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Preparation and Evaluation of Pharmaceutical Cocrystals of Pioglitazone HCl

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ABSTRACT

Based on the BCS classification scheme pioglitazone HCl is a 2nd class API. Pioglitazone hydrochloride has a low solubility at room temperature. The goal of this study was to find a way to make pioglitazone HCl more water-soluble by preventing the development of its dihydrate using the co-crystal formation method. Improving pioglitazone HCl's physical properties, particularly its solubility, is a typical use of this method. The high concentration of hydroxyl groups in nicotinamide led to its selection as a co-crystal former; this means that it has the ability to establish hydrogen bonds with other substances. Co-crystal of pioglitazone HCl were prepared by using nicotinamide as a co-former by using solvent drop and solvent evaporation method. Prepared co-crystal were characterized using IR spectral study, DSC study, X-ray diffraction study and dissolution study. The expected enhancement of dissolution was achieved with the co-crystal formation due to complete inhibition of dihydrate formation.

INTRODUCTION

In severe situations, a solid tablet that breaks down or disappears in the mouth without requiring water or crunching can be used as a medicine delivery method that dissolves quickly. A variety of techniques have been used to clarify intermolecular interactions and characterize pharmaceutical cocrystals. It is known that the solubility of cocrystals in water can reach 1,000 times that of drugs. There has also been a trend in the solubility of coformers over drugs (Scoformer/Sdrug) and the solubility of cocrystals (SA=Scocrystal/Sdrug). To describe a cocrystal's capacity to change a drug's solubility at a specific pH, concentration of the solubilizing agent, temperature, etc., a dimensionless solubility number called the cocrystal solubility benefit, or SA, is entered.

Experimental Work

Drug Authentication:

Description

Color: Patients typically reject systems that are not visually attractive, thus a comprehensive investigation is required to ensure that each batch of formulations has the same chromatic characteristics.

Olfactory perception and palatability: If an active substance is not palatable or has an unpleasant fragrance, it can be covered up by coatings or flavorings, which is not acceptable. However, this masks the taste or hides strong odors.

Melting point determination

The temperature at which a material changes state from a solid to a fluid at standard air pressure is known as its liquefying point. Using Thiele's cylinder technique, which involves setting a little amount of the medicine in a closed capillary cylinder with one end closed and putting it in a liquefying point apparatus, the softening mark of pioglitazone hydrochloride was found.

Solubility study

Solubility, which refers to the solute's capacity to dissolve in a solvent and structure a homogeneous system, is a significant calculate deciding the drug's planned focus in the

systemic dissemination and the normal pharmacological response. By introducing an excess of the drug to 10 milliliters of distilled water in glass tubes that were sealed with aluminum foil, the solubility of the drug was assessed. The resulting suspension was filtered after being agitated for 48 hours on a mechanical shaker. After diluting the resulting filtrate with distilled water, a UV spectrophotometer was used for spectrophotometric analysis.

Spectroscopic studies:

UV spectroscopy

Preparation of Standard Solution:

To create a standard stock solution with a concentration of 1000 µg/ml, 50 mg of the pure drug was accurately measured, dissolved in methanol, and then the volume was increased to 50 ml using methanol. A variety of concentrations of 5, 10, 15, 20, and 25 µg/ml were achieved by properly diluting portions of the standard stock solution with distilled water. The scanning frequency for these was 200 to 400 nm.

Selection of Analytical Wavelength:

Using a UV Spectrophotometer, several dilutions ranging from 2-10µg/ml were made from the standard stock solution 'B' and scanned in the 400-200nm wavelength range.

Preparation of calibration curve for Pioglitazone hydrochloride in methanol -

Consisting of focus levels of 2, 4, 6, 8, and 10µg/ml, the standard stock solution is used. The absorbance of the previously mentioned solutions was measured at 267.5 nm, and an absorbance vs focus adjustment bend was produced.

Fourier Transform Infrared Spectroscopy (FTIR):

Using the KBr powder press method, the FT-IR spectra of pioglitazone hydrochloride were recorded to verify their purity on the FTIR spectrophotometer (FTIR 8400S, Shimadzu). Dried potassium bromide was used to do the baseline correction. Over the 4000-400 cm-1 range, the instrument was operated under dry air purge with a resolution of cm-1. The primary drug peaks in the scans were assessed for their existence. The principal peaks of the published infrared spectra were compared with the identified peaks.

Differential Scanning Colorimeter (DSC):

To confirm the virtue of Pioglitazone HCl, a DSC thermogram was performed. Differential Scanning Calorimetry (METTLER TOLEDO, Star SW 920) was used to record the DSC thermogram. In a climate of nitrogen stream (40 mL/min), was warmed at a scanning pace of 100C/min in an aluminum skillet that had been pleated and had a punctured cover somewhere in the range of 30 and 3500C. Indium was used to align the DSC for temperature and enthalpy, and void pans were used for the baseline.

Selection of co-crystal former and its ratio

Ten coformers with the ability to form hydrogen bonds (good proton donor and acceptor) were chosen based on mechanochemistry: 4-hydroxy benzoic acid, nicotinamide, salicylic acid, oxalic acid, succinic acid, citric acid, caffein, hippuric acid, succinic acid, and tartaric acid. However, in terms of practical application, nicotinamide and hippuric acid led to improved water solubility for Pioglitazone HCl and nicotinamide were tested with different ratios of API:conformer (1:1, 1:2, and 1:3) primarily to choose stoichiometric ratios of successful conformers. Ratios of 1:2 and 1:3 indicated higher solubility in water. but not in the way of additional conformers; for this reason, a 1:1 ratio is thought to be secure and efficient when creating cocrystals.

Compatibility studies of drug and coformer :

Here's how a compatibility study typically works and the role of excipients:

1. Selection of Excipients: Excipients are carefully chosen based on their intended function in the formulation. Common excipients include binders, fillers, disintegrants, lubricants, and preservatives.

2.Compatibility Testing: Compatibility testing involves evaluating the interactions between the active pharmaceutical ingredient (API) and the excipients. This can be done through various techniques such as physical compatibility testing (visual inspection, microscopy), chemical compatibility testing (HPLC, LC-MS), FT-IR and thermal analysis (DSC, TGA).

Fourier Transform Infrared Spectroscopy (FTIR) study :

Utilizing KBr powder, the FT-IR spectra of pure pioglitazone HCl and nicotinamide, glipizide and stearic acid were acquired using an FT-IR spectrophotometer (Shimadzu, FTIR-8400S, Japan). The device was operated with a dry air purge, and scans were taken over a 4000-400 cm-1 zone at a speed of 2 mm/sec with a resolution of 4 cm-1. The main drug peaks, drug peaks that shifted or vanished, and new peaks that appeared as a result of coformer interaction were all assessed in the scans.

Differential Scanning Colorimeter (DSC)

To verify their compatibility, a DSC thermogram of nicotinamide and pioglitazone hydrochloride,(a physical combination of 1:1) was performed. Differential Scanning Calorimetry (METTLER TOLEDO, Star SW 920) was used to record the DSC thermogram. In an environment of nitrogen flow (40 mL/min), the physical mixture of drug and coformer (7 mg) was heated at a scanning rate of 100C/min in a crimped aluminum pan with a punctured lid between 30 and 3500C. DSC thermograms of the drug and coformer physical combination.

Preparation of co-crystal

Liquid assisted grinding :

The stoichiometric proportion of Coformer and API was consolidated, crushed in a mortar and pestle, and pulverized for 30 minutes while adding 2 ml of methanol as a solvent. The powder was then permitted to dry at room temperature before being subjected to extra examination.

Solvent evaporation :

The process of solvent evaporation was used to make the cocrystals. The stoichiometric ratios of Coformer and API were dissolved in 25 milliliters of methanol and warmed to 100 degrees Celsius for two hours while stirring continuously. Next, insolubles were removed from the solution by separating it. After that, the separated solution was left to evaporate at surrounding temperature delicately.

Characterization of co-crystal of Pioglitazone hydrochloride

Fourier transform infrared spectroscopy and Differential scanning calorimetry was performed.

X-ray diffraction

An X-ray powder diffractometer (PXRD) analysis of the produced mixtures validates the production of the novel solid phases. Since no two solids have exactly the same two theta lines, the difference in the two theta lines indicates the emergence of new solid phases, which is confirmed by their difference. The Spinner PW3064 sample stage was employed to record PXRD spectra. Samples were scanned from 10° to 40° in 2˚ increments, with a step size of 0.045° and a step length of 0.5 sec.

Evaluation of co-crystal

Solubility analysis

Excess of each material is put in glass tubes sealed with aluminum foil and placed in 10 ml of distilled water. final suspension shaken on a mechanical shaker for 48 hours before being filtered. After diluting the resulting filtrate with distilled water, a UV spectrophotometer was used for spectrophotometric analysis.

Dissolution study

Pioglitazone HCl cocrystal

Using a USP apparatus II dissolution vessel (TDL 08L, Electrolab, India) filled with 900 ml of 0.1 N HCl at 37 °C and 100 rpm, an intrinsic dissolution investigation was carried out. Cocrystal dissolution experiments lasted up to 30 minutes. Samples were taken out at intervals of five minutes, and measurements were made at 267.5 nm using a UV spectrophotometer (V-630, Jasco, Japan).

Result and discussion

Drug authentication

Appearance, colour :

It was discovered that the powder sample was a crystalline, white to off-white powder.

Melting point :

A melting point of 198–200^0 C was discovered. It suggests that the drug was pure.

Solubility :

Insoluble in water, but easily soluble in methanol, dichloromethane, and ethanol at low concentrations. It complies with I.P. as it is.

UV-Visible spectroscopy :

The dissolve pioglitazone hydrochloride in methanol showed an absorbance maximum (λmax) at 267.5 nm as shown in **figure**

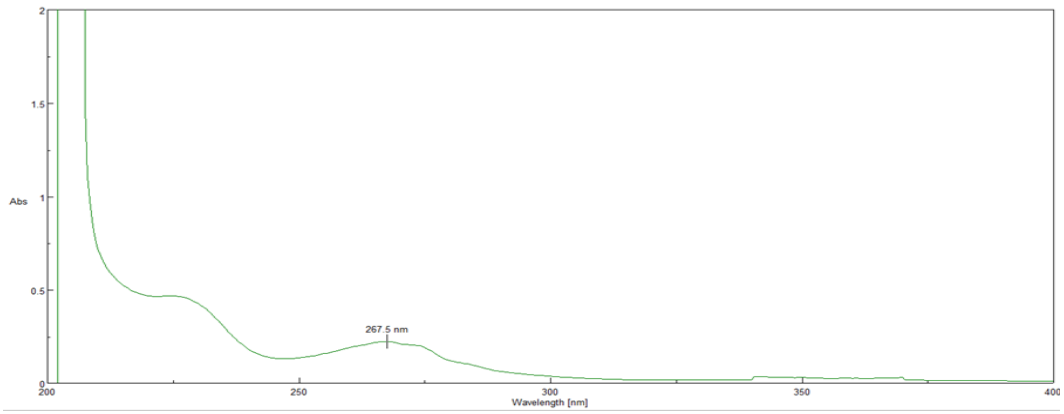

Figure UV spectra of pioglitazone hydrochloride in methanol.

FT-IR Spectroscopy :

Sr. No	Reported IR peak of pioglitazone hydrochloride (cm^{-1})	Description	Observed IR peak of pioglitazone hydrochloride (cm^{-1})
1	3100-3500	N-H Stretching	3425.69
2	3000-3100	Ar-CH Stretching	2955.04
3	1670-1820	C=O Stretching	1689.70
4	1400-1600	C=C stretching	1612.54
5	1050-1150	C-O Stretching	1242
6	1080-1360	C-N Stretching	1319.35
7	1600-1800	C=N Stretching	1743.71
8	700-750	C-S Stretching	717.54
9	800-900	Cl	848.71

Reported IR peak of pioglitazone hydrochloride & Observed IR peaks of pioglitazone hydrochloride showed in table.

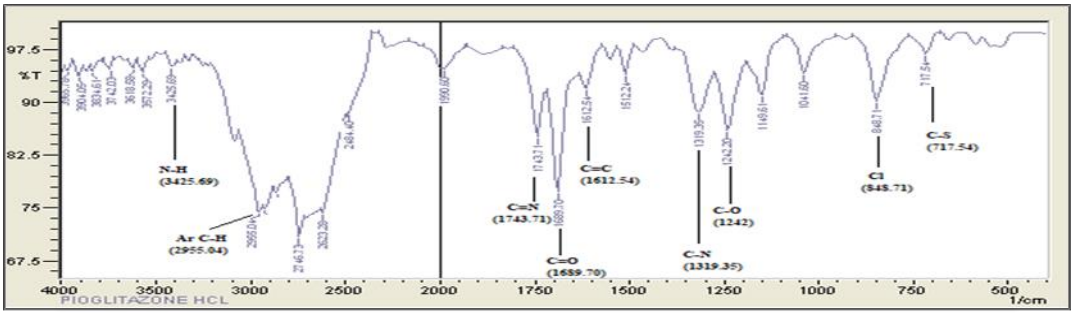

Figure FT-IR spectrum of pioglitazone HCl.

Differential scanning calorimetry (DSC) studies of Pioglitazone HCl :

DSC thermogram for Pioglitazone HCl showed melting point at 200.06 ^{0}C. Show in **figure**

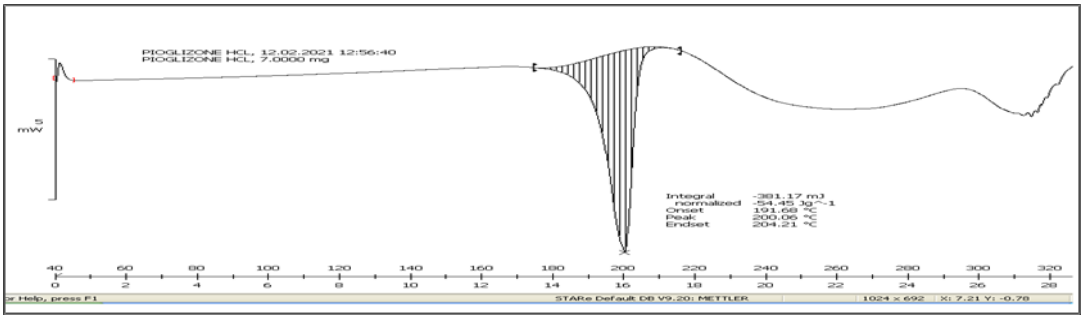

Figure DSC thermogram of Pioglitazone HCl.

Calibration curve of pioglitazone HCl by using UV spectrophotometer

Calibration curve of pioglitazone HCl in methanol

The alignment bend of pioglitazone HCl was ready in methanol. Table shows the various grouping of pioglitazone HCl with their respective absorbance at λ max 267.5 nm and figure 7.4 shows the alignment bend with regression coefficient 0.998, slope 0.02. the result indicate that there is a direct relationship between fixation (0,2,4,6,8,10µg/ml) and absorbance.

Table Data for calibration curve of pioglitazone HCl in methanol.

Sr. No.	Concentration (µg/ml)	Absorbance at 267.5 nm
1	0	0
2	2	0.0608
3	4	0.1200
4	6	0.1685
5	8	0.2229
6	10	0.2705

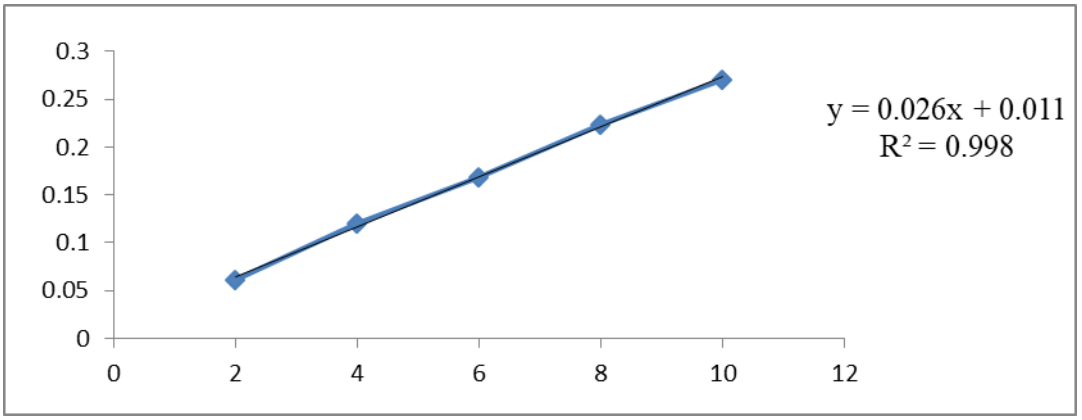

Figure Calibration curve of pioglitazone HCl in methanol.

Co-former characterization

NICOTINAMIDE

Description

The sample of nicotinamide is white crystalline powder that complies with IP. Vitamin B3 comes as nicotinamide, also known as niacinamide, which is used as a pharmaceutical and healthful supplement.

IR spectroscopy

Table Reported and observed IR peck of nicotinamide

Sr. No.	Reported IR peak (cm^{-1})	Description	Observed peck (cm^{-1})
1	3300-3500	-NH Stretching	3363.97
2	1080-1360	C-N Stretching	1396.51
3	1600-1700	C=N Stretching	1681.56
4	1600-1690	C=O Stretching	1620.26

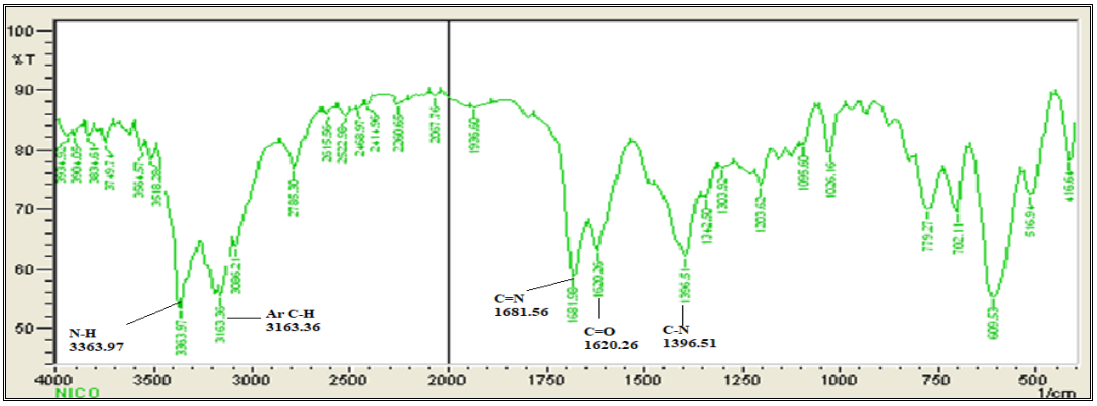

Figure FT-IR spectrum of nicotinamide.

Differential scanning calorimetry

The DSC thermogram of nicotinamide shows the melting point at 131.99^{0}C. showed in figure

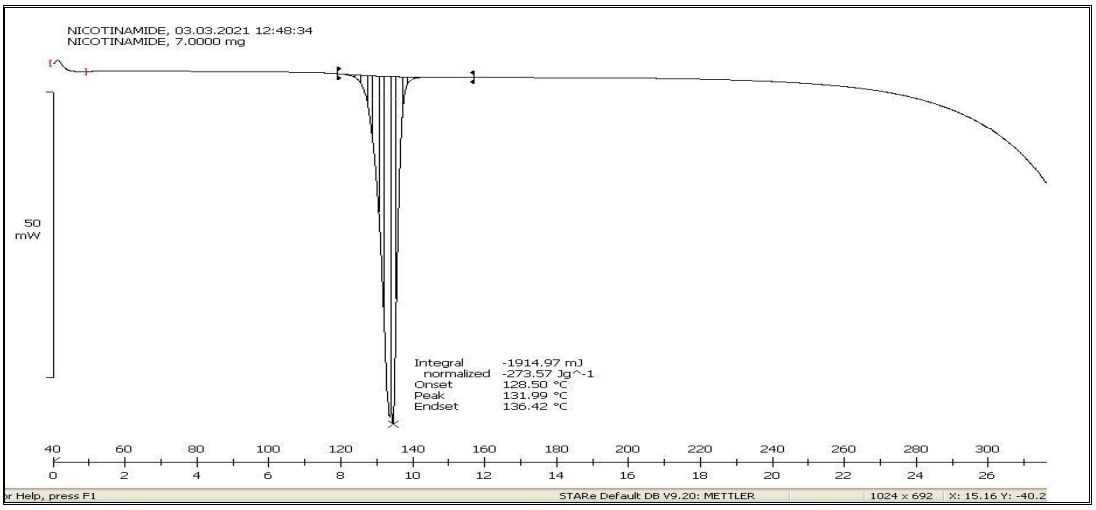

Figure DSC thermogram of nicotinamide

Drug-coformer interaction/compatibility study

The purpose of the drug coformer compatibility studies was to verify the drug's compatibility with the coformer that would be used to generate the co-crystal. The majority of these investigations are FTIR studies.

FT-IR spectroscopy

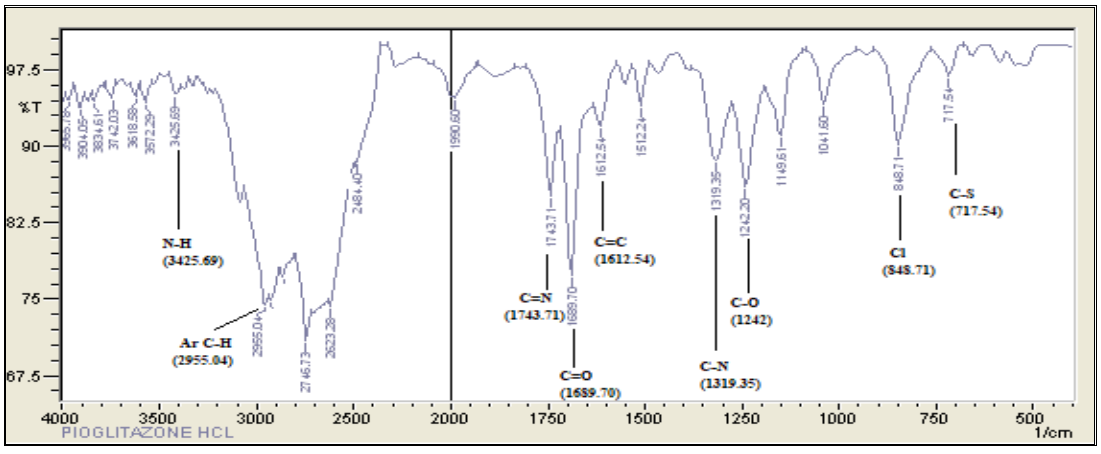

Figure FT-IR spectrum of plain pioglitazone HCl.

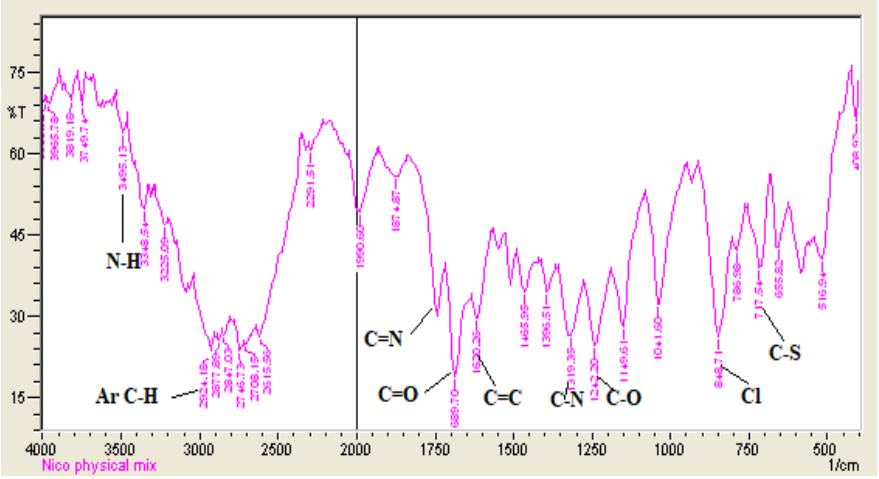

Figure FT-IR spectrum of drug and coformer.

There is no chemical interaction between the medication and coformer because the physical combination of pioglitazone hydrochloride and nicotinamide preserved the entire pioglitazone hydrochloride absorption peak.

Characterization of co-crystal

Fourier transform infrared (FT-IR) spectroscopy

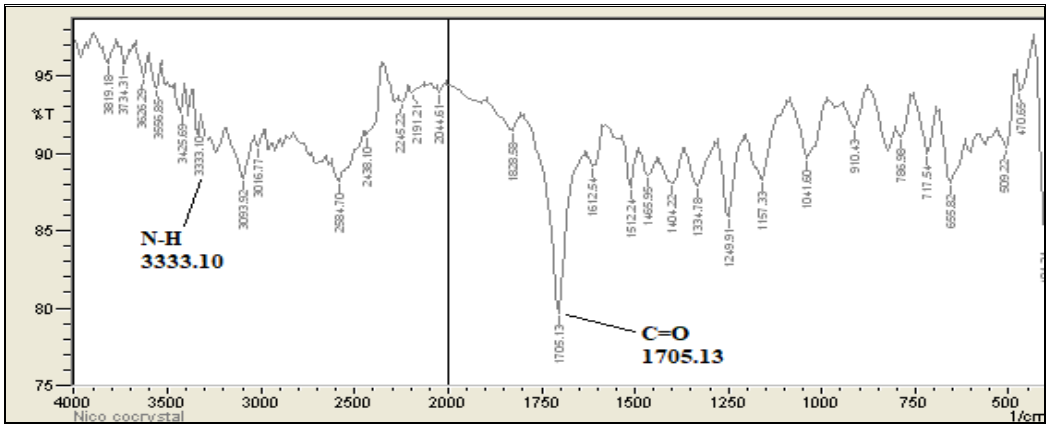

Figure FT-IR spectrum of PGZ:NTM co-crystal

The PGZ co-crystal's infrared spectroscopy revealed a clear change in the drug's absorption peaks. A shift of 3333.10 cm-1 was discovered to be the typical peak for -NH vibration at 3425.69 cm-1, while a shift of 1705.13 cm-1 was determined to be the peak due to C=O stretching at 1659.70 cm-1. The co-crystal spectrum was found to lack the band range of 1605 to 1593 cm-1, which is indicative for -NH deformation and was seen in the PGZ drug spectra at band at 1743.71 cm-1.

Differential Scanning Calorimetry

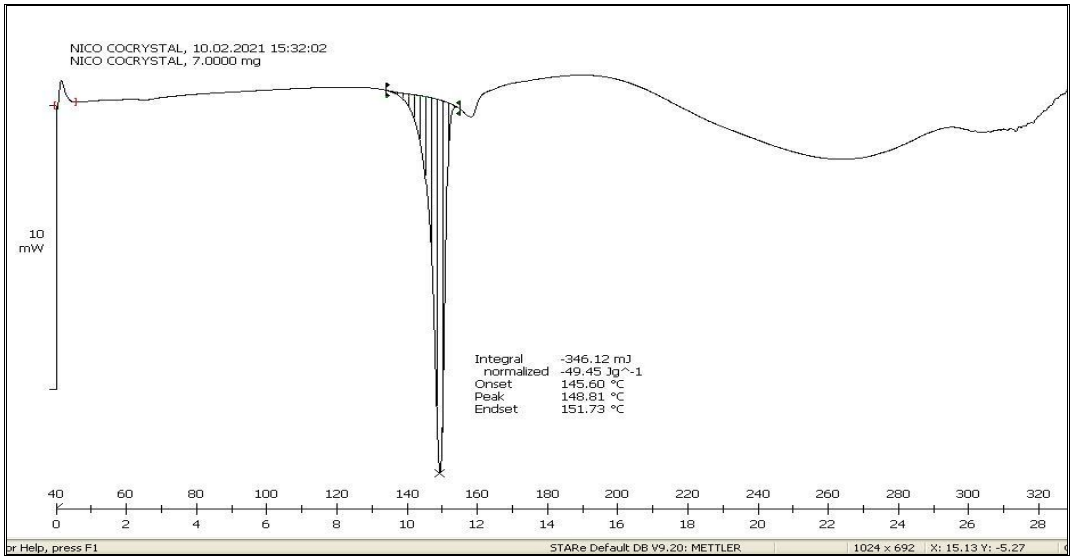

Figure DSC thermogram of PGZ:NTM co-crystal.

The co-crystal's DSC thermogram showed a melting endotherm at 148.81^{0}C. There was not another peak seen. Therefore, there is no chemical interaction between nicotinamide and pioglitazone HCl;

X-ray diffraction

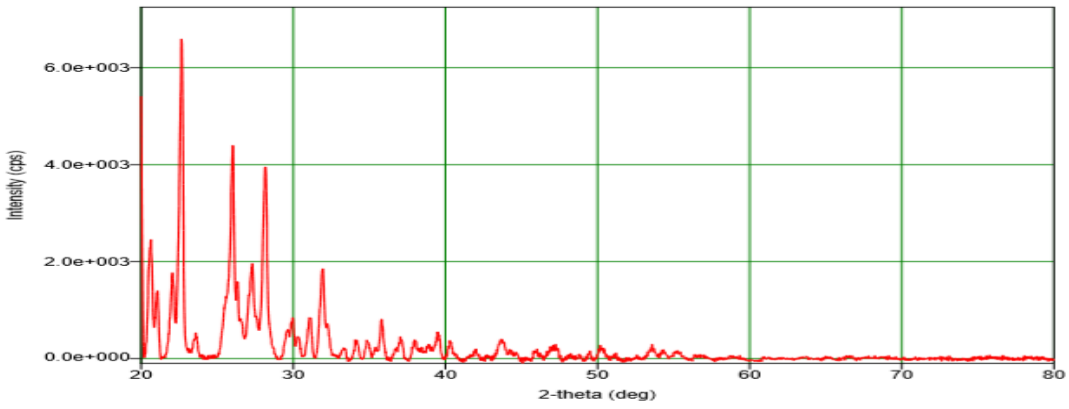

Figure X-ray diffraction pattern of Pioglitazone Hydrochloride.

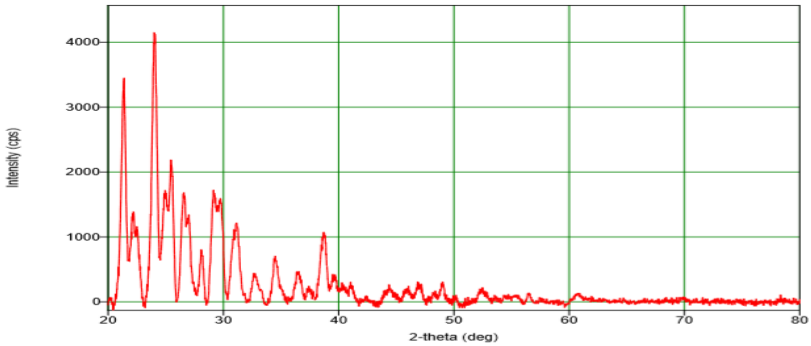

Figure X-ray diffraction pattern of PGZ:NTM co-crystal.

This is the main method of inquiry used to verify the occurrence of a new crystalline phase. Every molecule has a unique XRD pattern, sometimes referred to as its fingerprint. As a result, this method is highly helpful for identifying newly created crystalline phases. As a result, the XRD pattern changes as a new crystalline phase forms. The experimental section contains a description of the procedure. The PGZ and PGZ cocrystals' PXRD pattern is shown in Figures 8.9 and 8.10. The pure PGZ's PXRD pattern showed distinctive diffraction lines at 19.98, 20.62, 21.05, 22.11, 22.69, 23.62, 25.65, 26.02, 26.33, 26.57, and 27.30 to 2θ values. With 2θ values at 21.36, 22.12, 22.55, 24.03, 24.94, 25.51, 26.48, 26.91, 28.10, 29.15, 29.72, and 31.08, the PGZ:NTM revealed multiple distinct interference peaks that differed from the PGZ and coformers used. This indicates that the newly formed solid phases are pure. The creation of new solid phases is confirmed by the appearance of the distinctive peaks of the coformers and PGZ and the new characteristic diffraction peaks.

Evaluation of co-crystal

Solubility analysis

The solubility analysis of all prepare co-crystal are given in table.

Table solubility and increased ratio of prepared co-crystal system.

Co-crystal system	Method	Solubility (mg/ml)	Increased ratio (fold)
PGZ	-	0.00278 ± 0.0023	-
PGZ:NTM	Solvent evaporation	0.029 ± 0.011	10.60 Fold
PGZ:NTM	Liquid assisted grinding	0.0814 ± 0.023	29.30 Fold
PGZ:BZA	Solvent evaporation	0.0122 ± 0.0026	4.39 Fold
PGZ:BZA	Liquid assisted grinding	0.01463 ±0.00012	5.26 Fold
PGZ:SUA	Liquid assisted grinding	0.0076 ± 0.0025	2.73 Fold
PGZ:SAA	Liquid assisted grinding	0.0086 ± 0.003	2.82 Fold
PGZ:HPA	Liquid assisted grinding	0.0264 ± 0.0012	9.52 Fold

Solubility study of Pioglitazone HCl with nicotinamide, benzyl alcohol, Salicylic acid and Hippuric acid cocrystal resulted in increase in solubility.

Dissolution study of co-crystal

The accompanying table 4.5 reports the results of comparing the drug's dissolution from co-crystal with that of the drug alone and in 0.1N HCl. The ensuing results made it abundantly evident that there had been a notable rise in the solubility of nicotinamide and pioglitazone HCl as a result of the drug's co-crystallization and total prevention of dihydrate formation.

Sr.No.	Time (min)	% cumulative release	
		Plain drug	PGZ:NTM co-crystal
0	0	0	0
1	5	18.51(±0.04)	42.64(±0.03)
2	10	19.00(±0.03)	54.38(±0.03)
3	15	20.30(±0.05)	57.86(±0.07)
4	20	20.88(±0.05)	63.67(±0.06)
5	25	28.54(±0.06)	80.23(±0.04)
6	30	38.83(±0.04)	92.56(±0.04)

Table 4.5 % Cumulative release of plain drug and PGZ:NTM co-crystal

From above data it was concluded that co-crystal showed more dissolution enhancement than plain drug. The composition of co-crystal where PGZ:NTM were in proportion 1:1 exhibit superior dissolution profile. Hence these composition were selected for immediate release tablet preparation in further study.

Conclusion

Utilizing nicotinamide as a co-former and the solvent drop and solvent evaporation methods, co-crystals of pioglitazone HCl were produced. The produced co-crystal was examined using IR spectroscopy, DSC analysis, X-ray diffraction analysis, and dissolution analysis. Due to total prevention of dyhydrate formation, co-crystal formation produced the anticipated improvement in dissolving.

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