[UCI]I804:21031-200000605636

Thesis for the Degree of Master of Engineering

Degradation control of biodegradable Poly(lactide)s by physical and chemical modifications

by

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February 2022

Degradation control of biodegradable Poly(lactide)s by physical and chemical modifications
(폴리락타이드의 물리적·화학적 개질을 이용한 분해성 조절)

Advisor : Prof. Won-Ki Lee

by

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A thesis submitted in partial fulfillment of the requirements
for the degree of

Master Engineering

in Department of Polymer Engineering, The Graduate School,
Pukyong National University

February 2022

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February 25, 2022

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김가연

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요약

생분해성 고분자 polylactides (PLAs)의 분해성은 상업적 응용 분야에 있어서 제품의 수명에 큰 영향을 미친다. 이러한 분해성을 제어하기 위해, 친수성 glycolide를 lacitde와 공중합하여 poly(lactide-co-glycolide) (PLGA)를 합성하였다 본 연구에서는 PLGA monolayer의 효소 분해와 가수분해 속도를 Langmuir 기법을 이용하여 glycolide 조성에 따른 분해성을 체계적으로 연구하였다. 알칼리분해에서는 PLA보다 친수성의 증가로 공중합체에서 더 빠른 분해성을 보였다. Proteinase K가 l-LA에 선택적으로 분해를 시킴에도 불구하고 PLGA monolayer는 l-PLA monolayer보다 더 빠른 효소 분해성을 보였다.

생분해성 고분자인 poly(butylene succinate) (PBS) 는 길이가 긴 유연한 사슬로 이루어진 연성 고분자로 빠른 가수 분해 특성을 보였다. PBS의 유연성과 강도를 보완하기 위해 이를 개질시킨 poly(butylene succinate-co-butylene adipate-co-ethylene succinate-co-ethylene adipate) (PBEAS) 가 개발되었다. 상대적으로 느린 가수 분해성을 갖는 PLA를 이용하여 l-PLA/PBS와 l-PLA/PBEAS 혼합물의 가수 분해 거동과 상용성을 분자 수준에서 연구하였다. PBS와 PBEAS의 가수분해 속도는 l-PLA의 함량을 조절하여 조정할 수 있으며 생분해성 고분자 간의 상용성이 가수분해에 영향을 미치는 것을 알 수 있었다.

목적에 맞는 생분해성 고분자를 설계하기 위해서는 이러한 초기 분해성 조절에 관한 연구가 선행되어야 한다. 실제 분해는 고분자의 매우 얇은 표면층에서 시작되기 때문에 해당 연구에서는 Langmuir 기술을 이용하여 분자 수준에서 초기 분해성을 연구하였다. 생분해성 고분자 단분자을 이용하여 transition 압력이나 온도, 분해 매체 등을 변화하여 연구함으로 짧은 시간에 분해거동을 이해함으로써 새로운 생분해성 고분자의 상업적 설계에 기초자료로 활용할 수 있을 것이다.

Chapter 1. Introduction

Petroleum-based polymers have been widely used because of their favorable properties of durable, lightweight, and inexpensive materials. However, huge wastes from non-degradable and disposable plastics, which have toxic pollutants, cause serious environmental problems in plants, animals, and humans for a long time. Overall, in the USA, the number of recycled plastics is relatively small-three million tons for an 8.7 percent recycling rate in 2018 (The United States Environmental Protection Agency) [1]. Most of the corrected ones are ends up in landfills or incineration. Some discarded plastics are recognized as a severe anthropogenic issue in coastal and marine ecosystems.

Plastics made from fossil funnels require a lot of energy for synthesis and processing which results in global warming [2-4]. Additionally, disposal of plastic wastes by landfill and incineration has resulted in soil pollution and toxic gases, respectively. To minimize these issues, degradable and renewably derived polymers are significantly captivated in the fields of biomedical and commercial applications. The most widely researched biodegradable polymers are poly(lactide) (PLA), poly(butylene adipate terephthalate) (PBAT), poly(glycolide) (PGA), poly(e-caprolactone) (PCL), and poly(butylene succinate) (PBS), which have nontoxicity and biocompatible properties [5-8]. These biodegradable polyesters are usually degraded by enzymatic or hydrolytic degradation of an ester bond or both, leading to low molecular weight oligomers, dimers, and monomers and finally mineralized to CO_2 and H_2O [5-10]. However, it is imperative to control the degradation rate of degradable polymers for pharmaceutical or commercial applications. The 1-2 % of weight loss of bio polyesters has a dramatic effect on the service life because their mechanical properties decreases to 66 % [9]. Accordingly, the mechanical properties of bio-polyesters are rapidly loose amid the initial degradation. Therefore, tuning the degradation rate of bio polymers during the applications is receiving more consideration and it can be regulated by chemical or physical modifications like copolymerization, blending, plasma processing, and specific interactions.

The use of PGA is limited by its hydrolytic instability and insolubility in most organic solvents. Thus, it is copolymerized with LA, which has a relatively slow degradation rate to use in the field of drug delivery polymers as nanocarriers, sutures, implants, and medicine as an absorbent material widely. The various application of PLGA in the pharmaceutical industry has increased as numerous drug delivery formulations due to its biocompatibility, biodegradability, and tunable degradation properties. Additionally, it is possible to control the solubility and thermal properties of the PLGA copolymer by changing the lactide/glycolide ratios, molecular weight, and end-cap functional groups of the starting material [14].

Although there are numerous studies on the degradation of PLGA, very few studies have been conducted at the molecular level [15-17]. It is important to analyze the initial degradation behavior at the molecular level using the Langmuir monolayer because the degradation starts in a very thin surface layer of biopolyester. In this study, PLGA monolayer films have been investigated at the air/water as functions of degradation medium, alkaline, enzyme, and surface pressure. This study aimed to collate research on optimizing the synthesis procedure by changing parameters like the lactide/glycolide ratios that can affect the degradation behaviors at the molecular level, and therefore a great deal of deliberation should go for designing the system for the specific implementation and can be expanded to a broader range of commercial applications.

Apart from that, we focused on the blending of polyesters polymers also for potential applications. Generally, most of the wasted fishing nets (WFN) are made of polyamide (nylon6), polyethylene (PE), or polypropylene (PP), and these do not be degraded for centuries. These plastics in the ocean not only damage habitats or cause marine safety accidents, but they can also negatively impact the marine ecosystem through 'ghost fishing' - the accidental or intentional loss of fishing gear [26]. Since biodegradable PBS has soft and fast hydrolytic properties, its commercial application was limited. To improve its weak points, a modified poly(butylene succinate-co-butylene adipate-co-ethylene succinate-co-ethylene adipate) (PBEAS) and mixtures with other biopolymers are developed. In this study, we prepare the mixtures with the biodegradable l-PLA, which has a relatively slow degradation rate and investigated the compatibility and hydrolytic behavior of the l-PLA/PBS and l-PLA/PBEAS mixtures by the Langmuir system at the air/water interface.

Chapter 2. Theoretical background

2.1. Biodegradable polymers

Degradable polymers generally refer to polymers that are decomposed by microorganisms or light and are largely divided into disintegrable plastic, photodegradable polymers, and biodegradable polymers. Biodegradable polymers are mainly degraded at main chain bonds that can be hydrolyzed by microorganisms in water or soil, and as the degradation progresses, the molecular weight is reduced and finally regenerated into monomers or degraded into water and CO_2 (Figure 1). Mostly, these polymers can be found both naturally and synthetically made, and consist of amide, ester, urea, and urethane groups in the main chain (Figure 2). Biodegradable polymers have properties and degradation mechanisms according to their exact structure. Among them, aliphatic polyesters obtained from microorganisms or chemical synthesis are concerned because they exhibit sufficient degradability while having physical and chemical properties.

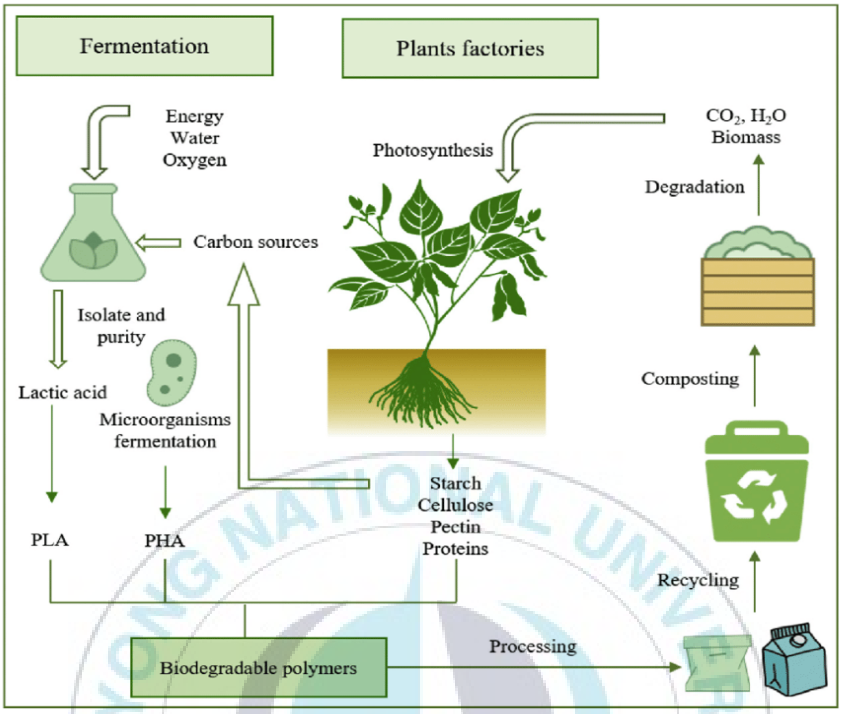


Figure 1. Cyclic biological process of biodegradable polymers [27].

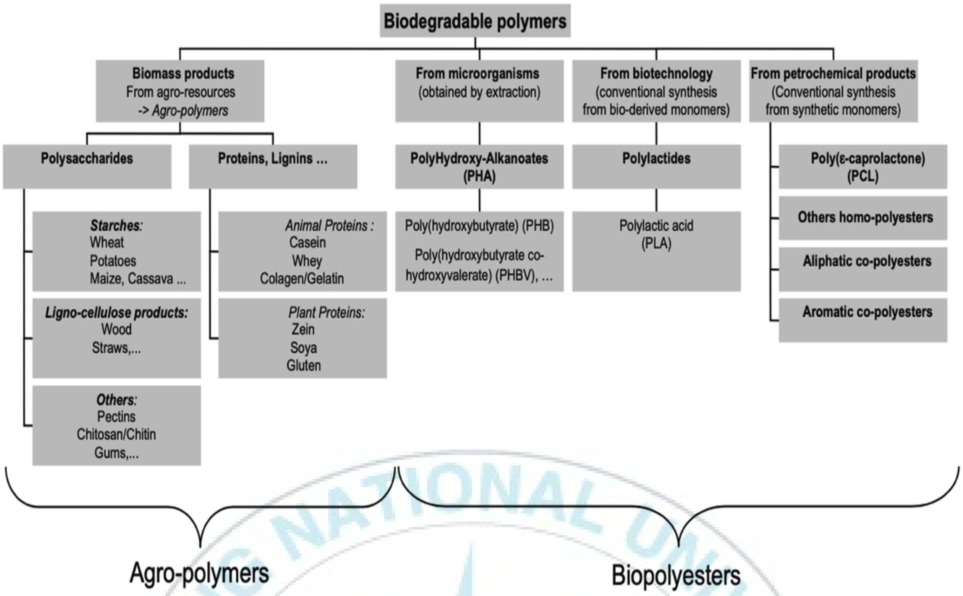


Figure 2. Classification of main biodegradable polymers [28].

2.2. Polylactide

Bio-degradable PLAs are produced from renewable resources such as corn, cassava, sugarcane, or other fermented plant starch (Figure 3). Since energy can be saved by about 30 % and CO_2 emission can be reduced to 1/6~1/10 compared to petroleum-based plastic, the prospect of PLA is brighter as a countermeasure in following the CO_2 emission policy (Table 1). PLA is degraded abiotically or by enzymes such as protnase and most effectively proteinase K from Tritirachium album. In addition, PLA is used in a large variety of consumer products (disposable products) and medical applications due to non-toxicity and biodegradability.

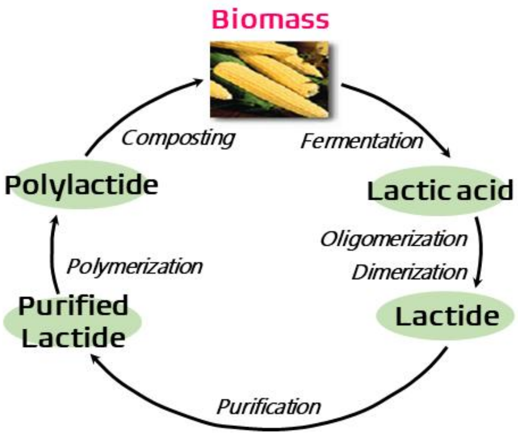


Figure 3. Schematic representation of PLA production [29].

Table 1. Resources to make 1 pound of polymer material

Resin	Energy	Emission	Water
PLA(Corn)	7.39 kWh	0.27 lbs of CO2	8.29 gallons
PP(Plastic)	9.25 kWh	1.7 lbs of CO2	5.16 gallons
PET(Plastic)	10.17 kWh	2.8 lbs of CO2	7.44 gallons
Styrofoam	11.17 kWh	2.5 lbs of CO2	20.53 gallons

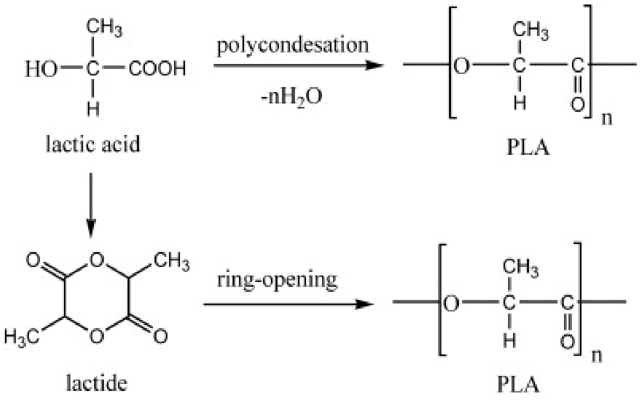
2.2.1. Synthesis of PLA

PLA can be synthesized with lactic acid or lactide monomers using two major polymerization routes (Scheme 1).

1) The direct condensation of lactic acid monomers is carried out in bulk by distillation of condensed water, with or without catalyst. Because the condensation reaction is reversible, it leads to low molecular weight and poor mechanical properties. Therefore, the removal of water is needed to gain high molecular weight.

2) Ring-opening polymerization of lactide is the most common route to PLA. The end-points of polymer chains address lactide monomers to form the longer polymer chains using a metal alkoxide as Sn-based or Zn-based catalyst, resulting in high molecular weight PLA.

In addition, there are two different methods of ring-opening polymerization, bulk polymerization and solution polymerization. The bulk polymerization method is simple and widely used in industries at the commercial scale to obtain a high molecular weight polymer. However, it is very challenging to control the molecular weight because of the automatic acceleration reaction in absence of solvents. Although, the solution polymerization method is easier to control polydispersity index (PDI) by adjusting the reaction time, temperature, amount of solvent, and catalyst concentration (Figure 4).



Scheme1. Routes of poly(lactic acid) (PLA) synthesis from lactic acid [30].

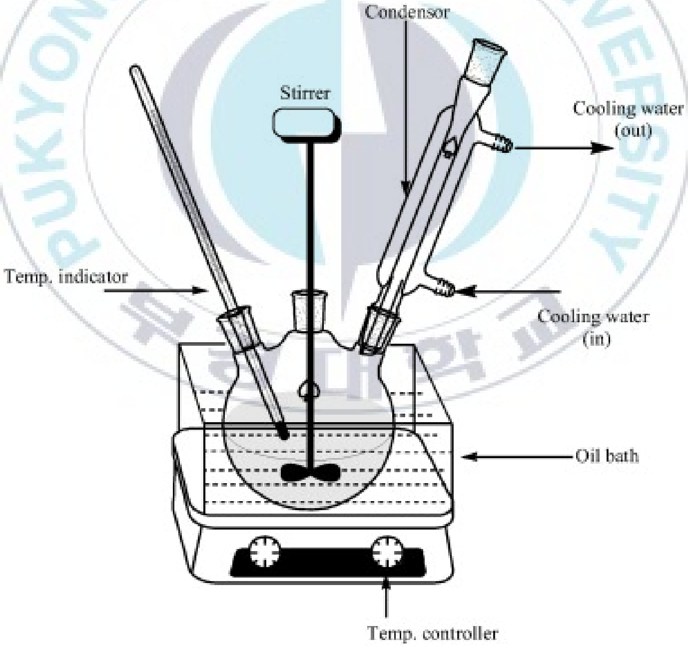
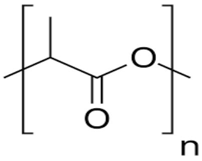


Figure 4. Synthetic tools for solution polymerization of PLA [31].

2.2.2. Properties of PLA

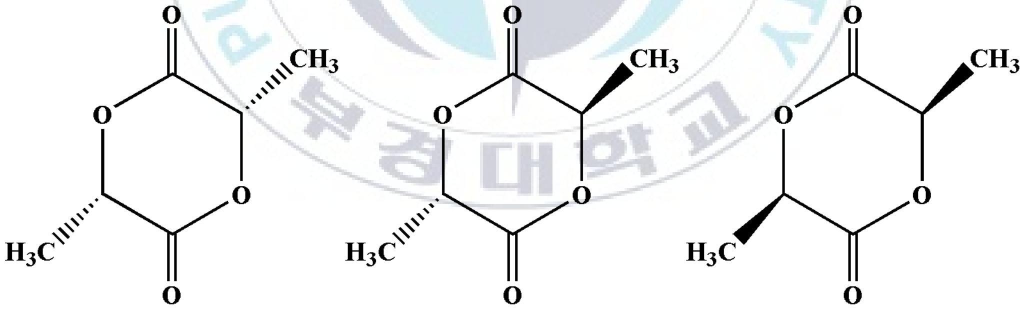
PLA is widely used as biopolymer for several applications because it has a similar melting temperature to commercial plastic and excellent properties (Table 2). Most of the PLA are semi-crystalline polymers with 55 ~ 65 ℃ glass transition temperature and melting point ca. 175 ℃. However, it is brittle that is not accordant with many applications. To overcome these weak points, physical and chemical modifications, copolymerization, blending, alloying, or adding additives and fillers have been designed.

Table 2. Properties of PLA

PLA	Properties
Structural formula	
Chemical formula	$(C_3H_4O_2)_n$
Density	1.210~1.430 g/cm^3
Melting temperature (T_m)	150~180℃
Glass transition temperature (T_g)	50~65℃
Crystallization temperature (T_c)	100~120℃

2.2.3. Stereochemical PLA

Lactides have three isomers of L, D, and meso types due to the chiral nature of lactic acid (Figure 5). Therefore, it is possible to synthesize PLAs having various properties and crystalline structures through copolymerization of stereochemical lactides. Furthermore, stereocomplex can be formed by blending of equimolar l-PLA and d-PLA. It represents high heat resistance, tensile strength, and the resistance to degradation increased.



L-lactide Meso-lactide D-lactide

Figure 5. Stereoisomeric forms of lactide.

2.3. Poly(glycolide)

PGA, which is the simplest linear and aliphatic polyester, is a biodegradable and thermoplastic polymer. PGA is mainly used in copolymerization with lactic acid, ε-caprolactone, and trimethylene carbonate because of its insolubility of common solvents and hydrolytic instability. They are widely used as materials for absorbable sutures and are being evaluated in the biomedical field.

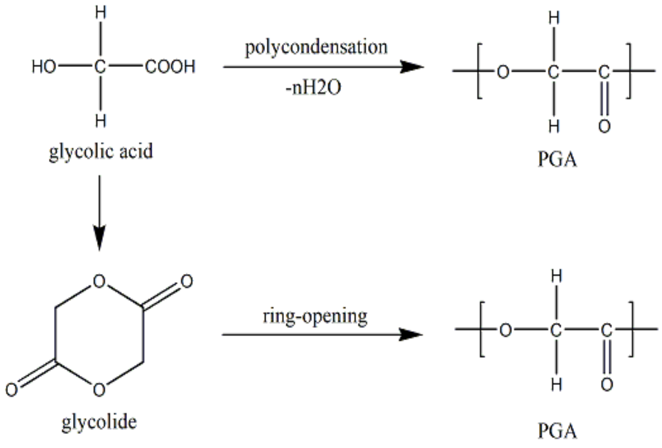
2.3.1. Synthesis of PGA

PGA can be synthesized through different monomer types with different materials (Scheme 2).

1) Polycondensation of glycolic acid is heated at atmospheric pressure and temperature of about 175-185 ℃ until water ceases to distill. Then pressure is reduced, keeping the temperature for about two hours. As a result, the low molecular weight PGA is obtained.

2) Ring-opening polymerization of glycolide can produce a high molecular weight. Sn-based catalyst is the most commonly used initiator since it is approved by the FDA (Food and Drug Administration).

3) Solid-state polycondensation of halogenoacetates results in the PGA and small crystals of salt. Polycondensation is heated at the temperature of about 160-180 ℃ with halogenoacetates, like sodium chloroacetate. While the reactions are in progress, the salt can be removed by washing the product with water.

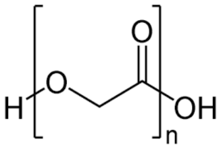


Scheme 2. Routes of poly(glycolic acid) (PGA) synthesis from glycolic acid.

2.3.2. Properties of PGA

PGA has a similar structure to PLA but different degradability, physical and mechanical properties (modulus 7 GPa) due to the absence of methyl group on the alpha carbon [9]. Furthermore, PGA has a high degree of crystallinity (45-55 %), high thermal properties (Tm 225-230 ℃), and high gas barrier properties (Table 3) [10]. However, the use of PGA is limited by its hydrolytic instability and insolubility in most organic solvents. Thus, it is copolymerized with PLA, which refers to Poly(lactide-co-glycolide) (PLGA) synthesized from its constituent monomers lactide and glycolide. The various application of PLGA in the pharmaceutical industry can control the degradation properties by varying the ratio between its monomers.

Table 3. Properties of PGA

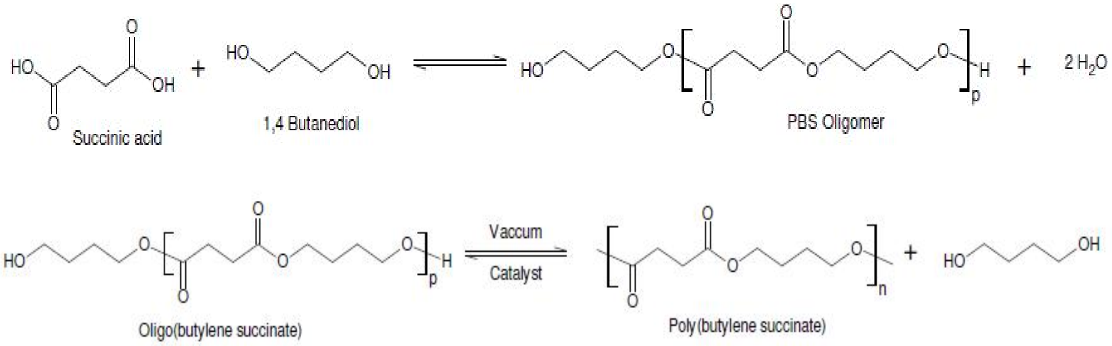
PGA	Properties
Structural formula	
Chemical formula	$(C_2H_2O_2)n$
Density	1.530 g/cm^3
Melting temperature (T_m)	225~230 °C
Glass transition temperature (T_g)	35~40℃
Crystallization temperature (T_c)	130℃

2.4. Poly(butylene succinate)

PBS is a biodegradable polyester, semi-crystalline thermoplastic, and cost-efficient alternative. It has excellent melt processability, biodegradability, chemical, and thermal resistance. PBS can be used in the field of textiles into melt blow, multifilament, monofilament, flat, and also in the field of plastics into injection-molded products, and in the medical field. Otherwise, PBS is widely used for food packaging, plant plots, fishing nets, and fishing lines. Therefore, PBS is a promising polymer for various potential applications.

2.4.1. Synthesis of PBS

PBS has two main routes for synthesis (Schem 3): The esterification process from succinate diesters and the direct esterification process from the diacid. Commonly, the direct esterification of succinic acid with 1,4-butanediol is widely used to obtain PBS. It consists of a two-step process. First, esterification occurs between the excess of diol and the diacid with the elimination of water. Second, these oligomers are trans-esterified with a catalyst such as titanium, zirconium, tin, or germanium derivatives under a vacuum state.

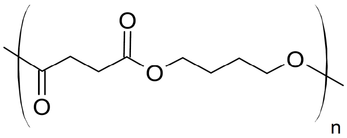


Scheme 3. Synthetic routes of PBS (Up: Step I, Down: Step II).

2.4.2. Properties of PBS

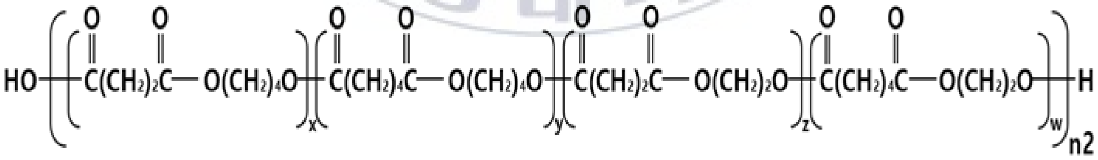
PBS has biodegradability, good melt processability, and high heat resistance, and compatibility with a fiber (Table 4). PBS has much more flexible since it has a lower melting point (115~160 ℃) and glass transition temperature (-45~10 ℃). Therefore, it is possible to gain the performance which can't be shown by itself as the compound with other resin and materials. The mechanical properties are comparable with those of widely used high-density polyethylene and isotactic polypropylene.

Table 4. Properties of PBS

PBS	Properties
Structural formula	
Chemical formula	$(C_8H_{12}O_4)_n$
Density	1.26 g/cm^3
Melting temperature (T_m)	115~160℃
Glass transition temperature (T_g)	-45~10℃
Crystallization temperature (T_c)	100~120℃

2.4.3. Poly(butlyene succinate-co-butlyene adipate-co-ethylene succinate-co-ethylene adipate)

The conventional PBS fishing nets used must be more flexible, stiff, and mechanically robust for a specific purpose. Thus, PBEAS which was modified from PBS was developed by adding adipic acid and ethylene glycol by the ANKOR Bioplastics (Korea) as shown in Figure 6. It is an eco-friendly bioplastic for fisheries and has suitable properties as fishing nets materials and price competitiveness.



$$HO\left[\left(\overset{O}{\overset{\|}{C}}(CH_2)_2\overset{O}{\overset{\|}{C}}-O(CH_2)_4O\right)_x\left(\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}-O(CH_2)_4O\right)_y\left(\overset{O}{\overset{\|}{C}}(CH_2)_2\overset{O}{\overset{\|}{C}}-O(CH_2)_2O\right)_z\left(\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}-O(CH_2)_2O\right)_w\right]_{n2}H$$

Figure 6. Structure of PBEAS.

2.5. Langmuir-Blodgett films

Langmuir-Blodgett film is a thin organic film with one molecular thick formed nanometer-scale system. These films can have different electrical, optical, and biological properties. Thus, it is very useful to create functional coatings, sensors, and biological membranes. Recently, it has been demonstrated that Langmuir‐Blodgett is an effective technique even to produce ultra-thin films of emerging two-dimensional layered materials on a large scale. Langmuir forms monolayers when the materials possess a hydrophilic head-group, which is water-soluble, and a hydrophobic tail-group in the molecule. A polymer for monolayer should be soluble in a hydrophobic solvent with low boiling temperature and is covered on the water when the solution dropped on the water (Figure 7). At this time, the solvent evaporates and monolayers are formed at the air/water interface. Since most biodegradable polyesters have hydrophilic/hydrophobic balance, they can be applied in the Langmuir system (see Figure 7).

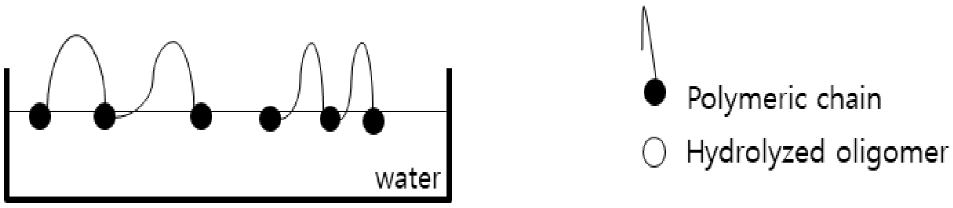


Figure 7. Monolayer of polymer on a water surface.

2.5.1. Surface Pressure-Area Isotherms

Surface pressure-area (π-A) isotherms have the mammoth advantage for studying the polymer monolayers on a subphase of deionized water. This surface pressure is defined as the differentiation between the surface tension of water and surface tension in the presence of a monolayer of the material, which was measured by the Wilhelmy method [19]. Particular orientation and packing of molecules on the subphase surface correspond to the specific state as follows (Figure 8) :

i) In the gaseous phase, the molecules are far apart as the notably decompressed monolayers formed without any orientation and interaction between the molecules. ii) As increasing surface pressure, the molecules approach each other and the interactions between them occur. But they are not properly arrayed, suggesting the transition from gaseous to a liquid expanded state (LE). iii) As the barrier moves further with more pressure, it leads to a phase transition from the liquid expanded state to the liquid crystal phase. The interaction between the molecules becomes stronger and the molecules are oriented into densely packed packings of crystalline domains to form liquid crystalline (LC) phase. The plateau region in the isotherm depicts the coexistence of LE-LC, and it means a transition of phase and formation of three-dimensional structure [2,23].

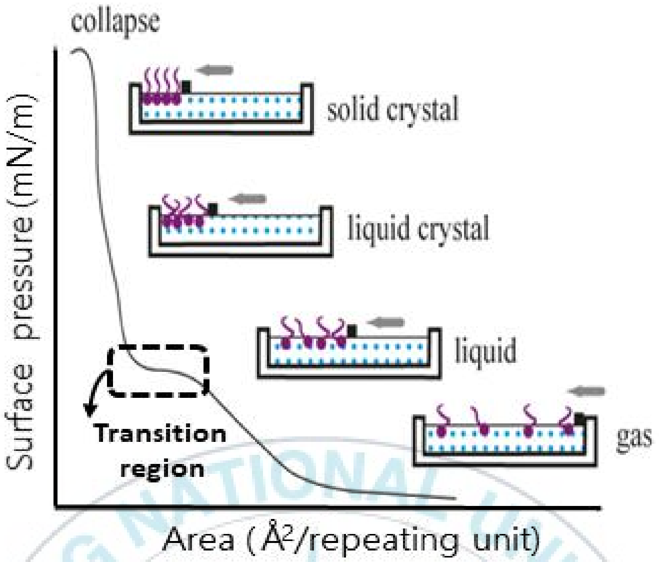


Figure 8. Surface pressure-area (π-A) isotherms of monolayers.

2.5.2. Kinetic curve

Langmuir system allows a fast and beauteous route to determine the hydrolytic kinetics of biodegradable polymers at a molecular level [4-6, 24]. The state of the biodegradable polymer monolayer was monitored and analyzed on a Langmuir trough (Figure 9). To study the hydrolytic degradation of monolayers, a dilute polymer solution with a volatile solvent was spread on a subphase. After compressing monolayers by the barrier to a surface pressure, the occupied area of the chain segments at a constant surface pressure decreases during the degradation since the biopolymers are from a water-soluble by-product. Therefore, A/A_0 value with time reflects the hydrolytic rate, where A and A_0 mean the occupied areas at time t and 0, respectively. The degradation medium in a subphase can be controlled by the concentration of enzyme and active ion.

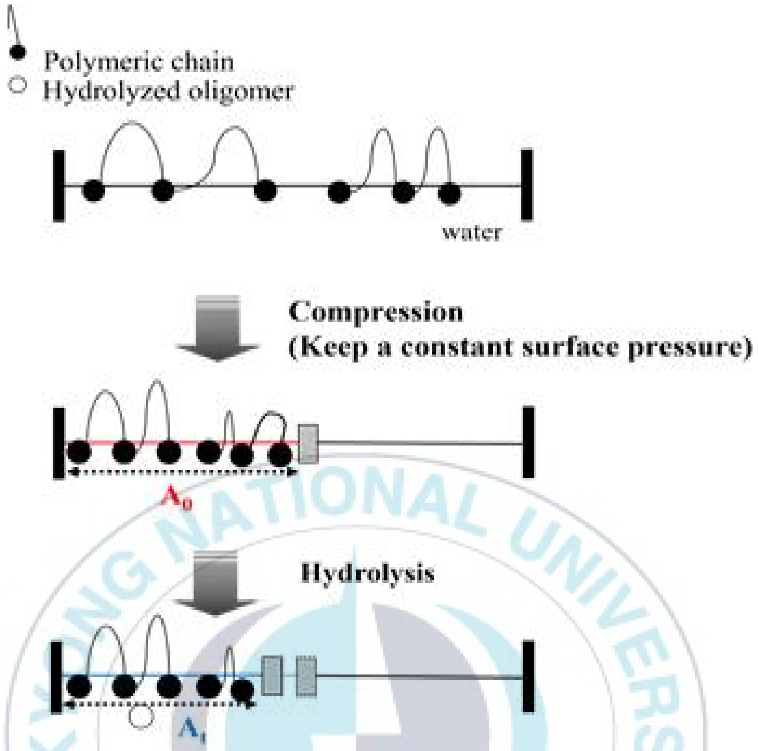


Figure 9. Schematic representation of hydrolyzable polymeric monolayers on the water subphase.

2.6. Control of the degradation rate

In the case of biodegradable polymers, mechanical properties are rapidly lost when degradation begins. Therefore, the initial degradation rate is an essential factor in determining the life of a product in commercial application. The main factors affecting the hydrolysis or biodegradation rate of biodegradable polymers (homo- and copolymers) include molecular weight, comonomer and composition, crystallinity, and crystalline size, tchain orientation, etc. Therefore, the degradation rate can be controlled by copolymerization, blending, plasma processing, or specific interactions.

2.6.1. Copolymerization

A copolymer is composed of two (or more) species of monomers unit. The properties of copolymer depend strongly on how these units are arranged along the chain. There are classified into linear copolymers (including alternating copolymers, random copolymers, block copolymers) and branched copolymers (including graft copolymer, star-shaped copolymer). The composition and type of the copolymer depend on these reactivity ratios rA of monomer A and rB of monomer B and follow the Mayo-Lewis equation. Much research has been studied with regards to the degradation according to effects of incorporation comonomer, such as hydrophilic comonomer and hydrophobic comonomer.

A-A-B-B-B-A-B-A-A-B-B-A	Random copolymer
A-B-A-B-A-B-A-B-A-B-A-B	Alternated copolymer
A-A-A-A-A-A-B-B-B-B-B-B	Block copolymer
A-A-A-A-A-A | B-B-B-B-B-B	Graft copolymer

Figure 10. Type of copolymers.

2.6.2. Blend

Polymer blends are blended physical mixtures of two or more polymers. The purpose of the blend is to improve the disadvantage of the conventional polymers and create new materials. Polymer blends can largely be divided into three categories: immiscible polymer blends (heterogeneous), compatible polymer blends, miscible polymer blends (homogeneous). To obtain better properties by blending, the mixtures should exhibit some compatibility or miscibility. Typical methods to confirm the compatibility of polymer blends include thermal behavior of glass transition temperature (DSC, DMA), morphology (SEM, TEM, AFM), and measurement of the optical clarity. Blending with biopolymers shows a good biodegradable and effective way to modify its properties. Also, it may be a much easier and faster way to achieve property compared to copolymerization.

Chapter 3. Degradation behavior of poly(lactide-co-glycolide) monolayers

3.1. Experimental

3.1.1. Materials

The l- and d-lactide were purchased from Purac (The Netherlands). Glycolide and Tin (II) 2-ethylhexanoate were purchased from Sigma-Aldrich (USA). Chloroform, toluene, and methanol were obtained from Samchun (Korea). All chemicals were of reagent grade and without further purification.

The alkaline hydrolysis of monolayers was carried out by adding NaOH (Icatayama Chemicals, Japan) to maintain the pH subphase. Furthermore, the enzymatic degradation of monolayers was carried out in 25 mM Tris-HCl buffer (pH8.6) with proteinase K from Tritirachium album (Sigma-Aldrich, USA). The pH of the buffer solution was adjusted by adding HCl solution (Samchun, Korea), and the pH of all solutions was measured using an electrode-equipped pH meter.

3.1.2. Synthesis

PLGAs were synthesized by ring-opening bulk polymerization of lactide and glycolide with the presence of tin (II) 2-ethylhexanoate as a catalyst. Weighed amounts of lactide, glycolide and 2 wt% of catalyst were added to the polymerization vessel, and it was carried out in a vacuum-sealed vessel at 140 ℃. Although a bulk polymerization method is simple and widely used in industries at the commercial scale to obtain a high molecular weight polymer, it is very challenging to control the molecular weight because of automatic acceleration reaction in absence of solvents. However, the solution polymerization method is easier to control a polydispersity index (PDI) by adjusting the reaction time, temperature, amount of solvent, and catalyst concentration. Many experimental conditions and variables were changed to obtain a desired molecular weight polymer.

For solution polymerization, a total of 5 g of lactide and glycolide was added to the 250 ml round bottom flask. Briefly, weighed amounts of lactide, glycolide, and 500 ㎕ of catalyst tin (II) 2-ethylhexanoate (7 wt% of monomer) were added in 15 ml of toluene. Toluene is selected as a solvent for polymerization because the high boiling point and the chain transfer constant value are lower than other solvents. The higher chain transfer constant of the solvent directly affects the final molecular weight of the polymer, which results in a decrease in the degree of polymerization. The flask was heated in an oil bath to 110 ℃ and allowed to react for 24h. Although the reaction temperature exceeded

110 ℃ or higher, a condenser was usedto prevent the evaporation of the solvent. After polymerization, the resultant product was dissolved in 15 ml of chloroform solvent and non-solvent methanol was used to precipitate for removing unreacted monomers. The final polymerized product was collected by filtration and desiccated under a vacuum. However, the glycolide composition over the 20 mol% was not dissolved in the toluene due to its high crystallinity, and thus, the bulk polymerization method has been used for synthesizing the PLGA over 20 mol% of glycolide content.

3.1.2. Measurement

The number of average molecular weight (Mn) and polydispersity index (PDI) were evaluated by Gel permeation chromatography (GPC, Shimadzu Corp) in chloroform at a flow rate of 0.8 ml/min at 40 ℃ and polystyrenes (Shodex® STANDARD SM-105, Showa Denko K.K.) were used as standards. The composition of the copolymers was identified with a Fourier transform nuclear magnetic resonance spectrometer (FT-NMR, JEOL, JNM ECZ-400) using $CDCl_3$. The thermal properties were conducted at a heating rate of 10 ℃/min and a cooling rate of -10 ℃/min by Differential scanning calorimetry (DSC 1, Mettler Toledo) under a nitrogen atmosphere.

Monolayer properties were studied by using a computer-controlled KSV-NIMA Langmuir probe system (trough size: 580×145×4 mm^3). All samples were separately prepared at a concentration of 1 μmol/mL. The water was purified by an ultrapure water system (UNIONS, Sinhan Science), and approximately 450 ml of deionized water (DI, 18.2 M•cm) was used as a subphase liquid. After carefully spreading, the solvent could evaporate for 1min to minimize hydrolysis when compression. In all experiments, the compression rate of barriers was 10 cm^2/min.

3.2. Results and discussion

3.2.1. Chemical compositions

Figure 11 depicts the ^{1}H-NMR spectra of the PLGA copolymers. It represents those copolymers that were successfully synthesized through the peak corresponding to the methyl group $-C\underline{H}-$ protons (peak at 5.2) of the LA and the methylene group $-C\underline{H}_2-$ protons (peak at 4.8) of the GA. The composition of synthesized PLGAs was confirmed by the integral of these two peaks.

The detailed compositions of the copolymers used in this study are listed in Table 5. In other literature, the ratio of the GA in the copolymer was higher than that of the in-feed monomer because GA has higher reactivity than the LA in ring-opening polymerization [11-13]. However, the solution polymerization method in this experiment was not showing a similar tendency because the monomers differ appreciably in solubility and diffusion rate with comparing the bulk polymerization. Generally, the same reactivity ratios apply whether the polymerization is carried out in bulk, solution, suspension, or emulsion system. Therefore, deviations of copolymer composition can only be expected from concentration differences in polymerization sites [20].

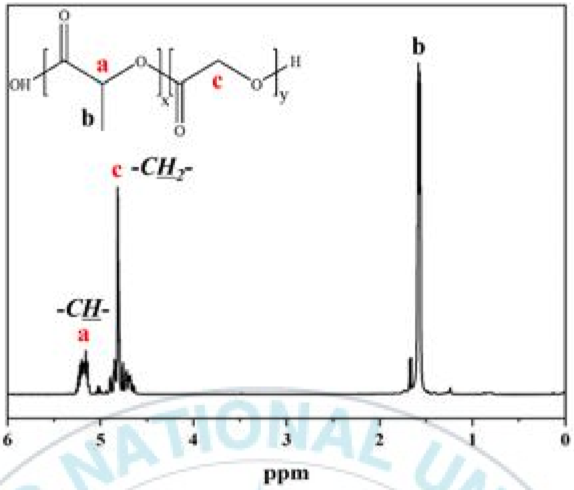


Figure 11. The ^{1}H-NMR spectrum and structure of the PLGA copolymer.

Table 5. Composition of copolymers used in this study

	In feed (mol%)		Product (by NMR) (mol%)		Sample Code
	LA	GA	LA	GA	
l-LA-co-GA	95	5	98	2	PLGA2
	90	10	92	8	PLGA8
	85	15	87	13	PLGA13
	80	20	82	18	PLGA18
	*70	30	54	46	PLGA46
d-LA-co-GA	80	20	80	20	PDGA20
	*70	30	58	42	PDGA42

*Bulk Polymerization

3.2.2. Thermal properties

Figure 12 represents the thermal properties of the synthesized polymers. To observe the changes in crystallinity as the amount of GA changes, the heating and cooling rates were kept constant to ± 10 ℃ /min to the maximum crystallinity. It is observed that small incorporation of the GA in PLA chains can decrease T_m and crystallinity because both PLA and PLGA are semicrystalline (Table 6). The incorporation of the GA in the PLGA copolymers makes it difficult to fold the chains, which deteriorates the perfectness of the crystal. The representative DSC thermograms illustrate that the decrease in T_g supports the increase in chain mobility and the regularity of the chain decreases as the amount of the GA increases. It evidenced that PLGA copolymers$\geq$13 mol% are amorphous and exhibit T_g, but no T_m [21], and this thermal behavior implies that the PLGA copolymers were successfully synthesized. The detailed thermal properties and molecular weights of the synthesized PLGA copolymers are summarized in Table 6.

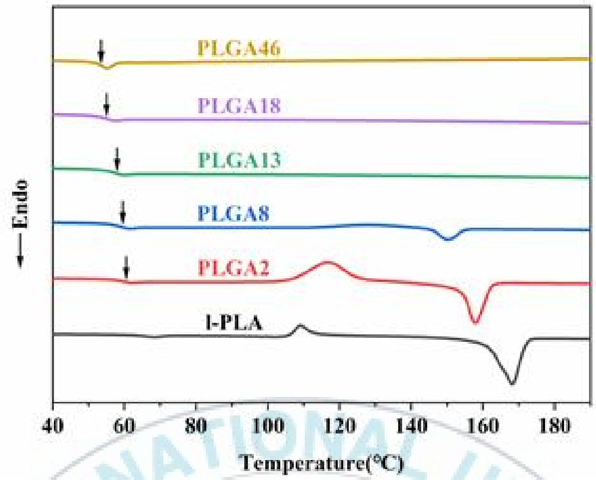


Figure 12. DSC curves of synthesized polymers. The arrows represent the T_g taken as the middle point.

Table 6. Characterization of the materials used in this study

	Mn	PDI	Tg	Tm	Crystallinity (%)
l-PLA	28K	1.6	–	169.6	44.7
PLGA2	27K	2.3	60.5	158.2	4.4
PLGA8	27K	2.3	59.3	150.3	2.8
PLGA13	26K	2.4	58.0	–	
PLGA18	16K	3.8	54.9	–	
PLGA46	23K	2.1	53.6	–	
PDGA20	28K	2.2	55.0	–	

3.2.3. Surface Pressure-Area isotherms of monolayers

Figure 13 shows the π-A isotherms of the l-PLA and PLGA monolayers on a deionized water subphase. The transition region of l-PLA was observed at 9.2 mN/m, and it is proportionally changed as increased in the GA unit. PGA has a single methyl group compared to PLA, and there is no significant difference in repeating units. Accordingly, there was a similar molecular behavior of PLGA monolayers from 8 mol to 18 mol on the air/water interface, while PLGA46 was collapsed at 15.8 mN/m without any transition region. It indicates that the transition region decreases as the crystallinity of the copolymer decreases, and it is not being observed as the copolymer turns completely amorphous at the molecular level. However, Tm was not observed at PLGA copolymers$\geq$13 mol% in DSC findings since it was measured on a rough scale, which may indicate the existence of crystal chains in monolayer, even though they are random chains. Since the lowest transition region was approximately 6.5 mN/m, the monolayers were performed below that surface pressure to proceed with degradation in a stable state.

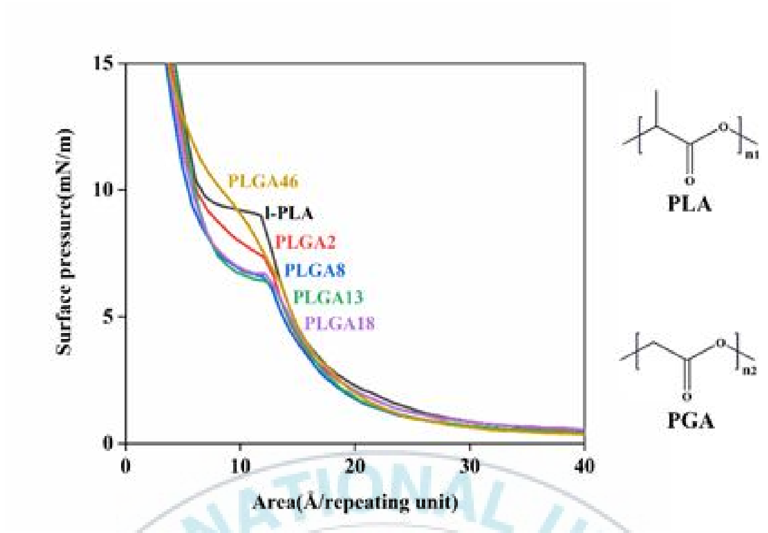


Figure 13. Pressure-area isotherms of l-PLA and PLGA monolayers on subphase of deionized water.

3.2.4. Alkaline hydrolysis of monolayers

Firstly, the effects of subphase pHs (ion concentration), 11.3 and 11.5, on the hydrolytic behavior of monolayers have been studied at a constant surface pressure of 5 mN/m. Although l-PLA and PLGAs with similar M_n, alkaline hydrolysis rate increased with the GA composition in the copolymer (Figure 14). Generally, alkaline hydrolysis of biodegradable polyesters is affected by their hydrophilicity [28-31]. Water contact angles of l-PLA and PLGA46 cast films were 72° and 66°, respectively. Therefore, the monolayer is more submerged in subphase as the GA units increase in the copolymer, and it provides more sites to hydroxide ions for the attack. Moreover, the low steric hindrance due to the absence of the methylene group of the GA unit would have been easier than LA for hydroxide ions to attack. A noticeable point is PLGA46 has almost very similar hydrolytic kinetic behaviors, regardless of pHs. However, for better understanding the hydrolytic behavior of monolayers on alkaline subphase, many experiments were carried out with different pHs with a constant pressure of 5 mN/m.

As illustrated in Figure 15, it shows A/A_0 values of l-PLA, PLGA18, and PLGA46 at 60 minutes according to pHs. For the l-PLA monolayer, the A/A_0 value was decreased linearly up to pH 11.7, while PLGA18 and PLGA46 monolayer were decreasing first and significantly slower after pH 11.5 and pH 11.3, respectively. Also, the A/A_0 value of PLGA46 with pH 11.7 was larger than the pH 11.5 one. Similarly, PLGA18 was exposed to a higher pH (pH 12), and it shows similar behavior as PLGA46 (not shown here). From the results of that alone, it can be considered that the amounts of ions over the critical point prevented the hydrolysis of PLGA monolayers, and increasing the GA units leads to faster supersaturation. To conclude, it seems that additional degradation experiments from various aspects are needed.

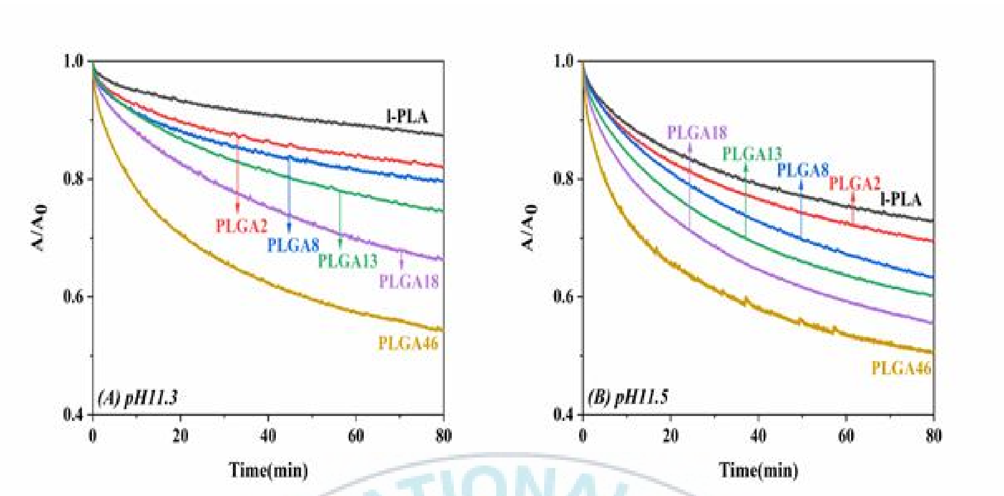


Figure 14. Area ratio vs time for l-PLA and PLGA monolayers maintained at 5 mN/m on subphase pH 11.3 (A) and pH 11.5 (B).

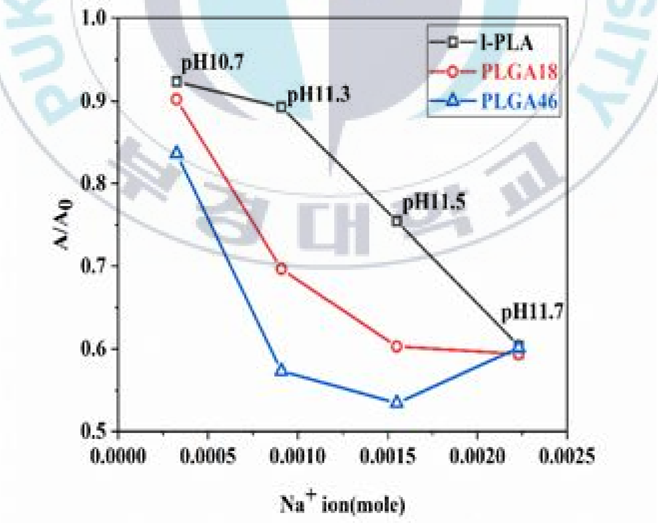


Figure 15. Area ratio vs pHs for monolayers maintained at 5 mN/m when the time is 60 minutes.

Figure 16 shows a plot of the Area vs time of l-PLA and PLGA monolayers at various constant surface pressure at pH 11.3, and the blue points represent the area at 5 mN/m for 60 min holding time. There was no significant difference in hydrolysis kinetics despite the different surface pressure. In contrast to the surface pressure stated, the hydrolysis of monolayers occurred faster when they hold.

It is important to realize that the Na+ ions play a significant role under subphase because monolayers take place in non-selective attacks from ions in alkaline hydrolysis. The occupied area was decreased with the increase in constant surface pressure; it means that the Na+ ions in contact with the monolayer were declined. As shown in Fig.16-D, 0.00090984 moles (pH 11.3) of Na^+ ions were in contact with hold time, while it was dramatically decreased when the monolayer was under constant surface pressure of 3 mN/m and 5 mN/m. Therefore, the Na^+ ions can attack the many sites on a holding time, and according to that hydrolysis was occurred faster than constant surface pressures.

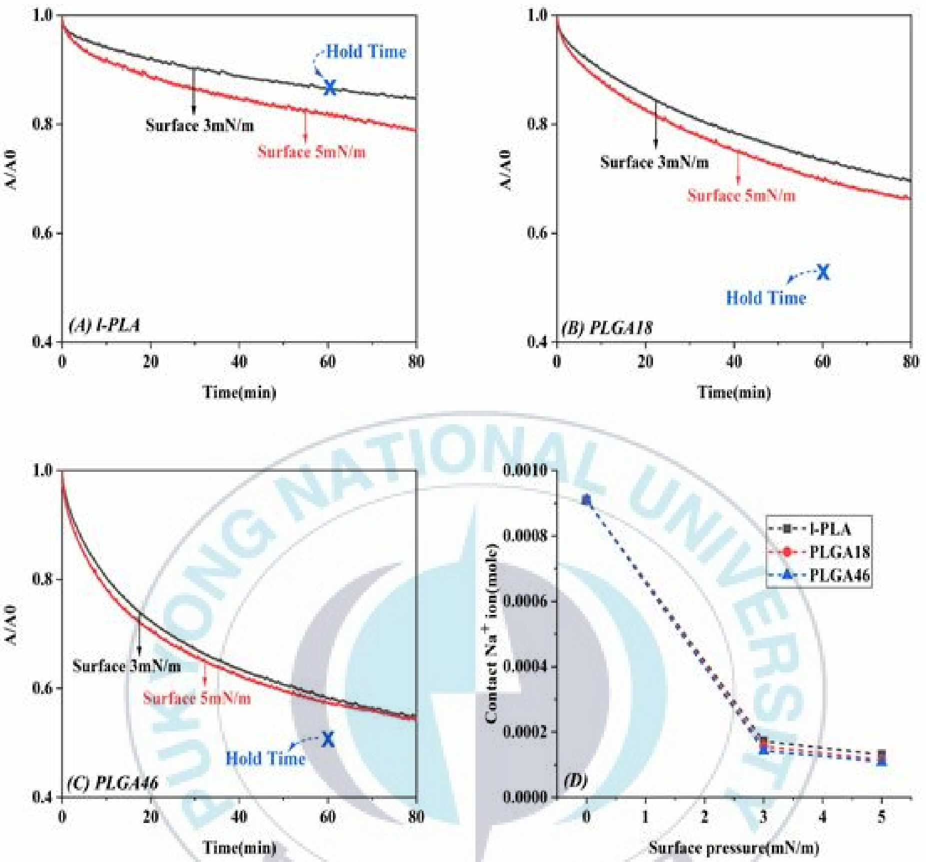


Figure 16. Area vs time for l-PLA (A), PLGA18 (B), PLGA46 (C) monolayers on the subphase of pH 11.3, respectively, and contact Na^+ ions vs surface pressure (D) for these monolayers.

3.2.5. Enzymatic degradation of monolayers

The Langmuir technique manifested to be a phenomenal technique to acquire insights into the interaction between the polymer chains and enzymes. It was proved that enzymes require a minimum packing density of the polymeric substrate to become active [24]. Proteinase K can catalyze the degradation of l-PLA in amorphous regions, although the folded chains in the crystalline region are highly stable to enzymatic cleavage. While PGA is known to degrade specific enzymes, especially exoenzymes like lipase, esterase, and endopeptidase [26, 27]. The enzymatic degradation of l-PLA and PLGA monolayers was examined at 5 mN/m on the subphase with 0.02mg of proteinase K as shown in Figure 17. The enzymatic degradation rate of PLGA increases with GA composition, and PLGA46 was depicted as the fastest degradation rate.

It has been known that proteinase K can catalyze the degradation of l-LA units but cannot catalyze the degradation of d-LA ones. As shown in Figure 17-B, the dl-PLA containing 20 mol of d-lactide showed a delay in degradation rate even though it is amorphous. Although PLGA18 and PLGA46 were equally amorphous, and they showed faster degradation than l-PLA. We established two possible assumptions: i) the GA shows activity on proteinase K, and ii) the GA accelerates the degradation of l-PLA. To prove this, we synthesized PDGA copolymers containing 20 mol% and 42 mol% compositions of GA and carried enzymatic degradation experiments. The d-PLA, PDGA20, PDGA42 were all approximately 90% (A/A_0=0.90), 88% (A/A_0=0.88), and 85% (A/A_0=0.85), respectively after 80 min of degradation. These results evidenced that proteinase K has not catalyzed the GA. As mentioned above, as the GA units are increasing in the copolymer, the monolayer is more submerged in the subphase due to its hydrophilicity, and it helps to be attacked by the enzymes that selectively degrade l-LA [6,28]. Other studies used the term “Catalytic effect” because GA plays a role in promoting the degradation of PLA, and this tendency was also observed in the Langmuir system [29].

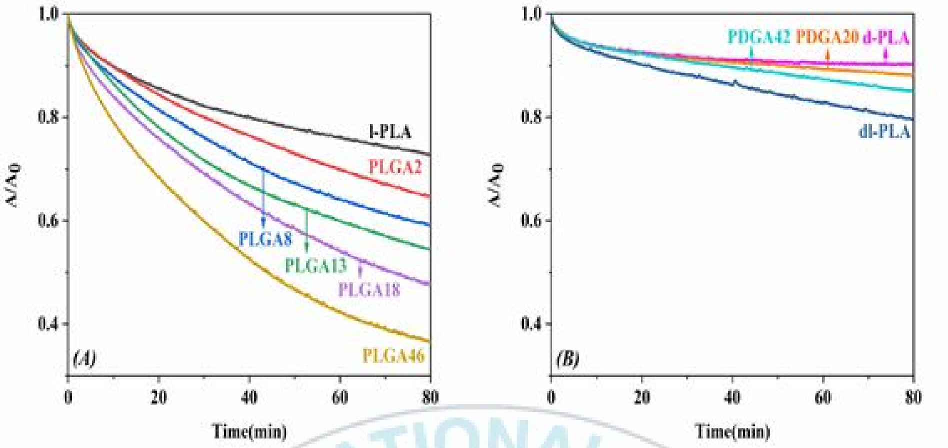


Figure 17. Area ratio vs time for monolayer films maintained at 5 mN/m on subphase with 0.02 mg of proteinase K.

For investigating the effect of surface pressure on enzymatic degradation behavior compared to alkaline hydrolysis behavior, the monolayers were preceded at various surface pressures and 60 min of hold time. As shown in Figure 18, enzymatic degradation shows a different tendency than alkaline hydrolysis. The monolayers were degraded hardly after 60 min of hold time, but the proportion of degradation was faster as the surface pressure increased. This state is related to the comparative size of alkaline ions and proteinase K; the Na^+OH^- ions are much smaller than proteinase K (ca.29 kDa) and can hydrolyze the monolayers at low constant surface pressure [7]. In contrast, proteinase K can be activated above the critical contact area at high constant surface pressure. Therefore, the activity increases due to contact with enzymes in the subphase at high constant surface pressure. We hypothesize that the PLGAs monolayers are seriously affected by the constant surface pressure in enzymatic degradation, unlike alkaline hydrolysis (Figure 19).

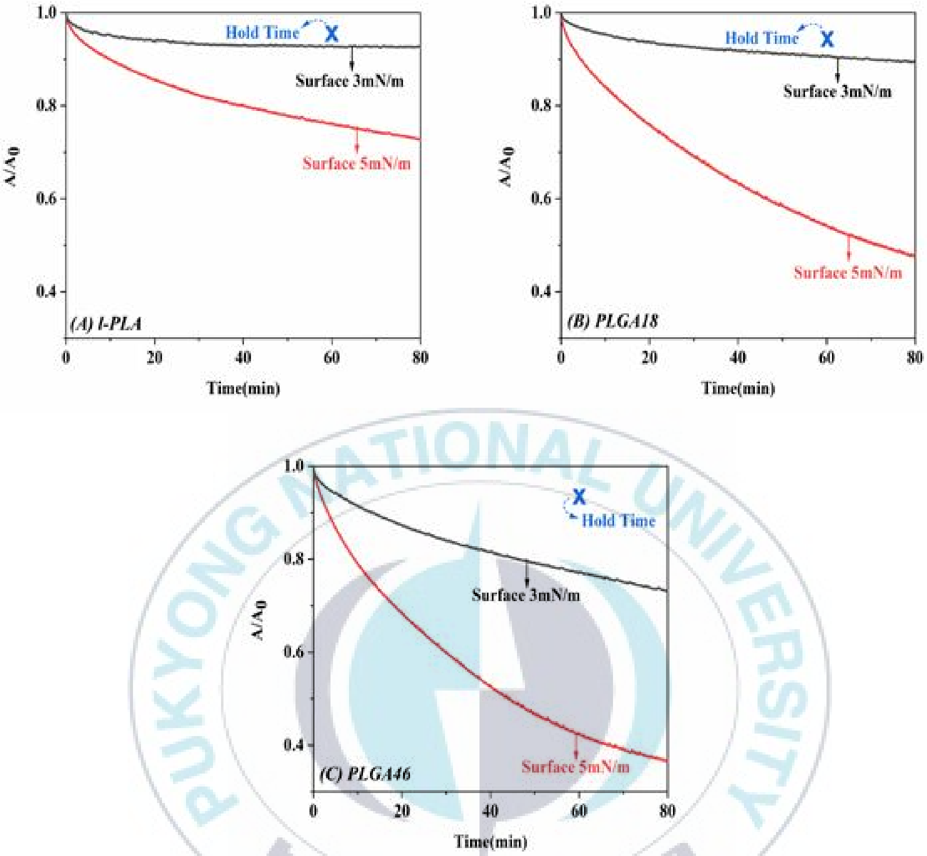


Figure 18. Area ratio vs time for l-PLA (A), PLGA18 (B), PLGA46 (C) monolayers on the subphase with 0.02 mg of proteinase K.

3.3. Conclusion

The Langmuir technique was used to study the alkaline and enzymatic degradation behavior of PLGA monolayers maintained at a constant surface pressure on different subphases. Both alkaline hydrolysis and enzymatic degradation resulted in faster degradation as GA composition increased even though GA is not active for proteinase K. PLGA copolymer showed a catalytic effect on l-LA refereeing degradation since the composition of GA increases. Although, the monolayers demonstrated different degradation behavior under the various constant surface pressure.

In the case of alkaline hydrolysis, the contact area between monolayer and ions means that the concentration of ions exposed to the monolayer is high when holding state. However, there was no difference in hydrolysis under pressure because the portion where the monolayer is more submerged, even though the contact area was greatly reduced. In contrast, enzymatic degradation occurred at high surface pressure because it needs more contact area between enzymes and submerged chains. Generally, this is the reason for the study results in that alkaline hydrolysis occurs simultaneously in the crystalline and amorphous regions, whereas enzymatic degradation preferentially occurs in the amorphous region [7, 18].

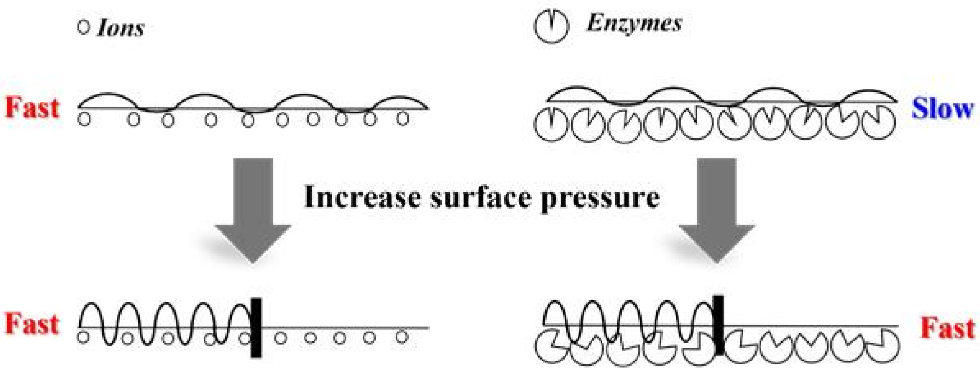


Figure 19. Schematic representation for different degradation behavior of biodegradable polyester monolayers.

Chapter 4. Hydrolytic behaviors of poly(lactide)/poly(butylene succinate) and poly(lactide)/poly(butylene succinate-co-butylene adipate-co-ethylene succinate-co-ethylene adipate) mixtures

4.1. Experimental

4.1.1. Materials

The PBS and PBEAS were provided from Ankor Bioplastics (Korea). PLA (L-lactic acid/D-lactic acid: 98.6/1.4) with an average molecular weight of 200,000 was purchased from Natureworks LLC. All chemicals were purified by the dissolution/precipitation method using chloroform as a solvent and methanol as a non-solvent. Chloroform (99.8%) and methanol were obtained from Samchun (Korea). Sodium hydroxide was obtained from Icatayama Chemicals (Japan). For the measurements of mechanical properties, the PBS, PBEAS, and l-PLA films were prepared with the compression press at the 150-160 ℃ molding temperature under 8-9 MPa of pressure for 2-3 min of press time. The thickness of the films was maintained to 250-300 ㎛.

4.1.2. Measurement

The mechanical properties were measured by the Tinius Olsen (H1KT, USA), equipped with a 100 Kgf load sensor applying a stretching rate of 5 mm/min. Five film samples were cut using a dog-bone shape mold press with a gauge length of 10 mm, and width of 2 mm for tensile tests. The thermal properties were conducted at a heating rate of 10 ℃/min and a cooling rate of -300 ℃/min by different scanning calorimetry (DSC, Mettler Toledo, England) under a nitrogen atmosphere.

Monolayers were studied by using a computer-controlled KSV-NIMA Langmuir probe system (KN 1006). All solutions were separately prepared in a concentration of 1 mol/mL and mixture solutions were obtained by stirring for 3 days. The mixture composition was fixed by 50/50 by mol% unless otherwise specified. Deionized water (DI, 18.2 M•cm) was used as a subphase liquid. The water was purified by an ultrapure water system (UNIONS, Sinhan Science). After spreading, the solvent could evaporate for 1 min to minimize hydrolysis when compression. The compression rate of barriers was 10 cm^2/min in all experiments.

4.2. Results and discussion

4.2.1. Mechanical properties

Biodegradable PBS can be produced by polycondensation of fossil or bio-based succinic acid and 1,4-butanediol. It behaves as a ductile polymer at room temperature because of low glass transition temperature (-35 ℃). However, the conventional PBS fishing nets used must be more flexible, stiffness, and mechanically robust. Thus, PBEAS (modified from PBS) has improved mechanical properties with an average tensile strength at break and elongation break of 40 MPa and 600 %, respectively.

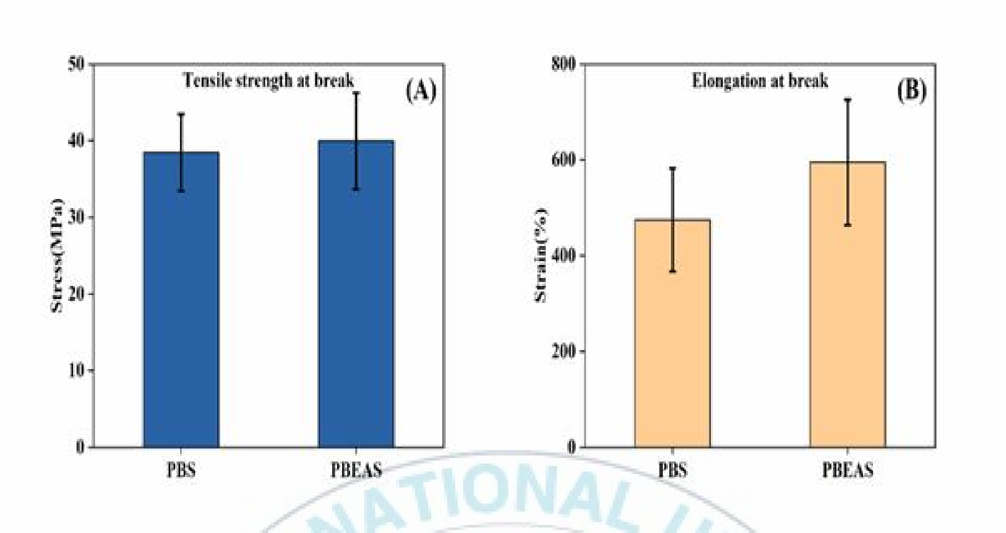


Figure 20. Mechanical properties of PBS and PBEAS films: (A) Tensile strength at break and (B) % strain.

4.2.2. Thermal properties

The mixture of l-PLA/PBS was widely studied because of their complementarity, improving the toughness of PLA and the stiffness of PBS. To obtain in properties by mixing, homogeneous mixing or interaction between both components is required and it disturbs the aggregation and crystal formation of a component. Therefore, the compatibility of a mixture can be analyzed by their T_g and/or T_m [33, 34]. The mixtures of PBS with l-PLA result in a very little change in T_g and T_m as shown in Figure 21 and Table 7. It would be difficult to mention their compatibility because both polymers are semi-crystalline ones with high crystallinity. Usually, the high crystallinity of a polymer increases its T_g and an interaction of a mixture occurs in the amorphous region. Although the T_g of l-PLA is 61.2℃, semicrystalline l-PLA/PBS and l-PLA/PBEAS mixtures a little decrease to 60.8 ℃ and 59.1 ℃, respectively, as shown in Table 7, there would be partial compatibility.

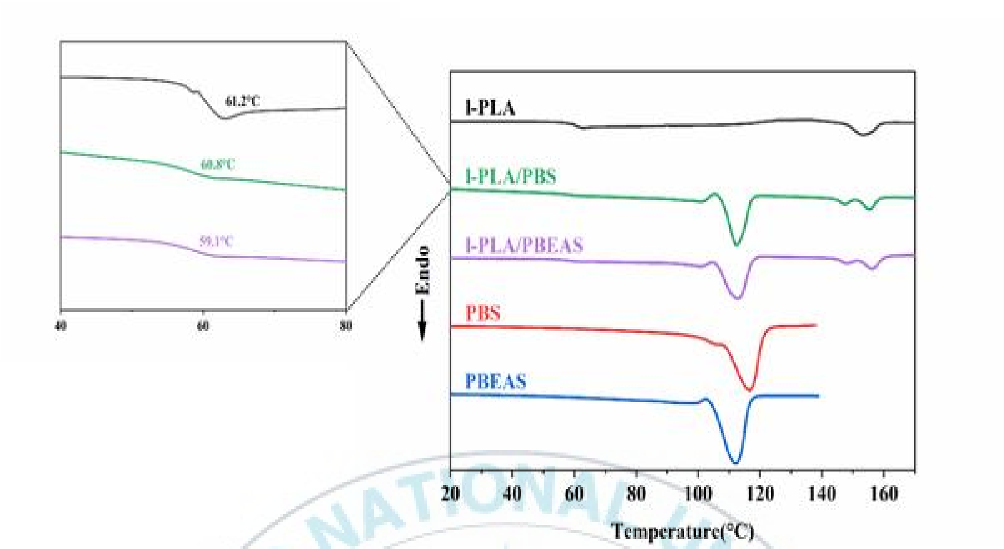


Figure 21. DSC curves of l-PLA, PBS, PBEAS, l-PLA/PBS, and l-PLA/PBEAS mixture films after melt quenching.

Table 7. Thermal properties of homopolymers and their mixtures

Sample	T_g (℃)	T_m (℃)	ΔH(J/g)
l-PLA	61.2	153.3	8.5
l-PLA/PBS	60.8	155.5/112.7	8.2/31
l-PLA/PBEAS	59.1	156.3/113.2	7.5/24.3
PBS	-	116.8	59.3
PBEAS	-	112.5	50

4.2.3. Surface pressure-Area isotherms

Figure 22 represents the π-A isotherms for l-PLA, PBS, and PBEAS monolayers on subphase of deionized water. The π-A isotherms of l-PLA, PBS, and PBEAS monolayers showed transitions of approximately 9.7 mN/m, 5.7 mN/m, and 5.9 mN/m, respectively. Before the transition, the occupied area per monomer of the PBS and PBEAS monolayers is much larger than l-PLA because the PBS and PBEAS consisted of two ester groups (hydrophilic) and ethylene and butylene groups (hydrophobic). Additionally, PBS and PBEAS have a long plateau region in the isotherm because of their long-chain backbone and chain folding structure at the air/water interface [35].

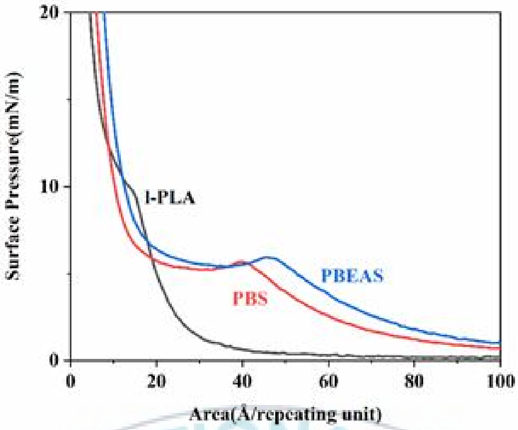


Figure 22. π-A isotherms of monolayer films on subphase of deionized water.

4.2.4. Compatibility of l-PLA/PBS and l-PLA/PBEAS mixtures (MIX, UNMIX)

To study the compatibility of l-PLA/PBS and l-PLA/PBEAS, π-A isotherms of mixture monolayers were measured in two different ways. The first type is well-mixed (MIX) monolayers after mixing for 3 days at room temperature and the second one is unmixed (UNMIX) monolayers by separately spreading each solution on the subphase. If both isotherms are different, an isotherm of the mixture monolayers will be partially compatible or incompatible. As shown in Fig.23-A, the UNMIX monolayers depict the two transitions, which correspond to the transition of l-PLA and PBS, respectively. Moreover, the transitions of l-PLA/PBS MIX monolayer occurred approximately at 9.9 mN/m and 6.5 mN/m, which were higher than the transition pressures of neat l-PLA and PBS monolayers (9.7 mN/m and 5.7 mN/m, respectively) because the PBS transition is delayed by other adjacent chains [35]. Therefore, the l-PLA/PBS mixture monolayers have shown partial compatibility and the existence of some molecular interaction between l-PLA and PBS.

However, the π-A isotherms of l-PLA/PBEAS MIX monolayers showed different behavior from l-PLA/PBS ones (Fig.23-B). Even though the π-A isotherm of PBEAS monolayer had a flat (5.7 mN/m) and long (from 45 to 20 in Area) transition behavior, the π-A isotherm of the l-PLA/PBEAS MIX monolayer shows sharply sloped behavior in the range from 7.5 to 9 mN/m which corresponds to the transition of PBEAS in the mixture. This indicates that the transition of PBEAS in the monolayers is strongly disturbed by adjacent l-PLA monolayers and the PBEAS monolayers in the mixture are not aggregated. From the isotherm behaviors, the l-PLA/PBEAS mixture monolayer shows better compatibility than the l-PLA/PBS one.

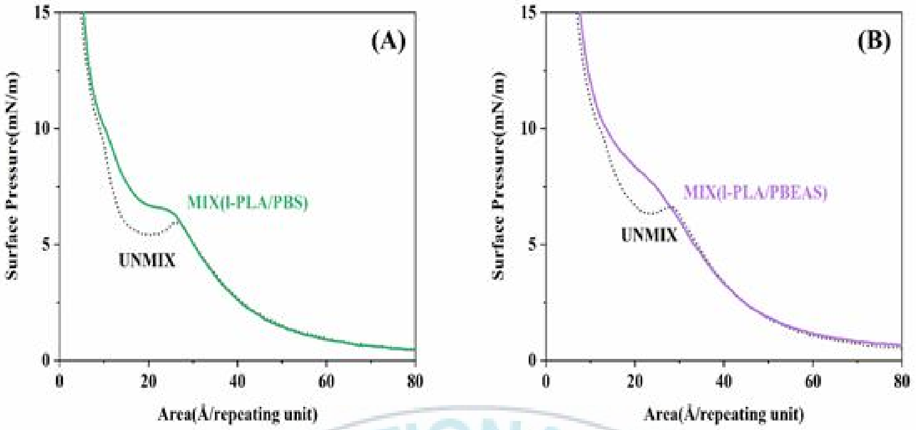


Figure 23. π-A isotherms of MIX and UNMIX monolayers on subphase of deionized water: (A) l-PLA/PBS and (B) l-PLA/PBEAS.

4.2.5. Hydrolytic degradation of monolayers

Langmuir technique is useful for measuring the hydrolytic kinetics of biodegradable polyester at the molecular level [35-38]. The A/A_0 value with hydrolytic time reflects the degradation rate, where A and A_0 mean the occupied areas at time t and 0, respectively. As shown in Figure 24, PBS and PBEAS monolayers showed a much faster alkaline hydrolysis rate than the l-PLA monolayer. It would be due to larger occupied areas of PBS and PBEAS than l-PLA. The large the occupied area is the more alkaline ions in the subphase attack the occupied monolayers.

To investigate the hydrolytic behavior of mixture monolayers on subphase pH 9.0, the theoretical data of mixture were calculated using the following equation in the mixture system:

$$T_{Mix}=M_a \cdot A_a+M_b \cdot A_b$$

where a and b are the respective polymers for the mixture, M represents the mole fraction of polymer in the mixture, and A represents the experimental occupied area at specific surface pressure. The experimental kinetic rates of l-PLA/PBS and l-PLA/PBEAS mixture monolayers are much slower than their theoretical values. The significant dissimilarity between the experimental and theoretical data can be answered by the fact that the hydrolysis of PBS or PBEAS chain in the mixture is disturbed by the adjacent l-PLA chains and then the hydrolysis of mixtures is delayed. As mentioned above, these results support the existence of an interaction between PBS and

PBEAS with l-PLA.

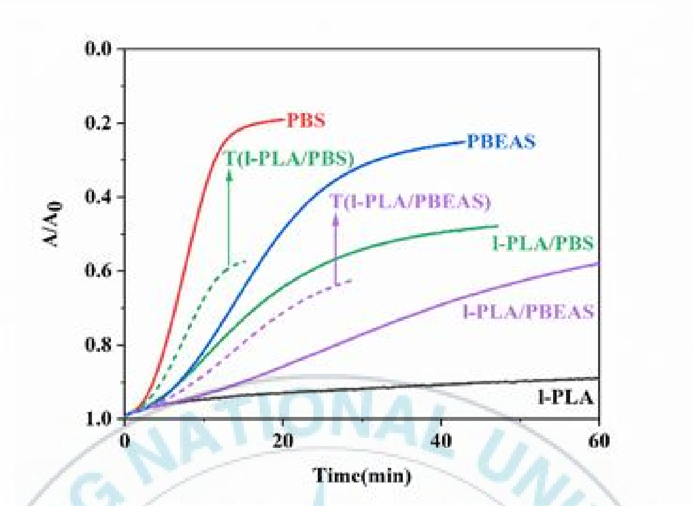


Figure 24. Area ratio vs time for monolayers maintained at 4 mN/m on subphase pH 9.0, T(mixture) indicates theroretially calculated data from their homopolymer's one.

4.2.6. Hydrolytic kinetics of binary monolayers (MIX,UNMIX)

Both mixture monolayers, l-PLA/PBS and l-PLA/PBEAS, showed different behaviors of the π-A isotherms on the deionized water. To understand the mixing state of the mixture monolayers, the experiments of MIX and UNMIX monolayers were conducted on the alkaline subphase with the same conditions. As shown in Figure 25, the hydrolytic rate of the UNMIX monolayers showed a much faster degradation rate than the MIX monolayers. This indicates that the UNMIX monolayers are in initial phase-separated status, and it possesses two-step kinetics. In the first step, the A/A0 rapidly decreased due to the preferred hydrolysis of PBS or PBEAS region and in the second step, it became very slow, like the hydrolytic behavior of l-PLA. This reveals that initially, UNMIX monolayers were possessed a phase-separation morphology, and it results in the hydrolysis of the PBS or PBEAS (step1), while in the second step, the interaction between l-PLA/PBS or l-PLA/PBEAS increases as the remaining chain are rearranged as like MIX monolayers.

The two-step kinetics was observed in the MIX monolayer of l-PLA/PBS (Fig.25-A), while one-step kinetics was observed in the MIX monolayer of l-PLA/PBEAS (Fig.25-B). These results also support that the interaction between l-PLA and PBEAS monolayers is stronger than the interaction between l-PLA and PBS monolayers at the molecular level. Therefore, the MIX monolayer of l-PLA/PBEAS represents delayed the hydrolysis rate because the alkaline ions are difficult to access the ester bond of monolayers when the chains appeared side-by-side in the mixture system.

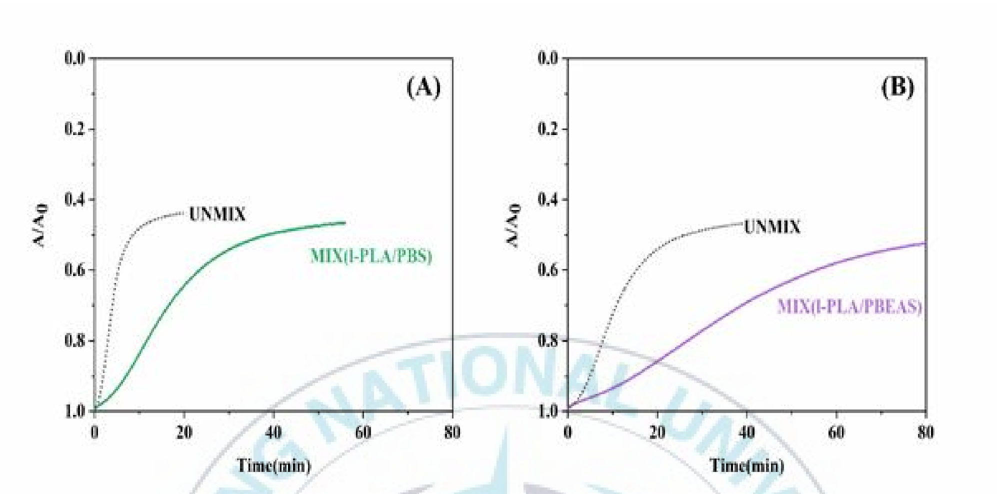


Figure 25. Area ratio vs time of (A) l-PLA/PBS and (B) l-PLA/PBEAS mixtures at 4 mN/m on the subphase of pH 9.0.

4.3. Conclusion

Langmuir technique is a versatile tool when it comes to mimicking and understanding the compatibility and hydrolytic behavior of polymeric materials at the air/water interface. In this study, l-PLA was mixed with the biodegradable PBS and PBEAS to study the compatibility and control the degradability. The compatibility of PLA/PBS (50/50 by mol%) and l-PLA/PBEAS (50/50 by mol%) monolayers were explained in terms of the transition and kinetic behavior. DSC thermograms of both mixtures exhibit slight changes in T_g may reveal their partial miscibility in the amorphous phase. It was confirmed that the compatibility of PBEAS and l-PLA was better than that of PBS and l-PLA. Therefore, at a constant pressure, PBEAS mixture showed slower degradation than PBS one at the subphase of pH 9.0 because there is more interaction between l-PLA and PBEAS.

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