3.9 *In-vitro* dissolution studies

Dissolution studies were conducted for all the formulation via USP dissolution apparatus II paddle type, using phosphate buffer pH 6.8 as dissolution medium. It had been observed from the drug release profile more than 90 % drug was released within 20 min. Formulation PTZN6 containing 5 % crospovidone and 4% of Emcosoy showed 99.31 amount of drug release within 20 min which was formulated by the direct compression method.

Table 5.9 *In- vitro* releases rate profile of Pioglitazone tablets (PTZN1-PTZN3)

Time (min)	PTZN1	PTZN2	PTZN3
0	0	0	0
5	25.3 ± 0.32	43.5 ± 0.49	34.91 ± 0.33
10	47.6 ± 0.43	66.3 ± 0.51	46.45 ± 0.75
15	56.3 ± 0. 56	75.2 ±0 .34	59.23 ± 0.17
20	67.3 ± 0.78	89.8 ± 0.44	72.34 ± 0.81
30	80.3 ± 0.34	99.46 ± 0.62	85.73 ± 0.65

45	95.1 ± 0.67	_	99.47 ± 0.72
60	95.7 ± 0.82	_	_

Mean ± SD (n=3)

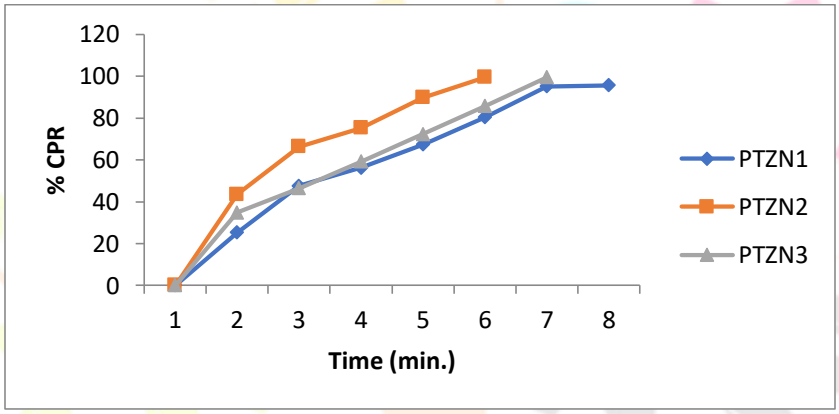

Figure 5.11 Comparative *in-vitro* release of formulation PTZN1 to PTZN3.

Table 5.*10 In-vitro* released rate profile of Pioglitazone tablets (PTZN4-PTZN6)

Time (min)	PTZN4	PTZN5	PTZN6
0	0	0	0
5	33.16 ± 0.78	45.23 ± 0.51	49.48 ± 0.65
10	41.45 ± 0.55	61.57 ± 0.45	69.33 ± 0.53
15	53.15 ± 0.26	73.61 ± 0.48	80.56 ± 0.52
20	66.28 ± 0.29	81.29 ± 0.40	99.31 ± 0.61
30	79.22 ± 0.64	89.21 ± 0.59	_
45	87.43 ± 0.27	99.46 ± 0.42	_
60	99.74 ± 0.29	_	_

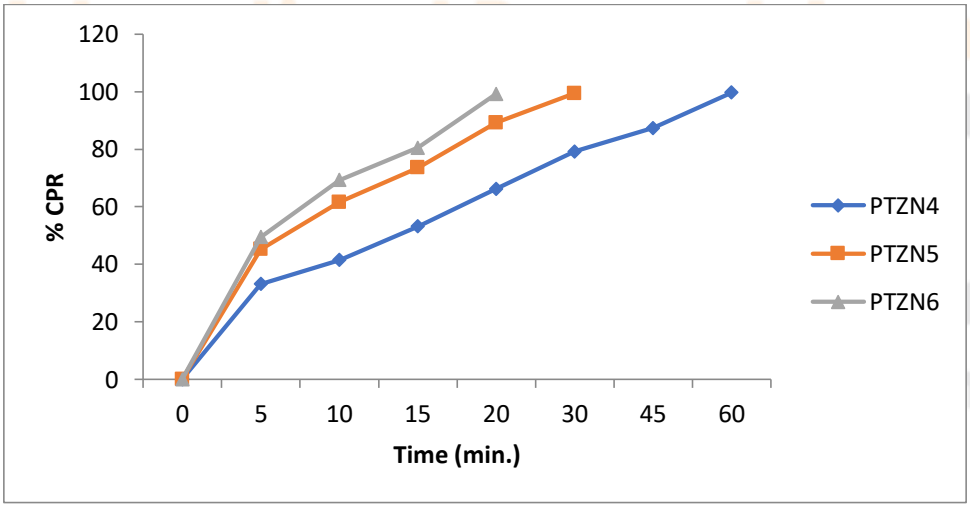

Figure 5.12 Comparative *in-vitro* release of formulation PTZN4 to PTZN6.

Table 5.11 *In-vitro* released rate profile of Pioglitazone tablets (PTZN7 – PTZN9)

Time (min)	PTZN7	PTZN8	PTZN9
0	0	0	0
5	17.8 ± 0.24	19.07 ± 0.20	24.45 ± 0.42
10	24.72 ± 0.32	23.75 ± 0.55	38.97 ± 0.41
15	33.33 ± 0.36	40.46 ± 0.09	41.28 ± 0.19
20	42.58 ± 0.34	50.25 ± 0.06	51.53 ± 0.17
30	52.05 ± 0.24	67.1 ± 0.28	72.04 ± 0.62
45	69.47 ± 0.75	79.3 ± 0.67	87.1 ± 0.62
60	82.34 ± 0.42	90.34 ± 0.39	98.6 ± 0.18

Mean ± SD (n=3)

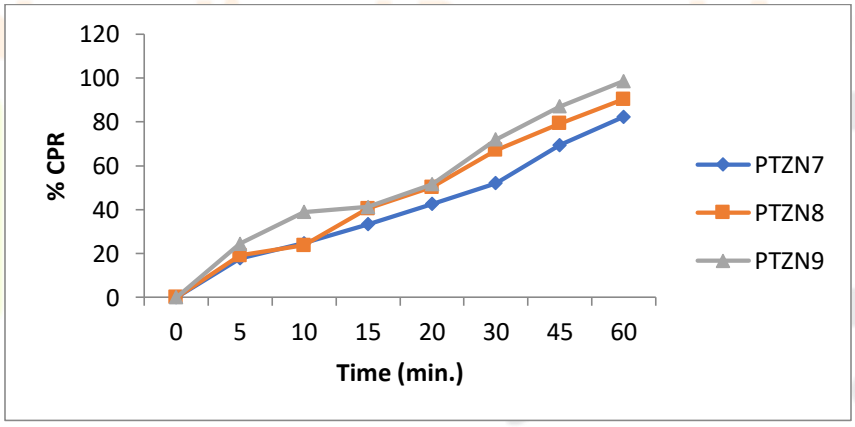

Figure 5.13 Comparative *in-vitro* release of formulation PTZN7 to PTZN9.

From the above data it had been concluded that formulations PTZN6 containing crospovidone and Emcosoy formulated by direct compression method showed fastest drug release when compare to the all other formulation the best selected formulation PTZN6 was chosen for comparison with marketed formulations. Formulation PTZN6 was compare with two different marketed formulations of different brands. Compression

indicated that the prepared formulation PTZN6 containing 5 % crospovidone and 4 % Emcosoy showed 99.31 ± 0.61 % drug release in 20 min whereas marketed formulation MKT1 and MKT2 showed 85.65 ± 0.50 % and 80.78 ±0.41 % drug release with in 20 min which was less than formulation PTZN6.The comparison of percent drug release of optimized formulation with marketed is shown in the Table 5.12.

Table 5.12 Comparison of percentage drug release of optimized formulation with marketed formulation

Time (min)	PTZN6	MKT1	MKT2
0	0	0	0
5	49.48 ± 0.65	45.31 ± 0.45	41.53 ± 0.42
10	69.33 ± 0.53	61.21 ± 0.82	56.99 ± 0.11
15	80.56 ± 0.52	70.44 ± 0.21	65.45 ± 0.19
20	99.31 ± 0.61	85.65 ± 0.50	80.78 ± 0.41

Mean ±SD (n=3)

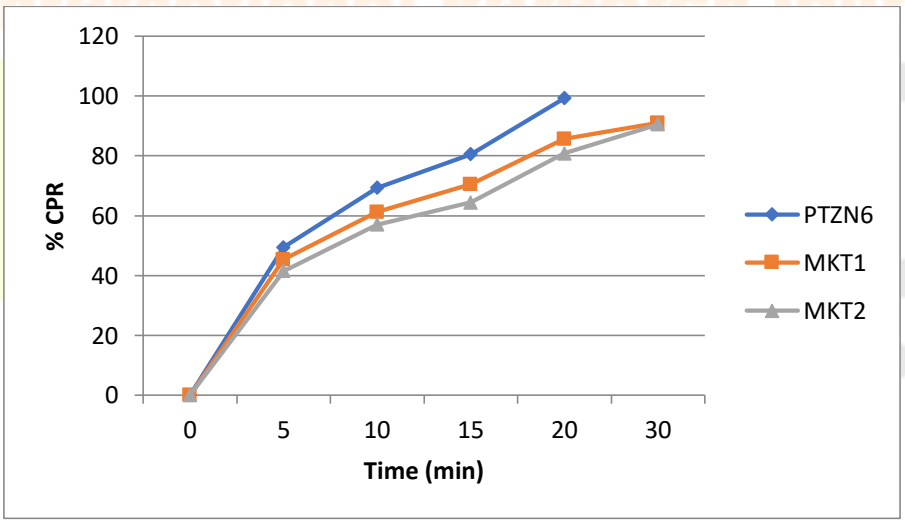

Figure 5.14 Comparative *in-vitro* release of formulation PTZN6 with marketed formulation.

Summary and Conclusion

Administration of drug using FDT has been generated interest due to its excellent rapid release in the oral cavity, easy to formulate, patient suitability and safety in order to overcome the problems like dysphagia. The

FDT also helps in improving the bioavailability of the drug due to the exposure from mouth to stomach. Fast dissolving tablets are considered to be contempory dosage forms. Fast dissolving concept developed to overcome some of the problems that existed in conventional solid dosage form i.e. difficulty in swallowing of tablets in pediatric and geriatric patients who constitute a large proportion of world's population.These dosages also form and their route of administration results in better efficacy, rapid onset of action, enhanced bioavailability, and improves patient compliance.The aim of this study was to optimize and formulate fast disintegrating tablets (FDTs) of Pioglitazone using different superdisintegrants by using method i.e. direct compression method. The tablets are formulated using three superdisintegrants viz., Emcosoy, crospovidone and Croscarmellose sodium in different concentrations.Pioglitazone is a diabetic drug (thiazolidinediones type, also called "glitazone") used along with a proper diet and exercise program to control high blood sugar in patients with type 2 diabetes. It works by helping to restore your body's proper response to insulin, thereby lowering your blood sugar. Pioglitazone decrease insulin resistance in the periphery and in the liver resulting in increase insulin-dependent glucose disposal and decreased hepatic glucose output. Whereas Emcosoy is used as super disintegrant for fast dissolving tablets and is free from sugar moieties, these properties makes this superdisintegrants as one of the best choice for diabetic patient. The results of experimental studies of Pioglitazone fast dissolving tablets proved that the powder blend of Pioglitazone showed good flow properties and the tablet evaluation tests are within the acceptable limits. IR spectral analysis proved that there was no drug excipient interaction. Post-compression parameters and in-vitro dissolution studies were carried out. Formulation PTZN6 was compare with two different marketed formulations of different brands. Compression indicated that the prepared formulation PTZN6 containing 5 % crospovidone and 4 % Emcosoy showed 99.31 ± 0.61 % drug release in 20 min whereas marketed formulation MKT1 and MKT2 showed 85.65 ± 0.50 % and 80.78 ±0.41 % drug release within 20 min which was less than formulation PTZN6.The comparison of percent drug release of optimized formulation with marketed formulation. So, it can be concluded that the as the concentration of superdisintegrants in the formulation increased the disintegration time was decreased.Whereas from the dissolution studies it was evident that the formulation (F6) showed better and optimized and desired drug release pattern i.e. 99.31% in 20 minutes.Considering *in-vitro* disintegration, % friability and % drug released, crospovidone and Emcosoy can successfully utilized for preparation of fast dissolving tablets.Hence it can be concluded that using crospovidone and Emcosoy as superdisintegrants prepared by direct

compression would be quite effective in providing faster onset of action without the need of water for swallowing of fast dissolving tablets containing Pioglitazone.

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