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ABSTRACT

PROCESS-STRUCTURE-PROPERTY RELATIONSHIPS OF RESORBABLE DESAMINO TYROSINE DERIVED POLYMERS: EFFECT OF BACKBONE CHEMISTRY AND ASSEMBLY ON DRUG DELIVERY

by
Pinar Nebol

The selection the correct biomaterial for a specific medical application plays an important role for the success of both application and the device. Since different applications require different properties, investigation and improvement of biomaterials with different properties are very important. L-tyrosine derived polymers enable the manipulation of the properties of the material by changing backbone or pendent chain structure. L-tyrosine derived polyarylate is one of the class of these materials.

This study investigates the behavior of the tyrosine derived polyarylates under in vitro conditions. The change of structure caused by incubation in phosphate buffer solution and the effect on the release of p-nitroaniline (PNA) (model drug) has been investigated, primarily with differential scanning calorimetry (DSC). In addition the release profile of PNA has been investigated by UV/visible spectroscopy.

Two different polyarylates were used. poly[(desaminotyrosine dodecyl esterl) dodecondioate] designated Poly(DT 12, 10) and, poly[(desaminotyrosine octyl ester) sebacate] designated Poly(DT 8, 8).

The results obtained from this study indicates that incubation caused significant changes in the solid state organization of the Poly(DT 8, 8). Tg is seen in dry polymers but disappears after the beginning of the incubation, indicating a phase change in the polymer. The enthalpy of phase change of the Poly(DT 8, 8) increases and lay off state in about one half a day. However, in contrast of Poly(DT 8, 8), the enthalpy of Poly(DT 12,

10) doesn't change significantly. According to these results, it is concluded that a phase change occurs in Poly(DT 8, 8) by incubation. The incubation in dry conditions also indicates a phase change in Poly(DT 8, 8), and this is accelerated by the presence of moisture. The incorporation of the model drug did not affect the observed enthalpy change of either of the polymers investigated.

PROCESS-STRUCTURE-PROPERTY RELATIONSHIPS OF RESORBABLE DESAMINO TYROSINE DERIVED POLYMERS: EFFECT OF BACKBONE CHEMISTRY AND ASSEMBLY ON DRUG DELIVERY

by
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Thesis
Submitted to the Faculty of
New Jersey Institute of Technology
in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Biomedical Engineering

Department of Biomedical Engineering

May 2008

APPROVAL PAGE

PROCESS-STRUCTURE-PROPERTY RELATIONSHIPS OF RESORBABLE DESAMINO TYROSINE DERIVED POLYMERS: EFFECT OF BACKBONE CHEMISTRY AND ASSEMBLY ON DRUG DELIVERY

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Dedicated to the dearest ones in my life;

My lovely family, they are my luck, my friends and my best supporters…
My precious Caner Yilmaz, he is the love in my hearth, color in my eyes and happiness in my life…

ACKNOWLEDGMENT

It is my pleasure to thank all the people who made this thesis possible.

First, I would like to express my utmost gratitude to my thesis advisor Dr. Michael Jaffe. Throughout my thesis study, he provided encouragement, sound advice, good teaching and lots of good ideas. I would also like to thank Kimberly Griswold for her support and help for this research.

I express my sincere thanks to Dr. George Collins for his comments, guidance, valuable input, and being a part of my committee.

I would like to thank to Dr. Richard Foulds and Dr. Treena Arinzeh for being a part of my committee.

I would like to pay special thank to Dr. Zohar Ophir, Dr. Willis Hammond and Joe Pickton for their kindness and help with this research and laboratory work.

I would like to thank Yelda Alkan, Ali Avni Cirik, Nizamettin Avci and Angana Benerjee who have generously supported me throughout the study. I wish to give a loving thank you to Caner Yilmaz for helping me get through these difficult times, and for all the emotional support, comradery, love and care he provided. Finally, I would like to acknowledge my parents and family for without them I would not have the talents and opportunities to succeed.

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CHAPTER 1

INTRODUCTION

Biodegradable polymers have gained great importance over the last few year. This is basically caused by the advantages of the degradable polymers over non-degradable polymers. The first advantage is relatively mild foreign body reaction caused by biodegradable polymers since they gradually degrade in the body and do not release harmful residues if they are biocompatible. The second advantage is the ability to regenerate tissue which can be available for the use in tissue engineering. In addition, the properties they possess make them available to use for many medical implants, drug delivery material [1].

Many different biodegradable polymers have been investigated for different applications. The most widely used biodegradable polymers are polyglycolic acid, polylactic acid and their copolymer polyglycolic acid/ polylactic acid (PGA, PLA, PGLA) (i.e. polyester based plymers), polycaprolactone (PCL), polyhydroxybutrate (PHB), polyhydrocybutrate-co-valerate (PHBV), polyorthoester and polyethyleneoxide (PEO) [2, 4].

The properties of the material used in biomedical applications play a vital role in the success of the application. Hence it's important to choose a material having appropriate properties for specific applications. Therefore to be able to customize the properties of the material for a desired application is desirable. Homo-poly(amino acids) show good biocompatibility since they are developed from natural amino acids. However, they have many disadvantages like poor degradation, processing difficulties, and insolubility in common organic solvents [4, 5]. To overcome these

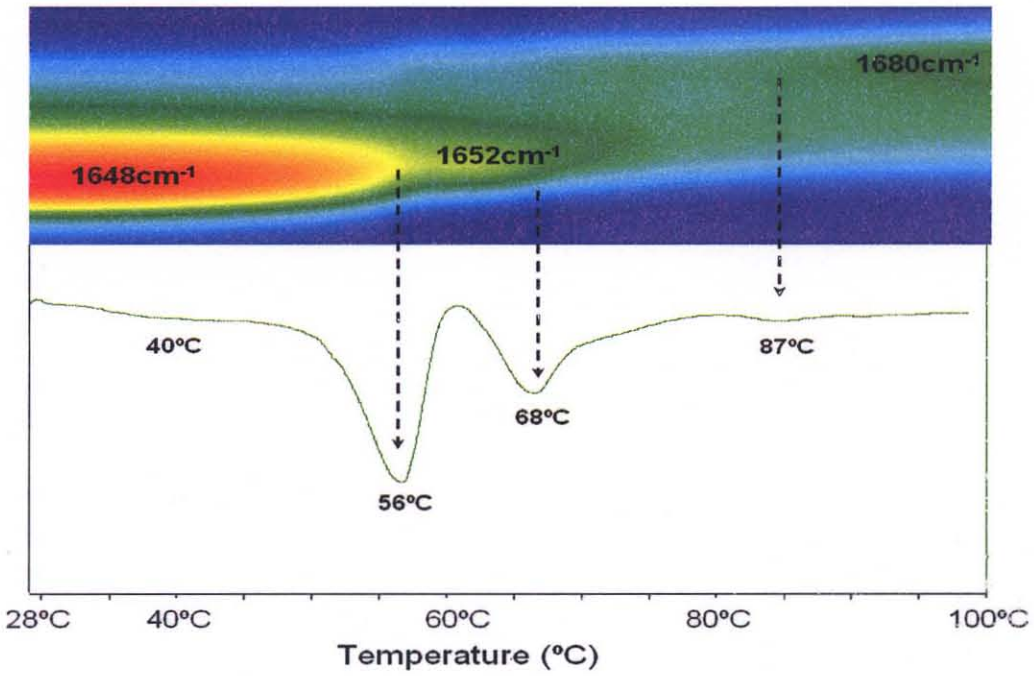

Figure 2.4 The overlap of DSC and temperature dependent FT-IR results of poly (DT 12,10) [6].

From the results of Figure 2.4, it can be concluded that hydrogen bonding is affected by temperature. Combining the DSC and FTIR results, it is reasonable to assume that organization in Poly(DT 8, 8) is associated with H bonding [6].

In the previous studies of the Jaffe group, it is seen that as methylene groups R and Y are small, then the material is amorphous If the number of methylene groups at these two sites increased, the material shows some level of non-crystalline organization and loses its strict amorphous properties [6, 36, 39].

increases, the ability of the material to reorganize itself increases [36]. The other important result that obtained is the effect of moisture on the reorganization of these polymers [38]. Yoo et al., investigated the thermal property of Poly(DT 8, 8) under various conditions. In order to see the effect of moisture on the structure of Poly(DT 8, 8), samples were treated under both wet and dry conditions [38]. When the samples were kept under vacuum and the moisture content is held to between 0.2-0.02%, a single glass transition point were obtained under dry conditions. When the samples were kept in aqueous environment an endothermic peak develops, and becomes more distinguishable with larger energy. The author concluded these finding as the plasticizing effect of moisture on structure formation of polyarylates; the presence of moisture makes the material more flexible and ease its reorganization [38].

The aim of this study is to examine the structural changes of several L-Tyrosine derived polyarylates under in-vitro conditions and relate this behavior to drug elution profiles.

CHAPTER 2

THEORY and PRINCIPLE

2.1 Biomedical Materials and Their Applications

With increased lifestyle (stress level, accidents and change in food habit) there is an increase in the individuals' need for biomedical applications. This augmentation allows scientists to focus on biomedical products such as artificial organs, biocompatible devices and products designed to increase the effect of drug therapy [47]. Biomaterials can be defined in several different ways but in general it is said to be a synthetic material which is used to replace a part or a function of a living system contacting with living tissues, blood or biological fluid. It can also be defined as a substance (other than drugs) or combination of substances which substitutes for the role of any organ or tissue [1].

Several examples can be given for biomaterials produced and used in the medical market. Table 2.1 and Table 2.2 summarize common applications of biomaterials in both organs and body systems [1].

Table 2.1 Biomaterials in Organs [1]

Organ	Examples
Hearth	Cardiac pacemaker, artificial heart valve, total artificial heart
Lung	Oxygenator machine
Eye	Contact lens, intraocular lens
Ear	Artificial staps, cochlea implant
Bone	Bone plate, intramedullary rod
Kidney	Kidney dialysis machine
Bladder	Catheter and stent

Table 2.2 Biomaterials in Body Systems [1]

System	Examples
Skeletal	Bone plate, total joint replacement
Muscular	Sutures, muscle stimulator
Circulatory	Artificial heart valves, blood vessels
Respiratory	Oxygenator machine
Integumentary	Sutures, burn dressing, artificial skin
Urinary	Catheters, stent, kidney dialysis machine
Nervous	Hydrocephalus drain, cardiac pacemaker, nerve stimulator
Endocrine	Microencapsulated pancreatic islet cells
Reproductive	Augmentation mammoplasty, other cosmetic replacement

The target function and the in-vivo environment of the material in the body play an essential role in the selection of the raw material. Considering these factors the biomaterial to be utilized, might be produced from metals, polymers, ceramics and composites [1]. The material selected should meet all of the requirements for the particular application [33]. The biomaterial selection is an important issue because if the selection is inappropriate the health of the patient could be affected quite adversely. This selection will depend on the properties of the material, design of the device and the biocompatibility of the material used. Biocompatibility is basically the reaction of the body to the foreign material. If the biocompatibility of the device is low it will irritate the tissues in the environment and provoke an abnormal inflammatory response [1].

Biocompatibility is an essential factor for biomedical devices to be safe for the use as medical device [16]. Since each medical device has different requirements appropriate material should be chosen for the specific application. In recent years, scientists focused on biomaterials and devices produced from them and tried to improve their performance. Biodegradable polymers played important roles in these

studies and contributed a lot to their improvement. Through the development of devices lots of problems occurred, such as the incompatibility of the foreign material irritation of degradation products and infections caused from the operation [47]. Those problems might be overcome by the selection of the appropriate raw material.

The mechanical properties and the degradation behavior of the polymers is the main criteria to be considered for selection depending on the requirements of the specific devices [17]

Medical applications of biopolymers can be categorized into three subgroups;

- Extracorporeal uses; catheters, artificial kidney membranes, wound dressing and artificial skin etc…
- Permanently Implanted Devices; Sensory, cardiovascular, orthopaedic and dental devices etc…
- Temporary Implants; Degradable sutures, implantable drug delivery systems etc… [47].

In the literature there are 4 different terms used to describe the disintegration of the material in a living organism. These are biodegradation, bioerosion, bioabsorption and bioresorption. It is not always easy to distinguish exactly by which process materials disintegrate in a living organism. Simply biodegradation can be referred as chemical degradation of the material caused by biological agent (enzyme, cell or microorganisms) [33]. However, bioerosion is defined as conversion of water-insoluble materials to fragments under physiological conditions. The terms bioresorption and bioabsorption are used when a polymeric material or its degradation products are removed by cellular activity in a living organism [33].

2.2 Drug Delivery Systems

The oral usage of the drug may not always be completely beneficial. However, the local delivery of a drug provides advantages to the patient. Medicinal support is always required for the patient after the application of the medical device. To increase the efficiency of the drug, the studies on the targeted delivery of the drug have been realized. The major advantage of the controlled local delivery of the drug is to minimize the side effects [33]. Figure 2.1 illustrates the drug concentration in blood plasma for the effectiveness of the drug.

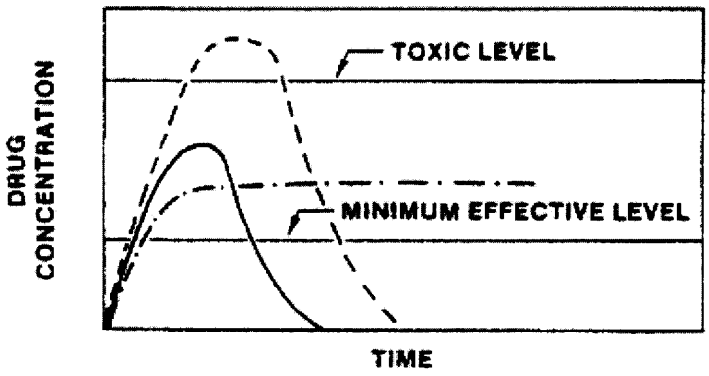

Figure 2.1 Drug concentration following absorption of therapeutic agent as a function of time. (———) safe dose, unsafe dose (– – –), controlled release (– · – · –) [33].

Unsafe dosage exceeds the maximum tolerable drug concentration and reaches a toxic over-dosing level. If a safe dose is used the concentration does not exceed the max level. However, the effect continues for a short period of time and the drug is ineffective because of under-dosing. Ideally, the controlled release of the drug provides a constant release over the entire period of time (between overdose and underdose concentrations, Figure 2.1). This provides a longer effect time in the tolerable region where the drug is best utilized [33]. By the usage of the controlled release, it is possible to avoid potential toxic over-dosing and periodic ineffective under dosing [18].

Degradable polymeric biomaterials can often enable the most effective use of the drug, and sometimes its only effective use, by routes which include: providing sustained effective systemic concentrations of the drug (i.e. avoiding the periodic potentially toxic over-dosing that can occur at the beginning of a dosing period and preventing the periodic ineffective under-dosing that can occur at the end of the dosing period); providing high concentrations of the drug only in the local vicinity of the drug-release depot, avoiding unwanted concentrations and effects of the drug at locations far away from the disease treatment site; protecting the drug from the body's metabolism and clearance mechanisms as the drug is being released; targeting the drug to particular cells and sites within the body; and targeting the drug to particular organelles and sites within individual cells [18].

2.2.1 Biodegradable Polymers in Drug Delivery

Biodegradable polymers are widely used in the drug releasing medical devices since they have good biocompatibility and drug transport properties. Polyester based polymers are the most frequently investigated degradable polymers for drug delivery applications [19]. Local drug delivery systems are mainly used in the treatment of cardiovascular disease, diabetes, orthopaedics, and cancer [20].

Basically the most widely used biodegradable polymers are; polyglycolic acid, polylactic acid and their copolymer polyglycolic acid/ polylactic acid (PGA, PLA, PGLA) (i.e. polyester based plymers), polycaprolactone (PCL), polyhydroxybutrate (PHB), polyhydrocybutrate co valerate (PHBV), polyorthoester and polyethyleneoxide (PEO). Although these biodegradable polymers show good biocompatibility they might show significant inflammatory and proliferative response in some studies [3]. They considerably increased the biocompatibility of the surface of coated devices. However, they do not decrease noeintimal proliferation by

themselves. Therefore drug loaded polymers have been used for a very long time [3]. Thus, polymeric materials can increase the surface biocompatibility of the devices however; they will be more effective if they are used in accordance with a drug.

Biodegradable polymers in drug delivery have been used for different purposes. Most frequently they are used for antibacterial purposes in medical implants to prevent infections, in skeletal delivery systems, and in stent coating to prevent restenosis and coagulation [21-23]. H. Gollwitzer et al., coated medical implants with antibacterial poly D,L lactic acid. Kirschner-wires were coated by solvent casting. The antibacterial effect was provided by Gentamicin & Teicoplain. The number of viable bacteria was reduced in the antibiotics presence [21].

There are several studies with biodegradable polymers, which studies them as a drug matrix for medical devices and implants [2, 3]. Five different biodegradable synthetic polymers after implantation within porcine coronary artery are studied by Van der Giessen et al. in the coating of stents. The polymers used were; polycaprolactone (PCL), polyhydroxybutrate (PHB), polyhydrocybutrate-co-valerate (PHBV), polyorthoester, polyethyleneoxide/polybutylene-terephtalate and poly(glycolic acid) / poly(lactic acid). The results showed that all polymers induced a significant inflammatory and proliferative response after 4 weeks and drug release is achieved through disintegration of the polymer [42]. Lincoff et al. compared the drug release from both low and high molecular weight Poly-L-lactic acid (PLLA). According to the study, high molecular weight PLLA showed slower degradation and consequently there was no evidence of acute or chronic inflammation [43].

In biomaterials the material properties are extremely important in order to mimic the tissue that it will replace or in order to succeed in its specific application. Some of the materials will require fast degradation some of them slow degradation,

some of the products (like bone fixation devices) will require to bear load and some systems (drug releasing systems) will require rubbery structures [7].

Kohn and Langer developed new biodegradable polymers that can be used in vivo. The chemical structure of these polymers makes it possible to adjust the properties of polymers according to the specific application [4]. One major type of these polymers is L-Tyrosine derived polyarylates. The structure of these materials allows for adjusting the properties of the materials by changing the length of the backbone and pendent chain. The difference in these chains determines whether the material is rubbery or glassy at a specific temperature, the mechanical properties and degradation properties [4].

One important limitation for biodegradable polymers is the cytotoxicity of the degradation products. For examples diphenols gives good mechanical strength to the polymers when it is used in backbone However, polymers containing diphenol in their backbone cannot be used in vivo since they are cytotoxic [5]. The widely utilized biodegradable polymers derived from α–hydroxy acids (like poly-glycolic acid, poly-lactic acids) have similar limitation. Although they have approval for many applications in the USA, their degradation products can still be limit their applications. The acidic degradation product may cause the material to fail [8]. Kohn and Langer used Tyrosine which is a major nutrient instead of diphenol in the backbone of the polymer [5].

2.2.2 Chemical Structure of Polyarylates

Although some biodegradable polymers have FDA approval to be used in humans, they still have disadvantages of irritation to the body because of the degradation products. Since amino acids are naturally found in body, the idea of poly(amino acids) as polymeric biomaterials have gained importance. Many of the poly(amino acid)

have failed because of inappropriate physical and mechanical properties, in addition they still had immunogenic problems [2].

Tyrosine is an amino acid containing an aromatic hydroxyl group [5, 9]. In the formation of tyrosine derived polymers it is used as an alternative to diphenols [5]. Non-cytotoxic nature of tyrosine enabled to produce non-cytotoxic tyrosine based pseudo poly(amino acid) [2].

Tyrosine derived polyarylates are formed by 2 structural elements. The first allows the modification of the backbone structure and the second forms the pendent chain of the polymer [2]. It is seen in previous studies that variation in the size of the backbone and side chain causes dramatic changes in structure and properties of the polymers [10].

The nomenclature of the desaminotyrosyle-tyrosine derived polyarylates has been determined depending on the backbone and pendent structure of the polymer. According to the number of methylene group in the backbone and side chain, the name of the polyarylates can be determined. Poly(Desaminotyrosyl-tyrosine octyl sebacate) have octyl group at the side chain and octyl ester component on side chain derived from sebatic acid [6]. In order to facilitate to use of the name simple abbreviations are used as Poly(DT R, Y) where DT stands for desaminotyrosyl-tyrosine, R stands for number of hydrocarbons at the side chain and Y stands for number of hydrocarbons in the backbone chain [6].

In this study three types of polyarylates are used: Poly(DTD dodecondioate), Poly(DTO sebacate) and Poly(DTE succinate), designated Poly(12, 10), Poly(DT 8, 8) and Poly(2, 2), respectively. DTD stands for desaminotyrosine dodecyl ester, DTO stands for desaminotyrosine octyl ester and DTE stands for desaminotyrosine ethyl ester [6].

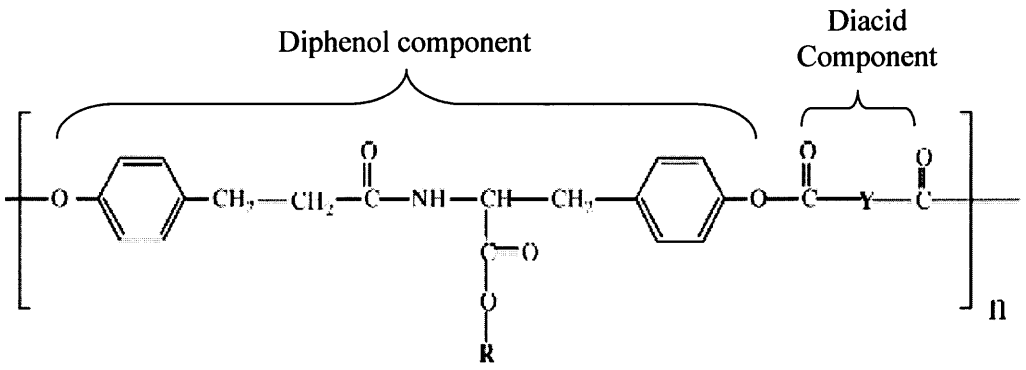

Figure 2.2 Tyrosine derived Polyarylate [5].

Figure 2.2 shows the chemical structure of the Desamino tyrosyl polyarylates [5]. Change in polymer backbone is created by the change in diacid structure in backbone and change in the diphenol component creates change in pendent chain. That's how a large number of polymer types created possessing various properties [5].

2.2.3 Morphology of Polymers

Polymers can typically have two different types of phases in solid state. These are amorphous and crystalline. However, polymers can not be completely crystalline and they will posses unordered amorphous regions thus they are called semi-crystalline [33, 34]. Figure 2.3 compares the behavior of the amorphous polymer and semi-crystalline polymer. It also shows the morphology of semi-crystalline polymer; the amorphous region in the crystalline region [34].

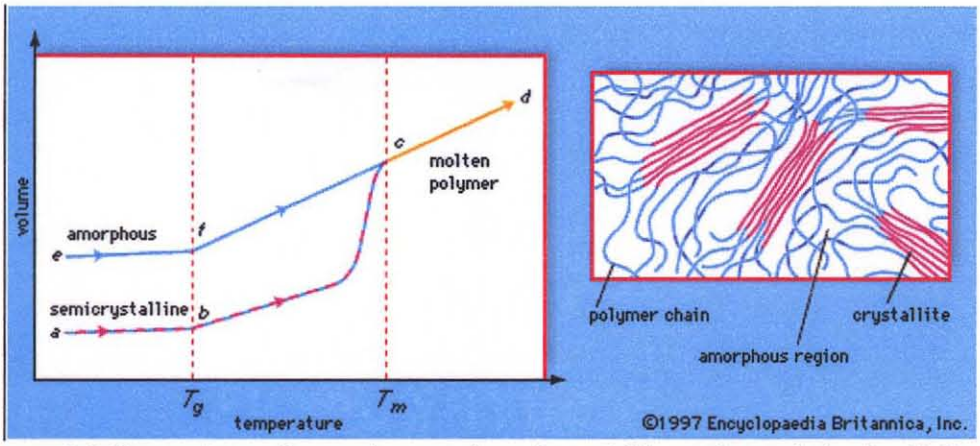

Figure 2.3 Comparison of amorphous and semi-crystalline polymer behavior [34].

The morphology of polymers is important criteria for determining the properties of the material to be used in medicine [33]. The degradation and drug release will be affected whether it is amorphous or semi-crystalline and also percent crystallinity of the material. Amorphous polymers will degrade faster compare to crystalline polymers because of faster erosion and the release of the drug will also be faster if release is dominated by degradation [35].

The morphology of the polymer can be complex and may have more than one phase in its structure. The material either crystalline or amorphous can have more than one distinct phase in its structure If a crystalline materials has more than one distinct phase it is called polymorphic materials. I an amorphous material has more than one distinct phase it is called polyamorphic material [40, 41]. Polymorphs are the materials possessing multiple crystalline phases with a phase boundary represented by phase equilibrium diagram. Therefore, there is a certain temperature and pressure that, free energies of two phases are equal and on one side one phase is more stable. Although this phenomenon is rarer for amorphous materials, there are examples that can be considered as polyamorphous materials [41]. Water is an example of polyamorphous materials and it is still under investigation by scientists [41]. If a

polyamorphic material is used in any application to produce a medical device, how the phases of the material changes should be considered in order to predict the properties of the device. Form the previous studies poly(DT 8, 8) showed different phase properties when it is exposed to different conditions [6, 24, 27, 36, 38, 39].

2.2.4 Drug Release Studies of L-Tyrsosine Derived Polyarylates and Polycarbonates

Since L-tyrosine derived polyarylates are relatively new polymers, there are limited resources in the literature on drug delivery. The majority of the existing studies are published by J. Kohn and his research group.

Yu and Kohn used two model drugs to investigate the release behavior of microspheres formed from Poly(DTB carbonate) and Poly(DTB carbonate) polyethylene glycol (PEG) copolymer. Fluorescein isothiocyonate-dextran (FITC-dextran) is used as high molecular weight hydrophilic model drug and p-nitroaniline as low molecular weight hydrophobic model drug. According to the results, FITC-dextran released with a small burst effect in the first hour then experienced a lag period having very slow release during 14 days. For the case of p-nitroaniline the release was much faster and presence of PEG accelerated the release of PNA [8].

In the literature there are studies with both L-tyrosine derived polyarylates and polycarbonates testing the hemocompatible coating by incorporation of anticoagulant into the coating. Huridin and prostacyclin were used as anticoagulant materials. Carbon fibers coated with drug incorporated polymer coating and blank polymer coating. Both showed decrease in coagulation compare to uncoated control fibers in addition drug incorporated ones prevented formation of thrombin at the surface [5].

Another remarkable study is the intracranial delivery of dopamine with long term controlled-release device which is made from Poly(DTH carbonate) [5]. Because

of the drug-polymer relationship Poly(DTH carbonate) showed prolonged release. The polymer matrix appeared to protect dopamine enabling prolonged release [5].

2.2.5 P-Nitroaniline as a Model Drug

In many studies in the literature p-nitroaniline (PNA) is used to model the drug behavior [8, 12, 14, 15]. There are a couple of advantages in using a model drug instead of using actual drugs. First it is cheaper compared to commercially available drug and can also behave like drugs having similar chemical structure.

Cheng and his coworkers used PNA to investigate the release behavior of cross-linked amino-acid containing poly-(anhydride-co-imide)s [14]. In another study PNA served again as a model drug with poly(sebacic anhydride-co-ethylene glycol). PNA was encapsulated into the polymer and release behavior was investigated under pH 7.4 and 4.0 [15].

The other advantage of PNA is its yellow color which makes it easy to monitor by simple UV/Visible sepectroscopy. This is one of the reason Kohn and Fiordeliso chose PNA as a model drug to investigate the release profile from tyrosine derived polyarylates [12]. PNA is also used in the study of Yu and Kohn. In the release studies of tyrosine-PEG-derived poly(ether carbonate)s microspheres. PNA served as low molecular weight hydrophobic model drug in this study [5, 8].

2.3 Thermal Analysis of Polymers

Differential scanning calorimetry is a technique widely used for thermal analysis of materials. It applies constant heat on both sample and reference and measures the change in temperature in both sample and reference [26]. For a material the change in temperature will be the same with reference unless there is no endothermic or exothermic reaction. If there is an exothermic reaction then the system uses the energy

released as a result of this reaction. Thus the increase in temperature of the sample is higher compare to the reference. If there is an endothermic reaction, then the change in temperature in sample is less compared to the reference since the system uses more energy to achieve the reaction [26].

Amorphous polymers or amorphous regions in polymers do not have enthalpy of melting since amorphous structures experience a smooth transition from a glassy state to a true liquid phase [31].

The structural behavior of various Desaminotyrosyle-Tyrosine derived Polyarylates has been studied widely by the Jaffe group. Figure 2.4 shows the behavior of Poly(DT 12, 10) with increasing temperature. It shows the overlap of FTIR and DSC results. From the FTIR results at low temperatures at wavelength of 1648 cm^{-1}, strong hydrogen bonding can be seen. As the temperature increases, this strong hydrogen bonding transforms to weak hydrogen bonding, and this is also seen in the DSC results as two endothermic peaks. When the temperature increases further, neither strong nor weak hydrogen bonding is distinguishable any more. Only free amide carbonyl bond was dominant [6].

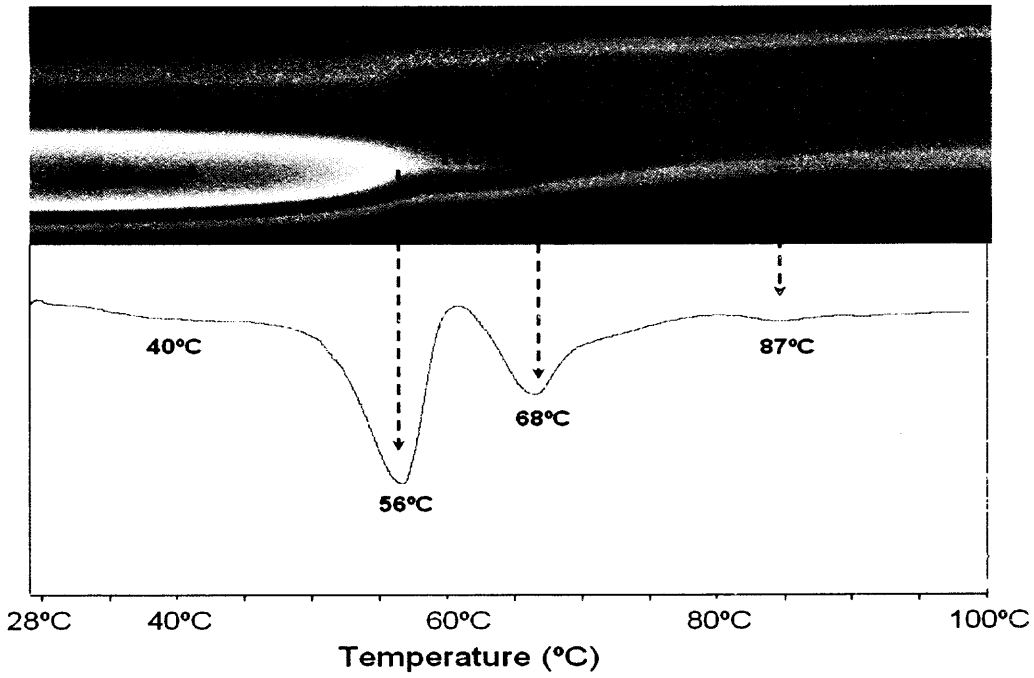

Figure 2.4 The overlap of DSC and temperature dependent FT-IR results of poly (DT 12,10) [6].

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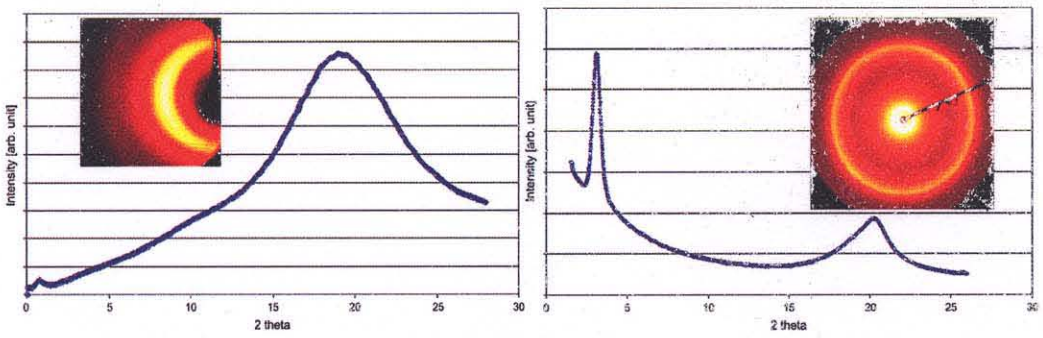

(a) (b)

Figure 2.5 X-Ray scattering data of (a) Poly (DT 2, 2) (b) Poly (DT 12, 10) [36].

Collins et al., studied the thermal characterization of polyarylates Poly(DT 12, 10) and Poly(DT 2, 2). Figure 2.5 shows the X-ray scattering data for Poly(DT 2, 2) and Poly(DT 12, 10). It is seen that both of the polymers showed a high angle peak around 20° of their 2θ angle. This peak is considered as a van der Waals peak and indicates amorphous properties. However, Poly(DT 12, 10) showed also a low angle peak unlike Poly(DT 2, 2). This peak is considered to be caused by long aliphatic chain in Poly(DT 12, 10), and considered to be a sign of some level of organization on the polymer, although it does not appear to have 3D periodicity, like crystalline structures [36]. This behavior is concluded with the existence of the complex amorphous structure formed by different types of phases [36].

This study revealed that, there are two modes of organization in the structure of Poly(DT 12, 10); Mode A and mode B. The polymer exists in mode A at room temperature having a specific H bonding arrangement. As the temperature increases than it reorganize itself and transforms to mode B [36].

There are several thermal event happens during heating of Poly(DT 12, 10) displayed by Collins et al., [36]. These events can be seen in Figure 2.6 which exhibit

the DSC result for POly(DT 12, 10) and Figure 2.7 which explains the events occur during heating of the polymer in the DSC.

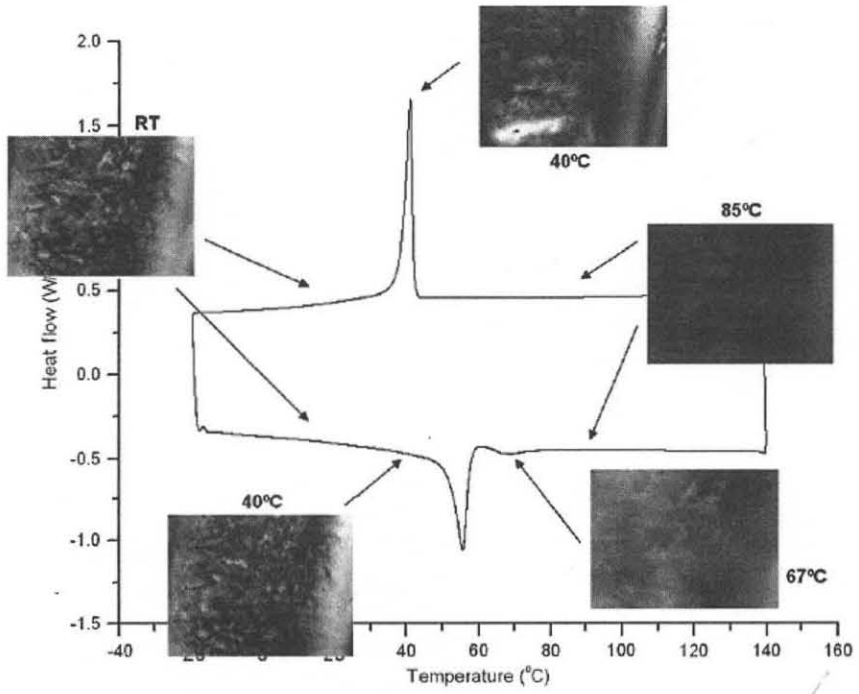

Figure 2.6 Overlay of optical pattern and DSC Poly(DT 12, 10) [36].

During heating of Poly(DT 12, 10), four thermal events occur. The first one is the rotational relaxation occur in mode A at around 40°C, and is given as event 1 in Collins' study. As the temperature increases mode A transforms to mode B at around 55°C and stated as event 2. If Poly(DT 12, 10) is continued to be heated a rotational relaxation occurs in mode B at around 67°C in which is stated as event 3. If it is heated further, mode B transforms to an unorganized mode of aggregation which is called as mode U by Collins and his coworkers. This last event is called as event 4 and occurs at around 85°C [36]. These series of events are displayed in Figure 2.7.

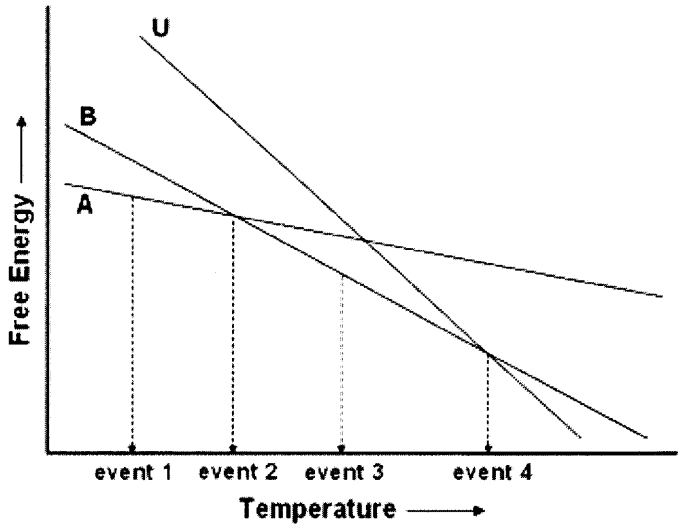

Figure 2.7 Free energy diagram for Poly(DT 12, 10) [36].

Considering these events occur during heating of Poly(DT 12, 10), in the study it is concluded that Poly(DT 12, 10) has two modes of hydrogen bonding in it structures and this modes depends on the temperature affecting the physical behavior of the polymer [36]. The change in temperature causes the polymer changes its phase from one mode to another and the change on these modes will affect the physical behavior of the polymers [36]. Therefore it's important to be able to predict the mode and the behavior of the change in mode of the polymer in order to predict the properties of the material to be used in the production of a medical device. This change in mode of organization the Poly(DT 12, 10) which is non-crystalline, supported the idea of polyamorphism for this material having different modes of amorphous aggregation [36].

Jaffe and his coworkers studied several different types of Polyarylates in Medical Device Concept Laboratory (MDCL). In one of their studies they investigated the dependence of the mesogenic order on the hydrogen bonding in the structure of the polymers. The hydrogen bonding through the backbone amide linkage

affects the organization of the internal aggregation of the polymer. According to their IR results, they concluded that the polymer re-organize itself. This reorganization is caused by the formation of hydrogen bonding of the esters through backbone of the polymer [24]. They concluded that the presence of the different phases in the polymer and the phase change between them will affect the performance of the polymer in-vivo conditions [24]. Therefore, it's important to predict the behavior of these polymers under in-vitro and in-vivo conditions.

CHAPTER 3

MATERIALS and METHODS

3.1 Materials

In this study two different L-tyrosine derived polymers were used: Poly(DTE dodecondioate), Poly(DT 12, 10) and Poly(DTO sebacate), Poly(DT 8, 8) were kindly purchased from New Jersey Center for Biomaterials and Medical Devices. Tetrahydofuran (THF) from Sigma is used as polymer solvent for Poly(DT 12, 10) and Poly(DT 8, 8). Soduim hydroxide from (NaOH) and potassium phosphate monobasic from Fisher-Scientific are used to prepare phosphate buffer (PBS) solution at pH 7.4. p-nitroaniline (PNA) purchased from Acros was used as model drug in drug release analysis.

3.2 Methods

The methods used in this study can be grouped in to three subgroups. Thermal analysis, degradation analysis of polyarylates and p-nitroaniline release analysis from polyarylates.

Based on previous trials a fifteen percent polymer wt/v ratio is used to prepare homogeneous polymer solutions. Five and 10% ratios had been used in preliminary trials and it is seen that the viscosity was low. Fifteen percent have appropriate viscosity to obtain suitable films. Glass plates were coated with Teflon sheets (with adhesive one side). After obtaining homogeneous polymer solutions, polymers films casted on these plates. The reason to use Teflon at coating surface is to be able to peel off the films easily. A twenty mill stainless steel doctor blade was used for casting each sample. Figure 3.1 shows the casted Poly(DT 8, 8) film with 10% PNA loading and doctor blade.

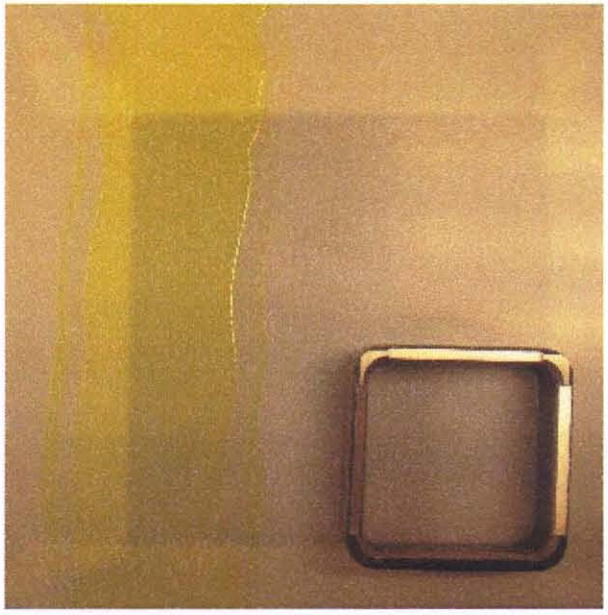

Figure 3.1 10% PNA loaded casted Poly(DT 8, 8) film on Teflon coated glass and stainless steel doctor blade.

Films are subjected to air drying for 24 hours and vacuum drying at 40°C in vacuum oven for additional 24 hrs. Dried films are than cut into 0.5 inch x 0.5 inch pieces to incubate phosphate buffer solutions.

3.2.1 Incubation of Polymer Films

Square polymer films were incubated in phosphate buffer solutions (PBS). PBS is prepared according to United States of Pharmacopedia (USP) standards at pH 7.4 [25]. 0.2 M sodium hydroxide and 0.2 M potassium phosphate monobasic is used and mixed according to USP standards. The polymer films are incubated at 37°C in 25 ml of PBS solutions. The films are removed at specified times, rinsed with deionized water and stored at 37°C for three more hours and prepared for DSC analysis.

3.2.2 Differential Scanning Calorimetry

"Differential scanning calorimetry" is used in thermal analysis of the polymers. In these experiment it is used to determine the enthalpy change of the material as a result of the incubation of the polymer films. Q100 Differential scanning calorimetry (TA Intrument) was used in the study. In the analysis, conventional DSC in heat-cool-heat mode was used for scanning in dry N_2 environment. Samples were encapsulated in standard aluminum pans between 5-8 mg. The first heating cycle gives information related to the effect of polymer processing [6]. The parameters used in DSC are summarized in Table 3.1.

Table 3.1 DSC Parameters for Thermal Analysis of L-tyrosine Derived Polyarylates

Parameters	**Temperature**
Start Temperature (°C)	-20
Heating Rate (°C)	10
Maximum Temperature (°C)	130
Cooling Rate (°C)	10
Minimum Temperature (°C)	-20

For each analysis, three repetitions have been performed to be able to see repeatability and precision. For each time point, results has been investigated with 95% confidence interval and shown by error bars in each figures.

3.2.3 Release of P-nitroaniline

The release profile of p-nitroaniline was monitored by uv/visible spectrophotometer. Standard curve has been prepared using the absorbance values at 382 nm for different PNA concentrations. The wavelength has been determined by scanning the solution having highest concentration in the range of 200-700 nm and the maximum peak has been found at 382 nm which is consistent with literature [14, 44-46]. The calibration curve and concentration equation was given in Results and Discussion Chapter. Three readings were performed for each sample and collection time points and absorbance values were recorded for each polymer type and drug ratios.

3.2.4 Gel Permeation Chromatography Analysis

In order to analyze the molecular weight of the polymers and thus the release mechanism of the drug, gel permeation chromatography (GPC) was used. GPC analysis were performed in THF (1 mL/min) using a Waters Breeze system equipped with a 717plus autosampler, a binary HPLC pump, a 2487 dual 1 absorbance detector, and a 2414 refractive index detector. A series of styragel columns which were kept in a column heater at 35 °C, were used for separation. The columns were calibrated with PS standards.

Polymer films were dissolved in THF (which is an appropriate solvent for these polymers for GPC analysis) and clear solution was obtained before GPC analysis. The weight of the polymer films were between 5-8 mg each time. In order to see the repeatability of the results random incubation times were selected and the test was repeated for each polymer type having different drug ratio.

CHAPTER 4

RESULTS and DISCUSSION

4.1 Effects of Incubation on Assembly of L-tyrosine Derived Polyarylates

4.1.1 Effects of Incubation on Assembly

The effects of incubation on assembly were investigated by DSC. The films collected at specific incubation times were run in DSC and their enthalpies were determined from endothermic peaks obtained during melting.

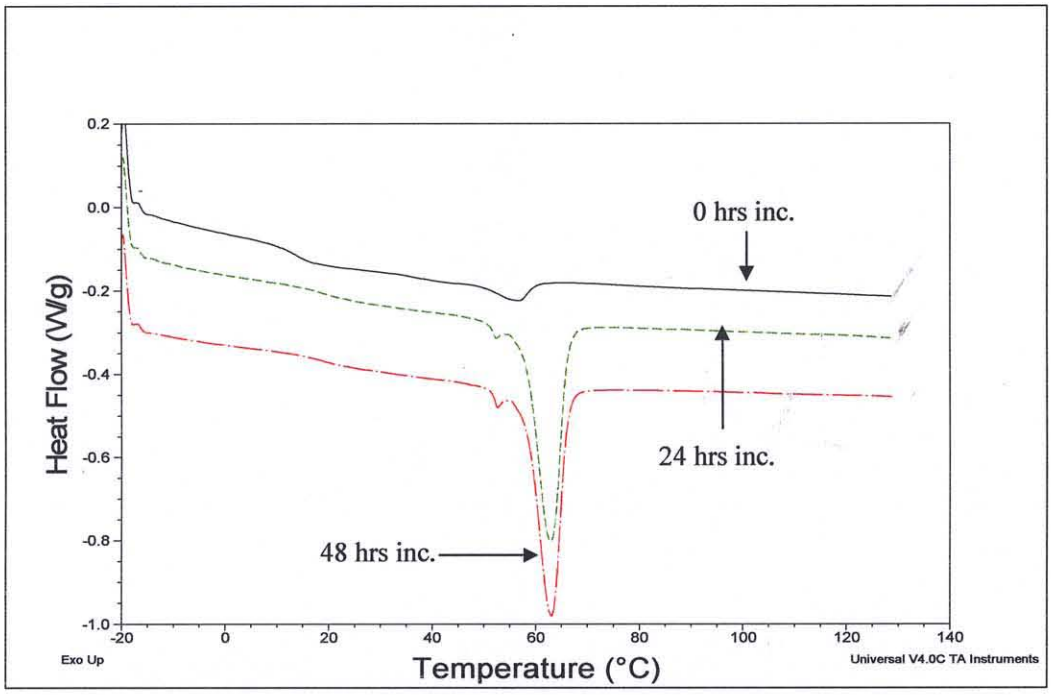

Figure 4.1 DSC Results of Poly(DT 8, 8) (0% PNA) with 0, 24 and 48 hrs of incubation.

Figure 4.1 shows the DSC results for the first heating cycle for Poly(DT 8, 8) with zero PNA concentration. As shown, the endothermic peak of the films changes for different incubation times indicating change of the enthalpy. At 0 hrs incubation a small endothermic peak was seen at around 60°C; after 24 hrs of incubation the

endothermic peak became much sharper at around 63°C. The Tg almost disappears after incubation although it is apparent with the 0 hrs data point, consistent with results of Yoo [6]. The endothermic peak shows that the heat flow increases significantly for 24 and 48 hrs of incubation compared to zero hrs incubation. However, for Poly(DT 12, 10) the endothermic peaks do not change significantly as it can be seen in Figure 4.2. A sharp endothermic peak was seen at around 63°C and a very small shallow peak was seen at around 85°C.

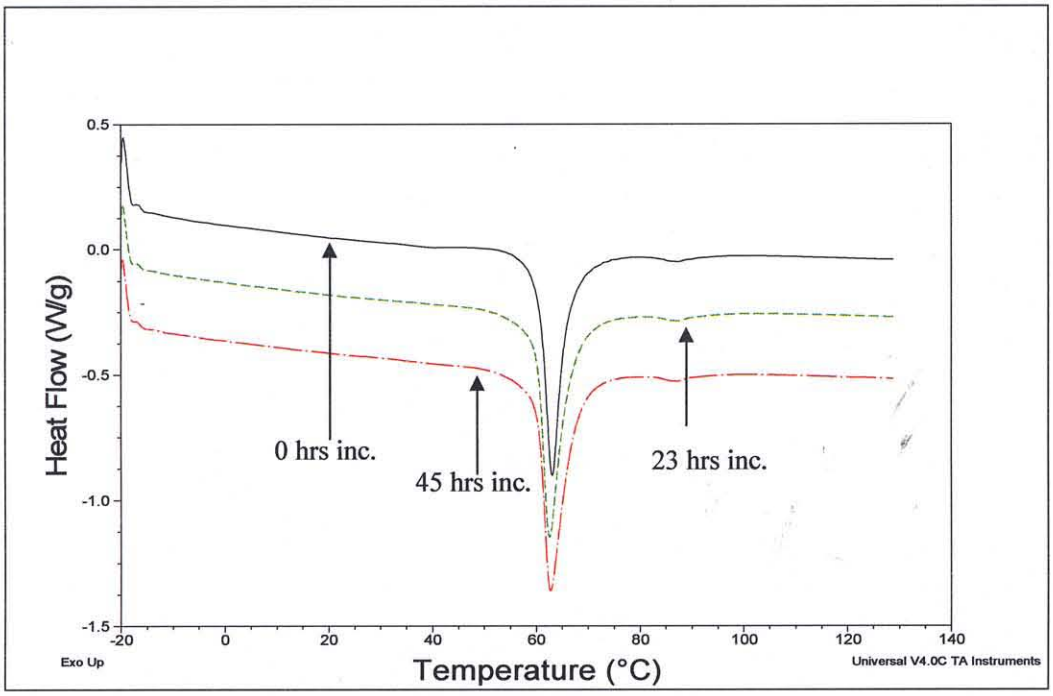

Figure 4.2 DSC Results of Poly(DT 12, 10) (0% PNA) with 0, 23 and 45 hrs of incubation.

Figures 4.3 and 4.4 show the enthalpy change of Poly(DT 8, 8) and Poly(DT 12, 10) respectively. The enthalpy values were calculated using linear baseline integration with TA Universal Analysis.

Incubation changes the enthalpy of Poly(DT 8, 8). In Figure 4.3 the exponential change in enthalpy of Poly(DT 8, 8) during the early stages of incubation

can be seen. It is also seen that the enthalpy increases and levels off after approximately 6 hrs. The change of the enthalpy with the incubation in a simulated aqueous body environment suggests the phase change of the polymer, reorganization in internal molecular aggregation, will occur in the first few hours of in-vivo use.

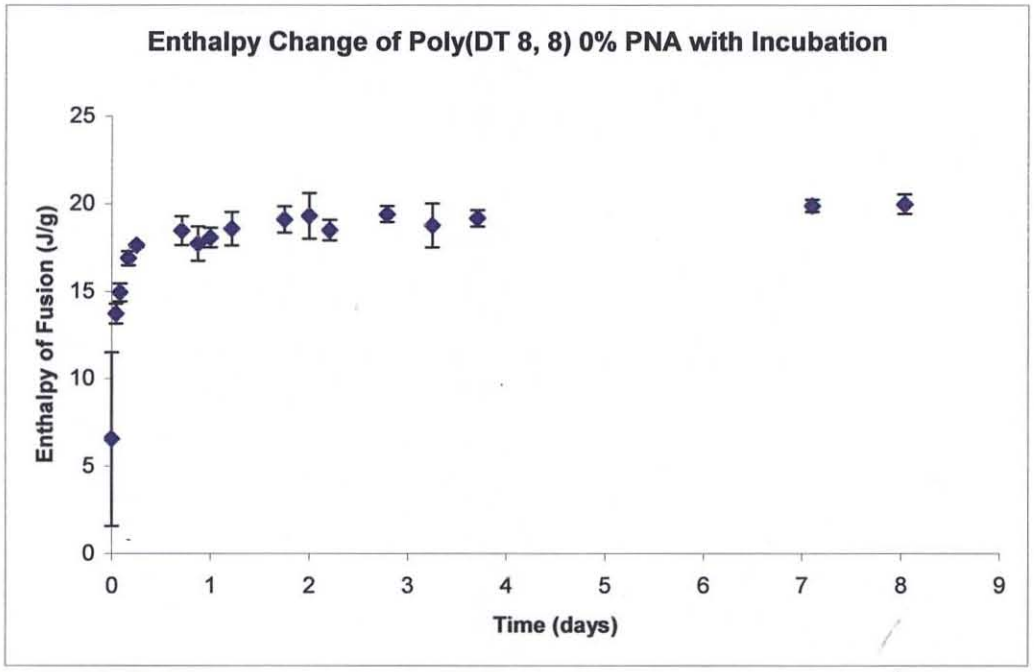

Figure 4.3 Enthalpy change of Poly(DT 8, 8) with incubation with 0% PNA.

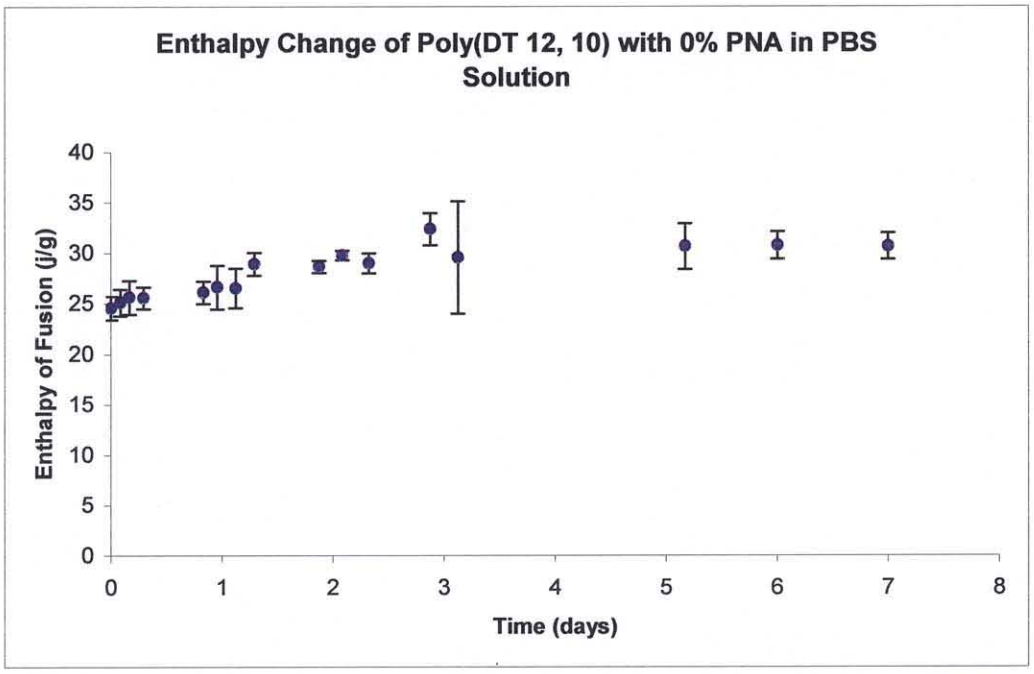

Figure 4.4 Enthalpy change of Poly(DT 12, 10) with incubation with 0% PNA.

Unlike Poly(DT 8, 8), the enthalpy values of Poly(DT 12, 10) do not change significantly with incubation. Figure 4.4 displays that; they follow a relatively constant pattern.

In Figure 4.5 the enthalpy values for these two polymers without PNA content was compared. As seen, the enthalpy does not change significantly in Poly(DT 12, 10), but Poly(DT 12, 10) has higher level off enthalpy value which is 30.5-31 J/g compare to Poly(DT 8, 8) which is approximately 19.5-20 J/g.

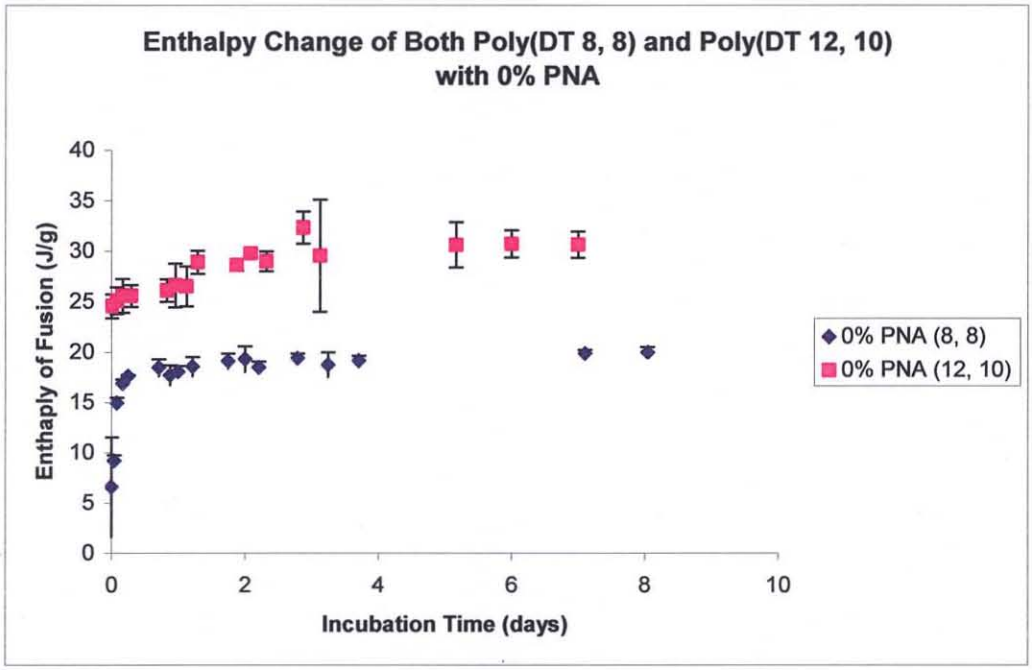

Figure 4.5 Enthalpy change comparison of Poly(DT 8, 8) and Poly (12, 10).

To be able to see the effect of incubation in the PBS for Poly(DT 8, 8), the polymer films also were tested under vacuum environment at 37°C. Figure 4.6 exhibit the enthalpy change of the samples under vacuum. According to the results, Poly(DT 8, 8) also has an increase in enthalpy under vacuum but it is seen that the increase in enthalpy in PBS is faster compared to increase in enthalpy under vacuum. Under vacuum Poly(DT 8, 8) reveals a delay in the increase of the enthalpy.

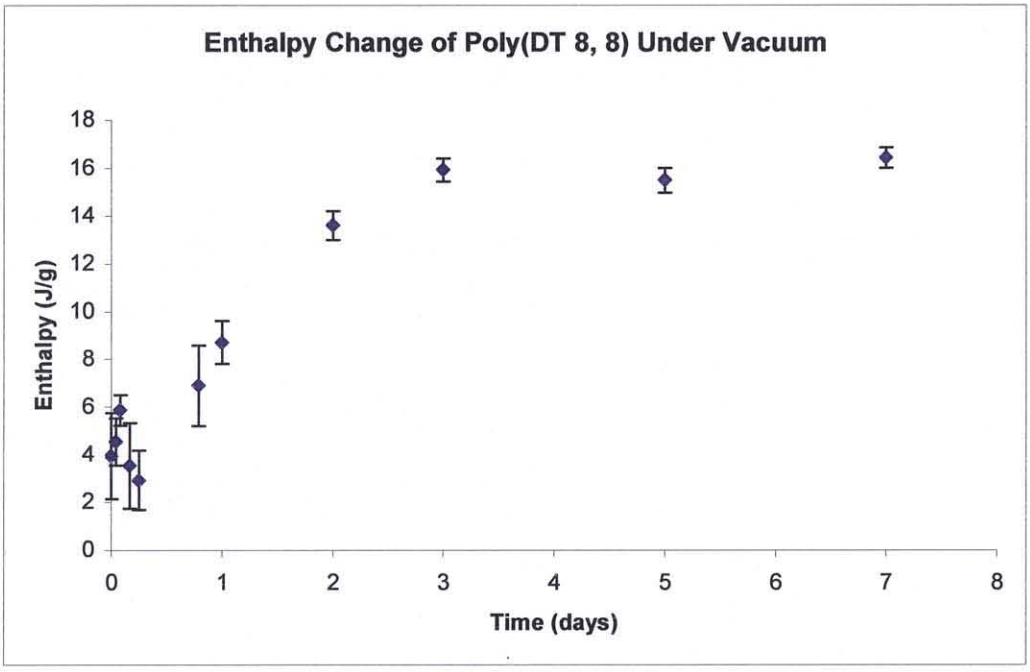

Figure 4.6 Enthalpy change of Poly(DT 8, 8) with 0% PNA under vacuum.

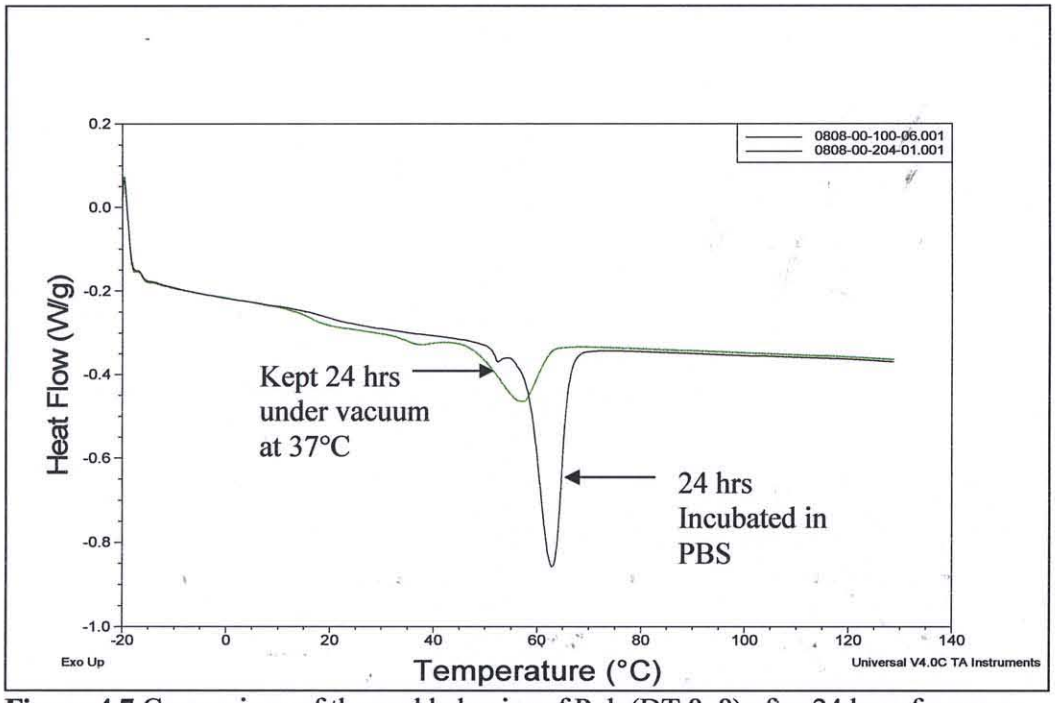

Figure 4.7 Comparison of thermal behavior of Poly(DT 8, 8) after 24 hrs of vacuum and incubated conditions.

In Figure 4.7 the comparison of thermal behavior of Poly(DT 8, 8) can be seen after 24 hrs of incubation at different conditions. The green line shows the behavior of the polymer film kept for 24 hrs at 37°C under vacuum. The black line shows the behavior of the polymer films incubated for 24 hrs in the PBS at 37°C. The Figure displays the difference on thermal behavior of Poly(DT 8, 8) treated differently. The film incubated in the PBS shows a sharp enthalpic peak at around 63.87 °C whereas polymer film kept under vacuum shows smaller enthalpic peak around 60°C. The glass transition point for Poly(DT 8, 8) under vacuum is more distinguishable. This difference can be a result of faster appearance of the phase change in Poly(DT 8, 8)' for the samples incubated in PBS. One can conclude that moisture increases the rate of the phase change of Poly(DT 8, 8) and causes reorganization in its structure. In Appendix D the DSC results for Poly(DT 8,8) with 0% PNA under dry conditions for each incubation time point were given for the first repetition.

It is also know that the increase in phase change enthalopy of Poly(DT 8, 8) occurs in any conditions. It also occurs when it is kept in room conditions. Although, It is not investigated in terms of kinetics in the study it is seen that if the polymer is kept in room conditions, this enthalpy change also occurs. The storage conditions of the polymers only affects how fast this change occurs.

In this study Poly(DT 8, 8) exhibited phase changing behavior having different rate, depending on environmental conditions. Consistent with the previous studies of Jaffe and his group, Initially Poly(DT 8, 8) has similar structure with Poly(DT 2, 2) showing amorphous properties. After incubation Poly(DT 8, 8) reorganizes itself and gain similar characteristic to Poly(DT 12, 10) [24, 27, 36, 38 ,39].

4.1.2 Effect of Drug Loading Combined with Incubation on Assembly

The effect of drug loading on polymer assembly has been investigated by incorporation of model low molecular weight hydrophobic drug p-nitroaniline for both Poly(DT 8, 8) and Poly(DT 12, 10). Two different polymer-to-drug (wt\wt) ratios were used; 5% and 10%.

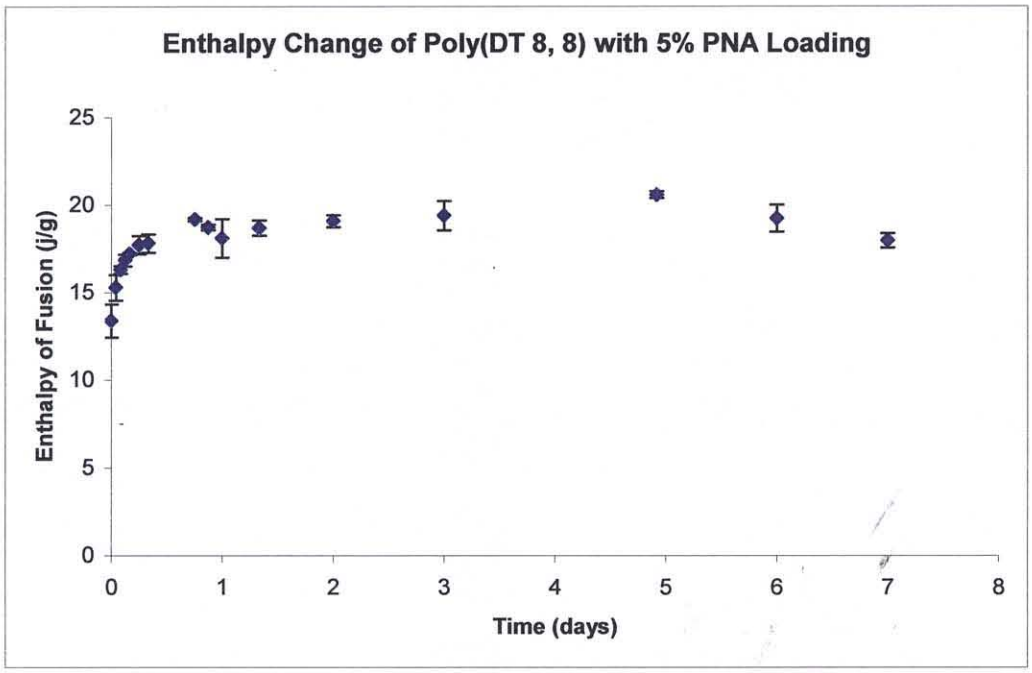

Figure 4.8 Enthalpy change of Poly(DT 8, 8) with incubation with 5% PNA.

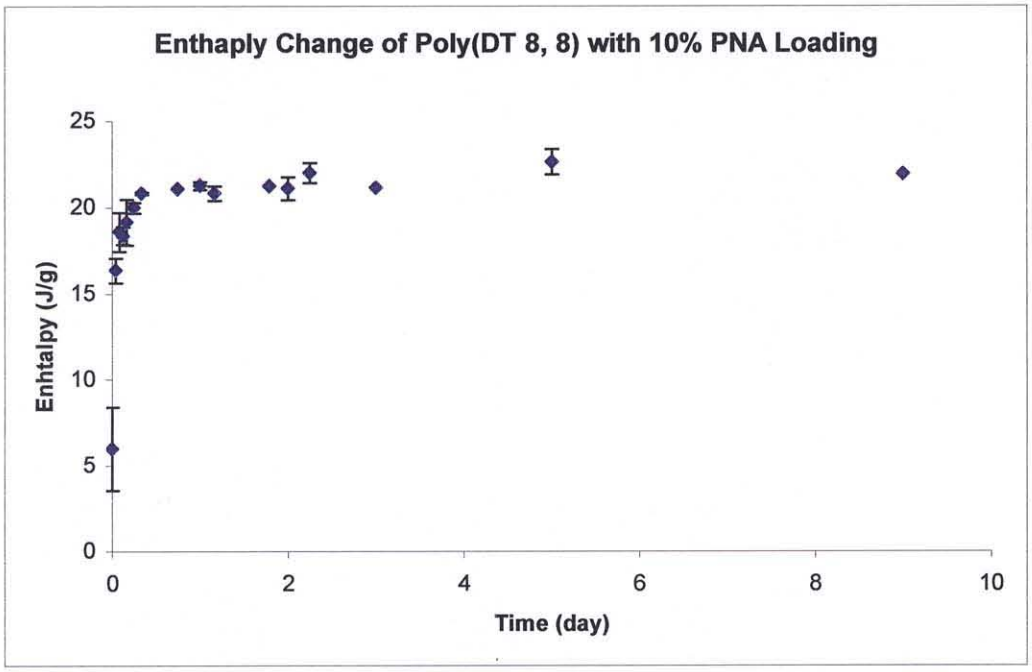

Figure 4.9 Enthalpy change of Poly(DT 8, 8) with incubation with 10% PNA.

Figures 4.8 and 4.9 exhibit the enthalpy change of the 5% and 10% drug loaded Poly(DT 8, 8) by incubation respectively. As can be seen, they follow similar pattern. Similar to 0% drug loaded poly(DT 8, 8) films, enthalpy increases gradually and reaches a constant value after incubation of approximately half a day.

Figure 4.10 shows the comparison of the enthalpy change of Poly(DT 8, 8) films having different drug loading ratios. It is seen that the enthalpy of the drug incorporated films tends to have higher values compared to blank samples, especially for 10% PNA loaded samples. In terms of the patterns that follow, the drug loaded samples and blank samples do not differ significantly, which shows that the rate and the behavior of the phase change of the Poly(DT 8, 8) films has not been affected by drug incorporation. In Appendix A, B and C the DSC results for Poly(DT 8,8) with 0%, 5% and 10% PNA for each incubation time point were given for the first repetition respectively.

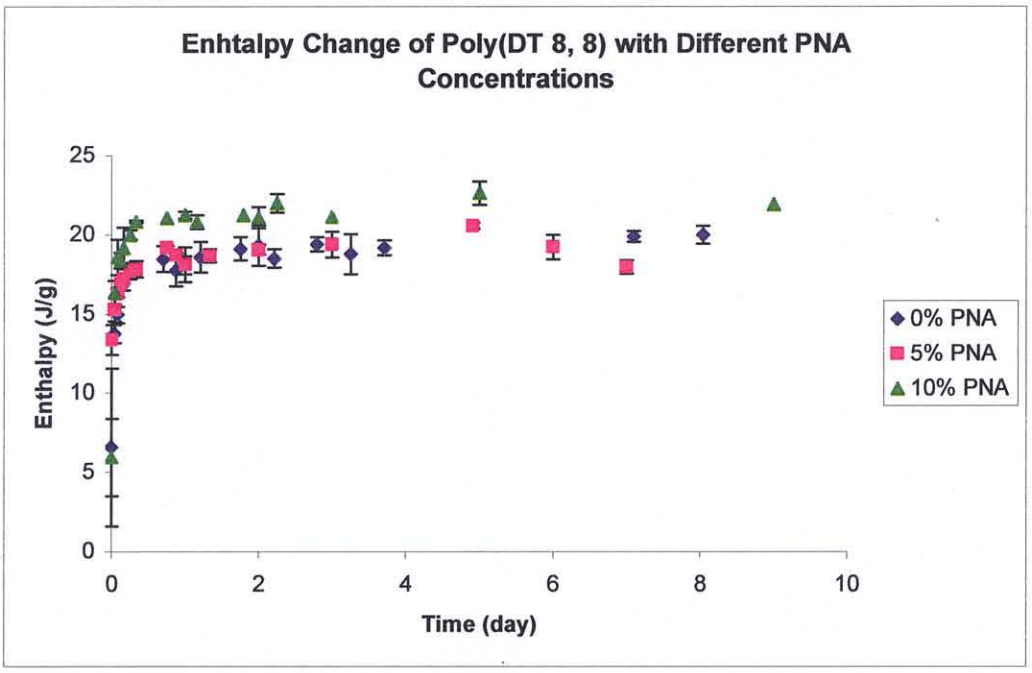

Figure 4.10 Enthalpy change of Poly(DT 8, 8) with incubation with 0% 5% and 10% PNA.

Figures 4.11 and 4.12 shows the enthalpy change of the 5% and 10% drug loaded Poly(DT 12, 10) by incubation respectively. Similar to Poly(DT 8, 8) the drug loaded samples for Poly(DT 12, 10) as well shows similar behavior with blank films.

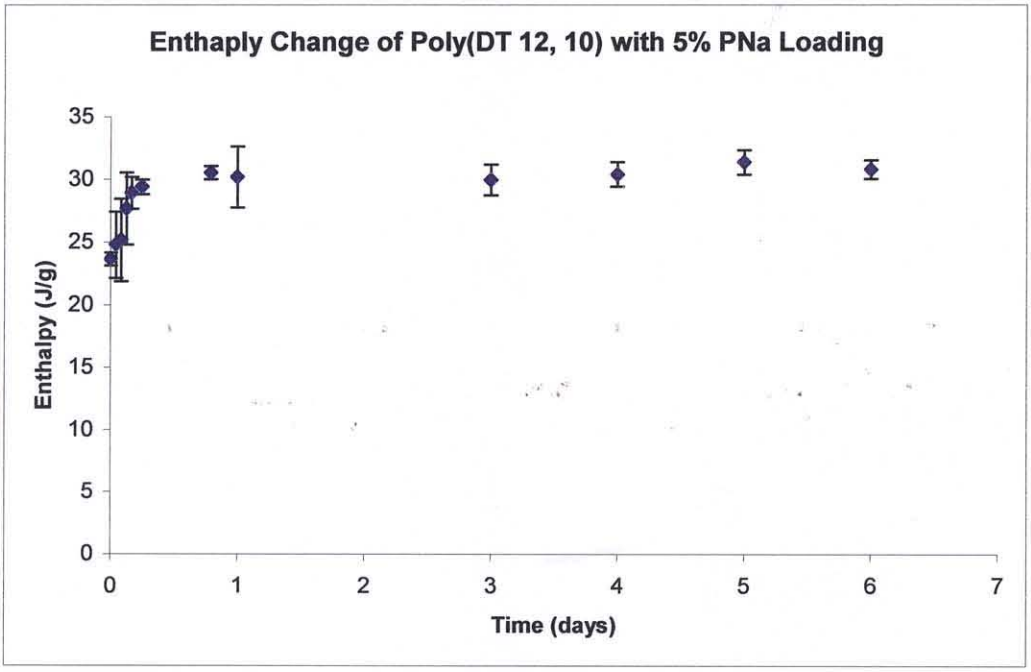

Figure 4.11 Enthalpy change of Poly(DT 12, 10) with incubation with 5% PNA.

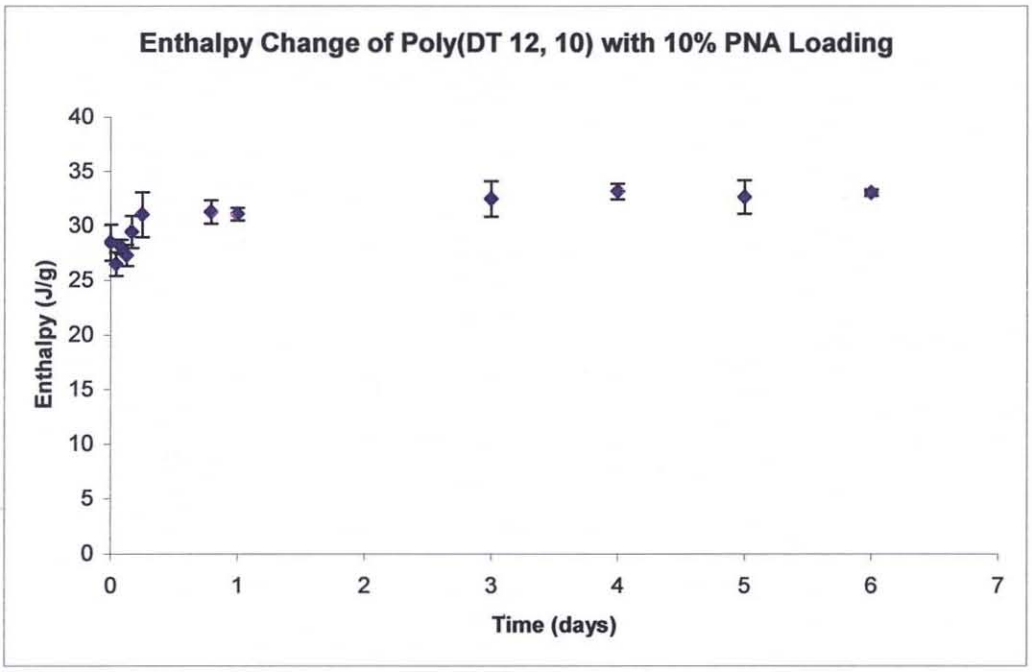

Figure 4.12 Enthalpy change of Poly(DT 12, 10) with incubation with 10% PNA.

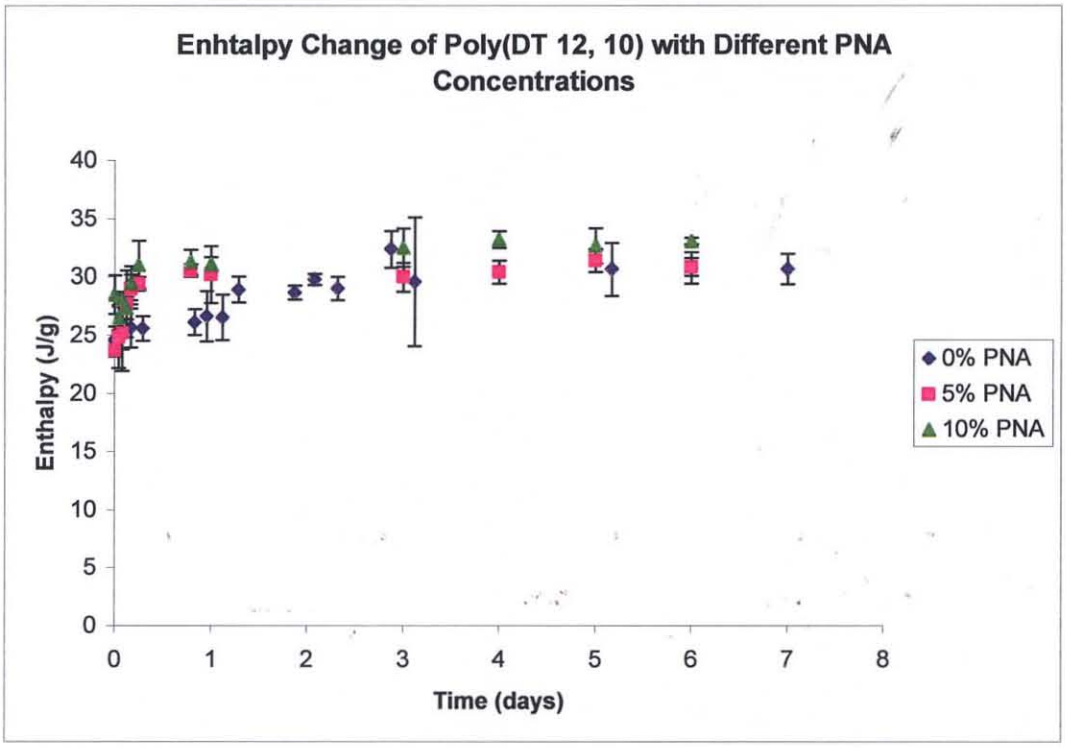

Figure 4.13 Enthalpy change of Poly(DT 12, 10) with incubation with 0% 5% and 10% PNA.

Figure 4.13 shows the comparison of enthalpy change between drug incorporated samples and blank Poly(DT 12, 10) samples. Consistent with the result of Poly(DT 8, 8); drug incorporated samples also experience the similar behavior in terms of rate and pattern of the enthalpy change by incubation but the drug incorporated samples tends to have slightly higher enthalpy especially for 10 % PNA containing films. In Appendix E, F and G the DSC results for Poly(DT 12, 10) with 0%, 5% and 10% PNA for each incubation time point were given for the first repetition respectively.

In order to understand better the effect of PNA incorporation into the both Poly(DT 8, 8) and Poly(DT 12, 10), PNA has also been tested with DSC. The DSC parameters used were the same for DSC run except the highest temperature which is selected as 165 °C to make sure that is slightly above the melting temperature of the p-nitroaniline. The melting temperature of PNA is 149 °C. Figure 4.14 shows the DCS result for PNA powder.

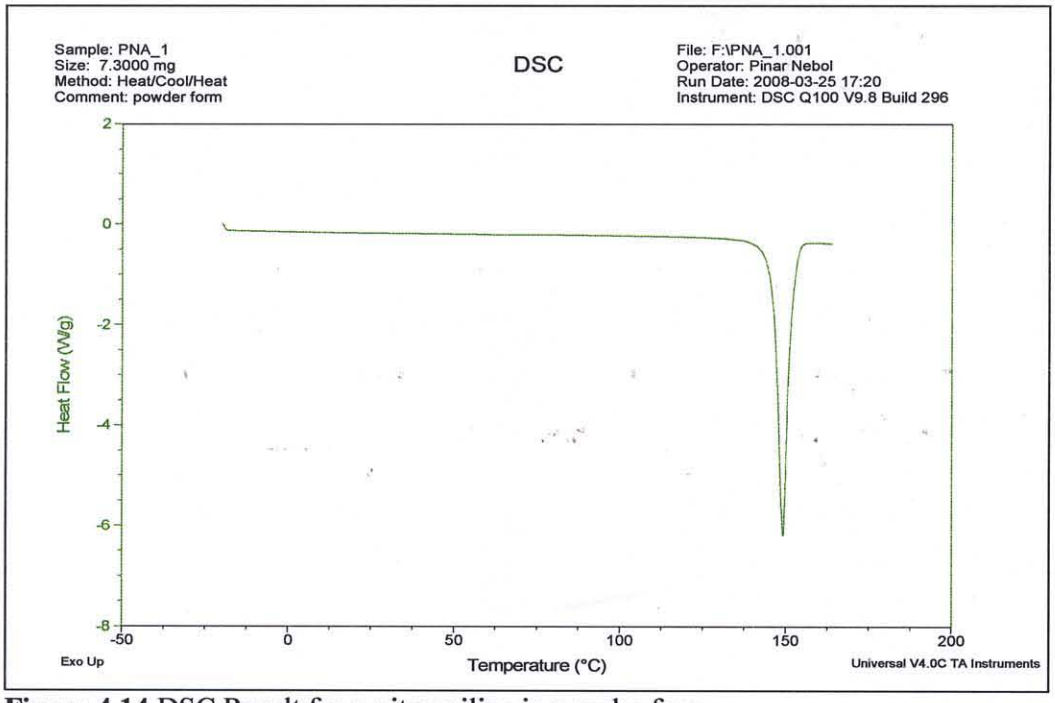

Figure 4.14 DSC Result for p-nitroaniline in powder form.

DSC result for PNA shows a single endothermic peak at the melting temperature of the model drug. There is no peak at the temperature that both Poly(DT 12, 10) and Poly(DT 8, 8) has endothermic peak. According to this result, one can conclude that the slight increase in the enthalpy of the drug incorporated polymers was not caused by the drug itself but the effect of the drug addition on the structure of the resulting polymeric films.

4.2 Gel Permeation Chromatography Results

Gel permeation chromatography is a chromatographic technique that separates the molecules depending on their size. It does not separate them directly depending on their molecular weight but their hydrodynamic volume. Then molecular weight of the samples can be determined using different standards. In this study polystyrene standards were used. The larger the molecular weights the faster it came out from the column since smaller molecules are retarded in the column. In order to see change in molecular weight of the polymers Gel Permeation Chromatographic analysis was performed.

The results showed that the molecular weight distribution range is quite broad since the peak obtained for each sample was not sharp which indicates large molecular weight distribution. This is an expected result for complex structures like polymers. It is reasonable to consider that 5-10% change in molecular weight can not be considered as change in molecular weight and conclude that there is no change and there is no degradation during incubation.

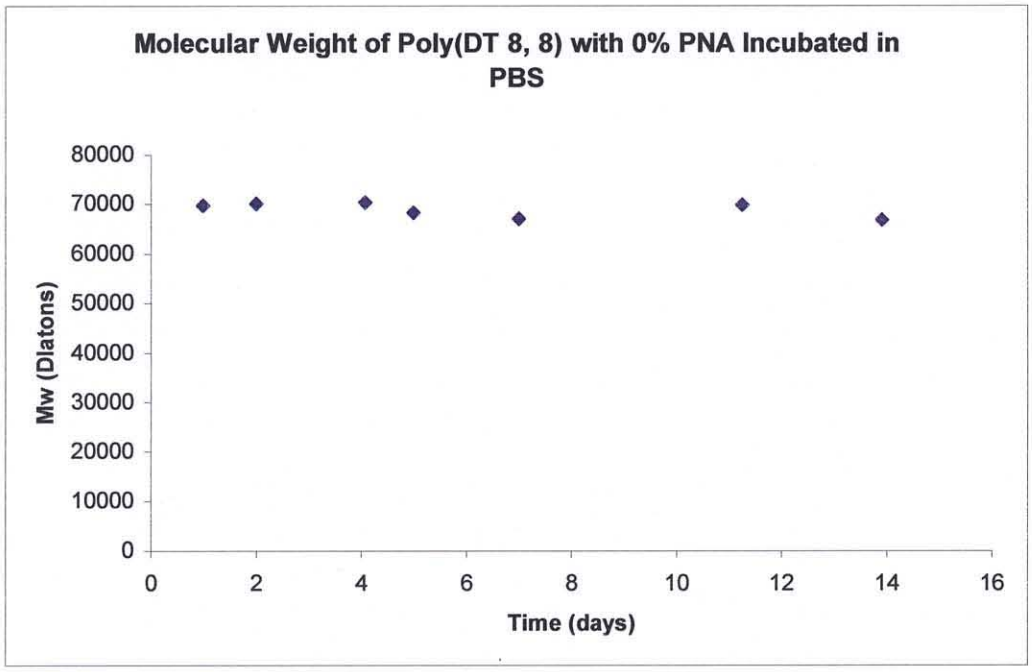

Figure 4.15 Molecular weight of incubated Poly(DT 8, 8) with 0% p-nitroaniline.

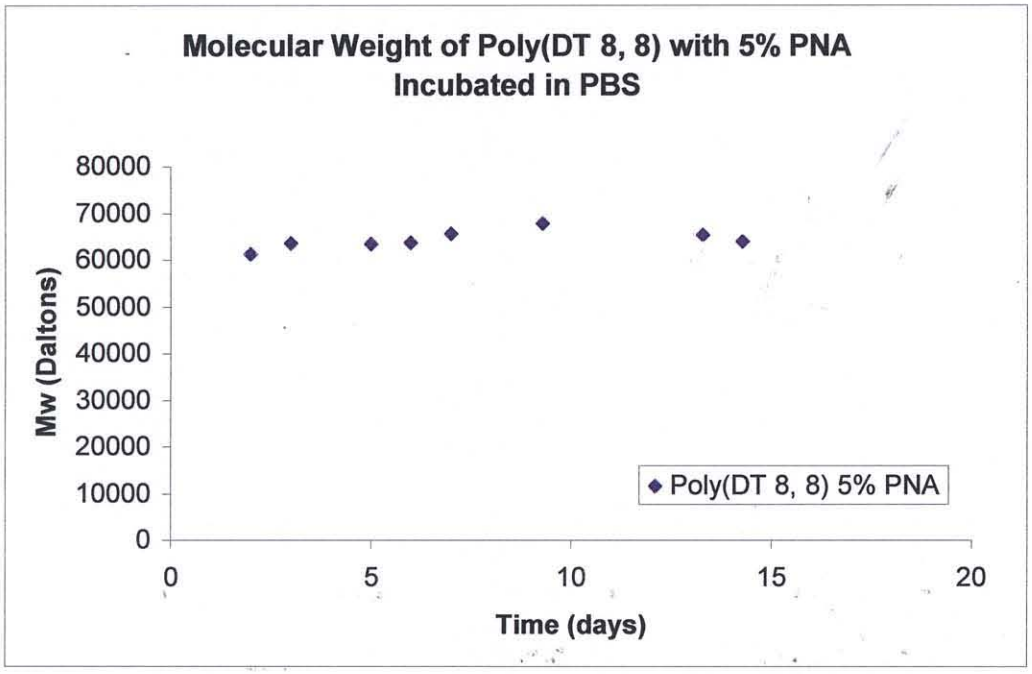

Figure 4.16 Molecular weight of incubated Poly(DT 8, 8) with 5% p-nitroaniline.

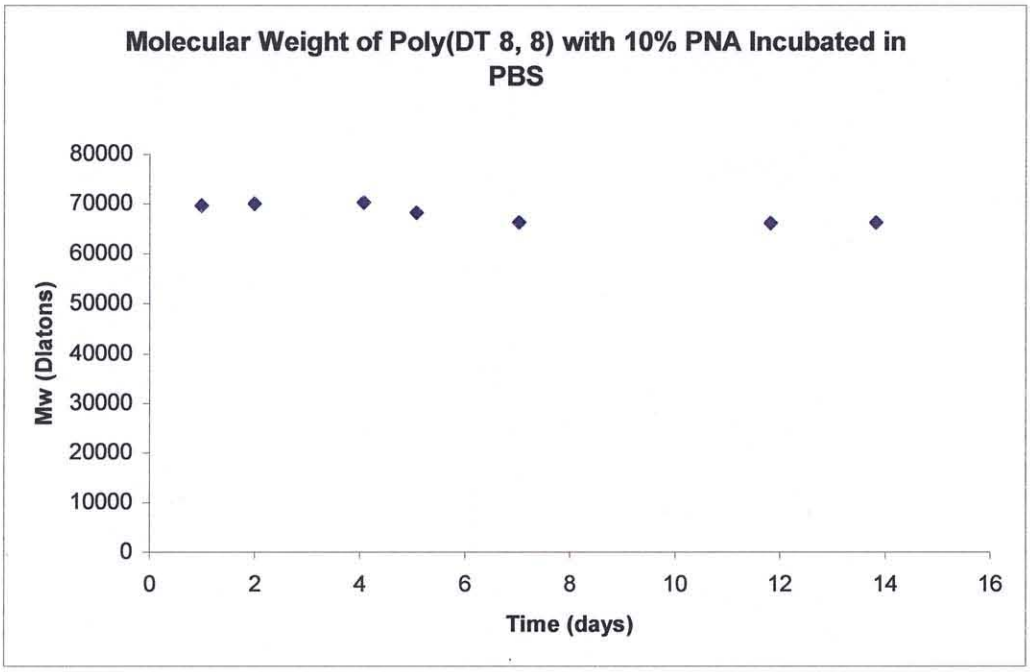

Figure 4.17 Molecular weight of incubated Poly(DT 8, 8) with 10% p-nitroaniline.

Figures 4.15, 4.16 and 4.17 show the change in molecular weight of the Poly(DT 8, 8) with 0%, 5% and 10% PNA respectively by incubation in PBS. All three figures indicate that the change in molecular weight is negligible during incubation time. Therefore one can conclude that the release of the p-nitroaniline occurs with diffusion controlled manner rather that degradation controlled manner.

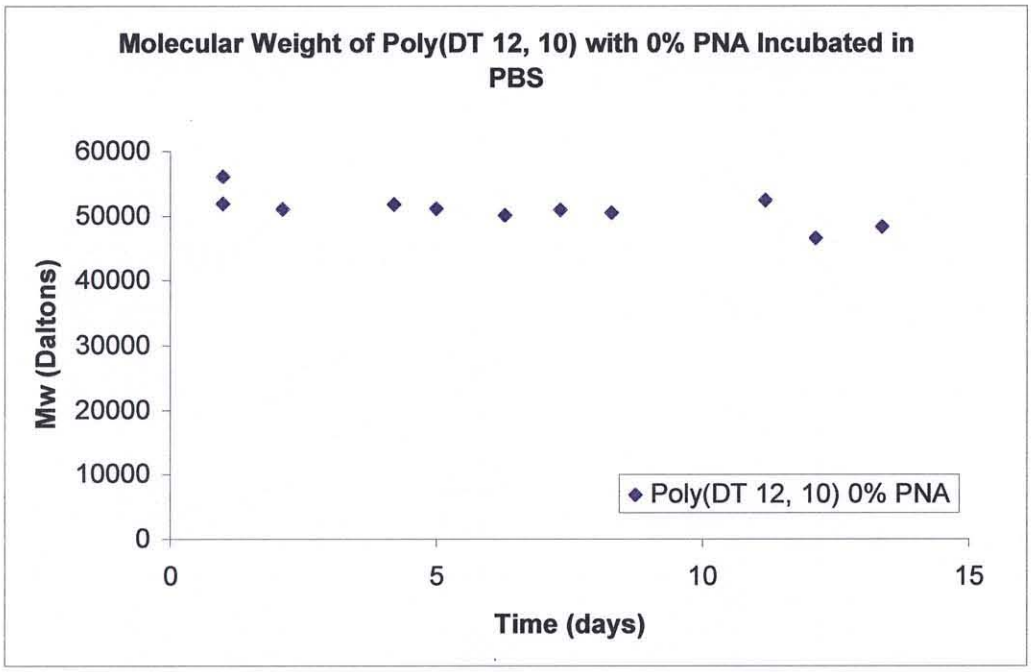

Figure 4.18 Molecular weight of incubated Poly(DT 12, 10) with 0% p-nitroaniline.

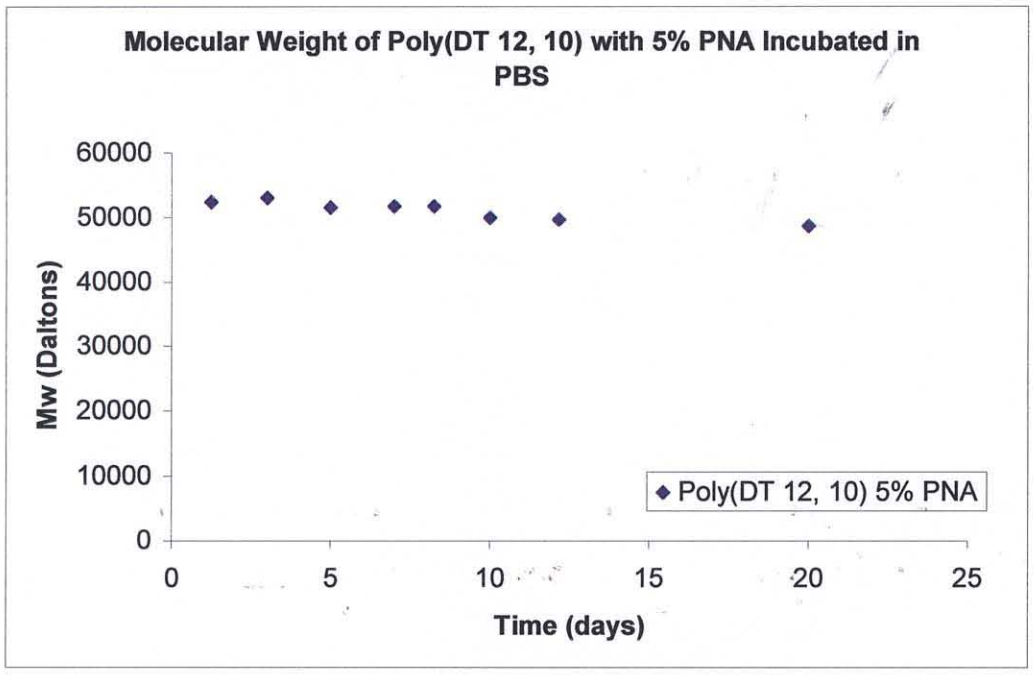

Figure 4.19 Molecular weight of incubated Poly(DT 12, 10) with 5% p-nitroaniline.

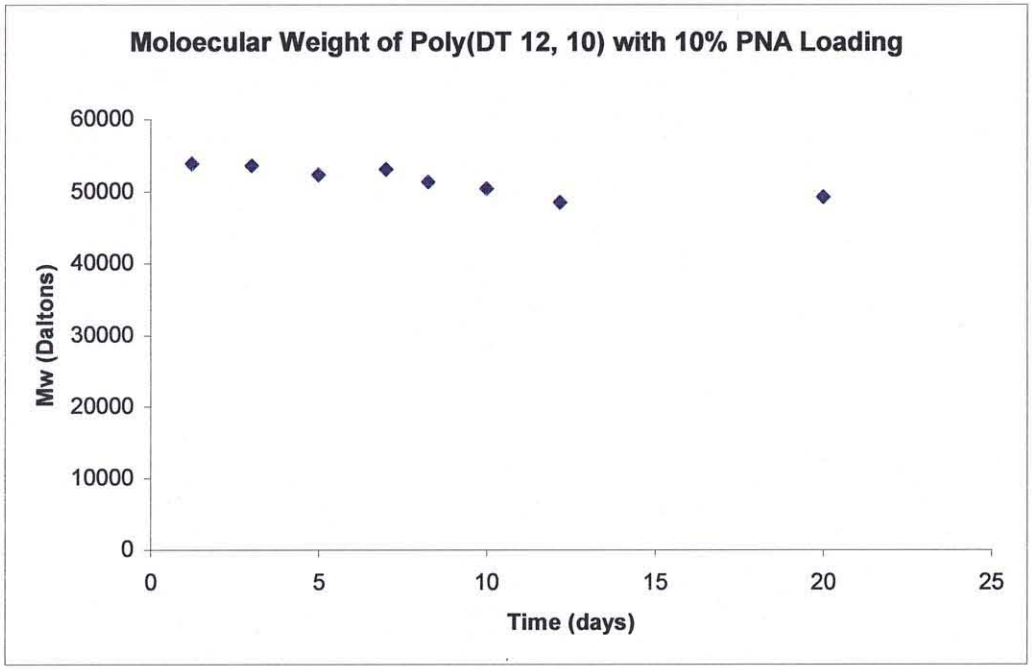

Figure 4.20 Molecular weight of incubated Poly(DT 12, 10) with 10% p-nitroaniline.

Figures 4.18, 4.19 and 4.20 show the molecular weight change during incubation of the Poly(DT 12, 10) with 0%, 5% and 10% PNA respectively. From each figure it can be concluded that the molecular weight of the polymer films stays constant during the incubation since the change is smaller than 10% for Poly(DT 12, 10) similar to Poly(DT 8, 8). Since the molecular weight of Poly(DT 12, 10) stays constant it can be concluded that the release from Poly(DT 12, 10) is also controlled by diffusion.

4.3 P-nitroaniline Release Results

The release of PNA was monitored by UV/Vis spectrophotometer. The calibration curve has been constituted with different concentrations and the amount of PNA released to the incubation solution was calculated using the equation obtained from

that calibration curve. The equation obtained is given below in Equation 1 and the calibration curve is given in Figure 4.21.

$$C[PNA] = 0.0099 * Absorbance \qquad \textbf{Equation (1)}$$

The concentration of p-nitroaniline has been calculated using the Equation 1. The weight of PNA has been calculated as mg in the PBS, and the weight percentage of the PNA released from the film has been calculated. For this calculation it is assumed that the drug has been uniformly dissolved in the polymer film and polymer to drug ratio (wt/wt) is same in every part of the films.

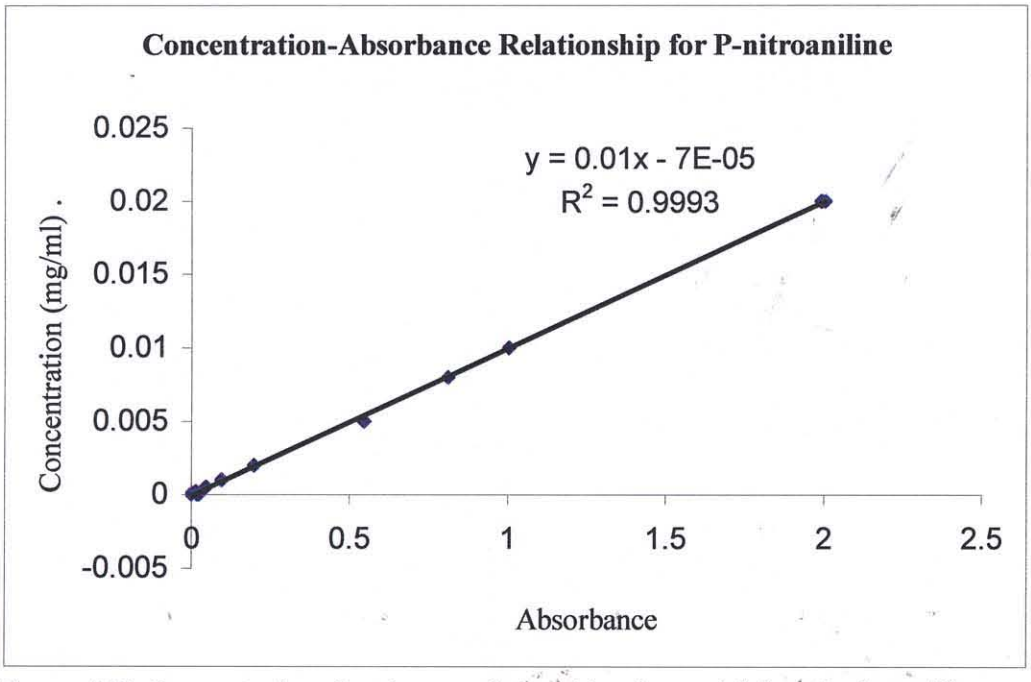

Figure 4.21 Concentration absorbance relationships for model drug P-nitroaniline.

The release profile of PNA from 10% (polymer/drug wt/wt) drug containing Poly(DT 8,8) and Poly(DT 12, 10) is shown in Figure 4.22 and Figure 4.23 respectively. As seen from the both Figure, p-nitroaniline releases quite quickly. The

time length requires for Poly(DT 12, 10) to reach equilibrium is shorter compare to Poly(DT 8, 8). Poly(DT 12, 10) reaches its equilibrium concentration at about 360 min whereas, Poly(DT 8, 8) reaches its equilibrium concentration approximately in 400 min (6-7 hrs). Figure 4.24 displays the comparison of the release profile of PNA from both Poly(DT 12, 10) and Poly(DT 8, 8). The difference in time length required to reach the equilibrium can be seen well in Figure 4.24. It's remarkable that the length of time that the release reaches equilibrium from the polymer is close to the length of time that the change in enthalpy in the Poly(DT 8, 8) films reaches steady state. Approximately 85.5% of PNA released from 10% PNA loaded Poly(DT 8, 8) and 92% of PNA released from 10% PNA loaded Poly(DT 12, 10). Poly(DT 12, 10) has slightly higher total release compared to Poly(DT 8, 8).

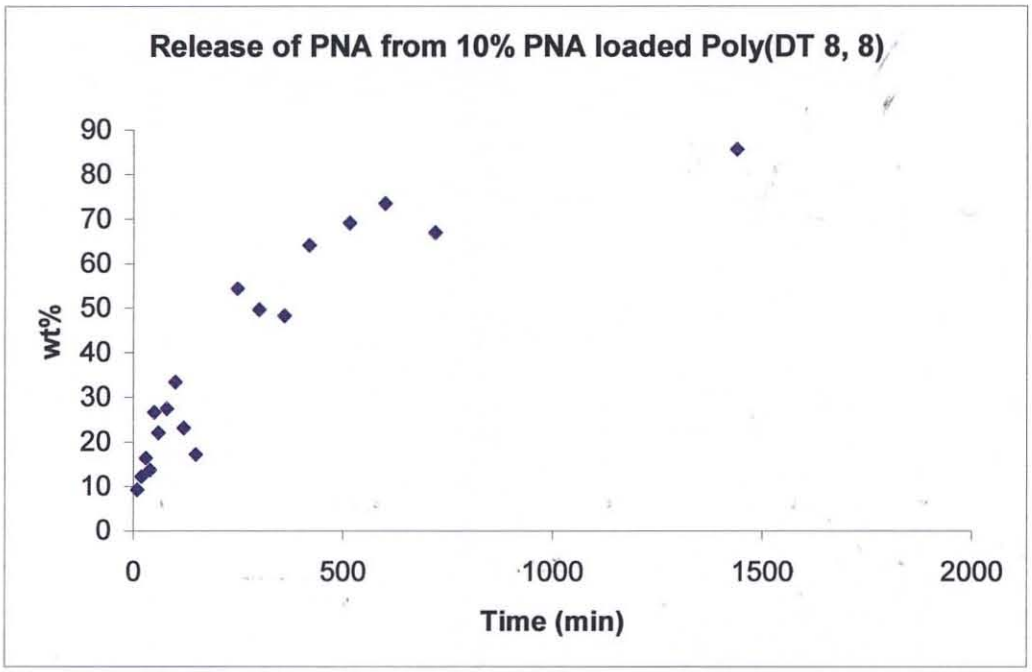

Figure 4.22 Release profile of p-nitroaniline from 10% drug containing Poly(DT 8, 8).

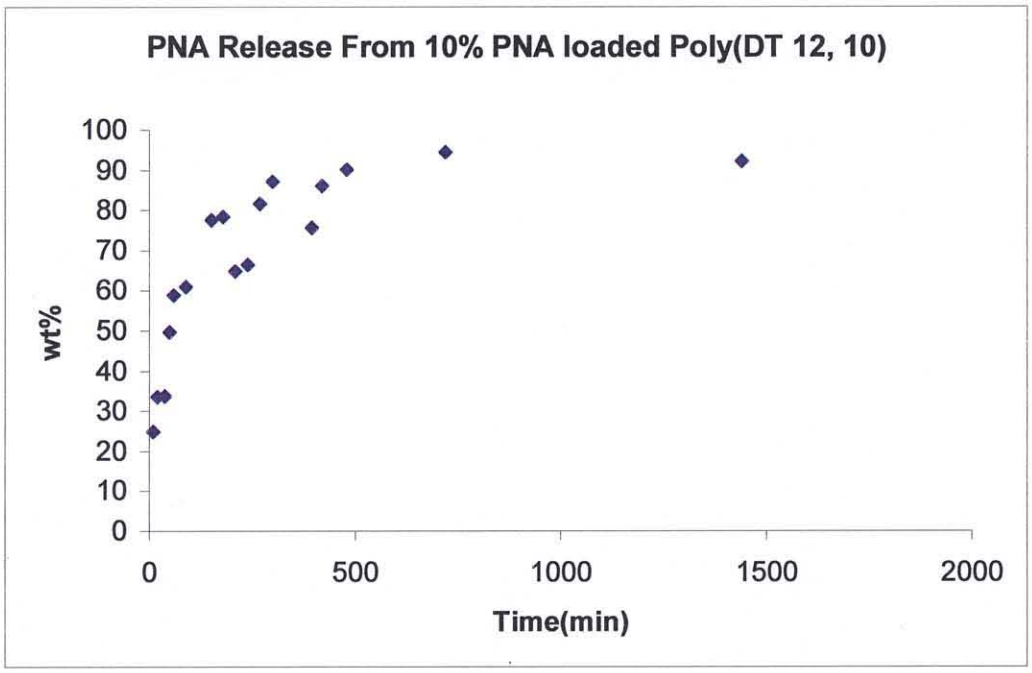

Figure 4.23 Release profile of p-nitroaniline from 10% drug containing Poly(DT 12, 10).

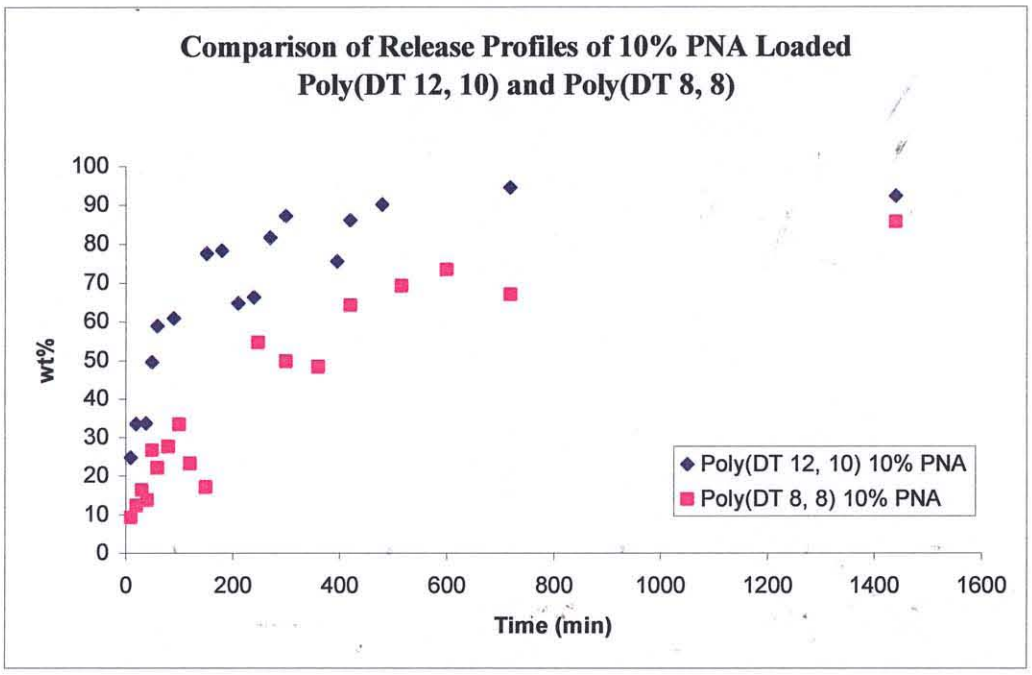

Figure 4.24 Comparison of the release profile of p-nitroaniline from 10% drug containing Poly(DT 8, 8) and Poly(DT 12, 10).

The release profile of PNA from 5% (polymer/drug wt/wt) drug containing Poly(DT 8,8) and Poly(DT 12, 10) is shown in Figure 4.25 and Figure 4.26 respectively. Similar to 10% PNA loaded samples the release is very quick and PNA concentration reaches equilibrium in a very short period of time. In addition similar to 10% loaded samples the time length requires for Poly(DT 12, 10) to reach equilibrium is shorter compare to Poly(DT 8, 8). Poly(DT 12, 10) reaches its equilibrium concentration at about 400 min whereas, Poly(DT 8, 8) reaches its equilibrium concentration approximately in 600 min (6-7 hrs). Figure 4.27 displays the comparison of the release profile of PNA from both Poly(DT 12, 10) and Poly(DT 8, 8). Approximately 81% of PNA released from 5% PNA loaded Poly(DT 8, 8) and 89% of PNA released from 5% PNA loaded Poly(DT 12, 10). Although total percent releases are very close to each other, Poly(DT 12, 10) has slightly higher release compared to Poly(DT 8, 8) as in the case of 10% drug loaded samples.

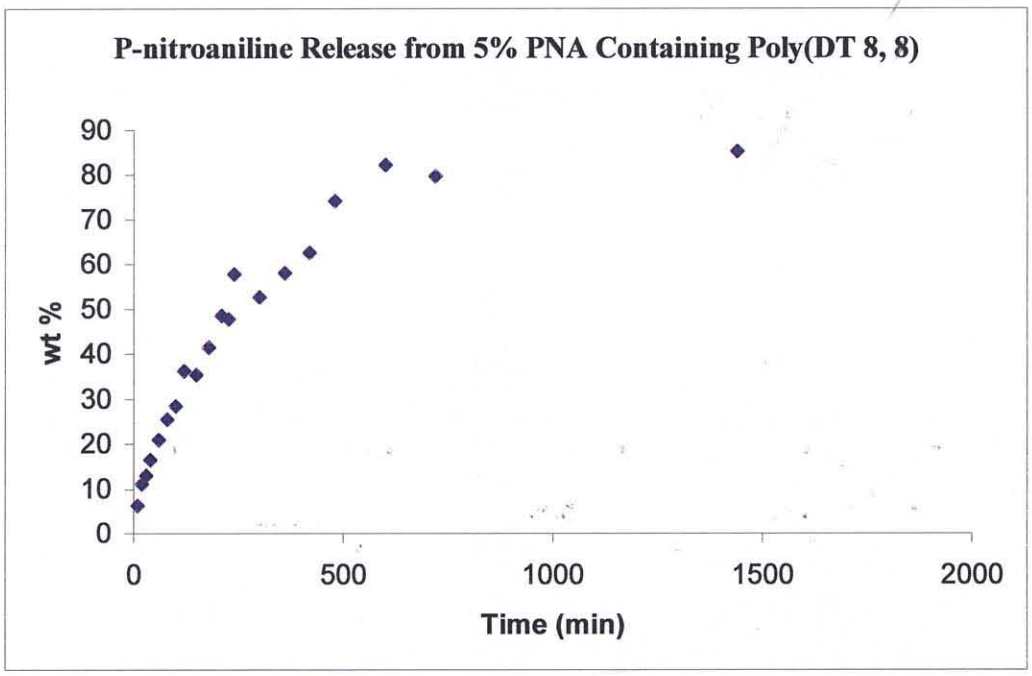

Figure 4.25 Release profile of p-nitroaniline from 5% drug containing Poly(DT 8, 8).

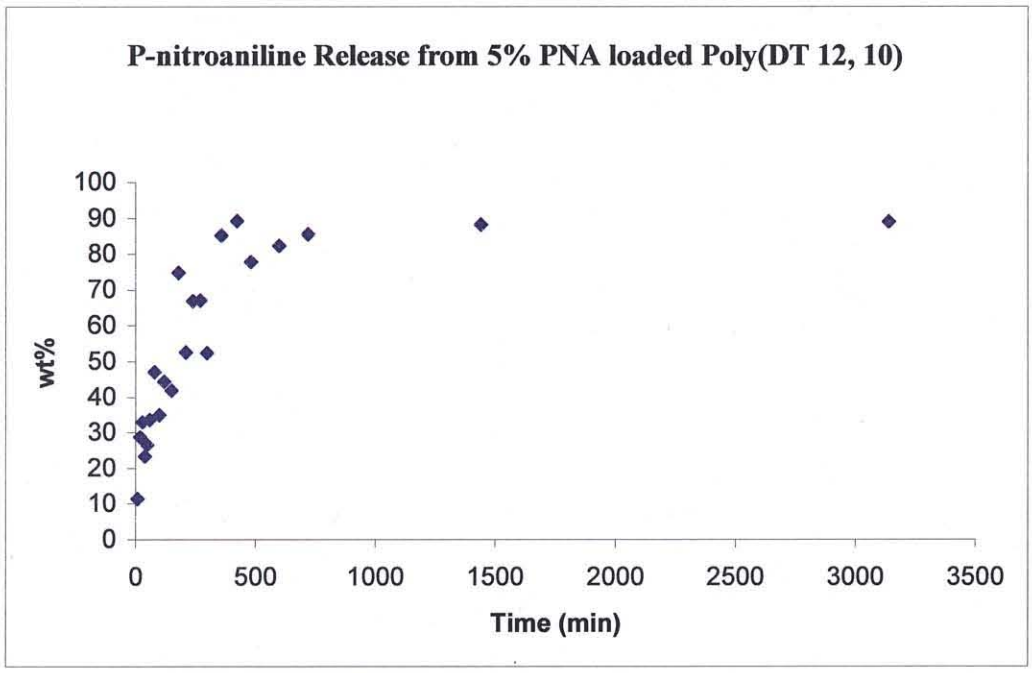

Figure 4.26 Release profile of p-nitroaniline from 5% drug containing Poly(DT 12, 10).

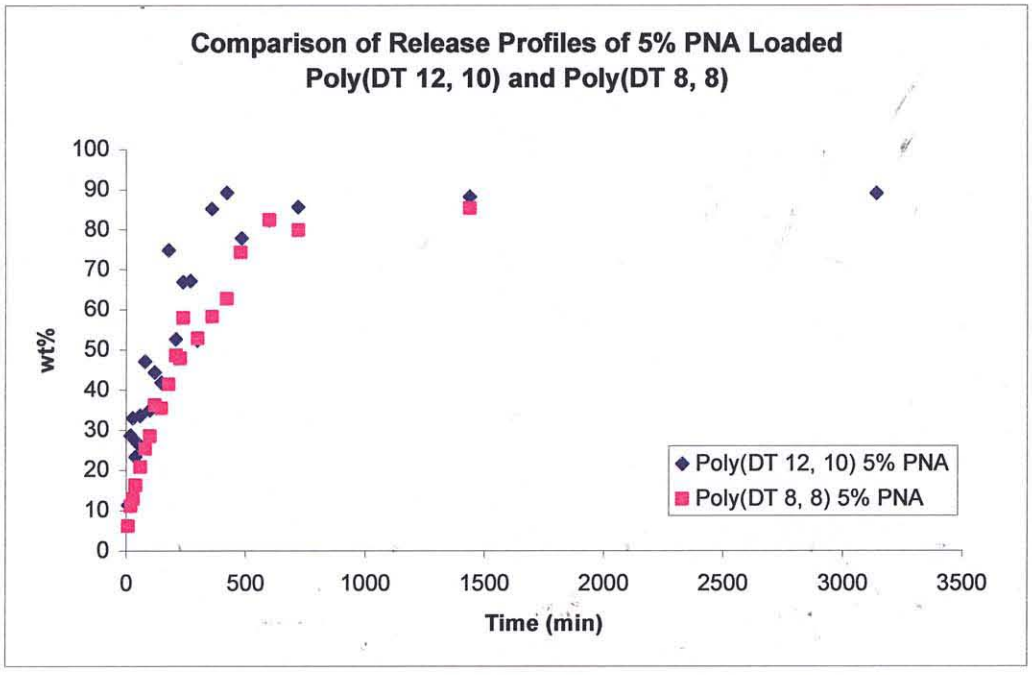

Figure 4.27 Comparison of the release profile of p-nitroaniline from 5% drug containing Poly(DT 8, 8) and Poly(DT 12, 10).

4.4 Discussion

According to the DSC results, Poly(DT 12, 10) showed an endothermic peak upon heating and an exothermic peak upon cooling; Poly(DT 8, 8) on the other hand showed only an endothermic peak consistent with previous work [24, 36]. Consistent with the previous study of Collins et al., Poly(DT 12, 10) doesn't show a change in heat capacity upon heating that could be considered as a glass transition point [36], although Poly(DT 8, 8) showed a change in heat capacity around 15°C that can be considered as glass transition temperature. Yoo et al. investigated the effect of the water treatment for different molded polyarylates of varying backbone chain lengths, including the Poly(DT 8, 8) composition. Similar to this study, the glass transition point is observed in the second DSC heating while only a sharp endothermic peak is observed in the first heating cycle [27]. The disappearance of the Tg point with the increase in the endothermic melting peak upon heating indicates reorganization in Poly(DT 8, 8) during incubation in the PBS.

A number of desaminotyrosil derived polymers have been studied by Jaffe's group. Unordered Poly(DT 2, 2) and Poly(DT 2, 4) will behave as amorphous polymers and Poly(DT 12, 10) as ordered will behave as an organized. Therefore Poly(DT 12, 10) should have a slower elution time compared to amorphous polymers. Poly(DT 8, 8) on the other hand, will first behave as an amorphous polymer; then depending on the application and storage conditions it will reorganize itself and it will have a structure similar to Poly(DT 12,10), and the release should change. Thus it will show changing elution profile which should be considered upon producing a medical device requiring specific properties. Depending on these facts, it was expected that Poly(DT 12, 10) would show slower elution profile compared to Poly((DT 8, 8).

However, on the contrary it showed a faster elution profile and reached equilibrium faster than Poly(DT 8, 8).

The rate of reorganization in Poly(DT 8, 8) has been investigated and the results showed that it experiences very fast exponential ordering in PBS at 37°C and reaches steady state value in almost half a day. Initially it has an fully amorphous structure and with incubation it reorganizes itself in a half a day. However, when is kept under vacuum at 37°C, it showed much slower reorganization; and it experienced slow reorganization after approximately one and a half day. The change in polymer also shows that the storage conditions of a device produced from Poly(DT 8, 8) are also extremely important in terms of internal aggregation of the polymer and this should play important role for the elution profile of a drug and the degradation rate of the polymer. The effects of temperature and moisture on the ordering of Poly(DT 8, 8) have already been studied by Yoo et al. [6]. It has been seen that the moisture content of the polymer is directly related to the structural change and the endothermic peak formation in Poly(DT 8, 8) and also that with moisture, Poly(DT 8, 8) experiences easier structural reorganization [6]. The previous results are consistent with the current study indicating that the incubation of the Poly(DT 8, 8) increases the speed of the phase change.

In this study the effect of the drug incorporation on the structural behavior of both polymers has also been investigated. The results indicate that the incorporation of a low molecular weight model drug has not been significantly affected the structural behavior (the shape of the enthalpy change), but the drug containing films tends to have slightly higher enthalpy compared to blank samples for both polymers especially for 10% loading.

The DSC result for PNA powder showed an endothermic peak at about 149-150 °C which is the melting temperature of p-nitroaniline. The results suggest that the increase in enthalpy of the poly(DT 8, 8) and Poly(DT 12, 10) casted films is not caused by the drug itself. It might be the result of the effect of the drug loading on the structure of the material. However, this hypothesis needs further analysis.

According to the results obtained from the GPC analysis, the change in molecular weight of the polymer films during 10-15 days of incubation is negligible as expected for both Poly(DT 8, 8) and Poly(DT 12,10). Therefore it is clear that the release of the model drug, p-nitroaniline, is controlled by diffusion for both polyarylate types. This result is consistent with the previous studies of the Kohn group.

The release of the model drug is quite fast and reaches constant concentration in almost 6-7 hours in both cases. However, Poly(DT 12, 10) releases faster compare to Poly(DT 8, 8) which was not an expected result. It was expected that the initial amorphous structure of Poly(DT 8, 8) would cause faster release in the beginning. However since the reorganization of the Poly(DT 8, 8) is fast, one can conclude that it is not an effect for the release of a material. In other words reorganization is too fast to be a significant effect in the release profile. Then the release should be a result of internal molecular structure. From previous studies it is known that the reorganization in polyarylates is associated with hydrogen bonding [6]. It is also clear that Poly(DT 12, 10) is a larger monomer compared to Poly(DT 8, 8) since there are more methylene group in both backbone and side chain structure [6]. Hence when hydrogen bonding occurs the space between molecules will be larger in Poly(DT 12, 10) compared to Poly(DT 8, 8) which will create more space for drug to move. As indicated before it is also clear that the elution occur by diffusion. Then It is

reasonable for Poly(DT 12, 10) to have faster since PNA molecules can move easier. As mentioned before from the previous studies it is known that Poly(DT 2, 2) and Poly(DT 2, 4) does not show any hydrogen bonding associated reorganization. They remain amorphous. The reason for this might be that the shorter the molecule the less flexible it is and the more difficult to make hydrogen bonding. As chains length increases Polyarylates starts to form hydrogen bonding in their internal structure.

Figure 4.28 displays the 5% model drug remaining in the polymer films after incubation in PBS. The elution stops at approximately 400 min for 5% drug loaded samples of Poly(DT 12, 10) and 600 min for Poly(DT 8, 8).

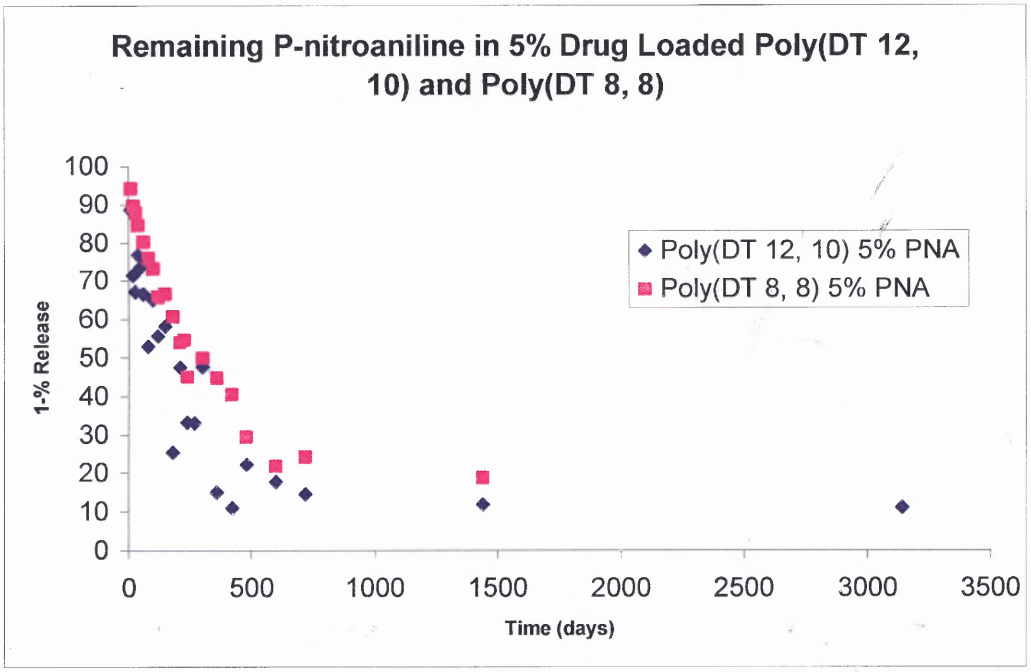

Figure 4.28 %Drug Remaining in 5% PNA loaded Poly(DT 12, 10) and Poly(DT 8, 8).

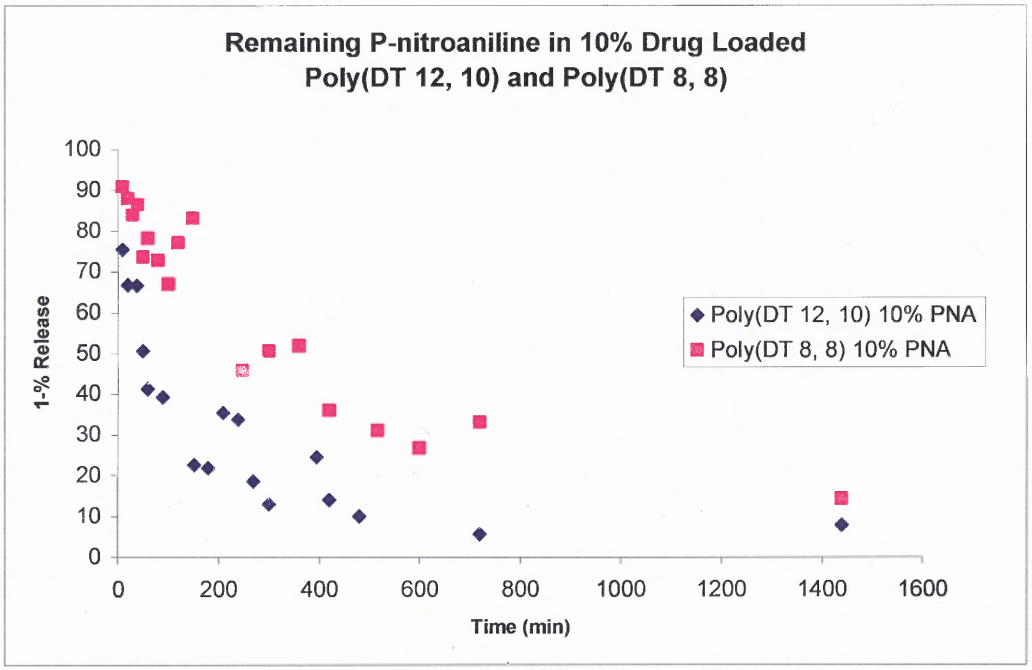

Figure 4.29 %Drug Remaining in 10% PNA loaded Poly(DT 12, 10) and Poly(DT 8, 8).

Figure 4.29 displays the 10% model drug remaining in the polymer films after incubation in PBS. The elution stops at approximately 360 min for 10% drug loaded samples of Poly(DT 12, 10) and 400 min for Poly(DT 8, 8).

Figure 4.30 shows the release profile from 5% PNA loaded Poly(DT 8, 8), as seen it shows almost constant release through the release time. In Figure 4.31 the release profile of 5% PNA loaded Poly(DT 12, 10) can be seen. Unlike Poly(DT 8, 8), Poly(DT 12, 10) showed almost instant release of PNA. It showed a release profile like a burst effect.

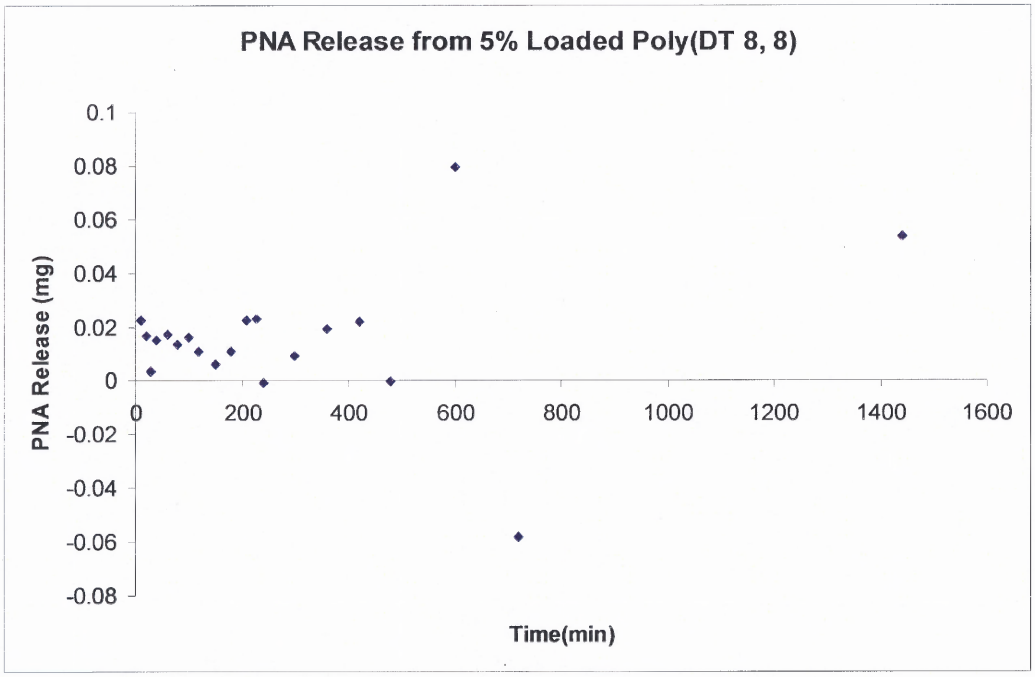

Figure 4.30 Drug Release from 5% PNA loaded Poly(DT 8, 8).

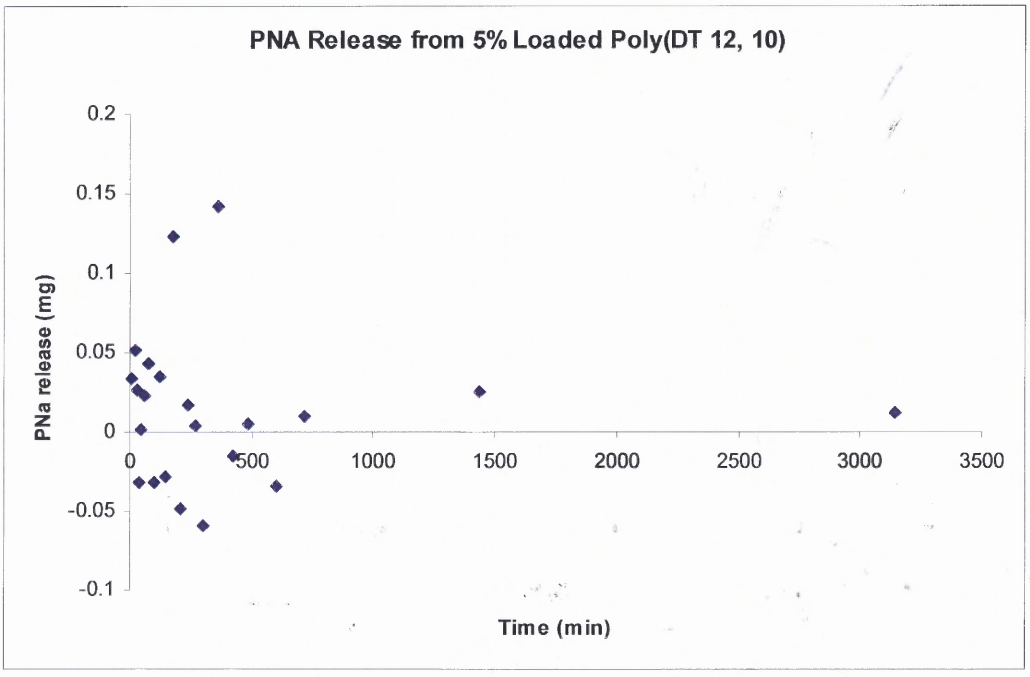

Figure 4.31 Drug Release from 5% PNA loaded Poly(DT 12, 10).

Figure 4.32 and 4.33 displays the release profile of 10% PNA loaded Poly(DT 8, 8) and Poly(DT 12 10), respectively. Both of the polymers showed an instantaneous release when they are loaded with 10% PNA; with 10% loading Poly(DT 8, 8) showed a difference in release behavior. It released the drug similar to Poly(DT 12, 10) like burst effect. From this result one can conclude that drug loading percentage is important in terms of release behavior. 10% loading can be too much for Poly(DT 8, 8) and that might be the reason for the fast release.

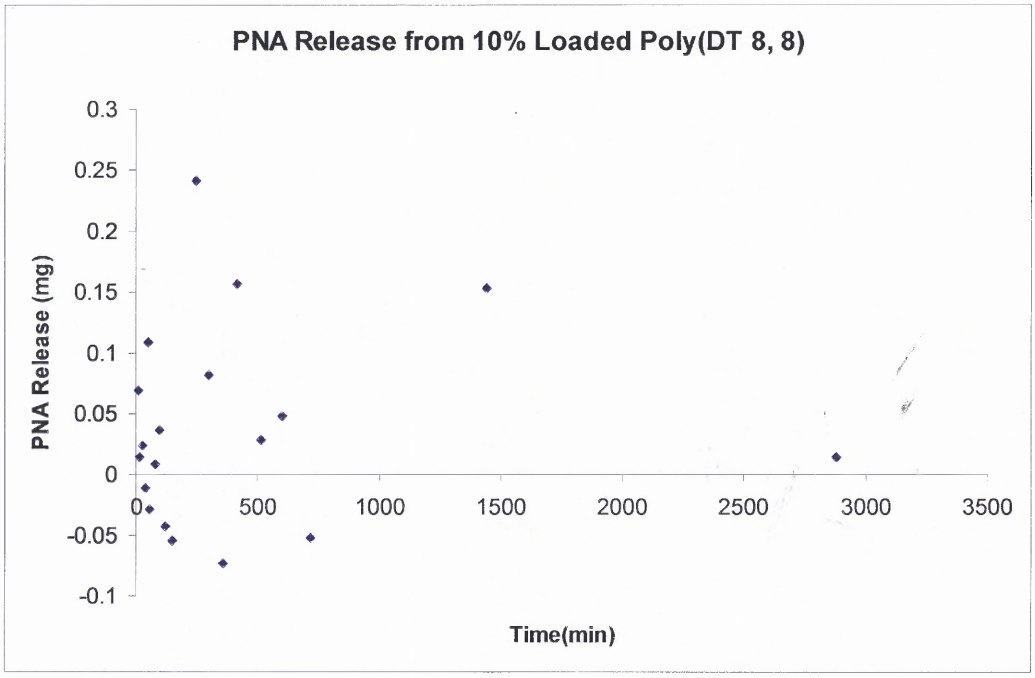

Figure 4.32 Drug Release from 10% PNA loaded Poly(DT 8, 8).

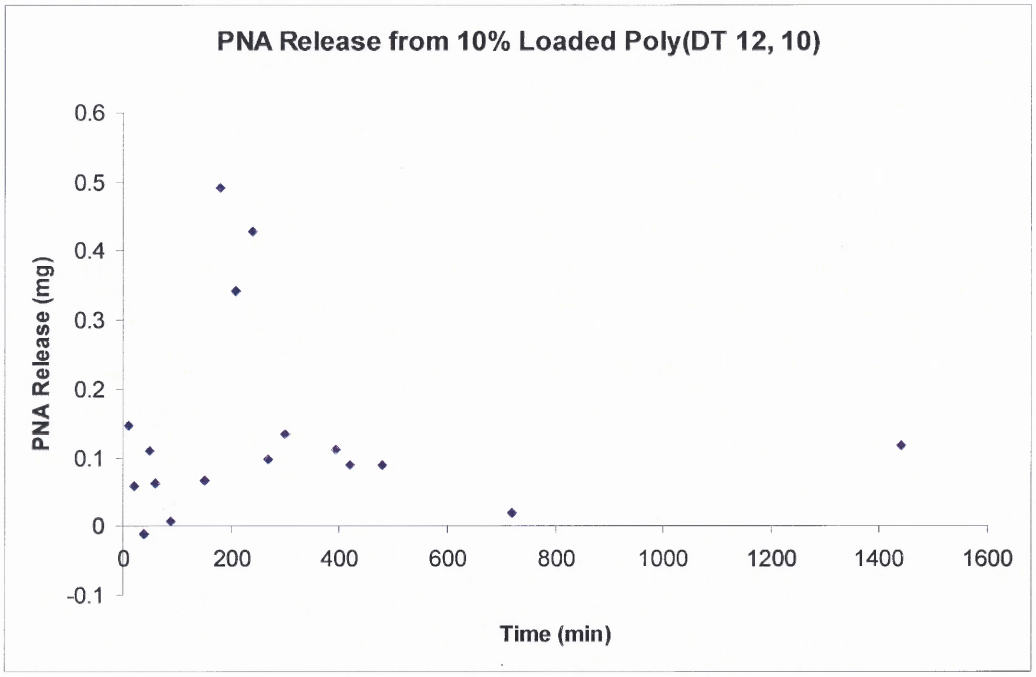

Figure 4.33 Drug Release from 10% PNA loaded Poly(DT 12, 10).

CHAPTER 5

CONCLUSION

In this study the effect of incubation on Poly(DT 8, 8) and Poly(DT 12, 10) was investigated and the results associated with the drug release properties of both materials. In addition the degradation behavior of the polymers has been investigated.

DSC results showed that Poly(DT8, 8) has amorphous structure and reorganize during incubation and gain a non-crystalline ordered structure. Unlike Poly(DT 8, 8), Poly(DT 12, 10) has an ordered structure similar to steady state structure of Poly(DT 8, 8). This result is consistent with the previous studies carried out by MDCL lab.

In order to investigate the effect of structure on the release properties on the polymers, model drug p-nitroaniline (PNA) was used. The release of the drug is a diffusional phenomenon which was shown by Gel Permeation Chromatography analysis. The change in molecular weight during the release time of was negligible, which will reveal that the release is not a result of degradation of the polymers.

The elution profile has been monitored by using Uv/Visible spectrophotometer. The elution of the PNA is very fast as it was expected according to the previous studies in the literature. The release is even faster from Poly(DT 12, 10) for both 5% and 10% drug ratios, which was an unexpected result in this study. The percent release from 5% loaded samples was 81% and 89% for Poly(DT 8, 8) and Poly(DT 12, 10) respectively and from 10% loaded samples it was 85.5% and 92 % for Poly(DT 8, 8) and Poly(DT 12, 10) respectively.

APPENDIX A

RAW DATA OF DSC RESULTS OF POLY(DT 8, 8) WITHOUT DRUG LOADING

DSC results of 0% p-nitroaniline loaded Poly(DT 8, 8) and measured enthalpy of phase change.

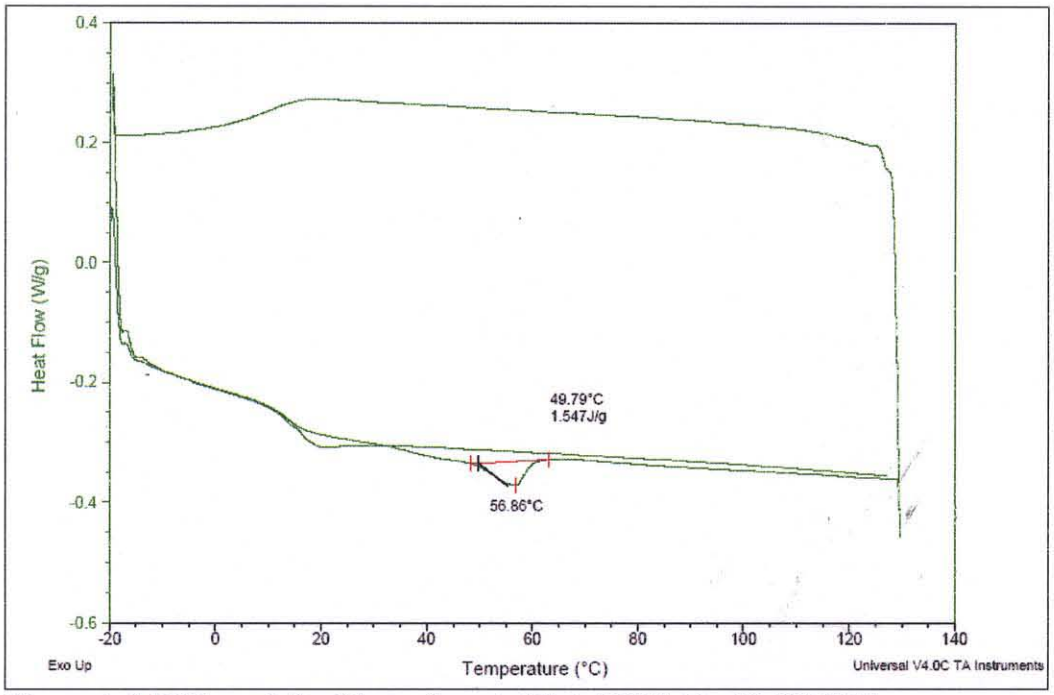

Figure A.1 DCS result for 0 hours incuated Poly(DT 8, 8) with 0% PNA.

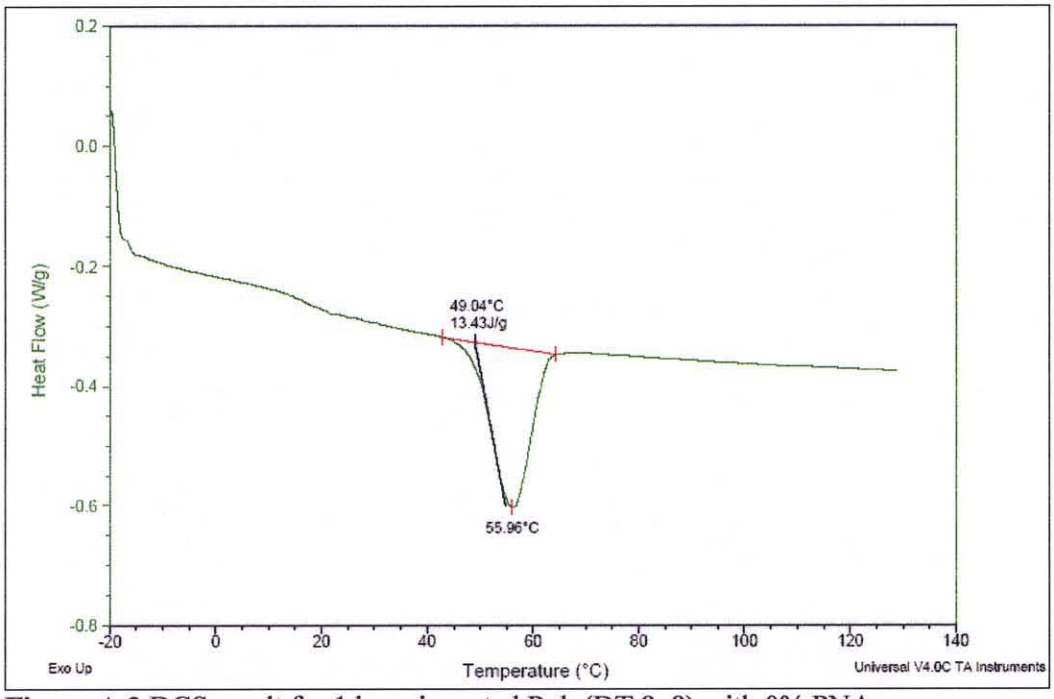

Figure A.2 DCS result for 1 hour incuated Poly(DT 8, 8) with 0% PNA.

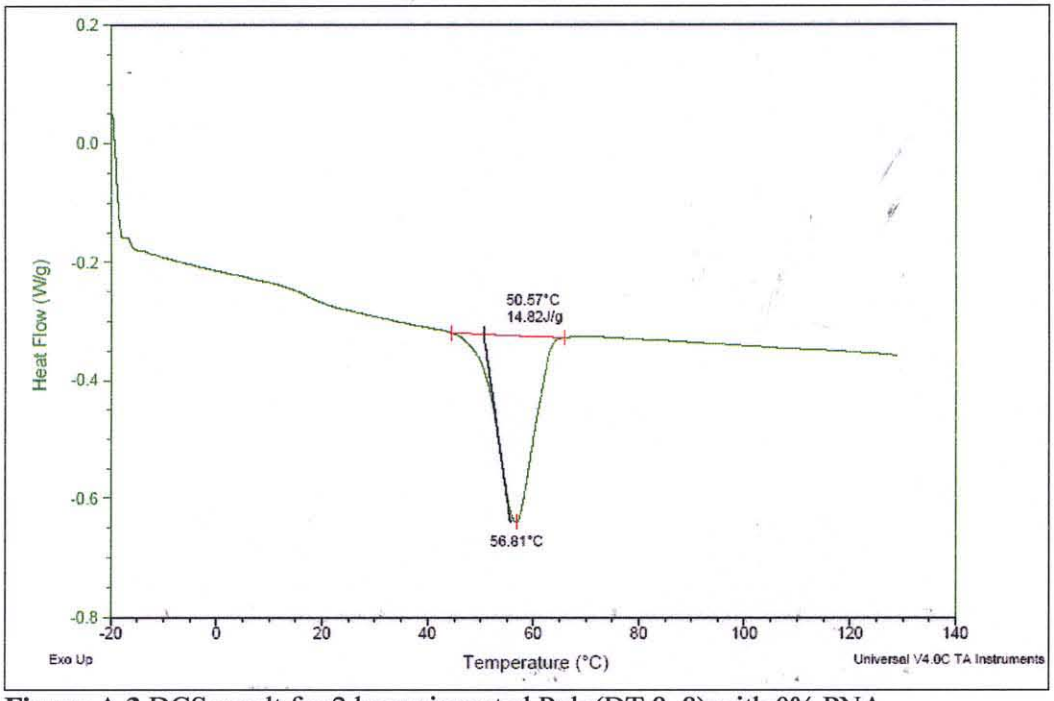

Figure A.3 DCS result for 2 hours incuated Poly(DT 8, 8) with 0% PNA.

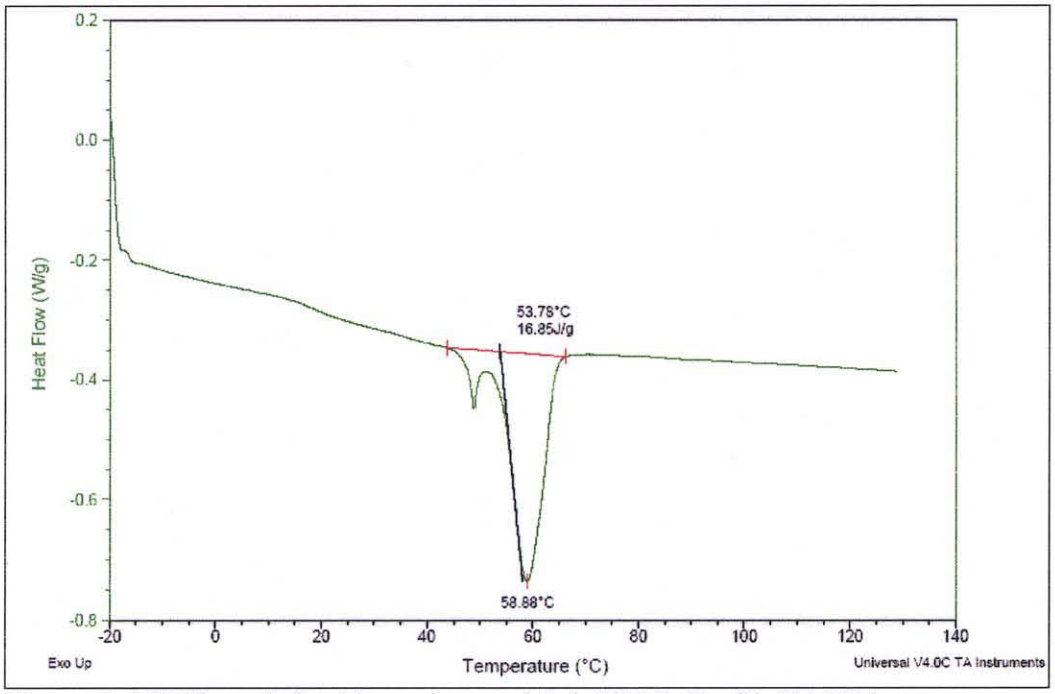

Figure A.4 DCS result for 4 hours incuated Poly(DT 8, 8) with 0% PNA.

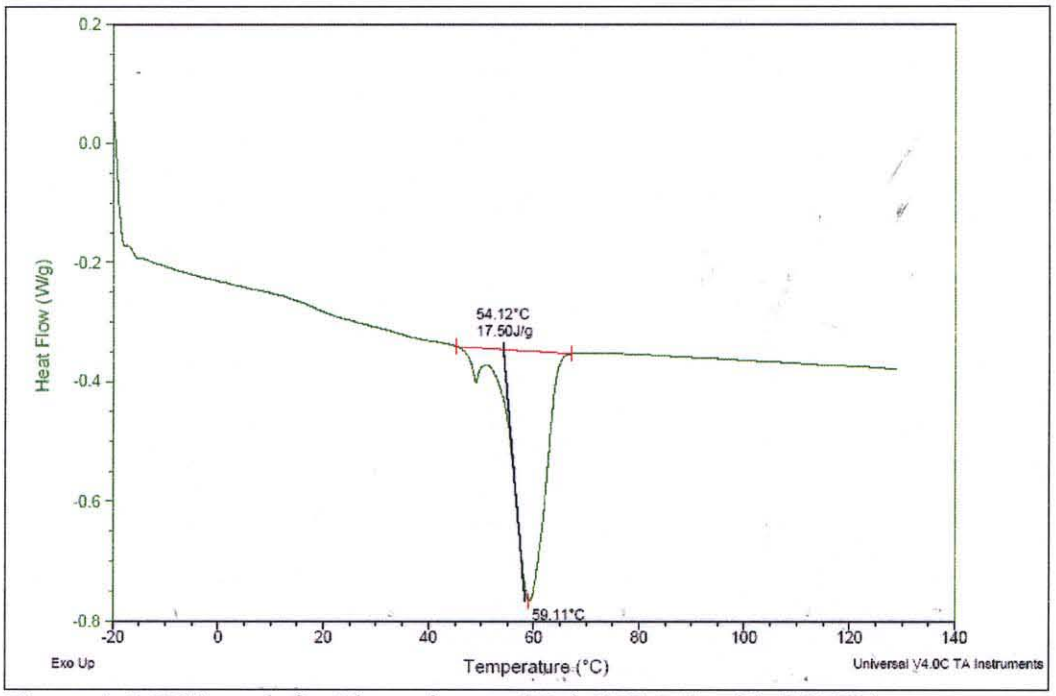

Figure A.5 DCS result for 6 hours incuated Poly(DT 8, 8) with 0% PNA.

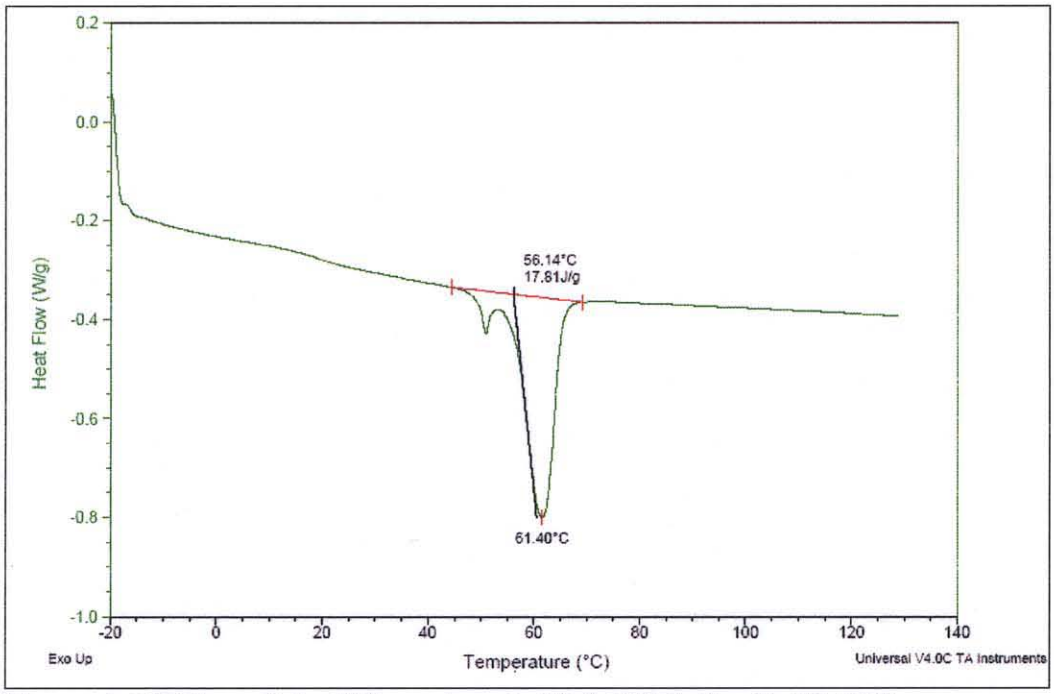

Figure A.6 DCS result for 17 hours incuated Poly(DT 8, 8) with 0% PNA.

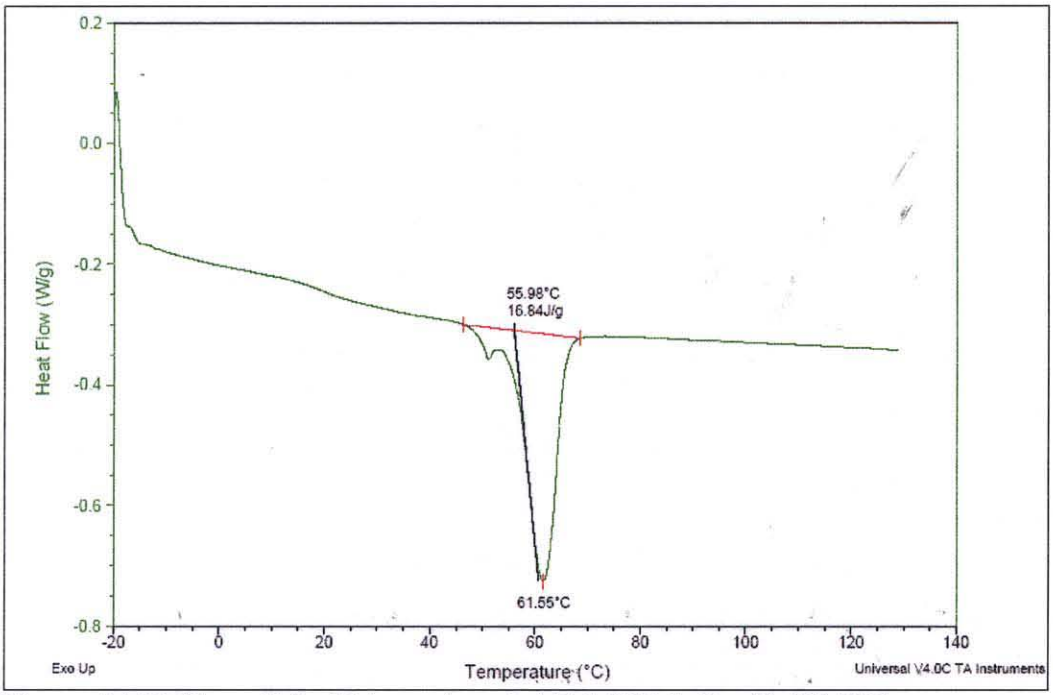

Figure A.7 DCS result for 21 hours incuated Poly(DT 8, 8) with 0% PNA.

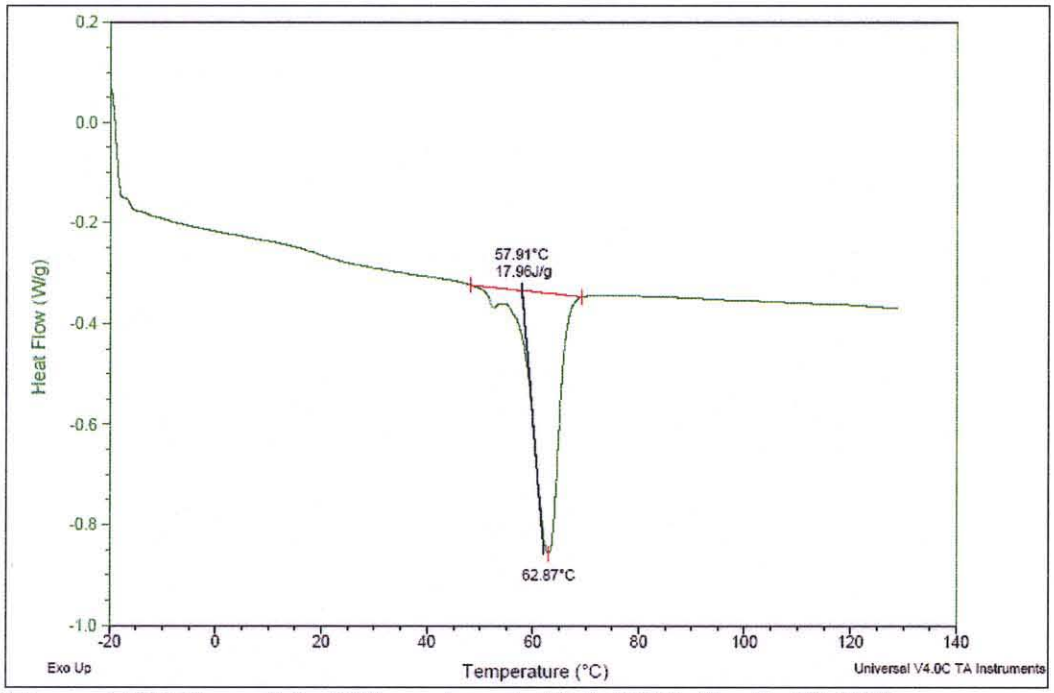

Figure A.8 DCS result for 24 hours incuated Poly(DT 8, 8) with 0% PNA.

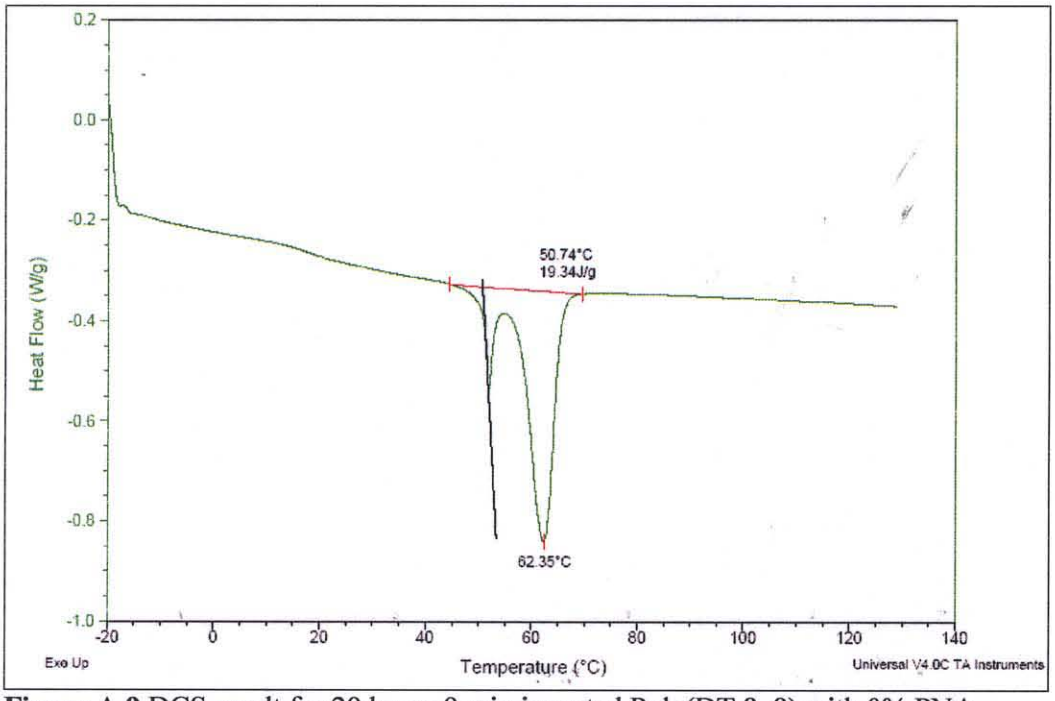

Figure A.9 DCS result for 29 hours 9 min incuated Poly(DT 8, 8) with 0% PNA.

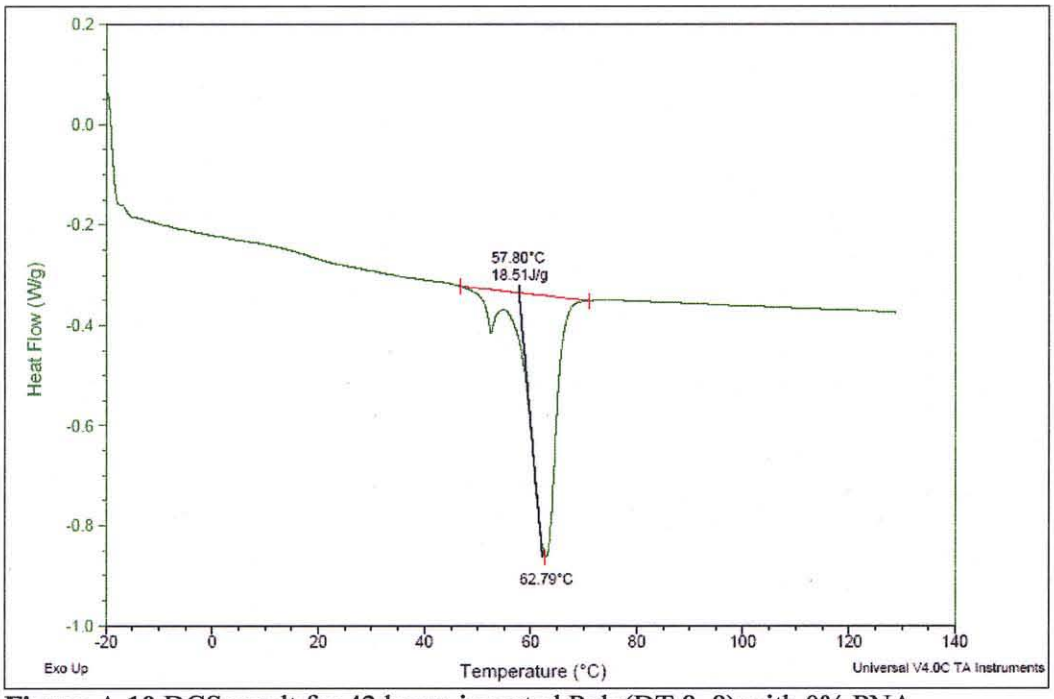

Figure A.10 DCS result for 42 hours incuated Poly(DT 8, 8) with 0% PNA.

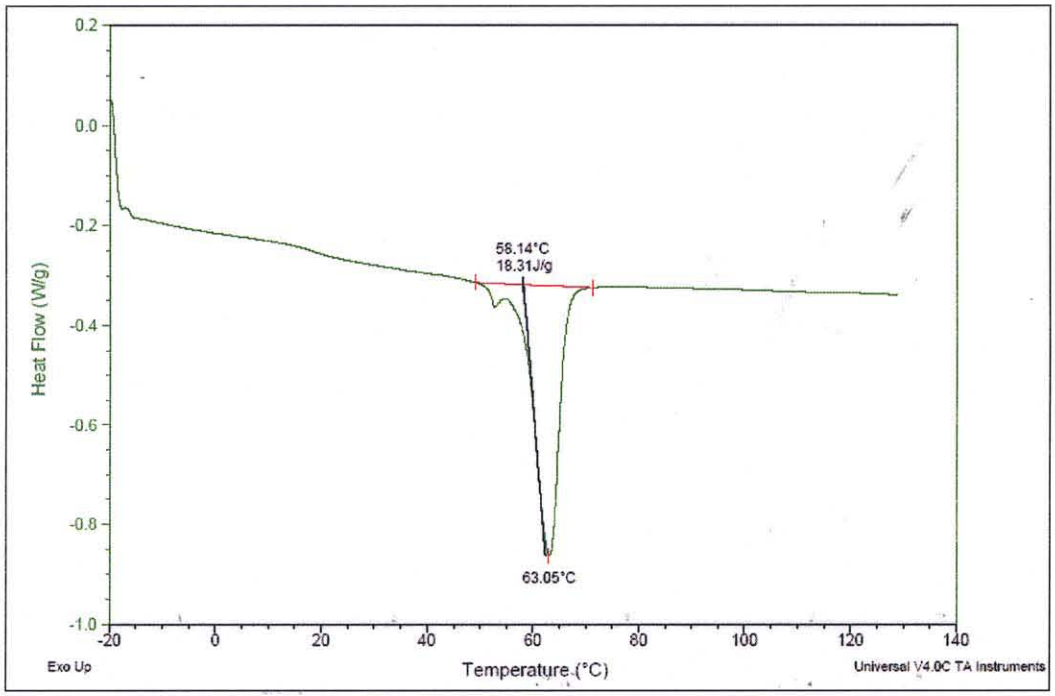

Figure A.11 DCS result for 48 hours incuated Poly(DT 8, 8) with 0% PNA.

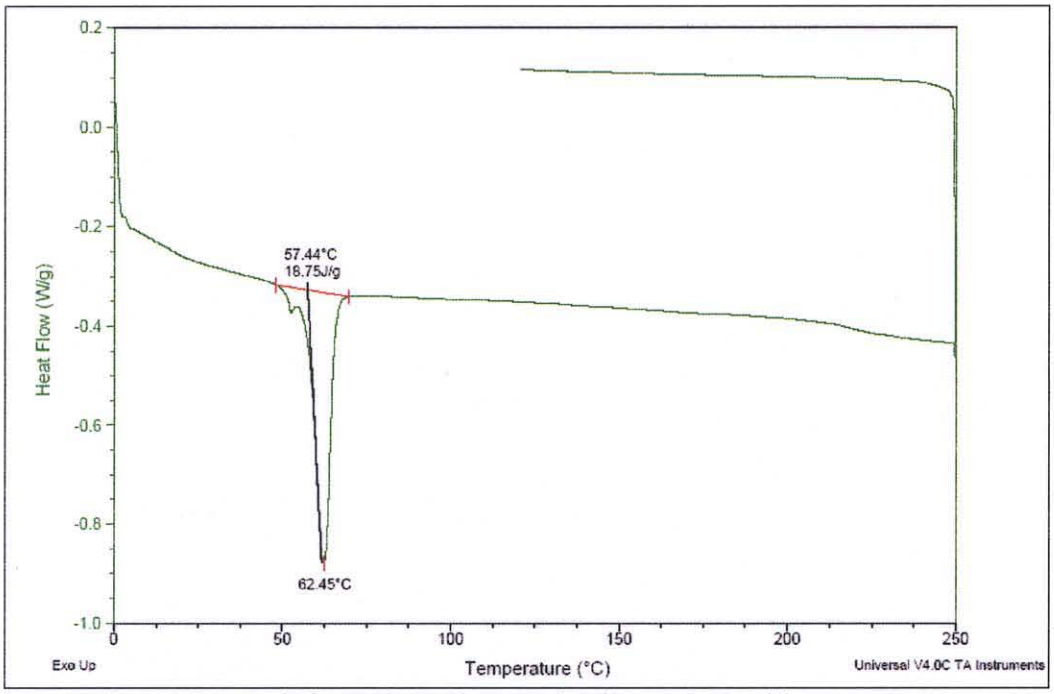

Figure A.12 DCS result for 53 hours incuated Poly(DT 8, 8) with 0% PNA.

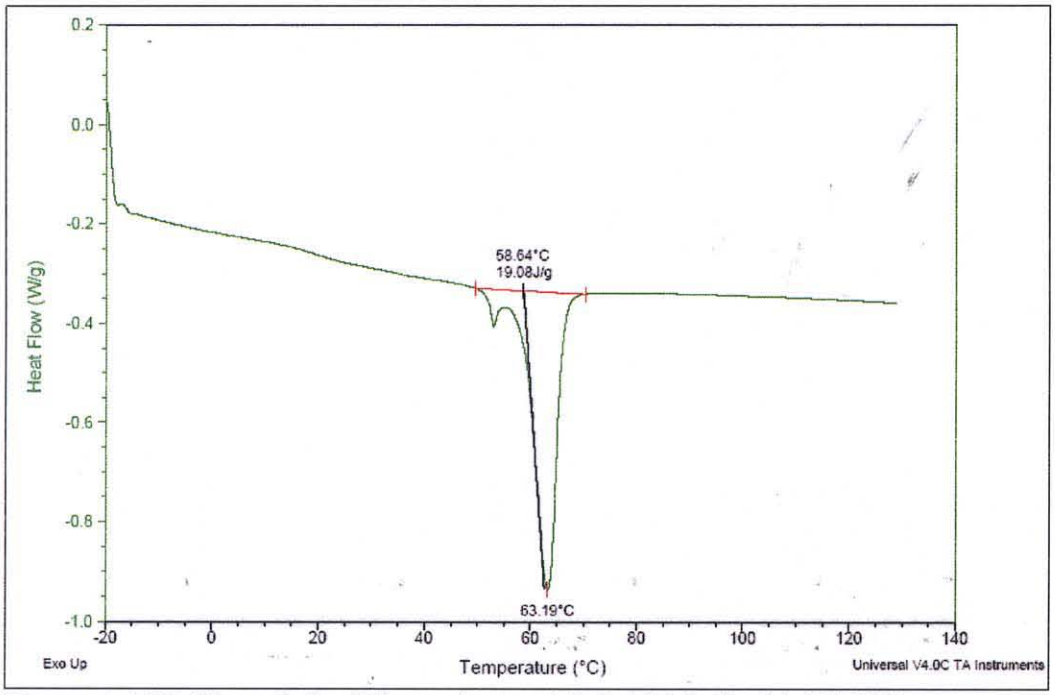

Figure A.13 DCS result for 67 hours incuated Poly(DT 8, 8) with 0% PNA.

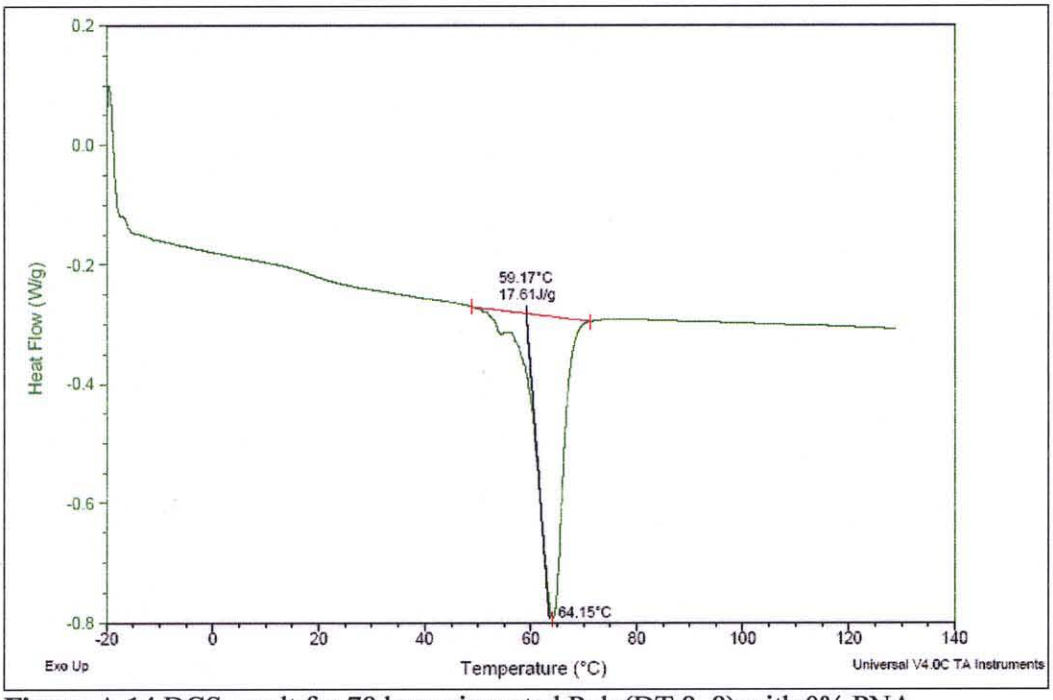

Figure A.14 DCS result for 78 hours incuated Poly(DT 8, 8) with 0% PNA.

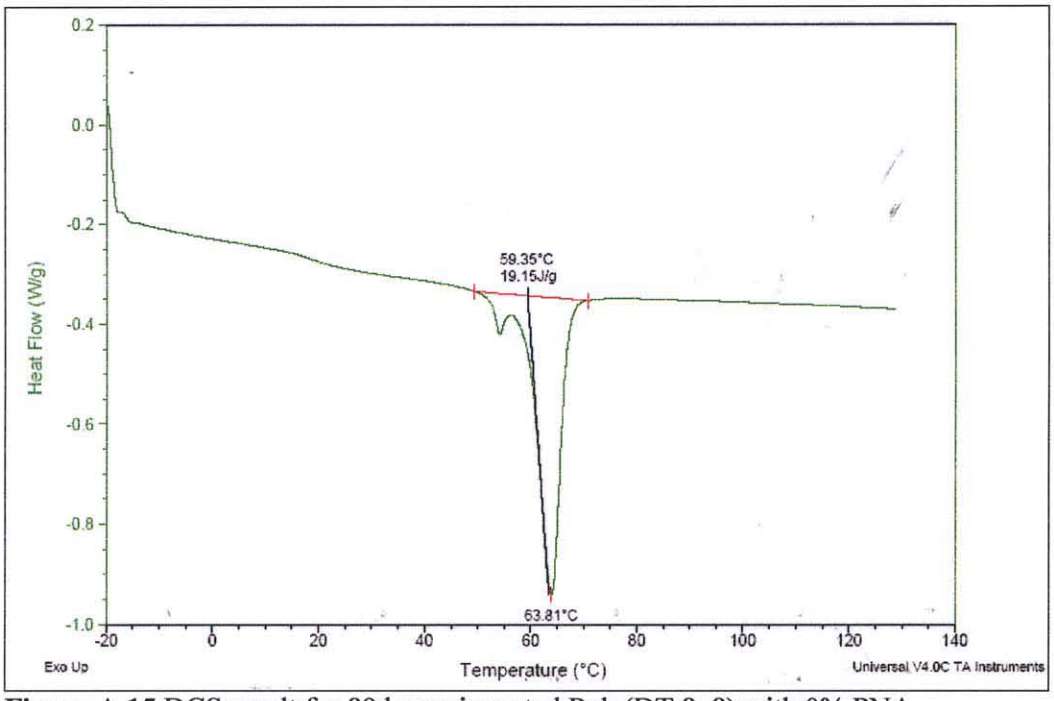

Figure A.15 DCS result for 89 hours incuated Poly(DT 8, 8) with 0% PNA.

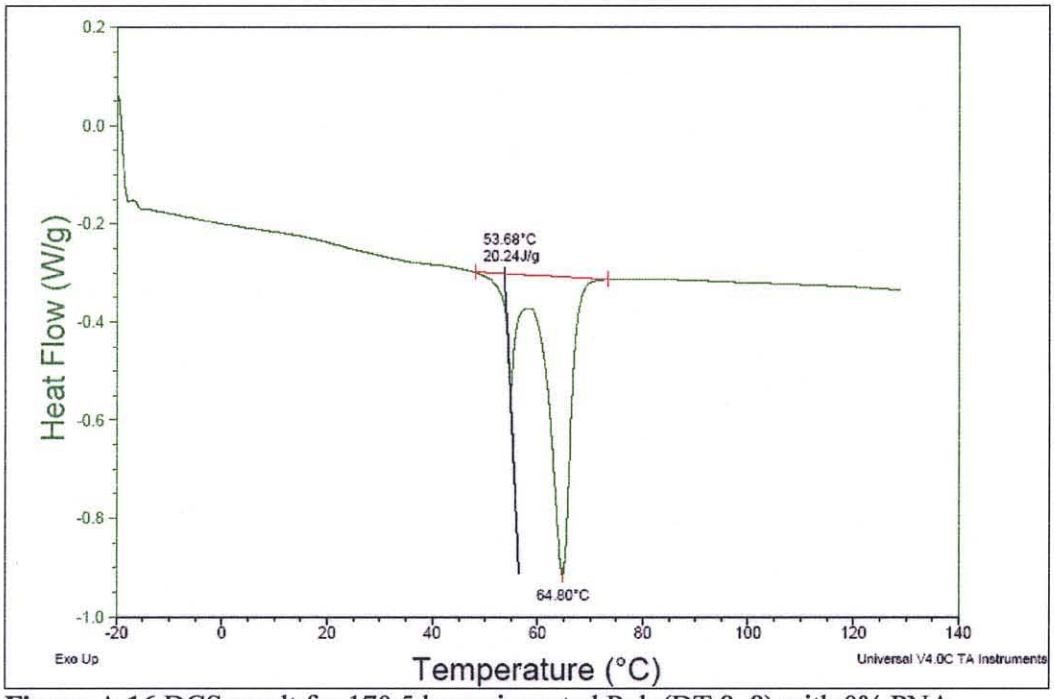

Figure A.16 DCS result for 170.5 hours incuated Poly(DT 8, 8) with 0% PNA.

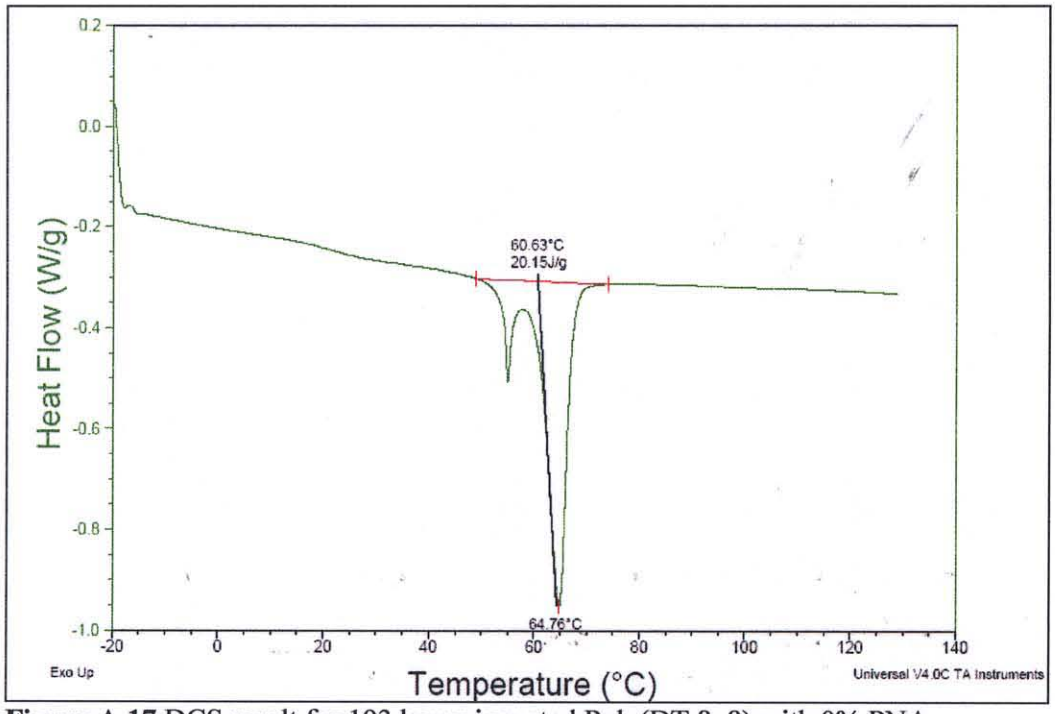

Figure A.17 DCS result for 193 hours incuated Poly(DT 8, 8) with 0% PNA.

APPENDIX B

RAW DATA OF DSC RESULTS OF POLY(DT 8, 8) WITH 5% DRUG LOADING

DSC results of 5% p-nitroaniline loaded Poly(DT 8, 8) and measured enthalpy of phase change.

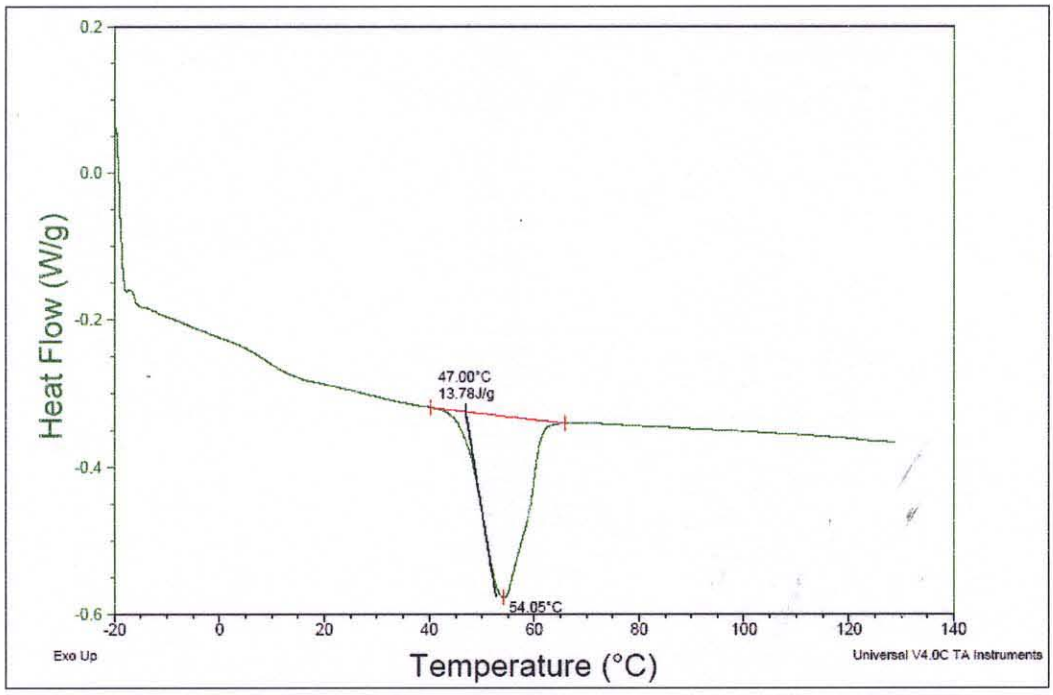

Figure B.1 DCS result for 0 hours incuated Poly(DT 8, 8) with 5% PNA.

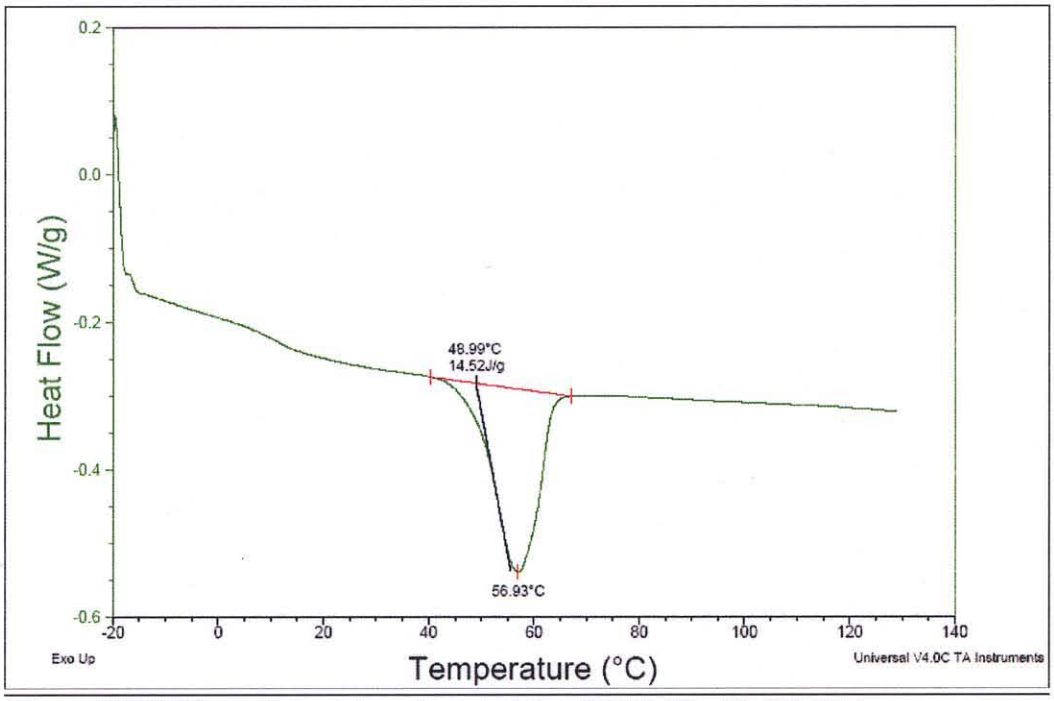

Figure B.2 DCS result for 1 hour incuated Poly(DT 8, 8) with 5% PNA.

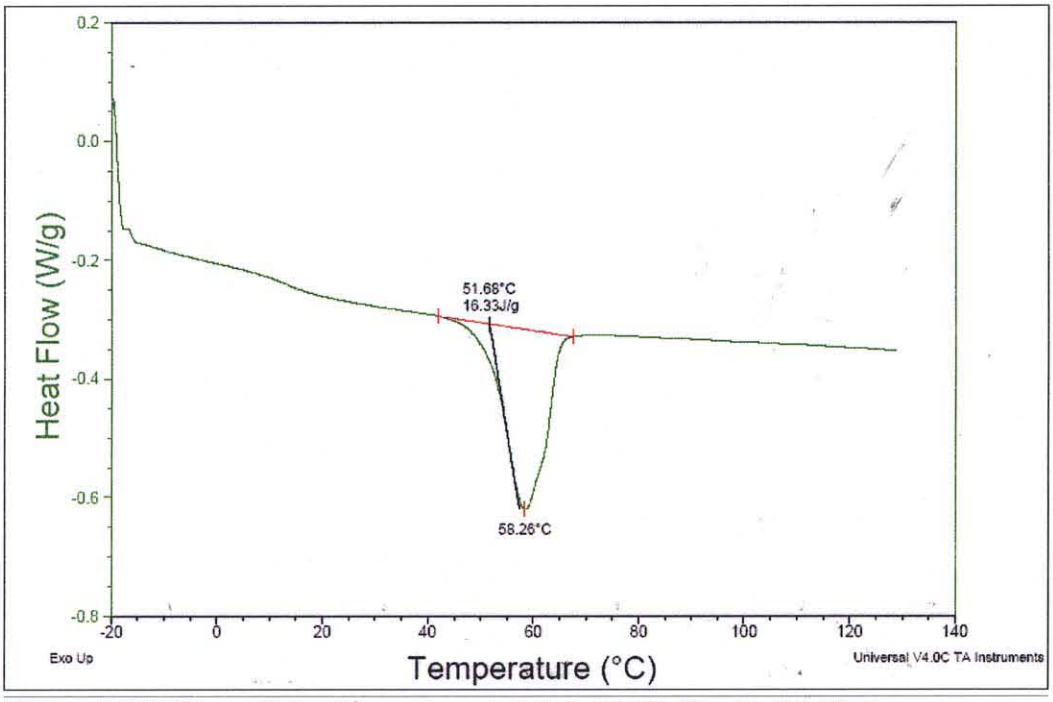

Figure B.3 DCS result for 2 hours incuated Poly(DT 8, 8) with 5% PNA.

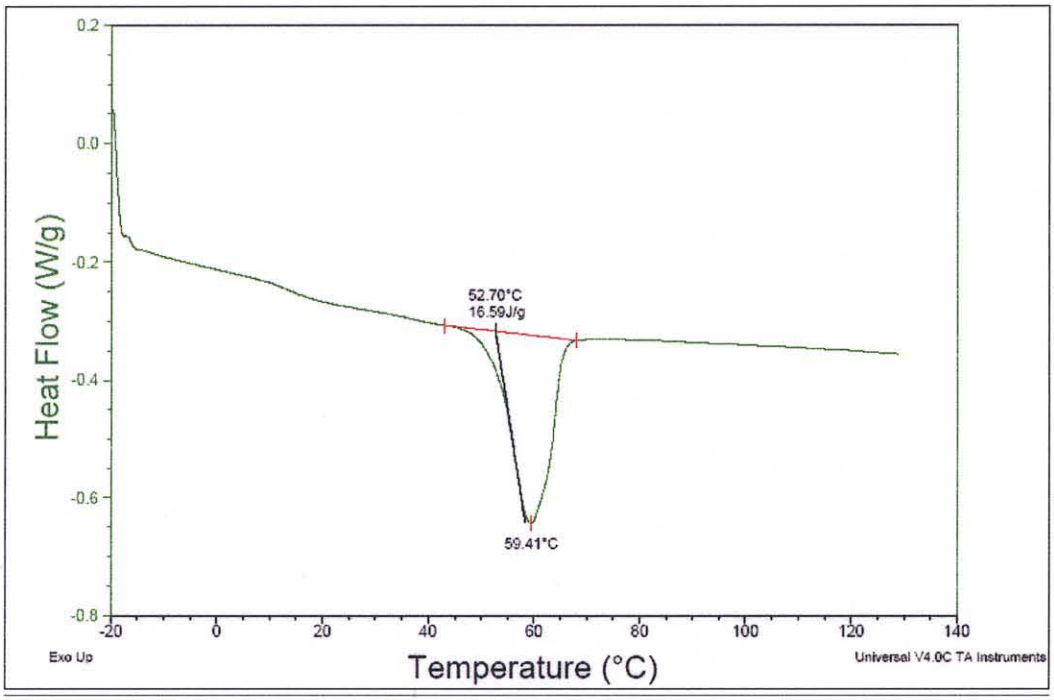

Figure B.4 DCS result for 3 hours incuated Poly(DT 8, 8) with 5% PNA.

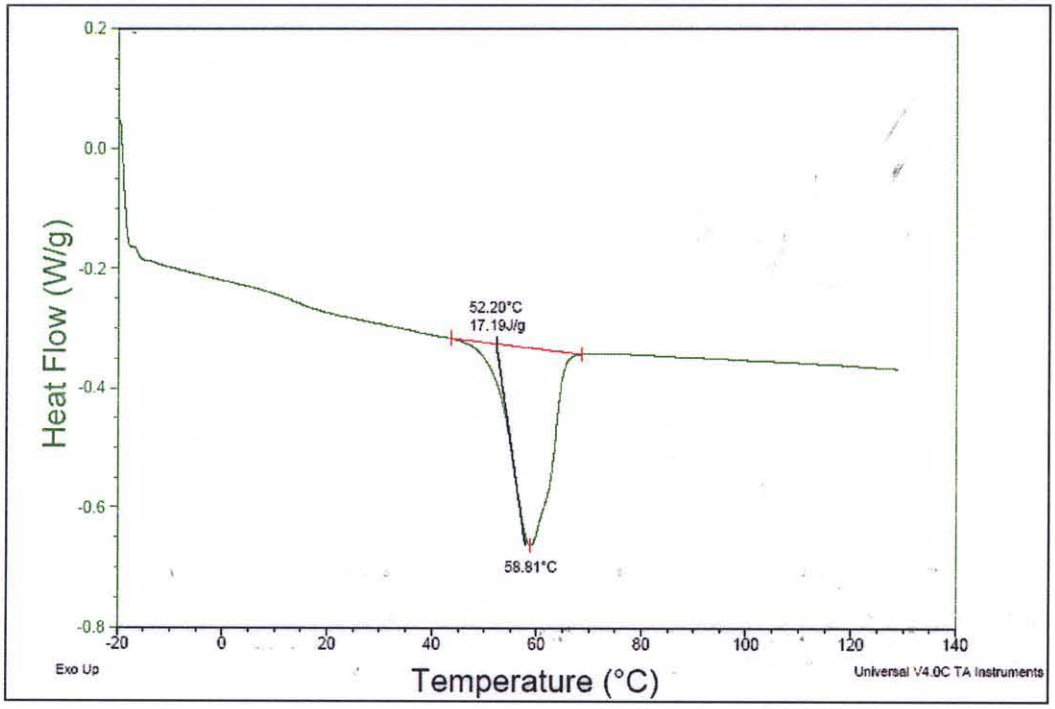

Figure B.5 DCS result for 4 hours incuated Poly(DT 8, 8) with 5% PNA.

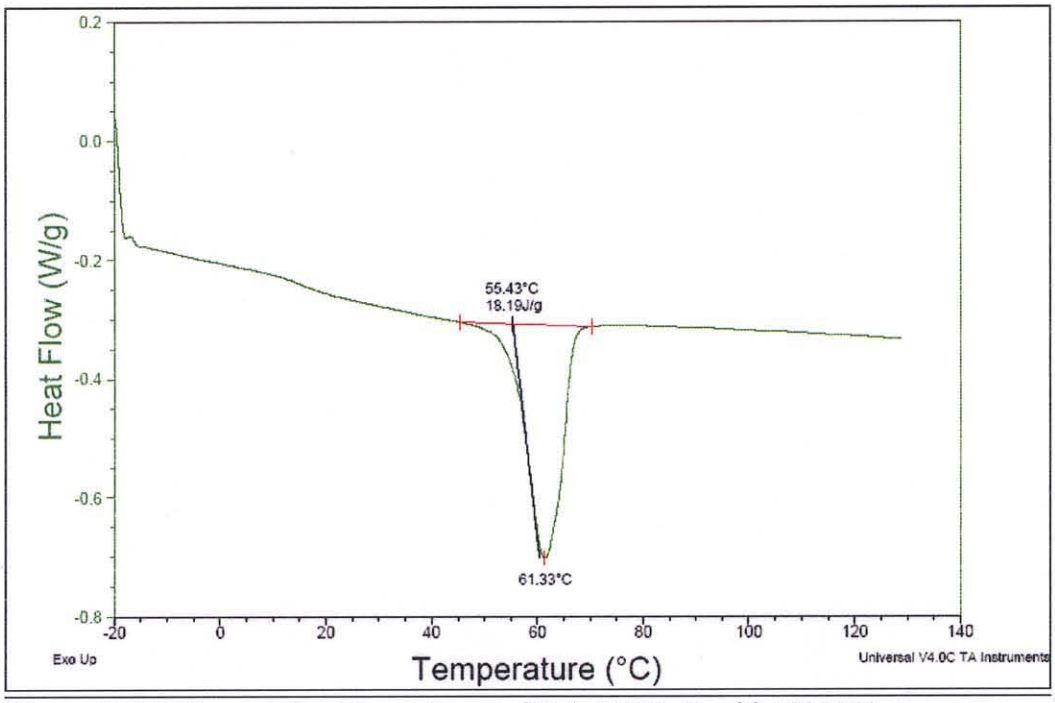

Figure B.6 DCS result for 6 hours incuated Poly(DT 8, 8) with 5% PNA.

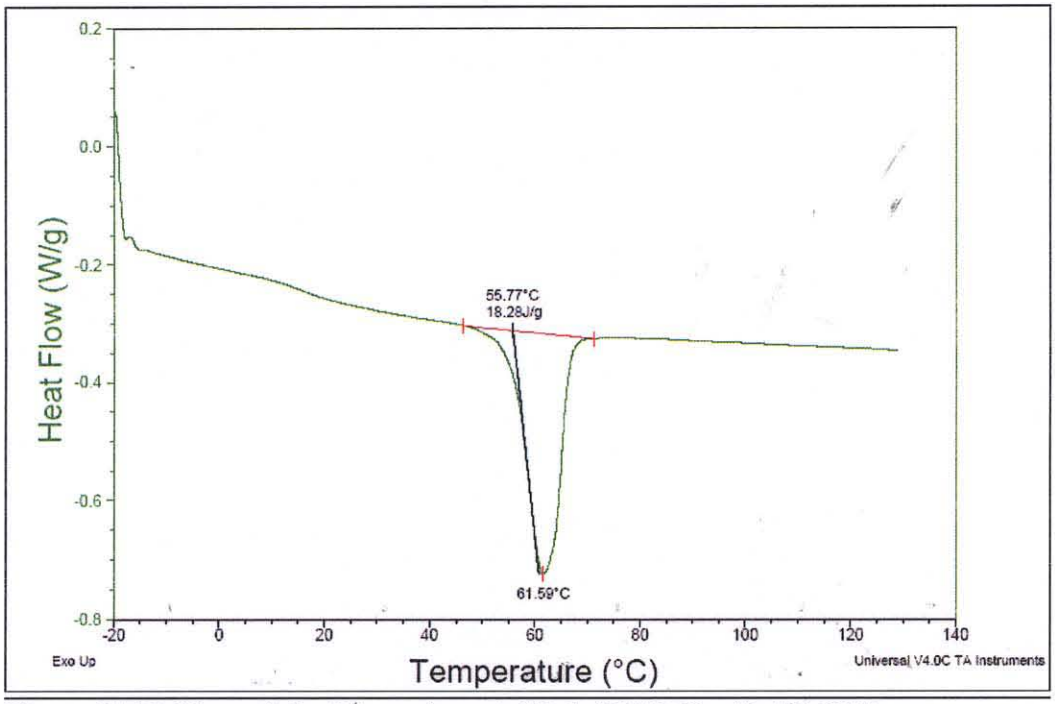

Figure B.7 DCS result for 8 hours incuated Poly(DT 8, 8) with 5% PNA.

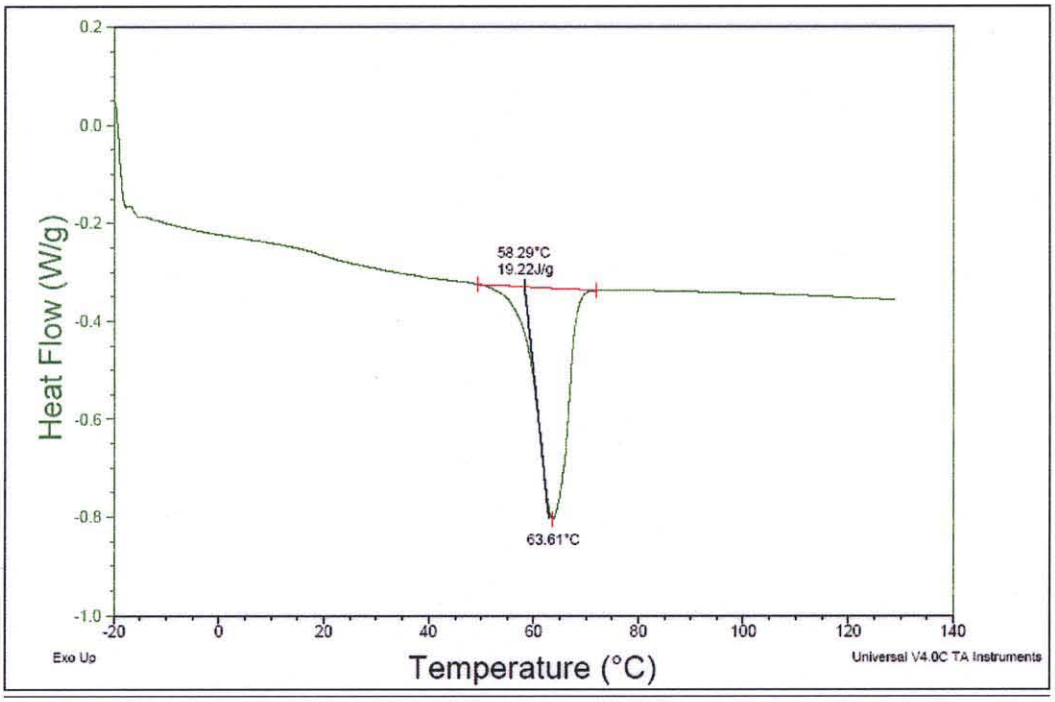

Figure B.8 DCS result for 18 hours 6 mins incuated Poly(DT 8, 8) with 5% PNA.

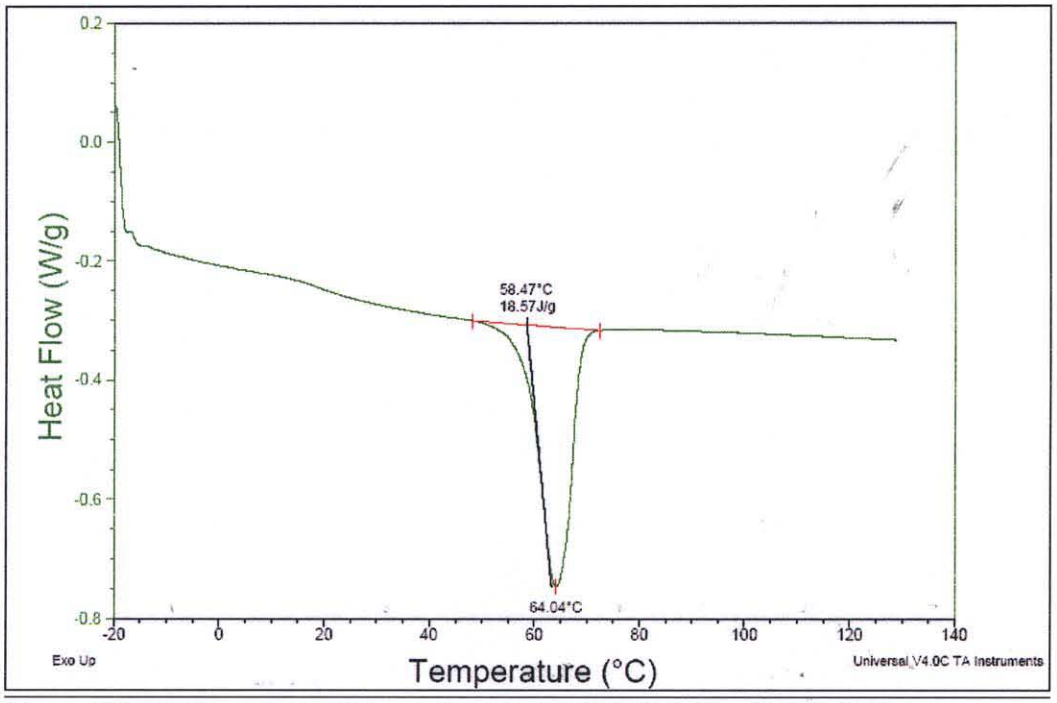

Figure B.9 DCS result for 21 hours incuated Poly(DT 8, 8) with 5% PNA.

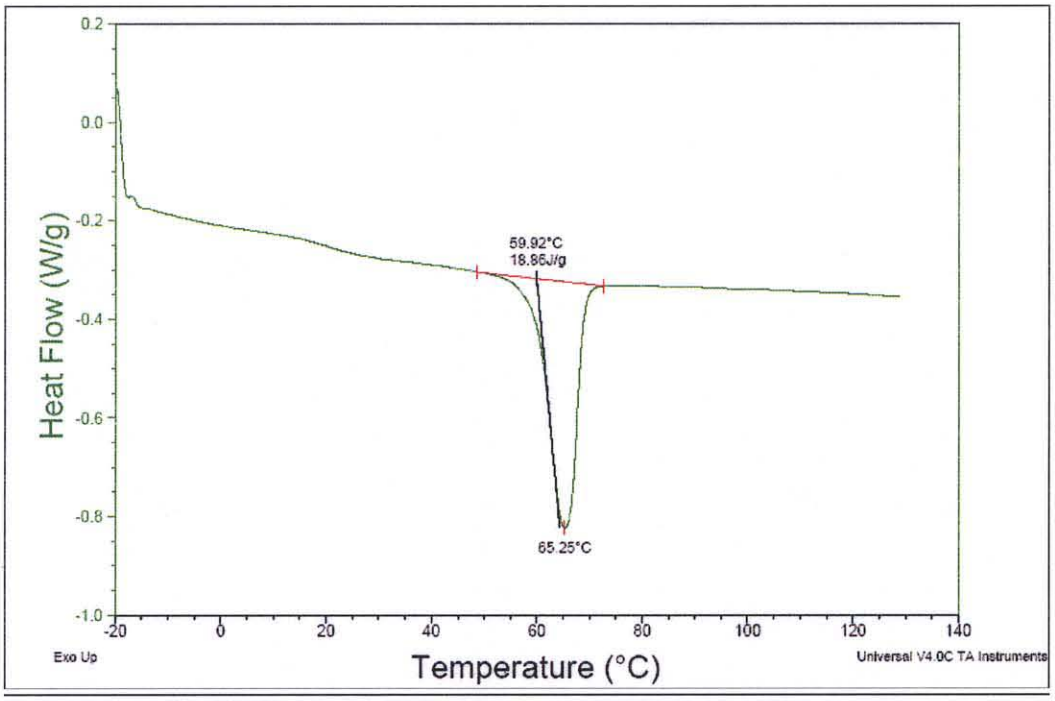

Figure B.10 DCS result for 32 hours incuated Poly(DT 8, 8) with 5% PNA.

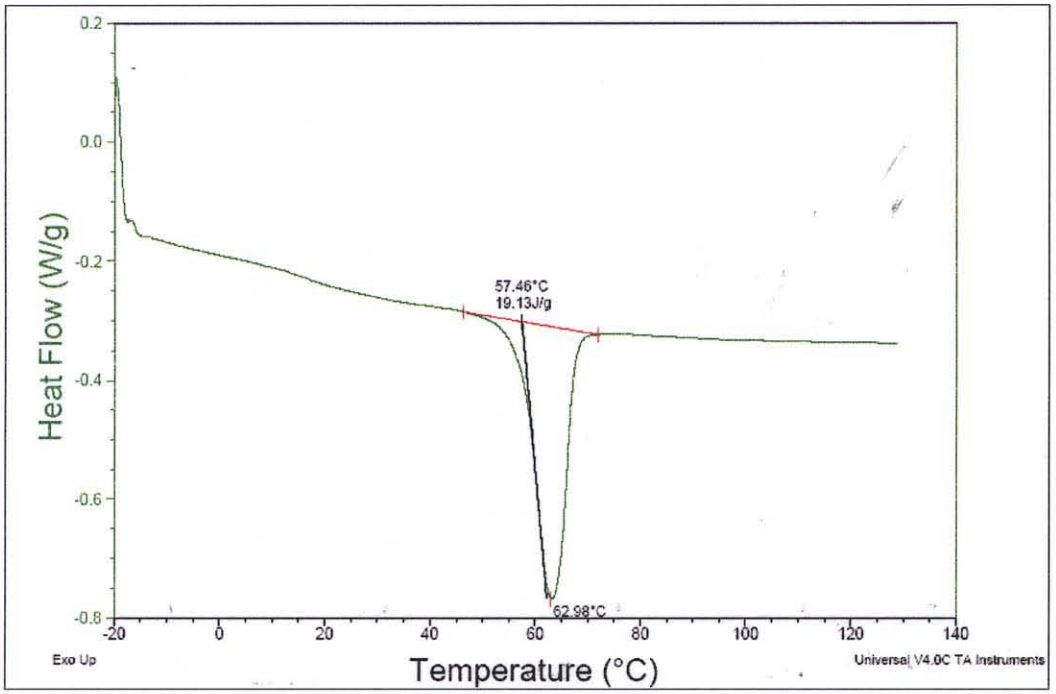

Figure B.11 DCS result for 48 hours incuated Poly(DT 8, 8) with 5% PNA.

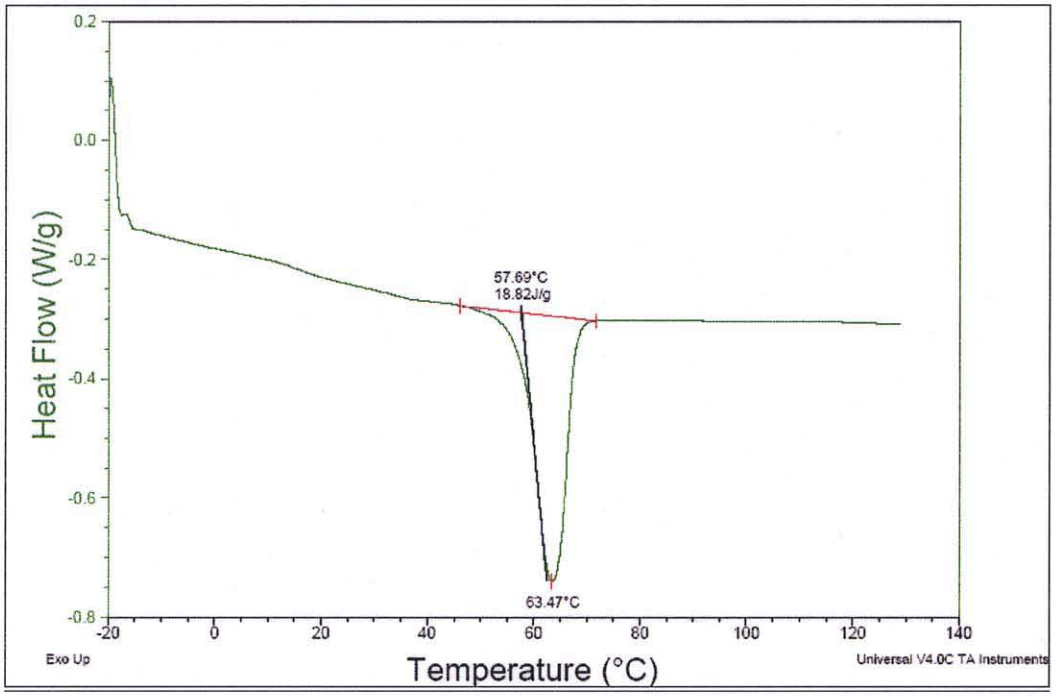

Figure B.12 DCS result for 72 hours incuated Poly(DT 8, 8) with 5% PNA.

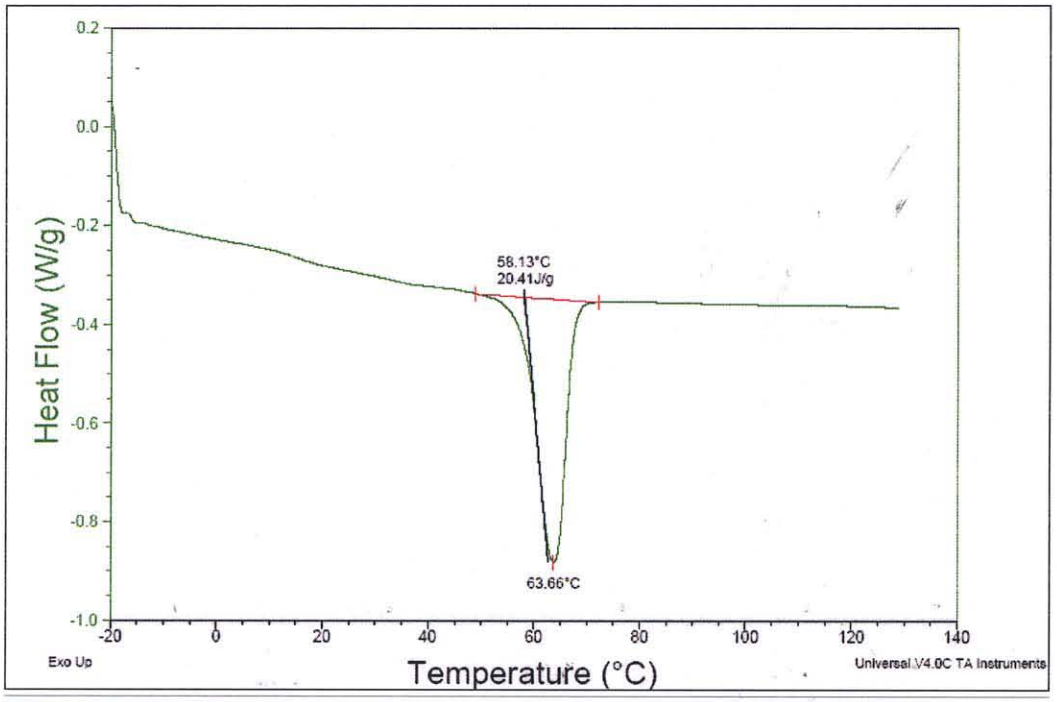

Figure B.13 DCS result for 118 hours incuated Poly(DT 8, 8) with 5% PNA.

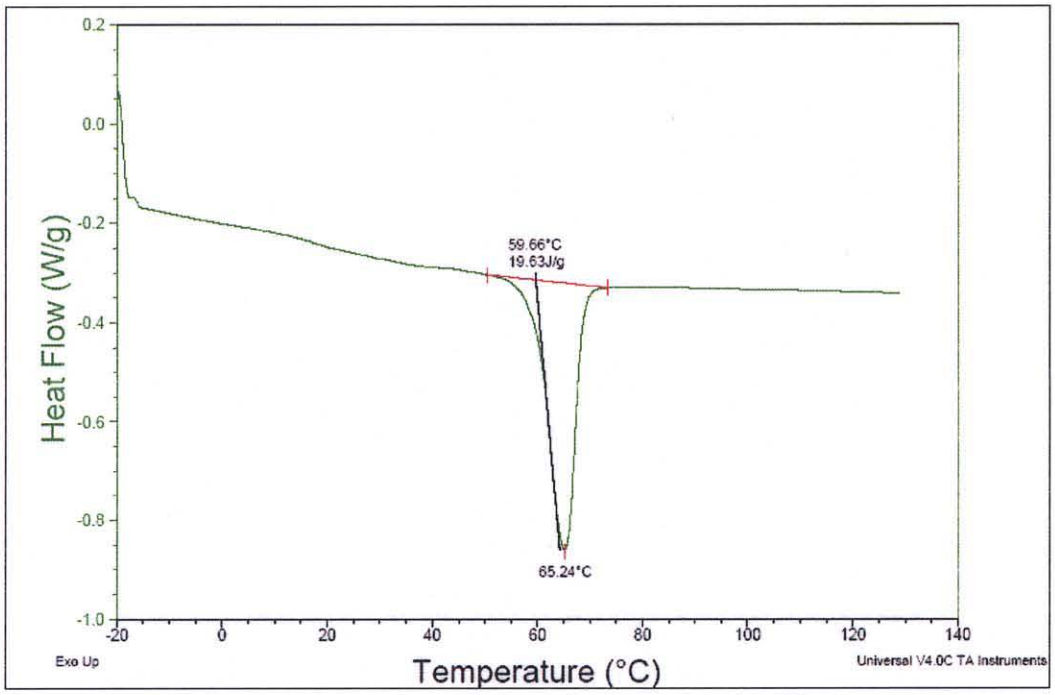

Figure B.14 DCS result for 144 hours incuated Poly(DT 8, 8) with 5% PNA.

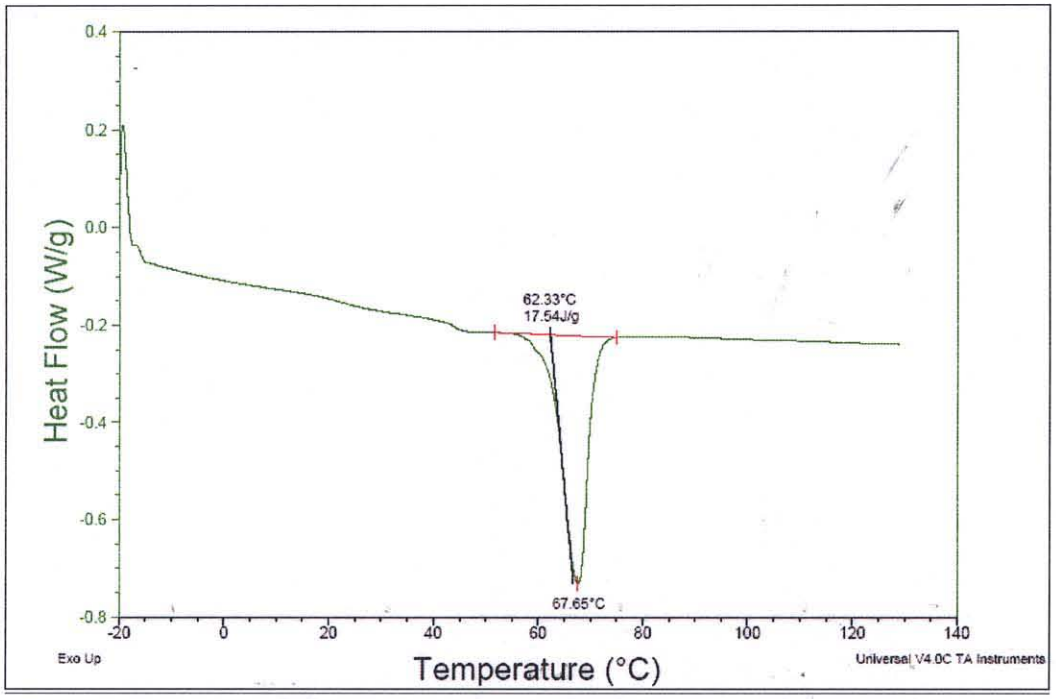

Figure B.15 DCS result for 168 hours incuated Poly(DT 8, 8) with 5% PNA.

APPENDIX C

RAW DATA OF DSC RESULTS OF POLY(DT 8, 8) WITH 10% DRUG LOADING

DSC results of 10% p-nitroaniline loaded Poly(DT 8, 8) and measured enthalpy of phase change.

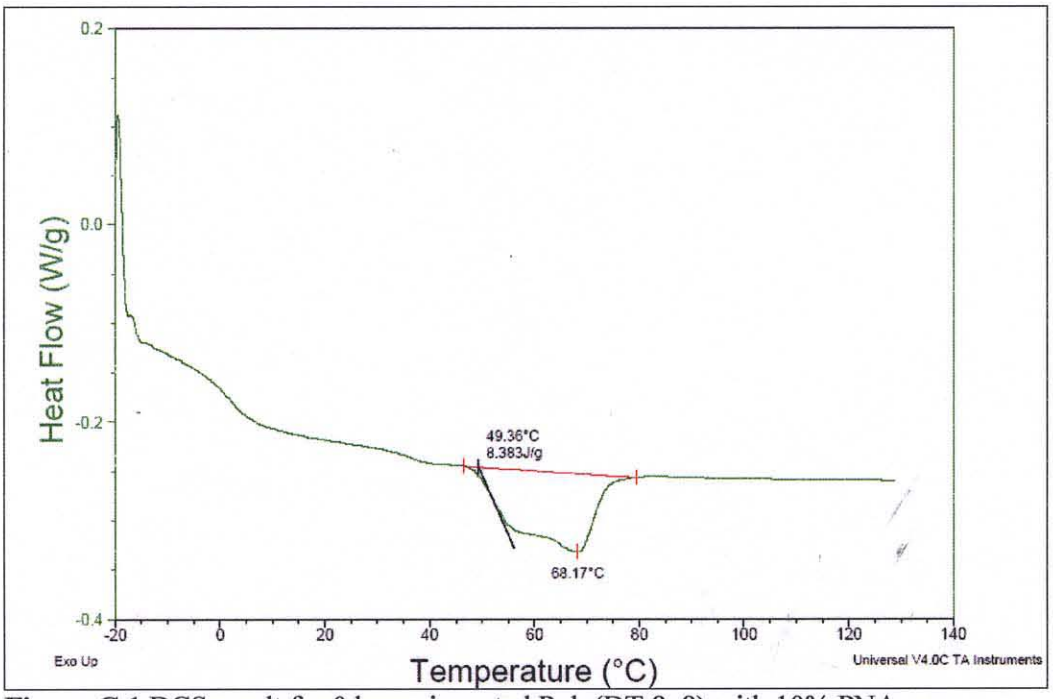

Figure C.1 DCS result for 0 hours incuated Poly(DT 8, 8) with 10% PNA.

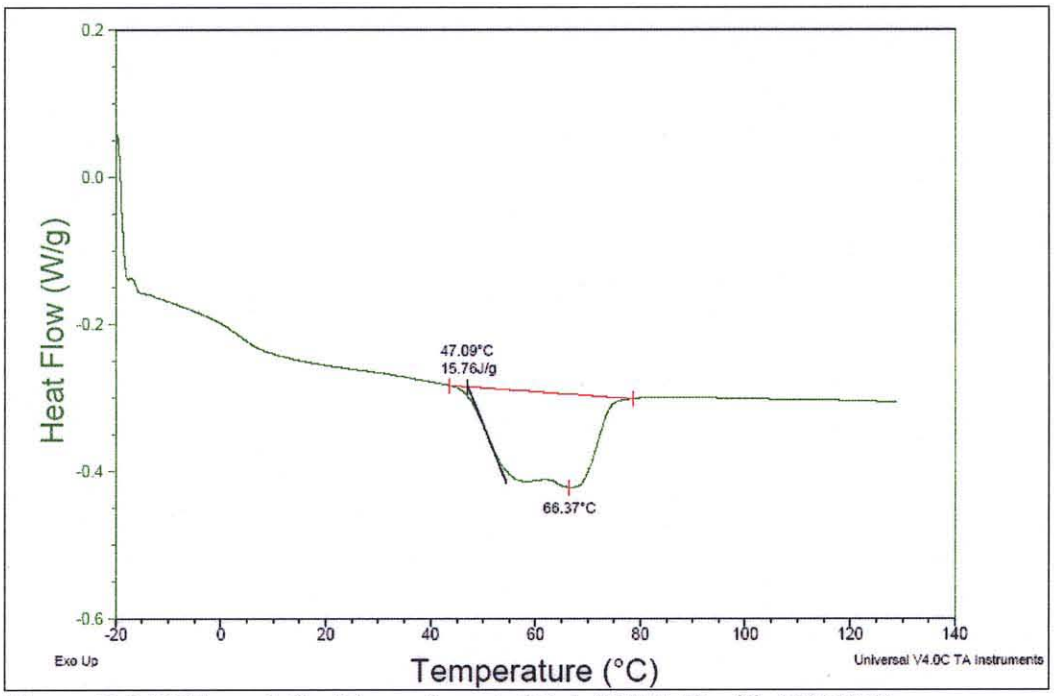

Figure C.2 DCS result for 1 hours incuated Poly(DT 8, 8) with 10% PNA.

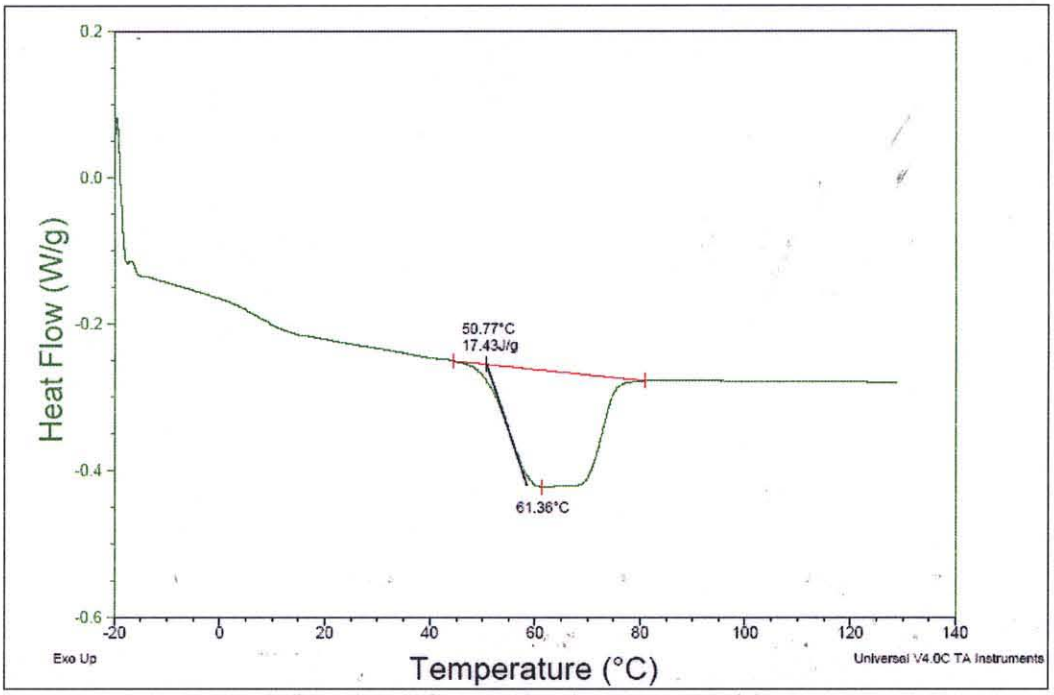

Figure C.3 DCS result for 2 hours incuated Poly(DT 8, 8) with 10% PNA.

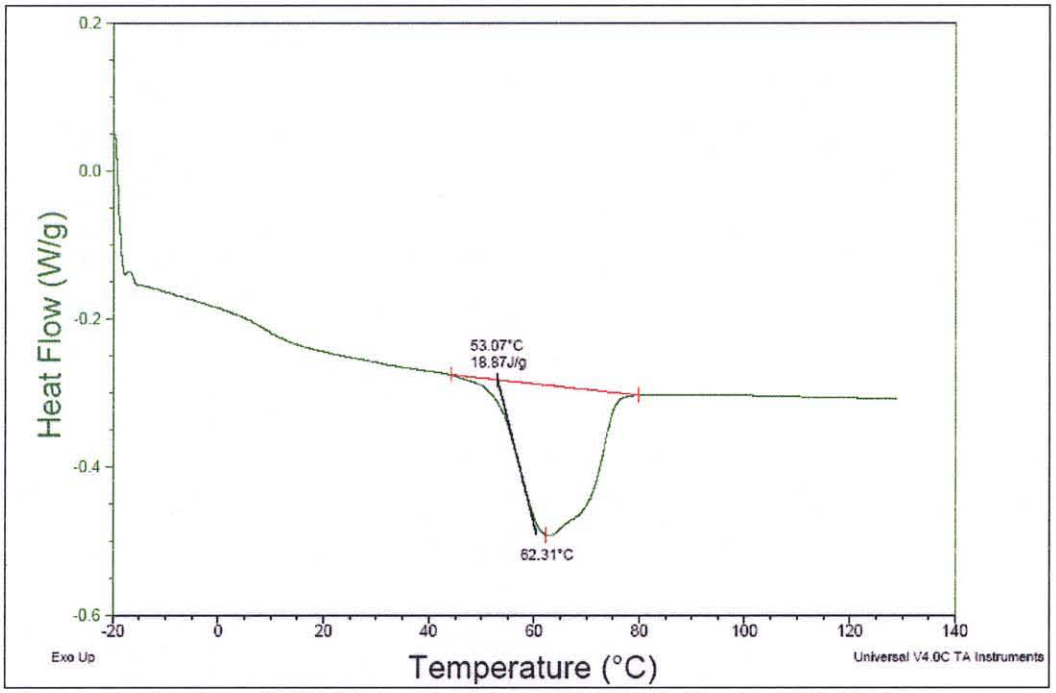

Figure C.4 DCS result for 3 hours incuated Poly(DT 8, 8) with 10% PNA.

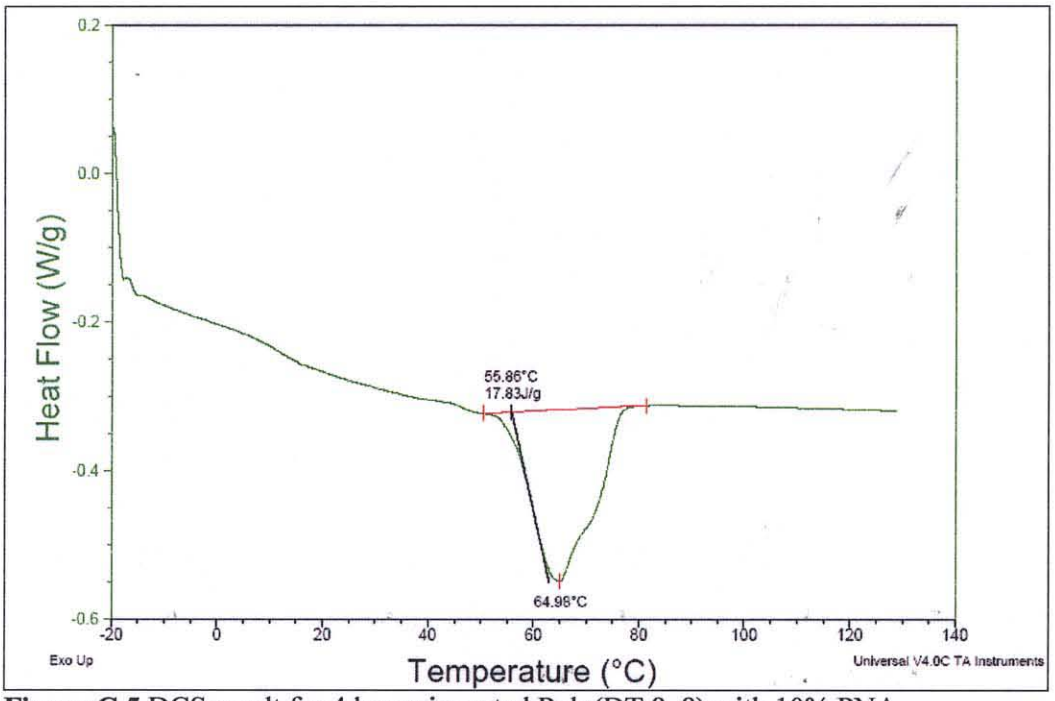

Figure C.5 DCS result for 4 hours incuated Poly(DT 8, 8) with 10% PNA.

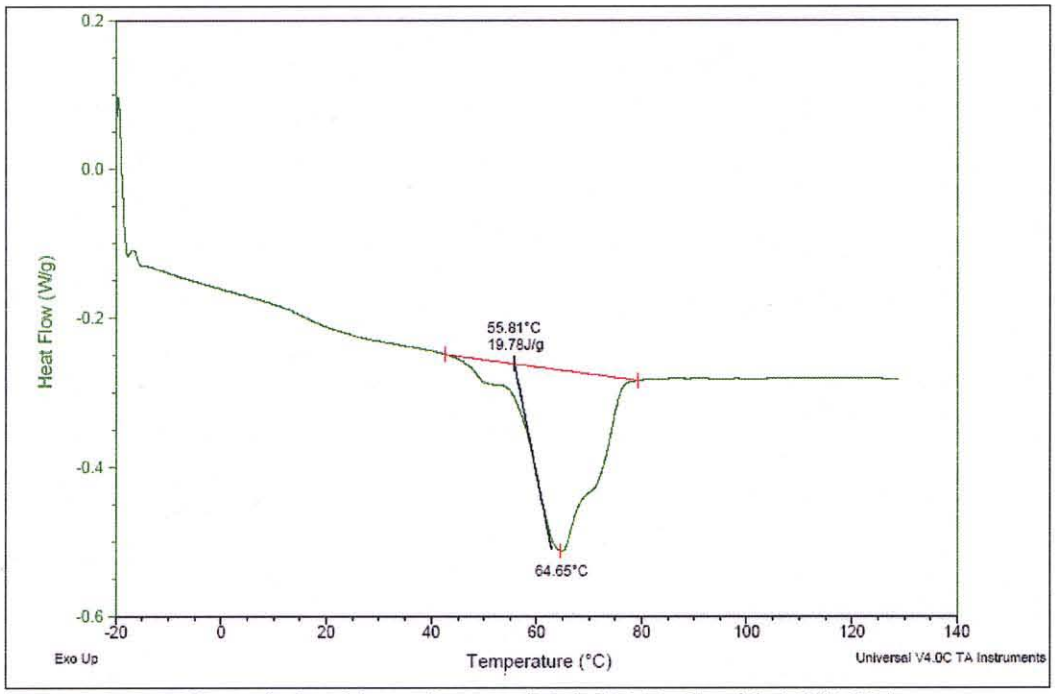

Figure C.6 DCS result for 6 hours incuated Poly(DT 8, 8) with 10% PNA.

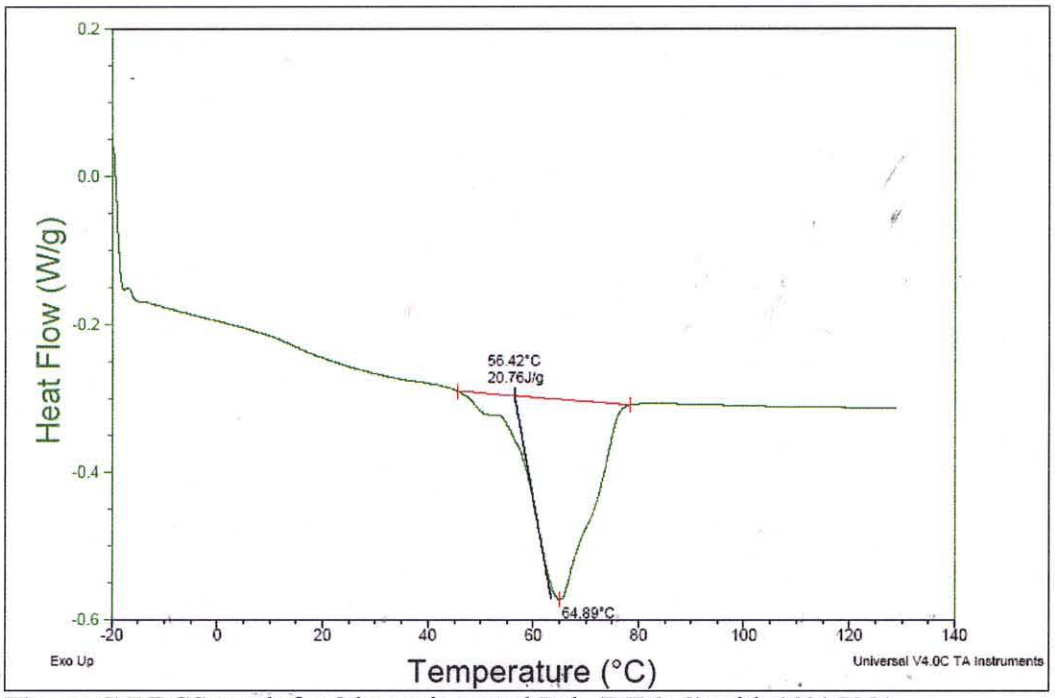

Figure C.7 DCS result for 8 hours incuated Poly(DT 8, 8) with 10% PNA.

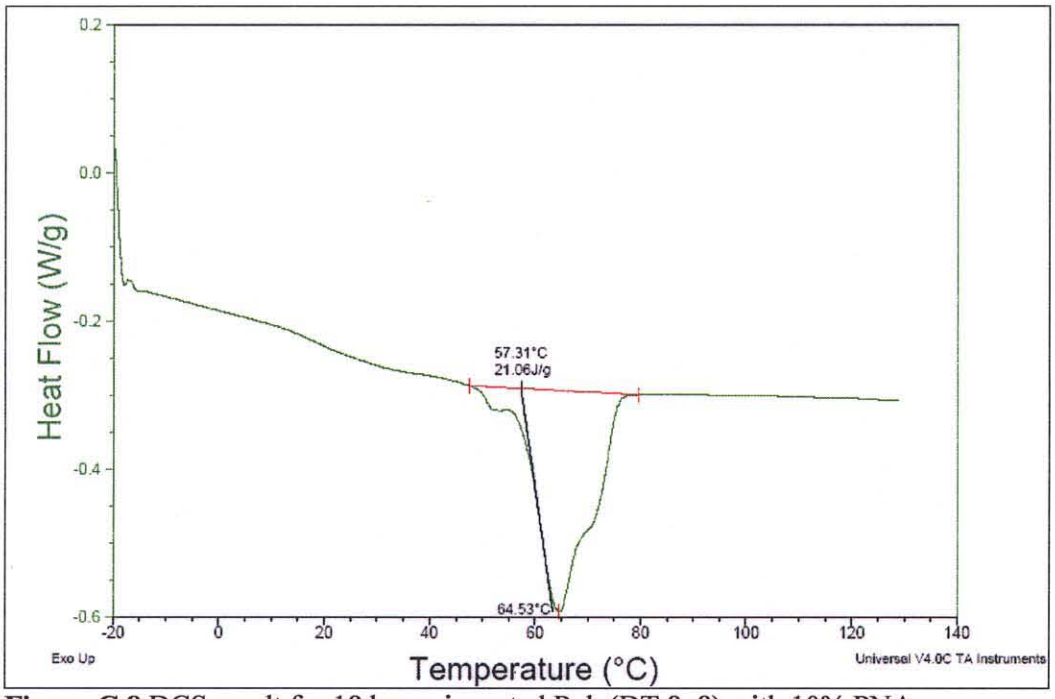

Figure C.8 DCS result for 18 hours incuated Poly(DT 8, 8) with 10% PNA.

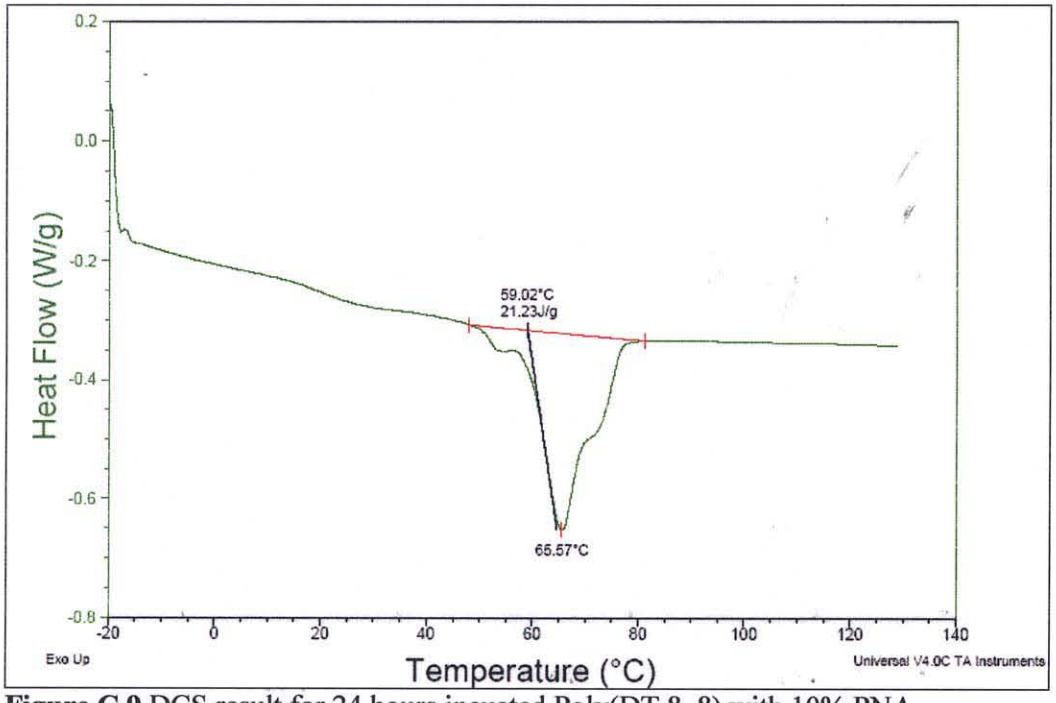

Figure C.9 DCS result for 24 hours incuated Poly(DT 8, 8) with 10% PNA.

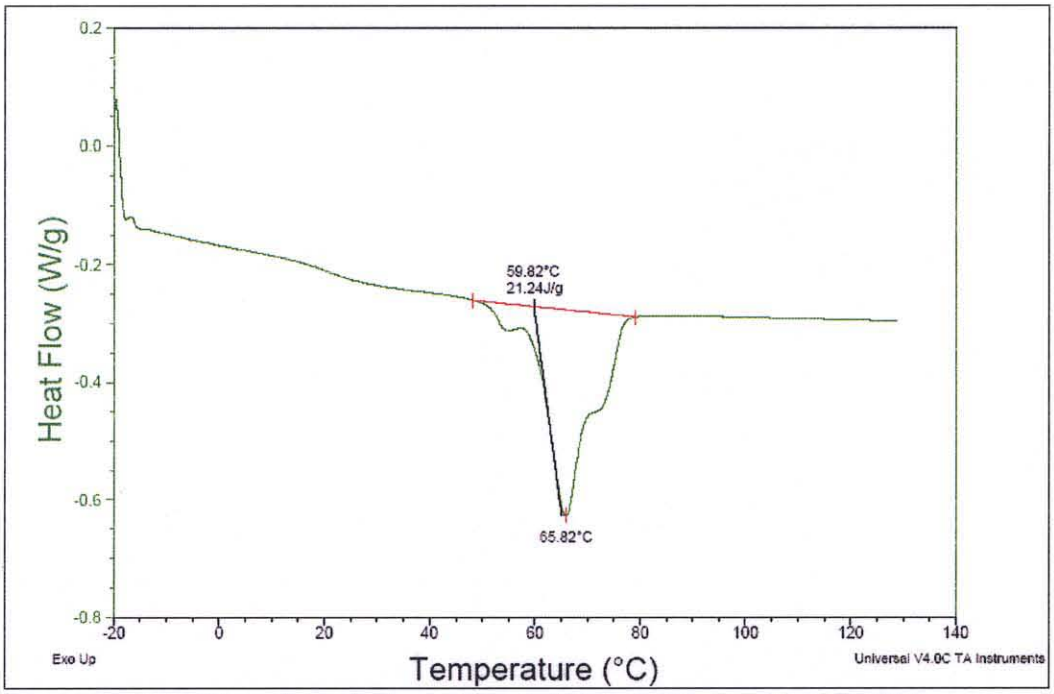

Figure C.10 DCS result for 43 hours incuated Poly(DT 8, 8) with 10% PNA.

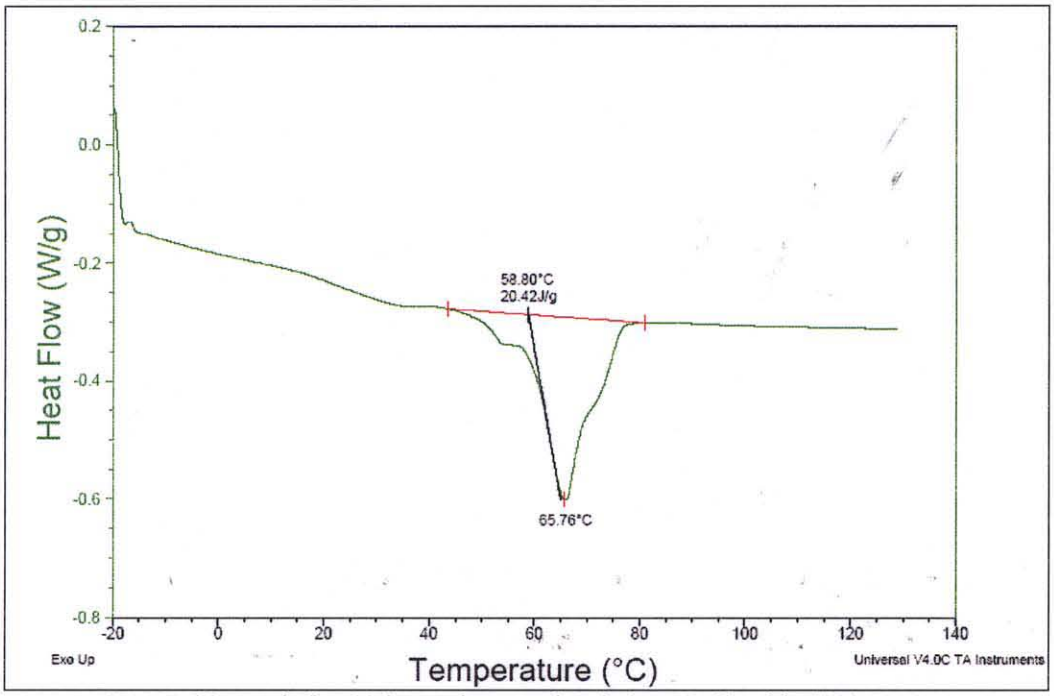

Figure C.11 DCS result for 48 hours incuated Poly(DT 8, 8) with 10% PNA.

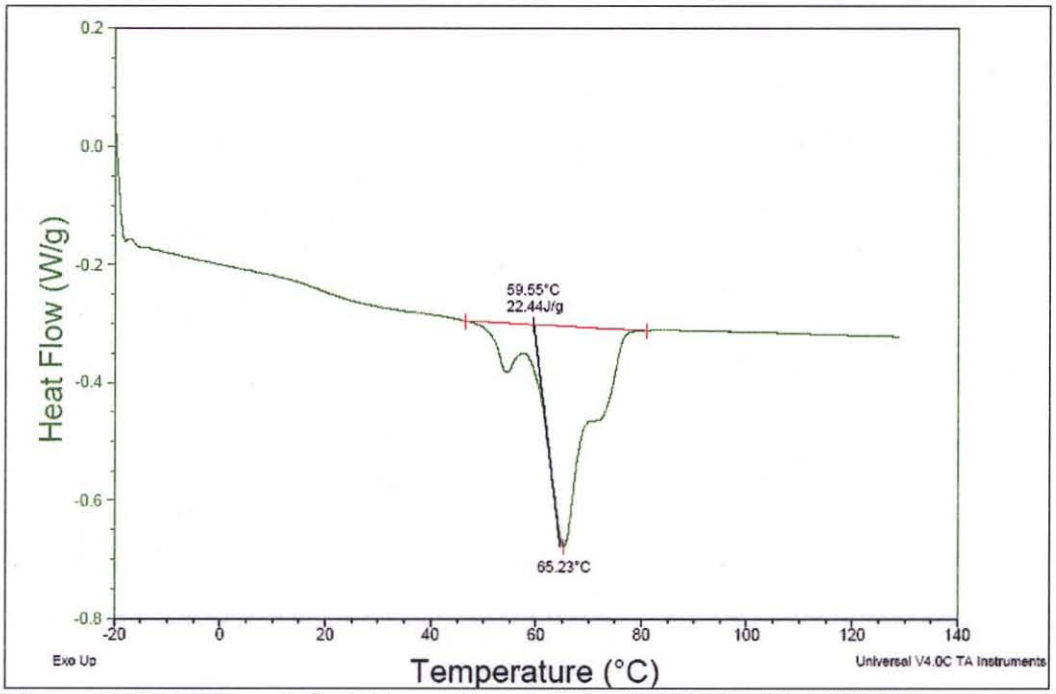

Figure C.12 DCS result for 54 hours incuated Poly(DT 8, 8) with 10% PNA.

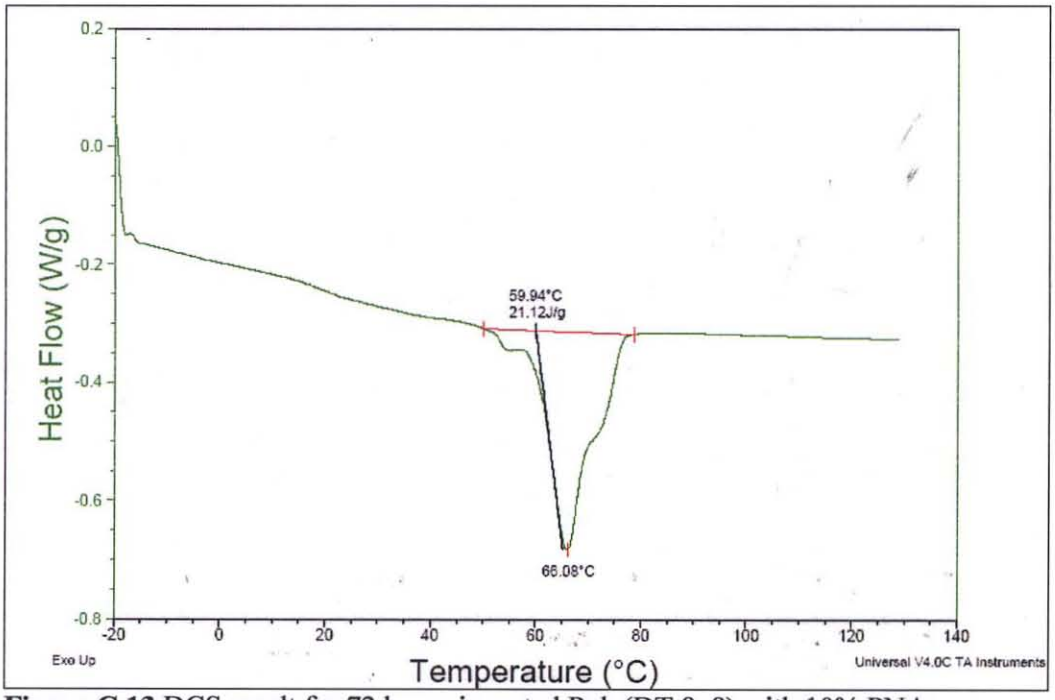

Figure C.13 DCS result for 72 hours incuated Poly(DT 8, 8) with 10% PNA.

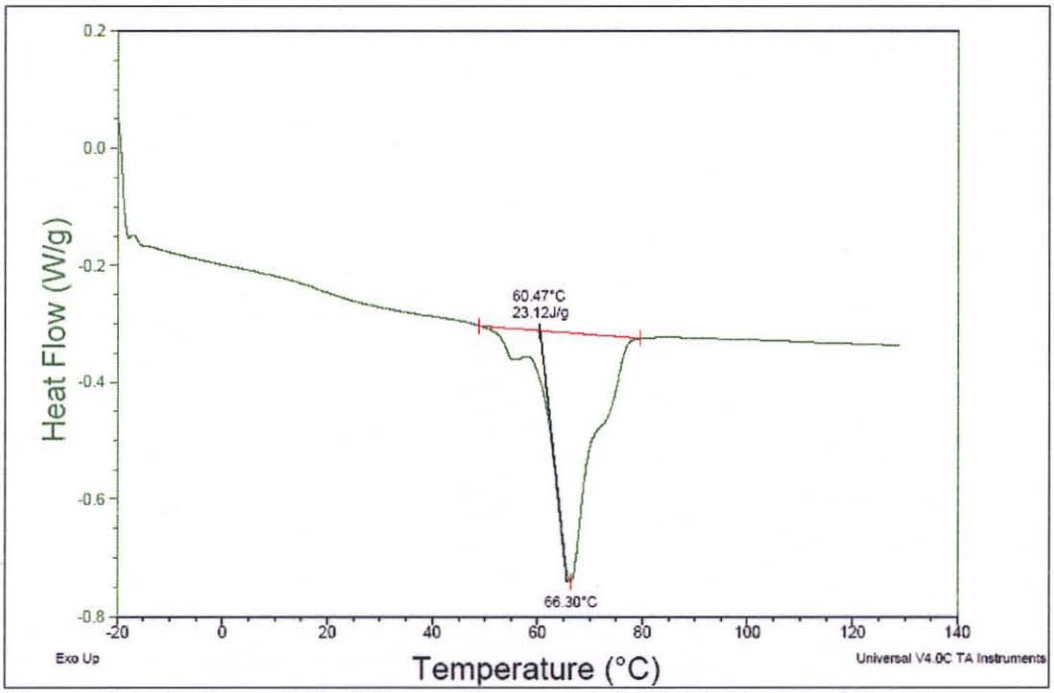

Figure C.14 DCS result for 120 hours incuated Poly(DT 8, 8) with 10% PNA.

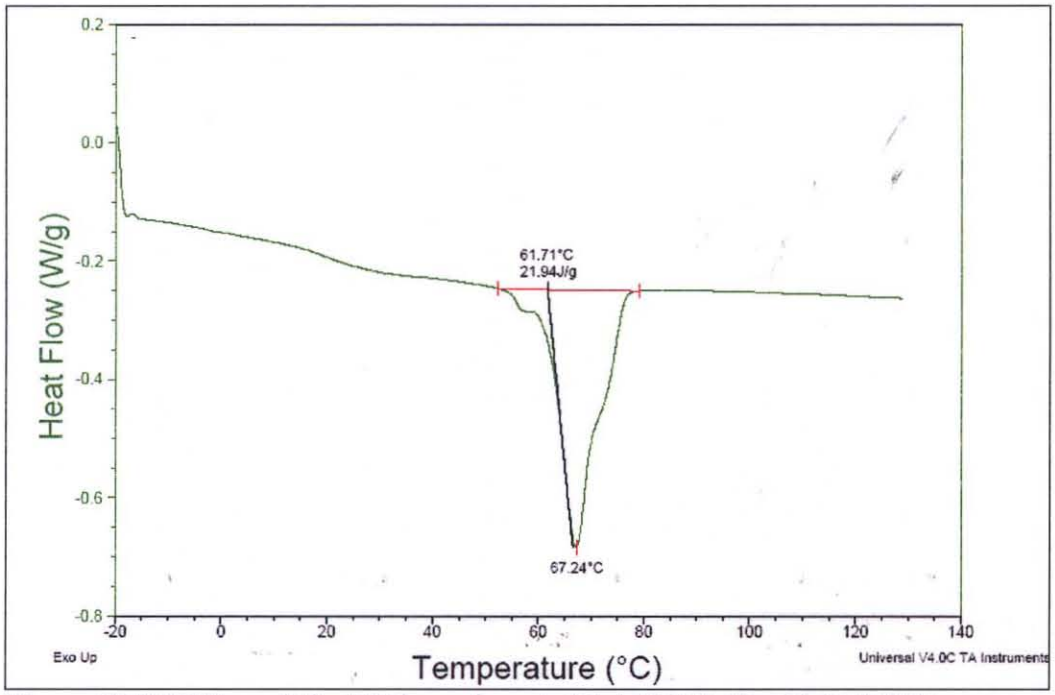

Figure C.15 DCS result for 216 hours incuated Poly(DT 8, 8) with 10% PNA.

APPENDIX D

RAW DATA OF DSC RESULTS OF POLY(DT 8, 8) WITH 0% DRUG LOADING UNDER VACUUM CONDITIONS

DSC results of 0% p-nitroaniline loaded Poly(DT 8, 8) under vacuum conditions and measured enthalpy of phase change.

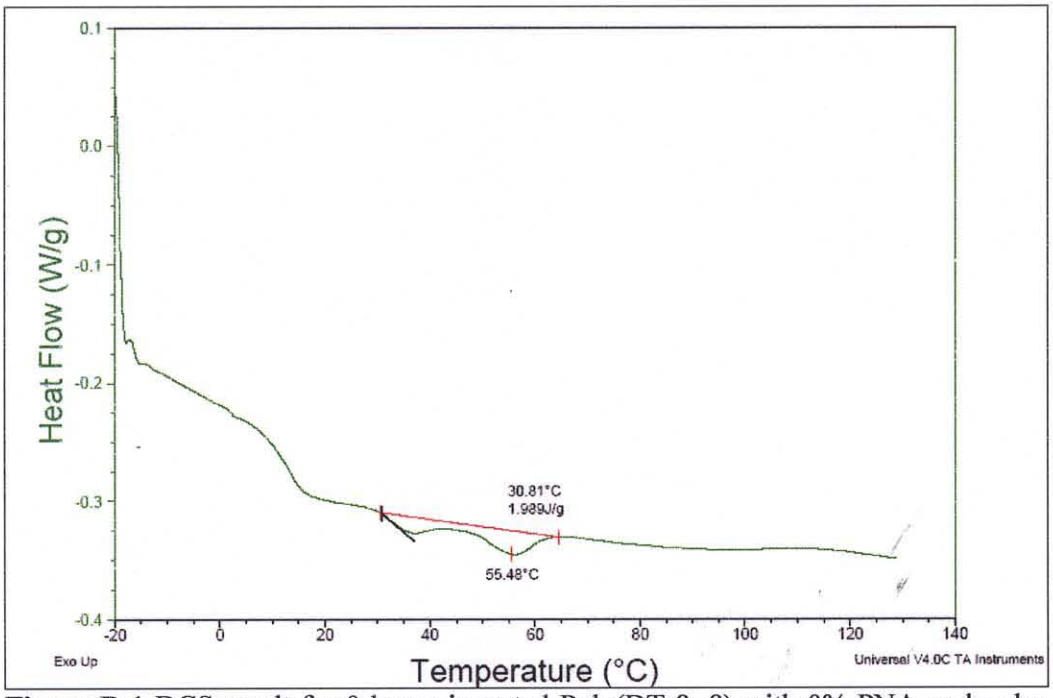

Figure D.1 DCS result for 0 hours incuated Poly(DT 8, 8) with 0% PNA under dry conditions.

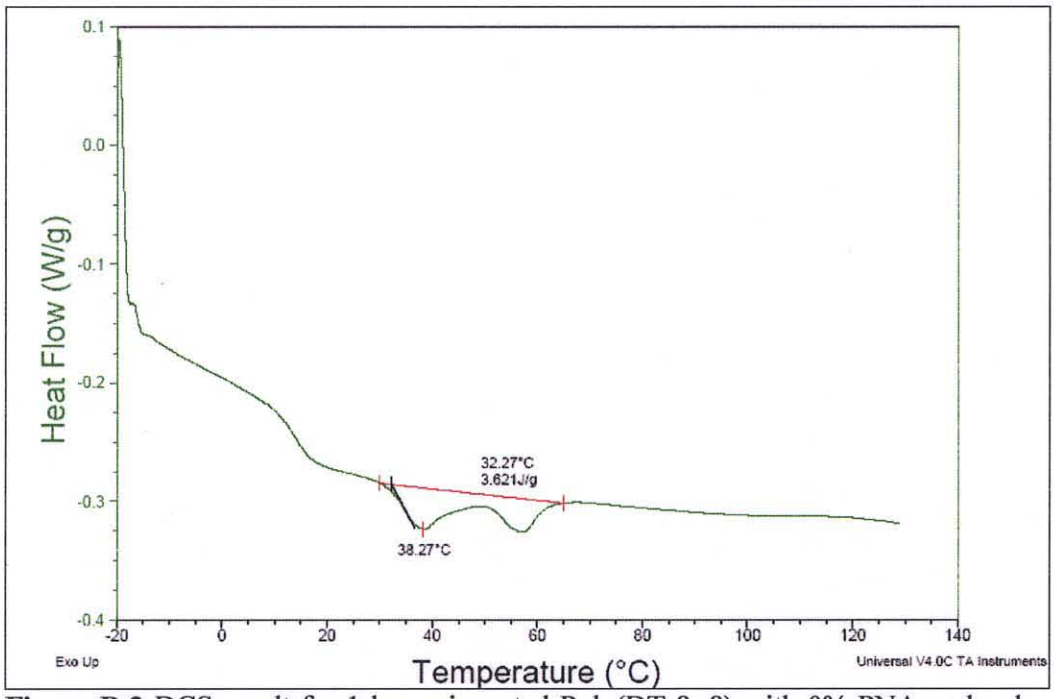

Figure D.2 DCS result for 1 hours incuated Poly(DT 8, 8) with 0% PNA under dry conditions.

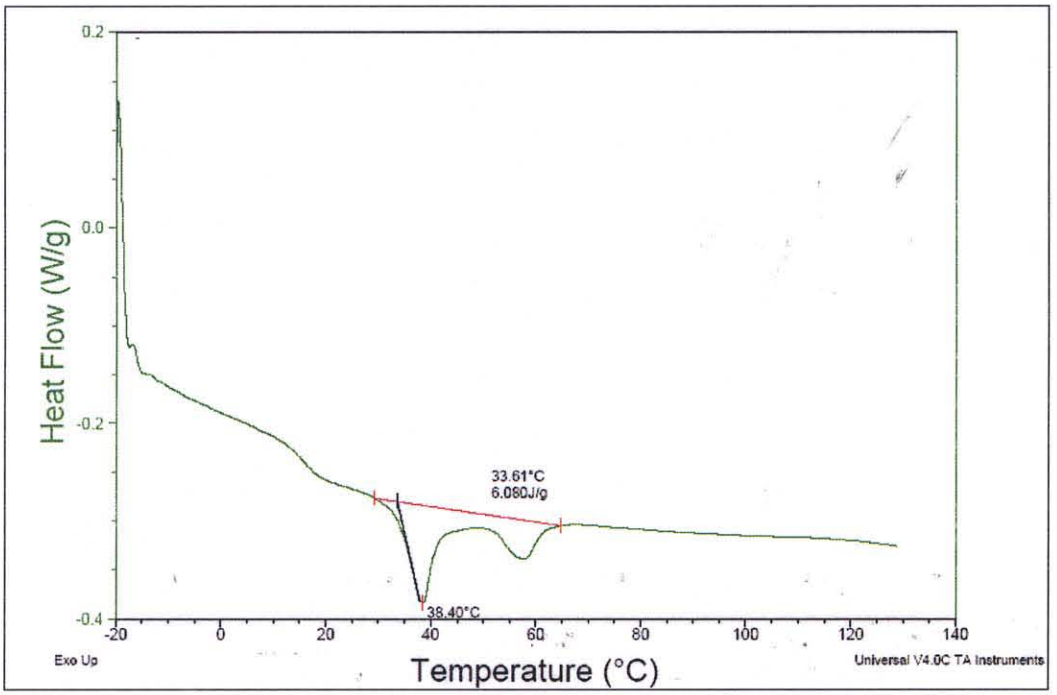

Figure D.3 DCS result for 2 hours incuated Poly(DT 8, 8) with 0% PNA under dry conditions.

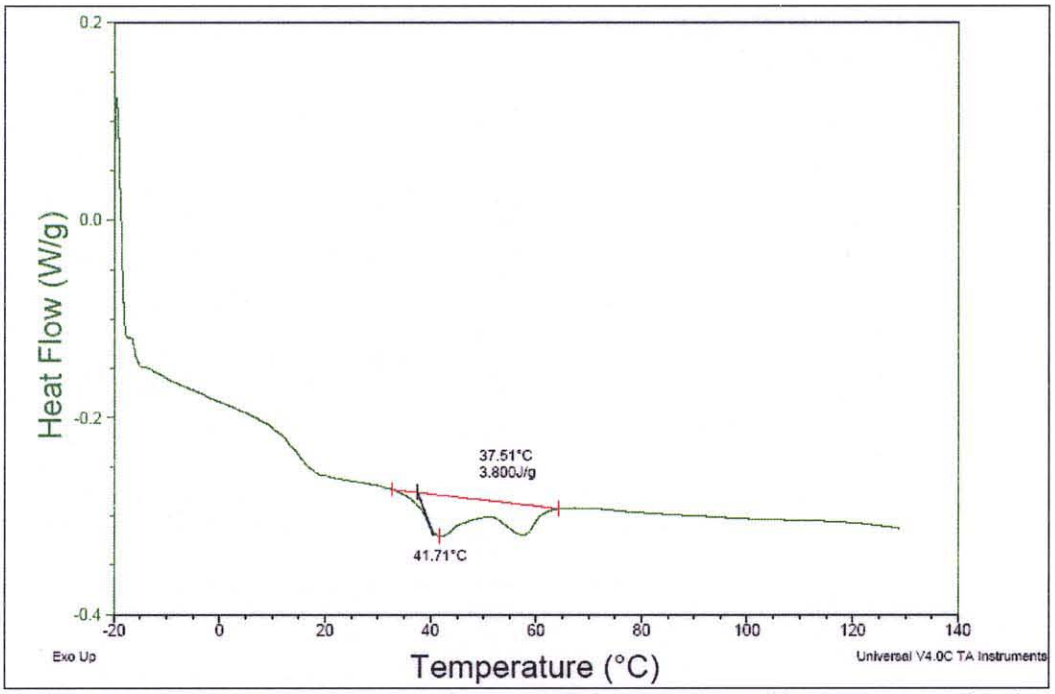

Figure D.4 DCS result for 4 hours incuated Poly(DT 8, 8) with 0% PNA under dry conditions.

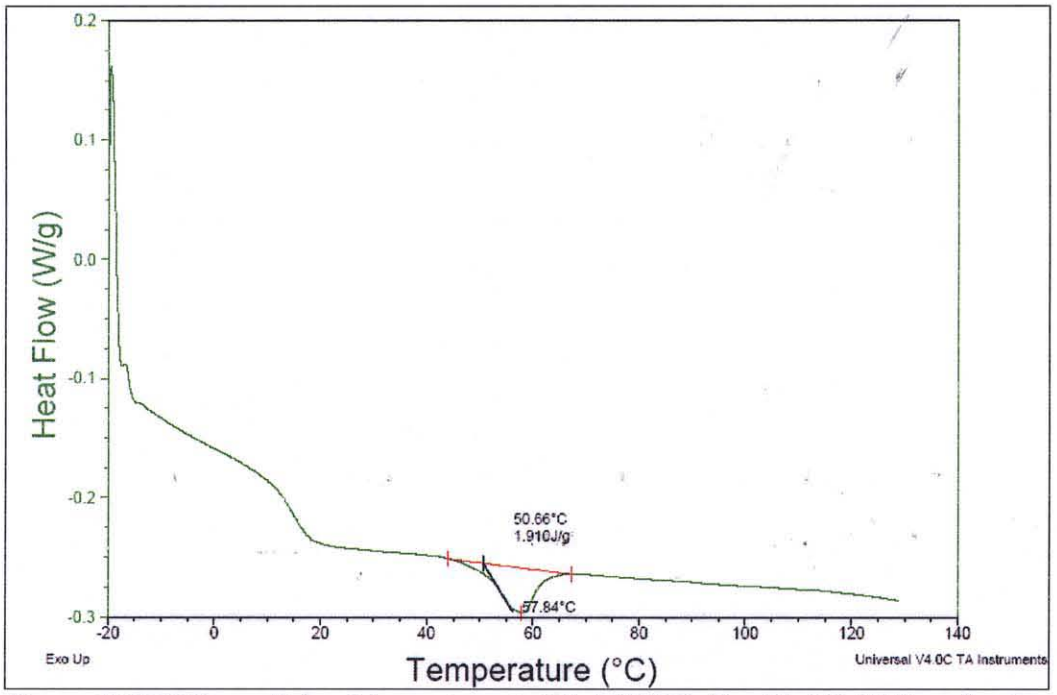

Figure D.5 DCS result for 6 hours incuated Poly(DT 8, 8) with 0% PNA under dry conditions.

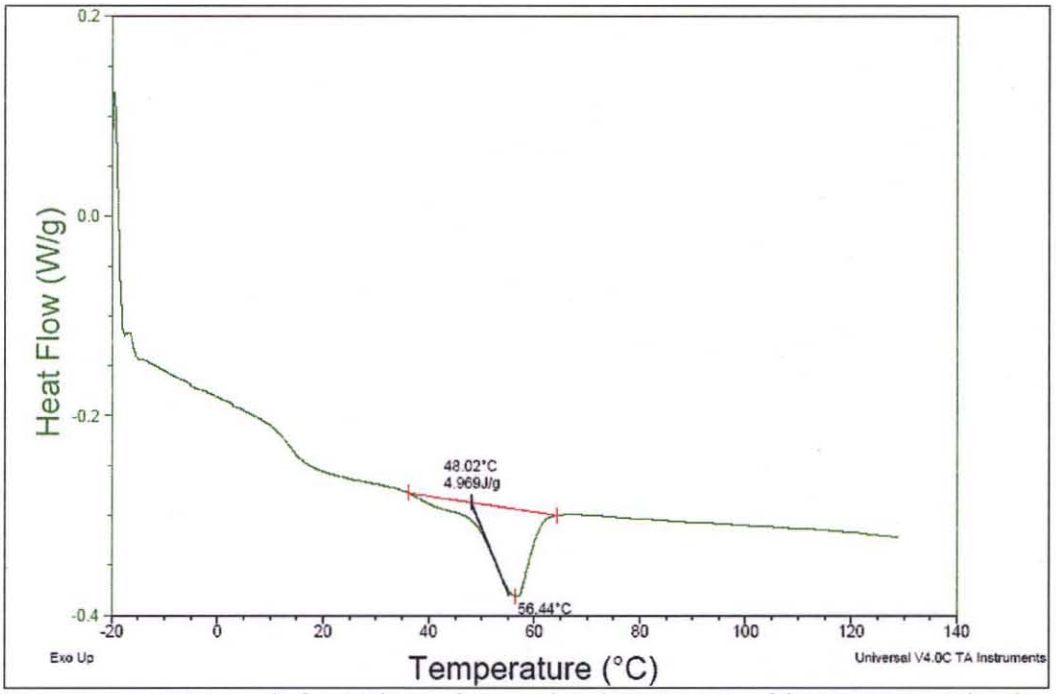

Figure D.6 DCS result for 19 hours incuated Poly(DT 8, 8) with 0% PNA under dry conditions.

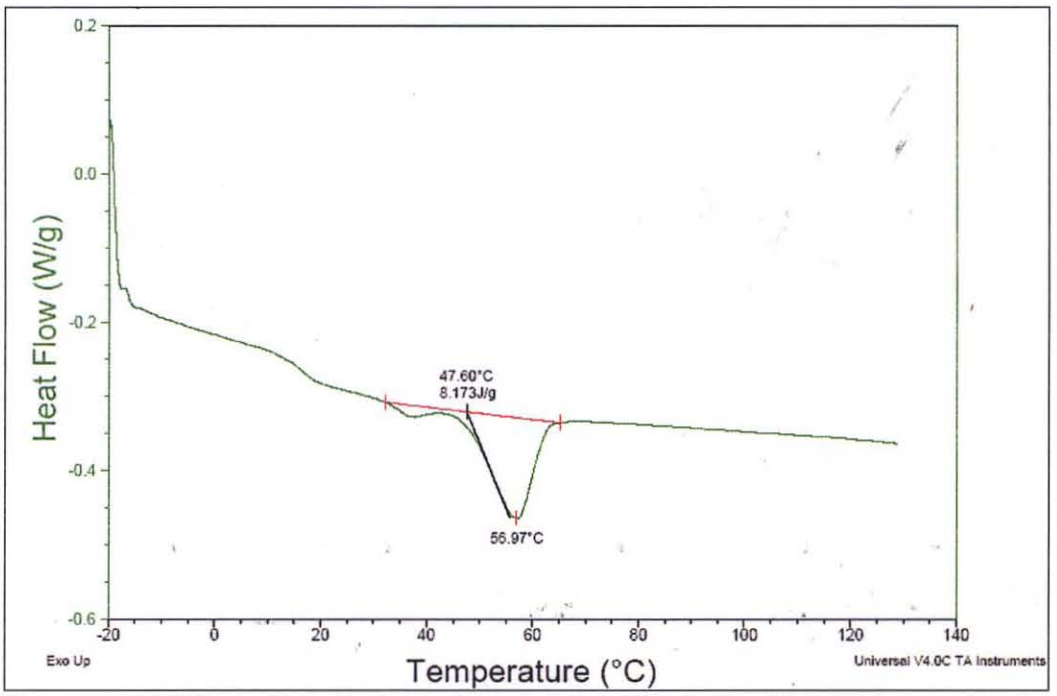

Figure D.7 DCS result for 24 hours incuated Poly(DT 8, 8) with 0% PNA under dry conditions.

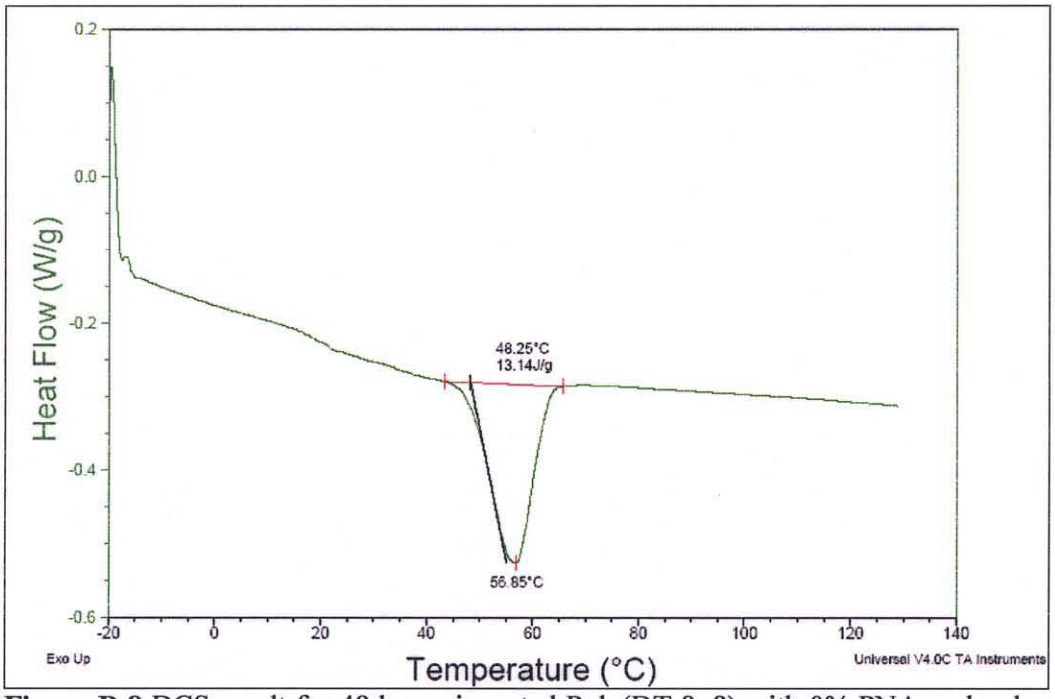

Figure D.8 DCS result for 48 hours incuated Poly(DT 8, 8) with 0% PNA under dry conditions.

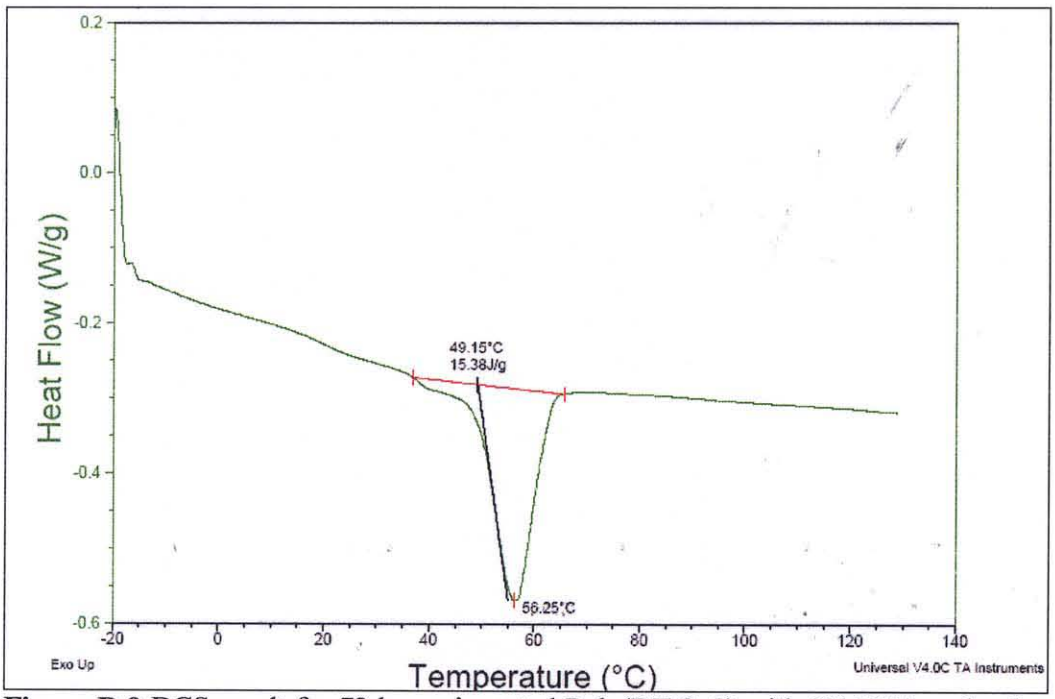

Figure D.9 DCS result for 72 hours incuated Poly(DT 8, 8) with 0% PNA under dry conditions.

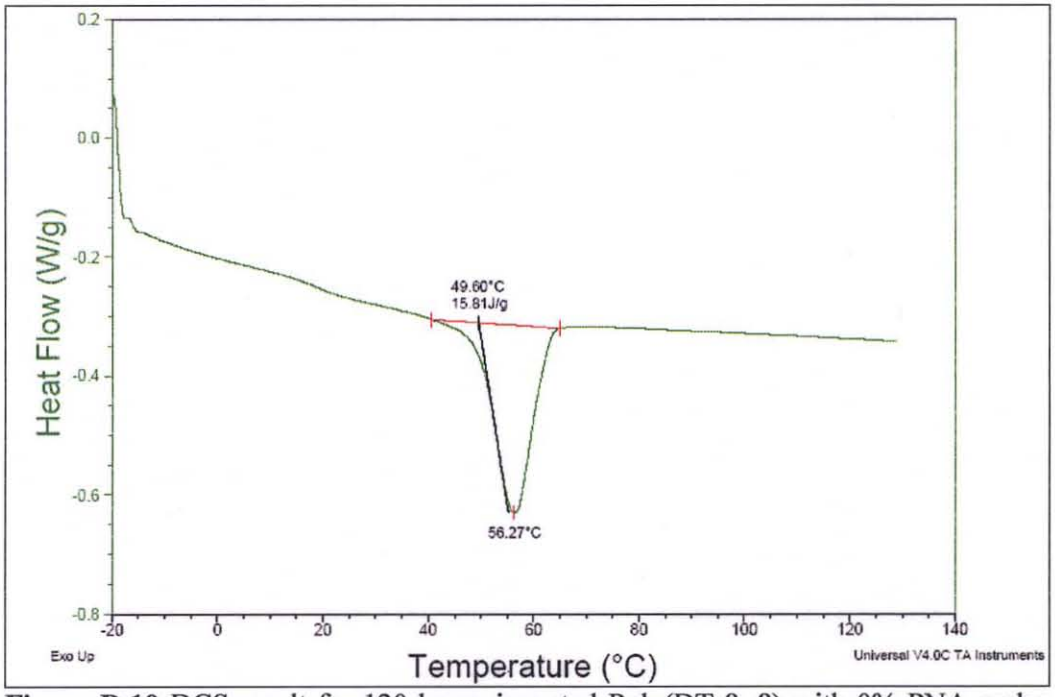

Figure D.10 DCS result for 120 hours incuated Poly(DT 8, 8) with 0% PNA under dry conditions.

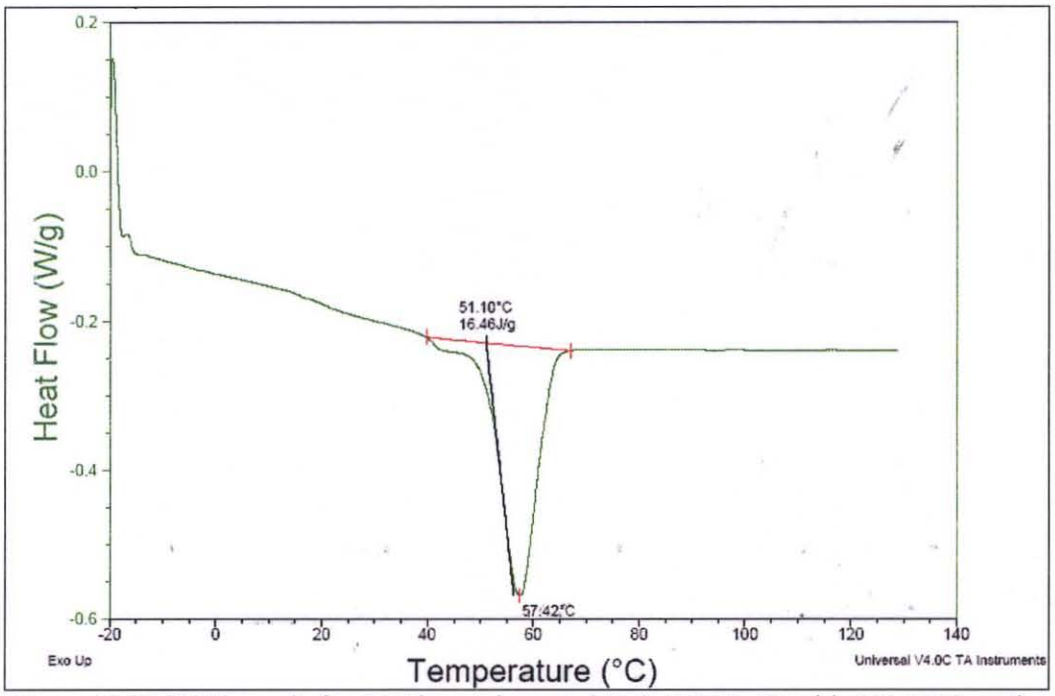

Figure D.11 DCS result for 168 hours incuated Poly(DT 8, 8) with 0% PNA under dry conditions.

APPENDIX E

RAW DATA OF DSC RESULTS OF POLY(DT 12, 10) WITH 0% DRUG LOADING

DSC results of 0% p-nitroaniline loaded Poly(DT 12, 10) and measured enthalpy of phase change.

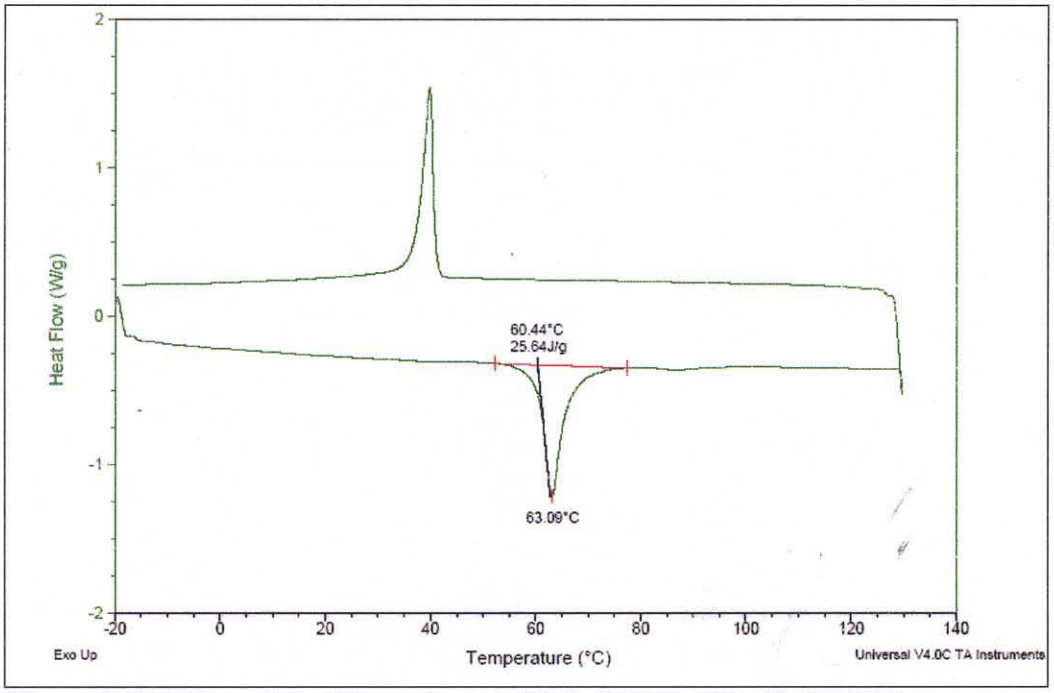

Figure E.1 DCS result for 0 hours incuated Poly(DT 12, 10) with 0% PNA.

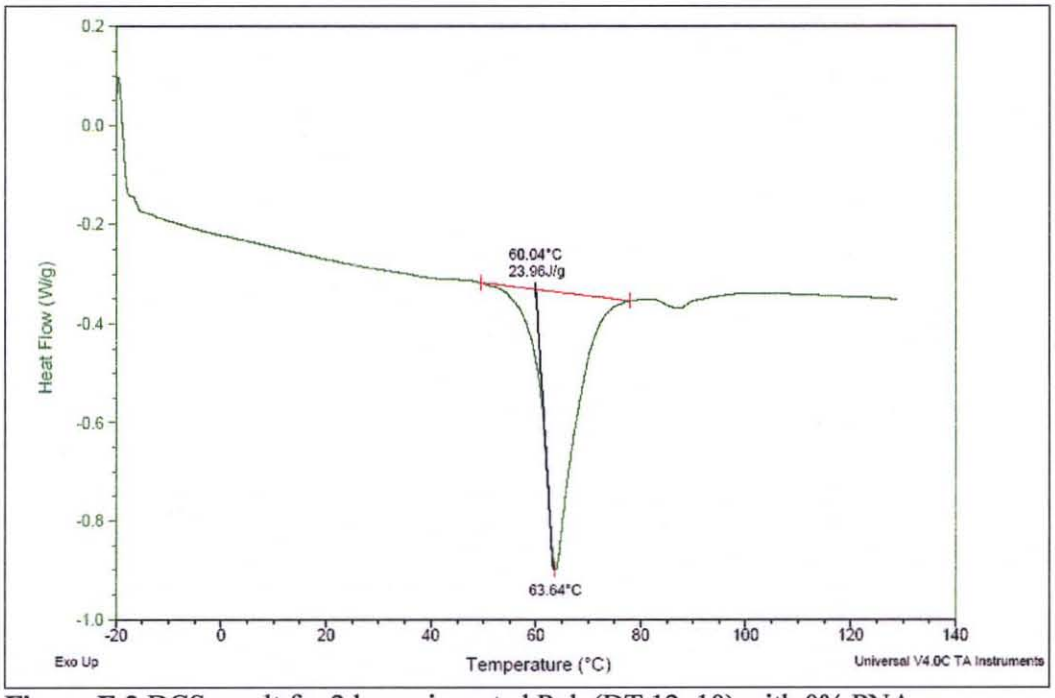

Figure E.2 DCS result for 2 hours incuated Poly(DT 12, 10) with 0% PNA.

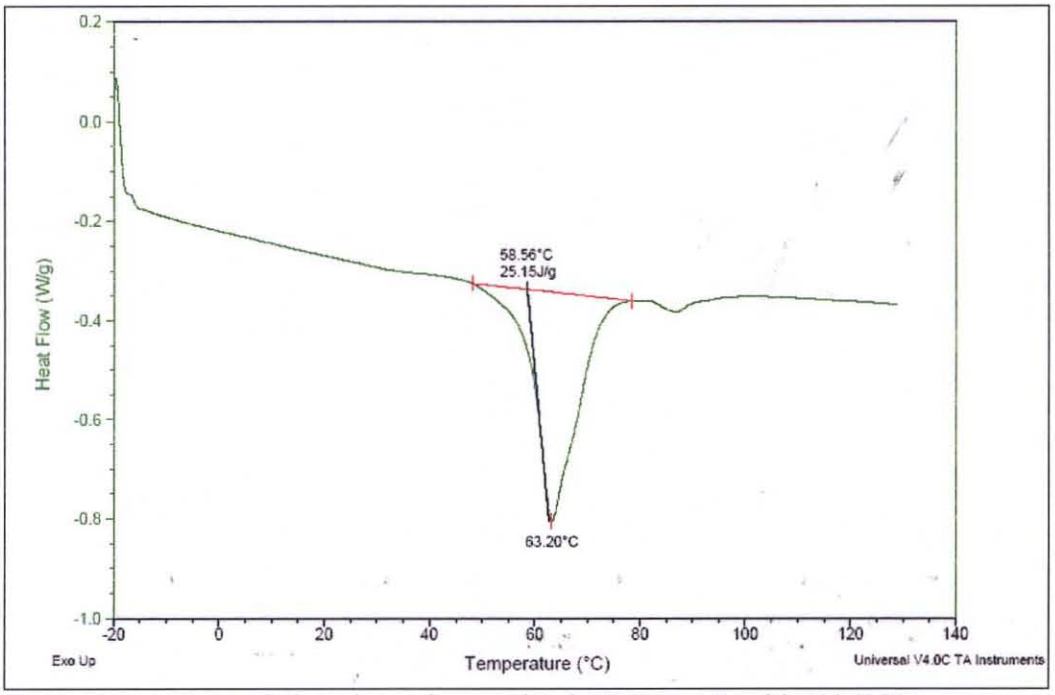

Figure E.3 DCS result for 3 hours incuated Poly(DT 12, 10) with 0% PNA.

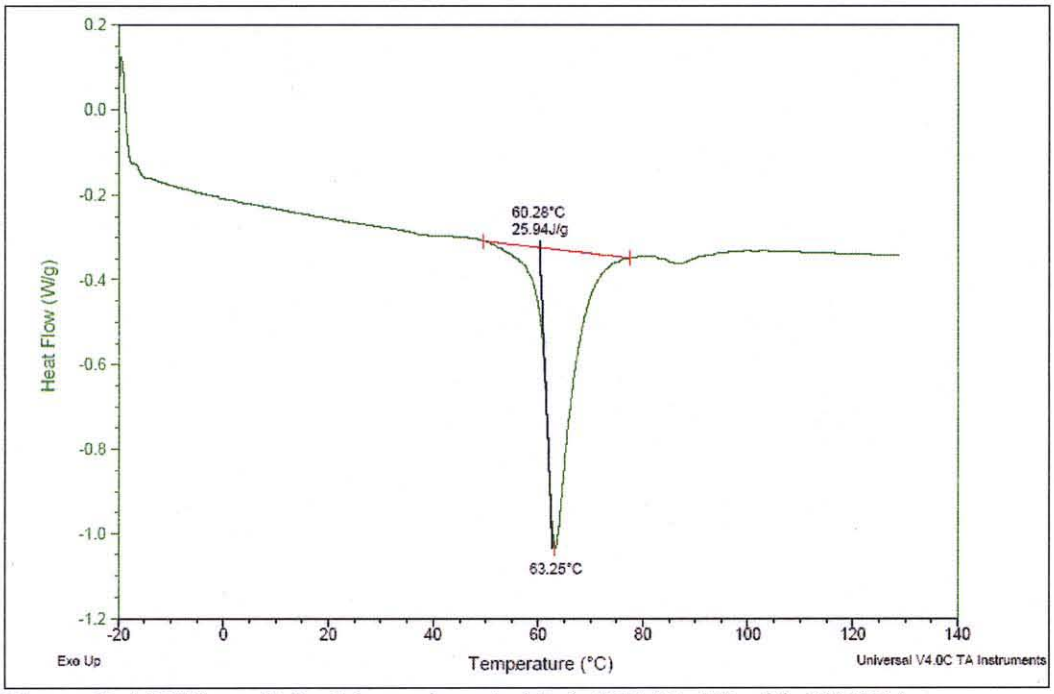

Figure E.4 DCS result for 7 hours incuated Poly(DT 12, 10) with 0% PNA.

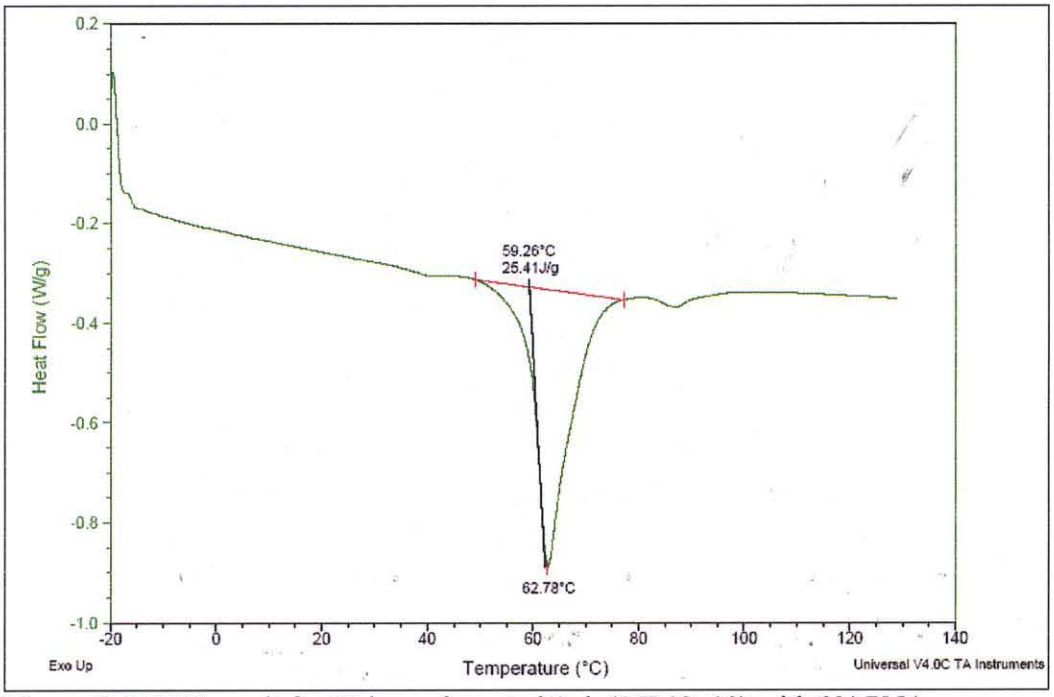

Figure E.5 DCS result for 20 hours incuated Poly(DT 12, 10) with 0% PNA.

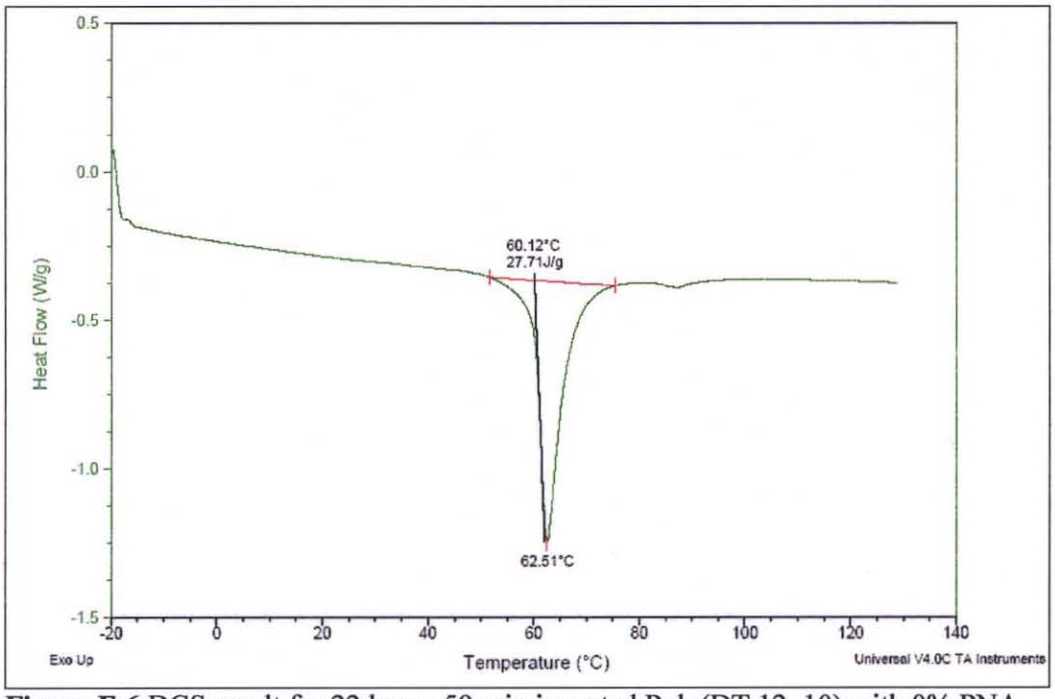

Figure E.6 DCS result for 22 hours 59 min incuated Poly(DT 12, 10) with 0% PNA.

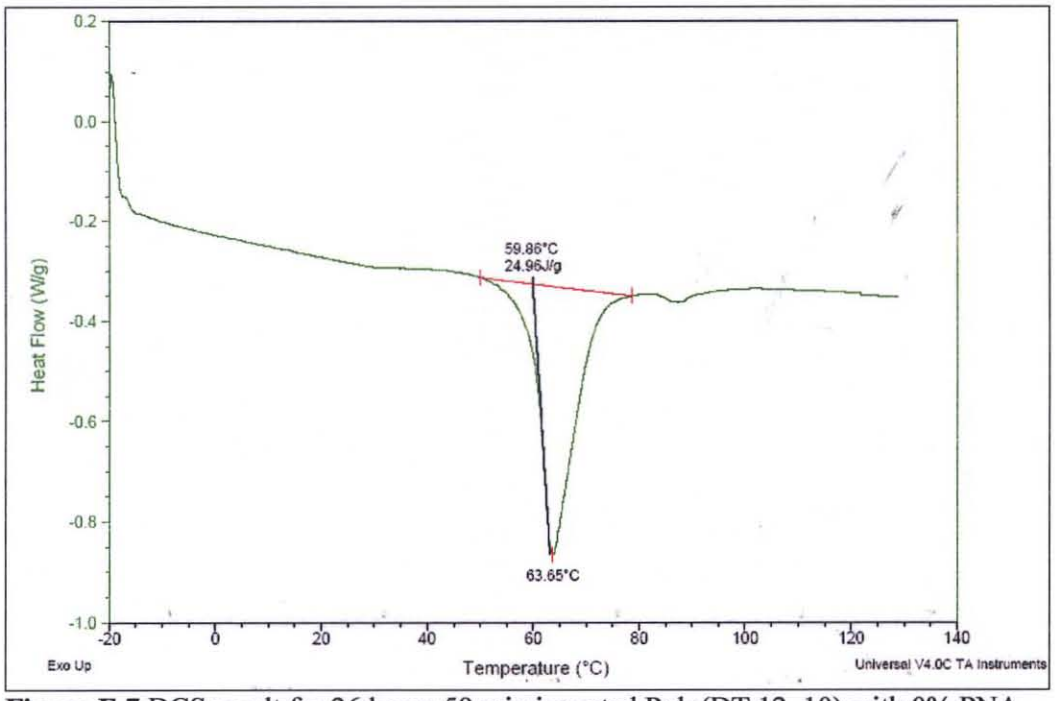

Figure E.7 DCS result for 26 hours 59 min incuated Poly(DT 12, 10) with 0% PNA.

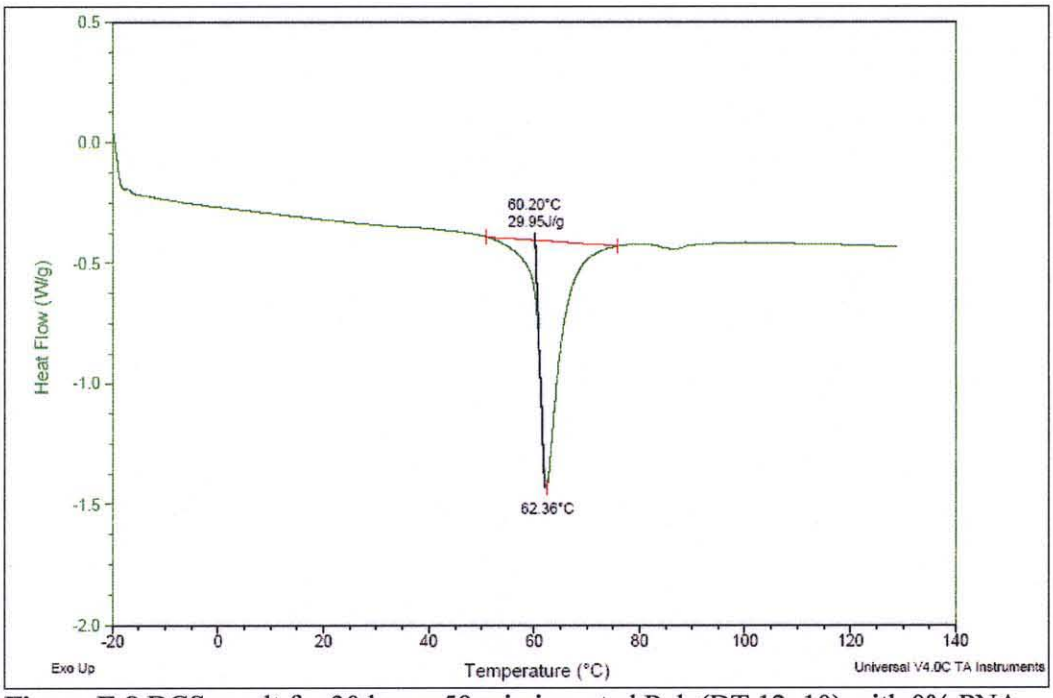

Figure E.8 DCS result for 30 hours 59 min incuated Poly(DT 12, 10) with 0% PNA.

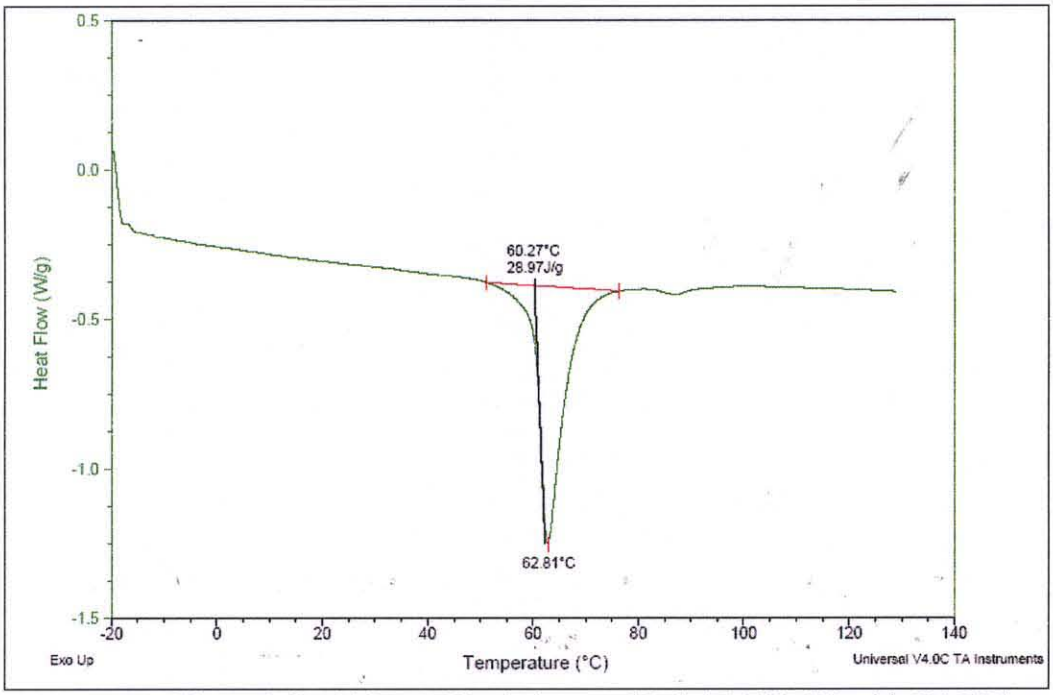

Figure E.9 DCS result for 44 hours 59 min incuated Poly(DT 12, 10) with 0% PNA.

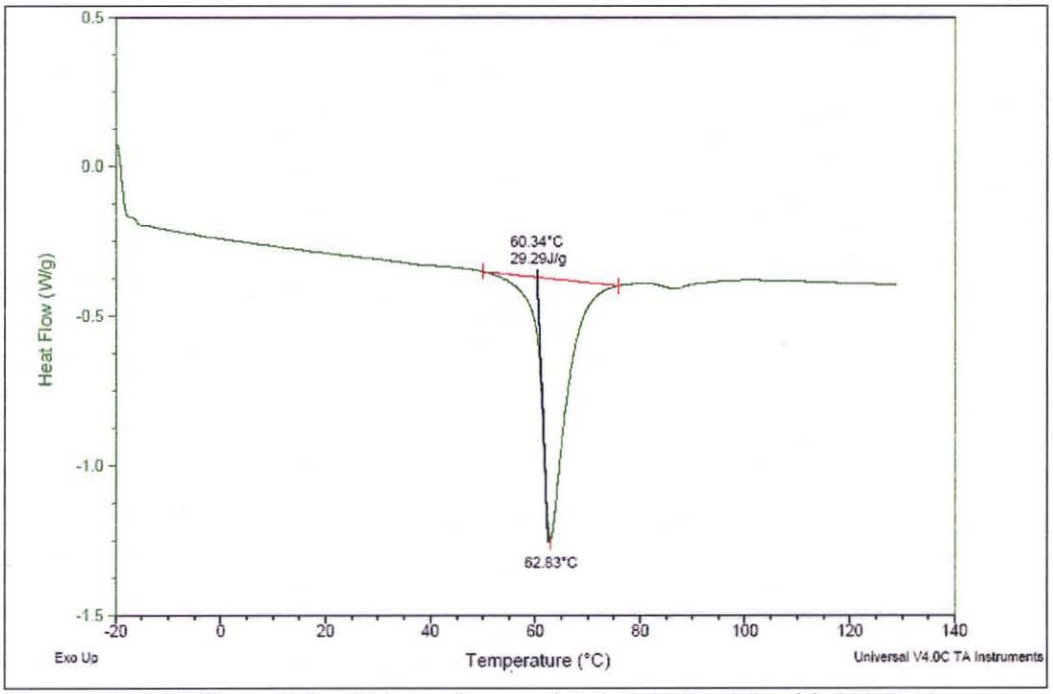

Figure E.10 DCS result for 50 hours incuated Poly(DT 12, 10) with 0% PNA.

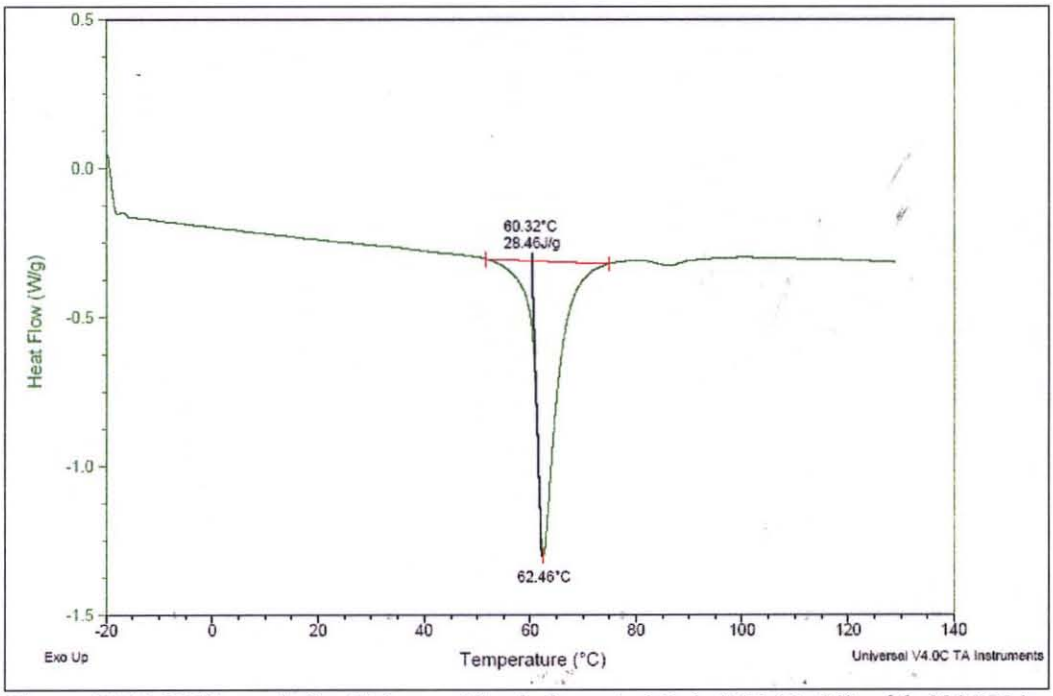

Figure E.11 DCS result for 55 hours 44 min incuated Poly(DT 12, 10) with 0% PNA.

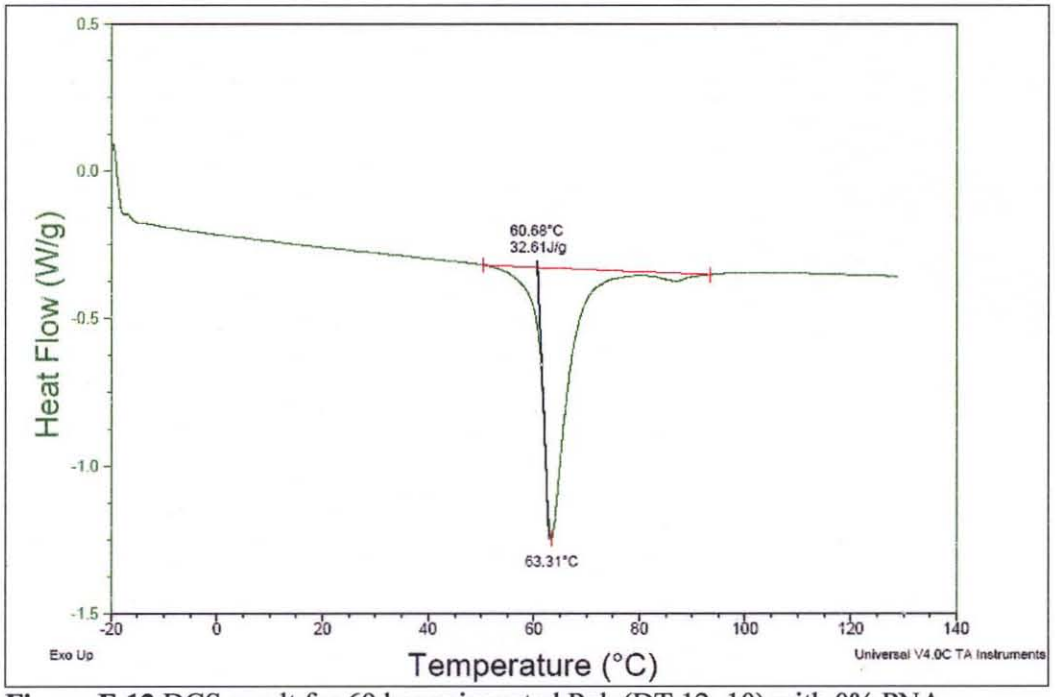

Figure E.12 DCS result for 69 hours incuated Poly(DT 12, 10) with 0% PNA.

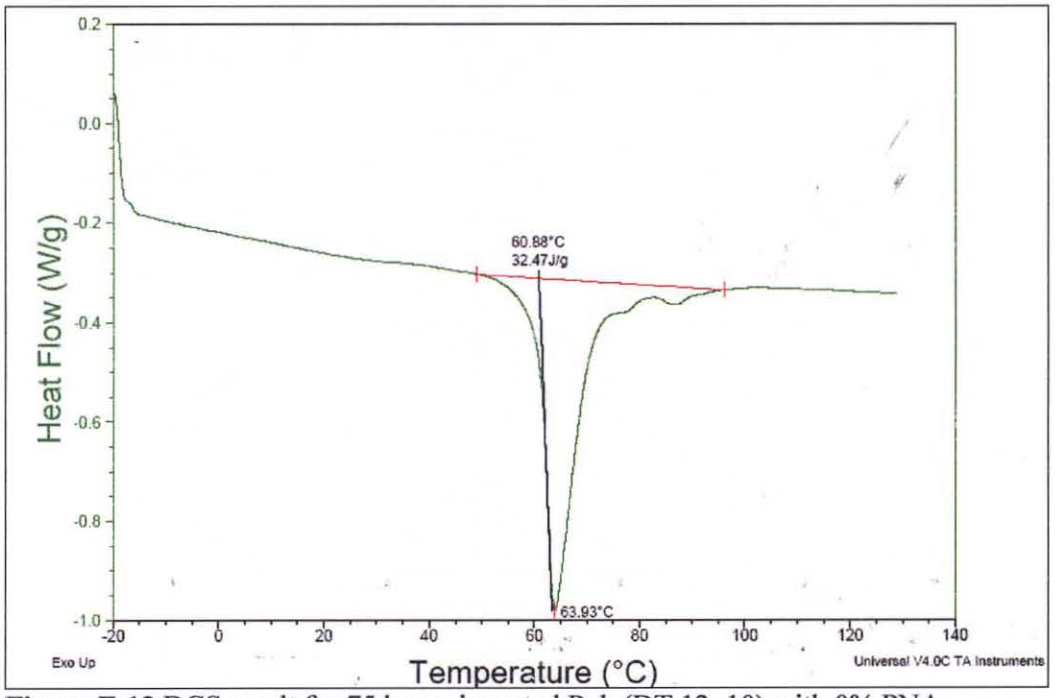

Figure E.13 DCS result for 75 hours incuated Poly(DT 12, 10) with 0% PNA.

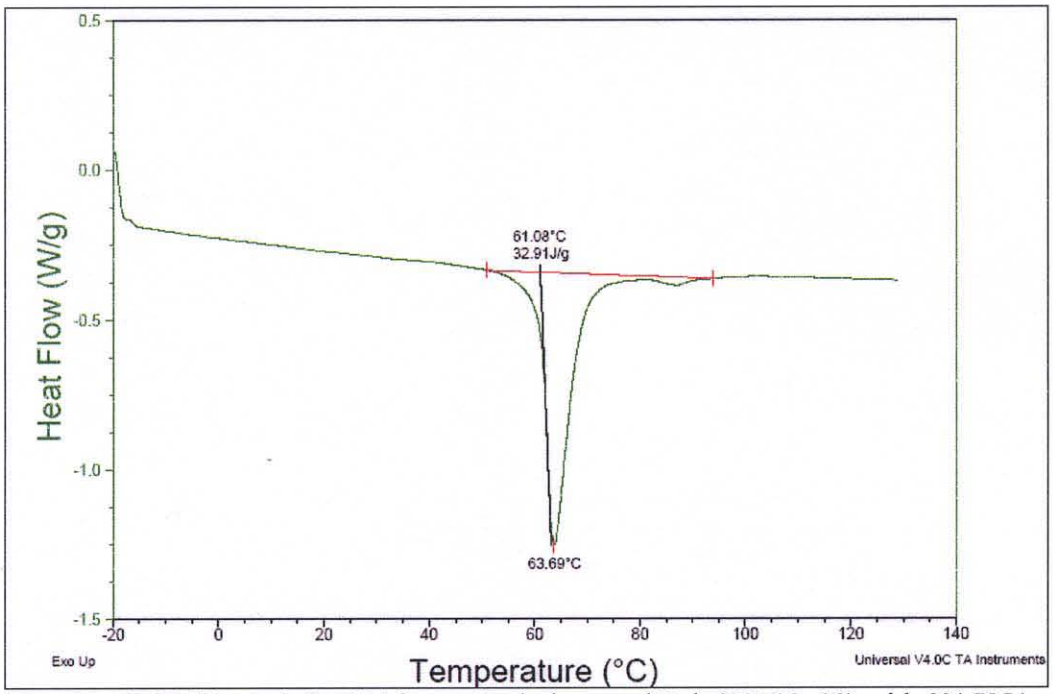

Figure E.14 DCS result for 124 hours 7 min incuated Poly(DT 12, 10) with 0% PNA.

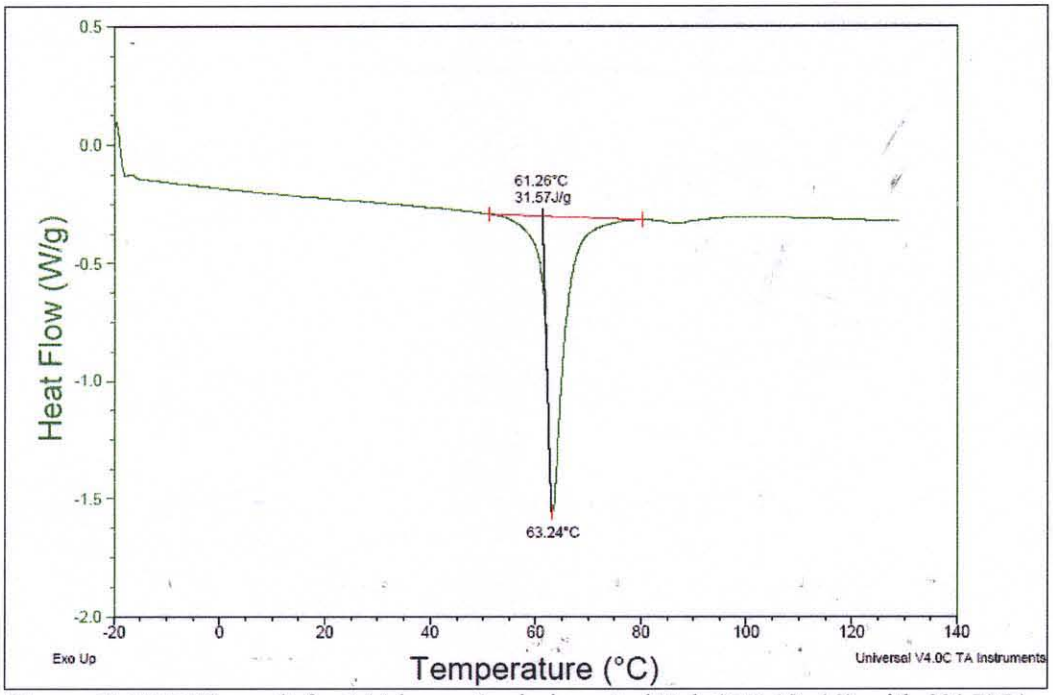

Figure E.15 DCS result for 144 hours 4 min incuated Poly(DT 12, 10) with 0% PNA.

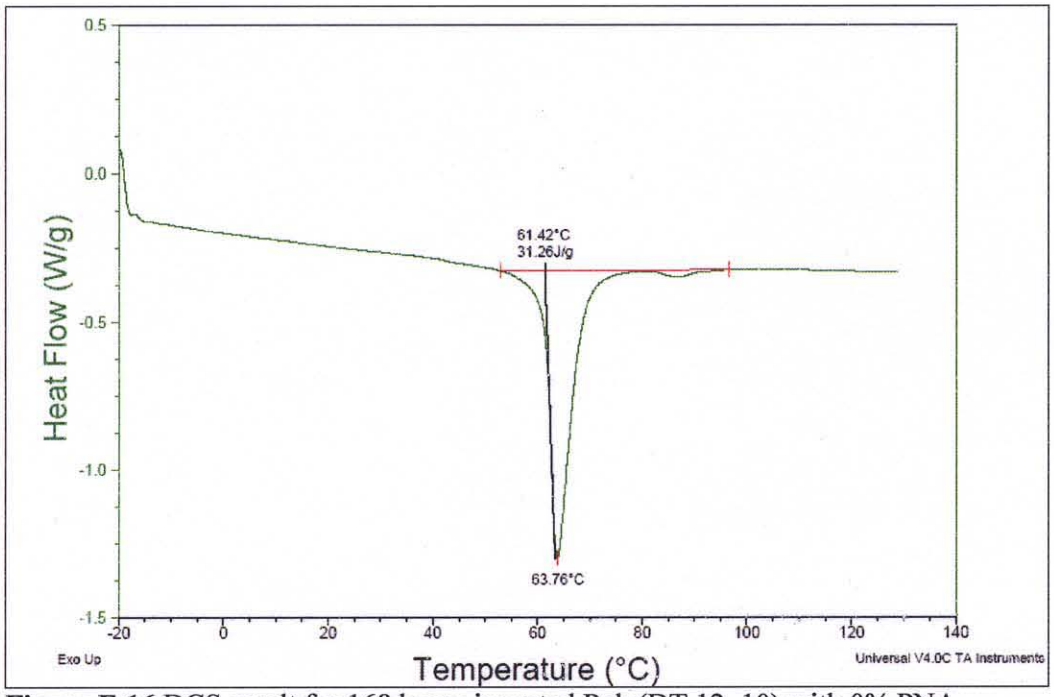

Figure E.16 DCS result for 168 hours incuated Poly(DT 12, 10) with 0% PNA.

APPENDIX F

RAW DATA OF DSC RESULTS OF POLY(DT 12, 10) WITH 5% DRUG LOADING

DSC results of 5% p-nitroaniline loaded Poly(DT 12, 10) and measured enthalpy of phase change.

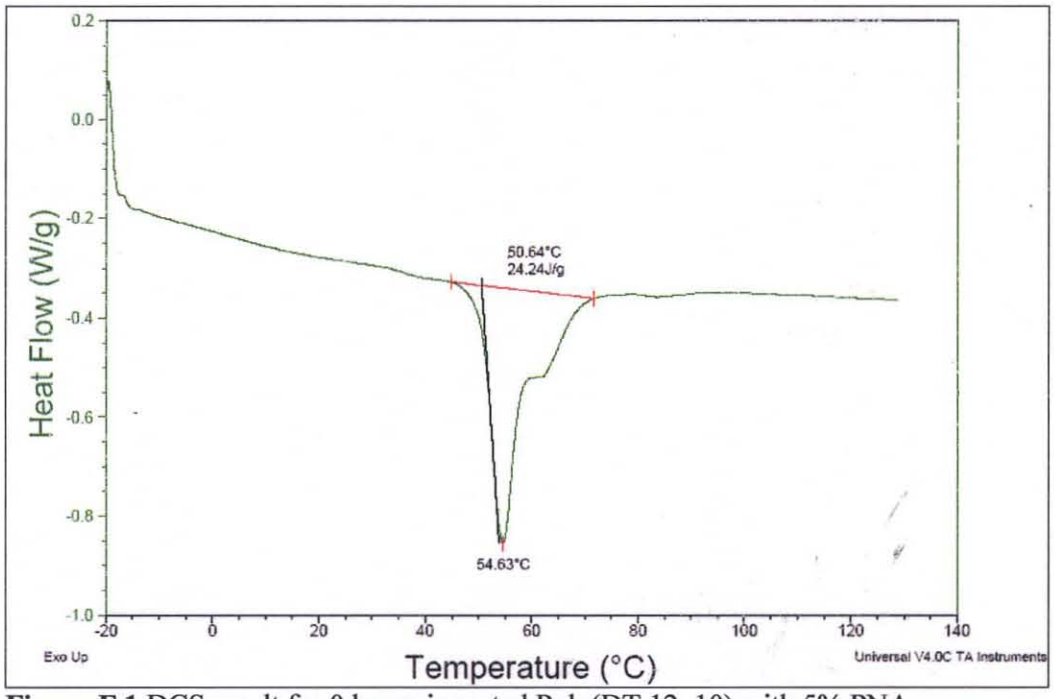

Figure F.1 DCS result for 0 hours incuated Poly(DT 12, 10) with 5% PNA.

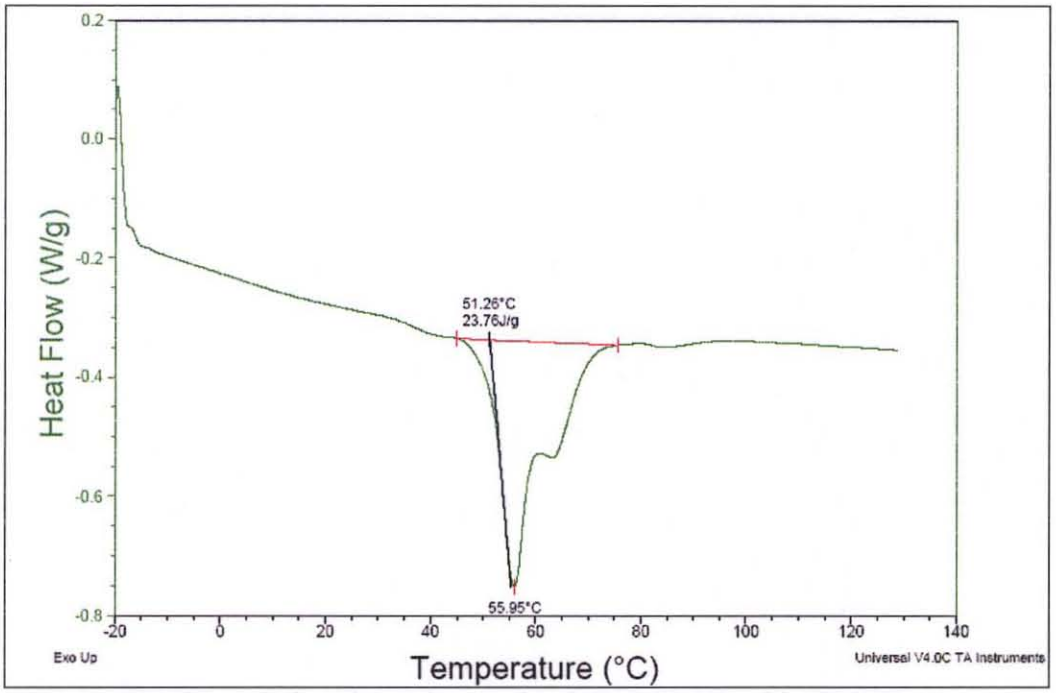

Figure F.2 DCS result for 1 hours incuated Poly(DT 12, 10) with 5% PNA.

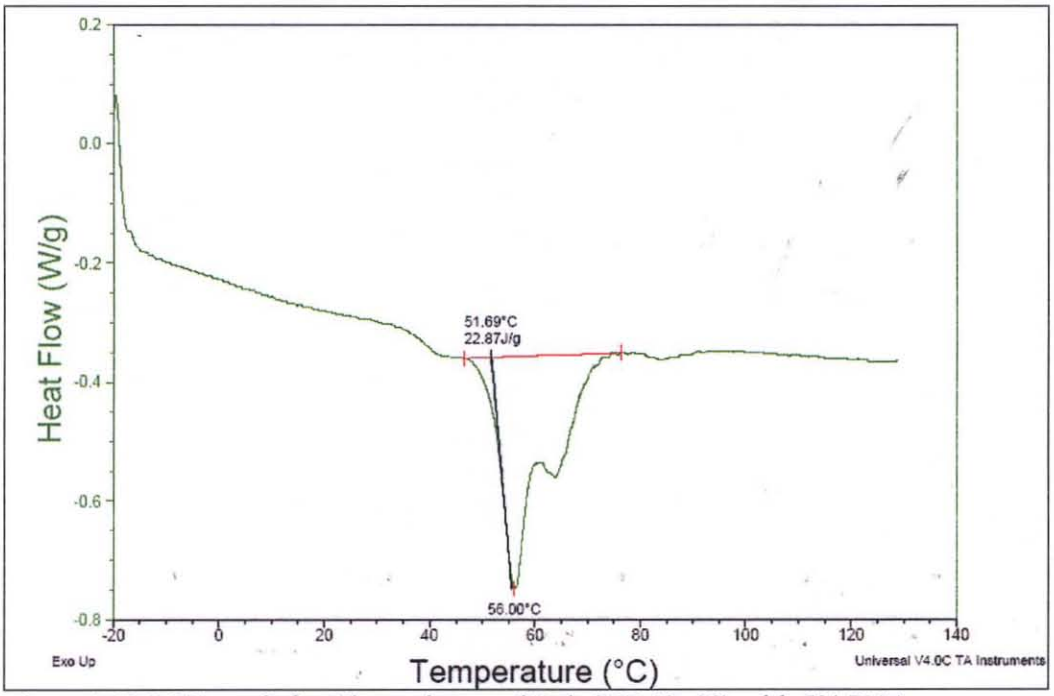

Figure F.3 DCS result for 2 hours incuated Poly(DT 12, 10) with 5% PNA.

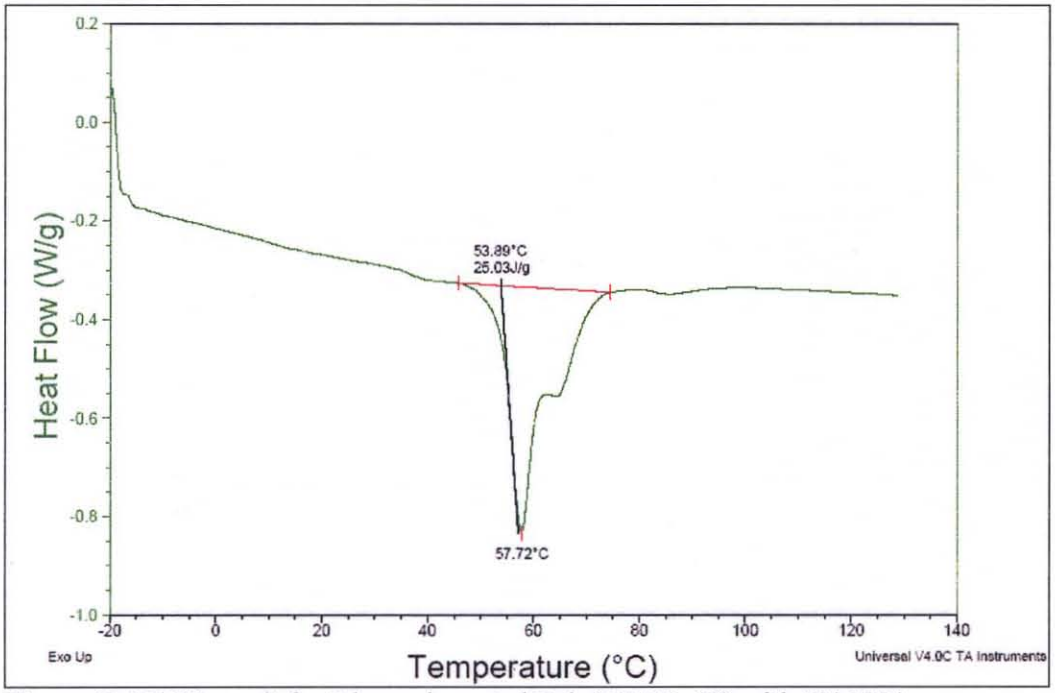

Figure F.4 DCS result for 3 hours incuated Poly(DT 12, 10) with 5% PNA.

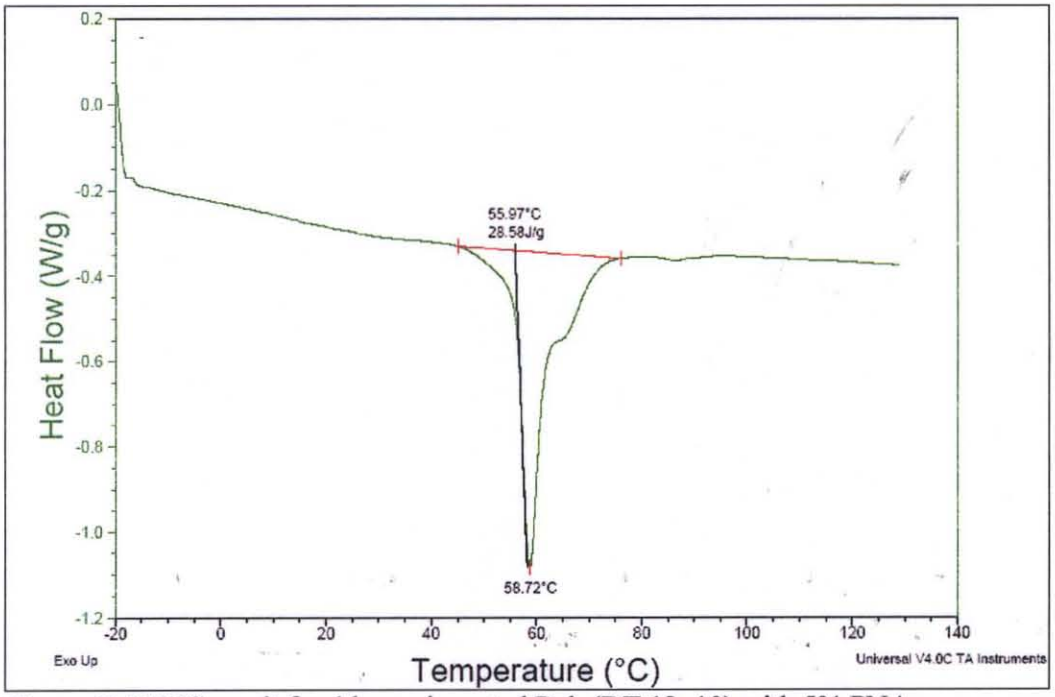

Figure F.5 DCS result for 4 hours incuated Poly(DT 12, 10) with 5% PNA.

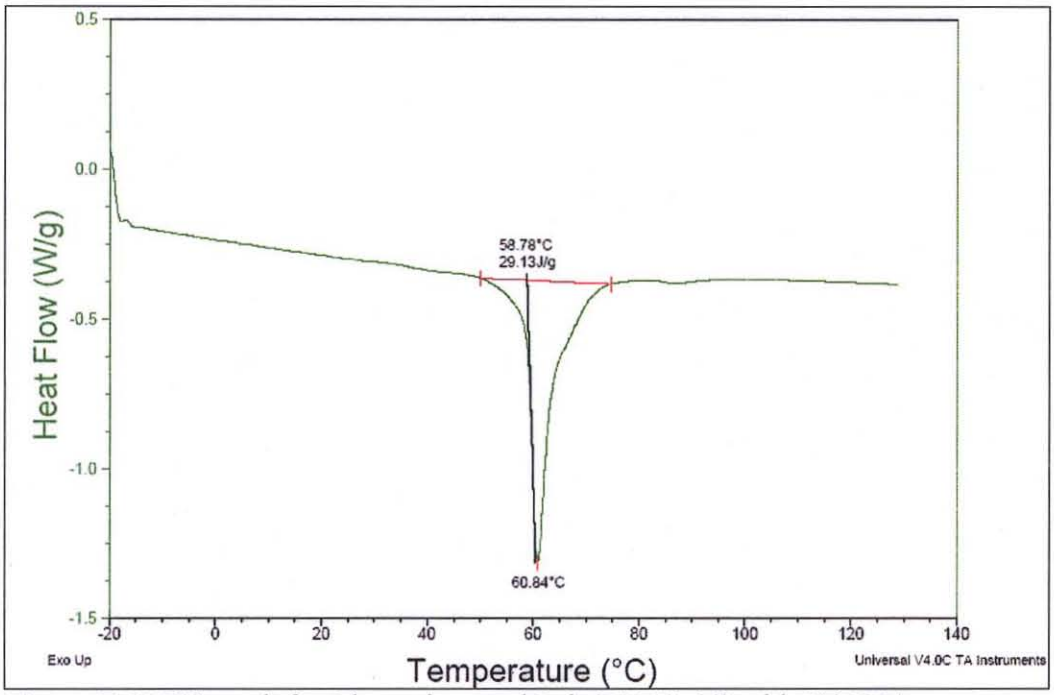

Figure F.6 DCS result for 6 hours incuated Poly(DT 12, 10) with 5% PNA.

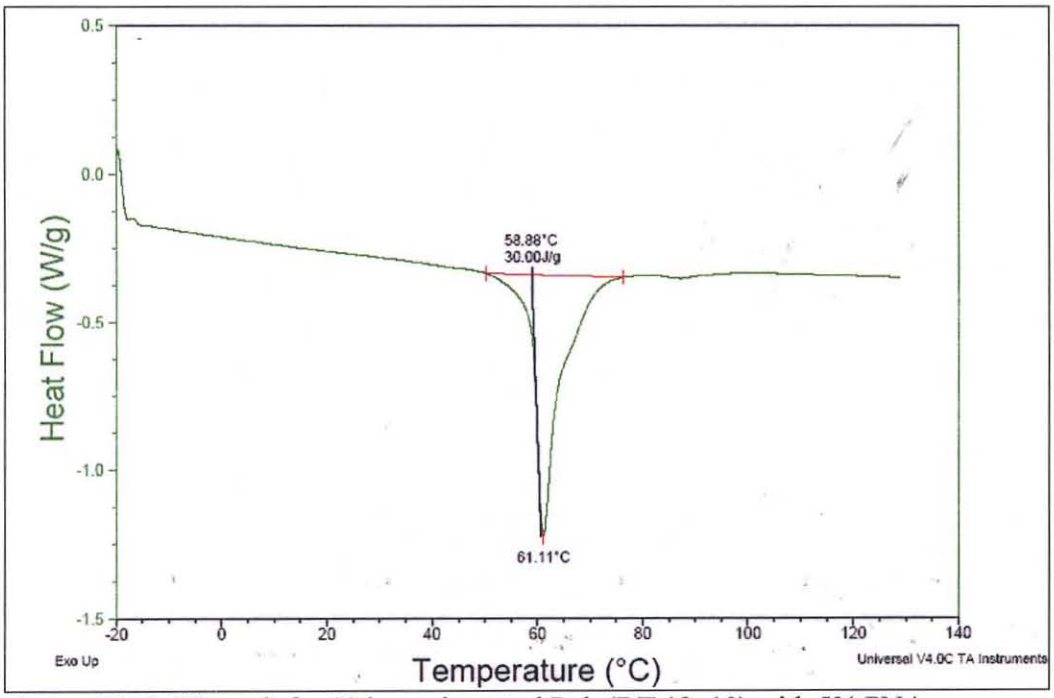

Figure F.7 DCS result for 19 hours incuated Poly(DT 12, 10) with 5% PNA.

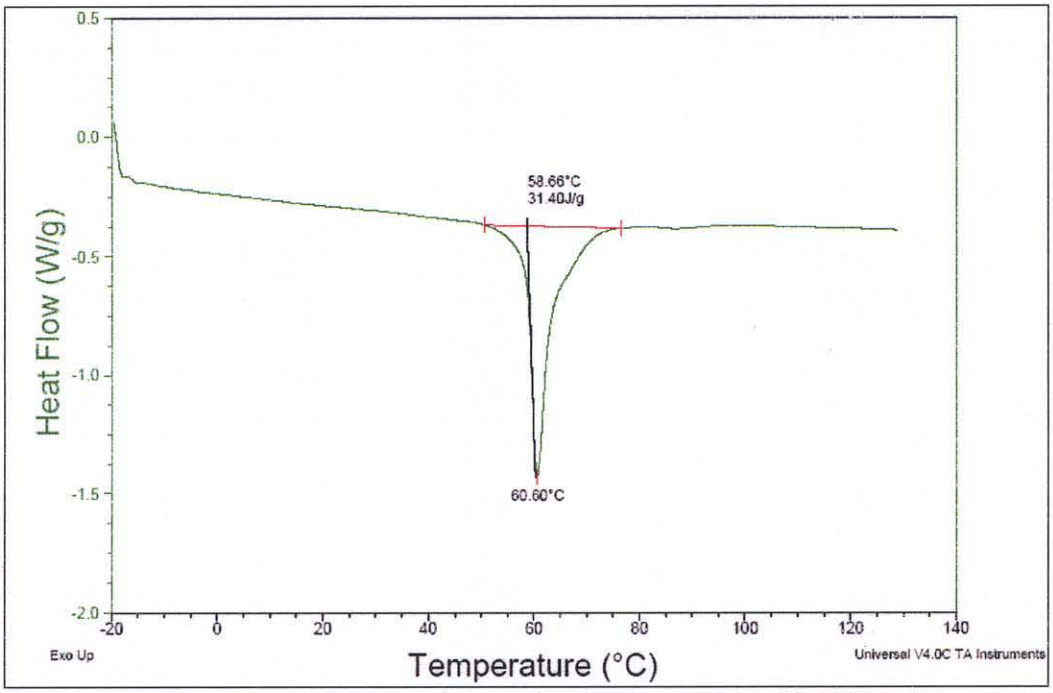

Figure F.8 DCS result for 24 hours incuated Poly(DT 12, 10) with 5% PNA.

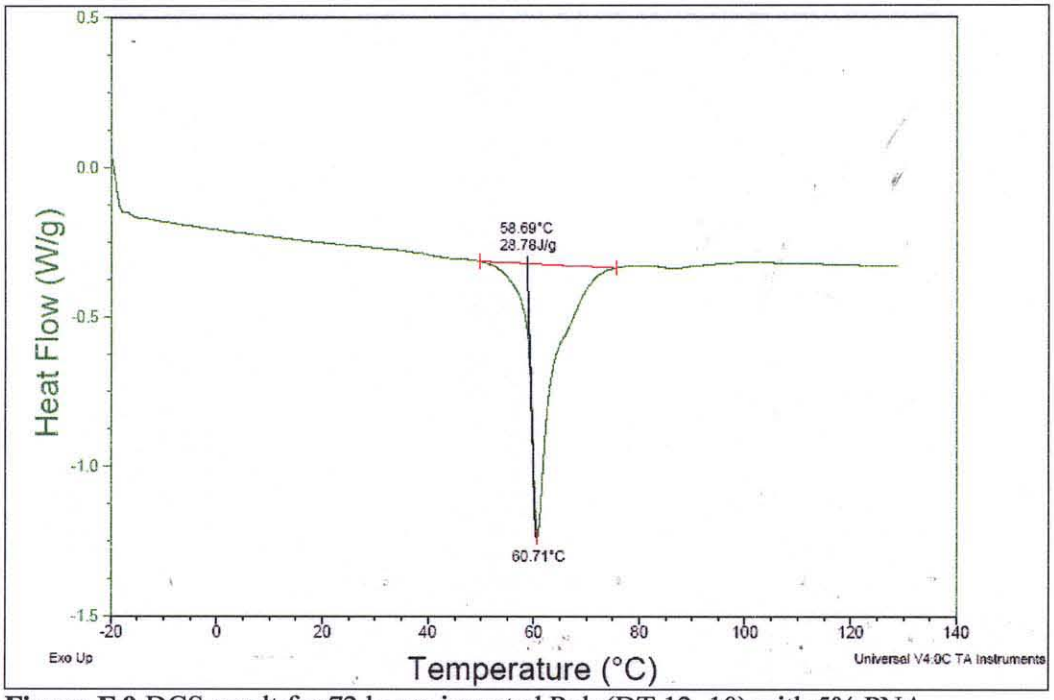

Figure F.9 DCS result for 72 hours incuated Poly(DT 12, 10) with 5% PNA.

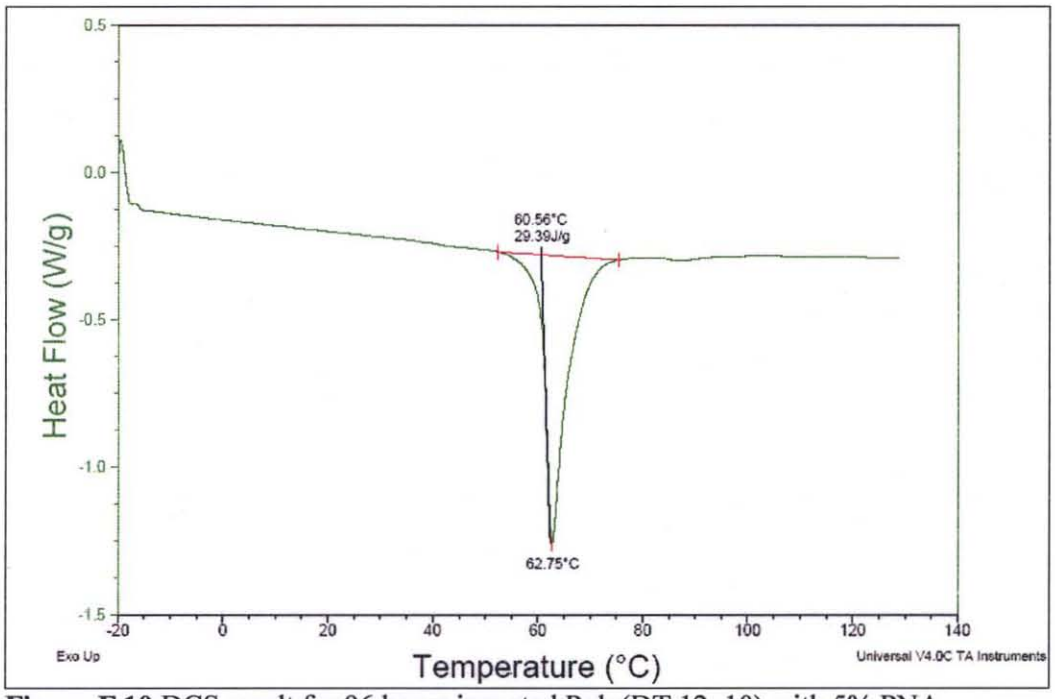

Figure F.10 DCS result for 96 hours incuated Poly(DT 12, 10) with 5% PNA.

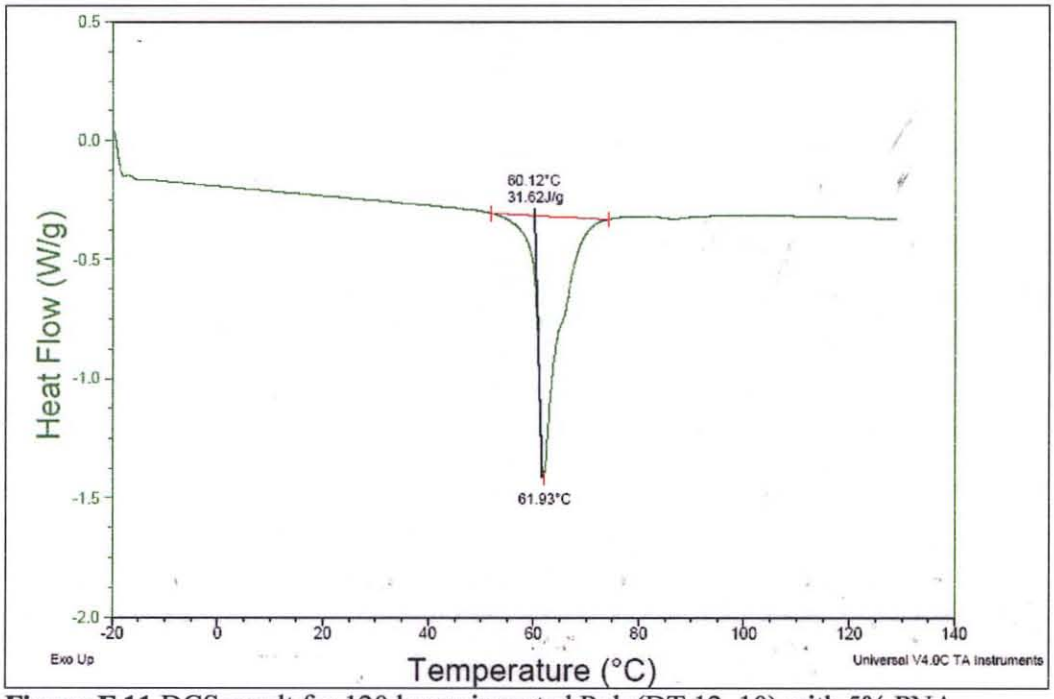

Figure F.11 DCS result for 120 hours incuated Poly(DT 12, 10) with 5% PNA.

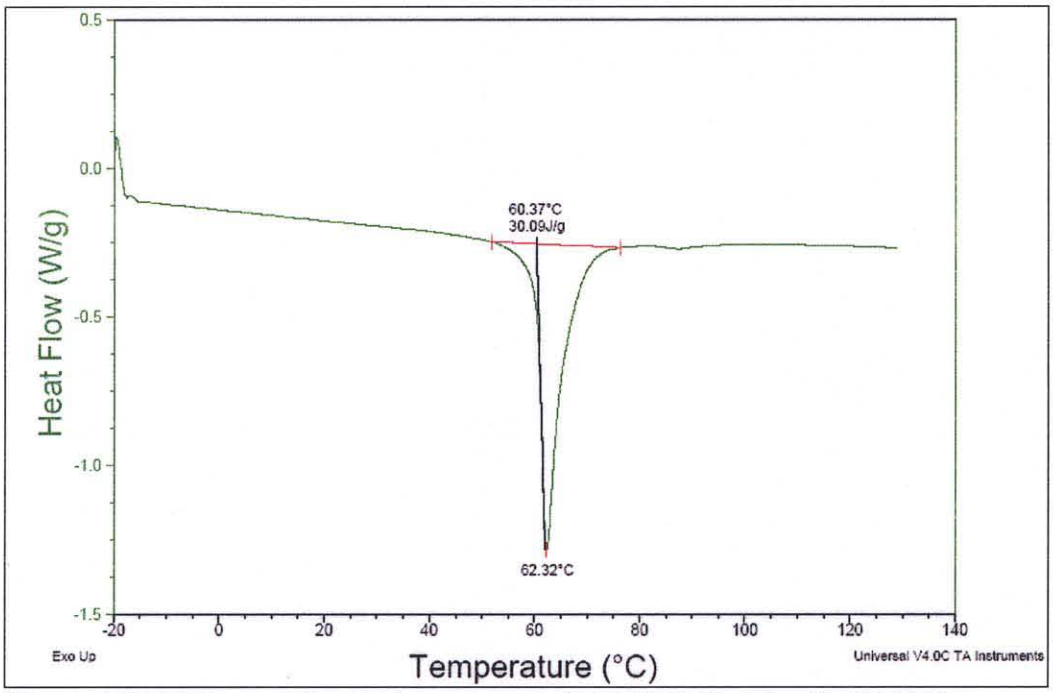

Figure F.12 DCS result for 144 hours incuated Poly(DT 12, 10) with 5% PNA.

APPENDIX G

RAW DATA OF DSC RESULTS OF POLY(DT 12, 10) WITH 10% DRUG LOADING

DSC results of 10% p-nitroaniline loaded Poly(DT 12, 10) and measured enthalpy of phase change.

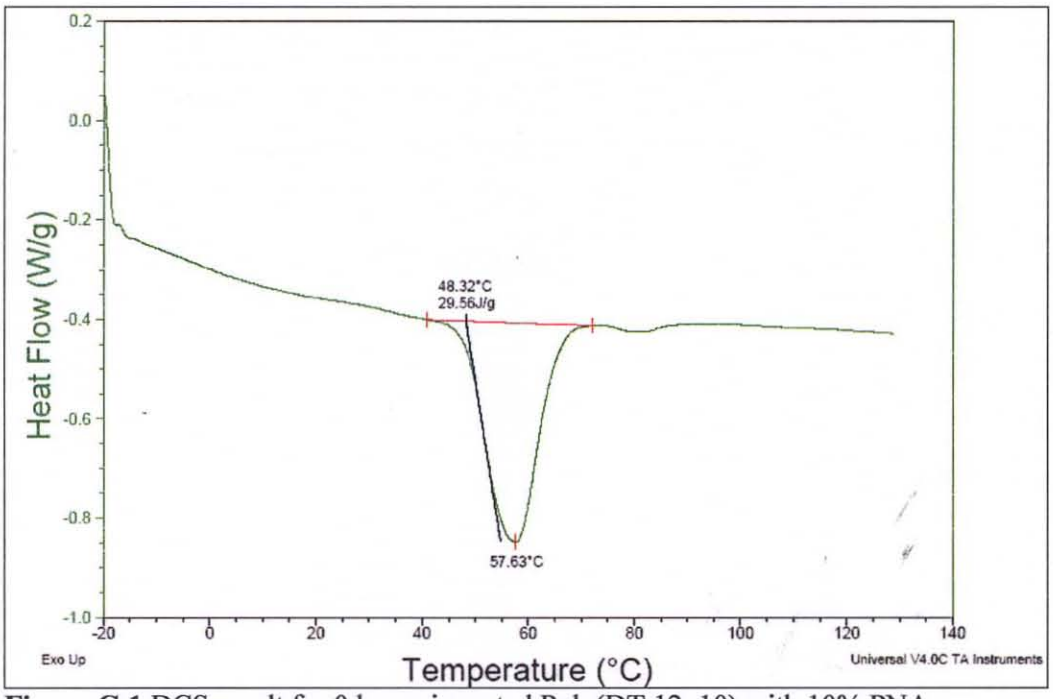

Figure G.1 DCS result for 0 hours incuated Poly(DT 12, 10) with 10% PNA.

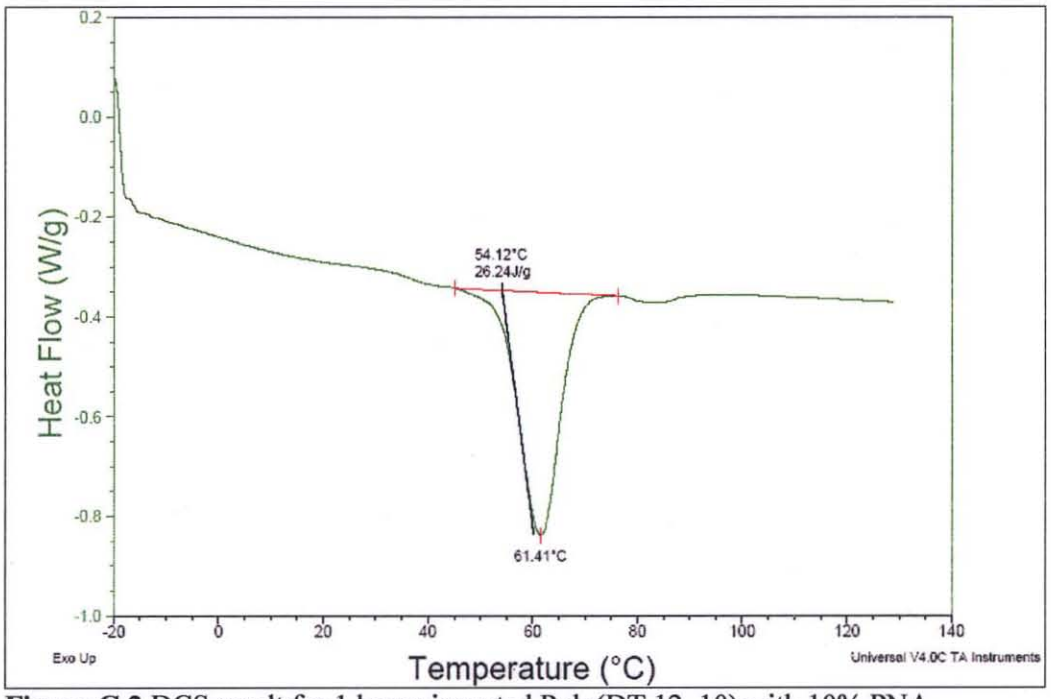

Figure G.2 DCS result for 1 hours incuated Poly(DT 12, 10) with 10% PNA.

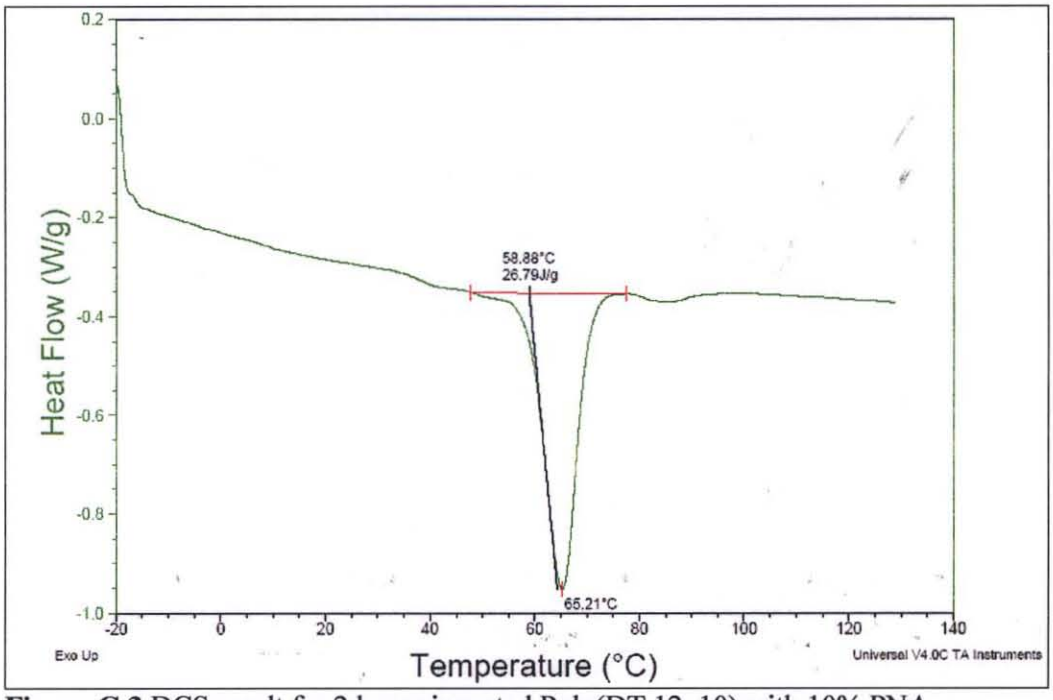

Figure G.3 DCS result for 2 hours incuated Poly(DT 12, 10) with 10% PNA.

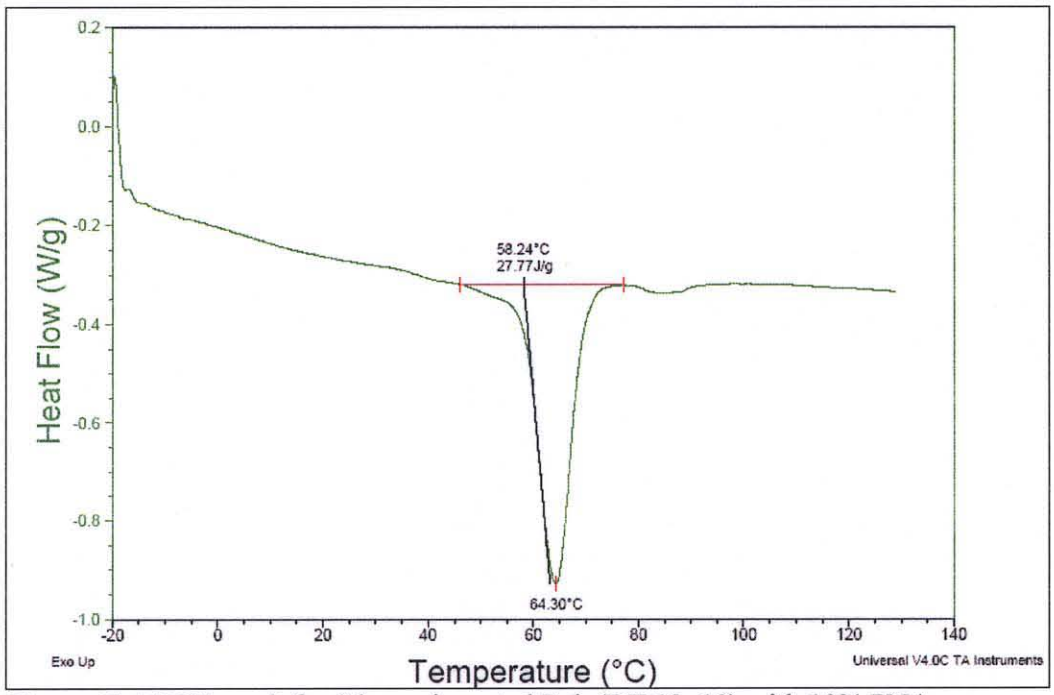

Figure G.4 DCS result for 3 hours incuated Poly(DT 12, 10) with 10% PNA.

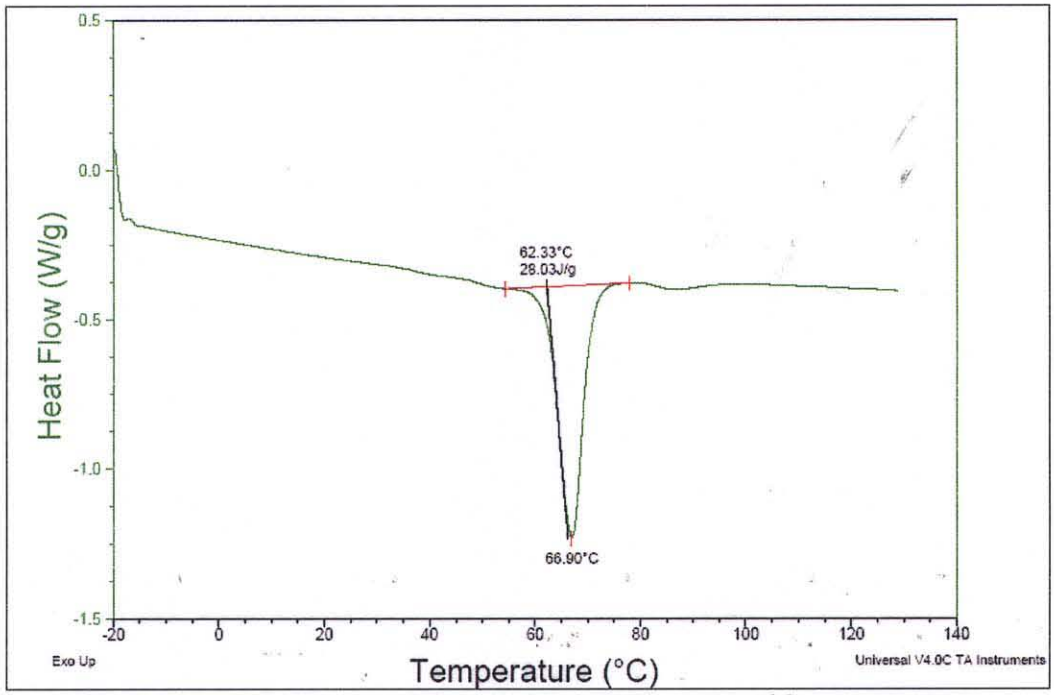

Figure G.5 DCS result for 4 hours incuated Poly(DT 12, 10) with 10% PNA.

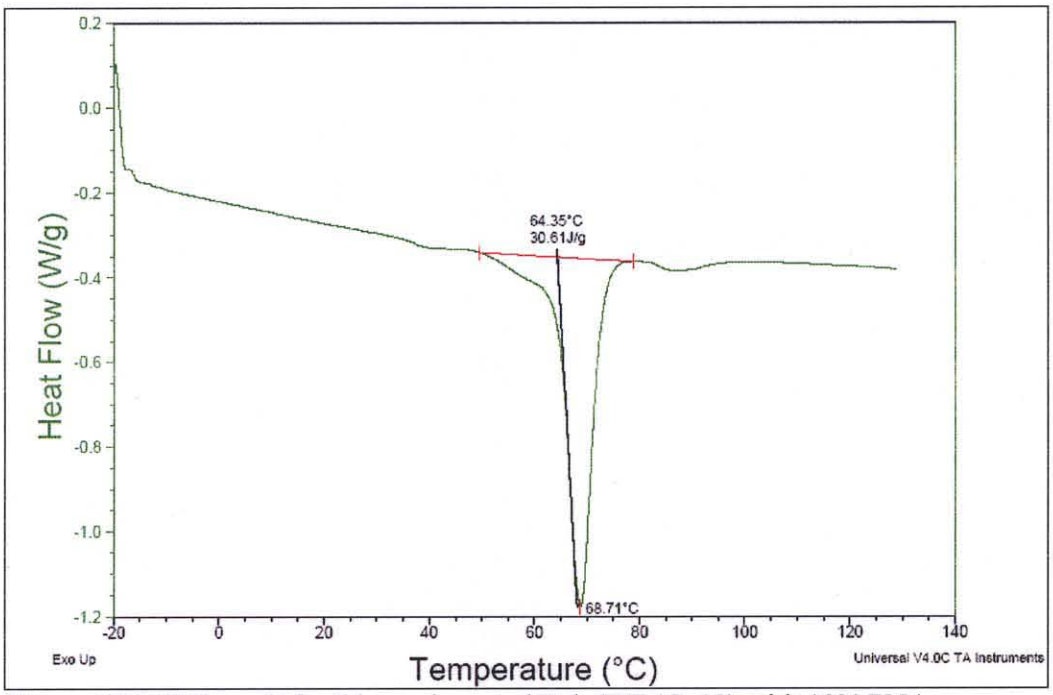

Figure G.6 DCS result for 6 hours incuated Poly(DT 12, 10) with 10% PNA.

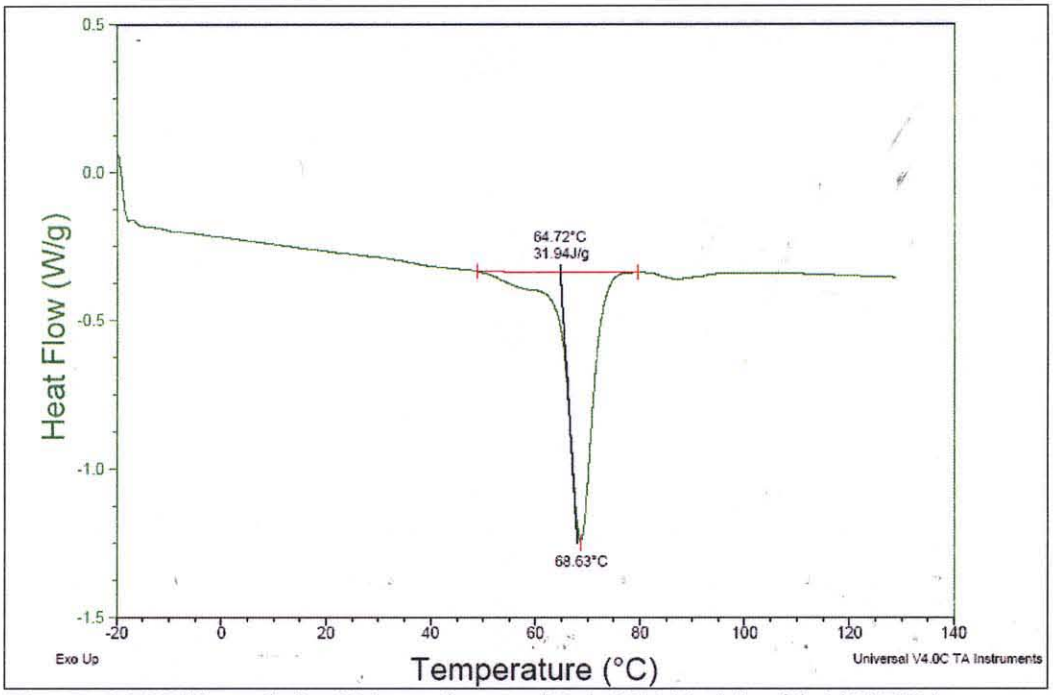

Figure G.7 DCS result for 19 hours incuated Poly(DT 12, 10) with 10% PNA.

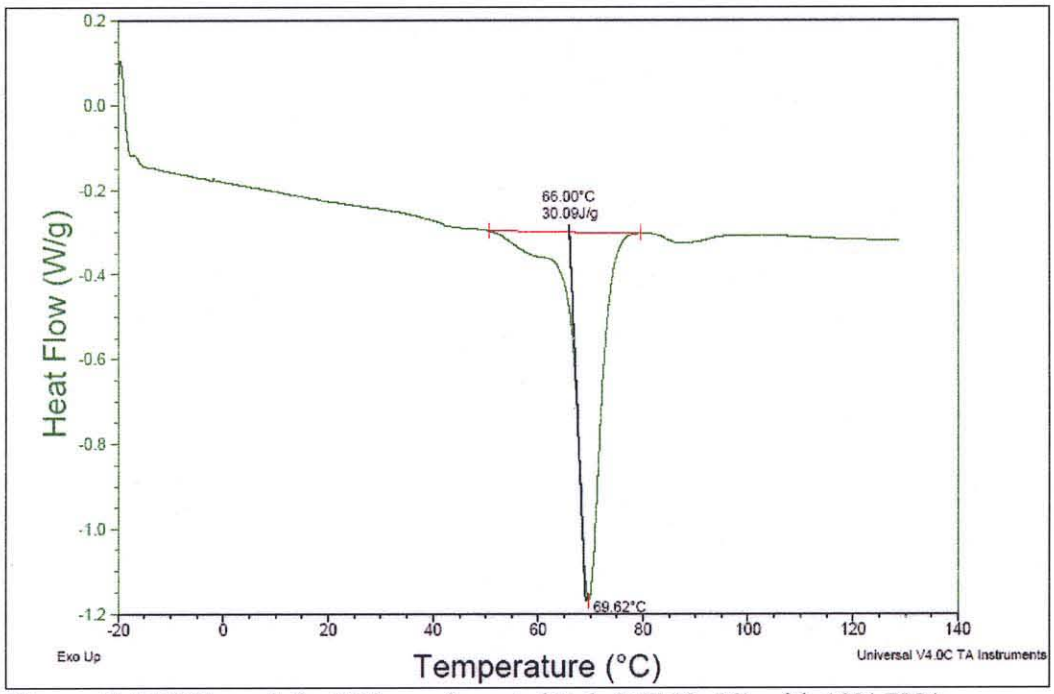

Figure G.8 DCS result for 24 hours incuated Poly(DT 12, 10) with 10% PNA.

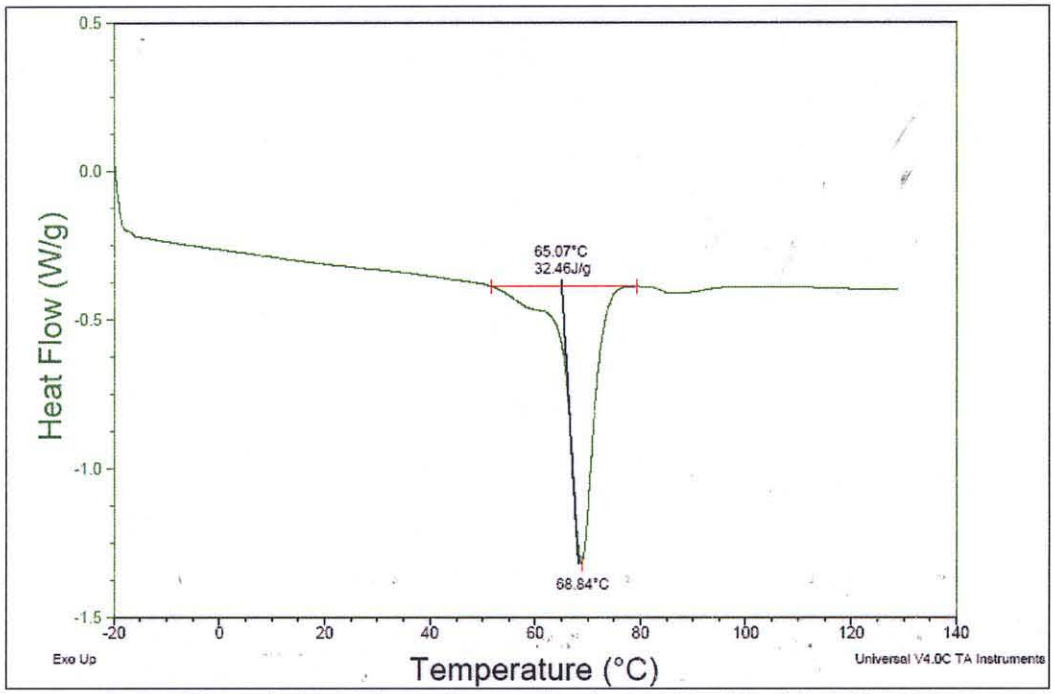

Figure G.9 DCS result for 72 hours incuated Poly(DT 12, 10) with 10% PNA.

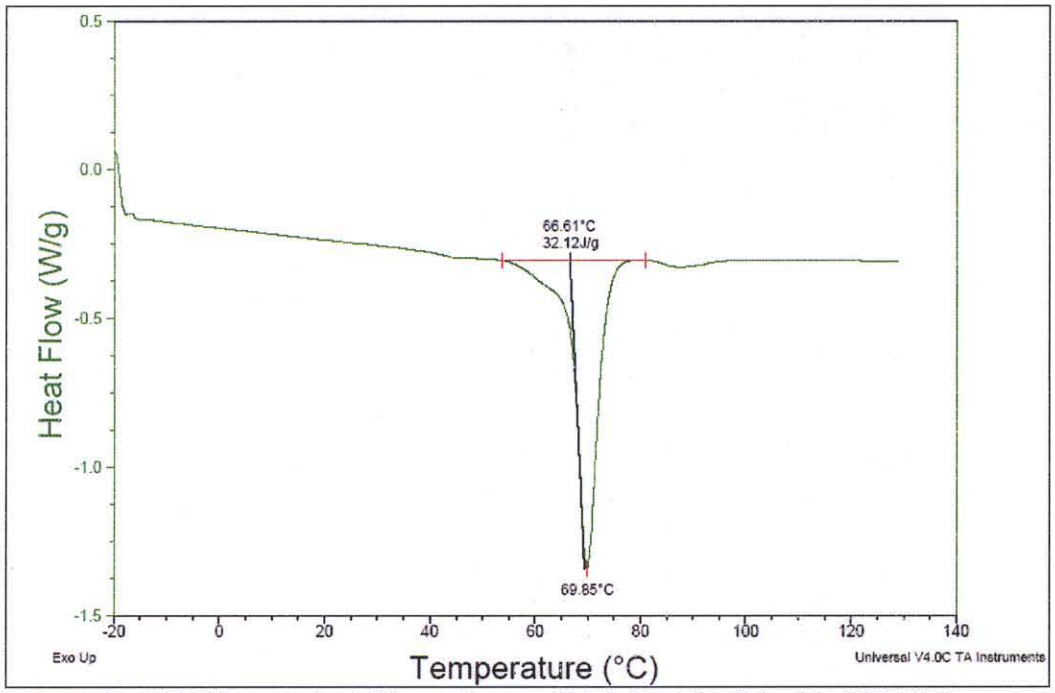

Figure G.10 DCS result for 96 hours incuated Poly(DT 12, 10) with 10% PNA.

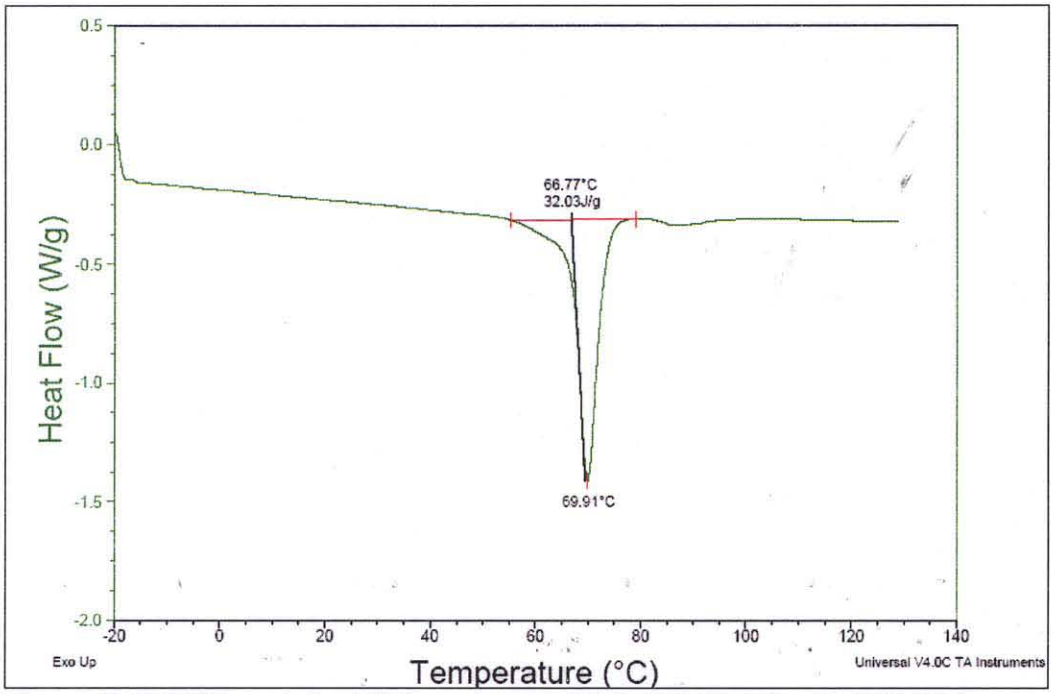

Figure G.11 DCS result for 120 hours incuated Poly(DT 12, 10) with 10% PNA.

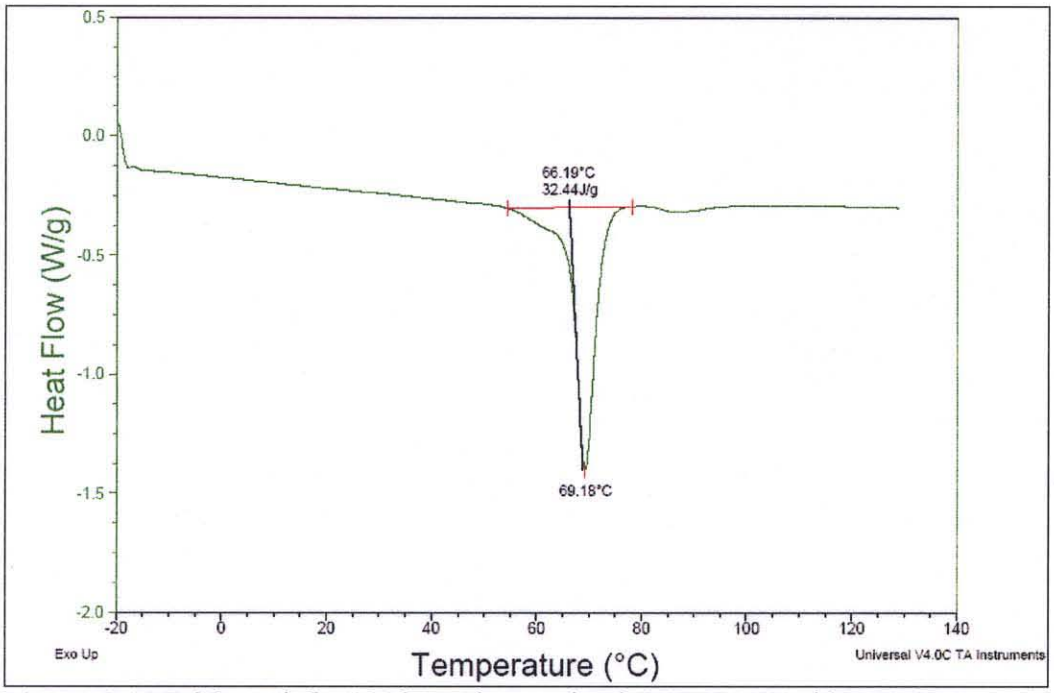

Figure G.12 DCS result for 144 hours incuated Poly(DT 12, 10) with 10% PNA.

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