공학석사학위논문

Preparation of Poly Lactic Acid Stereocomplex Particles by ASES using Supercritical CO_2 and Application to Drug Encapsulation Process

초임계 이산화탄소를 역용매로 하는 ASES를 통한 폴리 젖산 입체 복합체의 제조 및 약물 캡슐화 공정으로의 응용

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Abstract

Preparation of poly lactic acid stereocomplex particles by ASES using supercritical CO_2 and application to drug encapsulation process

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Poly lactic acid (PLA) is a representative biodegradable polymer which is getting spotlight as a substitution of petrochemical plastic. However, low thermal stability of PLA makes mass-production difficult. To overcome this problem, many processes have been studied to enhance thermal stability by stereocomplexation between two enantiomers of PLA (PLLA and PDLA). Those are melt crystallization, solution casting, and precipitation into organic anti-solvent. Flim form or fibrous form of PLA stereocomplex can be obtained by these processes. However, these processes need high temperature, long process time, or excess organic solvent.

In this study, a preparation of spherical PLA stereocomplex particles was achieved successfully by Aerosol Solvent Extraction System (ASES) using supercritical CO_2 as an anti-solvent at mild temperature

condition (40℃) in tens of minutes. The prepared PLA stereocomplex was analyzed by Differential Scanning Calorimetry (DSC), Wide Angle X-ray Scattering (WAXS), and Field-Emission Scanning Electron Microscopy (FE-SEM). Kind of organic solvent dissolving PLAs, blending weight ratio of two enantiomers of PLAs, molecular weight of PLLA, and concentration of PLA solution were selected as variables which can affect properties of prepared PLA stereocomplex. As a result of experiment, dichloromethane was selected as proper organic solvent to dissolve PLAs. And almost PLAs participated in the formation of stereocomplex crystallites when blending weight ratio was 1:1. Besides, the less molecular weight of PLLA was employed, the more formation of stereocomplex crystallites was predominant than that of homo-crystallites. In case of concentration of PLA solution, it didn't affect to predominant formation of stereocomplex crystallites, but low concentration induced small particle size and low crystallinity.

On the other hand, PLA and PLA stereocomplex are also widely applied to drug delivery system (DDS) due to biodegradability. Based on the idea that spherical particles can be obtained in the ASES, preparation of spherical drug particles encapsulated by PLA stereocomplex was also carried out to control release rate of drug. Cetirizine (CTZ), which is used as antihistamines, is employed as a drug, and the processed CTZ encapsulated by PLA stereocomplex (CTZ complex) was analyzed by Energy Dispersive X-ray Spectrometer (EDS) and dissolution rate test. Through EDS mapping for chloride atom, which exists only in CTZ, not in PLA, on FE-SEM image, it was clarified that CTZ was well distributed on overall CTZ complex.

Furthermore, it was revealed that approximately 72.5% of CTZ content in CTZ complex was encapsultated perfectly from dissolution rate profile of CTZ complex. Additionally, CTZ content is thought to be partially encapsulated by PLA stereocomplex since initial dissolution rate was reduced complared to that of raw CTZ.

Therefore, preparation of PLA stereocomplex using ASES with supercritical CO_2 as anti-solvent shows remarkable points compared to conventional processes in terms of time, energy saving and environment-friendly. Especially, it is meaningful that ASES is a continuous process so that mass-production is available. Moreover, possibility of ASES as drug encapsulation process is confirmed by preparing CTZ complex successfully. It is thought that preparation of CTZ complex by ASES is a competitive process, considering synergy between residual solvent-free product and non-toxicity of PLA stereocomplex to human body.

Key words: Supercritical CO_2, ASES, Poly lactic acid, Stereocomplex, Thermal stability enhancement, Encapsulation, Cetirizine, Dissolution rate, Controlled release, Drug delivery system

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1. Introduction

Mankind lives in the era of mass production and consumption and also produces many wastes. Among these wastes, as for polymer wastes such as plastics, several years or decades are required to be decomposed of when they are buried in landfill sites. When they are incinerated, they generated noxious gas. For these reasons, biodegradable polymers which can be decomposed by microorganism are getting spotlight. Poly lactic acid (PLA), which is a representative of biodegradable polymers, has been used in various applications such as implant devices, tissue regeneration [1], internal sutures [2], or hygiene product [3], and drug delibery system (DDS) [4] because of its property of non-toxicity to human body [5]. Also, it is a strong point that PLA can be produced from renewable resources. Recently, mass-manufacturing facilities make it possible for PLA to be used as textiles, films, and a food packaging material [5-7]. However, it is difficult for PLA to replace existing mass-manufactured plastic polymers due to its unfavorable thermal properties. A melting point of PLA is reported as about 160~170℃ which is high temperature enough to be processed compared to commercial polymer. Nevertheless, its heat deflection temperature (HDT), which is crucial to a maximum continuous use temperature, is reported as about 55℃; HDT of PLA is as low as glass transition temperature [8]. This makes it difficult for PLA to replace commercial plastics at over a certain temperature. To overcome these drawbacks, a preparation of stereocomplex by blending two kinds of optical isomers (L-form and D-form of PLA) is proposed and has been studied. According to previous studies, a formation of

stereocomplex improves its thermal stability with significant increases in melting point (220~240℃) and HDT (160~170℃) [4,8-21]. When PLA stereocomplex is formed, it shows its intrinsic crystallinity, which is easily distinguished from the crystallinity of PLA homocrystallites. However, PLA stereocomplex can also shows properties of homopolymers if PLA crystallite is not perfectly removed by stereocomplexation. In this case, PLA stereocomplex shows not only thermal properties of PLA homopolymers but also those of PLA homopolymers [9,20,21]. For this reason, various processes for preparation of PLA stereocomplex without homocrystallites such as melt crystallization from bulk [14,19], solution casting [10,12,13,16,17,20,21] and precipitation into excess anti-solvent [9,11] have been studied in many literatures [4,8-21]. Recently, PLA stereocomplex formation using supercritical CO_2 assisted by co-solvent was reported [22]. However, processes mentioned above need high temperature, or long process time. Moreover, since all processes are batch type, it is difficult to mass-produce PLA stereocomplex. In addition, because the processed materials are obtained in a form of film, its application is limited.

In this study, aerosol solvent extraction system (ASES) using supercritical CO_2 as antisolvent is proposed as a new process for preparation of micron-sized PLA stereocomplex particles. Advantages of process using supercritical CO_2 are as follows. First, this process is economical in terms of energy and time consumption. Because the operating temperature is under 40℃ slightly higher than the critical temperature of CO_2 (31℃), an energy cost can be smaller compared with other conventional processes. Second, since ASES is a continuous

process, it is more suitable for mass production compared to other conventional processes. Third, ASES is reliable in respect to the removal of toxic residual solvent such as dichloromethane and chloroform which are preferred solvent dissolving PLA. It is achieved by powerful ability of supercritical CO_2 to extract organic solvent. Finally, products are obtained as powder, micron-sized PLA stereocomplex particles. This makes applicability of PLA stereocomplex broad compared to the film form. This study is distinguished from recent report using supercritical CO_2 [22] in regards to utilizing supercritical CO_2 as a solvent assisted by good organic solvent (rapid expansion of supercritical solution (RESS) with co-solvent, previous research), or an anti-solvent (ASES, this study).

By utilizing these advantages of ASES, the preparation of PLA stereocomplex was carried out in various conditions. Different kinds of solvents, change of blending weight ratio between PLLA/PDLA, and different molecular weight of PLLA were used. And then, the properties of prepared PLA stereocompleces were analyzed by differential scanning calorimetry (DSC), wide angle x-ray scattering (WAXS), and field-emission scanning electron microscope (FE-SEM). Futhermore, by utilizing that products are obtained as micron sized particles, this process was applied to preparation of cetirizine (CTZ, as drug) particles encapsulated by PLA stereocomplex (CTZ complex). The CTZ complex could be applied to controlling a drug release rate. Prepared CTZ complex were analyzed by dissolution rate test and energy dispersive spectroscopy (EDS/FE-SEM) to confirm weather CTZ was well-encapsulated by PLA stereocomplex.

2. Research background

2.1. Poly lactic acid (PLA)

Lactic acid is obtained by fermentation of corn starch or sugar cane. When PLA is polymerized from lactic acid monomer, it is difficult to obtain high molecular weight PLA due to hydrolysis. To obtain high molecular weight PLA, two lactic acid molecules form cyclic dilactate ester(lactide) first, and then PLA is polymerized from lactides by ring-opening polymerization. PLA produced by such a process has similar mechanical properties to polyethylene terephthalate (PET) which is a widely used plastic commercially [8].

Important features of PLA are its biodegradability in human body and compostability by microorganism in soil [7]. For these reason, PLA has been getting the spotlight as a substitute for polymeric material obtained from oil-based plastics like PET, PBT (Polybutylene terephthalate), and PP (Polypropylene). However, low HDT (55℃) of PLA which is lower than its glass transition temperature is an obstacle to applications at over a certain temperature. To enhance properties of PLA, blending of PLLA and PDLA has been proposed.

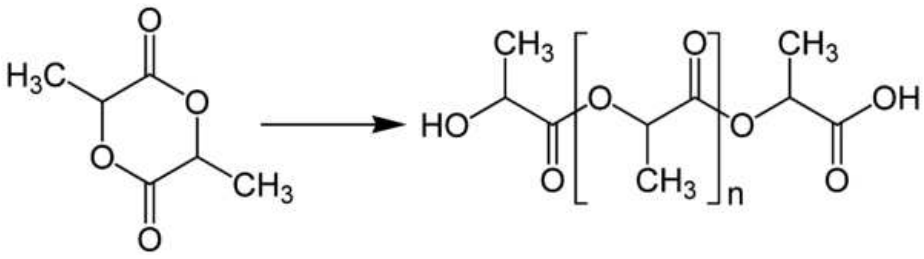

Figure 1. Catalytic and thermolytic ring-opening polymerization of lactide(left) to poly lactic acid(right)

2.2. Stereocomplexation

A formation of PLA stereocomplex(stereocomplexation) by blending PLLA and PDLA enhances various properties such as melting temperature (220~240℃), HDT (160~170℃), and thermal resistance [17]. Also, hydrolysis resistance is enhanced by stereocomplexation. PLA stereocomplex has higher number average molecular weight (M_n), tensile strength, and shows lower weight reduction under long time hydrolysis circumstance compared to PLA [16].

PLA stereocomplex has its crystallinity(2θ = near the 12^o, 21^o, and 24^o) distinguished from that of PLA(2θ = near the 15^o, 17^o, and 19^o) when analyzed by WAXS [18].

The solution casting is a representative process to prepare PLA stereocomplex. This batch process is done by evaporating a solution dissolving PLLA and PDLA. It takes at least two days and generally one weak for the solution casting process at mild or high temperature condition [10,12,13,16,17,20,21]. Additionally, some studies reported solution casting which was accompanied with annealing at high temperature (200~210℃) during several hours to obtain PLA stereocomplex without any trace of PLA homocrystallites [10,20].

Table 1. Comparison of general properties of bio-based polymers and oil-based polymers [8]

		Bio-based polymer				Oil-based polymer		
		PLLA	s-PLA	PBS	PHA	PET	PBT	PP
Density	g/cm^3	1.26	-	1.26	1.14	1.38	-	0.91
T_m	℃	160-170	220-240	114	60	260	220	164
T_g	℃	58-60	65-72	-32	-60	80	50	5
HDT	℃	55	160-170	97	56/47	120-160	-	110
Tensile strength	MPa	68	90	57	61	57	62	32
Elongation at break	%	4	30	700	730	300	10	500

s-PLA: PLA stereocomplex, PBS: poly butylene succinate, PHA: poly 3-hydroxalkanoate, PET: poly ethylene terephthalate, PBT: poly butylene terephthalate, PP: poly propylene

2.3. Supercritical fluids

2.3.1. Definition of supercritical fluids

Supercritical fluid is defined as state where substance is above its critical temperature (T_c) and critical pressure (P_c). Properties of supercritical fluid is frequently considered to be intermediate between that of liquid and gas. When substance reaches to supercritical state, it is appeared that surface between liquid and gas is gone ambiguous. In this condition, supercritical fluid has intrinsic properties which are distinguished from liquid or gas. Its properties include merits of both liquid-like and gas-like properties. Advantages of liquid-like properties are high density and strong solvent power which result in high solubility. And advantages of gas-like properties are high diffusivity and low viscosity which facilitate rapid mass transfer and penetration to micro-sized structures.

Commonly, properties of solvent are determined by a kind of molecule and an interaction between molecules. In case of liquid solvent, it is difficult for the properties of solvent to be significantly changed due to its imcompressibility. However, solvent under supercritical state undergoes a large transition of properties such as density, viscosity, polarity, and diffusivity, et cetera with slightly variation of pressure near the critical point.

Supercritical fluid process which utilizes above advantages is an innovative technology that can be a solution of technical difficulties like

a low efficiency and a low quality in overall existing processes, including extraction, crystallization, drying, fractionation, absorption, distillation, et cetera.

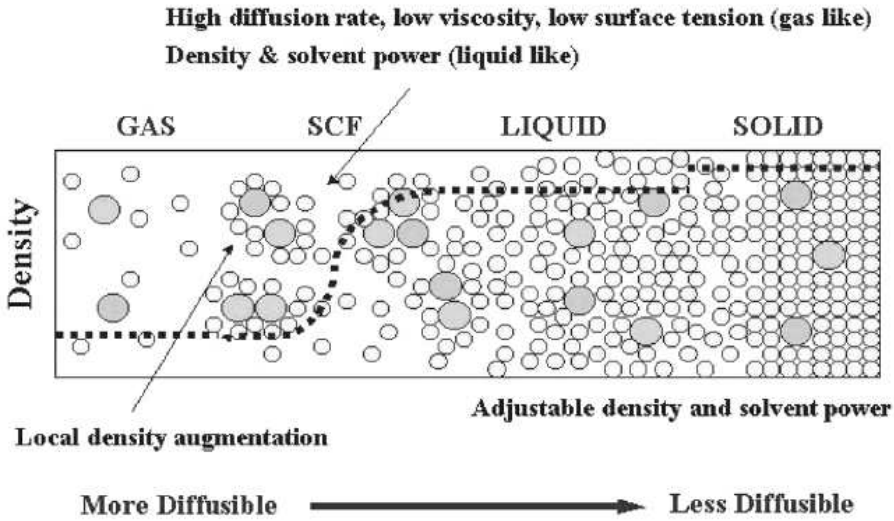

Figure 2. Fluctuation of density due to molecular association of supercritical fluid [23]

2.3.2. Properties of supercritical fluids

Critical point defined as T_c and P_c indicates end of gas-liquid coexistence curve in phase diagram. Phase transition from liquid to gas occurs generally with discontinuous change in properties. However, properties of supercritical fluid exist in a wide range of temperature and pressure. Therefore, properties can be changed continuously by controlling temperature and pressure under supercritical condition. Near the critical point, a slight variation of temperature or pressure results in a large change in properties of a substance. Figure 4 shows projection of gas-liquid coexistence curve on reduced density-pressure plane. Temperature and pressure are expressed as reduced values which are divided by critical temperature and critical pressure respectively. A left region of gas-liquid coexistence curve indicates two phases, and equilibrium of two phases is expressed by a vertical tie line. In this diagram, the region of supercritical fluid is expressed as a right side of isothermal line at $T_r = 1$ with $P_r > 1$. Supercritical fluid can have high solvent power like liquid. It is because the density of supercritical fluid can be as high as that of liquid by controlling temperature and pressure. Because density is used as index of solvent power, temperature and pressure can be utilized as variables for solubility of solute and solute fractionation from solvent. For example, the density of CO_2 decreases by 80% at 1.1 reduced temperature, as reduced pressure decreases from 3 to 1. Temperature and pressure conditions which are generally utilized in supercritical fluid processes are generally ranged in 1~1.2 reduced temperature and pressure higher than critical point. Diffusivity and viscosity have an effect on mass transfer rate.

Generally, diffusivity of supercritical fluid is at least 10 times higher than that of liquid. In case of viscosity, it is 10~100 times lower than that of liquid and similar to that of gas. It means diffusion via supercritical media is higher than liquid media. Furthermore, low surface tension of supercritical fluid can help fast diffusion to micropore structure. However, it does not mean that mass transfer rate in supercritical fluid is not limited. Extraction of solute from liquid to supercritical fluid is restricted by mass transfer rate in liquid, and this limitation of diffusion controls overall coefficient of mass transfer. Stirring is, therefore, still important to such a system.

Most of supercritical fluids utilized are low molecular weight gases having relatively low critical temperature. For this reason, processes for recovery of substance can be operated at an appropriate temperature when substance is stable. Above all things, most important advantage of supercritical fluid process is free-residual solvent process.

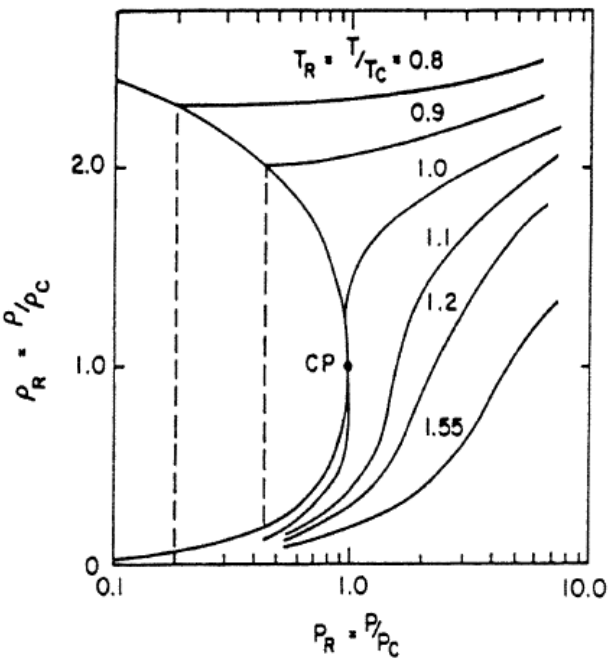

Figure 3. Phase diagram of pure substance in reduced density-pressure coordinates [24]

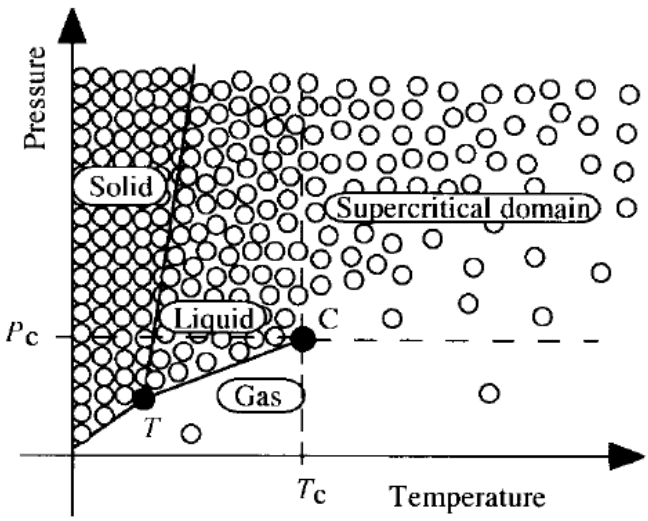

Figure 4. Schematic representation of a phase diagram [25]

Table 2. Order of magnitude of physical properties of gas, supercritical fluid, and liquid

	Density ($g\ cm^{-1}$)	Viscosity coefficient ($g\ cm^{-1}\ s^{-1}$)	Diffusion coefficient ($cm^2\ s^{-1}$)
Gas	10^{-3}	10^{-4}	10^{-1}
Supercritical fluid	10^{-1}~1 *Liquid-like*	10^{-4}~10^{-3} *Gas-like*	10^{-4}~10^{-3} *Liquid-like*
Liquid	1	10^{-2}	$< 10^{-5}$

2.3.3. Properties of supercritical CO_2

Industrially, CO_2 is favored as a supercritical fluid medium, because CO_2 has relatively low critical temperature and pressure (T_c = 304.15K, P_c = 7.38MPa) compared to water(T_c = 647.15K, P_c = 22.12MPa) or methanol (T_c = 512.6K, P_c = 8.09MPa). Also, it is cheap, noncombustilble, nontoxic, and recyclable. Therefore, development of eco-friendly and energy savable process is available by using CO_2. Especially, due to diffusion property of supercritical CO_2, it is being applied in various fields such as organic synthesis, electrochemical synthesis, and polymer synthesis. Also, a lot of studies are carried out in pharmaceutical field and industry of spice or food due to great extractability of supercritical CO_2 at mild condition. In case of protein, one of thermolabile substances, it needs to be treated at 0~50℃, since it is vulnerable to high and low temperature. If protein is dried by hot air drying or freeze drying, medicinal effect decreases rapidly. Furthermore, because 3-dimensional structure is also important to its activity, its effectiveness also decreases when its structure is broken by capillary force such as surface tension. For this reason, it is difficult to obtain active protein when it is treated with organic material like a surfactant. By using supercritical CO_2, these limitation can be overcome. As well as these advantages, supercritical CO_2 can be used to prepare particle with smaller size distribution.

Despite above advantages, little solubility of polar materials to supercritical CO_2 makes it difficult to utilize CO_2 as a solvent to polar substances. Various studies have been carried out to overcome this disadvantage. Among these studies, studies regarding micro and macro

emulsion are performed. In these technologies, polar materials like water are sprayed into CO_2 as nano ~ micro sized droplet. Various studies such as reaction, extraction, fractionation, and electric gilding have been carried out using this principle.

2.3.4. Particle preparation method using supercritical/ subcritical fluids

Long period usage of supercritical fluid in particle preparation technology has resulted in formation of various processes using mechanism of nucleation and growth. Processes of particle preparation using supercritical fluid are explained below in detail [23,26,27]. Among these processes, aerosol solvent extraction system (ASES) is utilized to obtain PLA stereocomplex particles and drug complex particles which are target materials in this study.

2.3.4.1. Rapid expansion of supercritical solution (RESS)

Hannay and Hogarth, at conference of Royal Society of London in 1897, reported a formation of snow-like materials when high pressured substance is emitted to atmosphere. Developed from this discovery, RESS is suggested for engineering application by Krukonis at American Instinute of Chemical Engineers in 1984.

This process is used when target material has a solubility to supercritical fluid. First, target material dissolves in supercritical fluid with high pressure, and then it is precipitated at exit with an abrupt decrease in pressure. This precipitation is done by difference in solubility ranging low pressure to high pressure. Principle of phase separation due to pressure difference is described in Figure 5 which is explaining principle of particles precipitation. Temperature of solution decreases as pressure is decreases, and particles are prepared in a boundary of fluid-solid (F-S) or that of liquid-liquid (L-L) according to a degree of reduction in temperature.

Shape of particles obtained by RESS varies with expansion nozzle, temperature, and pressure, and can be spherical, fibrous, and film form. If solubility of target material to supercritical fluid is low, co-solvent is used to enhance solubility. In this case, aggregation of particles can be observed. If polymers are abundant in solution, fibrous or film form of products are obtained in many cases. When supercritical fluid is expanded, a polymer is precipitated as liquid or solid phase. Fibrous polymer are obtained when they are precipitated as liquid phase, and a diameter of fibrous polymer is usually about 1~5mm.

One advantage of RESS is that several micro sized particles with relatively narrow size distribution can be obtained quickly. Besides, crystallization and drying are performed at the same time, and no residual solvent exists in particles. Also, it is simple to collect products. For these reasons, space for filtration, washing, and drying process can be saved. In spite of these advantages, RESS has some disadvantages; this process needs a large amount of supercritical fluid to obtain a small amount of particle, since most target materials have low solubility in supercritical fluid.

To treat organic compounds, CO_2, nitrous oxide, trifluoromethane, ethylene, and pentane can be used as supercritical solvent. To enhance solubility of organic compounds in supercritical solvent, several percentages of polar solvent can be used. RESS is a attractive process in lab scale due to its simplicity. However, it is difficult to control particle size distribution in industrial scale. Furthermore, RESS can be used in only limited field due to low solubility of solute in supercritical solvent.

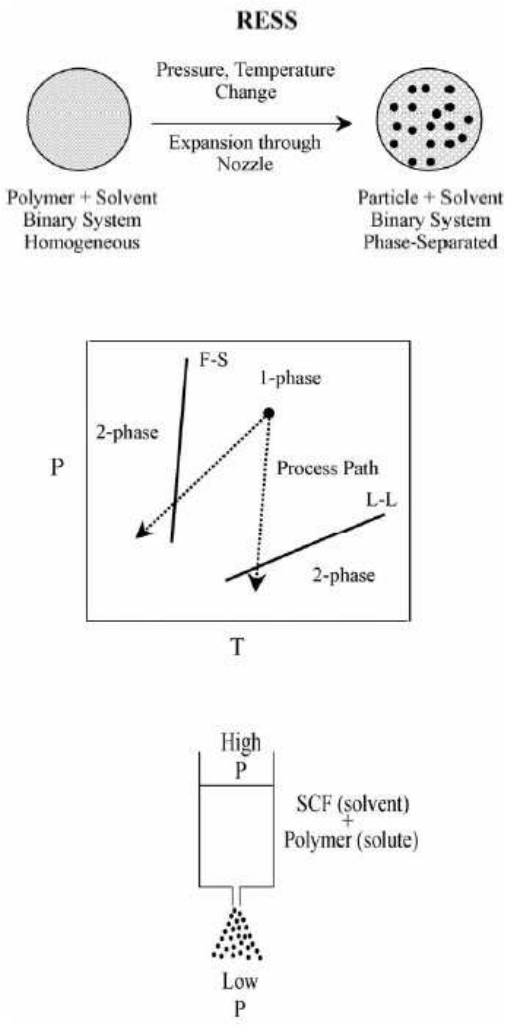

Figure 5. Schematic representations of the RESS process and its operational principles [26]

2.3.4.2. Gas anti-solvent (GAS)

A concept of GAS trace back to middle of 1950s. In 1954, Francis described precipitation effect in a binary and ternary system using liquid CO_2. GAS was proposed by Gallapher as a process for recrystallization of explosive using supercritical CO_2.

This process is used to recrystallize solute which does not dissolve in supercritical fluid. GAS is appropriate process for recrystallization of chemicals which are not soluble in supercritical fluid. First, organic solution dissolving target material is prepared, and then gas is sprayed into precipitator which contains organic solution. At this time, gas is used as anti-solvent of target material. Concentration of gas in solution increases as pressure increases. This results in precipitation of target material from organic solution. A phase of gas don't need to be supercritical state. As shown in figure 6, boundaries of solid/liquid and liquid/liquid, in case of using the gas as an anti-solvent, shift to higher temperature and pressure region. As a result, a system, which is one phase at first, experiencesva phase separation, and this leads to particle precipitation. The most distinguished difference between GAS and RESS is that GAS deals with a ternary system, whereas RESS deals with a binary system.

2.3.4.2. Supercritical anti-solvent (SAS)

This process is also known as aerosol solvent extraction system (ASES) or precipitation with a compressed anti-solvent (PCA). In this process, supercritical fluid is used as an anti-solvent of target material. First, a solution dissolving target material is prepared, and then this solution is sprayed into a precipitator which is already filled with supercritical fluid. Because sprayed solution is broken into fine droplets, a mass transfer rate between solution droplet and supercritical fluid is enhanced. This results in higher and faster supersaturation, which leads to rapid nucleation rate and precipitation of fine particles. After precipitation is finished. washing process is carried out by flowing supercritical fluid continuously to remove a residual solvent from particles.

SAS has many advantages. It is operated at lower temperature and pressure compared to RESS. And, it is competitive process for micronization of various medicines or proteins without residual solvent. Furthermore, oxidization is prevented, since process is isolated from oxygen and light. Due to this isolated operation environment, reproducibility is guaranteed. Continuous process is also available for mass-production of particles.

Meanwhile, solution enhanced dispersion by supercritical fluids (SEDS) was designed to obtain rapider precipitation rate compared to ASES. In this process, solution and supercritical fluid are sprayed via specially designed nozzle at the same time. This causes solution to be exposed to high-flowrate supercritical fluid, and leads to faster nucleation rate.

As a result, product with smaller particle size can be obtained compared to ASES.

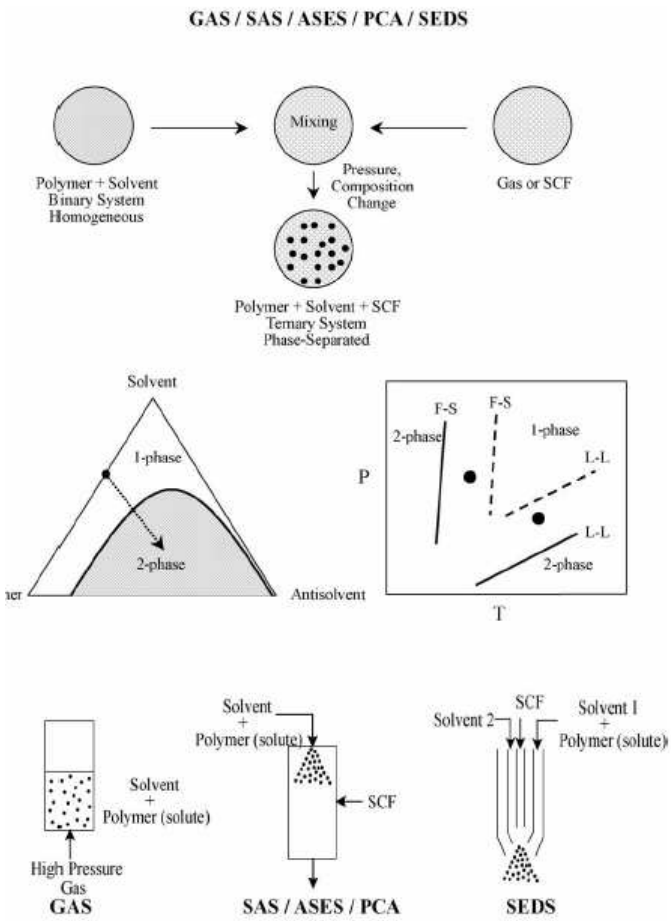

Figure 6. Schematic representations of the GAS, SAS, ASES, PCA and SEDS processes and their basic operational principles [26]

2.3.4.3. Particle from gas-saturated solutions (PGSS)

PGSS is designed to prepare particles which absorbs supercritical fluid up to dozen of weight percentages. In this process, a target material doesn't need to dissolve in supercritical fluid, but supercritical fluid has to dissolve in liquid phase. First, gas-saturated solution/suspension is prepared by dissolving supercritical fluid in solution. And then, gas-saturated solution/suspension is sprayed into expansion chamber via nozzle and rapidly depressurized. As a result, fine particles without residual solvent can be obtained.

PGSS is applicable to preparation of complex particles, and has a merit of a little amount of supercritical fluid usage.

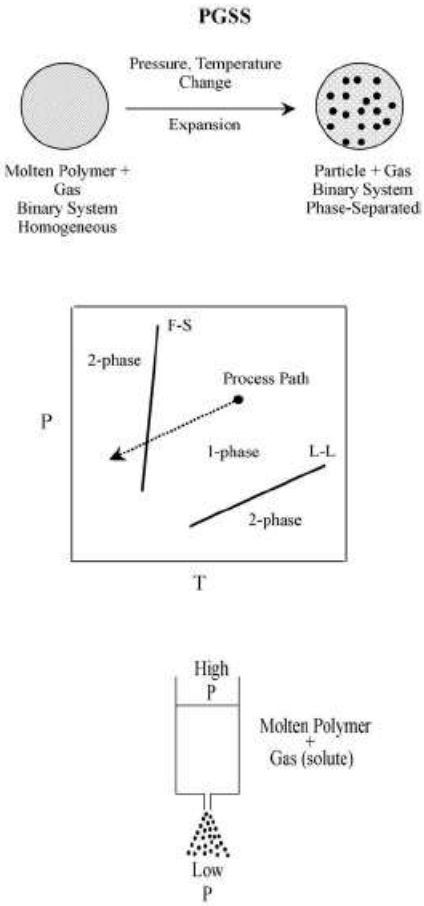

Figure 7. Schematic representations of the PGSS process and its basic operational principles [26]

3. Preparation of PLA stereocomplex by ASES using supercritical CO_2

3.1. Experimental

3.1.1. Materials

PLLAs with M_w: 74,000, 100,000, 142,000Da and PDLA with M_w: 300,000Da were supplied by Cheil Industries Inc. in Korea. Dichloromethane (99.5%) and chloroform (99.5%) employed as organic solvent were purchased from Samchun Pure Chemical Co., Ltd. in Korea. Carbon dioxide (99.0%) used as anti-solvent were purchased from Hyup-Shin Gas Industry Co. in Korea.

3.1.2. Experiment apparatus and procedure

Figure 8 shows a schematic diagram of ASES apparatus. Pre-cooler was used to maintain temperature of CO_2 low at which CO_2 is at liquid phase. CO_2 was pressurized by CO_2 pump and heated by pre-heater up to experimental condition (40℃, 100bar, 50mL/min). Pressure was controlled by using back pressure regulator (26-1721-24, Tescom, USA), and temperature was measured by K-type thermocouple. High pressure cell (60ml, 115mm in width, 95mm in length, 240mm in height, made of SUS 316) was filled with pressurized and heated CO_2. The high pressure cell was maintained at experiment temperature (40℃), since it is equipped with two heat transfer jackets containing circulating medium. On the other hand, solution was prepared by dissolving PLLA and PDLA in organic solvent (dichloromethan or chlorofom) at the same time. Detailed solution conditions will be explained later. Solution was pumped by solution pump (1mL/min). In this apparatus, two solution pump line exist, but only one line was utilized in chapter 3. In chapter 4, all line was employed. Pumped solution was sprayed into high pressure cell filled with supercritical CO_2 via single nozzle, and this led to particle precipitation. After solution spraying was finished, CO_2 was continuously supplied to high pressure cell during 15 minutes to wash out residual organic solvent in particles. Precipitated particles were deposited at 0.45μm pore sized membrane filter (Type FHLP, PTFE, Merck Millipore Ltd, Korea) while mixture of CO_2 and organic solvent continuously flowed to gas-liquid separator through back pressure regulator. In the separator, gasified CO_2 and organic solvent were separated, and CO_2 was vented. When

washing process was finished, particles could be collected from filter after depressurization.

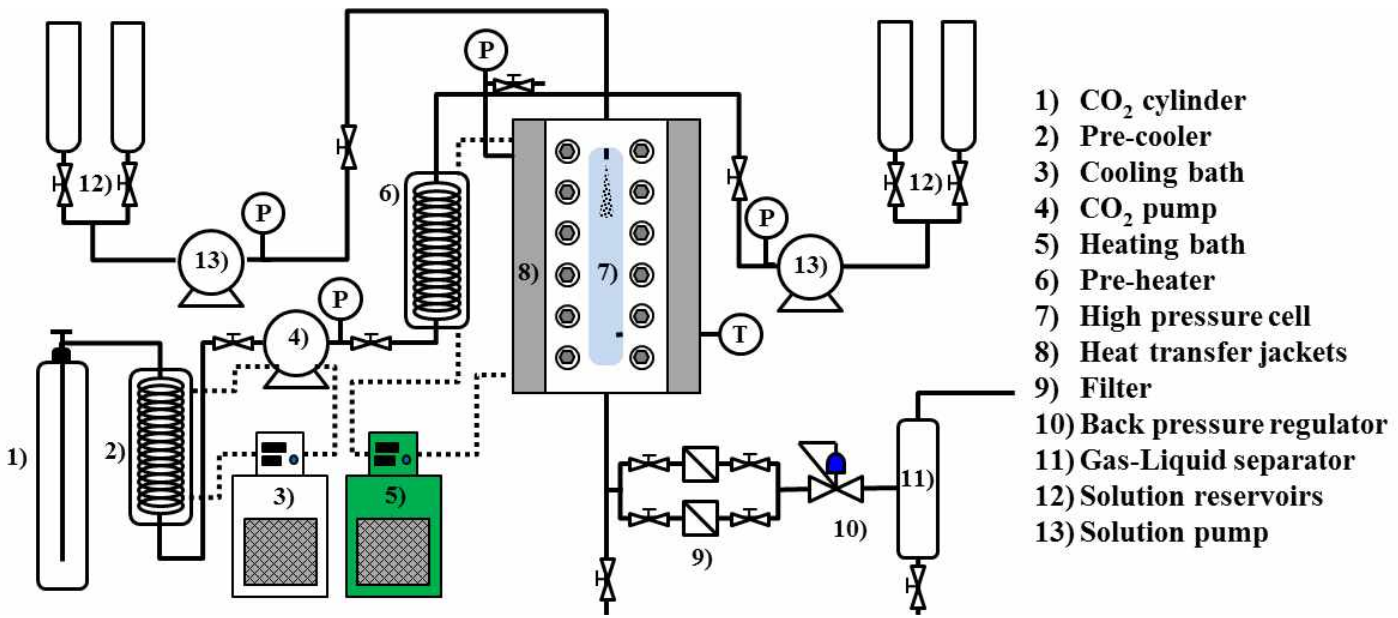

Figure 8. Schematic diagram of ASES apparatus

3.1.3. Characterization

3.1.3.1. Differential scanning calorimetry (DSC)

The melting point of raw PLAs and PLA stereocomplexes were measured by DSC (TA Instrument Inc., DSC Q100, USA). About 1~3mg of the samples was used to prepare DSC pan. The temperature was increased from 40℃ to 250℃ at a ramp rate of 5℃/min under 50mL/min nitrogen (99.999%, Hyup-Shin Gas Industry Co., Korea) flow condition.

3.1.3.2. Wide angle X-ray scattering (WAXS)

Crystallinity of raw PLAs and PLA stereocomplexes were analyzed by WAXS (Bruker AXS Inc., D/D8 DISCOVER with GADDS, Germany). The WAXS measurements were performed at 25℃, 40kV, and 45mA. Measurement 2θ range was 0~40 in 0.02 stepsize.

3.1.3.3. Field emission scanning electron microscopy (FE-SEM)

The images of PLA stereocomplexes were obtained by FE-SEM (Carl Zeiss, SUPRA 55VP, Germany) with energy dispersive X-ray spectrometer (EDS, Bruker, XFlash Detector 4010, Germany) attachment. Samples were prepared by spreading PLA stereocomplex powder on carbon tape and coating with platinum using a sputter coater

(BAL-TEC, SCD 005, USA). FE-SEM was operated at 2kV and magnification was 10k times.

3.2. Results and discussions

3.2.1. Selection of proper solvent

It was first attempted to select a proper solvent which dissolves target material. In solution casting process, Dichloromethane (MC) and Chloroform ($CHCl_3$) have been used generally as a solvent dissoving PLA. In this study, to select more appropriate solvent for ASES, two experiments were conducted. One used dichloromethane and the other one used chloroform. Both experiment was carried out using PLLA (100,000Da), PDLA (300,000Da). 2wt% of PLA (PDLA/PLLA = 1) solutions were prepared. DSC and WAXS were used for analysis.

As described in figure 9, product from experiment using MC showed only melting behavior of PLA stereocomplex (s-PLA) (218.5℃). However, in case of product from experiment using $CHCl_3$ melting behavior of homo-crystallite (177.9℃) besides that of PLA stereocomplex (218.7℃) was observed slightly. It seemed that homo-crystallite remained in product from $CHCl_3$ solution.

From WAXS profiles as showed in figure 10, on the other hand, both products showed peaks of PLA stereocomplex (MC: 12.1^o, 20.7^o, 24.0^o, $CHCl_3$: 12.2^o, 20.7^o, 23.7^o). However, they also showed peak of PLA (MC: 16.7^o, $CHCl_3$: 16.5^o). This result indicates that stereocomplex crystallites were formed predominantly, but homo-crystallites also existed. In spite of crystallinity peak of PLA homopolymers, product didn't show melting behavior of PLA when precipitated from MC

solution. In addition to this, formation of PLA stereocomplex was more predominant when recrystalized from MC solution judging from peak intensity of stereocomplex crystallites compared to homo-crystallites. Also, crystallinity of PLA stereocomplex from MC solution was much higher than that from $CHCl_3$ solution.

From these results, MC was selected as a proper organic solvent in ASES. In the following experiments, only MC was used to prepare PLA solution.

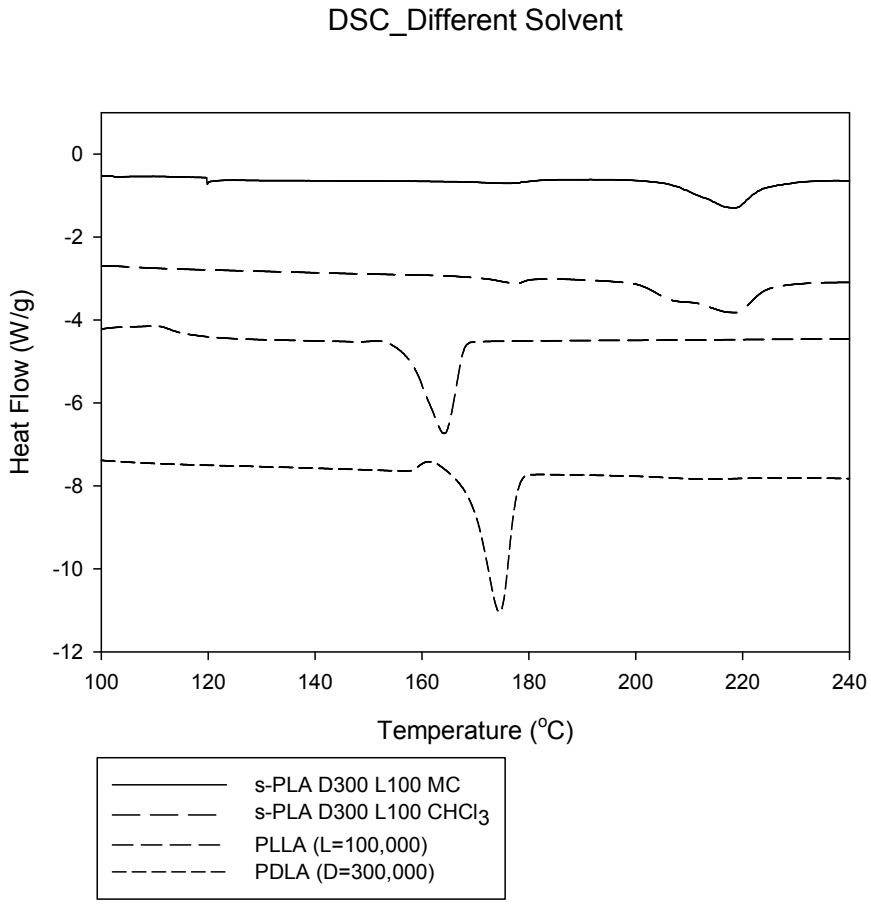

Figure 9. DSC curves of raw PLAs and PLA stereocomplexes with different solvent

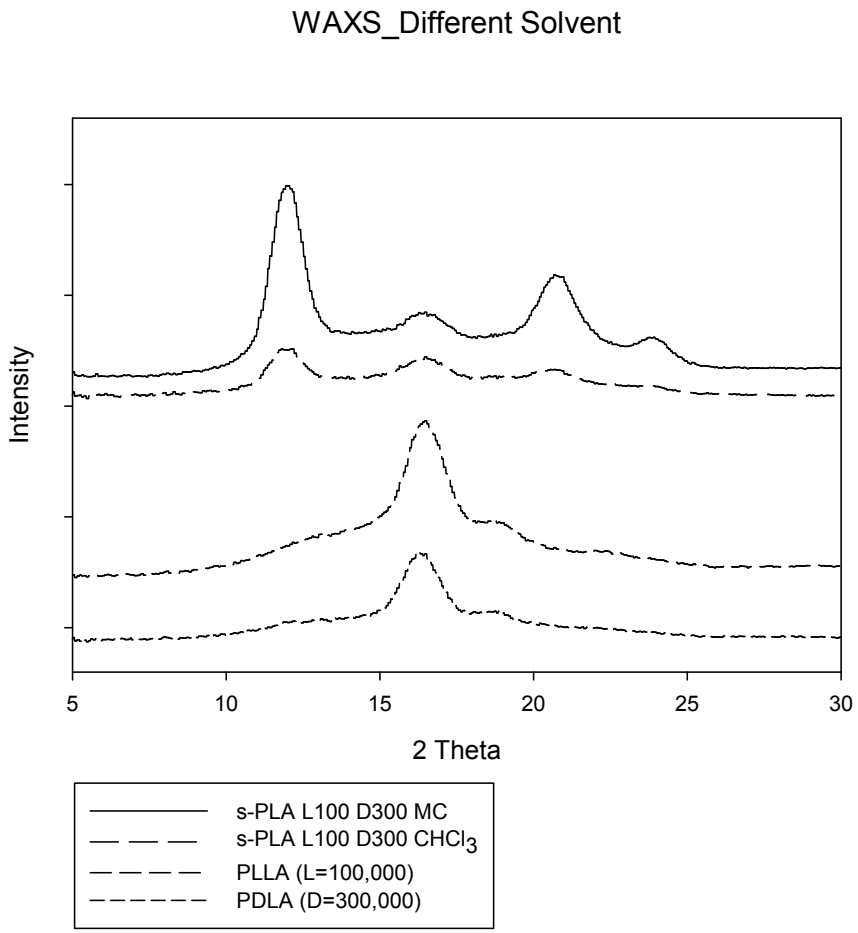

Figure 10. WAXS profiles of raw PLAs and PLA stereocomplexes with different solvent

3.2.2. Effect of PLLA/PDLA weight ratio

According to literatures, optimum blending ratio of PLLA to PDLA for preparation of PLA stereocomplex is 1:1 weight ratio [9,11,21]. To clarify that 1:1 weight ratio is also optimal in ASES, various experiments with different weight ratio condition were conducted. Weight ratio of PDLA (300,000Da) to PLLA (142,000Da) varied from 3:1 to 1:3. And 2wt% of PLA-MC solution was prepared. The DSC was used to confirm PLA stereocomplex was formed without any trace of PLA homo-crystallite. Analysis data is shown in figure 11.

From DSC analysis, it was confirmed that 1:1 weight ratio is optimal in ASES. When weight ratio of PDLA to PLLA was 1:1, product showed only melting behavior of PLA stereocomplex. However, melting behavior of PLA homopolymer was observed in addition to that of PLA stereocomplex when weight ratio was changed.

From these results, it is confirmed that 1:1 weight blending ratio of PDLA to PLLA is also applied to stereocomplexation by ASES. All other experiments were carried out with PLA solution dissolving enantiomeric polymers at the same weight ratio.

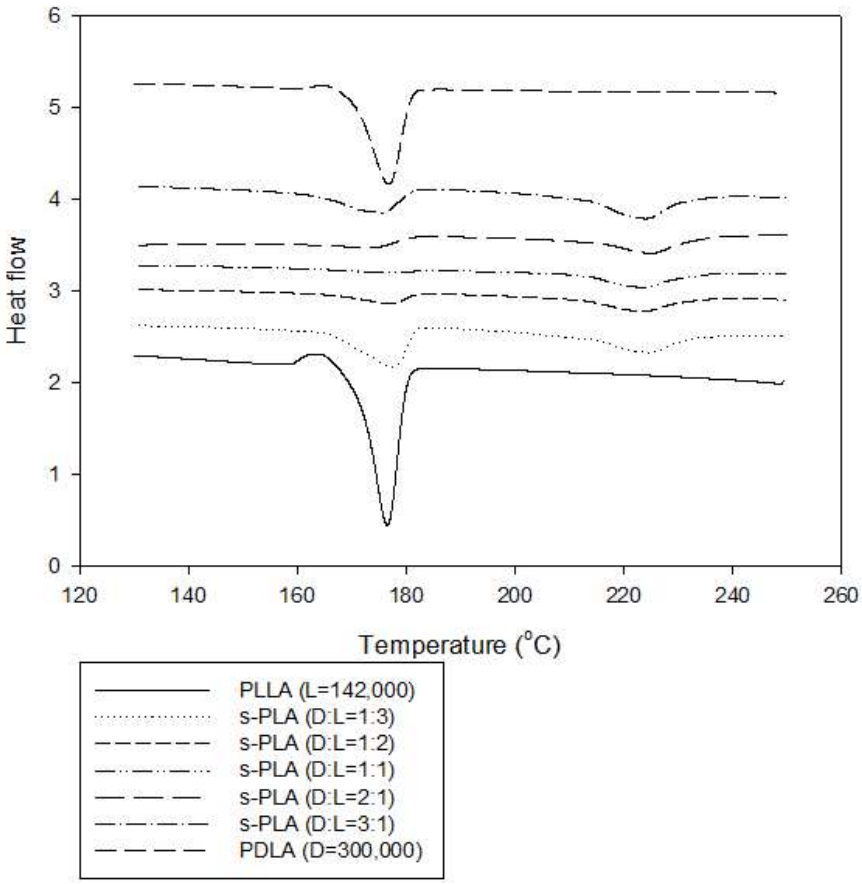

Figure 11. DSC curves of raw PLAs and PLA stereocomplexes with different weight blending ratio

3.2.3. Effect of PLLA molecular weight

In some literatures, molecular weight of PLA has an effect on priority between stereocomplexation and homo-crystallization in melt crystallization [14] and solution casting [12]. When the higher molecular weight of PLA was used, the lower tendency of stereocomplexation was observed. However, no relationship between molecular weight of PLA and priority was reported in precipitation into organic anti-solvent [11]. To confirm effect of PLLA molecular weight on properties of PLA stereocomplex in ASES, three PLLA having different molecular weight (74,000, 100,000, 142,000Da) were used to prepare products. Molecular weight of PDLA was 300,000 Da. 1:1 weight ratio of PDLA and PLLA were dissolved in MC as 2wt%.

From the DSC data shown in figure 12, PLA stereocomplex without melting behavior of PLA homopolymers was prepared though PLLA with different molecular weight was used (PLA stereocomplex with PLLA 74,000Da: 223.4℃, 100,000Da: 218.5℃, 142,000Da: 226.1℃). As for the tendency of stereocomplexation, the same tendency as in melt crystallization and solution casting was observed when ASES was used to prepare PLA stereocomplex. As shown in figure 13, the higher molecular weight of PLLA was used, the higher peak intensity ratio of homo-crystallites (PLA stereocomplex with PLLA 74,000Da: $15.7^{o}/16.5^{o}$(very little trace), 100,000Da: $16.5^{o}/16.5^{o}$, 142,000Da: $16.0^{o}/16.5^{o}$, same as peak of raw PLLA/PDLA each) to stereocomplex (PLA stereocomplex with PLLA 74,000Da: 12.0^{o}, 20.8^{o}, 23.9^{o}, 100,000Da: 12.0^{o}, 20.7^{o}, 23.9^{o}, 142,000Da: 12.0^{o}, 20.9^{o}, 23.8^{o}) was observed. This means stereocomplexation is prior to formation of

homo-crystallites when low molecular weight PLLA is used like solution casting process. However, different from solution casting process, ASES-processed products did not show thermal behavior of PLA homopolymer, although the products showed crystallinity of homo-crystallites. It is distinguished from other preparation processes [9,20,21].

On the other hand, products were obtained as powder in all experiment conditions, and spherical particles were observed by FE-SEM as shown in figure 14. This is difference between ASES and conventional preparation processes (melt crystallization and solution casting).

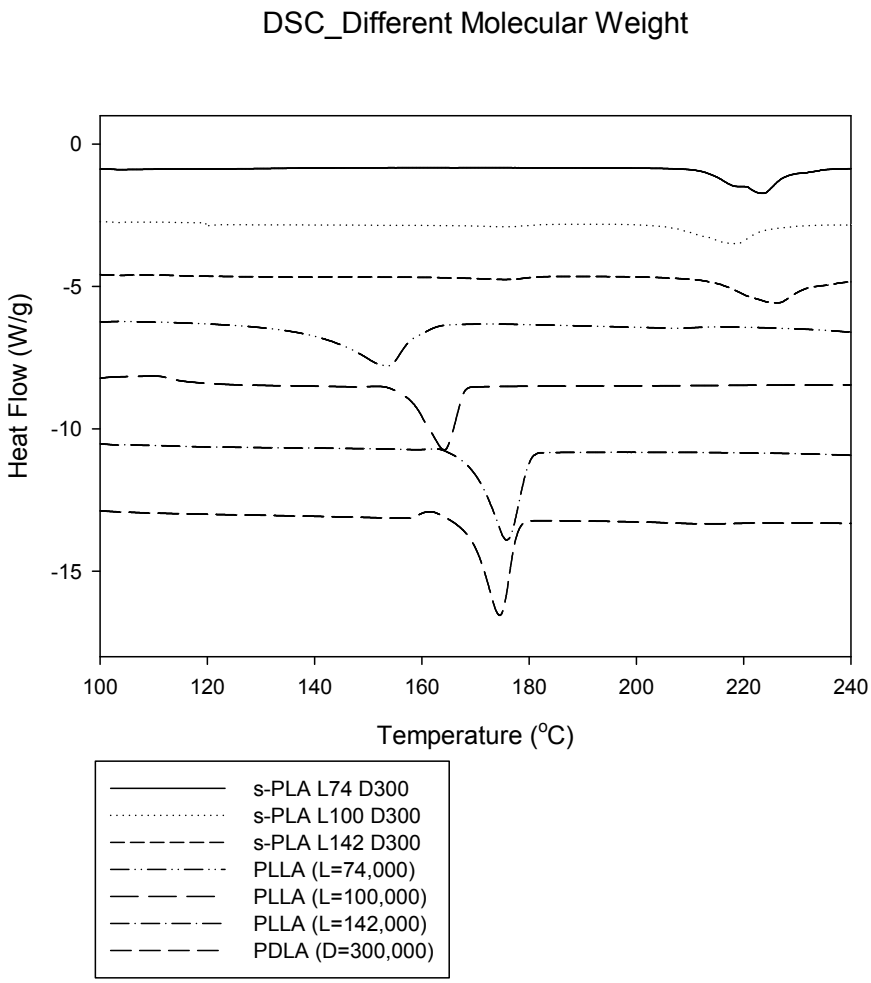

Figure 12. DSC curves of raw PLAs and PLA stereocomplexes with different molecular weight of PLLA

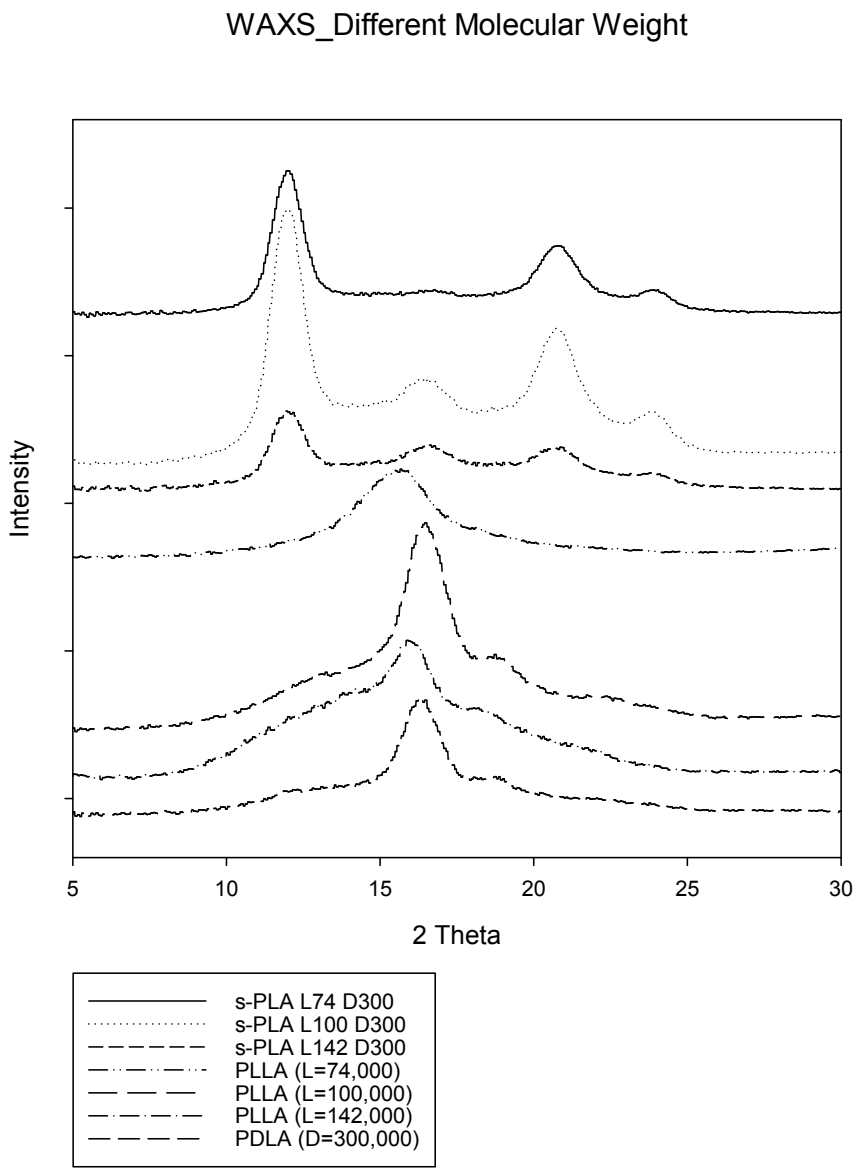

Figure 13. WAXS profiles of raw PLAs and PLA stereocomplexes with different molecular weight of PLLA

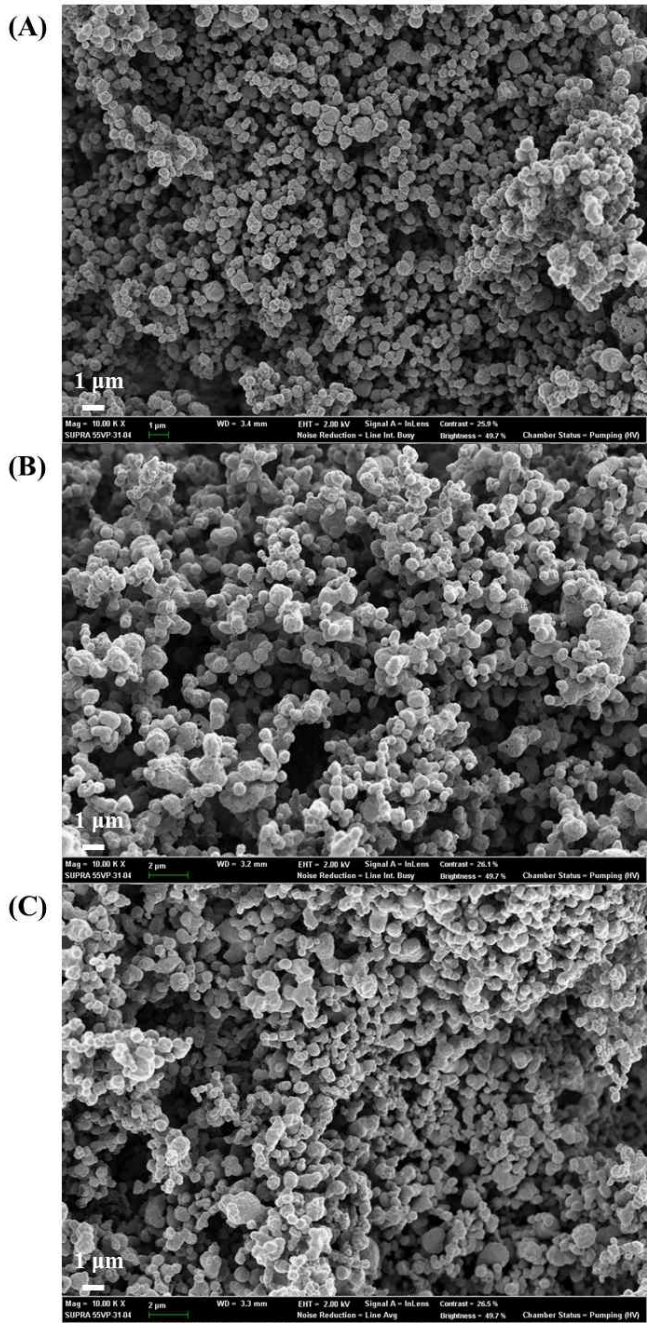

Figure 14. FE-SEM images of PLA stereocomplexes between PDLA (D: 300,000) and PLLA (A) L: 74,000, (B) L: 100,000, (C) L: 142,000

3.2.4. Effect of PLA solution concentration

According to literatures, in solution casting process, critical level of solution concentration where stereocomplexation is predominant is lower than the concentration level where homo-crystallites formation overwhelms [12]. Therefore, during solution casting process, sufficient low evaporation rate is important to give stereocomplex crystallites enough time for nucleation and growth. Therefore, long process time is required when solution casting process is used. With regard to the preparation of PLA stereocomplex from precipitation into anti-solvent, it was also reported that low solution concentration induced the predominant formation of stereocomplex crystallites [11].

When ASES was used to prepare PLA stereocomplex, it was difficult to confirm that low solution concentration is advantageous to form stereocomplex crystallites. As shown in figure 15, any evidence of stereocomplex crystallites formation was not observed as solution concentration was lowered. However, the less solution concentration was used, the less crystallinity of products and the smaller particle size were observed.

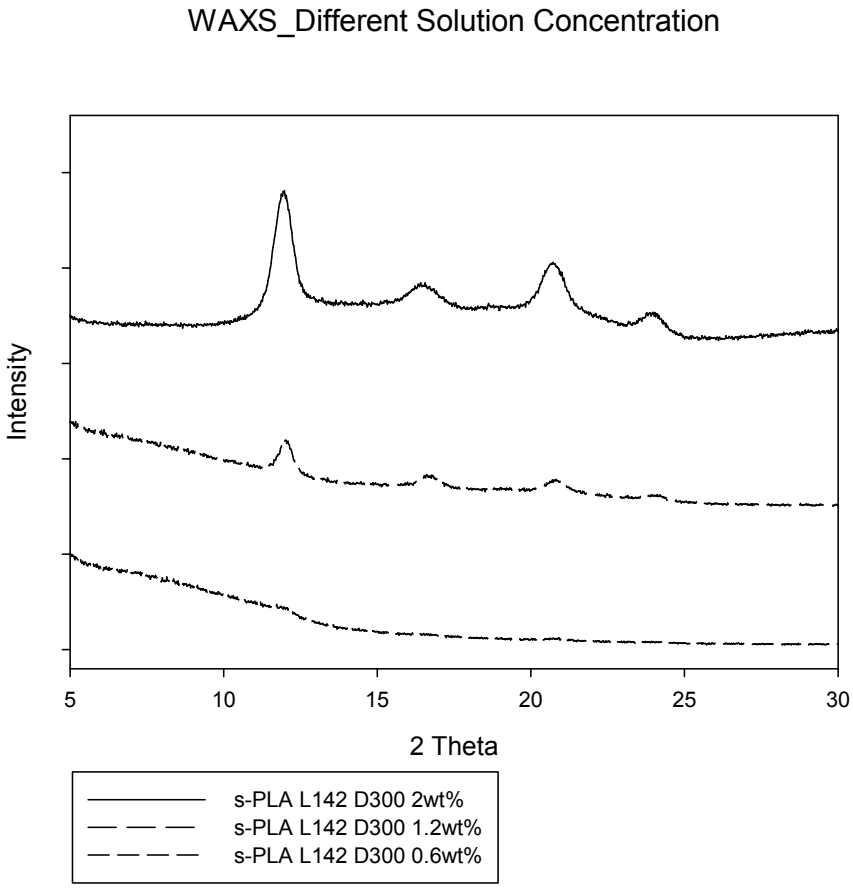

Figure 15. WAXS profiles of PLA stereocomplexes with different solution concentration

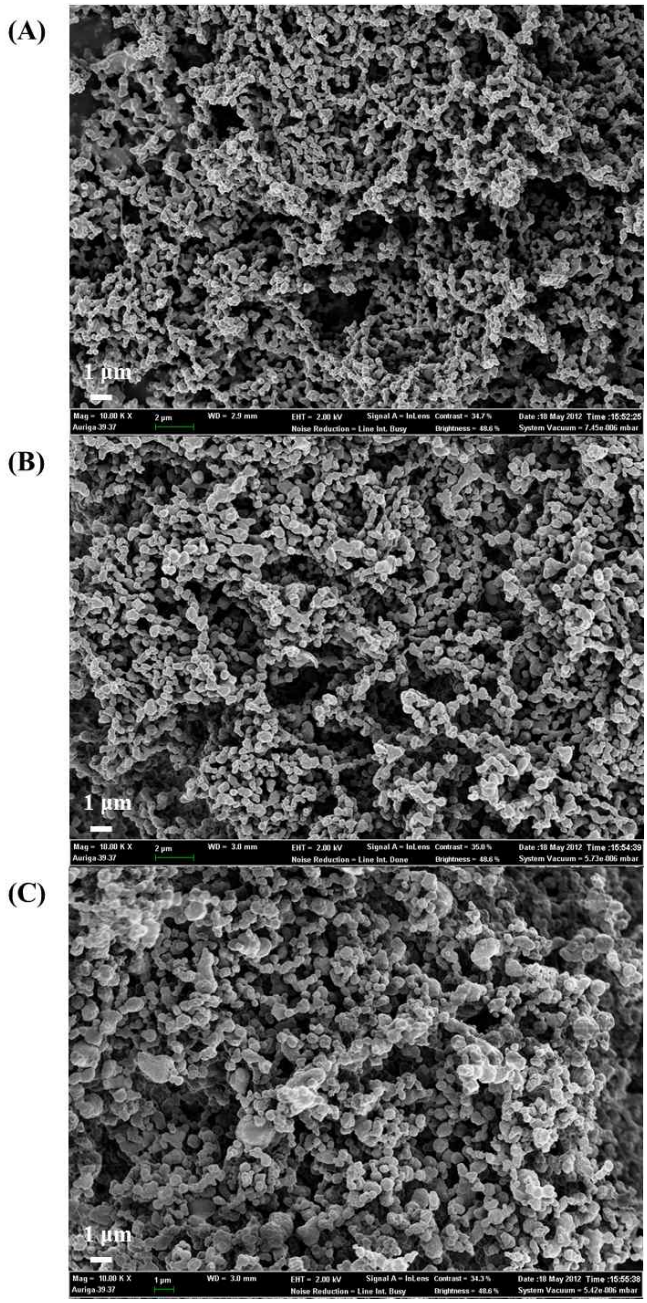

Figure 16. FE-SEM images of PLA stereocomplexes with different solution concentration (A) 0.6% (B) 1.2% (C) 2%

4. Application of ASES to drug encapsulation process

4.1. Experimental

4.1.1. Materials

PLLA with M_w: 100,000Da and PDLA with M_w: 300,000Da were employed as coating materials which were supplied by Cheil Industries Inc. in Korea. Cetirizine dihydrochloride (CTZ), which was employed as a drug encapsulated by coating materials, was purchased from Enzal Chemicals Co., Ltd. in India. Sodium diphosphate dibasic anhydrous (99.0%), dodecyl sulfate sodium salts (85.0%), dichloromethane (99.5%) and ethanol (99.7%), which were used as solute of buffer solution in HPLC analysis, surfactant dissolved in dissolution test medium, organic solvent for PLAs and CTZ each, were purchased from Samchun Pure Chemical Co., Ltd. in Korea. Methanol (HPLC grade), which was employed as eluent in HPLC analysis, was purchased from J.T. Baker® Chemicals. Phosphoric acid (>85wt% in water solution), which was used for titration of buffer solution, was purchased by Sigma-Aldrich, Co., LLC in Korea. The deionized water (DIW) was purified by ultra pure water plant (FR/Milli-Q Advantage A10) which was purchased by Merck Millipore Ltd., in Korea. Carbon dioxide (99.0%) used as anti-solvent were purchased from Hyup-Shin Gas Industry Co. in Korea.

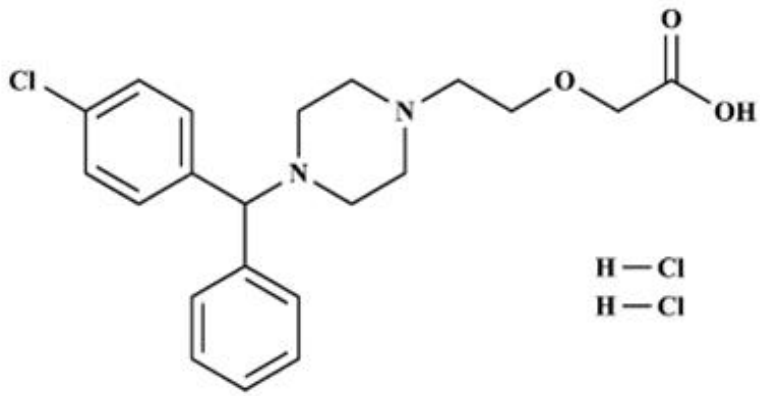

Figure 17. Structural formula of cetirizine dihidrochloride

4.1.2. Experiment apparatus and procedure

4.1.2.1. Preparation of CTZ particles encapsulated by PLA stereocomplex (CTZ complex)

The same ASES apparatus was utilized as in chapter 3. However, CTZ, which are active material, does not dissolve in MC. For this reason, ethanol (EtOH) was employed to dissolve CTZ. To prevent MC from working as anti-solvent to CTZ before solutions were sprayed into precipitator, PLA containing MC solution and CTZ containing EtOH solution were pumped at different solution lines as described in figure 8. However, these two solution were not sprayed via single nozzle. Each of solutions was sprayed via different site of co-axial nozzle as shown in figure 17. This co-axial nozzle was designed to enhance encapsulation efficiency. From inner nozzle, CTZ solution (EtOH) was sprayed, and PLA solution (MC) was sprayed via outer nozzle. The co-axial nozzle is designed for CTZ solution to be surrounded by PLA solution just before solutions were sprayed into supercritical CO_2. This process is distinguished from SEDS. The nozzle of SEDS is designed for solution to contact and be mixed with supercritical CO_2 just before solution is sprayed, to obtain faster precipitation rate than ASES. On the other hand, this co-axial nozzle was designed for solutions to contact supercritical CO_2 in high pressure cell for the first time just after solutions were sprayed. Therefore, this process is also called as ASES. The other process steps are same as that of chapter 3.

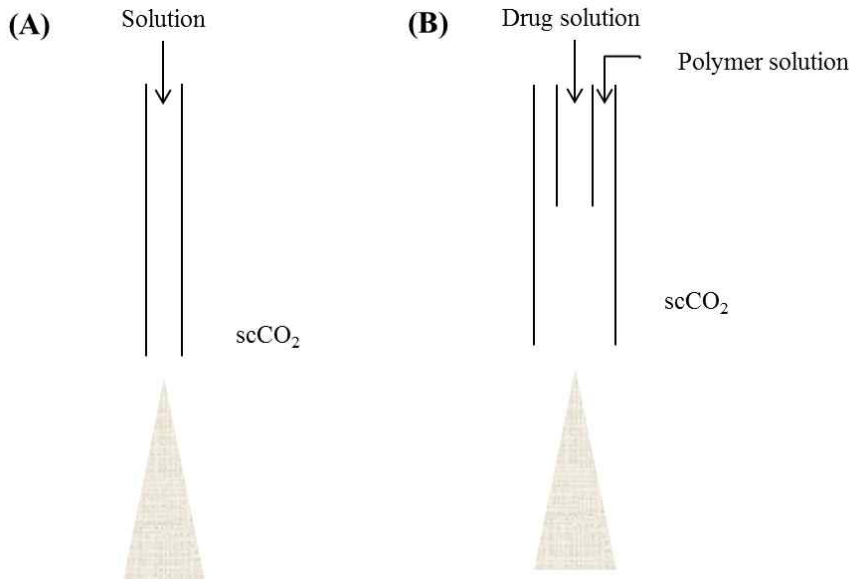

Figure 18. ASES nozzle for (A) single solution precipitation and (B) co-precipitation of two different solution(co-axial nozzle)

4.1.2.2. Drug loading calculation

The drug loading is defined as amount of CTZ contained in unit CTZ complex weight (mg CTZ / mg CTZ complex).

$$Drug\ loading = \frac{amount\ of\ CTZ\ (mg\ \ CTZ)}{unit\ \ CTZ\ complex\ \ weight\ \ (mg\ CTZ\ complex)}$$

To calculate drug loading of prepared CTZ complex, UV-Visible spectrophotometer (UV-VIS, Evolution 201, Thermo Scientific Inc., USA) was utilized. First, three random sampling consist of approximately 40mg of prepared CTZ complex were carried out. Then, three samples were dissolved in EtOH to dissolve only CTZ in CTZ complex. To break PLA stereocomplex structure encapsulating CTZ perfectly, sonication was conducted to CTZ complex-EtOH suspension during one day. After sonication, PLA stereocomplex was broken to colloid, and all CTZ could be dissolved in EtOH. Each samples were analyzed by UV-VIS after filtration by 0.45μm syringe filter (Millex-HV, PVDF, Merck Millipore Ltd., Korea). To confirm concentration of samples, calibration was done using raw CTZ solution (EtOH). Concentration of calibration solutions were 5, 10, 20, 40mg CTZ / 30mL EtOH. From calculated each drug loadings, average drug loading of prepared CTZ complex was calculated.

4.1.2.3. In-Vitro dissolution rate test

To investigate dissolution profile of CTZ complex, dissolution rate test was conducted. The dissolution rate test of CTZ complex was tested using a USP paddle method with a dissolution tester (DST-810, LABFINE INC., Korea) which was maintained as 37℃ during experiment. For dissolution rate test of CTZ complex, 900mL of DIW was prepared in a dissolution test bath. 0.9g of dodecyl sulfate sodium salts (SDS) was dissolved in 900mL of DIW to enhance solubility of CTZ in water [28]. The SDS did not interfere with the CTZ assay (UV-VIS and HPLC analyses). By doing this, CTZ complex settled down adequately for mass transfer without floating on medium. Stirring speed of paddle was 50rpm. Whenever 5mL aliquot was withdrawn, it was replaced by 5mL of DIW. After sampling, 5mL aliquot was immediately filtered through 0.45μm PVDF syringe filter. To compare with dissolution rate of CTZ complex, the other dissolution test bath with raw CTZ was prepared at the same way above. Amount of CTZ and CTZ complex added to dissolution test bath will be explained later in detail. Sampling times were chosen as 1min, 5min, 15min, 30min, 1h, 2h, 3h, 6h, 12h, 18h, 36h, 80h, 135h, 251h, 348h, 450h. Aliquots from samples after 18h, error by evaporation of medium was corrected using dissolution profiles of raw CTZ. Aliquots were analyzed by high performance liquid chromatography (HPLC).

4.1.3. Characterization

4.1.3.1. UV-Visible spectrophotometer (UV-VIS)

To confirm wavelength with highest peak intensity of CTZ and calculate drug loading of CTZ complex, UV-Visible spectrophotometer (UV-VIS, Evolution 201, Thermo Scientific Inc., USA) was utilized. Scan range was 200nm to 700nm wavelength with EtOH baselining. CTZ dissolved in EtOH showed highest peak at 260nm.

4.1.3.2. High performance liquid chromatography (HPLC)

To calculate concentration of samples obtained from dissolution test, high performance liquid chromatography (HPLC, Agilent 1200, Agilent Technologies, USA) was employed. Eluent was prepared by mixing methanol (MeOH) and sodium phosphate buffer solution (pH = 6.5) as 1:1 v/v. Flow rate of eluent was 0.8mL/min. And injection volume was 10μL. 5μm pore sized 4.6mm X 250mm C18 Column (Eclipse Plus C18 Column, Agilent Technologies, USA) was used, and temperature of column was 30℃. UV detector was operated at 260nm.

4.1.3.3. Energy dispersive X-ray spectrometer (EDS)

The images of CTZ complex was obtained by FE-SEM (Carl Zeiss, SUPRA 55VP, Germany) with energy dispersive X-ray spectrometer

(EDS, Bruker, XFlash Detector 4010, Germany) attachment. Sample was prepared by spreading CTZ complex powder on carbon tape and coating with platinum using a sputter coater (BAL-TEC, SCD 005, USA). FE-SEM was operated at 2kV and magnification was 10k times. EDS was operated at 10kV and magnification was 30k times.

4.2. Results and discussions

4.2.1. Preparation of CTZ complex

By co-axial nozzle precipitation using ASES, white powder products were collected from filter. Precipitated products were analyzed by FE-SEM and EDS. Since chloride atom exists only in CTZ, not in PLA stereocomplex, EDS mapping for chloride atom on SEM image of CTZ complex was conducted as shown in figure 18. From EDS mapping image, it was clarified CTZ was spread over all CTZ complex particles evenly. However, it is difficult to say that CTZ was well encapsulated by PLA stereocomplex from only this EDS mapping image. It was also possible red points in EDS mapping image represents CTZ particles without encapsulation. To confirm CTZ was well encapsulated by PLA stereocomplex, following analyses were carried out.

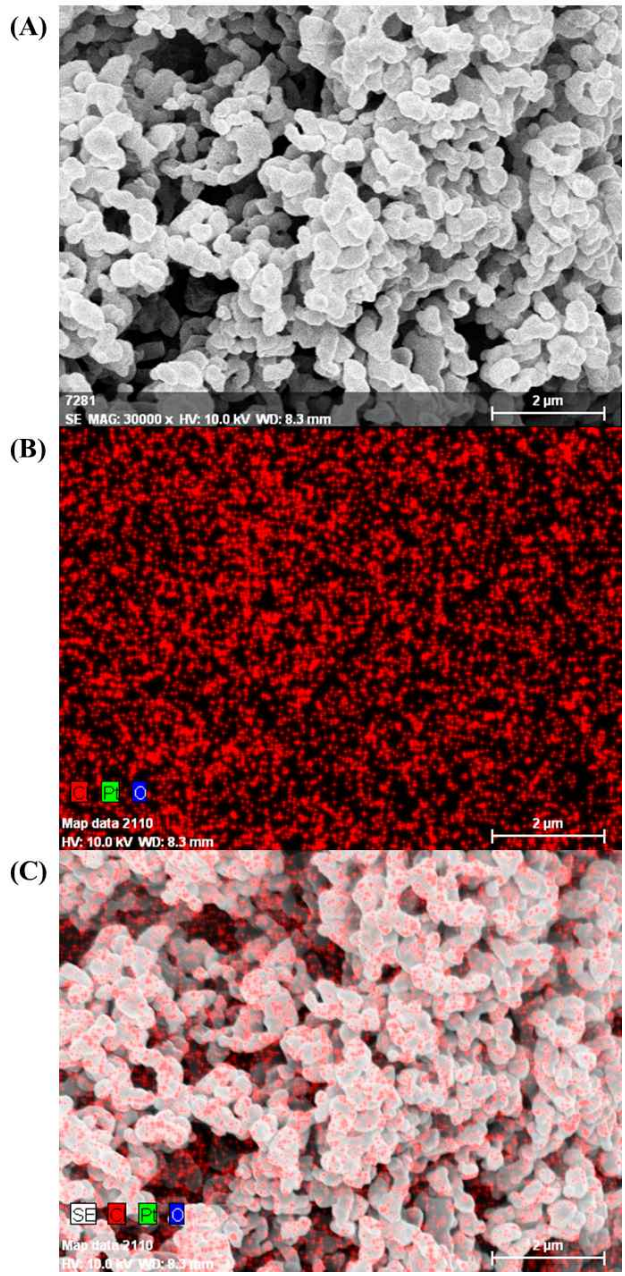

Figure 19. (A) FE-SEM image of CTZ complex, (B) EDS mapping for chloride atom, and (C) FE-SEM image of CTZ complex with EDS mapping for chloride atom

4.2.2. Drug loading calculation

40, 40.7, 42.2mg of CTZ complex were randomly sampled from prepared products. From calibration of raw CTZ solutions (EtOH) as shown in figure 18, drug loading of each samples were calculated. This is described in table 3. According to calculated data, about 21.79mg of CTZ was contained in 40mg of prepared CTZ complex. On the basis of calculated drug loading, next experiment was planned in detail.

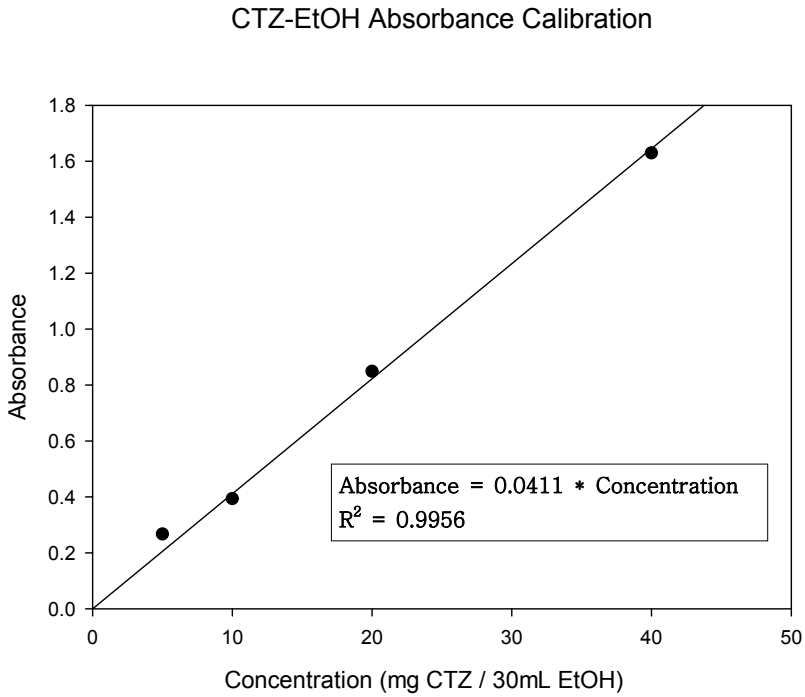

Figure 20. Calibration of cetirizine concentration using UV-VIS spectrophotometer

Table 3. Calculation of drug loading

Sampling weight (mg)	Absorbance	Calculated concentration (mg CTZ / 30mL EtOH)	Drug loading (mg CTZ / mg CTZ complex)	Drug loading per 40mg CTZ complex (mg)
40	0.8702	21.17	0.5293	21.17
40.7	0.8638	21.02	0.5164	20.66
42.2	1.021	24.84	0.5887	23.55

4.2.3. In-Vitro dissolution rate test

40mg of CTZ complex, equivalent to 21.79mg of CTZ from calculated data, and 21.79mg of raw CTZ were employed to each dissolution test baths. Each aliquots were sampled from dissolution rate test and analyzed by HPLC at condition described above. To correct an error from evaporation of water after 18h, corrected peak areas were used. Since all of raw CTZ were dissolved in medium at first one minute, peak areas of raw CTZ were utilized for correction of those of CTZ complex. It is assumed that amount of evaporated water of each baths were same. Dissolution profiles of CTZ complex and raw CTZ during initial one hour (figure 20) showed that approximately 27.5% of CTZ was partially encapsulated by PLA stereocomplex. From dissolution profile of raw CTZ, all CTZ was dissolved in dissolution medium during first one minute. However, 26.2% of CTZ in CTZ complex was dissolved in dissolution medium during 15 minutes. This means PLA stereocomplex partially encapsulates about 27.5% of all CTZ content and interferes with mass transfer of CTZ to dissolution medium. The rest of CTZ content was released gradually for hundreds of hours as shown in figure 21. This means approximately 72.5% of all CTZ content was perfectly encapsulated by PLA stereocomplex. It is estimated that perfectly encapsulated CTZ gradually diffused through minute pores of PLA stereocomplex.

By combining SEM image with EDS mapping for chloride atom and dissolution profile of CTZ complex, it is concluded that CTZ complex was prepared successfully by ASES. About 72.5% of all CTZ content is well prevented from initial rapid release. Although 27.5% of all CTZ

content was not coated perfectly, it is certain that partial encapsulation also had an effect on decrease in drug release rate.

Table 4. Dissolution rate test of CTZ complex (40mg)

Time	Peak area (Original)	Peak area (Evaporation correction)	Release percentage (%) (Correction)
0 min	0	0	0
1 min	4.14	4.14	19.23
5 min	5.61	5.61	26.05
15 min	5.64	5.64	26.19
30 min	6.05	6.05	28.10
1 h	5.92	5.92	27.49
2 h	6.03	6.03	28.00
3 h	6.09	6.09	28.28
6 h	6.24	6.24	28.98
12 h	6.27	6.27	29.12
18 h	6.79	6.65	30.88
36 h	7.24	6.90	32.04
80 h	8.41	7.77	36.09
135 h	9.23	8.24	38.27
251 h	11.86	9.72	45.14
345 h	14.72	10.89	50.57
450 h	17.94	12.66	58.79

Table 5. Dissoultion rate test of raw CTZ (21.79mg)

Time	Peak area (Original)	Peak area (Evaporation correction)	Release percentage (%) (correction)
0 min	0	0	0
1 min	21.52	21.52	99.94
5 min	21.55	21.55	100.08
15 min	21.50	21.50	99.85
30 min	21.48	21.48	99.76
1 h	21.51	21.51	99.90
2 h	21.52	21.52	99.94
3 h	21.61	21.61	100.36
6 h	21.39	21.39	99.34
12 h	21.62	21.62	100.41
18 h	21.99	21.52	100.00
36 h	22.57	21.52	100.00
80 h	23.31	21.52	100.00
135 h	24.10	21.52	100.00
251 h	26.27	21.52	100.00
348 h	29.10	21.52	100.00
450 h	30.50	21.52	100.00

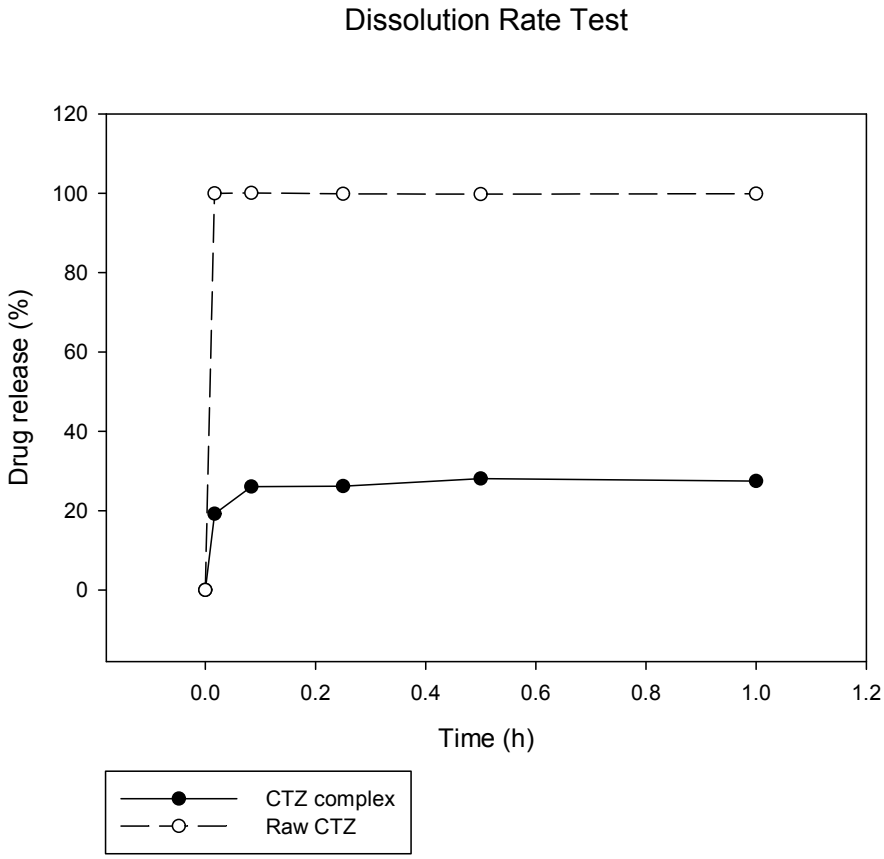

Figure 21. Dissolution rate test profiles (Initial 1 hour)

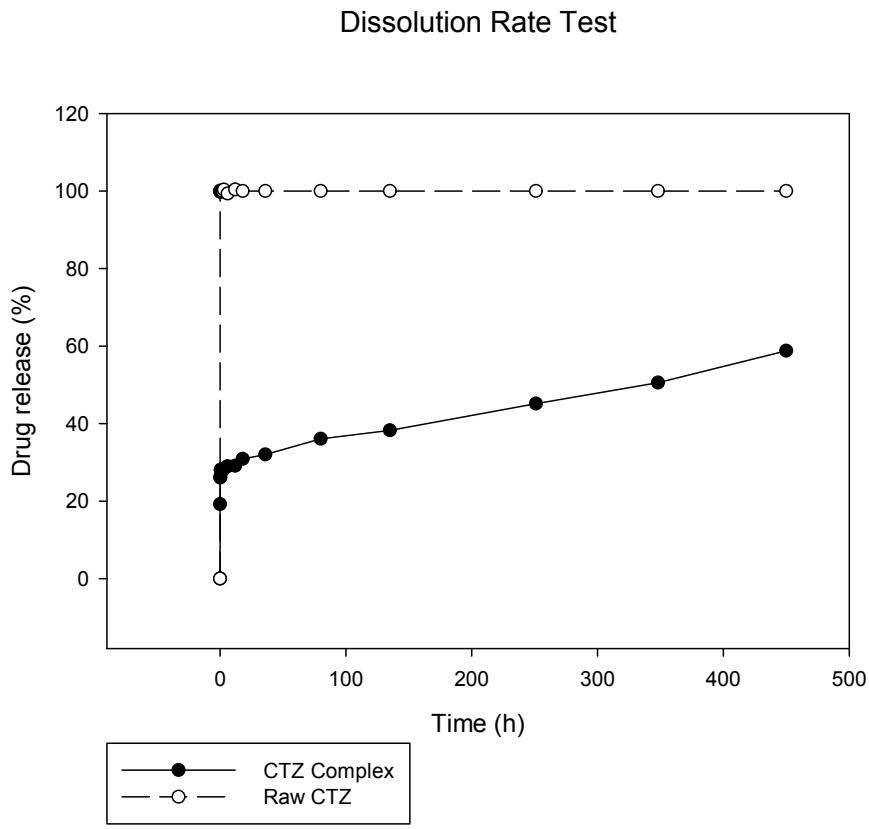

Figure 22. Dissolution rate test profiles (450 hours)

5. Conclusion

In this study, the preparation of PLA stereocomplex was carried out by ASES using supercritical CO_2 as anti-solvent. Spherical PLA stereocomplex particles were successfully obtained as products. The thermal behavior and crystallinity of prepared products were analyzed by DSC and WAXS. Between MC and $CHCl_3$, which are the widely employed organic solvents to dissolve PLA homopolymers, MC was selected as a proper solvent for preparation by ASES, since PLA stereocomplex precipitated from MC solution showed better thermal behavior and crystallinity than that precipitated from $CHCl_3$ solution. In terms of blending weight ratio of PLLA to PDLA and molecular weight of PLLA, the preparation of PLA stereocomplex by ASES showed the same aspect to the weight ratio optimalized in widely utilized processes. 1:1 weight ratio of PLLA to PDLA was best blending ratio for preparation of PLA stereocomplex using ASES. And low molecular weight of PLLA induced predominant formation of stereocomplex crystallites in ASES. Those are similar tendency which are shown in other preparation processes. However it was different from other preparation processes that products did not show thermal behavior of PLA homopolymer, although peak of homo-crystallites was shown in WAXS data. The concentration of PLA solution had an effect on crystallinity of prepared products. The products showed lower crystallinity as lower concentration of solution was used. The concentration of solution had nothing to do with predominant formation of specific crystallites in ASES. It was also distinguished from other widely utilized processes.

In this study, the application to preparation of cetirizine particles (CTZ, used as active material) encapsulated by PLA stereocomplex (coating material) was also attempted, which was on the basis that spherical particles were obtained as products. From EDS mapping image and dissolution profile, it was concluded that approximately 72.5% of CTZ content was perfectly encapsulated by PLA stereocomplex. Futhermore, the rest of CTZ content was also partially coated by PLA stereocomplex. As a result, CTZ was not released to water rapidly compared to raw CTZ.

Preparation of PLA stereocomplex by ASES using supercritical CO_2 is meaningful in that continuous, green process and expansion of application range of PLA stereocomplex can be achieved. In addition to this, ASES can show strong advantage at pharmaceutical field in terms of micronization without residual organic solvent. taking into account a synergy of merits described above, the success in drug encapsulation with considerable efficiency by ASES is thought to be a worthy progress.

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국 문 초 록

폴리 젖산 (Poly lactic acid, PLA)은 대표적인 생분해성 고분자로 기존의 석유 화학 기반 플라스틱을 대체할만한 고분자로 각광받고 있다. 그러나 플라스틱으로써 폴리 젖산은 낮은 열적 안정성으로 인해 대량 생산이 어렵다는 단점을 지니고 있다. 이를 극복하기 위하여 폴리 젖산의 두 광학 이성질체 (L-폴리 젖산과 D-폴리 젖산)를 혼합하여 입체 복합체 (PLA stereocomplex)를 만들어 열적 특성을 향상시키는 많은 연구가 진행되어 왔다. 대표적인 제조방법으로 Melt Crystallization, Solution Casting, Precipitation into Organic Anti-solvent 등을 들 수 있는데, 이를 통해 필름 형태 또는 섬유상 형태의 폴리 젖산 입체 복합체를 얻을 수 있다. 하지만 공정에 높은 온도와 긴 시간, 또는 과량의 유기 용매가 필요하다는 단점이 있다.

첫 번째로, 본 연구에서는 초임계 이산화탄소를 역용매로 하여 Aerosol Solvent Extraction System (ASES)을 통해 온건한 온도조건 (40℃)에서 짧은 시간 (수십 분)내에 구형 입자 형태의 폴리 젖산 입체 복합체를 성공적으로 제조하였으며, 시차주사열량계 (DSC), 광각 X-선 산란분석기 (WAXS), 전계방출주사전자현미경 (FE-SEM)등을 통해 제조된 입체 복합체의 물성을 분석하였다. 제조된 폴리 젖산 입체 복합체의 물성에 영향을 주는 변수로써 폴리 젖산을 녹이는데 사용된 유기 용매의 종류, 폴리 젖산의 두 광학 이성질체의 혼합 무게 비율, 사용된 L-폴리 젖산의 분자량, 그리고 폴리 젖산 용액의 농도가 이용되었다. 실험 결과, dichloromethane (MC)이 ASES에서 가장 적절한 용매로 선택되었다. 한편, 두 광학 이성질체의 혼합 무게 비율이 1:1일 때 대부분의 폴리 젖산이 입체 복합체 형성에 참여하였음을 확인하였으며, 또 낮은 분자량의 L-폴리 젖산이 이용될수록 입

체 복합체의 결정화가 단일 고분자의 결정화보다 우세하게 일어남을 확인하였다. 폴리 젖산 용액의 농도의 경우 특정 결정화 우세에 영향을 주지는 않는 것으로 관찰되었으나 농도가 낮아질수록 입자의 크기가 작아지고 결정성이 작아지는 경향을 보였다.

한편, 폴리 젖산 또는 폴리 젖산 입체 복합체는 인체 내에서 분해되기에 약물 전달 시스템 (DDS)에서도 널리 응용되고 있다. 두 번째로, 본 연구에서는 ASES를 통한 생산물이 구형 입자 형태임에 착안하여 폴리 젖산 입체 복합체가 코팅이 된 구형 약물 입자를 제조해 보았다. 항히스타민제 (Antihistamines)로 널리 이용되고 있는 세티리진 (Cetirizine dihydrochloride)이 약물로써 이용되었으며, 제조된 약물 복합체는 에너지 분산형 X선 분광기 (EDS)와 용출률 시험 (Dissolution Rate Test)을 통해 약물 복합체의 코팅 효율을 분석해보았다. EDS를 통해 세티리진의 염소 원소를 FE-SEM 사진에 도표화해본 결과, 약물 복합체 전반에 걸쳐 세티리진이 고르게 분포하고 있음이 파악되었다. 또한, 용출률 시험을 통해 전체 세티리진의 약 72.5%가 폴리 젖산 입체 복합체에 의해 확실하게 코팅이 되었음을 확인되었으며, 나머지 27.5%의 세티리진도 부분적으로 코팅이 되어 용출 속도가 감소되었음을 확인할 수 있었다.

초임계 이산화탄소를 역 용매로 하는 ASES를 이용한 폴리 젖산 입체 복합체의 제조 공정은 시간과 에너지 절약 및 친환경성에서 기존의 제조 공정들에 비해 뛰어난 점을 보이며 특히 연속식 공정이기에 설비의 규모가 크지 않더라도 대량 생산이 가능하다는 점에서 의미가 있다. 또한 ASES을 통하여 폴리 젖산 입체 복합체로 코팅된 세티리진 입자도 성공적으로 제조함으로서 약물 입자 코팅 공정으로써 가능성을 확인하였다. ASES를 이용한 입자의 제조법이 잔류 유기 용매 문제에서 자유롭다는 점과 폴리 젖산 입체 복합체가 인

체에 무해하다는 점이 시너지 효과를 낼 수 있다는 점을 고려하면, ASES를 통한 폴리 젖산 입체 복합체로 코팅된 약물 입자 제조 공정이 충분히 경쟁력 있다고 판단된다.

주요어: 초임계 이산화탄소, ASES, 폴리 젖산, 입체 복합체, 열적 안정성 향상, 캡슐화, 세티리진, 용출률, 방출 조절, 약물 전달 시스템

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