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Research Article

Compatibility Testing of Nateglinide with Different Grades of Cellulose Ethers and Excipients Used in Sustained Release Formulations

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ABSTRACT
Compatibility testing was done to assess interaction between Nateglinide (NTG) and different pharmaceutical excipients and polymers, which are used in a sustained release formulation to manufacture tablet. To evaluate the compatibility between drug, excipients and polymers, different techniques such as Differential Scanning Calorimetry (DSC), Infrared Spectroscopic study (IR) and Isothermal stress testing (IST) study were employed. The results of DSC curves showed that, all excipients and polymers are compatible with the NTG. Except DSC curves of magnesium stearate, which shows certain interaction with the NTG, however, it overcome in the results of IR and IST studies, which showed that all the excipients, polymers used in this study are compatible with the NTG.

Keywords: Isothermal stress testing (IST), Nateglinide, Compatibility study.

INTRODUCTION

Nateglinide, a D-phenylalanine derivative is an anti-diabetic drug that is quick but short acting and controls postprandial blood glucose (PBG) effectively. Nateglinide belongs to the meglitinide class of anti-diabetic drugs used to treat type 2 diabetes by stimulation of pancreatic beta cells that results in the release of proinsulin. Nateglinide is rapidly and completely absorbed following oral administration. Chemically, it is (2R) -2-[trans-4-isopropyl-cyclohexanecarbonyl) - amino] -3-phenyl-propionic acid (Figure 1)[1, 12,13,15,16]

Studies of drug-excipient compatibility represent an important phase in the preformulation stage of the development of all dosage forms. The potential physical and chemical interactions between drugs and excipients can affect the chemical, physical, therapeutic properties and stability of the dosage form. The excipients and polymers are generally used in dosage form to ease in administration of the drug, to facilitate the formulation of the drug product, to increase the stability of the formulation. Excipients or polymers may interact with drugs that gives rise to changes in the chemical nature, solubility, absorption and therapeutic response of drugs. Therefore, the stable and effective solid dosage form depends on the selection of the occupants which can be achieved through the study of the interaction between the drug and excipients in the solid state. Differential scanning calorimetry (DSC) is rapidly used as a tool for the evaluation of the drug–excipient compatibility. However, caution needs to be exercised in the interpretation of DSC results.

This is because of the requirement of high temperature conditions and the lack of moisture in conducting these experiments. Hence, conclusions based on the DSC results alone may be misleading and to avoid this another methods such as IR spectroscopic study and Isothermal stress testing (IST) study is commonly employed for evaluating the drug–excipient compatibility[1,2].

IST involves storage of drug–excipient blends with or without moisture at a temperature (50°C) for a specific period of time (3weeks) to accelerate the ageing of drug and interaction with excipients. The IST has specific application in the pharmaceutical industry where the interaction between drug and excipients is visually observed and the drug content determined quantitatively. However, the disadvantage of this method is time consuming and laborious. Ideally, all the techniques, DSC, IR and IST should be used in combination during the compatibility studies for the selection of the excipients.

In this study, DSC, IR and IST study were used for evaluating the compatibility of NTG with selected excipients which are used in the sustained release formulation. In case where the DSC curve is suspected, infrared (IR) spectrum of pure drug was compared with that of drug–excipient mixture and pure accident. Excipients found to be compatible with each other.

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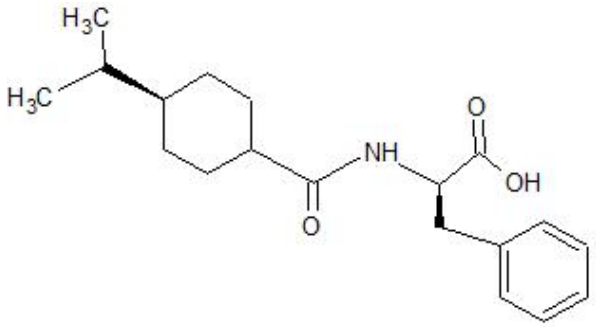

Figure 1: Structure of Nateglinide.

Excipients which were included in the prototype formula were tested using the technique of IST.

MATERIALS AND METHODS

Materials

Nateglinide USP, a gift sample from CIPLA Pharmaceuticals, Kurkumbh, Pune, India. HPMCK100M and HPMCK4M (Methocel) was a kind gift sample by Ashland Inc., USA. Microcrystalline Cellulose PH101, Microcrystalline Cellulose PH102 (Avicel), Talc, Lactose, Magnesium stearate was procured from commercial suppliers. Methanol and Water used throughout the study is of HPLC grade (Merck Inc.) and are procured from commercial suppliers.

Methods

Differential Scanning Calorimetry (DSC)

A differential scanning calorimeter (Mettler, Toledo) was used for thermal analysis of drug and mixtures of drug – excipients and drug- polymer. The selected excipients and polymers were mixed in an appropriate ratio. Individual samples of drug, excipients and polymers as well as mixtures of drug – excipients and drug- polymer were weighed directly in the DSC aluminium crucible and scanned in the temperature range of 40°C-350°C under an atmosphere of drug nitrogen. The heating rate was 2°C/min. and the curves obtained in the study were observed for any interaction[4, 5, 8, 10,11,14].

IR Spectroscopy

IR spectra of drug and mixture of drug – excipients and drug- polymer were recorded on in the range of 400nm-200nm using potassium bromide discs[1,3].

Isothermal Stress Testing (IST)

For Stressed Samples

The pure drug (NTG), selected polymer/s and occupant/s were weighed (1:1) in 4 ml glass vials (n = 3) and mixed on a vortex mixer for 2 min. for confirming homogenous mixing.

In each vial, 10 % of the distilled water was added and sealed using a Teflon-lined screw cap and stored at 50° C in hot air oven (Lab India, India).

For Control Samples

The pure drug (NTG), selected polymer/s and occupant/s were weighed (1:1) in 4 ml glass vials (n = 3) and mixed on a vortex mixer for 2 min. for confirming homogenous mixing.

The vials were sealed using a Teflon-lined screw cap and stored at 2-8° C in a refrigerator.

These sample/s were regularly examined for any change of colour. After 3 weeks (21 days) these samples were analysed quantitatively by using UV-visible spectrophotometer scanned between 400-200nm (Model UV-1800 Shimadzu)[2].

Linearity Range

Different aliquots of 5ppm to 50ppm were prepared and the solution is scanned in the range of 400nm to 200nm and absorbance is measured and graph is plotted concentration verses absorbance and linearity is calculated.

Preparation of Stock solution

10mg of pure Nateglinide was dissolved in 100ml of methanol (100ppm)

Preparation of Sample solution

0.5, 10, 15, 20, 25, 30, 35, 40, 45, 50 ml of stock solution was diluted to 10ml of methanol in 10ml volumetric flask to get respective ppm solutions.

RESULTS AND DISCUSSION

Compatibility Study

DSC

Selected DSC curves of drug and drug-excipients and drug-polymer mixtures are shown in Figure 2-30 for “0” days, “10” days, “20” days, “30” day’s intervals. The thermal behaviour of drug, respective excipients and the combinations are compared in the DSC curves. Peak transition temperature (Tpeak), Onset Temperature for various mixtures is summarized in Table 2.The majority of DSC thermograms of drug alone and in combination with different polymers shows the onset temperature of peak (T onset) [~130°C] and peak transition temperature (T peak) [~132°C].

The thermogram of NTG showed a sharp endothermic peak at 131.94°C and peak onset 130.68°C. (Figure 2) In the majority of thermograms, the melting endotherm of NTG (T onset and T peak) was well preserved with light broadening shifting towards the lower temperature range. This change in shape and shifting of peak towards a lower temperature range could be due to mixing of the drug with accidents and my not necessarily indicate potential incompatibility[6,7, 10,11,14].

The DSC thermogram of NTG and K100M showed a sharp endothermic peak at 132.56°C and peak onset at 129.99°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with K100M. (Figure 3)

The DSC thermogram of NTG and K4M showed a sharp endothermic peak at 132.27°C and peak onset at 130.05°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with K4M. (Figure 4)

The DSC thermogram of NTG and Microcrystalline Cellulose AVICEL PH101 showed a sharp endothermic peak at 131.72°C and peak onset at 129.30°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with AVICEL PH101. (Figure 5)

The DSC thermogram of NTG and Microcrystalline Cellulose AVICEL PH102 showed a sharp endothermic peak at 132.30°C and peak onset at 130.30°C. The endothermic peak of NTG was well preserved, this shows

that the NTG is compatible with AVICEL PH102. (Figure 6)

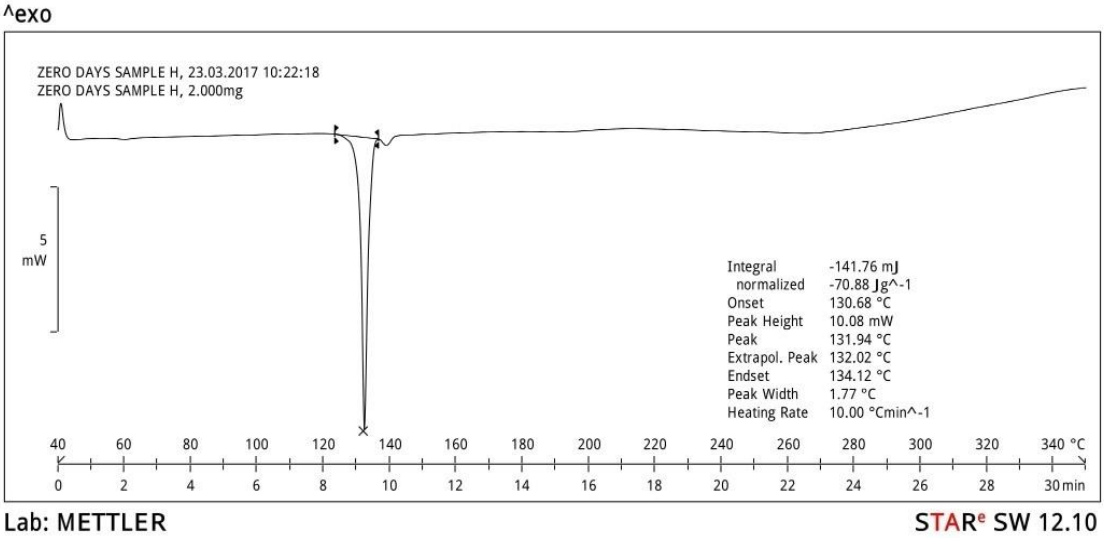

Figure 2: DSC thermogram of NTG ('0' days).

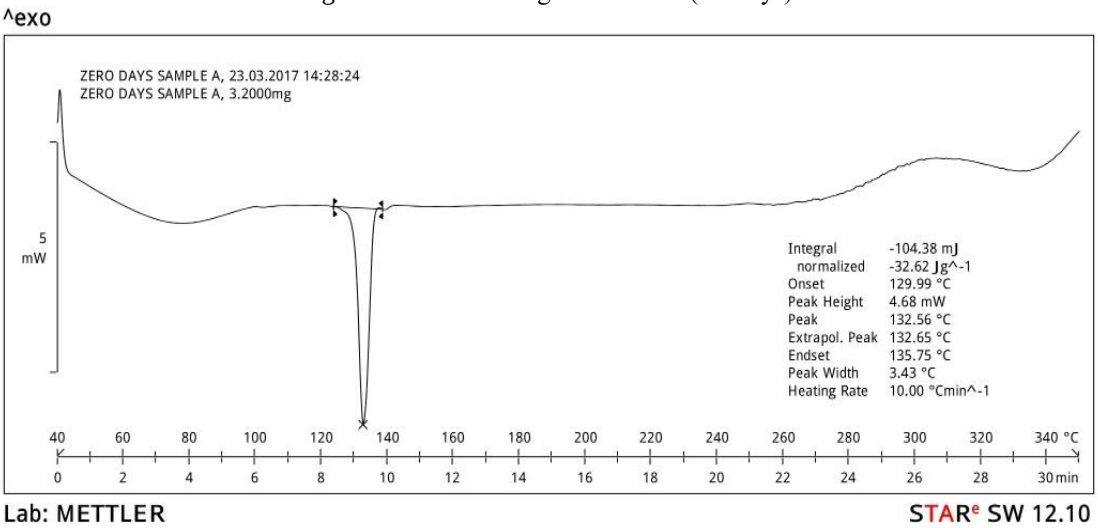

Figure 3: DSC thermogram of NTG + K100M ('0' days).

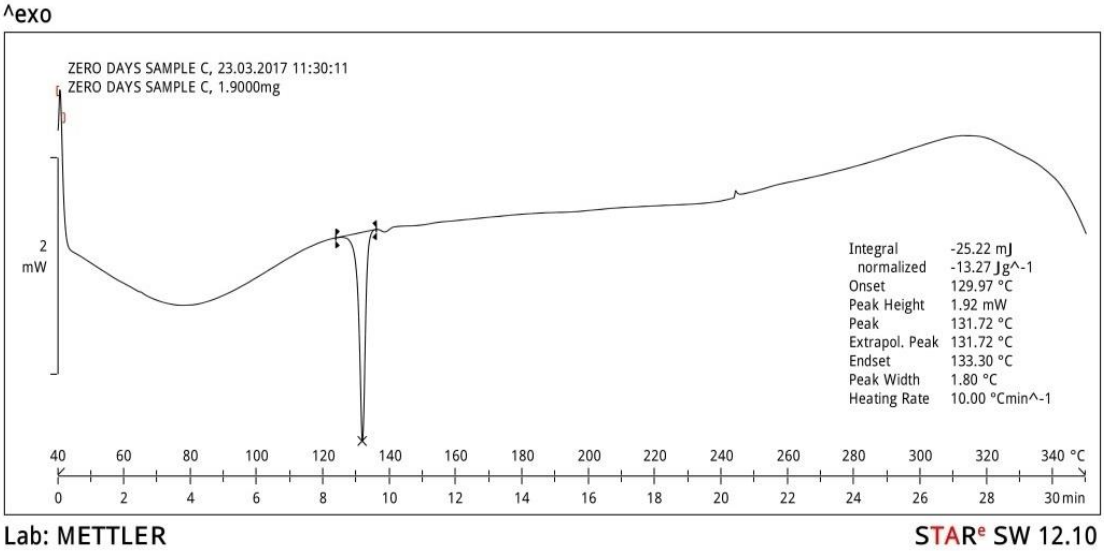

Figure 4: DSC thermogram of NTG + K4M ('0' days).

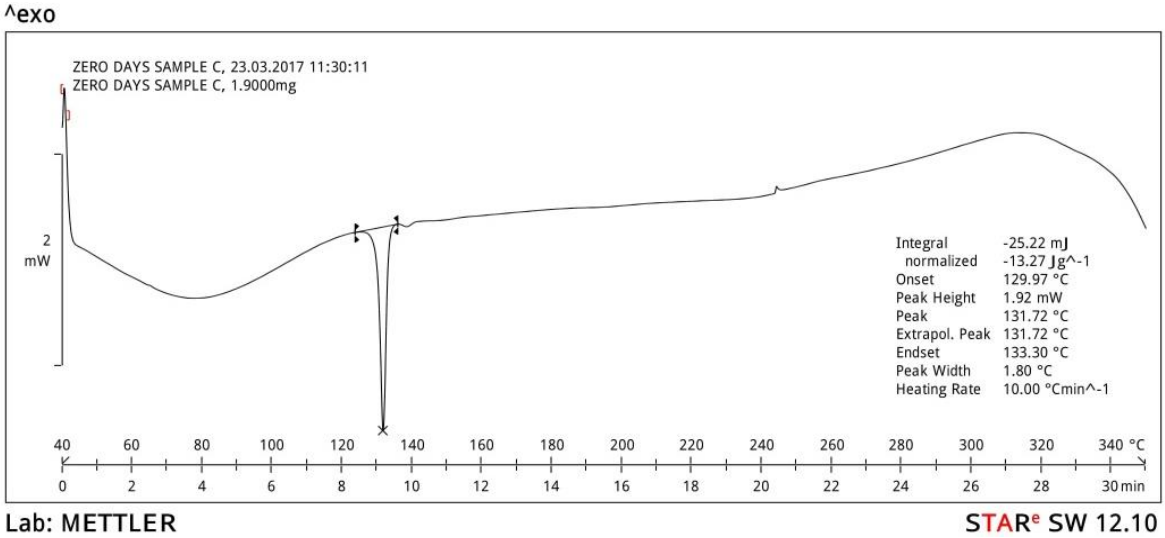

Figure 5: DSC thermogram of NTG + AVICEL PH101 (‘0’ days).

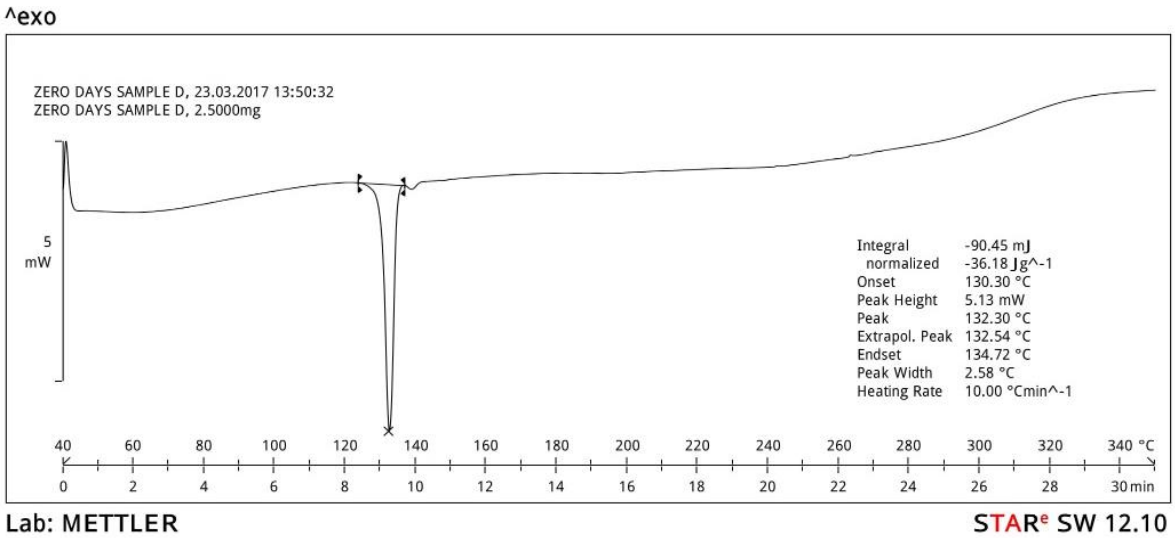

Figure 6: DSC thermogram of NTG + AVICEL PH102 (‘0’ days).

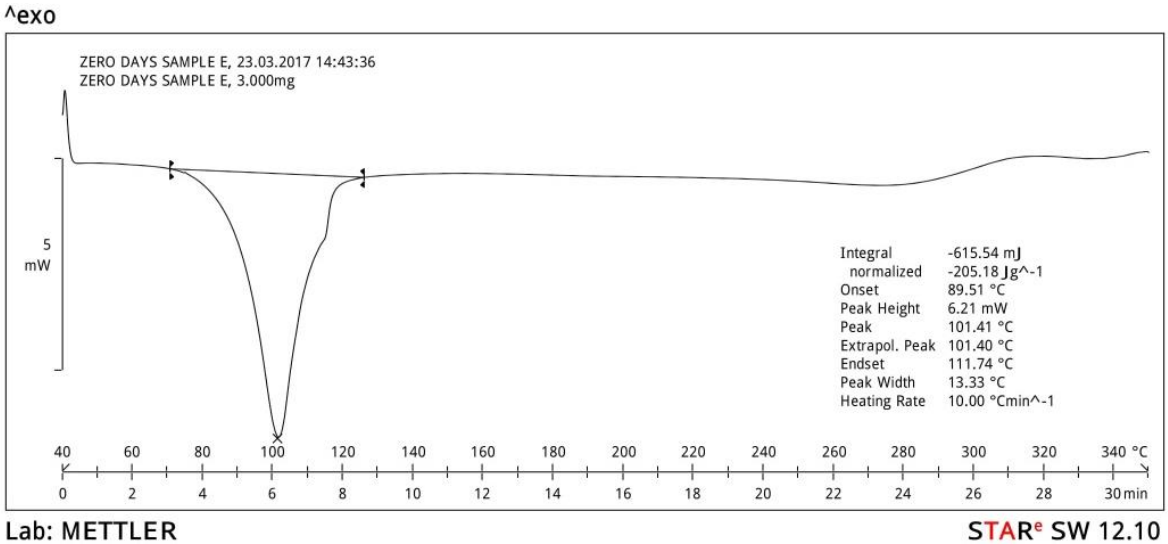

Figure 7: DSC thermogram of NTG + MG-S (‘0’ days).

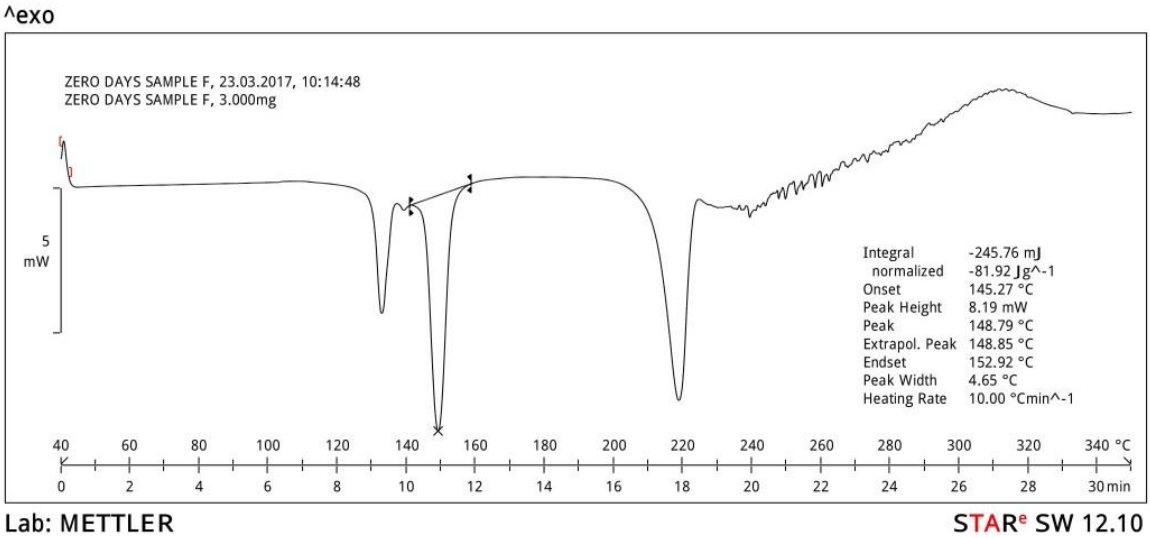

Figure 8: DSC thermogram of NTG + Lactose ('0' days).

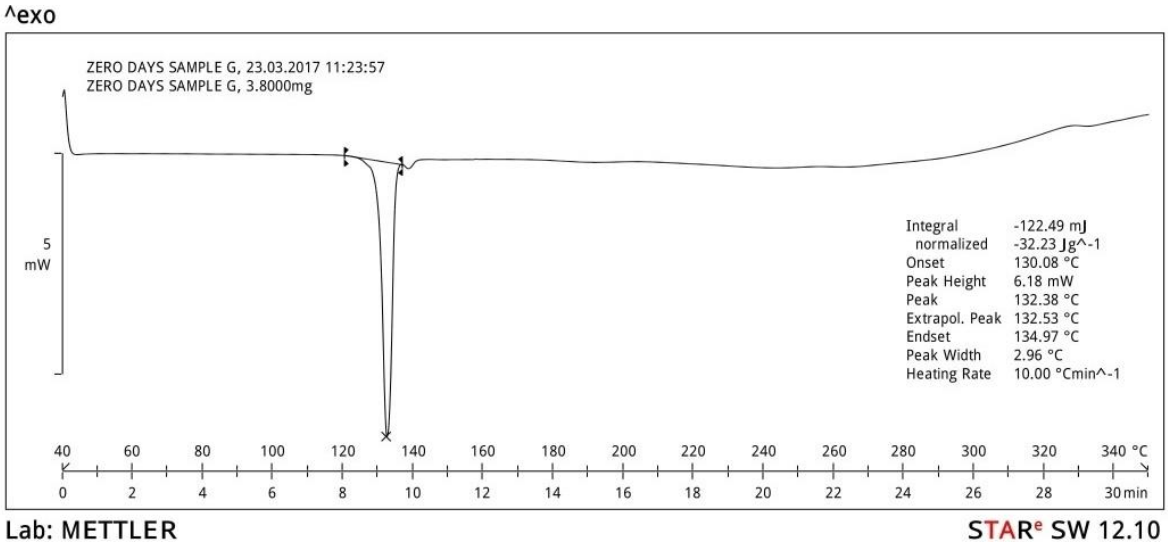

Figure 9: DSC thermogram of NTG +Talc ('0' days).

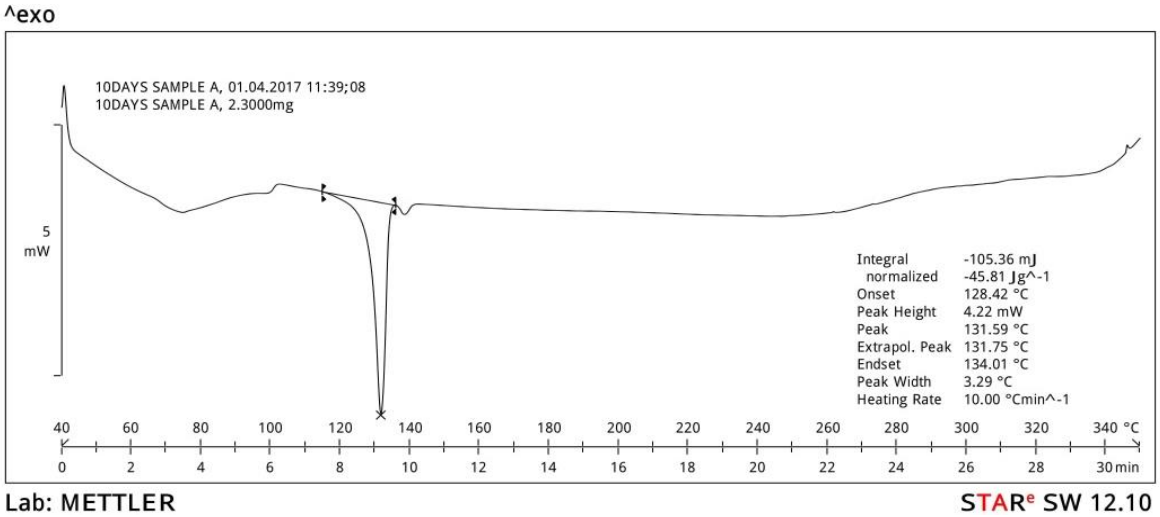

Figure 10: DSC thermogram of NTG + K100M ('10' days).

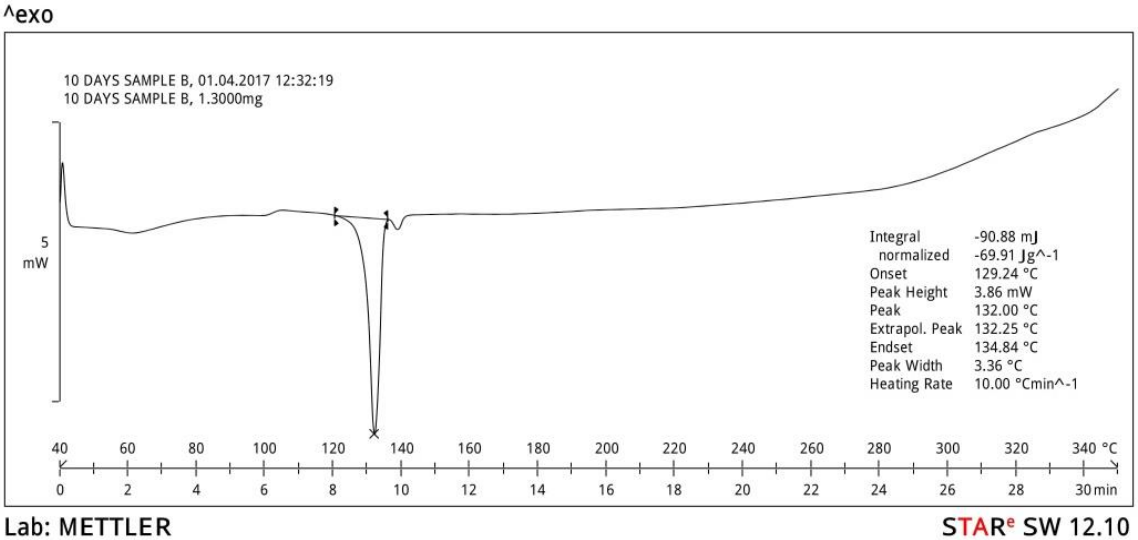

Figure 11: DSC thermogram of NTG + K4M ('10' days).

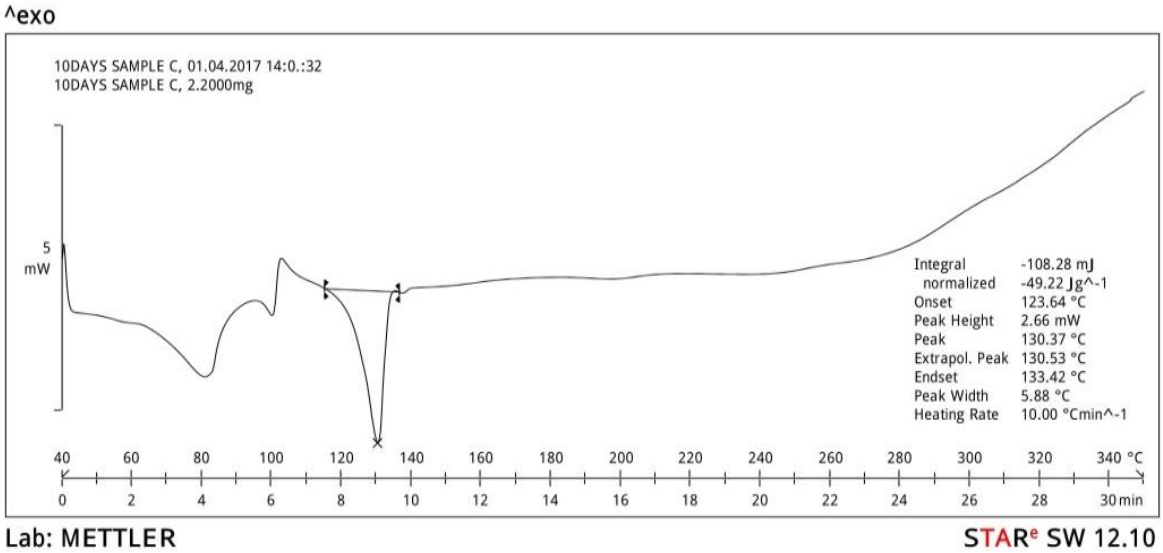

Figure 12: DSC thermogram of NTG + AVICEL PH101 ('10' days).

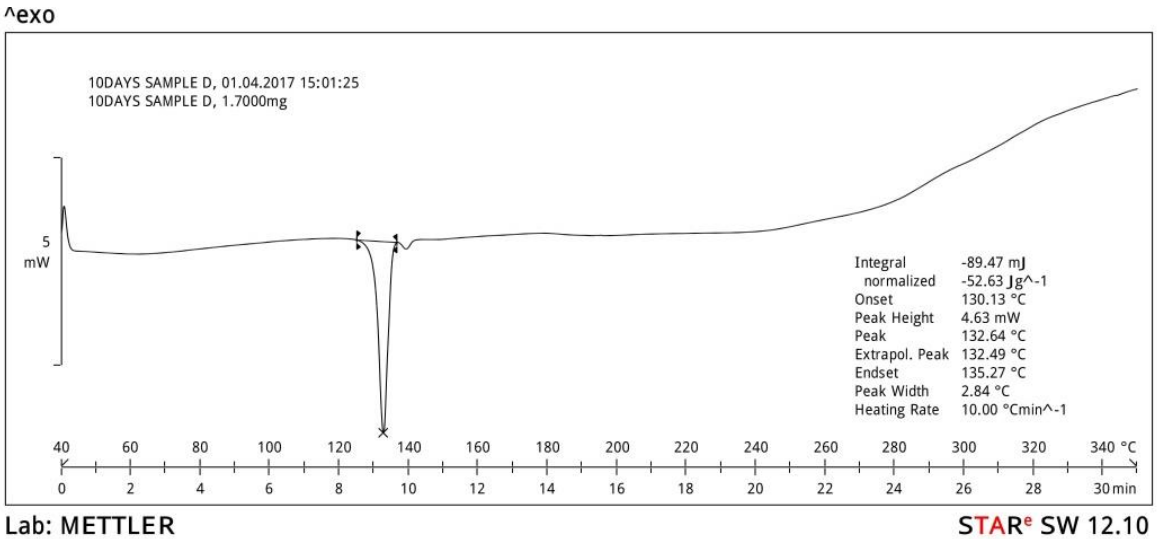

Figure 13: DSC thermogram of NTG + AVICEL PH102 ('10' days).

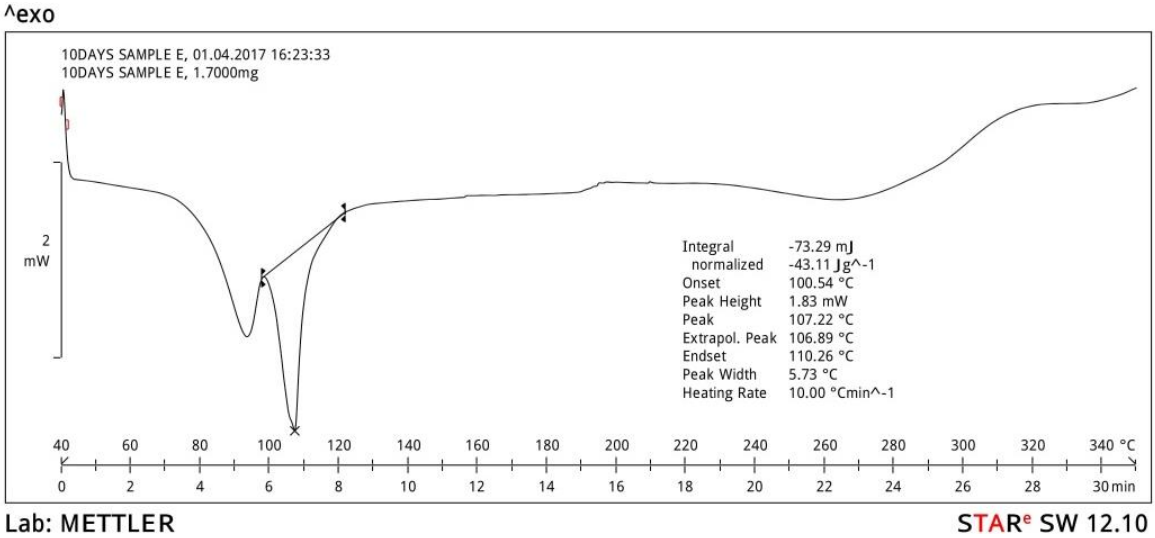

Figure 14: DSC thermogram of NTG + MG-S ('10' days).

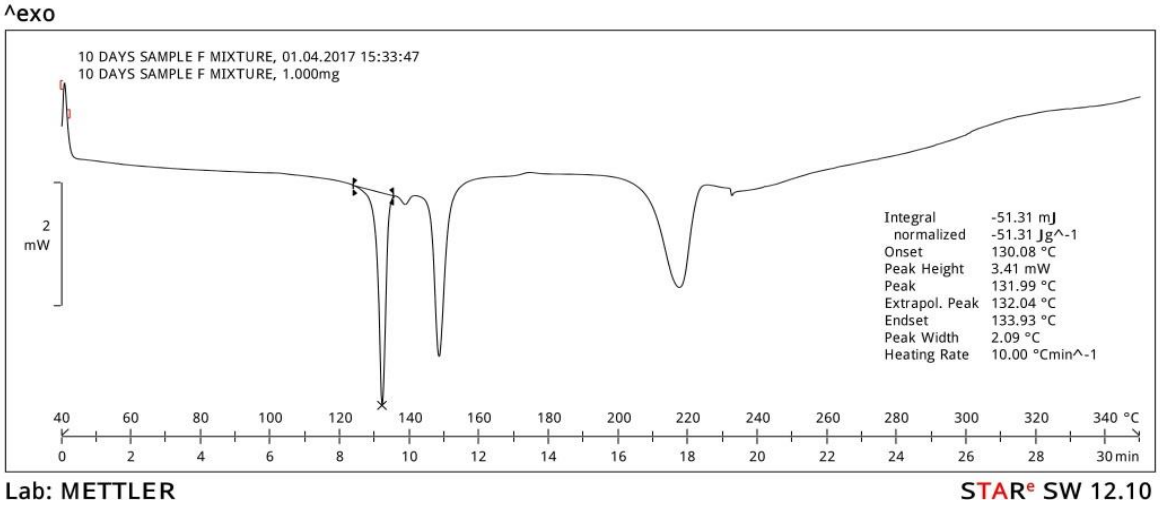

Figure 15: DSC thermogram of NTG + Lactose ('10' days).

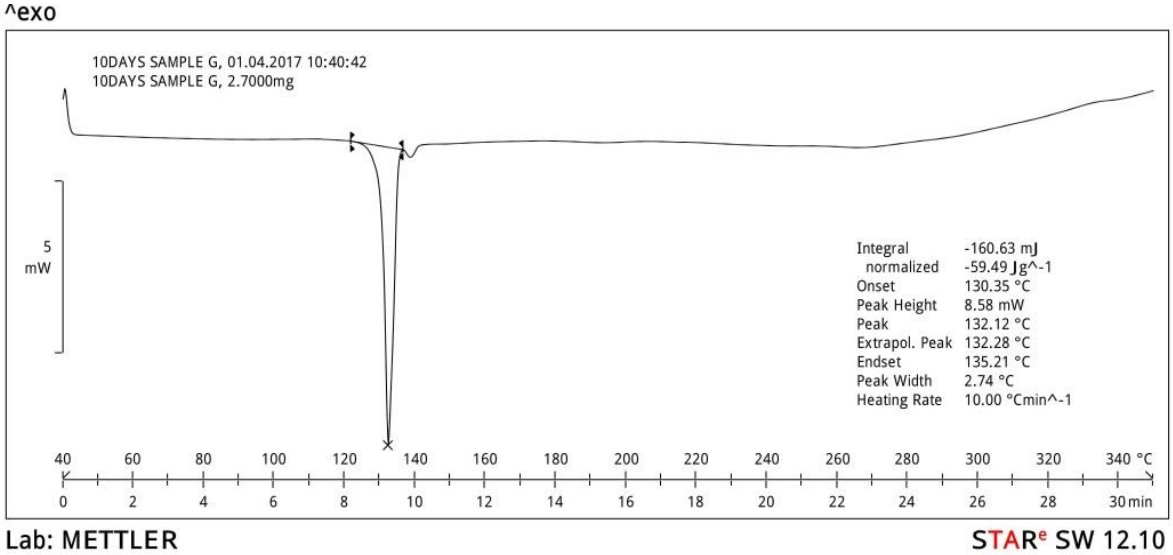

Figure 16: DSC thermogram of NTG +Talc ('10' days).

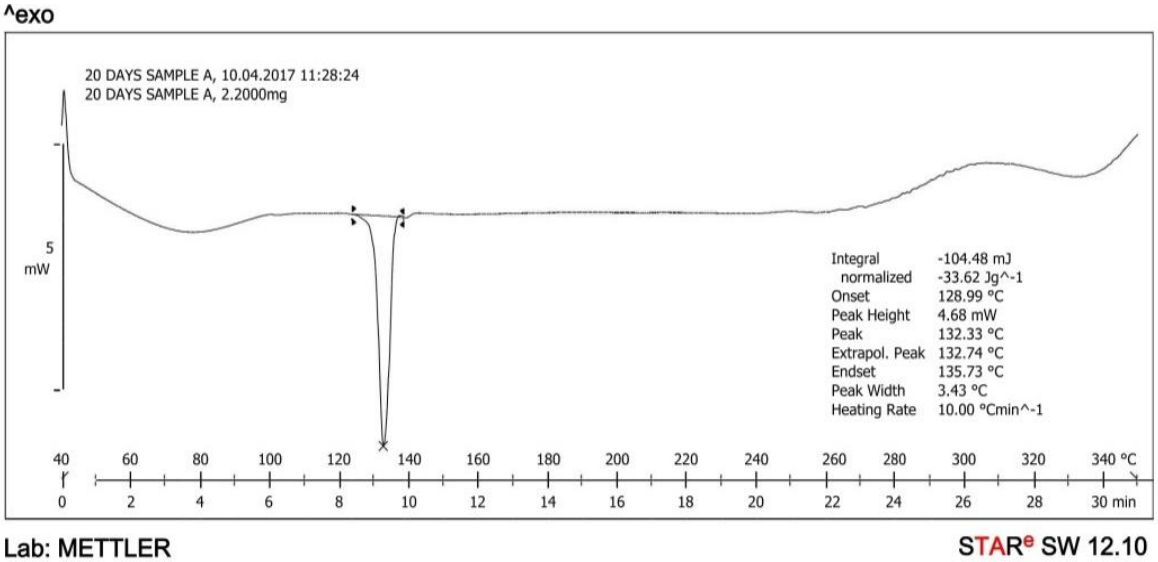

Figure 17: DSC thermogram of NTG + K100M ('20' days).

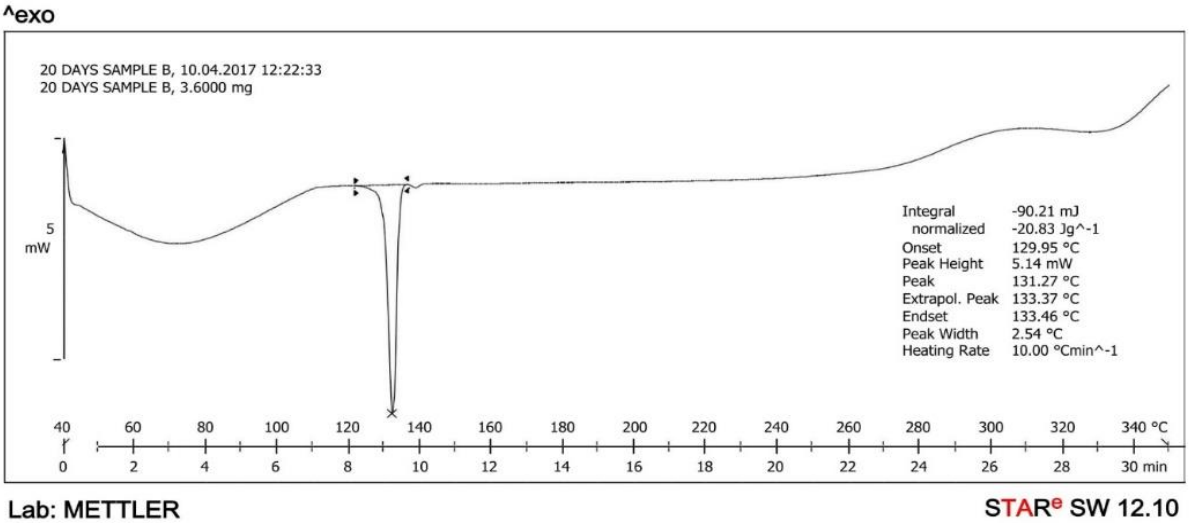

Figure 18: DSC thermogram of NTG + K4M ('20' days).

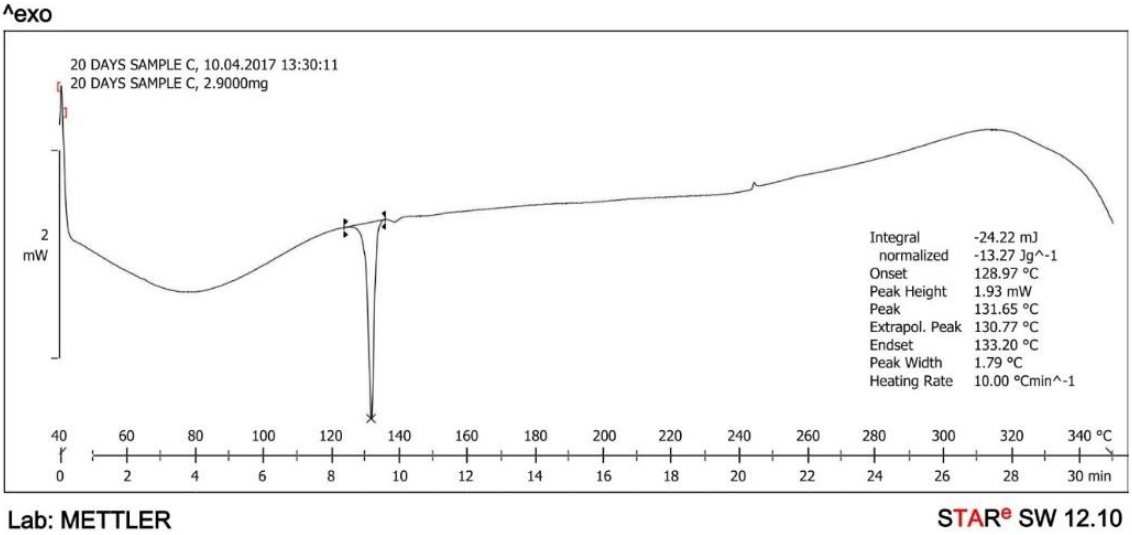

Figure 19: DSC thermogram of NTG + AVICEL PH101 ('20' days).

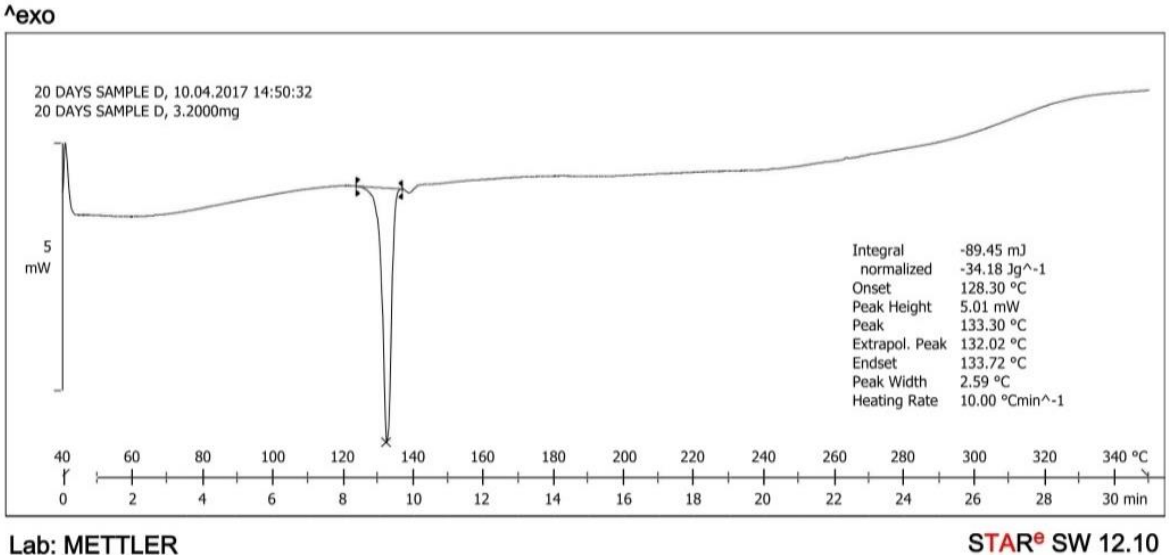

Figure 20: DSC thermogram of NTG + AVICEL PH102 (‘20’ days).

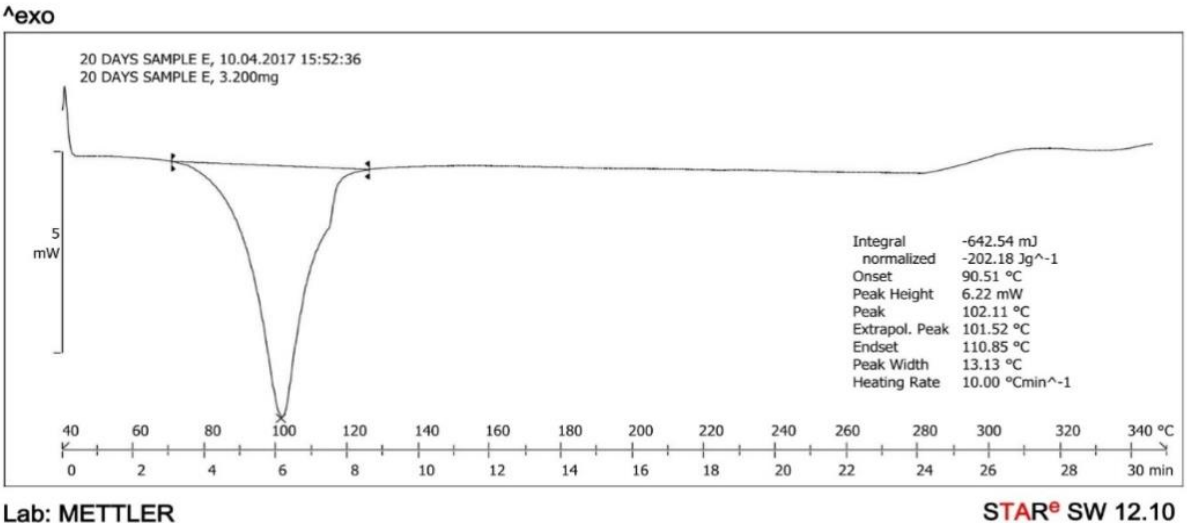

Figure 21: DSC thermogram of NTG + MG-S (‘20’ days).

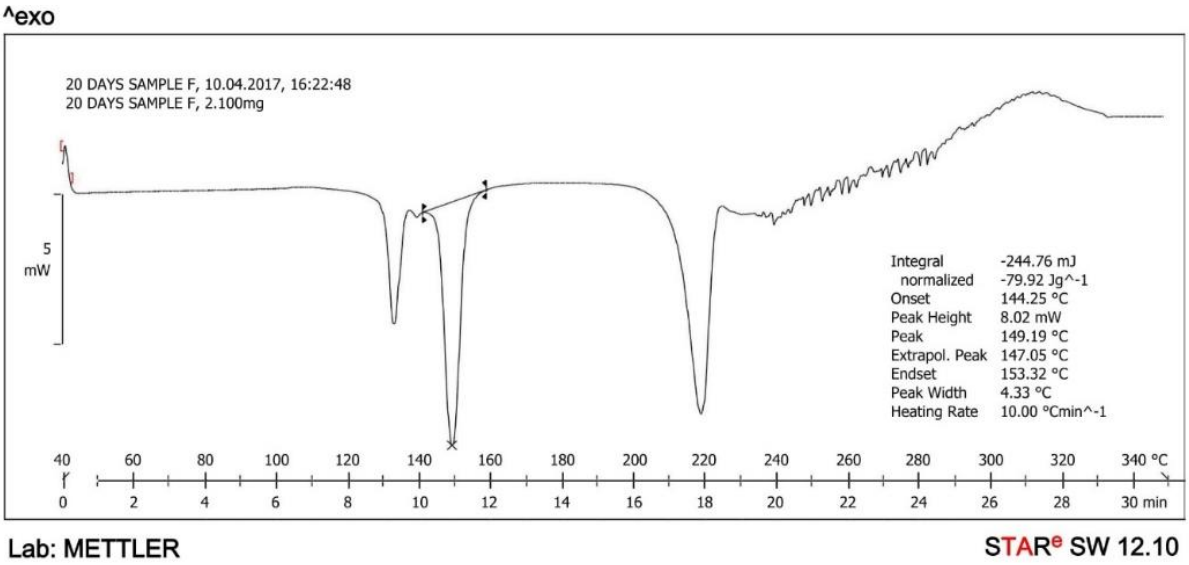

Figure 22: DSC thermogram of NTG + Lactose (‘20’ days).

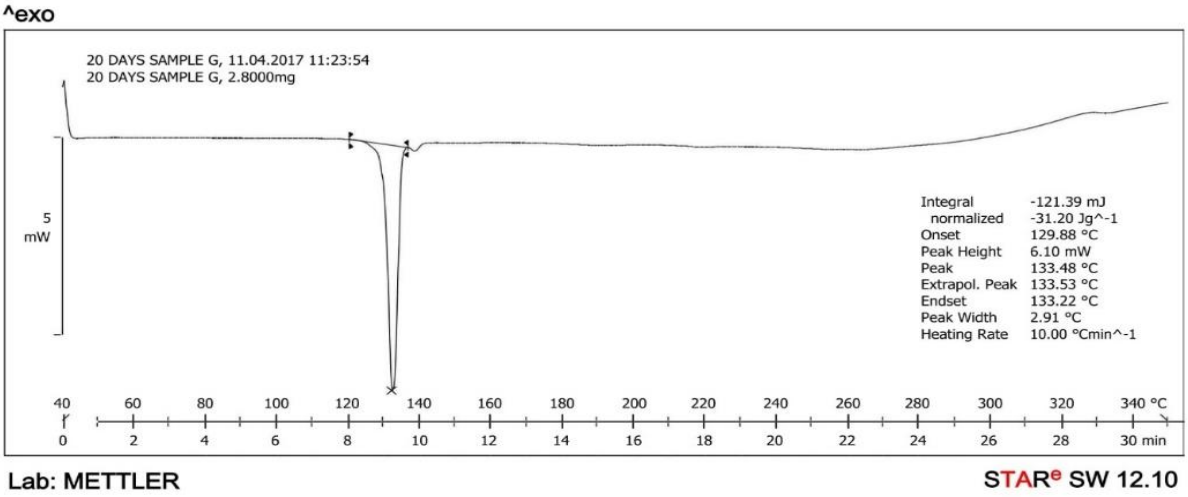

Figure 23: DSC thermogram of NTG +Talc ('20' days).

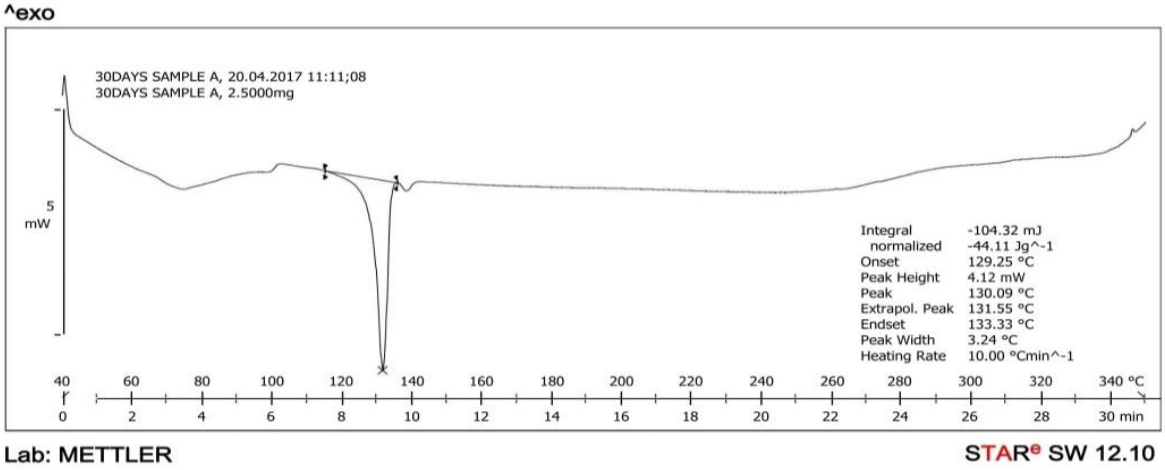

Figure 24: DSC thermogram of NTG + K100M ('30' days).

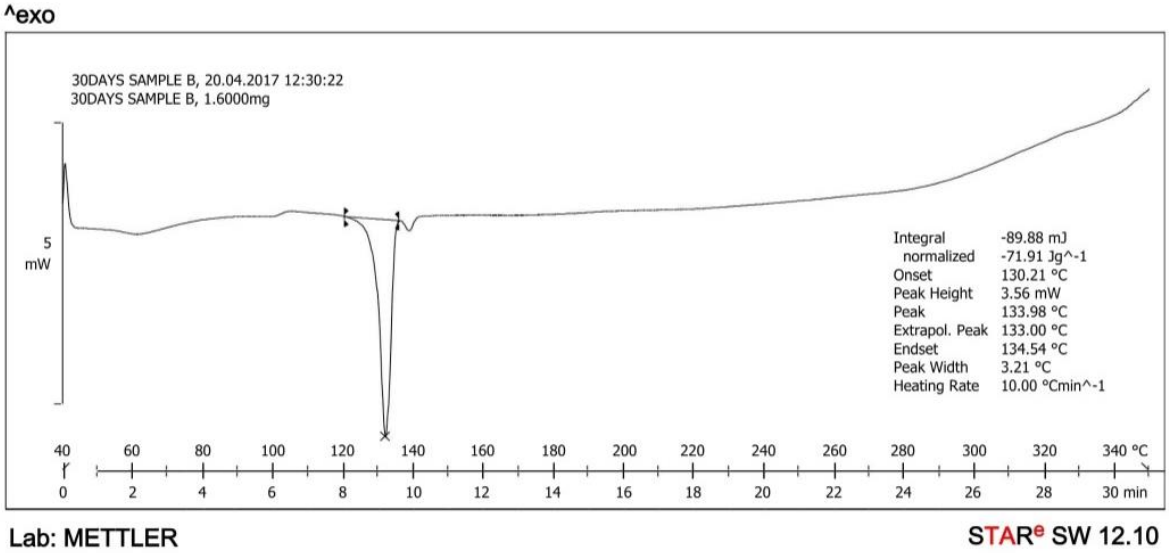

Figure 25: DSC thermogram of NTG + K4M ('30' days).

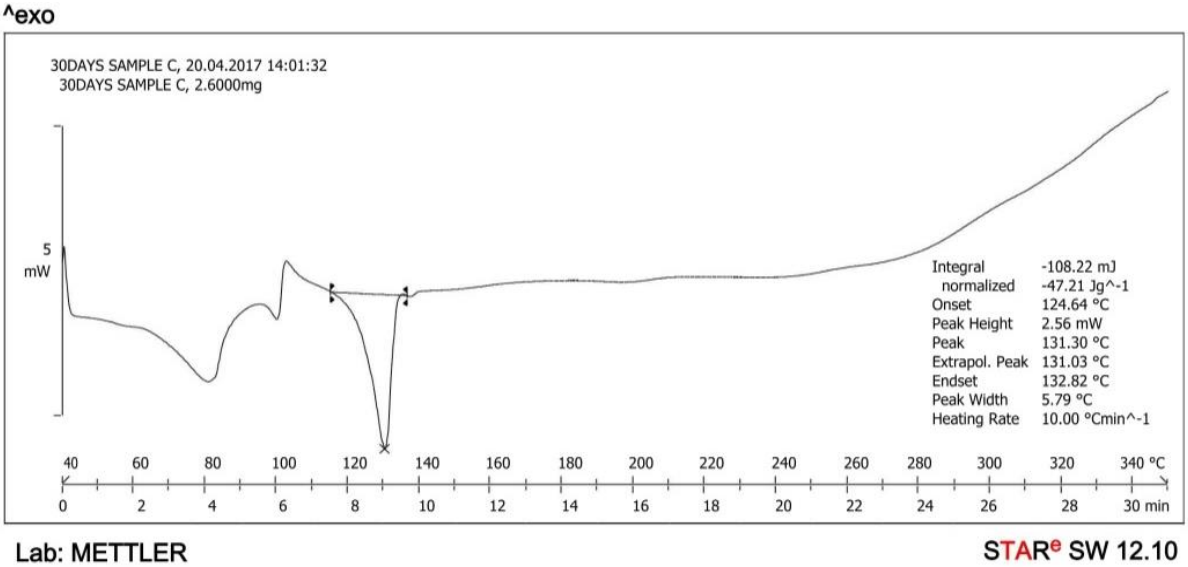

Figure 26: DSC thermogram of NTG + AVICEL PH101 ('30' days).

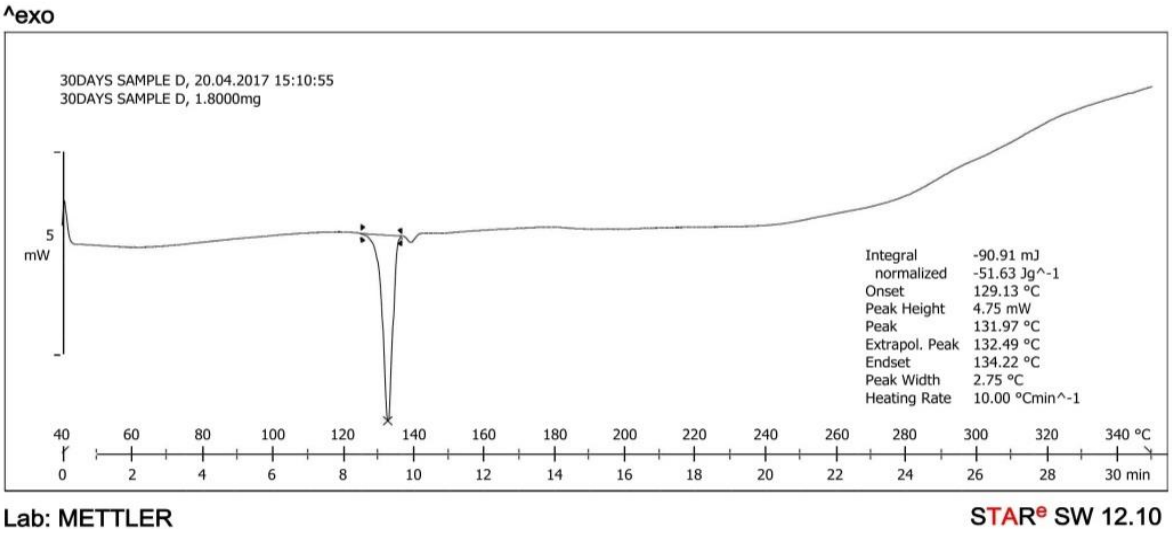

Figure 27: DSC thermogram of NTG + AVICEL PH102 ('30' days).

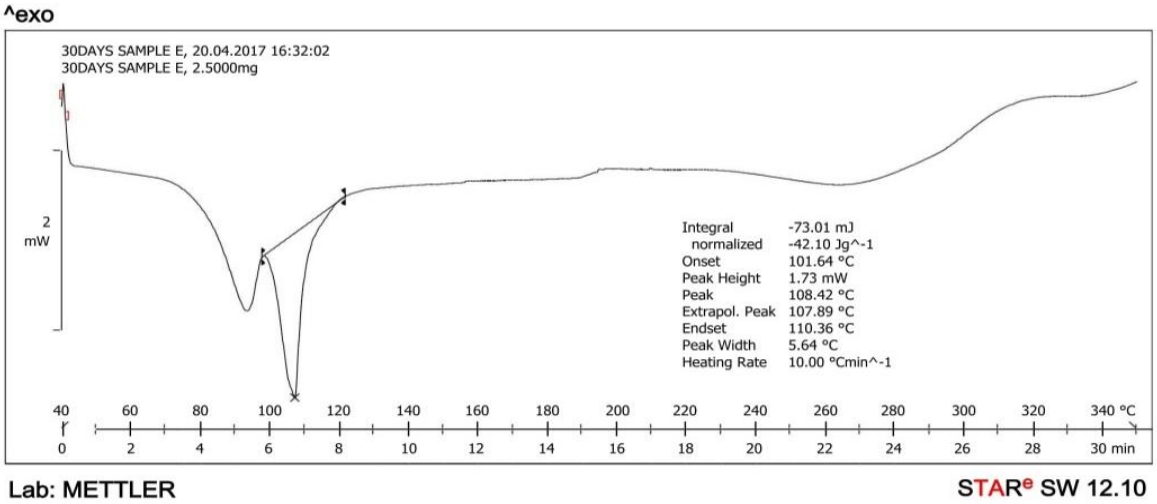

Figure 28: DSC thermogram of NTG + MG-S.

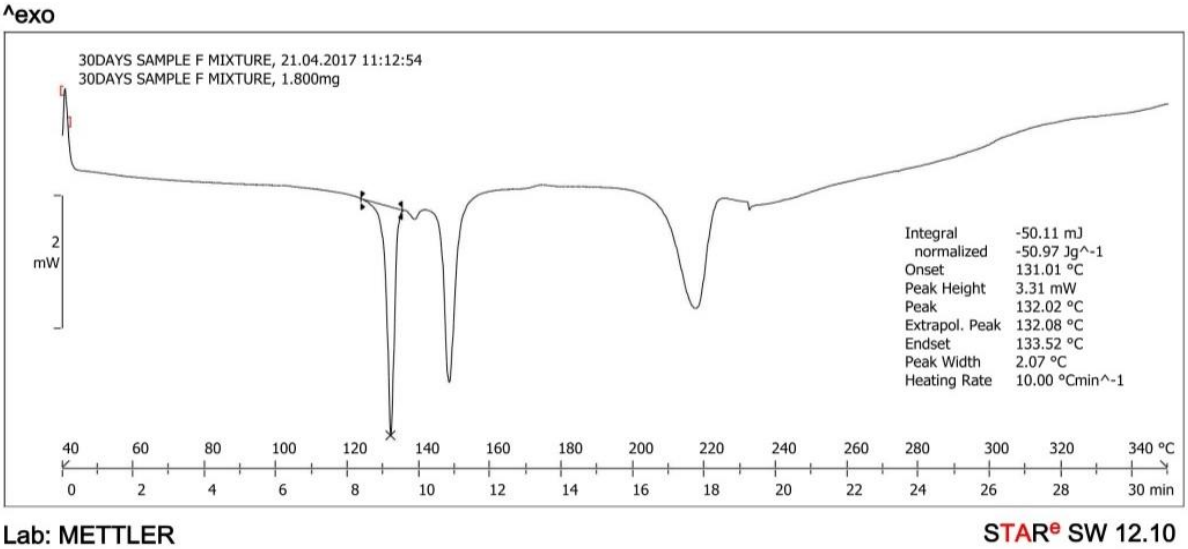

Figure 29: DSC thermogram of NTG + Lactose.

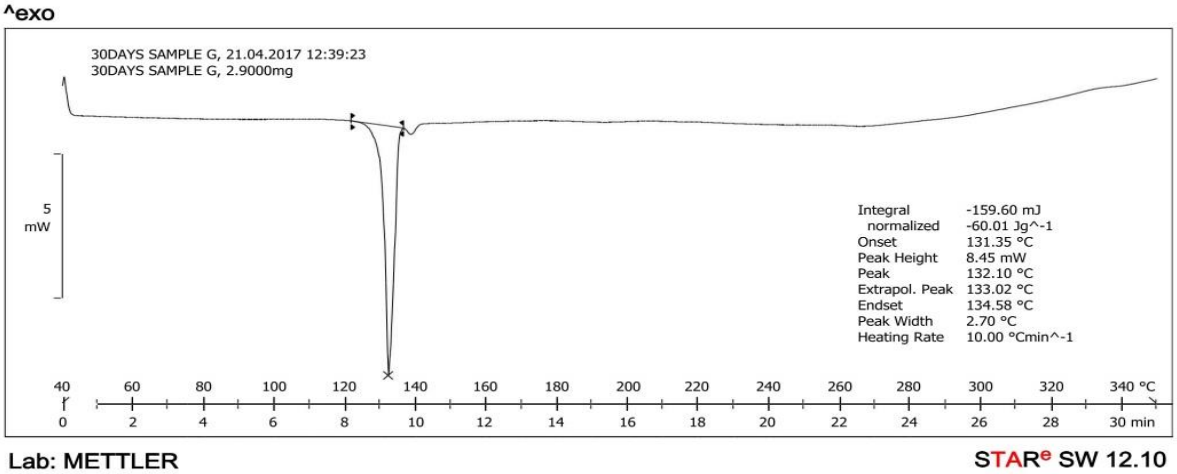

Figure 30: DSC thermogram of NTG +Talc.

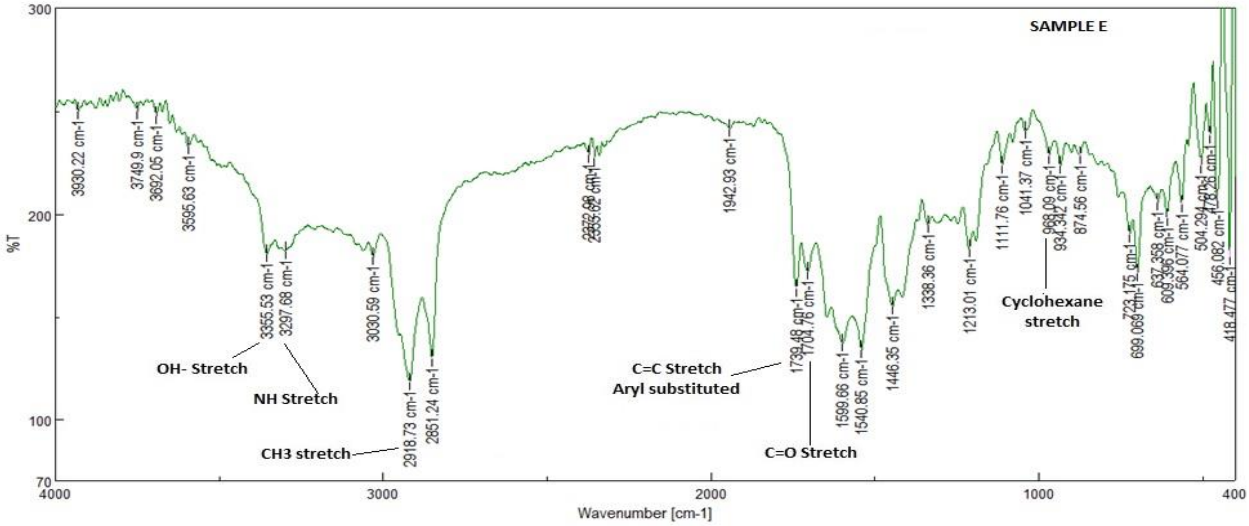

Figure 31: IR spectra of NTG +Magnesium Stearate.

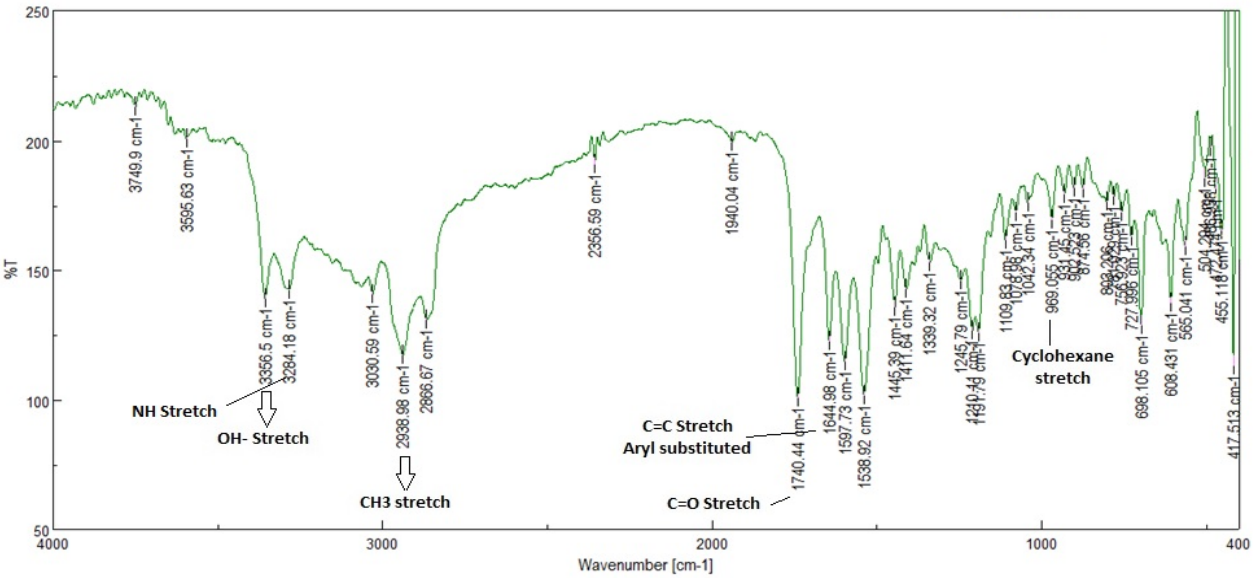

Figure 32: IR spectra of NTG.

The DSC thermogram of NTG and Magnesium Stearate (MG-S) showed a sharp endothermic peak at 101.41°C and peak onset at 89.91C with irregular thermogram. There is disappearance of the peak of NTG indicates that, there may be physical interaction between NTG and MG-S. Therefore, the NTG - MG-S mixture was subjected to IR study and its spectrum was compared with IR spectra of NTG, which indicates that there is no any physical interaction between NTG and MG-S. (Figure 31, 32)

The DSC thermogram of NTG and Lactose showed a sharp endothermic peak at 148.79°C and peak onset at 145.27°C which indicates dehydration of bound water. The DSC thermogram also showed the melting point peak at 220°C. This indicates that there is no physical interaction between NTG and Lactose. (Figure 8)

The DSC thermogram of NTG and Talc showed a sharp endothermic peak at 132.38°C and peak onset at 130.08°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with Talc. (Figure 9)

The DSC thermogram of NTG and K100M showed a sharp endothermic peak at 131.59°C and peak onset at 128.42°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with K100M. (Figure 10)

The DSC thermogram of NTG and K4M showed a sharp endothermic peak at 132.00°C and peak onset at 129.24°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with K4M. (Figure 11)

The DSC thermogram of NTG and Microcrystalline Cellulose AVICEL PH101 showed a sharp endothermic peak at 130.37°C and peak onset at 123.64°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with AVICEL PH101. (Figure 12)

The DSC thermogram of NTG and Microcrystalline Cellulose AVICEL PH102 showed a sharp endothermic peak at 132.64°C and peak onset at 130.13°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with AVICEL PH102. (Figure 13)

The DSC thermogram of NTG and Magnesium Stearate (MG-S) showed a sharp endothermic peak at 107.22°C and peak onset at 100.54°C with irregular thermogram. There is disappearance of the peak of NTG indicates that, there may be physical interaction between NTG and MG-S. Therefore, the NTG - MG-S mixture was subjected to IR study and its spectrum was compared with IR spectra of NTG, which indicates that there is no any physical interaction between NTG and MG-S. (Figure 31,32)

The DSC thermogram of NTG and Lactose showed a sharp endothermic peak at 131.99°C and peak onset at 130.08°C which indicates dehydration of bound water. The DSC thermogram also showed the melting point peak at 219°C. This indicates that there is no physical interaction between NTG and Lactose. (Figure 15)

The DSC thermogram of NTG and Talc showed a sharp endothermic peak at 132.12°C and peak onset at 130.35°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with Talc. (Figure 16)

The DSC thermogram of NTG and K100M showed a sharp endothermic peak at 132.33°C and peak onset at 128.99°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with K100M. (Figure 17)

The DSC thermogram of NTG and K4M showed a sharp endothermic peak at 131.27°C and peak onset at 129.95°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with K4M. (Figure 18)

The DSC thermogram of NTG and Microcrystalline Cellulose AVICEL PH101 showed a sharp endothermic peak at 131.65°C and peak onset at 128.97°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with AVICEL PH101. (Figure 19)

The DSC thermogram of NTG and Microcrystalline Cellulose AVICEL PH102 showed a sharp endothermic peak at 133.30°C and peak onset at 128.30°C. The

Table 1: Results of UV analysis of the samples under IST conditions after 3 weeks of storage.

Sr. No.	Sample	Ratio (Drug + Excipients / polymer)	% Drug Remaining	
			[B]Control Sample (2-8°C)	[C]Stressed Sample (50°C)
	A		101.64	99.6
	B		102.15	99.8
	C		101.25	99.48
	D		101.92	100.17
	E		101.96	99.56
	F		102.2	100.49
	G	1:1	101.44	99.67
	H		101.79	100.01

[A] Values are expressed as standard deviation
[B] Drug excipients/polymers blend without water and stored in refrigerator (2-8°C)
[C] Drug excipients/polymers blend with 10% added water and stored at 50°C for 3 weeks.

endothermic peak of NTG was well preserved, this shows that the NTG is compatible with AVICEL PH102. (Figure 20)

The DSC thermogram of NTG and Magnesium Stearate (MG-S) showed a sharp endothermic peak at 102.11°C and peak onset at 90.51°C with irregular thermogram. There is disappearance of the peak of NTG indicates that, there may be physical interaction between NTG and MG-S. Therefore, the NTG - MG-S mixture was subjected to IR study and its spectrum was compared with IR spectra of NTG, which indicates that there is no any physical interaction between NTG and MG-S. (Figure 31, 32)

The DSC thermogram of NTG and Lactose showed a sharp endothermic peak at 149.19°C and peak onset at 144.25°C which indicates dehydration of bound water. The DSC thermogram also showed the melting point peak at 220°C. This indicates that there is no physical interaction between NTG and Lactose. (Figure 22)

The DSC thermogram of NTG and Talc showed a sharp endothermic peak at 133.48°C and peak onset at 129.88°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with Talc. (Figure 23)

The DSC thermogram of NTG and K100M showed a sharp endothermic peak at 130.09°C and peak onset at 129.25°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with K100M. (Figure 24)

The DSC thermogram of NTG and K4M showed a sharp endothermic peak at 133.98°C and peak onset at 130.21°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with K4M. (Figure 25)

The DSC thermogram of NTG and Microcrystalline Cellulose AVICEL PH101 showed a sharp endothermic peak at 131.30°C and peak onset at 124.64°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with AVICEL PH101. (Figure 26)

The DSC thermogram of NTG and Microcrystalline Cellulose AVICEL PH102 showed a sharp endothermic peak at 131.97°C and peak onset at 129.13°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with AVICEL PH102. (Figure 27)

The DSC thermogram of NTG and Magnesium Stearate (MG-S) showed a sharp endothermic peak at 108.42°C and peak onset at 101.64°C with irregular thermogram. There is disappearance of the peak of NTG indicates that, there may be physical interaction between NTG and MG-S. Therefore, the NTG - MG-S mixture was subjected to IR study and its spectrum was compared with IR spectra of NTG, which indicates that there is no any physical interaction between NTG and MG-S. (Figure 31,32)

The DSC thermogram of NTG and Lactose showed a sharp endothermic peak at 132.02.19°C and peak onset at 131.01°C which indicates dehydration of bound water. The DSC thermogram also showed the melting point peak at 220°C. This indicates that there is no physical interaction between NTG and Lactose. (Figure 29)

The DSC thermogram of NTG and Talc showed a sharp endothermic peak at 132.10°C and peak onset at 131.35°C. The endothermic peak of NTG was well preserved, this shows that the NTG is compatible with Talc. (Figure 30)

Isothermal Stress Testing (IST)

The drug–excipient mixtures were tested using the technique of IST and the quantitative results obtained after UV analysis are shown in Table 1. It has been observed from the Table 2 that there is a little change in the drug content of the samples after storage of drug–excipient blends under stressed conditions of IST studies after 3 weeks of storage at stressed conditions, also the from DSC and IR study it clearly indicates that NTG was not degraded in drug–excipients mixture. Therefore, it was considered that the NTG and the excipients used are compatible with each other.

In case of NTG–magnesium stearate mixture, a definite conclusion could not be drawn based on the DSC results alone. However, the results of IST studies showed that the residual drug concentration was within the limit and in the IR spectrum of NTG–magnesium stearate mixture, the characteristic bands of NTG were well preserved confirming the compatibility.

CONCLUSION

The results of the compatibility studies confirmed that DSC and IR could be used as the intensive methods to evaluate and ascertain the compatibility between NTG, polymers and excipients. However, the techniques of IST

after storage of the mixture of NTG and individual excipients under stressed conditions should also be adopted in conjunction with DSC and IR studies to confirm conclusion. In this study, the DSC study along with IR spectroscopy and UVanalysis (for IST studies) were successfully employed to assess the compatibility of NTG with the excipients and polymers.

From overall results of the DSC studies an interaction was suspected between NTG and magnesium stearate. However, based on the results of IR spectroscopy and IST study, the possibility of incompatibility between NTG and magnesium stearate was completely ruled out. Thus, the methods of DSC, IR spectroscopy, and IST have been proved to be successful in the assessment of the compatibility of NTG, polymers and accidents which are used in the sustained release formulations.

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