PRE-FORMULATION STUDIES

4.1 Introduction:

Studies conducted before initiation of experiments in formulation development are known as Preformulation studies. Preformulation studies provide scientific rationale for successful and robust product development with specified objectives. These studies help to understand the probable interactions between drug and excipients and aid in designing the experimental trials to mitigate the same.

This chapter includes the identification and characterization studies for drug and excipients to be used in formulation development.

4.2 Materials

Granisetron HCl and Amisulpride were obtained from Sun pharmaceutical Industries Ltd (India). Poly(lactic-*co*-glycolic) Acid (PLGA), Polycaprolactone (PCL) and polyvinyl alcohol (PVA) were obtained as gift samples from Sun pharmaceutical industries ltd.

4.3 Instruments:

Ultra violet (UV)-Visible spectrophotometer- 1800 Shimadzu, Japan

Fourier transform infrared spectrophotometer- Model Cary 620 microscope and Cary 670 FTIR, Agilent, CA, USA

Differential Scanning Calorimetry - DSC-60, Shimadzu, Japan

4.4 Authentication of drugs and pre-formulation studies

Both the drugs were authenticated using UV spectroscopy, Fourier transform infrared (FT-IR) spectroscopy and differential scanning calorimetric (DSC) analysis.

4.4.1 Organoleptic properties:

The physical properties of Amisulpride and Granisetron are shown in table 4-1. The physical appearance was compared with the reported values.

Table 4-1 Organoleptic Properties of drugs [1, 2]

Organoleptic Properties	**Drugs**	
	Amisulpride	**Granisetron**
Physical state	Solid	Solid
Appearance	Powder	Powder
Colour	White	White
Observation	Matched with reported data	

4.4.2 Determination of Melting point [3]:

Melting point of both the drugs (Amisulpride and Granisetron) were determined by capillary method [3].

Amisulpride showed melting point of 128°C and that of Granisetron showed melting point of 301°C, which were in-line with the reported values.

4.4.3 Solubility Data:

Solubility data for both the drugs collected from literature have been presented in table 4-2.

Table 4-2 Solubility data [4-7]

Solubility in	**Drugs**	
	Amisulpride	**Granisetron**
pH 1.2	40 mg/ml	>25mg/ml
pH 5.5	27.84 mg/ml	>25mg/ml
pH 6.8	3.62 mg/ml	>25mg/ml
pH 7.4	2.4 mg/ml	>25mg/ml
Water	Practically insoluble (1gm in 10000 ml & above)	Freely Soluble (1gm in 1-10 ml)
Ethanol	Sparingly soluble (1 gm in 30-100 ml)	Slightly Soluble (1gm in 100-1000 ml)
Methanol	Soluble (1gm in 10-30 ml)	Slightly Soluble (1gm in 100-1000 ml)
Dichloromethane	Freely Soluble (1gm in 1-10 ml)	Sparingly soluble (1 gm in 30-100 ml)

4.4.4 UV Absorption Spectrum:

The UV- absorption spectra of Amisulpride was measured at concentration of 2µg/ml using UV-spectrophotometer in 0.1N Hydrochloric acid (HCl). The sample was scanned from 200-800 to determine maximum absorption wavelength (λmax) as shown in figure 4-1. It was observed that amisulpride showed λmax at 226.5 nm which was in-line with the reported value [8].

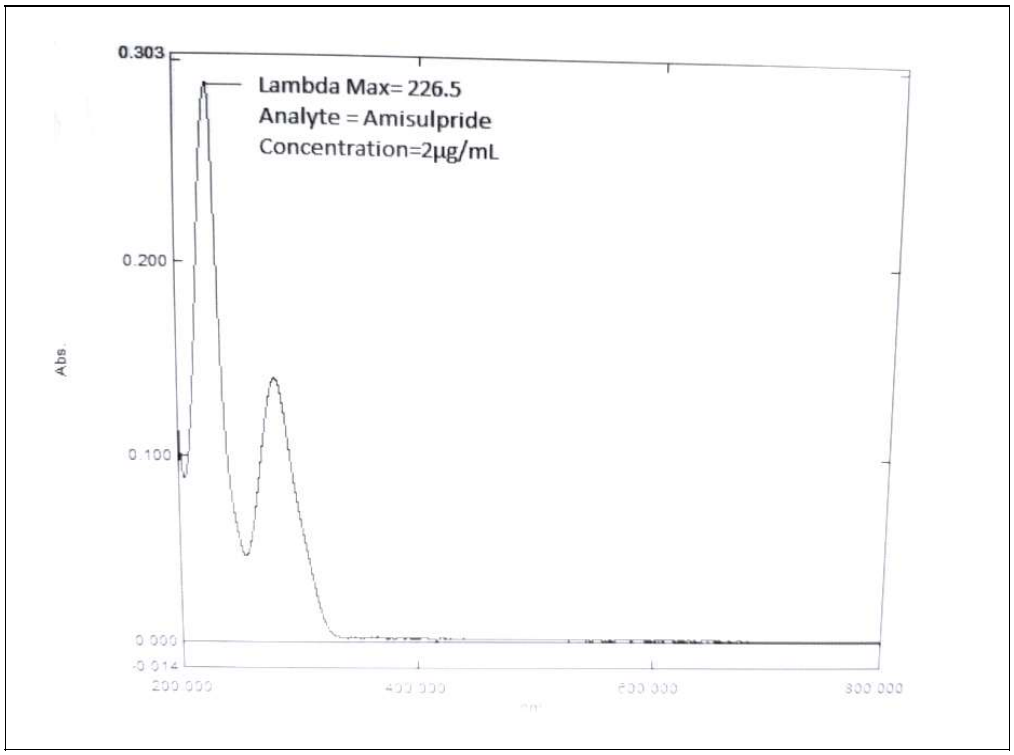

Figure 4-1 UV Spectrum of Amisulpride

The UV- absorption spectra of Granisetron HCl was measured at concentration of 4µg/ml using UV-spectrophotometer in 0.1N HCl. The sample was scanned from 200-800 to determine maximum absorption wavelength (λmax) as shown in fugure 4-2. It was observed that granisetron showed λmax at 302 nm which was in-line with the reported value [9].

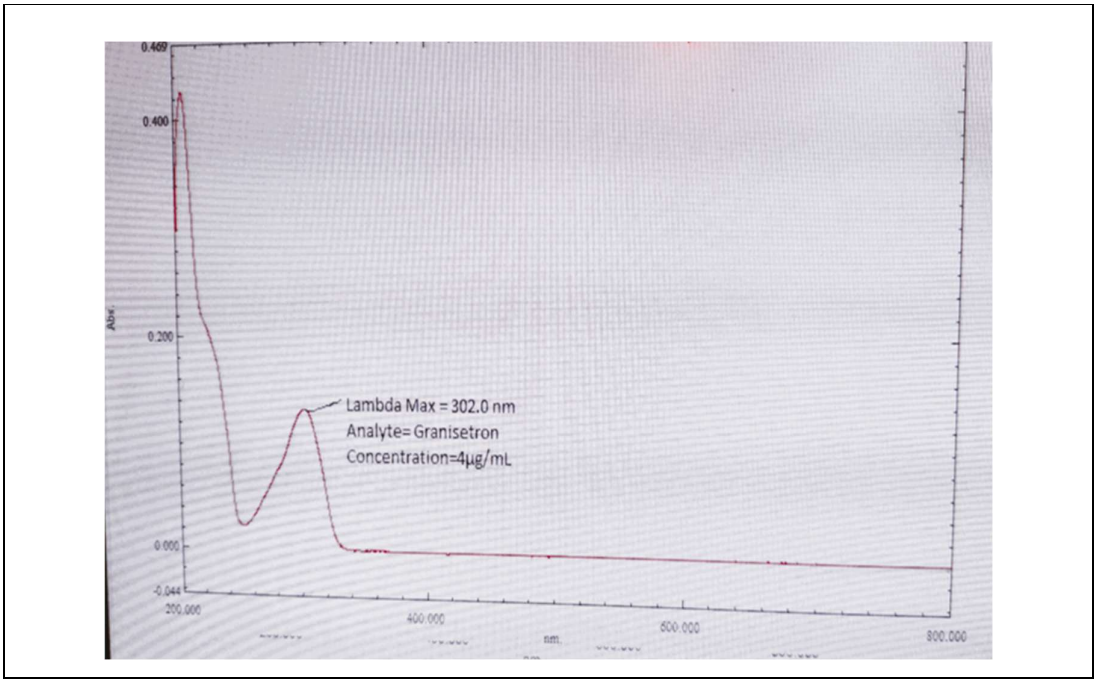

Figure 4-2 UV Spectrum of Granisetron

4.4.5 FTIR analysis:

The functional groups identification was performed using Fourier Transform Infrared spectroscopy (FTIR) (Model Cary 620 microscope and Cary 670 FTIR, Agilent, CA, USA) in Attenuated Total Reflectance (ATR) mode with a Germanium from 400 cm^{-1} to 4000 cm^{-1} range and 16 scans [10]. The FTIR spectra of Amisulpride, Granisetron, Poly(lactic-*co*-glycolic) Acid (PLGA), Polycaprolactone (PCL) and polyvinyl alcohol (PVA) are shown in Figure 4-3 (A to E). The characteristic peaks and their respective functional groups are shown in Table 4-3.

Figure 4-3A FTIR spectrum of Amisulpride

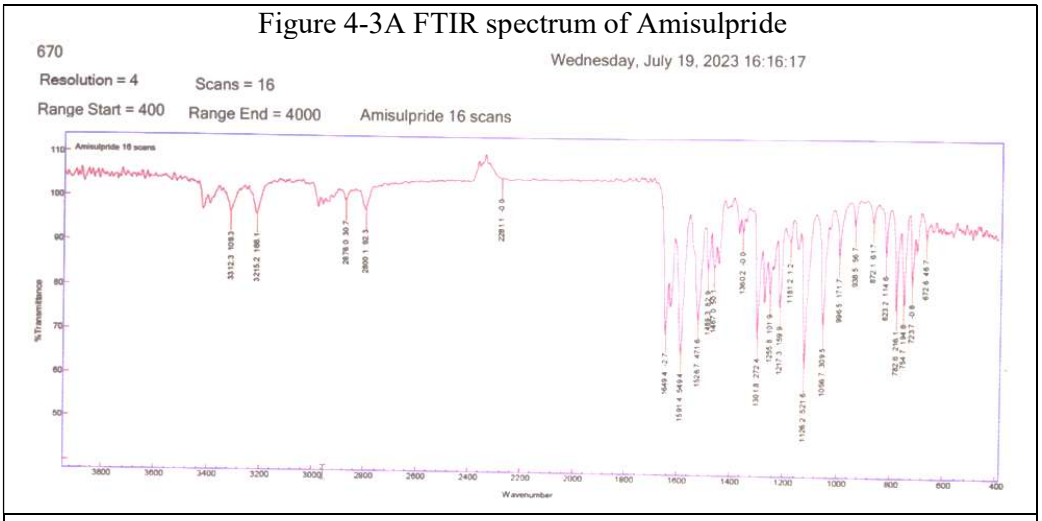

Figure 4-3B FTIR spectrum of Granisetron

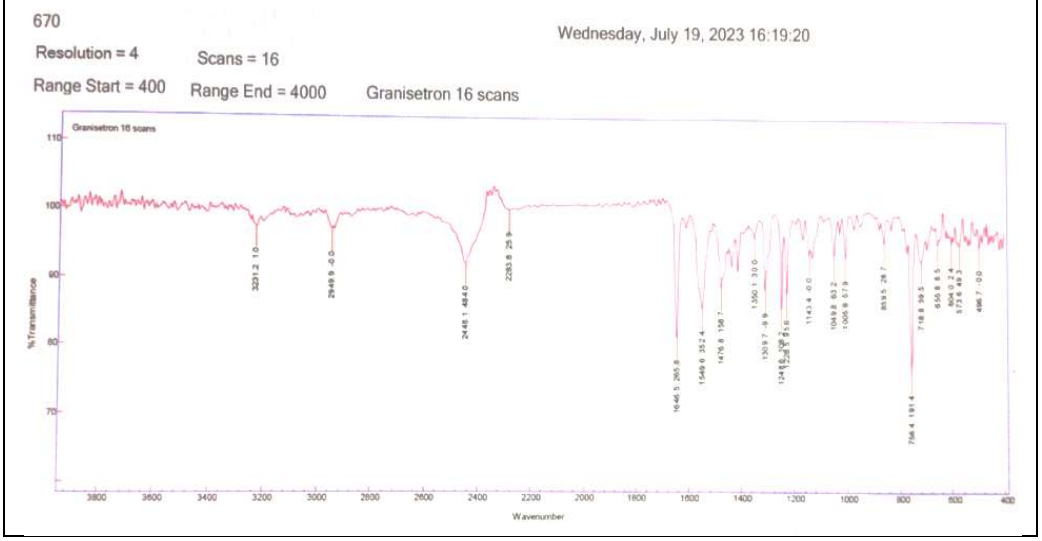

Figure 4-3C FTIR spectrum of Poly(lactic-*co*-glycolic) Acid (PLGA)

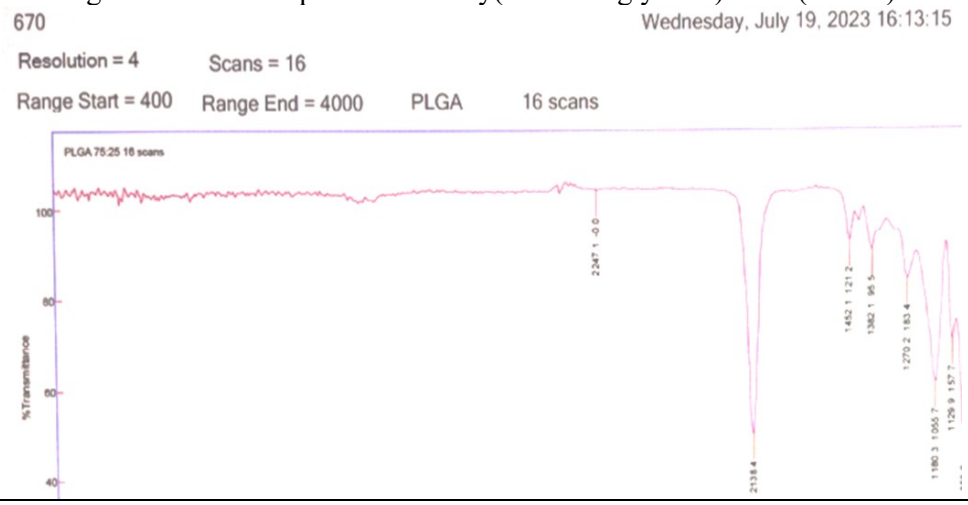

Figure 4-3D FTIR spectrum of Polycaprolactone (PCL)

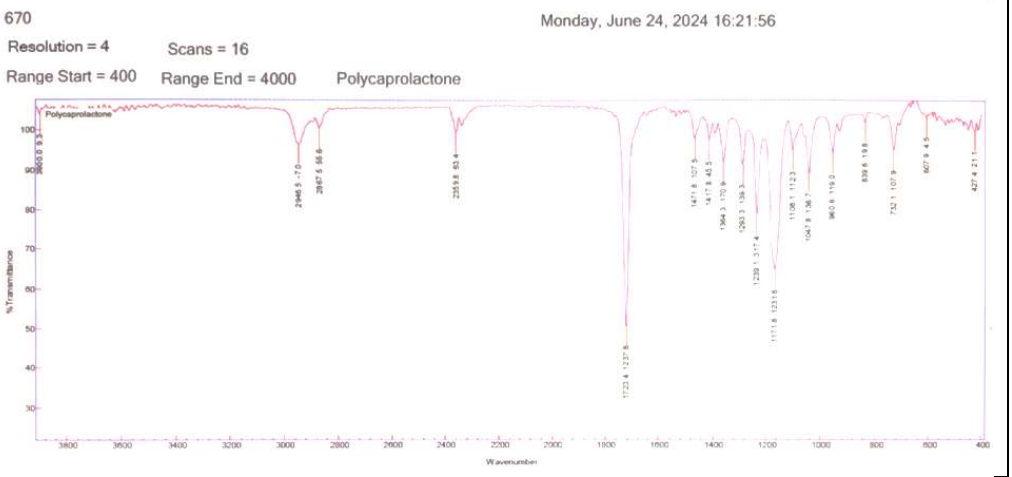

Figure 4-3E FTIR spectrum of Polyvinyl alcohol (PVA)

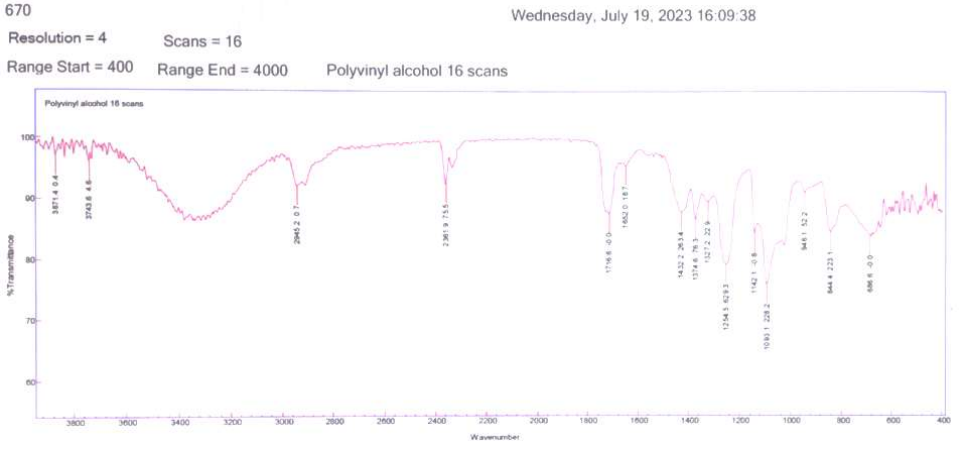

Figure 4-3 FTIR Spectra of A) Amisulpride B) Granisetron C) PLGA D) PCL E) PVA

Table 4-3 Characteristic FTIR peaks and corresponding functional groups

Sr. No.	Characteristic Peaks (cm^{-1})	Functional groups
Drug: Amisulpride		
1	3312	-NH stretching
2	3215	-NH stretching
3	1649	C=O stretching
4	1056	O=S=O stretching
Drug: Granisetron HCl		
1	3231	-NH stretching
2	1646	C=O stretching
3	1549	-CN stretching
Polymer: PLGA		
1	1749	C=O stretching
2	1452	C-H bends
3	1180	C-O stretching
4	1088	C-O-C stretching
Polymer: PCL		
1	1723	C=O stretching
2	1364	O-H stretching
3	1293	C-O& C-C stretching
4	1239	C-O-C stretching
Polyvinyl alcohol		
1	3280	OH stretching
2	1716	C=O stretching
3	1432	CH2 bending
4	1324	C-H deformation
5	1093	C-O stretching

All the observed spectra matched with the reported spectra and peak values [11-15].

4.4.6 Thermal analysis using DSC:

The thermal behaviour of amisulpride, granisetron, PLGA and PCL were determined by Differential Scanning Calorimetry (DSC-60, Shimadzu, Japan) using 10 °C/min scan rate from 0°C at 320°C, with nitrogen blanketing atmosphere [16]. DSC thermograms of Amisulpride, Granisetron, PLGA, PCL are shown in Figure 4-4 (A to D).

Figure 4-4A DSC data of Amisulpride

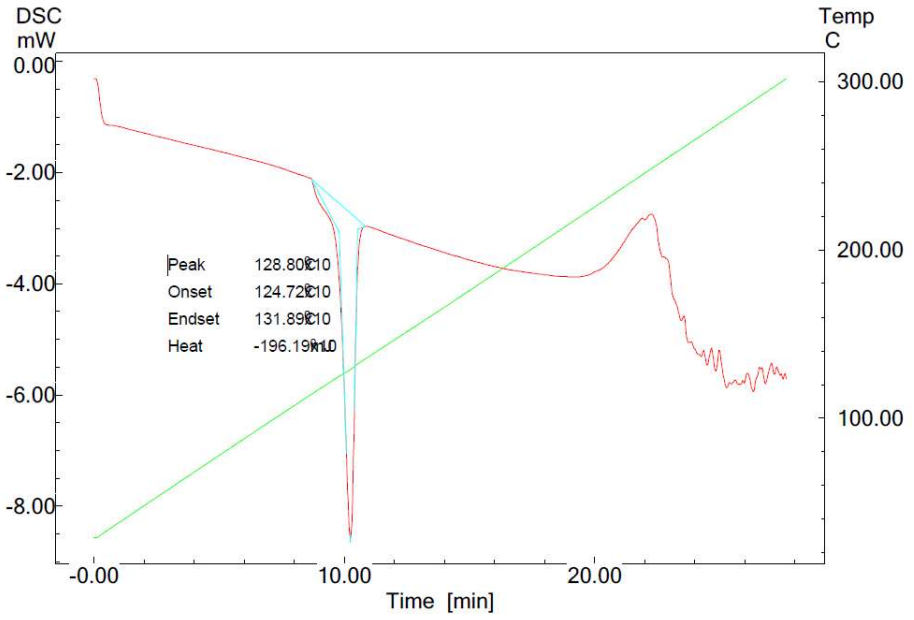

Figure 4-4B DSC data of Granisetron

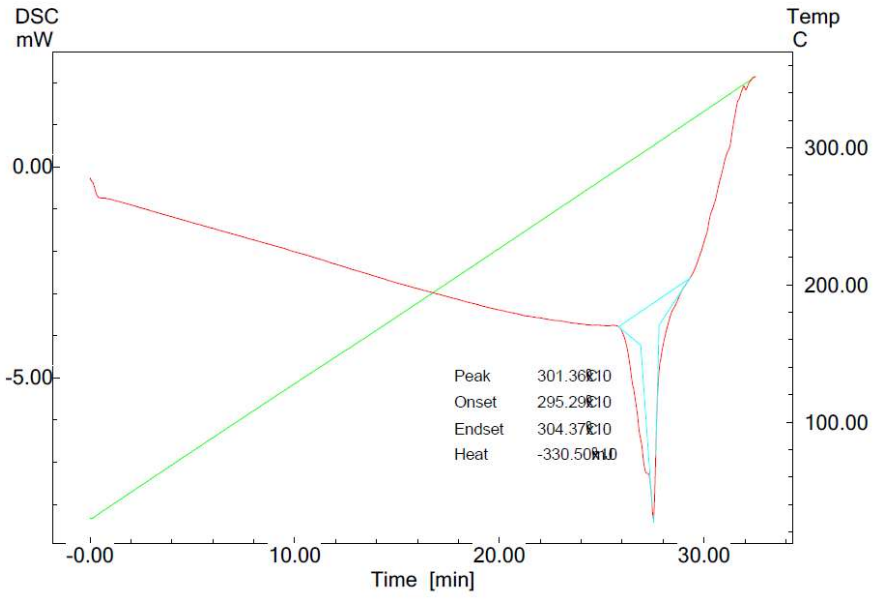

Figure 4-4C DSC data of PLGA

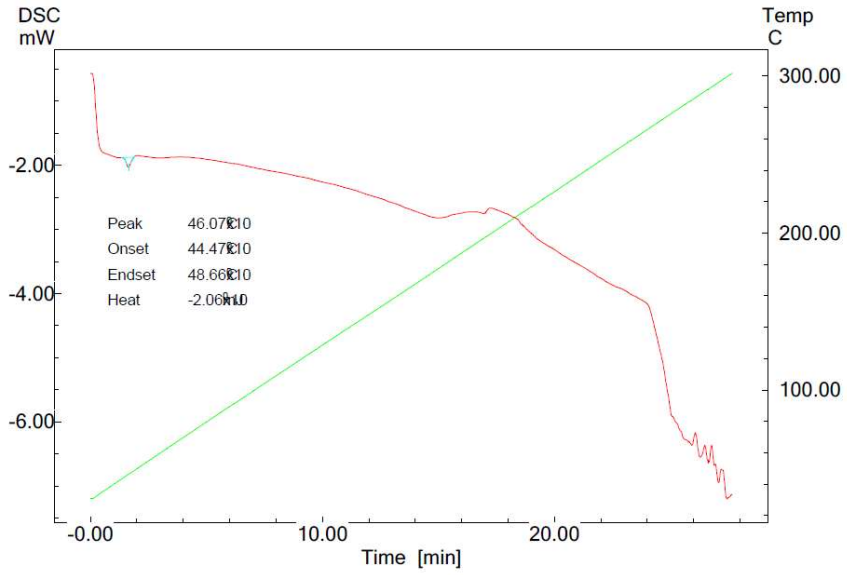

Figure 4-4D DSC data of PCL

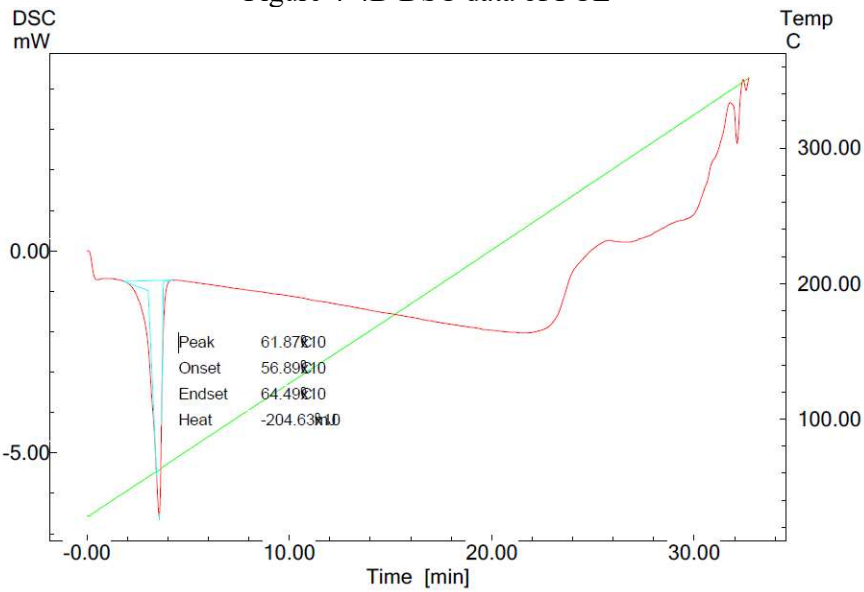

Figure 4-4 DSC data of A) Amisulpride B) Granisetron C) PLGA D) PCL

Amisulpride shows sharp endothermic peak at 128.8 °C and Granisetron shows endothermic peak at 301.36°C which confirms the identification of both the APIs [17,18]. PLGA being 100% amorphous polymer shows glass transition temperature (Tg) at 46.07°C [19]. PCL is a semi crystalline polymer, so its thermogram presents an endothermic peak at 61.87°C [20].

4.5 References:

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