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## RESEARCH ARTICLE

# QUANTIFICATION OF AMORPHOUS PHASE BY GRAVIMETRIC VAPOR SORPTION

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**ABSTRACT**

In the envisaged study, heat induced crystalline to amorphous phase generation and amorphous content quantification in crystalline form of Pantoprazole sodium sesquihydrate drug substance was studied by different analytical techniques like variable temperature Powder X-Ray diffraction (VT-PXRD), Thermo gravimetric Analysis (TGA) and Gravimetric vapor sorption analyzer (GVS). Amorphous Pantoprazole Sodium is obtained by dehydrating Pantoprazole Sodium sesquihydrate. Amorphous and Crystalline contents are varied to obtain different concentrations of Amorphous in Crystalline phase. The slope of the vapor sorption curves of the samples found to be characteristic to the concentration of amorphous phase. Linearity with a good correlation has been established between concentration of amorphous phase and slope of the sorption curve, the same linear equation has been used for cross-predictions and the results are found to be satisfactory.



## INTRODUCTION

Pharmaceutical solids can broadly classified as Amorphous and crystalline. In the pharmaceutical processes like milling, wet granulation, drying, re-crystallization as well as compaction, there is a possibility of generating disorder in the form of crystal defects or amorphous phase [1]. Amorphous materials in pharmaceutical formulations yield complex and challenging problems concerning the performance, processing, and storage of these products. For these reasons, fully characterizing the amorphous state is crucial. To understand the generation of amorphous phase and its detection and quantification is extremely important. Pantoprazole Sodium is mainly reported in two different forms are Monohydrate and Sesquihydrate. Upon the removal of bound water from Pantoprazole sodium Sesquihydrate, thermal and X-Ray data indicate the lattice undergoes an adjustment and the crystal integrity disappears. This study describes the formation of amorphous Pantoprazole Sodium by removing 1.5 mole of bound water with heat and discusses the associated physical changes that occur. These changes are found to be irreversible, and the crystal lattice does not return to its original state as the sample rehydrates or exposed to room temperature over a period of time. Amorphous rehydrated sample becomes deliquescent at higher relative humidity. GVS is a well-established method for the determination of water and organic vapor sorption isotherms. It is based on a highly sensitive gravimetric system, which measures the adsorption and desorption of extremely small amounts of probe molecule. Water vapor can act as a plasticizing agent in amorphous materials. Amorphous materials typically have a Higher Surface Area and Vapor Sorption affinity than their crystalline counterparts. The degree of amorphous content can be calculated by measuring the water uptake of (partially) amorphous materials at a particular humidity and compares it to a calibration curve measured from samples with known amorphous contents. Linearity model/Calibration curve were made by preparing different level spiked concentration of amorphous in crystalline phase (w/w) and exposed from 0 to 90% Relative Humidity (RH) at room temperature. The calibration curve can be used to determine the degree of amorphous in Pantoprazole Sodium semi crystalline material.

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## MATERIALS AND METHODS

Pantoprazole Na sesquihydrate (CAS Registry No: 138786-67-1, Molecular weight 432.36) is an Antiulcerative. Pantoprazole Na sesquihydrate obtained from R&D center Mylan Laboratories, it is sodium salt of 5-(difluoromethoxy)-2-[[(3, 4-dimethoxy- 2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole (Fig. 1)

### Variable Temperature PXRD (VT-PXRD)

X-ray powder diffraction was performed on the samples using the Bruker D8 advance X-ray diffractometer. The instrument was equipped with a 2.2 kW Cu anode X-ray tube, high temperature stage, and high-speed position sensitive detector

Fig-1

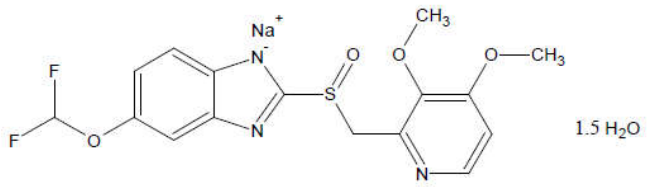


**Fig.1. Pantoprazole Sodium Sesquihydrate chemical structure**

(PSD). Cu Ka radiation (Wavelength = 1.5418A °) was used to obtain all powder diffraction patterns. A nickel filter was placed in the receiving path of the X-rays to remove the Kb radiation. Pantoprazole sodium sesquihydrate material was mounted and analyzed on a front loading sample holder, without any special sample preparation. Environmental conditions for the analysis were manipulated to facilitate drying the sample without removing it from the instrument. The sample was dehydrated by heating the material from 25°C to 115°C with 2 minutes gap interval between the scans. All scans were performed over the range of 4.6–40° 2 theta, with a step size and time per step of 0.02° 2theta and 0.16sec respectively.

### Thermo gravimetric analysis (TGA)

The analyses were performed on TGA Q5000 of TA Instruments (Lukens Drive, Delaware, USA), in Hi-Res (High Resolution) mode with dynamic test procedure under the nitrogen gas purge at a flow of 40 mL/min for balance and 60 mL/min for sample. Instrument was calibrated for temperature with Nickel (supplied by the TA instruments) and TGA balance was calibrated with certified weights (Denver Instrument-calibration weights, Denver, Colorado). The experimental conditions for dynamic test procedure, in which the samples were analyzed on the platinum pan, with a heating rate of 30◦C/min up to 125°C and resolution number of 4 with sensitivity value of 1.Data acquisition and analysis were performed using Universal Analysis 2000 software (TA Instruments).

### Gravimetric Vapor Sorption Analysis (GVS)

Gravimetric Vapor Sorption analyses were performed using IGAsorp Moisture Sorption Analyser from HIDEN ISOCHEMA, analysis experiments are performed by stepping the Relative Humidity (% RH) over a broad range from 10 to 90% at constant temperature (28°C). The relative humidity is controlled in the sample chamber dynamically by combining different flow rates of wet and dry gas streams prior to injection. The reservoir in the sample block is utilized to humidify a gas steam and thus produces the wet stream. The RH sensor is used to measure and control the relative humidity in the sample chamber. The RH can be varied between 0 and 95%. Any sample will come to an equilibrium moisture uptake capacity at a defined humidity and temperature. If either of these conditions is altered the sample will either release or take up moisture to maintain energetic equilibrium [7].

## RESULTS AND DISCUSSION

### Variable Temperature PXRD (VT-PXRD)

Overlaid Diffraction pattern of PXRD profiles were collected at every 10°C interval from 25°C to 115°C can be seen in Fig. 2, indicating the diffraction patterns are remained unchanged till the temperature about 95°C, at about 105°C the pattern show a change in the intensity of the peaks which are gradually decreasing, finally at 115°C the pattern completely changed to broad amorphous hallow [2].The study indicates the thermal events that occurred in that temperature range (95°C-115°C) resulted in collapse of crystal lattice which infers the phase change from crystalline Pantoprazole sodium sesquihydrate to Pantoprazole sodium amorphous.

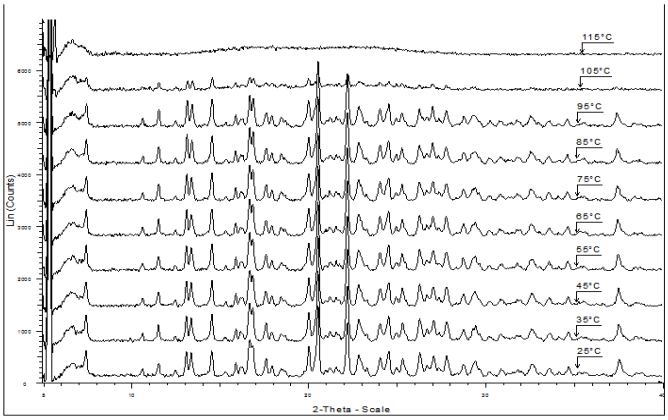


**Fig. 2 Overlaid Diffraction pattern of PXRD profiles collected at every 10°C interval from 25°C to 115°C**

### Thermo gravimetric analysis (TGA)

The TGA thermogram of the sample along with its 1st derivative curve is shown in the Fig.3. Total weight loss integrated from 29.6°C to 112.66°C is 6.576% (w/w). 1St derivative curve of TGA thermogram shows sharp weight loss onset at about 92°C and endset at about 112°C. In the similar temperature range VT-PXRD study indicated an abrupt change in the diffraction profile. The integrated weight loss during this inflation is found to be 5.571%; this weight loss corresponds to the water present in the crystal lattice, i.e. bound water weight loss [3, 4]. This kind of ion-coordinated water participates in an ion water bond which usually is much stronger than any hydrogen bonds present so called crystal bound water. Once it looses the crystal bound water it becomes amorphous and confirmed by PXRD.

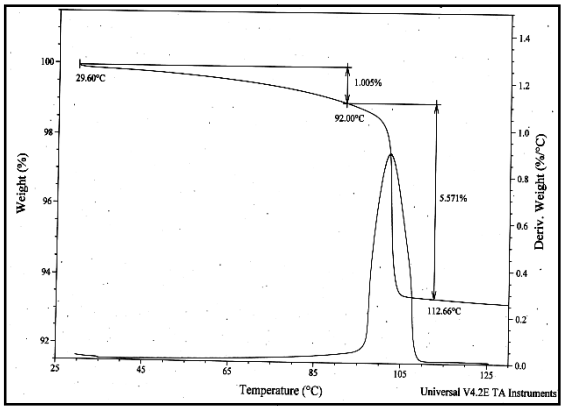


**Fig.3 TGA thermogram of Pantoprazole Sodium Sesquihydrate API**

### Gravimetric Vapor Sorption Analysis (GVS)

Different levels of Spiked concentrations are prepared by Weighing the required quantity of amorphous and crystalline Pantoprazole Sodium material and blended in different proportions (0-100% w/w) and mixed uniformly to ensure homogeneity and took about 15 mg of blend sample into the

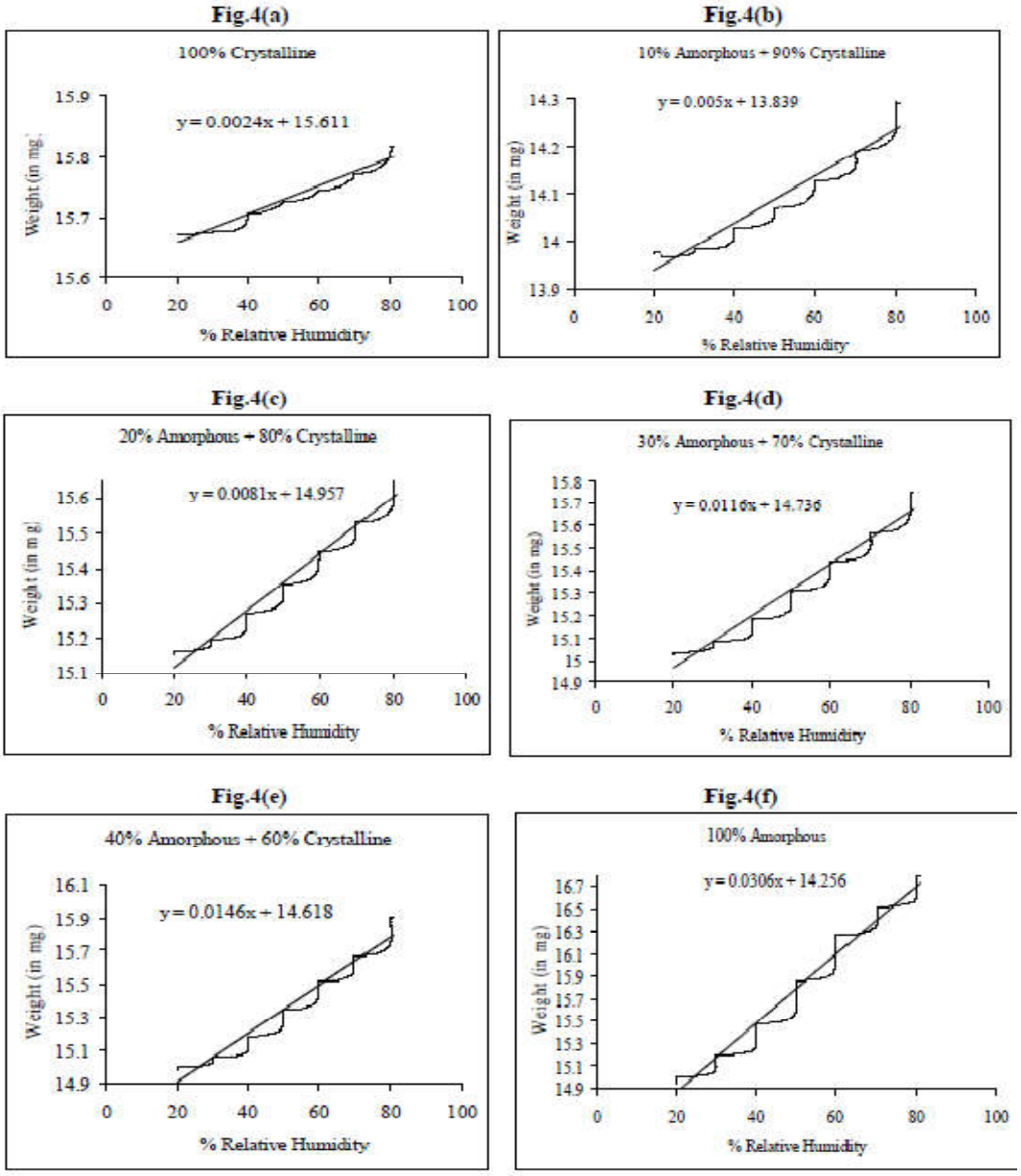


**Fig.4. The trend lines, slope along with linear equation for each spiked concentration**

Standard stainless steel mesh bucket having approximate diameter 15mm fine mesh. The environment around the sample was then set to 0%RH and the sample was allowed to equilibrate. The analysis was performed from 10% to 90% relative humidity by keeping 20 minutes holding time at each station at a constant temperature. For each sample weight is plotted against % Relative Humidity. The data considered for the calculations is in the relative humidity range of 20% to 80%. For each spiked concentration, the weight is plotted against % Relative humidity, the trend line was plotted and the linear equation is obtained. Fig.4 (a to f) represents the trend line, slope along with linear equation for each spiked concentration. The slope of the trend lines of each spiked concentration is considered for the linearity (Fig.5). Table-1 represents the slope and concentrations of all the spiked samples prepared, also predicted values of each concentration. The slope values of all concentrations are cross-predicted using the above obtained linear equation, the predicted results found to be close to the true values (Table 1).

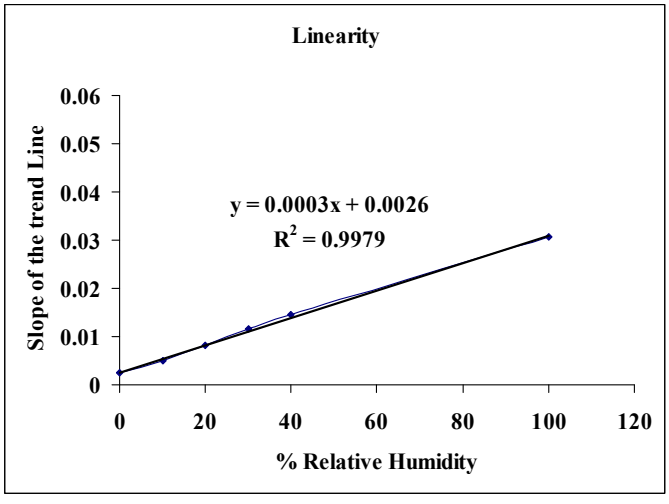


**Fig.5. Represents the linearity of the concentrations with slope of the trend line**

**Table 1: Slope for the Curve of different spiked concentrations**

| S. No. | Amorphous Content in Crystalline (w/w) | Slope | Cross PredictedValues (% Amorphous content in w/w) |
|---|---|---|---|
| 01 | 100% Crystalline | 0.0024 | -1 |
| 02 | 10% Amorphous + 90% Crystalline | 0.005 | 8 |
| 03 | 20% Amorphous + 80% Crystalline | 0.0081 | 18 |
| 04 | 30% Amorphous + 70% Crystalline | 0.0116 | 30 |
| 05 | 40% Amorphous + 60% Crystalline | 0.0014 | 40 |
| 06 | 100% Amorphous | 0.0306 | 93 |

## Conclusions

Information about Amorphous and crystalline phase ratio of given active pharmaceutical ingredient is crucial as the value may effect bio-pharmaceutical performance, the current study achieves this objective by using Gravimetric sorption analyzer, the results are very much close to the true values. The approach would help not only to understand the phase ratio, but also the sorption patterns under isothermal conditions at varying amount of amorphous content, which is very useful information for the formulation process environmental conditions optimization. The study has great relevance in case of formulation development with amorphous drug substances.

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