Transesterification as a plausible new route for PLGA

Thesis Report Submitted towards the partial fulfilment of B.S. - M.S. dual degree program

By

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20 March, 2018

Certificate

This is to certify that this dissertation entitled "**Transesterification as a plausible new route for PLGA**" towards the partial fulfilment of the BS-MS dual degree programme at the Indian Institute of Science Education and Research, Pune represents work carried out by **Harshita Soni (20131117)** at **Solvay Research & Innovation center, Gujarat, India** under the supervision of **Dr. G. Padmanaban, Research & Innovation Corporate Lab Manager**, during the academic year **2017-2018**.

Date: 20th March, 2018

Place: Vadodara, India

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Signature of Student

G. Padmanaban 20.3.18

Signature of Supervisor

Declaration

I hereby declare that the matter embodied in the report entitled "**Transesterification as a plausible new route for PLGA**" are the results of the work carried out by me at Solvay **Research & Innovation Center, India** and the Department of Chemistry, Indian Institute of Science Education and Research (IISER) Pune under the supervision of **Dr. G. Padmanaban** and the same has not been submitted elsewhere for any other degree.

Date: 20th March, 2018

Place: Vadodara, India

Signature of Student

Signature of Supervisor

Acknowledgement

After this long journey of master's thesis, the time has come for honest introspection. I owe my sincere thanks and deepest gratitude to my supervisor Dr. G. Padmanaban. I would like to thank him for his constant support, motivation, and help throughout the year. His enthusiasm and dedication toward scientific research always amazed me. Motivated by his esteemed guidance, led me to pursue research in my future.

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~ Harshita

Content

1. **Abstract**
2. **Introduction**
   - **2.1 Biodegradable Polymers**
     - **2.1.1 Natural biodegradable polymers**
     - **2.1.2 Synthetic biodegradable polymers**
   - **2.2 PLA, PGA and PLGA copolymers**
     - **2.2.1 Poly glycolic acid (PGA)**
     - **2.2.2 Poly lactic acid (PLA)**
     - **2.2.3 Poly (lactic-co-glycolic) acid (PLGA)**
   - **2.3 Aim of the thesis**
3. **Materials and Methods**
   - **3.1 Materials**
   - **3.2 Solvents**
   - **3.3 Instrumentation**
   - **3.4 General procedure**
4. **Results and Discussions**
   - **4.1 Synthesis and characterization of monomers**
   - **4.2 Synthesis and characterization of monomers**
5. **Conclusion**
6. **References**

List of Figures

Fig (1) Classification of biodegradable polymers

Fig (2) Structure of glycolic acid and glycolide

Fig (3) Structure of glycolic acid and glycolide

Fig (4) Conventional scheme for polycondensation of PLGA

Fig (5) Polycondensation scheme for PLGA

Fig (6) Schematic representation for monomer synthesis

Fig (7) ^{1}H NMR spectrum of isobutyl lactate monomer

Fig (8) ^{13}C NMR spectrum of isobutyl lactate monomer

Fig (9) Structure of synthesized monomers

Fig (10) ^{1}H NMR spectrum for PLA synthesized with n-propyl lactate monomer

Fig (11) ^{13}C NMR spectrum for PLA synthesized with n-propyl lactate monomer

Fig (12) Reaction setup for polycondensation

Fig (13) IR Spectrum for glycolic acid and its ester derivatives

Fig (14) IR Spectrum for lactic acid and its ester derivatives

Fig (15) ^{1}H NMR spectrum for PLGA copolymer with respective monomers

Fig (16) ^{13}C NMR spectrum for PLGA copolymer with respective monomers

Fig (17) ^{1}H NMR spectrum for PLGA copolymers

Fig (18) TGA analysis of PGA polymers

Fig (19) TGA analysis of PLA polymers

Fig (20) TGA analysis of PLGA polymers

Fig (21) DSC analysis of PGA polymer

Fig (22) DSC analysis of PLA polymer

Fig (23) GPC chromatogram for PGA, PLA and PLGA polymer

Fig (24) GPC chromatogram of PLGA polymers

List of Tables

Table No.	Description	Page No.
Table(1)	IR frequency values for lactic acid, glycolic acid and their ester derivatives	26
Table(2)	TGA analysis of PLGA polymers	31
Table(3)	M_n and M_w values of PLA polymer obtained from on GPC	32
Table(4)	M_n and M_w values of PGA polymer obtained from on GPC	33
Table(5)	M_n and M_w values of PLGA polymer obtained from on GPC	34

Abbreviations

PGA	Poly glycolic acid
PLA	Poly lactic acid
PLGA	Poly (lactic-co-glycolic) acid
ROP	Ring Opening Polymerization
NMR	Nuclear Magnetic Resonance
FT-IR	Fourier-Transform Infra-Red
TGA	Thermo Gravimetric Analysis
DSC	Differential Scanning Calorimetry
TLC	Thin Layer Chromatography
GPC- SEC	Gel Permeation Chromatography – Size Exclusion Chromatography
RI	Refractive Index
PMMA	Polymethylmethacrylate
HFIP	Hexafluoroisopropanol
MSA	Methane Sulfonic Acid

1. Abstract

Biodegradable polymers have a wide range of applications in biomedical and pharmaceutical areas as well as producing bio disposable packaging materials. As natural resources of these materials are limited, finding new methods of production is in progress. Here, we report a new method of synthesizing PLGA copolymer which is biodegradable polyester. PLGA copolymer is generally produced from lactic and glycolic acid or their cyclic dimers lactide and glycolide, in this report, we have attempted to use the methodology of melt transesterification as a tool for the polycondensation of ester derivatives of lactic and glycolic acid as monomers. Here, homopolymers of these monomers PLA and PGA were also produced in order to compare them with copolymers. To understand the influence of different structural parameter in the synthesis of these PLGA copolymers, we investigated different ester derivatives of both glycolic and lactic acid. These monomers were synthesized by esterification of lactic and glycolic acid. All the monomers and polymers were characterized by NMR, GPC, and DSC-TGA.

2. Introduction

2.1 Biodegradable polymers:

It is very well known that plastics are ideal for many applications including packaging, building materials, hygiene products, biomedical devices etc.; however, these plastics are resistant to microbial degradation which leads to waste disposal problems. In order to resolve this problem biodegradable materials are introduced in 1980's. The first catgut sutures were made from intestine sheep.

As the name suggests itself 'Biodegradable' means capable of decomposing into carbon dioxide, methane, water and other eco-friendly compounds and biomass.[1] Degradation process of these polymers occurs with both biotic and abiotic methods compared to non- biodegradable polymers, which involves cleavage of hydrolytically or enzymatically sensitive bonds in the polymer. Polymer structure, morphology, molecular weight, polymerization degree, environmental conditions, chemical treatment and radiations are the factors that affect biodegradation of these materials.[2] For application purpose biodegradable polymers can be used for several areas like packaging materials, drug delivery, bio-implants, tissue engineering etc.

These can be classified on the basis of their chemical composition, origin, synthesis method, application etc. Here is the main classification of these polymers:

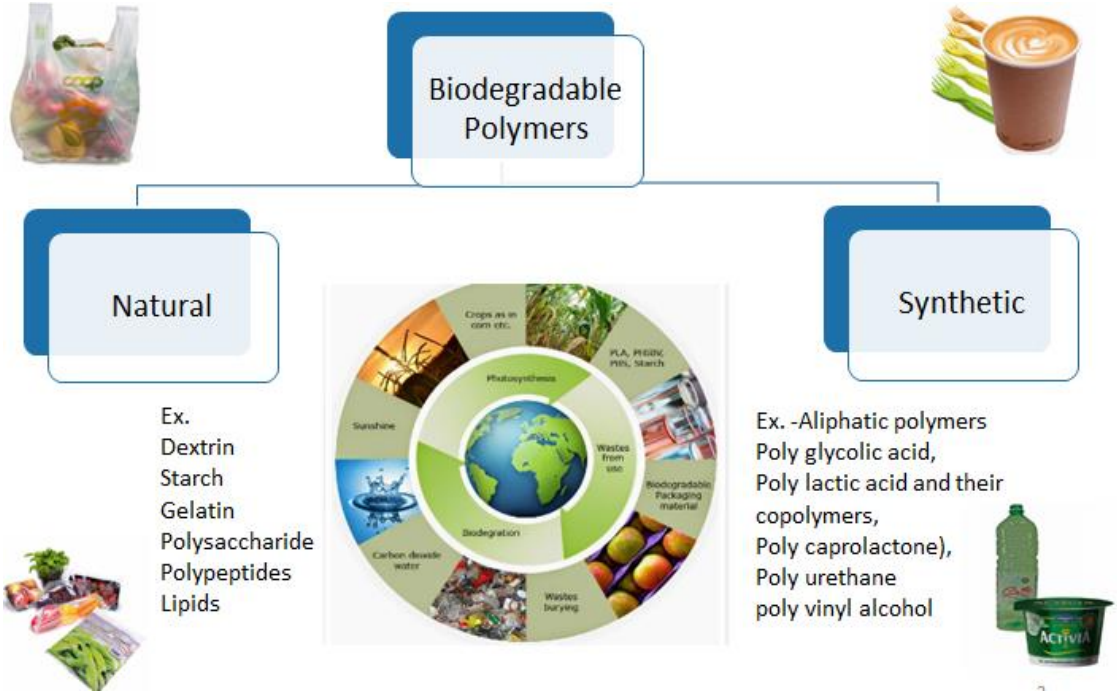


Figure 1: Classification of biodegradable polymers

2.1.1 Natural biodegradable polymers: Polymers which already exist in the nature or produced during the growth cycle of organisms fall under this category. Their synthesis generally involves enzyme catalysed chain growth polymerization reactions of activated monomers, which are typically formed within cells by complex metabolic processes (*e.g.,* polysaccharides like starch, cellulose, chitosan, proteins like soy, collagen, gels, silk, polynucleotides like DNA, RNA and bio fibres).[3]

2.1.2 Synthetic biodegradable polymers: These are derived from non-renewable resources with hydrolysable functions, ester – poly (glycolic acid) (PGA), poly (lactic acid) (PLA), copolymer of lactic and glycolic acid (PLGA), amide – polyamide 66, urethane (polyurethane) etc.

Irrespective of the category, the major advantage of these materials is their biocompatibility and biodegradability. Mechanical properties of these polymers depend on chemical composition used to produce them, storage and processing and application conditions.

Biodegradation of these polymers takes place via enzymes or chemical deterioration associated with living organisms. This process of degradation occurs in two steps. At first the fragmentation of the polymers happens into lower molecular mass species by either abiotic or biotic reactions which includes oxidation, photodegradation, hydrolysis, degradations by microorganisms etc. and then bioassimilation of these polymer fragments via microorganisms followed by mineralisation.[4]

2.2 PLA, PGA and copolymer PLGA:

2.2.1 Poly glycolide or polyglycolic acid (PGA):

It is the simplest linear aliphatic polyester. It was produced as the first synthetic absorbable suture, in 1962. It can be prepared by ring opening polymerization of cyclic lactone which is glycolide fig.(2), direct melt polycondensation of glycolic acid fig. (2) etc.[5,6] it has high degree of crystallinity and hence it is not soluble in most of the organic solvents. It has glass transition temperature of 35-40 °C, with a high melting point (200-230 °C). As it has less solubility and higher rate of degradation giving acidic products its biomedical applications are limited. To overcome all these aspects copolymers of this polymer have been derived with lactide, caprolactone, urethane etc. for biomedical devices.[7]

Figure 2: Structure of glycolic acid and glycolide

2.2.2 Poly lactide (PLA):

It is usually obtained by polycondensation of D-, L-, or racemic (DL) lactic acid directly or by ring opening polymerization of lactide[8], which is a cyclic dimer of lactic acid. Lactic acid has an additional methyl group compared to glycolic acid. The additional methyl group not only introduces chirality, but also makes PLA more hydrophobic polymer and more resistant to hydrolysis than PGA. Glass transition

temperature of commercially available PLA is 63.8◦C.[9] Different physical properties and biodegradability of PLA obtained from D- and L- isomers, these properties also depends of the chirality of lactide. PLLA is hard, transparent, semi-crystalline polymer having about 37% crystallinity and melting point 170-180 ◦C with a glass transition temperature 53 ^{0}C whereas PDLLA , poly (DL-lactide), is an amorphous polymer with no melting point and has glass transition temperature around 55 ◦C. Brittleness and poor thermal stability are disadvantages of PLA. This, semicrystalline, biodegradable materials have variety of applications in pharmaceutical, biomedical field as well as biodegradable plastics also.[10]

Lactic acid Lactide

Figure 3: Structure of glycolic acid and glycolide

2.2.3 Poly (lactic-co-glycolic acid) (PLGA):

It is a block copolymer of lactic acid and glycolic acid. It is a kind of aliphatic polyester, which can completely biodegrade into CO_2 and H_2O and is completely harmless and nontoxic to the environment. Also it has been FDA (Food and Drug Administration) approved for human therapy. It has been commercially available with varying ratios of lactic and glycolic acid for different applications. By changing the ratio of lactic to glycolic acid, amorphous and semi crystalline copolymers can be obtained. In the case of PLGA, not only the ratio of GA to LA, even the block length of these monomers in the copolymer also influences their properties including degradation, crystallinity etc. PLGA biodegrades through hydrolysis of its ester linkages in the presence of water and the degradation rate of these polymers depends on their hydrophobicity. The extra methyl group on lactic acid makes lactide rich PLGA copolymers less hydrophilic and hence degrade more slowly. When PLA co-polymerized with crystalline PGA, reduces the degree of crystallinity of PLGA, increase the rate of hydration and hydrolysis. So, when the ratio of monomer Lactic: Glycolic acid increases, the degradation rate of the copolymer decreases as PLA degrades slower than PGA as mentioned in above reason.

PLGA has a wide range of applications in biomedical and pharmaceutical areas, for example- implants for controllable drug release systems, orthopaedic, tissue engineering, interior bone fixation, artificial skin, tissue scaffolds.[11] PLGA copolymer can be synthesized using various methods such as Ring opening polymerization of lactide and glycolide, metal catalysis, solvent based polymerization etc. The general methodology to produce PLGA is shown in fig. (4)

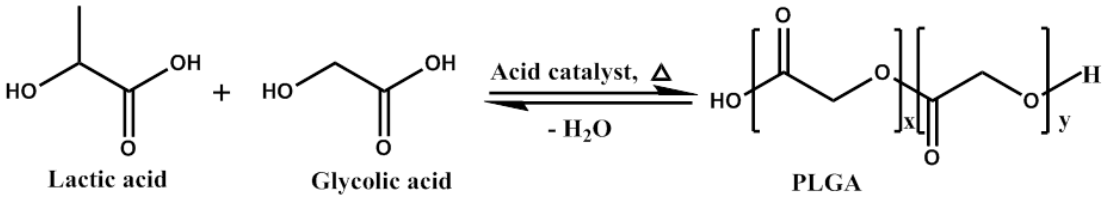


Fig 4: Conventional scheme of direct polycondensation of PLGA

2.3 Aim of thesis: The most common method to produce PLGA copolymers is ring opening polymerization of respective lactide and glycolide to result the copolymer with required properties. However, it is not a cost effective process. On the other hand, in conventional polycondensation method of PLGA synthesis, lactic and glycolic acids are copolymerized in the presence of an acid catalyst. The by-product in this process is water. The molecular weight of obtained polymer mainly depends on efficient removal of water from the reaction mixture. As removal of alcohols having lower boiling point than water is easier and any residual water could cause hydrolysis of the polymer backbone, especially when the GA content is high. In the present thesis we tried to synthesize PLGA polymers via polycondenstation polymerization of different lactates and glycolates (methyl/propanol/isopropyl/n-butyl/isobutyl esters) as monomers which is a trans-esterification reaction. Molecular weight of produced polymer also depends on the reactivity of the species forming in the reaction mixture during polycondensation. In these reactions, the by-product is the respective alcohol (methanol/ isopropanol/propanol/n-butyl/isobutyl/neopentyl alcohol) in which some of these have lower boiling point than water therefore removal will be easy and the produced copolymer would not be having water content present as by-product in the reaction mixture so the degradation will be slower due to hydrolysis compared to conventionally synthesized PLGA. The schematic representation of the present approach is demonstrated in figure (5).

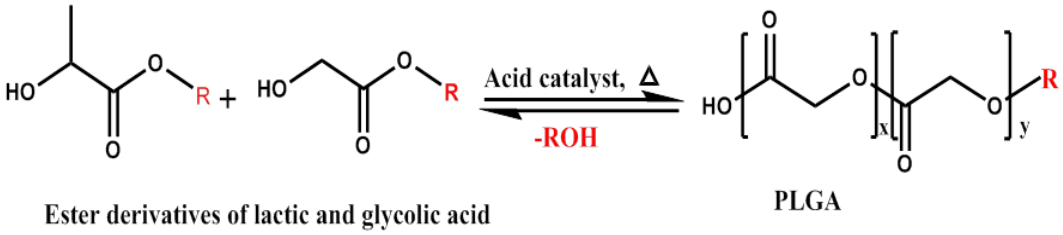


Figure 5: Polycondensation scheme for PLGA

3. Materials and Methods:

3.1 Materials: Lactic Acid (90% aqueous solution), glycolic acid (glypure), titanium tetra butoxide, methane sulfonic acid (MSA), potassium permanganate ($KMnO_4$), methanol, 1-propanol, 2-propanol, n-butyl alcohol, isobutyl alcohol, neopentyl alcohol, sulfuric acid, and molecular sieves (4 Å) were obtained from Sigma Aldrich

3.2 Solvents: Deuterated chloroform ($CDCl_3$), dimethyl sulfoxide (DMSO), hexafluoro isopropanol (HFIP), dichloromethane(DCM).

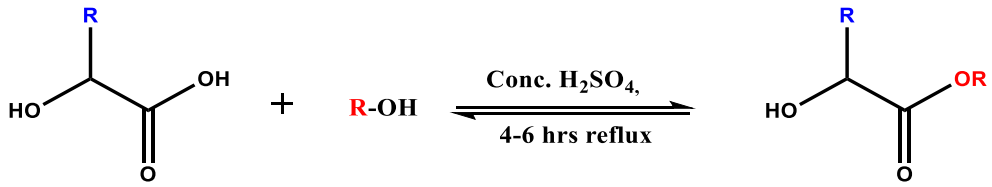
3.3 Instrumentation:

All the samples for ^{1}H NMR and ^{13}C NMR were prepared in $CDCl_3$ as a solvent and Trimethylsilane was used as an internal standard. The NMR spectra were recorded using a Bruker AV 400 multinuclear broadband spectrometer, 5mm probe solution state, 400 MHz for proton NMR and 100 MHz for carbon NMR, spectrum of all samples were obtained at a temperature of 25 °C. The values for chloroform at 7.26 ppm and 77.24 ppm respectively for ^{1}H NMR and ^{13}C NMR are used as references in the NMR spectra. Gel permeation Chromatography (GPC) was done using 0.05M potassium trifluoroacetate in HFIP mobile phase with 0.4 mL/min flow, column MINMAX-B, 2 columns in series with RI detector, column temperature 40 °C, injection volume 20 µl with PMMA standard, the solution was heated using water bath to make sure that the polymer dissolved. The obtained solution was filtered using 0.45 micron membrane filters to get rid of any bigger impurities. GPC was done using a column which was standardized by using PMMA. The thermal stability of the polymers were determined by using TGA Q500 with auto sampler, where the polymers were heated at 10°C/min under nitrogen atmosphere and DSC was done using DSC Q2000. FT-IR study of the monomers was done by using PerkinElmer FT-IR frontier spectrometer.

3.4 General procedures:

Monomer synthesis: Preparation of ester derivatives from acids is a common practice in organic chemistry and several methodologies were reported in the literature. Fisher esterification is one of the most common methods for the synthesis of esters, in which an acid and a suitable alcohol are reacted in the presence of an acid catalyst.[12] The reaction is in equilibrium condition. So as soon as the ester forms in the reaction and water as byproduct is possible that ester can reacts with water and gives acid back, so water removal from the reaction mixture is necessary in order to get ester as product.

Here we employed the same method for the esterification of α-hydroxy carboxylic acids (lactic and glycolic acids). In a typical procedure, the α-hydroxy carboxylic acid was dissolved in excess of alcohol (methanol, propanol, isopropanol, butanol, iso-butanol, neopentanol) and catalytic amount of acid catalyst (conc. Sulfuric acid) was added to the reaction mixture.[13] Molar ratio of this reaction is 1 eq lactic acid, 5 eq alcohols and 0.02 eq. sulphuric acid. The reaction mixture was kept stirring at reflux temperature for 4-6 hours. The progress of the reaction was followed by TLC and NMR. General scheme for synthesizing monomers is shown in figure (6).



For Glycolic acid R = H
Lactic acid R = CH_3

Fig (6): Schematic representation for monomer synthesis

Preparation of Isobutyl lactate: (20gm, 222.2mmol) lactic acid was dissolved in around 100 ml Isobutyl alcohol and 0.2-0.3 ml conc. sulfuric acid was added to this mixture and kept for heating for 4 to 6 hours at refluxing temperature (110-115 °C) to complete the esterification. [13] The reaction progress was monitored by thin-layer chromatography (TLC). After this, alcohols were removed using rotary evaporator. For getting final, product purification of the crude product was done using filtration column with pure DCM as mobile phase .The product formed was colourless liquid in nature and the yield got was 64.3%.Characterization of this monomers was done by FT-IR, NMR Spectroscopy and TGA analysis.

^{1}H and ^{13}C NMR spectrum of monomer isobutyl lactate is shown below in figures (7) & (8). ^{1}H NMR, δ ppm: 0.91(d, 6H, -CH $(CH_3)_2$), 1.4(d, 3H, -CH-CH_3), 1.9(q, 1H, -$(CH_3)_2$-CH), 3.9(d, 2H, -O-CH_2), 4.2(q, 1H, -CH_3-CH). ^{13}C NMR, δ ppm: 17.1, 20.6, 27.8, 66.9, 71.7, 175.2, here the peak appears at 0.9, 1.9, and 3.9ppm in ^{1}H NMR and 17.1, 27.8, 71.9 in ^{13}C NMR confirms the monomer formation.

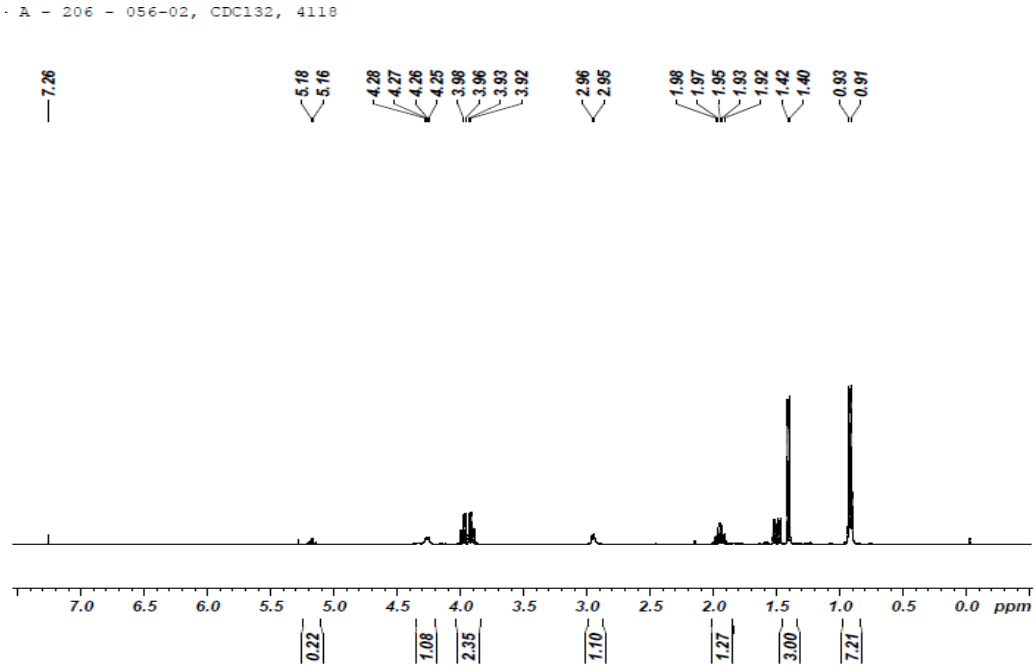


Figure 7: ^{1}H NMR spectrum of isobutyl lactate monomer

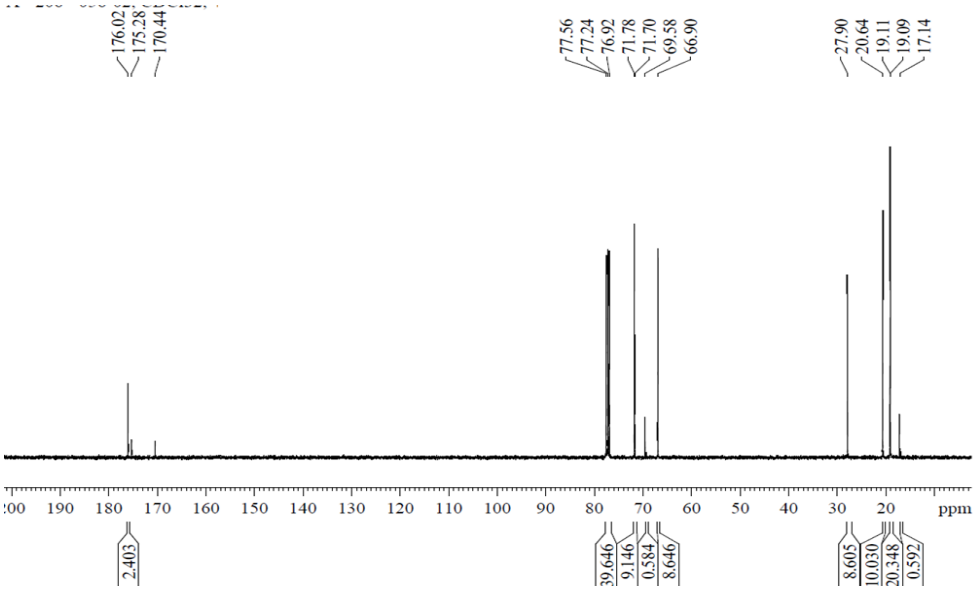


Figure (8): ^{13}C NMR spectrum of isobutyl lactate monomer

The same procedure was followed for preparation of ester derivatives of lactic acid and glycolic acid. Yield obtained for all the monomers was in the range of 40-70%. In figure (9), structure of all prepared monomers is demonstrated.

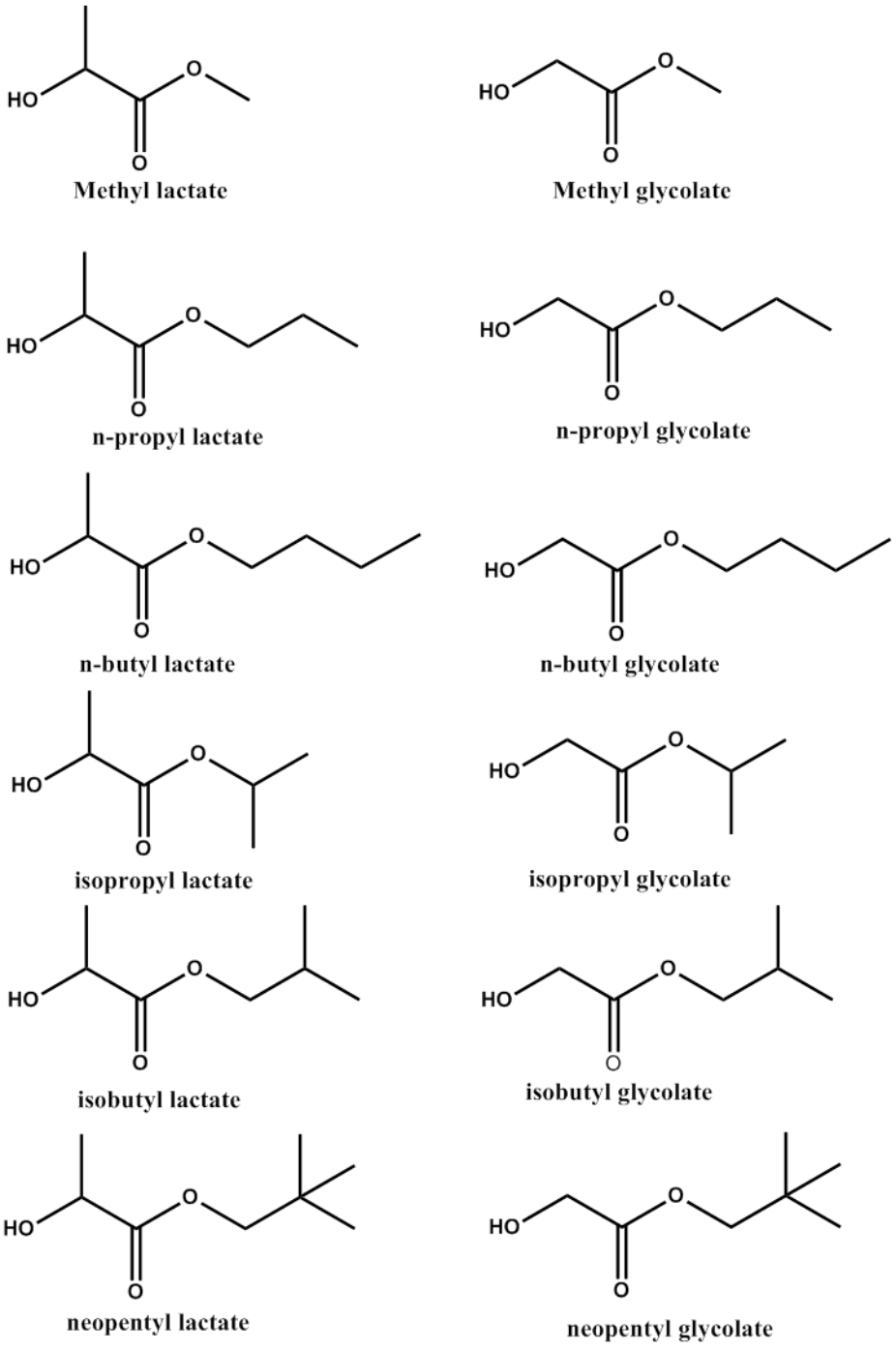


Fig 9: Structures of synthesized monomers

Polymer Synthesis:

Polyesters can be produced by direct esterification of a diacid with a diol, self-condensation of a hydroxy carboxylic acid, ring opening polymerization (ROP), metal catalysis, solvent based polymerization etc. Since polyesterification is an equilibrium reaction like other step growth polymerizations, water or by-product needs to be continuously removed from the reaction mixture in order to achieve high conversions and high molecular weight. Apart from this, the choice of the reaction temperature is also important to minimize side reactions.[14]

There are several methods of synthesizing PLA, PGA and PLGA as direct synthesis or melt poly condensation, ring opening polymerization etc. Of these methodologies, ROP is one of the most commonly used methods. However, from industrial point of view it is not a cost effective process. In order to obtain high molecular weight polymers, the cyclic dilactone monomers have to be extensively purified, using techniques such as high vacuum distillation. So herein we mainly focus on melt polycondensation method to synthesize polymers.

Generally in melt polycondensation polymerization, the monomers are polymerized in the presence of an acid catalyst, up to a certain temperature for several hours under inert conditions and vacuum is applied in order to efficiently remove the byproduct from the reaction mixture so that the equilibrium could be shifted towards the high molecular weight polymer.[15] Though hompolymer of lactic esters already have been reported but we have taken ester derivatives of lactic and glycolic acid for synthesis, as copolymers of these derivatives via ester polycondensation have not been reported earlier in the literature.

Here both homopolymers (PLA and PGA) and copolymer PLGA were Prepared via polycondensation method.

Synthesis of PLA and PGA: 4gm monomer was added to the two necked round bottom flask and 8-10 µl MSA (0.3 wt. %) was added to this monomer at 120°C in inert conditions, reaction temperature was increased to 190°C in 1 hr, vacuum was increased slowly up to 30-35Torr in 1hr, after this, reaction was continued for next 5 hrs and the product formed was a semi-solid compound and slightly brown in colour. These polymeric compounds were characterized by NMR, GPC, DSC and TGA.[16]

^{1}H and ^{13}C NMR spectrum for n-propyl lactate with the polymer PLA is shown in the figure (10) & (11). In the polymer formation, the monomer peak which appears around (4.0-4.2) ppm vanishes and polymer peak starts appearing at (5.0- 5.5) ppm which is not present in the monomer, so there is a significant peak shift from monomer to polymer in ^{1}H NMR, which gives the indication of polymer formation.[17]

In ^{13}C NMR of PLA in figure (11) we can see the peaks in region 10-30 ppm vanishes which is present in the monomer, this peak corresponds to the end group which is n-porpyl group This confirms the formation of polymer.

All the other homopolymerizations were done and characterized as the same method mentioned above.

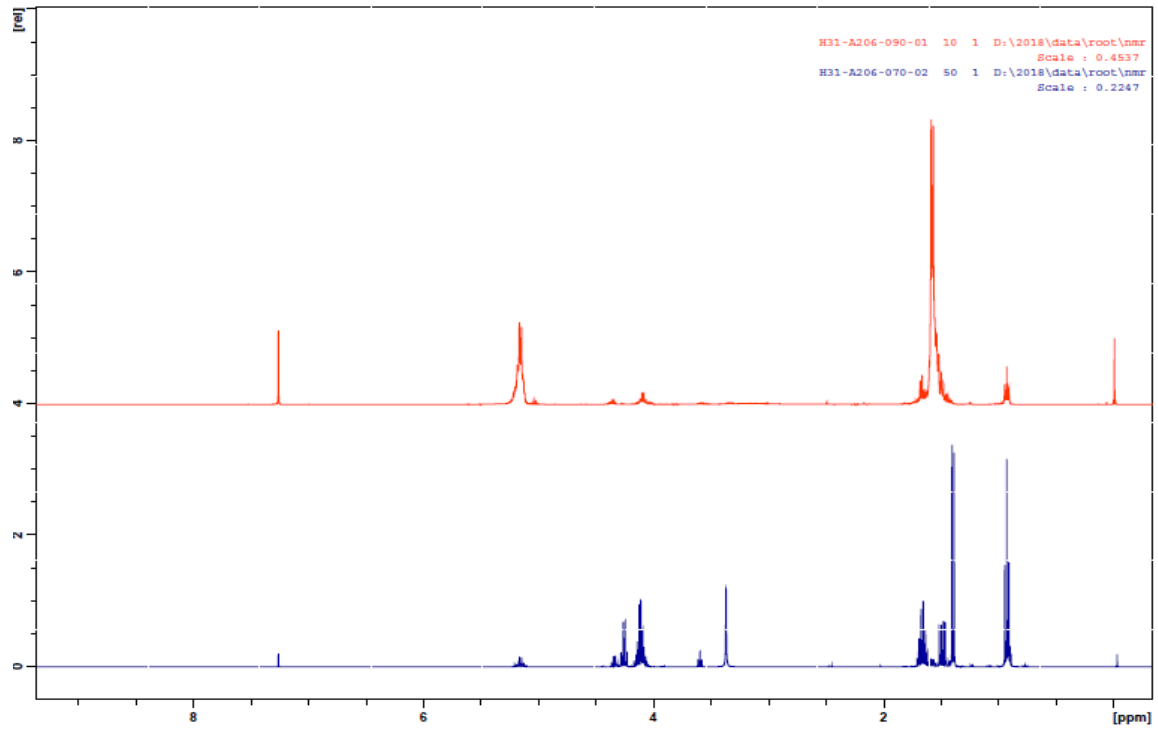


Figure 10: ^{1}H NMR spectrum for PLA synthesized with n-propyl lactate monomer

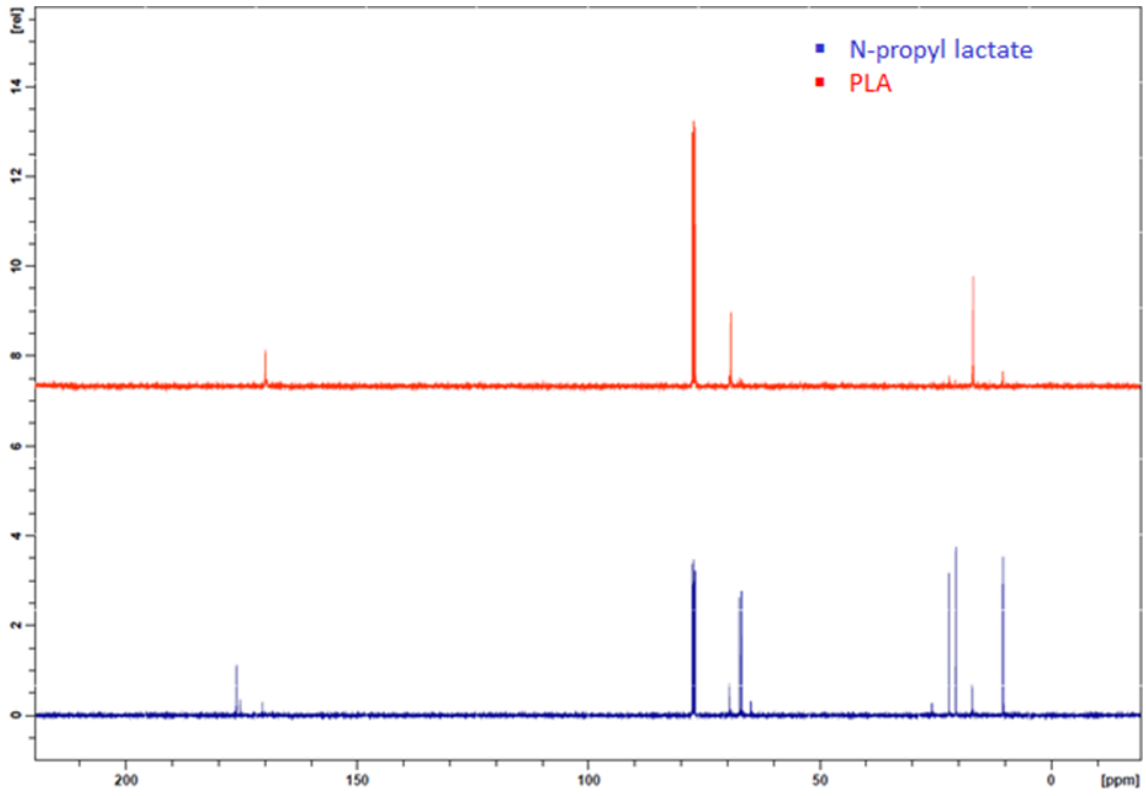


Figure 11: ^{13}C NMR spectrum for PLA synthesized with n-propyl lactate monomer

Synthesis of copolymer PLGA: For synthesizing PLGA 50:50 ratio (2gm) of monomers was taken in a two necked round bottom flask, in this 8-10 µl MSA (0.3 wt. %) was added at 120 °C in inert conditions, reaction temperature was increased to 190 °C in 1 hr, vacuum was applied increased slowly up to 30-35 Torr in 1 hr, after this, reaction was continued for next 5 hrs and the product formed was a semi-solid compound and slightly brown in colour. This polymeric compound was characterized by NMR, GPC, DSC-TGA, which are shown below. Reaction setup used for polycondensation is demonstrated in the following figure (12).

Figure 12: Reaction setup for polycondensation

4. Results and discussion:

4.1 Synthesis and characterization of monomers: All the ester derivatives of lactic and glycolic acid were synthesized using esterification of α-hydroxy carboxylic acids in the presence of catalytic amount of sulfuric acid. Purification of these monomers was performed through column chromatography and the products obtained were colorless liquids in nature. For all the monomers, the yield obtained was around 40-70%. All these monomers were characterized using NMR, IR spectroscopy and TGA analysis. Successful synthesis of the esters was confirmed by the appearance of new signals corresponding to the ester group in the ^{1}H NMR. Analysis of IR spectra also indicated a clear shift in the carbonyl stretching frequencies due the transformation of an acid into esters. For thermal properties, Thermo Gravimetric Analysis was done to assess the stability of these monomers against temperature.

TGA analysis of monomers: Thermo gravimetric analysis of monomers was done in order to get information about thermal stability, presence of any residual solvent in the monomer. Here from TGA analysis we found that there was some alcohol amount present in the monomer and the monomer were thermally stable upto 90°C.

IR spectra of monomers:

IR spectroscopy is an excellent analytical method to differentiate organic functional groups as these functional groups result different vibrational bands depending on the nature of the bond. We applied these analytical methods in combination with NMR to confirm the transformation of the starting material acids to corresponding esters. In fig we have shown the IR spectra for lactic acid, glycolic acid along with their ester derivatives. Lactic and glycolic acid have carboxylic acid functional group and their ester derivatives have ester group present in the structure. In these frequency Vs transmittance curves, we could see the carbonyl stretching bands of carboxylic acid functionality of glycolic acid and lactic acid at 1702.74cm^{-1} and 1719.02cm^{-1} respectively, and the monomers having carbonyl stretching band above 1720 cm-1 clearly indicated presence of ester functionalities in monomers, as shown in figure (13) & (14) or table (1), which confirms successfully synthesis of the monomers.

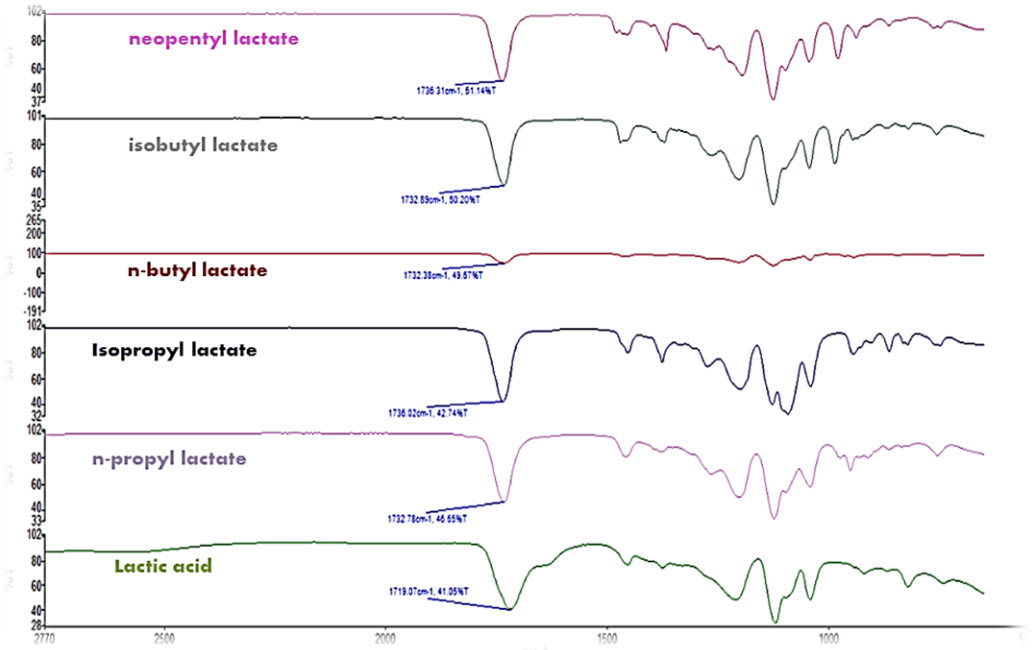


Figure 13: IR Spectrum for glycolic acid and its ester derivatives

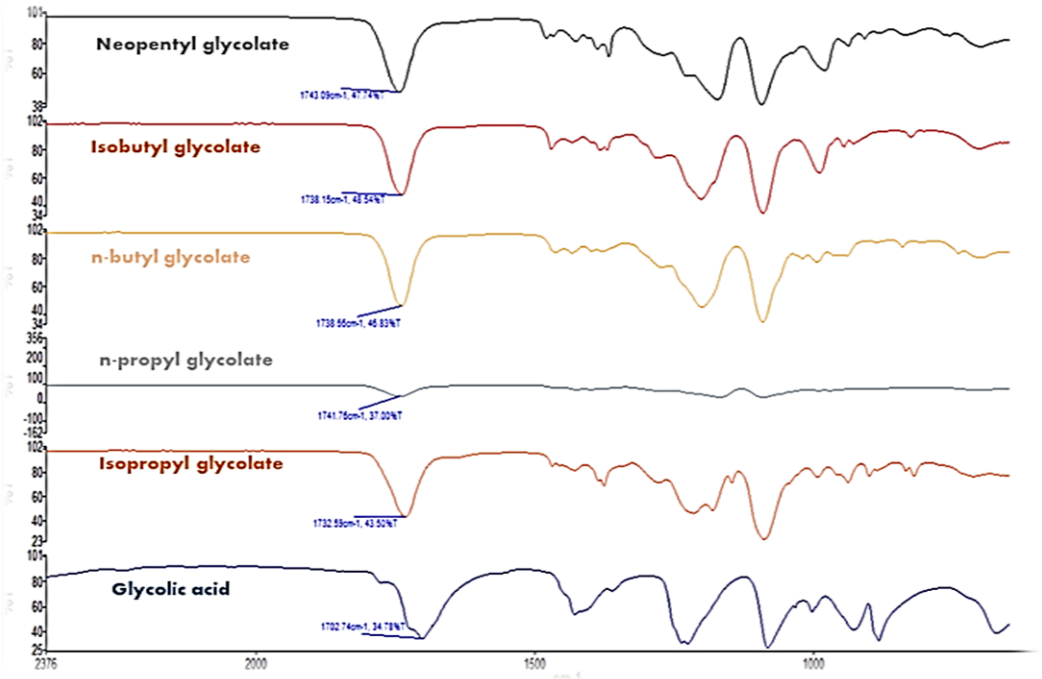


Figure (14): IR Spectrum for lactic acid and its ester derivatives

Table (1): IR frequency values for the carbonyl C=O stretching frequencies in lactic acid, glycolic acid and their ester derivatives

Compound	**Peak Shift (cm^{-1})**	**Compound**	**Peak shift(cm^{-1})**
Lactic acid	1719.07	Glycolic acid	1702.74
n-propyl lactate	1732.78	n-propyl glycolate	1732.59
Isopropyl lactate	1736.02	Isopropyl glycolate	1741.76
n-butyl lactate	1732.38	n-butyl glycolate	1738.66
Isobutyl lactate	1732.89	Isobutyl glycolate	1738.05
Neopentyl lactate	1736.31	Neopentyl glycolate	1743.09

Synthesis and characterization of polymers:

Both homopolymers PLA, PGA and copolymer PLGA were produced via polycondensation method. Homopolymer PGA prepared via polycondensation method from ester derivatives of glycolic acid, was dark brown or black solid in nature and was insoluble in most of the solvents (chloroform, DCM, acetone etc.) unlike PLA and PLGA. In the case og PGA reaction temperature was increased upto 210-215°C as reaction mixture starts solidifying after some hours because melting temperature is high for PGA. Due to more reactivity of GA compared to LA it is possible to have more blocks of GA than lactic acid in a unit of PLGA copolymer which we analysed using NMR. PLA and copolymer PLGA were soluble in $CHCl_3$, DCM, acetone and other organic solvents. Solubility of these PLGA polymers does not depend on the number of GA and LA blocks.[18] Characterization of all the polymers was done using NMR, GPC and DSC-TGA analysis.

NMR characterization of PLGA polymers:

Both ^{1}H and ^{13}C NMR of PLGA copolymers was done using solvent $CDCl_3$. In these NMR spectrums we could see the shift of $–CH_2$ protons of glycolic acid and -CH protons of lactic acid from monomer (4ppm) to polymer around 4-6 ppm; this was due to formation of ester through trans-esterification. Here in fig. (15) & (16) NMR of PLGA is shown which is synthesized from isobutyl substituted monomers.

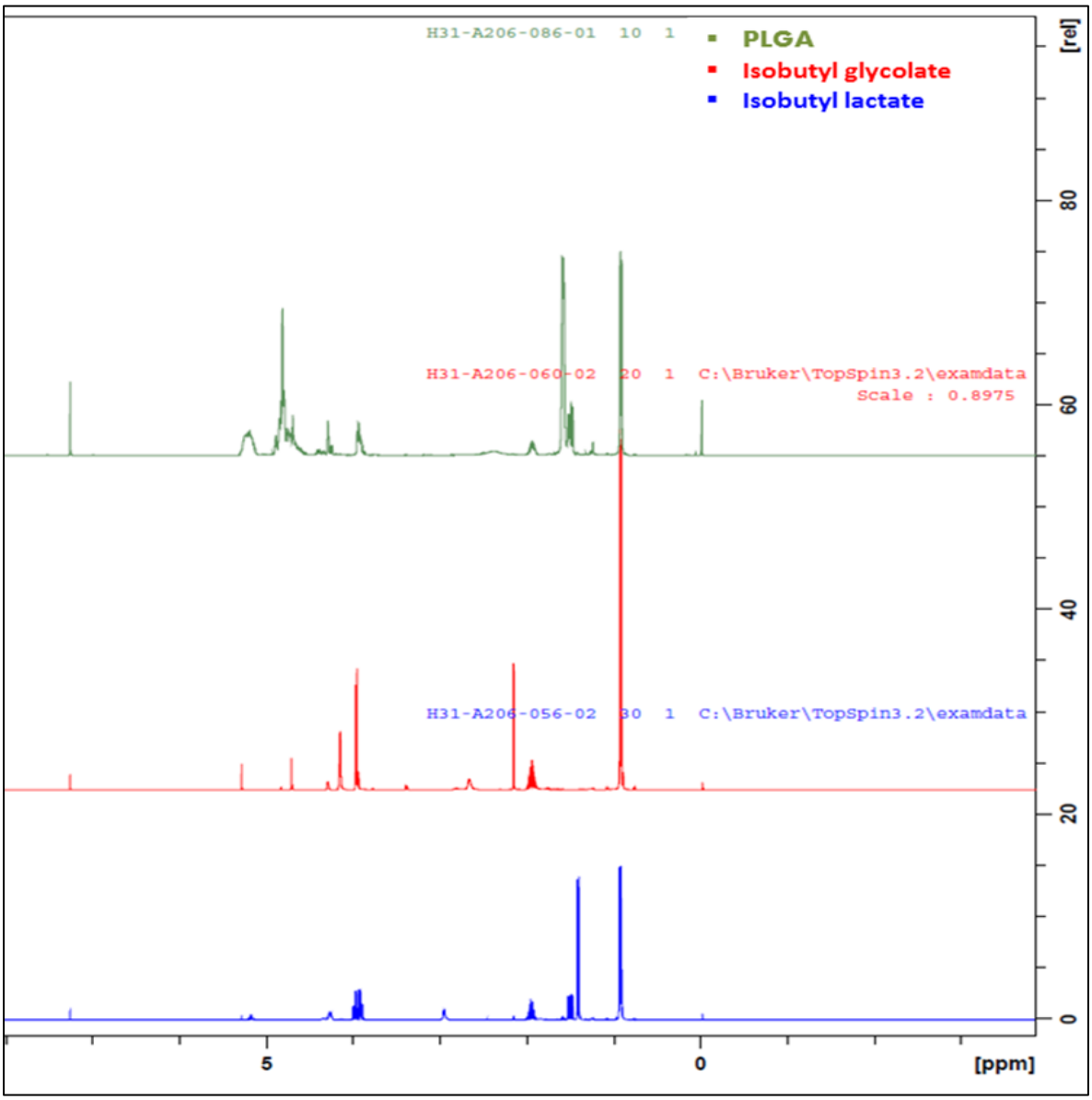


Figure 15: ^{1}H NMR spectrum for PLGA copolymer with respective monomers

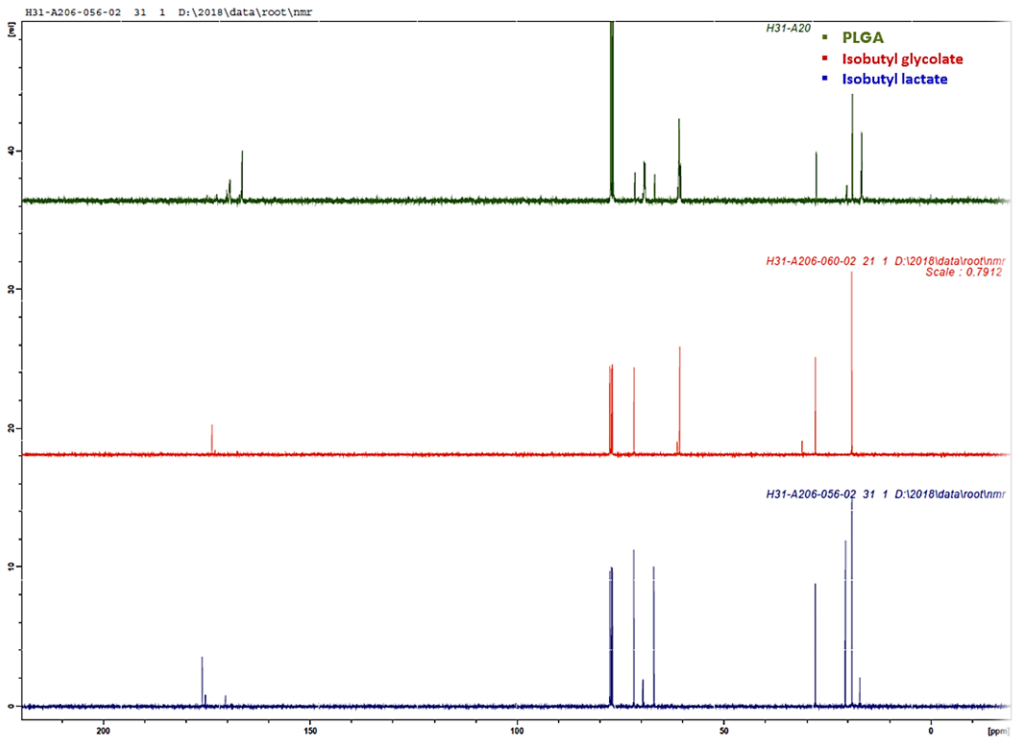


Figure 16: ^{13}C NMR spectrum for PLGA copolymer with respective monomers

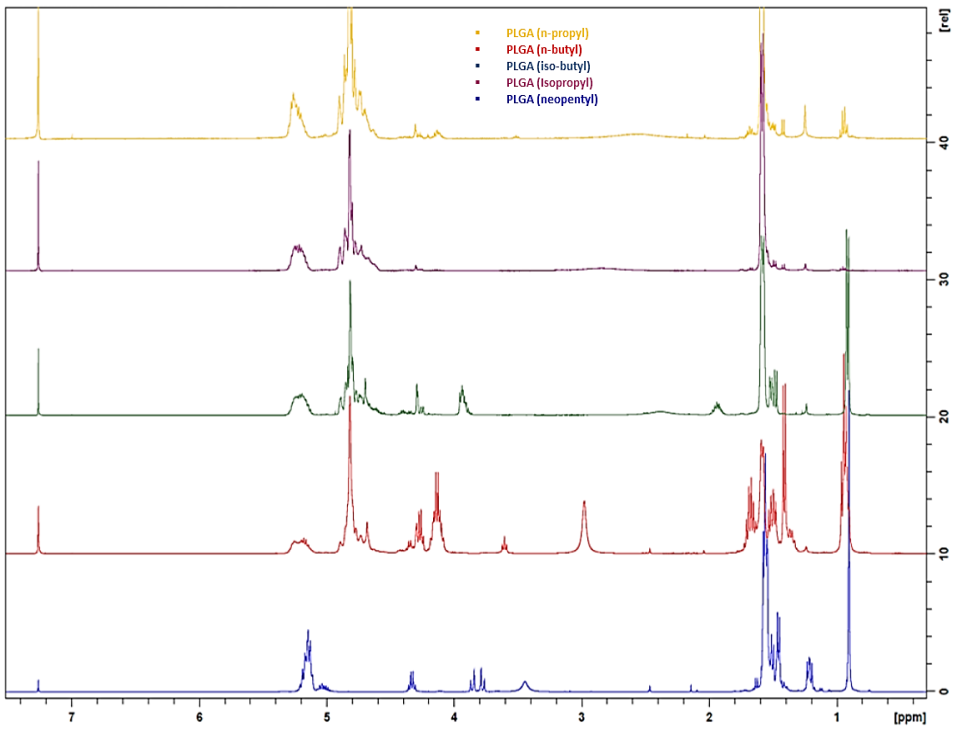


Figure 17: ^{1}H NMR spectrum for PLGA copolymers

Thermal stability of polymers:

Study of thermal stability of polymers was done using Thermogravimetric analysis (TGA). TGA measures the amount of weight loss of a given sample as a function of temperature. It is used to get the information like weight loss or gain due to decomposition, presence of volatiles and moisture content in the given material.

PGA polymers produced from n-propyl and isopropyl esters of glycolic acid got highest thermal stability than isobutyl, n-butyl, neopentyl ester derivatives. These polymers were stable upto 300 °C while others (derived from isobutyl, n-butyl and neopentyl ester) were stable up to around 200 °C. All these polymers degraded completely above 390°C, which is shown in the Figure 18.

All the PLA polymers were less thermally stable compared to PGA and PLGA copolymers and were completely degraded by 390 °C as shown in the fig 19.

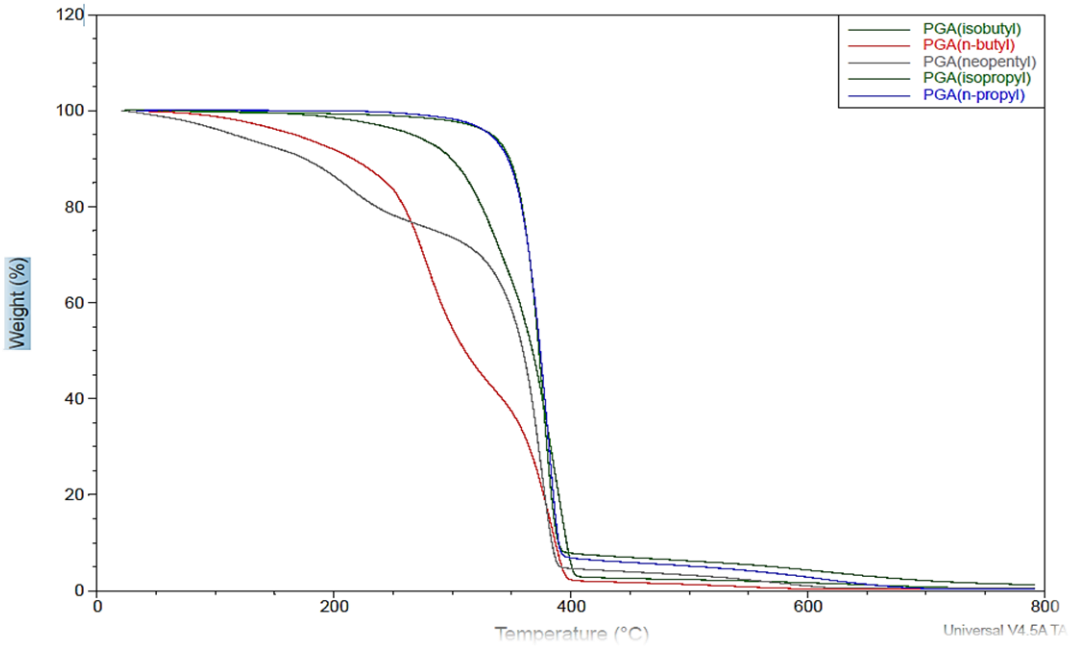


Figure 18: TGA analysis of PGA polymers

All the PLGA polymers were stable upto 250°C and completely degraded by 390 °C, which is shown in the temperature Vs weight% curve figure 20. In the table (2), the 10% weight loss temperature values have been shown.

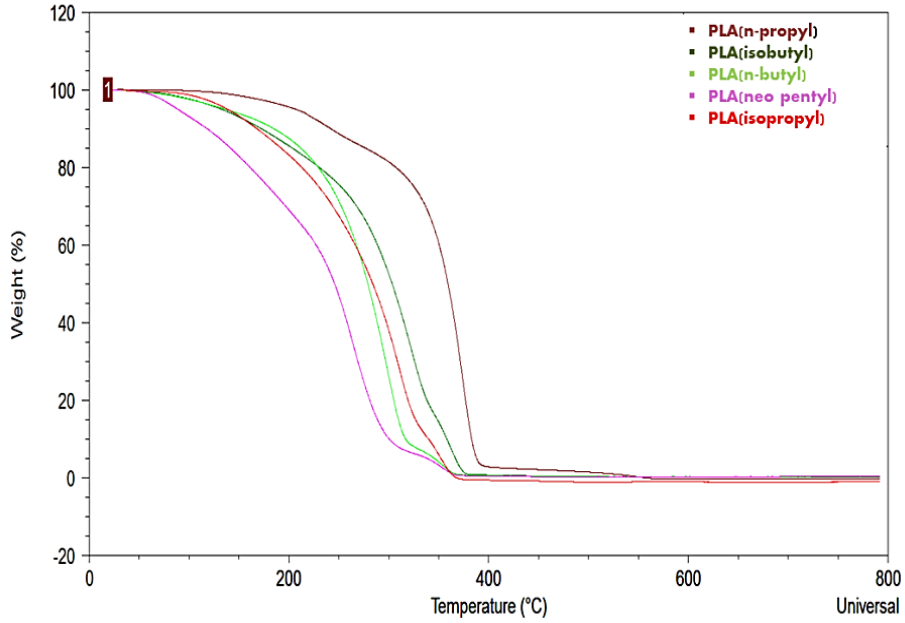


Figure 19: TGA analysis of PLA polymers

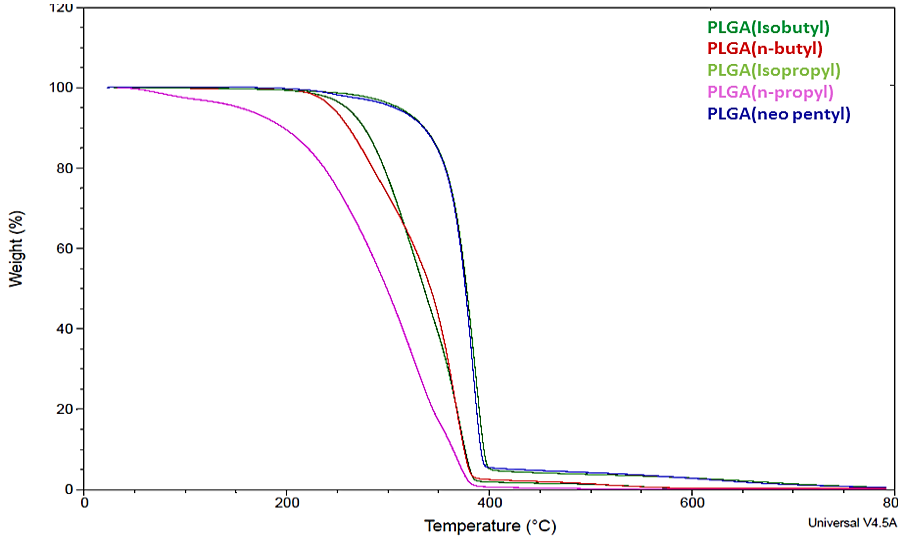


Figure 20: TGA analysis of PLGA polymers

There was a decrease in thermal stability of PLGA polymers derived with higher carbon chain substituted ester monomers than the lower ones, as shown in the curve that PLGA synthesized from propyl and isopropyl ester monomers having more thermal stability than PLGA formed from butyl, isobutyl and neopentyl ester monomers.

Table 2: TGA analysis of PLGA polymers

Polymer	10% wt. loss temperature(°C)
PLGA(n-propyl)	335.43
PLGA(isopropyl)	335.43
PLGA(n-butyl)	260.84
PLGA (isobutyl)	275.39
PLGA(neopentyl)	195.34

DSC analysis of polymers:

Differential scanning calorimetry was done for all the PGA, PLA and PLGA polymers. In this we study the response of polymer when it is heated, by using this technique glass transition temperature (T_g), melting temperature (T_m), crystalline temperature (T_c) of a polymer is obtained. In DSC a given sample is heated with a controlled steady rate such as 10 °C per minute and now heat flow is going to be measured as a function of temperature for the sample. Here temperature Vs heat flow curve illustrates the endothermic and exothermic event during the heating and cooling of the material between 0-400 °C. First endothermic step change gives the glass transition temperature and exothermic event gives melting temperature and during cooling cycle an exothermic peck gives the crystallization temperature for the material.

DSC analysis of PGA polymer derived from isobutyl glycolate is shown in fig. (21), where crystalline temperature (128.8 °C) and melting temperature (182.8 °C) is calculated.

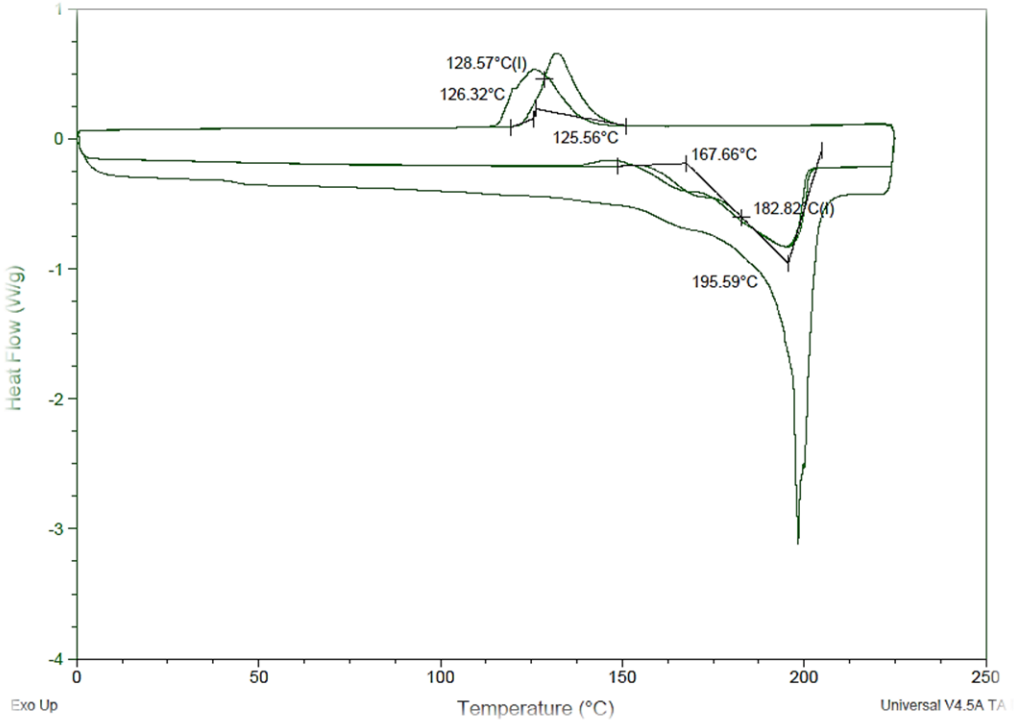


Figure 21: DSC analysis of PGA polymer

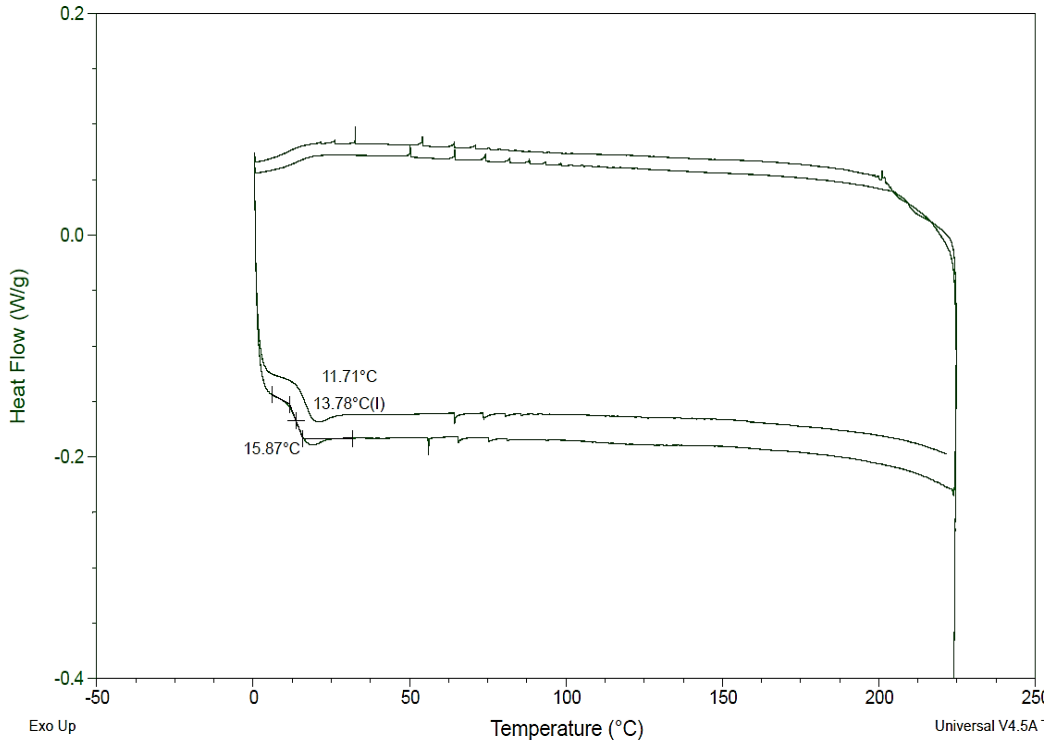


Figure 22: DSC analysis of PLA polymer

Here, PLA polymer synthesized was amorphous in nature and for most of the PLGA copolymers the value of glass transition temperature obtained within the range of 35 – 50 °C.

Molecular weight of polymers:

Molecular weight of all the polymers was obtained using Gel permeation chromatography (GPC), using HFIP as a solvent and polystyrene as a standard. Molecular weight of PLA polymers obtained had less molecular weight than PGA and PLGA polymers, the values are given in the table(3).

Table 3: M_n and M_w values of PLA polymer obtained from on GPC

Polymer	**M_n (g/mol)**	**M_w (g/mol)**	**PDI**
PLA(n-propyl)	4600	8400	1.8
PLA(isopropyl)	1200	1700	1.3
PLA(n-butyl)	1050	1200	1.1
PLA (isobutyl)	1100	1300	1.2
PLA(neopentyl)	1000	1350	1.3

Some of the PGA polymers were not properly soluble; here molecular weights of PGA polymers are shown in the table (4).

Table 4: M_n and M_w values of PGA polymer obtained from on GPC

Polymer	**M_n (g/mol)**	**M_w (g/mol)**	**PDI**
PGA(n-propyl)	not soluble		
PGA(isopropyl)	3800	6900	1.7
PGA(n-butyl)	1500	2100	1.6
PGA (isobutyl)	3400	5700	1.4
PGA(neopentyl)	2300	3000	1.2

Molecular weight of PLGA copolymers obtained from GPC by propyl and isopropyl ester monomers were the highest among all the other ester monomers and Neopentyl ester was lowest. PDI value for all PLGA polymers obtained within the range of 1.2 – 2.4. GPC chromatogram shows the decrease in retention time due to

high hydrodynamic volumes of bigger polymers. M_n, M_w and polydispersity values are given in the table (5).

Table 5: M_n and M_w values of PLGA polymer obtained from on GPC

Polymer	**M_n (g/mol)**	**M_w (g/mol)**	**PDI**
PLGA (n-propyl)	7400	16900	2.2
PLGA (isopropyl)	8900	22000	2.4
PLGA (n-butyl)	2800	4100	1.4
PLGA (isobutyl)	2900	4500	1.5
PLGA (neopentyl)	1900	2400	1.2

From these observations we could say that all polymers molecular weight obtained from higher substituted carbon chain was less in compare to the lower one, reason could be that the removal of the higher carbon chain alcohol was difficult as the boiling point is higher.

Number average molecular weight (M_n) obtained by GPC technique and NMR technique was not same; the value of M_n given by GPC was higher than NMR estimated values. This is called as overestimation of molecular weight and this phenomenon is explained as that GPC works on the principle of calculating hydrodynamic volume. The instrument is first calibrated by a known polymer weight and then depending on the hydrodynamic volume of the polymer we give molecular weight is calculated, here polystyrene was used as a standard. The hydrodynamic volume of PLA, PGA and PLGA polymers some of Mn calculated by NMR may not be same as the hydrodynamic volume of polymers used of same (Mn) so the GPC shows underestimation and overestimation of molecular weights.

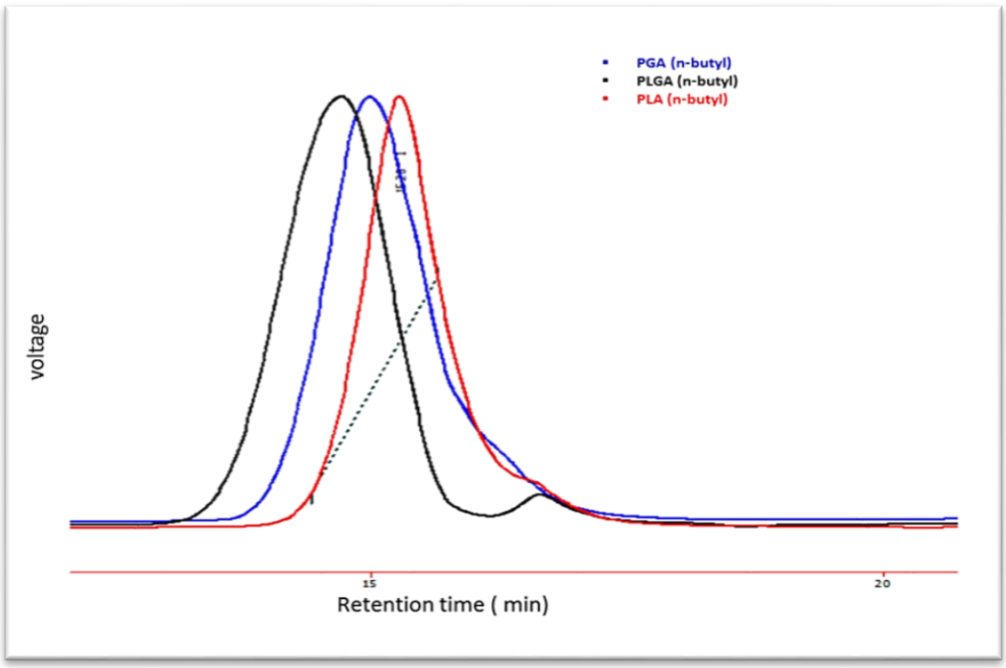


Figure 23: GPC chromatogram for PGA, PLA and PLGA polymer

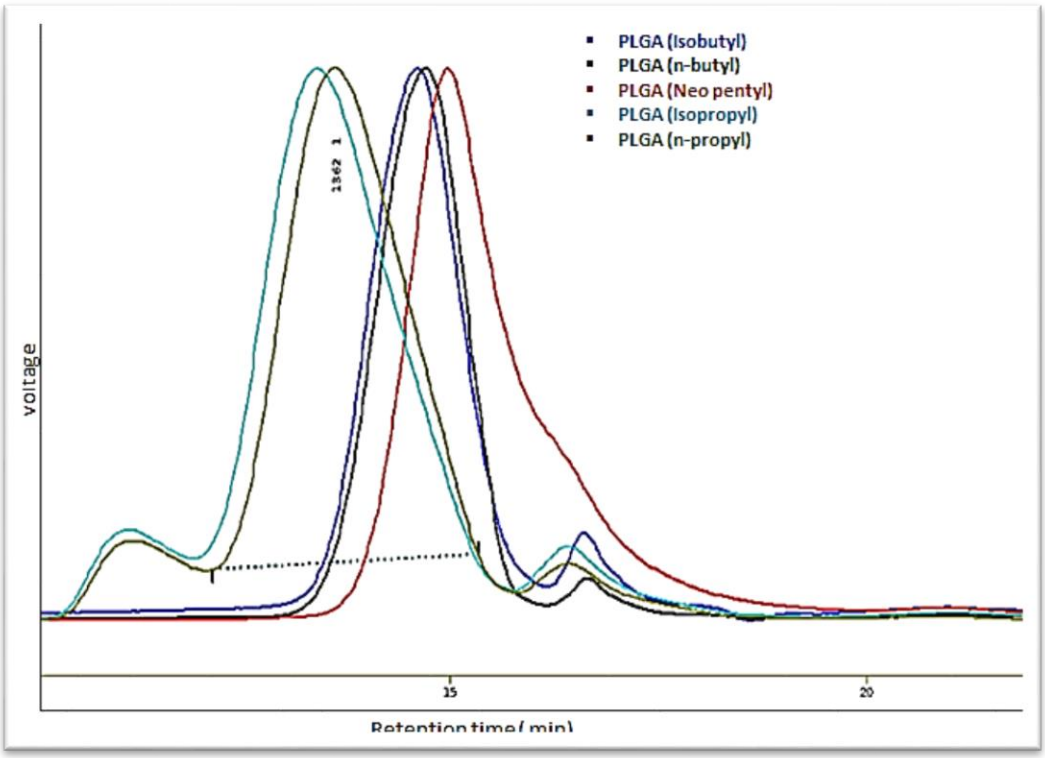


Figure 24: GPC chromatogram of PLGA polymers

5. Conclusion:

Poly lactic acid (PLA), poly glycolic acid (PGA) and copolymer PLGA were successfully synthesized via transesterification using different substitution (methyl, n-propyl, isopropyl, n-butyl, isobutyl, neopentyl) of ester derivatives of lactic and glycolic acid. Both monomers and polycondensation products formed from these reactions were characterized by ^{1}H NMR, ^{13}C NMR, FT-IR, DSC-TGA analysis. Among all the polymers, polymers derived with n-propyl and isopropyl substituted ester derivatives were most thermally stable above 390 °C and had highest molecular weight compared to others.

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MS Thesis Report

(Form for Thesis Supervisor)

Name of the student: _Harshita Soni_____ Reg number___ 20131117__

Title of the Thesis: _Transesterification as a plausible new route for PLGA _____

Review Report

(Please provide your comments below)

The family of PLGA copolymers and homopolymers have traditionally been made by the R.O.P. of the cyclic dilactones, i.e., lactide & glycolide. There are a number of limitations to this approach, so Harshita was given the task to look at transesterification as a plausible route for the preparation of the copolymers and homopolymers of PLGA family. This project involved significant synthesis & purification of the monomers, followed by polymerization under different conditions in order to obtain a good polymer. Harshita did a good job in taking up this interesting challenge, and delivering good results. She has shown that, it is indeed possible to look at transesterification as a plausible route to make PLGA and PGA. The preliminary results which originated from her work are very encouraging.

Harshita has prepared a number of esters of lactic and glycolic acids by reacting lactic and glycolic acids with the corresponding alcohol. Once the esters were made, the challenge was to polymerize them using appropriate transesterification catalyst. After screening a number of catalysts, methane sulfonic acid (MSA) was found out to be the best catalyst for this process. She showed that the thermal properties of PLGA and PGA prepolymers prepared from certain esters, viz. n-propyl esters, were comparable to those prepared via direct polycondensation of the α-hydroxy acid monomer(s). Her results are quite exciting from the industry point of view, since they open up different vistas of synthesis of this important biodegradable & biocompatible family of polymers.

During her stint at my lab as MS intern, I was observing whether she is able to adapt to the challenges of doing research in a constrained environment, such as a chemical industry, where the safety norms are followed very strictly, and the working hours are restricted. Harshita was quick to the task, by doing her work in a safe and diligent manner. She also managed to plan her work and finish it during the normal work hours of Solvay Research & Innovation centre, Vadodara. She was quite perseverant, which permitted her to learn from a bunch of failed reactions during a significant number of initial days. She was sincere, hard-working, and calm, which helped her to get blended with the team quite quickly.

G. Padmanaban

Date: 23 April 2018 Signature of the Supervisor

Place: Vadodara Name: G. Padmanaban

(a) Please save this report as .pdf file and upload in SAM under report

(b) Marks out of 100(for a weightage of 20%) for continuous evaluation and for thesis are to be uploaded directly in SAM. Please do not indicate or include marks in this report.

MS Thesis Report

(Form for TAC Examiner)

Name of the student: **Harshita Soni** Reg Number: **20131117**
Title of the Thesis: **Transesterification as a plausible new route for PLGA**

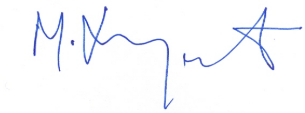
Review Report

(Please provide your comments below)

Harshita has developed the melt transesterification polycondensation reaction for poly(L-lactide)s and poly(L-glycolide)s which are important classes of industrial biodegradable polymers. L-lactic acid and L-glycolic acid were converted into carboxylic esters and self-polycondensed to yield the polymers. The structures of the monomers and polymers were characterized by 1H and 13C-NMR spectroscopy. The molecular weights were determined by GPC. It is interesting to see the that the molecular weights of the polymers could be tuned depending upon the carboxylic ester monomer employed in the polymerization reaction. More efforts towards the kinetics of the polymerization or end group analysis by MALDI-TOF would have provided significant insight into the molecular weight building process. Further, the molecular weights reported in tables 3 to 5 should be corrected to two digit; for example, the values in 4604 in table 3 should read as 4600 g/mol. Further, the molecular weights should be given units as g/mol. Her contribution in the development of PLGA and PLLA are significant and I strongly recommend his thesis work for awarding MS degree

Recommendations (Please tick (√) appropriate choice)

(i) Recommend in the present form



Date: 24.4.2018

Signature

Place:

Name: M. Jayakannan