ISSN: 2755-6328

Research Article

Open Access Journal of Pharmaceutical Sciences and Drugs

Solid-State Screening and Development of Ranolazine Polymorph under different Conditions

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Received: May 20, 2025; **Accepted:** May 29, 2025; **Published:** June 04, 2025

ABSTRACT

Purpose: The study sought to determine whether a polymorphism of RNZ could enhance the medication's water solubility and permeability.

Methods: Pure drugs (RNZ) were reconstituted from different solvents in order to determine the influence of the solvents, and the resulting crystals were examined for infrared. By maintaining RNZ crystal at 0°C, 40°C, as well as 70°C with 75% relative humidity, the effects of moisture and temperature were ascertained. The crystals were then examined for infrared changes in the RNZ polymorph, which was produced using the solvent evaporation process. Utilizing FT-IR, DSC, XRD, and POM, the enhanced polymorph was characterized chemically and physically. The effects of crystalline on the moisture and temperature on crystalline phases were investigated, as well as the solubility of crystal shapes in water.

Results: When comparing the data from the DSC thermograms of a pure medication (RNZ) and a polymorph, one endothermic peak was It is located at 122°C and has been observed. There was no sign of a glass transition or a presence of any kind of crystallization in this spectrum. The polymorph that has been recrystallized from ethanol showed only one endothermic peak at 137 °C in its DSC thermogram. The diffraction lines of a drug of pure substance (RNZ) matched those of the polymorph, per the XRD analysis. FT-IR confirmed that the solvents employed to purify RNZ showed variations in the crystal lattice.

Conclusion: There were variations within the crystal lattice of the solvents employed to purify RNZ. Examining the variables influencing RNZ polymorphic transition was fascinating. For form II, the change was observed at RH=75% (±5), but both forms demonstrated dependability at varying ambient temperatures.

Keywords: Furious Transfer Infra-Red Spectroscopy, Differential Scanning Calorimeter, X-ray Diffraction, Polymorph, Solubility and Polarized Optical Microscopy

Abbreviations

CYP	:	Cytochrome
RNZ	:	RNZ

Introduction

RNZ inhibit potassium and sodium channel blockers, and it acts as an Antianginal drug [1]. Because of poor bioavailability of verbal medications (35 to 50 percent), the pharmacokinetic profile of oral medicine administration is tiny and unpredictable. It is pretty beneficial because of its short half-life (between 2 and 6 hrs), high clearance (more than 70%), and efficient hepatic first-pass cytochrome P-450 3A (CYP3A) metabolism and cytochrome CYP2D. RNZ is designated as a Class II drug by the Biopharmaceutics Classification System (BCS), signifying that it has minimal solubility and permeability [2]. RNZ plasma concentrations are extremely unpleasant and fluctuate after oral therapy, according to published studies [3,4]. Therefore, it is necessary to improve RNZ solubility, oral bioavailability, permeability, and dissolution rate [5].

Scientists created and carried out a few mixtures to increase the permeability and solubility of RNZ, in line with the information they presented in earlier study articles. This contains floating

Citation: Sunita Vaidya, Surendra Agrawal, Pranita Jirvankar, Sandip Sonavane. Solid-State Screening and Development of Ranolazine Polymorph under different Conditions. Open Access J Pharma Sci and Drug. 2025. 1(1): 1-7. DOI: doi.org/10.61440/OAJPSD.2025.v1.06

microspheres and tablets with a longer release time. After carefully reviewing these research publications, it was found that the researchers simply decreased the frequency of dose increases and enhanced patient compliance without investigating the solubility, permeation, or systematic evaluation of RNZ [6,7]. We used a new and suitable formulation process and/or approach to address this important issue and enhance RNZ's solubility and bio permeability. The Greek terms poly (many) with morph (shape) are the roots of the word polymorphism. The capacity of a substance to function in a minimum of two crystal phases with different the molecular configuration or just configurations inside a crystal lattice is so defined.

It basically means that the same molecule occurs in different polymorphs in distinct ways. It is referred for as packing polymorphism if the difference results from packing, and conformational polymorphism if it results from conformational changes [8]. Polymorphism causes molecules to have diverse configurations in the unit cell of their crystal, resulting in variable physical properties [9]. The polymorphism of drugs has been an important issue in the pharmaceutical industry [10]. The interior solid-state structure of polymorphic forms varies, despite their similar chemical content. Varied polymorphic forms of a medicinal ingredient might have varied aqueous solubility; these include dissolution rates, melting temperatures, physicochemical stability, and a host of other properties. Drug compounds in polymorphic form have different internal solid-state structures but the same chemical structure. Because crucial characteristics like solubility as well as drug stability rely on the solid-state structures, it is imperative and required that polymorphic drug forms be systematically evaluated and characterized. Different crystalline forms or solvates may be produced by varying the crystallization conditions (temperature, pressure, concentration, rate of crystallization, seeding of the crystallization medium, presence and concentration of impurities, etc) [11]. Polymorphism is a major occurrence in the pharmaceutical sciences since it can affect a wide range of API properties such as flowability, tableting, dissolving rate, solubility, stability and even biological performance such as efficacy and toxicity [12]. The literature contains a number of examples demonstrating how physical layout affects different physicochemical and biological characteristics of drugs and excipients. For instance, Wille et al. discovered six varieties of cocoa butter, every single with a notably distinct melting point. As a result, for the creation of formulations based on this excipient, selecting a specific polymorphic form and, avoiding intervention is critical [11]. According to Poornima et al., solid form A, which was acquired using the antisolvent approach, underwent a solid-solid change from Form I to Form II, whereas the generated Pioglitazone hydrochloride polymorph, which was exists in Form I of PGH and formed crystals using chilling and solvent evaporation processes. The dissolution rate is improved [13]. Two polymorphs containing caffeine-glutaric acid, [l]Form I and Form II, were created by Thakuria et al. and dissociated under controlled humidity. Taking into account this degree of knowledge, there are currently substantial regulatory concerns about the physicochemical characteristics, stability and product performance of pharmaceuticals that are susceptible to polymorphism [14]. As a "proof-of-concept" effort, the current study examines the potential. Making a polymorph to improve the permeability and solubility of RNZ RNZ polymorphs were produced via the solvent evaporation method. The fully manufactured polymorph was characterized using FT-IR, DSC, XRD, as well as polarized optical microscopy.

Materials and Methods

Materials

A bulk drug with a purity of more than 99.86 percent was supplied by RNZ Jubilant Life Sciences Ltd., located in Noida. and the laboratory produced the RNZ polymorph. Potassium dihydrogen phosphate, ethanol, methanol, isopropanol, acetonitrile, and dimethyl formamide were supplied by Loba Chemicals Pvt. Ltd., located in Mumbai, India. Liquid paraffin and other extra materials were supplied by Lodha Group (Mumbai).

Methods (Preparation of RNZ Polymorphism)

Solvent evaporation techniques were used to create the RNZ polymorph [8]. The form of crystalline powder of the natural medication for RNZ was dissolved with various solvent, such as dimethyl formamide, methanol, ethanol, isopropanol, isopropanol + water, methanol + water (8:2), and so forth, although being continuously agitated to complete all of the crystallization. Methanol, ethanol, isopropanol+water, methanol + water (8:2), and isopropanol dimethyl formamide RNZ was crystallized independently. The solvent was evaporated for 72 hours in three distinct conditions: at ambient temperature, at 70°C, and under vacuum. The crystals were gathered and stored at room temperature in amber glass bottles covering silica pellets in desiccators. Since these crystals' melting points were discovered to be between 120 and 122°C, an FT-IR spectra were not obtained for them. The crystals were gathered and stored at room temperature in amber glass containers under silica pellets in desiccators. Since these crystals' melting points were discovered to be between 120 and 122°C, an FT-IR spectra were not obtained for these compounds. Tiny amounts of the two solvents crystals were extracted, and their melting points and FT-IR analyses were performed.

Physico-chemical Characterization of RNZ Polymorph

Fourier-Transform Infrared Spectroscopy

An FT-IR spectrophotometer was used to investigate and comprehend the molecular-level cooperation between functional groups between RNZ and polymorph samples (Model:8400S Shimadzu Corporation, Kyoto, Japan). In summary, 2% of the collected specimen of isolates was ground in a mortar and pestle using FT-IR-grade potassium bromide to create the disc used for the FT-IR analysis. Each combination was compressed into thin, uniform, clear discs using a small hand presses equipment (Shimadzu, Kyoto, Japan, MHP-1, P/N-200-66747-91). According to previously published literature, an analytical technique was used [15].

Differential Scanning Calorimetry

Applying the differential scanning calorimeter (Model: DSC2920 TA apparatus) as well as a method that our teams have previously documented. Parts of the formulation, including RNZ and polymorph, were assessed to look into their performance and thermal interaction [16]. Individual specimens Two milligrams were carefully weighed and placed in an aluminum skillet fitted with a covertube bender, as shown below. After being weighed, the samples were placed inside the DSC apparatus, which had already been calibrated for heat flow and carrying capacity

using standard indium. to remove any impact caused by retained moisture. Dried nitrogen gas was consistently pumped into the specimen-analyzing compartment during an amount about 50 mL/min (N2). The temperature range that was investigated was 100 to 150 °C. Six degrees Celsius each minute was the rate at which the samples were heated. The equipment's software reads DSC thermograms including the associated heating settings.

X-ray diffraction

The crystalline performance of the RNZ and polymorph was investigated using an x-ray diffractometer (model: PW 1729) in terms of their XRD spectra. (The methodology outlined in the literature for sample preparation, analysis, and spectrum interpretation was strictly adhered to [17].

Polarized Optical Microscopy

On a microscopic slide, a little quantity of RNZ as well as its polymorph was preserved for observation at a 10x magnification. Nikon ECLIPSE LV100N polarizing microscope plus Nikon DS-Fi2 camera as well as analyzer software (model: Nikon Corporation, Japan) was used to view and capture the polarized light image at room temperature. The polarized light picture is uniformly black when a solid crystalline structure isn't present [18].

Solubility Study of Crystalline Forms in Water

Separately, 50 mg of the RNZ bulk medication and 50 mg of the polymorph were mixed together in 25 ml water in a 50 ml volumetric flask. For 30 minutes, a glass rod was used to physically dissolve the crystal in water. After an hour using a sonicator (model: Sonicator-5L50, PCI, Mumbai, India), the flasks were refilled with water to reach the proper volume. The resulting solution was filtered and the amount of dissolved drug was determined by diluting the filtered solution with water in order to get the concentration of 100µg/ml by UV-Vi's spectrophotometer (Model: UV 2401 PC Shimadzu Corporation, Kyoto, Japan) at 226 nm [19].

Impact of Humidity and Crystallization Temperature on the Crystalline Formations

For a month, polymorph was kept in an oven at 0°C, 70°C, and 40°C, respectively. Each sample was taken in small quantities and subjected to FT-IR analysis. (model: Shimadzu Corporation, Kyoto, Japan; FT-IR 8400S).

Humidity's Impact on Crystal Formations

By maintaining the polymorph between a room temperature as well as at a humidity level of 75%, the impact of relative moisture on crystalline stability was researched. Small quantities of every sample were evaluated with time using FT-IR (model: FTIR-8400S, Shimadzu Corporation, Kyoto, Japan).

Results and Discussion

Preparation of RNZ Polymorphism

The purifying and crystal-forming process is called crystallization. One of the many factors influencing the final crystal shape is the kind of solvent used. Dimethyl formamide, methanol, ethanol, isopropanol, isopropanol+water, as well as methanol + water (8:2) combined all used separately to crystallize the RNZ bulk drug. These solvents were selected in light of the literature review, which showed that they were employed to purify RNZ throughout the synthesis process. Following trial-and-error recrystallization in various solvents, the crystals were created, and they were then evaporated at ambient temperature, at 70°C, or under vacuum. The crystal produced by evaporating ethanol at 70°C had the melting point of 138°C, that was less than the initial melting point. The endothermic peak found in the DSC spectra of the original medication (MP. 122°C) as well as derivative polymorph (MP. 137°C) further supported it. It was also discovered that the morphological behavior of these crystals, as determined by an imaging device at 400X magnification, differed from that of the RNZ bulk drug. Changes in the flexing and stretching frequency of absorption of numerous peaks were visible in the same infrared spectrum. Changes in the polymorph's crystal structure are also supported by the development of certain new bands as well as the removal of some old bands. Comparing the polymorph to the bulk medication, the X-ray diffractogram showed similar alterations. In contrast to the proposed RNZ large medication, crystals produced via evaporation from various Solvents didn't exhibit any modifications to the morphological behavior or melting point any changes in melting point or morphological behavior. Similar to the RNZ bulk medication, the infrared spectra showed a similar number and strength of peaks.

The compound's crystal shape did not alter upon recrystallization from the aforementioned solvents under vacuum.

Fourier-Transform Infrared Spectroscopy

The interaction of the function groups of several distinct RNZ and polymorph components is confirmed by the FT-IR analysis. FT-IR spectroscopy was utilized to evaluate the RNZ bulk medication and its polymorph. Among the most widely used methods for clarifying crystalline polymorphism The FT-IR spectra of the bulk substance RNZ and its RNZ polymorph are displayed in Figures No. 1 and 2. cm-1 is the unit of measurement. In the FT-IR spectrum, the RNZ groups with functions showed distinctive bands. FT-IR spectra recorded on pure drug (RNZ), polymorph, and those acquired under various conditions were examined and compared. The proposed vibrations of the molecule's different functional groups are contrasted with the observed wave number. depicted in Figure No. 1. N-H stretching, chemically aromatic C-H stretching, asymmetric aliphatic C-H stretching, symmetric aliphatic C-H stretching, coupled vibration from CO stretching, aromatic C+C stretching, and C-H def. scissoring are all depicted by the absorption peaks at 3367.48, 3049.25, 2929.67, 2862.17, 1704.96, 1541.02, and 1444.58. N-H deformation, scissoring of the C-H bend, C-O-C stretching, C-H bend (wagging or twisting), rocking, and secondary N-H stretching are all represented by the absorption peaks shown at 3330.84, 1685.67, 1591.16, 1463.87, 1330.79, 1124.42, and 742.54 in Fig. No. 2. It shows that tiny variations in wave number result in distinct chemical and physical characteristics, which suggests a separate RNZ polymorph. Illustrations 1, 2, 3, 4, 5, 6, and 7 It shows the N-H stretching bonding at 3328.91 cm-1 for the bulk medication, which changed to 3334.69 cm-1 after a month of polymorph storage at 70°C. For numerous summits, similar alterations were noted under these circumstances. Some bonds vanished, while others new bonds were even noticed. Under the same circumstances, the signal's strength also altered. When a bulk medication is recrystallized utilising isopropanol along with different solvents, the FT-IR spectra fails to support the development of polymorph.

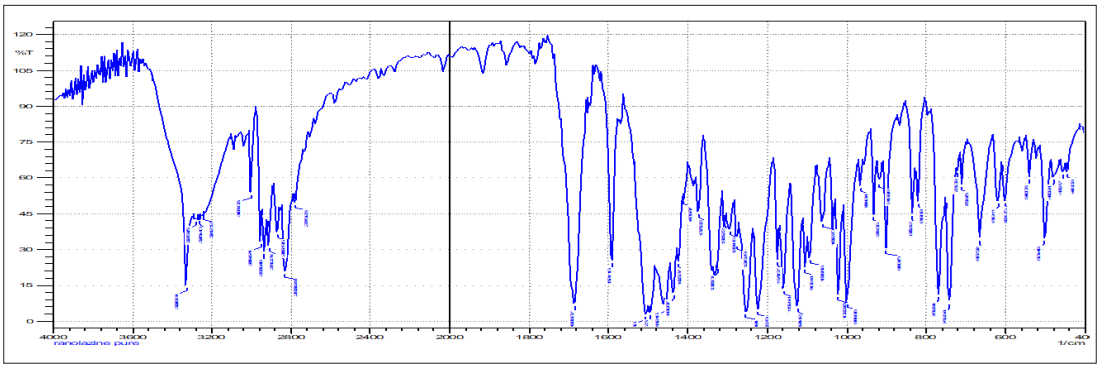

Figure 1: FT-IR spectrum of RNZ bulk drug

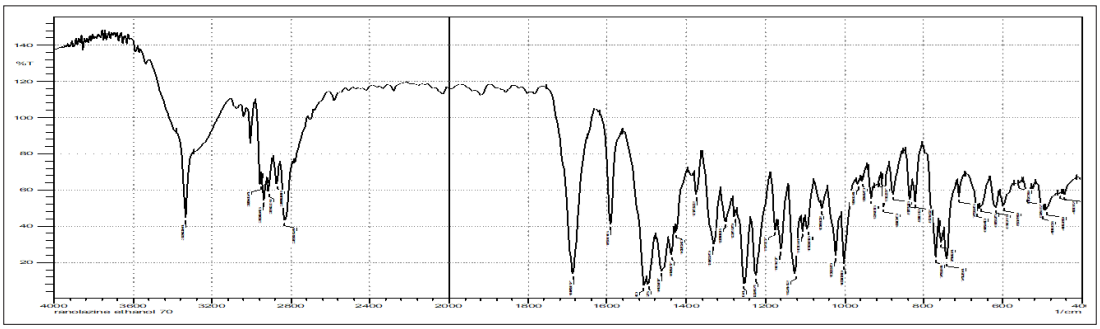

Figure 2: FT-IR spectrum of RNZ recrystallized from ethanol (at 700C)

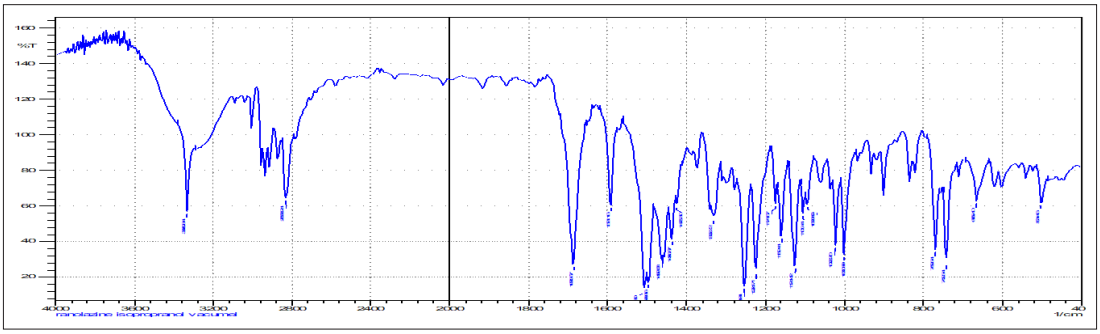

Figure 3: FT-IR spectrum of RNZ recrystallized from isopropanol (under vacuum)

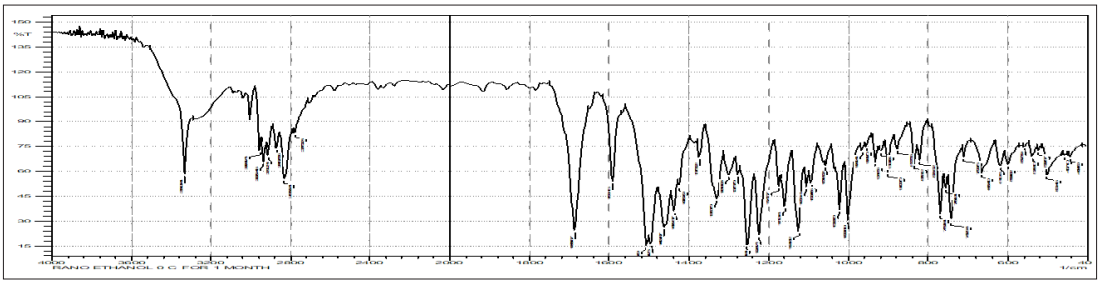

Figure 4: FTIR spectrum of RNZ after thermal study (1 month, 0°C)

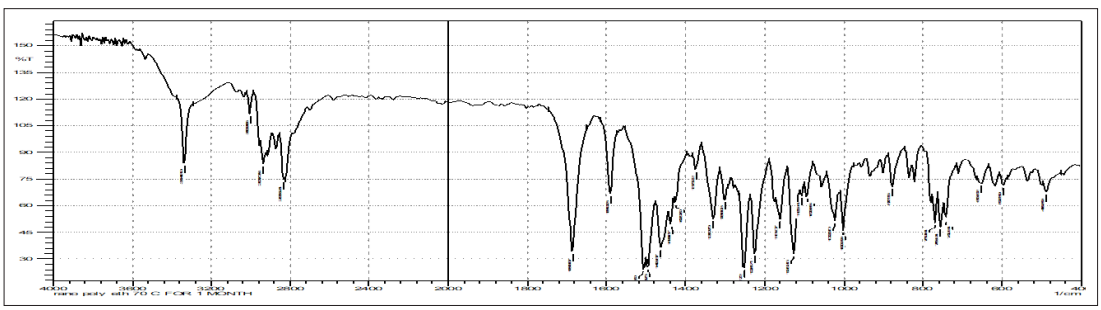

Figure 5: FTIR spectrum of RNZ after thermal study (1 month, 70°C)

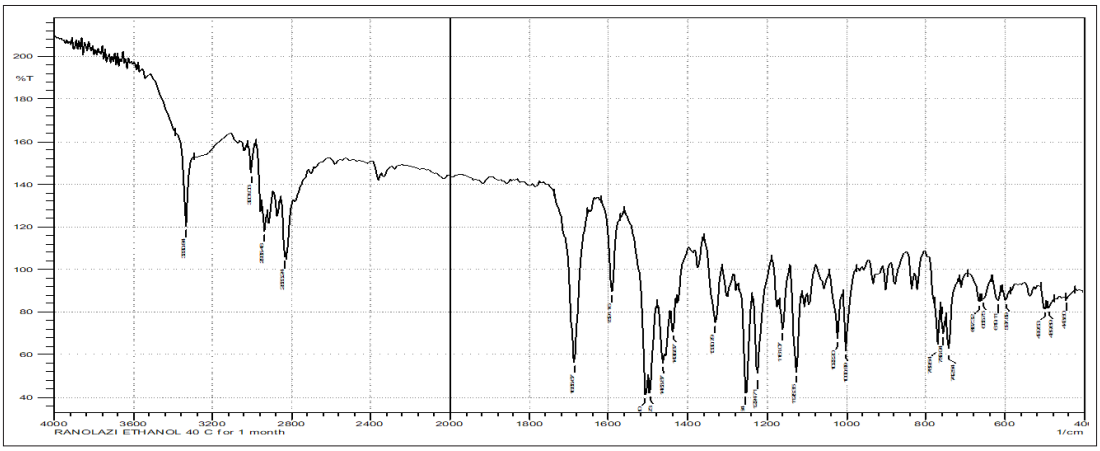

Figure 6: FTIR spectrum of RNZ after thermal study (1 month, 40ºC)

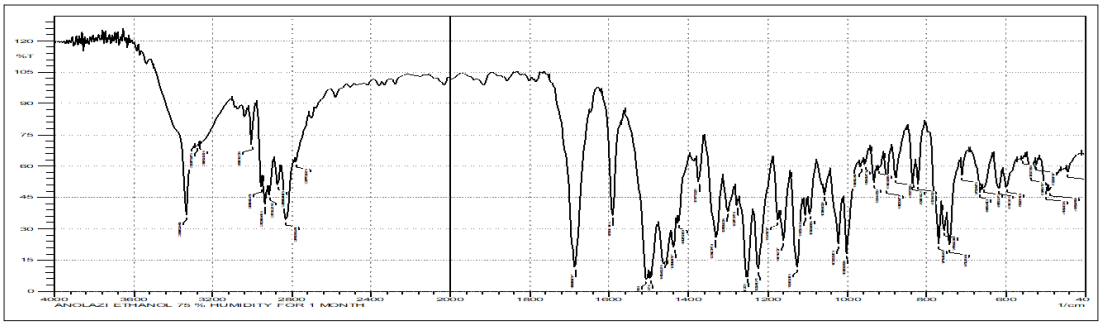

Figure 7: FT-IR spectral analysis of RNZ after humidity study (1 month, RH75% RH)

Differential Scanning Calorimetry

DSC was used to examine the thermal properties of the pure drugs RNZ and Polymorph. Figures 8 and 9 display the DSC thermograph corresponding to the RNZ bulk medication and its polymorph. RNZ's DSC thermograph displays an extensive endothermic symmetric peak around 122.15 0C, that represents the point of melting of the bulk drug, after an initial evaporation of moisture traces. A glass transition has not been observed. The enthalpy in fusion (H) for this peak was determined to be -79.55J/g. The RNZ changing from crystalline into anhydrous could be the cause of this. Prior research findings provided significant support for the conclusions. The RNZ polymorph's DSC thermograph showed a prominent endothermic peak around 124.13 0C, indicating that the polymorph's crystal lattice differs from the bulk drugs. It is evident from this peak's observed enthalpy of fusion of -79.26J/g that the solvent significantly affects the drug's crystallization behavior.

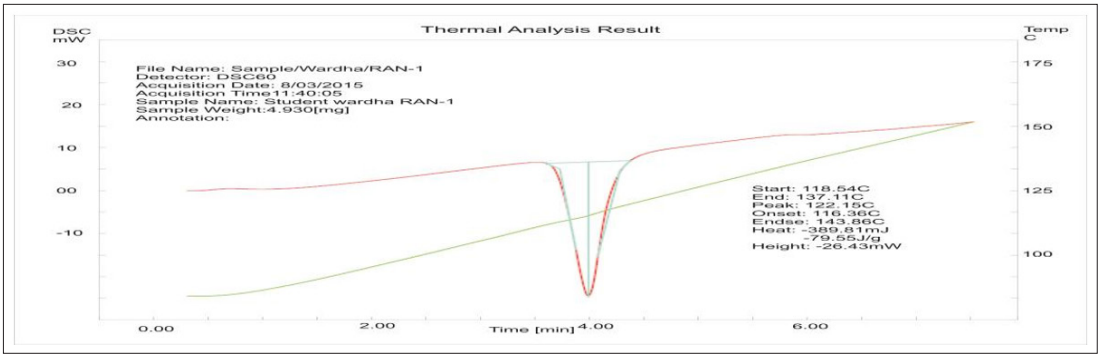

Figure 8: DSC thermogram of RNZ bulk drug

X-ray Diffraction

The X-ray diffraction findings were in agreement with the crystal shape of the medication and its polymorph. Figure. The diffractogram spectra with bulk drug RNZ as well as its polymorph are shown on a 2¸ scale in Figures 10 and 11. A number of sharp-pointed peaks were visible at different points in the diffractogram.On a scale of 36.4293, 37.4438, 38.5660, 39.7772, 43.7021, 45.3993, and 47.7750, a 2¸ of bulk medication RNZ indicates crystalline nature. The RNZ polymorph of the XRD spectrum (Fig. 11) Diffractograms showed a number of peaks in various places. At 21.4546, 22.2888, 23.3152, 23.9420, 24.4443, 25.2896, 26.2741, 28.0017, 29.9764, 32.1484, and 47.6275 on a 2¸ scale, both the RNZ and polymorph diffractograms show that the bulk medication is crystalline. The drug's diffractogram saw a substantial alteration. In addition, the position and intensity of the diffractions vary. It is determined whether the drug as well as its polymorph both crystalline in nature based on the amount and power of diffractions

as well as well-resolved lines on both diffractograms. The ray diffraction patterns of these compounds are crystalline in nature. The X-ray diffraction patterns of these elements are shown in Figures 9 and 10. It showed clear lines of diffraction from 0 to 30 degrees (2Θ).

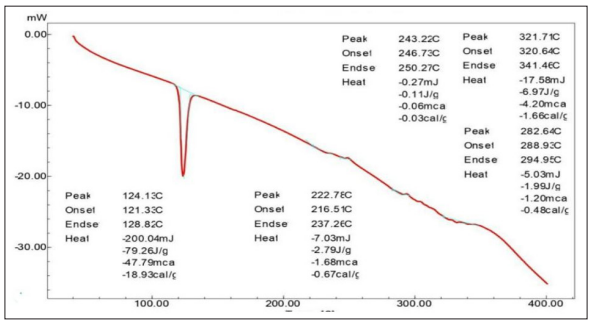

Figure 9: DSC thermogram of RNZ polymorph

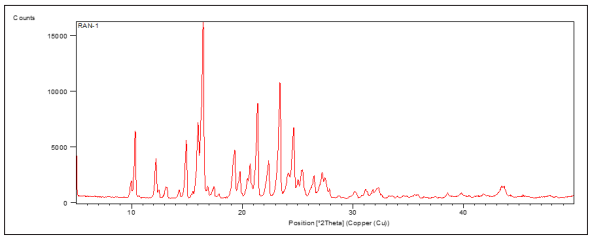

Figure 10: XRD diffractogram of RNZ bulk drug

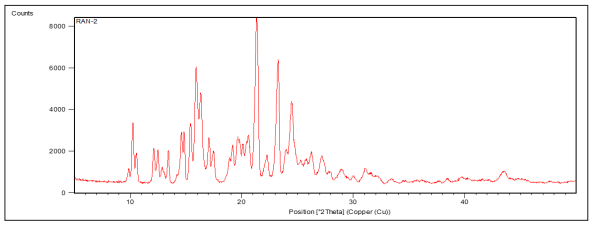

Figure 11: XRD diffractogram of RNZ polymorph

Polarized Optical Microscopy

A POM analysis was used to characterize RNZ and polymorph. If there is no crystal-like structure present, the POM image is completely black. POM images may be utilized to identify the presence of crystals. Crystals were discovered in the POM images displayed in Figures No. 12 and 13. The imaging device at 10X magnification was used to determine the structure of the RNZ bulk medication and its polymorph. On the other hand, the POM picture and visual observations revealed a variety of crystals among polymorphs, which is supported by the POM analysis results.

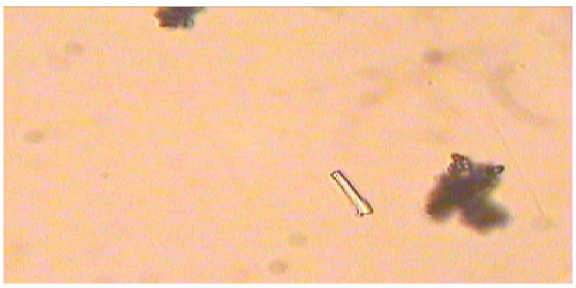

Figure 12: Crystal shape of RNZ bulk drug

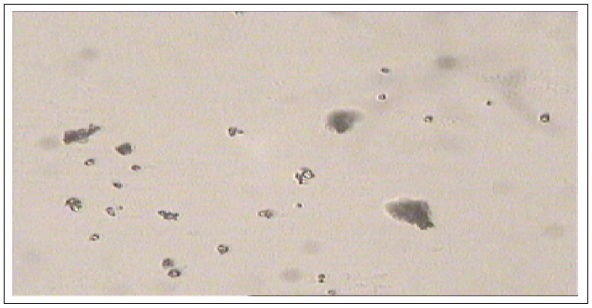

Figure 13: Crystal shape of RNZ polymorph

Solubility Study of Crystalline Forms in Water

Table No. 1 The RNZ polymorph and the bulk drug RNZ's water solubility study are shown. Because of its low solubility as well as the high permeability profile of the BCS Class II category, pure RNZ was found to have a water solubility of around 0.1288 ± 2.23608 mg/ml. Higher soluble in water and a larger solubility range of 0.1506± 2.23606 mg/ml were noted for the RNZ polymorph. RNZ's water solubility can be improved by the polymorph as well as the drug's amorphous state in its carrier.

Table 1: Solubility of RNZ crystalline forms in water

Sr. No.	Sample	Solubility*(mg/ml)
1.	RNZ	0.1288 ± 2.23608
2.	RNZ Polymorph	0.1506± 2.23606

*Values are represented as mean ± S. D., (n = 3)

Effect of Temperature on Crystalline Form

Thermal transformations must be evaluated in order to be evaluated, polymorph of RNZ was kept in an oven at 0oC, 40oC and 70oC for a month. Their thermal stability was determined by melting point and FT-IR spectroscopy. The melting point determined by the capillary method (136oC) did not reveal any difference from the melting point of the prepared polymorph. FT-IR spectrum.

Effect of Relative Humidity on the Crystalline Form

This study was place in a specified setting with a specific relative humidity. RH= 75% (±5). The appearance of polymorph was noted on FT-IR spectrum after one month. RNZ is exposed to variable humidity conditions to form monohydrate, but no significant effect was observed in the IR spectrum of polymorph when stored at 75% (±5).

Conclusion

Physicochemical characterization by FT-IR spectroscopy, DSC, XRD and POM enabled differentiation of RNZ bulk drug and its prepared polymorph. The solvents used for the purification of RNZ exhibited differences in the crystal lattice as supported by FT-IR, DSC and XRD study. It was fascinating to look into the elements that influence RNZ polymorphism transformation. Transformation was noted at RH=75% (±5) for form II while both the formed showed stability at different temperature.

Acknowledgement

Not Applicable.

Author Contributions

Sunita Vaidya wrote the main manuscript, Surendra Agrawal guided wrote manuscription, Pranita Jirvankar performed analysis, Sandip Sonawane drafting manuscript.

Datta Availability

All data generated or analysed during this study are included in this published article.

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