CHAPTER IV

RESULTS AND DISCUSSION

4.1 Preparation of the L-lactide

L-lactide synthesis was divided into two steps. The first step was to produce low molecular weight PLLA. In the second step, L-lactide was produced by ring formation by decomposition of low molecular weight PLLA.

The L-lactide crystal was characterized by NMR technique. From ^{1}H NMR spectrum in Figure A-1 (Appendix A), chemical shift at 5.14 ppm was assigned to -C<u>H</u>CH_3 group, and 1.66 ppm for -$CHC\underline{H_3}$ group. Moreover, ^{13}C NMR spectrum in Figure A-2 (Appendix A) indicated the peak at 168 ppm for –COO group, 72 ppm for –COH group, and 15 ppm for CH_3 group.

4.1.1 Synthesis of low molecular weight PLLA

The reaction was set under nitrogen atmosphere, L-lactic acid (88 wt%) was first heated with toluene-4-sulfonic acid monohydrate in a silicone oil bath at 140°C for 2 hours until temperature reached 100°C so that water present in L-lactic acid solution was removed and condensed into the condensate reservoir, followed by a gradual temperature rise up to approximately 140°C for 2 hours to remove water and by product (Figure 4.1). The solution was changed from white clear liquid to very light yellow liquid. The vacuum pressure was applied for 30 minutes, and then temperature increased to 160°C until water ceases to distill, to further remove water from the reaction. The GPC chromatogram of low molecular weight PLLA is shown in Figures B-1 (Appendix B).

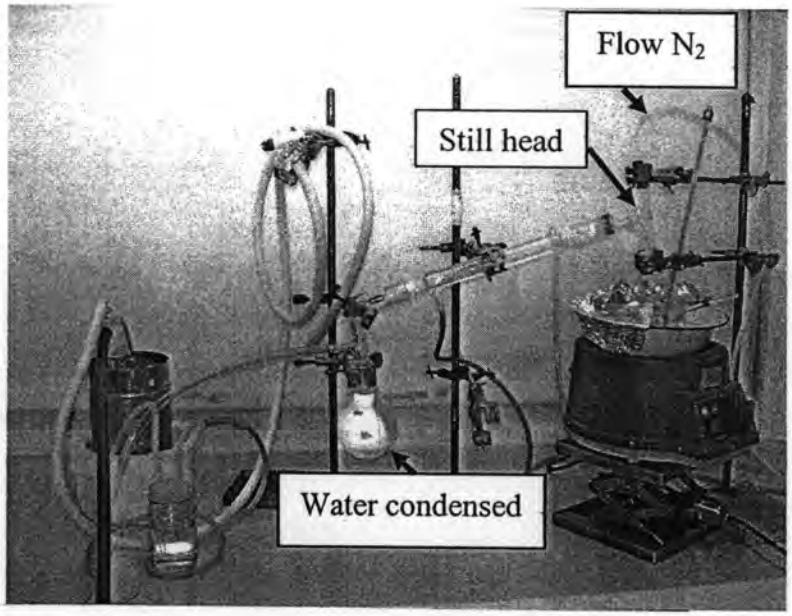

Figure 4.1 Experimental setup for low molecular weight PLLA synthesis.

4.1.2 Ring formation of L-lactide from low molecular weight PLLA using Zn dust as a catalyst.

Zn dust was added into the light yellow liquid obtained in 4.1.1. The mixture was heated to 160°C, and mechanically stirred for 30 minutes or until water stopped to condense into the condensate reservoir (Figure 4.2). Then, the temperature was increased to 220-230°C and the pressure was then reduced to 760 mmHg. This condition was maintained until white solid crystal of L-lactide was formed in the air condenser. The L-lactide crystal was removed and washed with cold de-ionized water to remove excess L-lactic acid and then vacuum filtered and white solid crystal of L-lactide was obtained at 25-35 % yield. The L-lactide crystal was purified by recrystallization in ethyl acetate, resulting in formation of white needle-like crystal (Figure 4.3). The difference in solubility of L-lactic acid, low molecular weight PLLA, and L-lactide was used as a purification basis during the recovery of L-lactide crystal from L-lactic acid and contaminants. The L-lactide crystal was crystallized and separated from L-lactic acid monomer with cold ethyl acetate (Table 4.1). The recovery percentage of L-lactide was 60-75% after recrystallization.

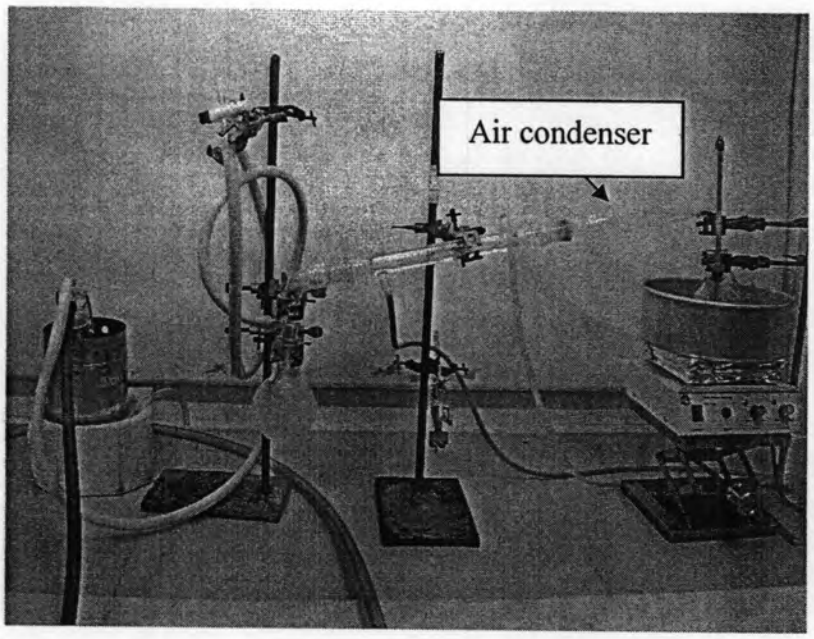

Figure 4.2 Experimental setup for L-lactide ring formation.

Table 4.1 Solubility of monomer or polymer prepared.

Monomer or polymer	Solubility			
	Cold EtOAc	CH_2Cl_2	MeOH	H_2O
L-lactic acid	S	S	S	S
L-lactide	NS	S	S	S
Poly(L-lactide)	NS	S	NS	NS

S = Soluble and NS = Non-soluble

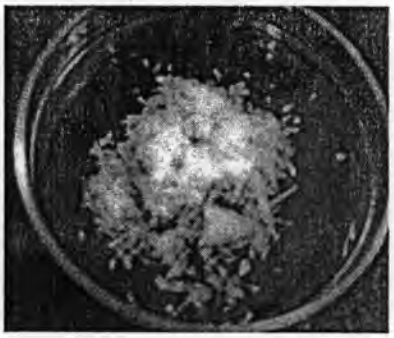

Figure 4.3 L-lactide crystal.

4.2 Polymerization of PLLGA

PLLGA was synthesized by ring opening polymerization, using stannous octoate as a catalyst. In order to find the optimum copolymerization condition, the effects of catalysts, reaction time, catalyst concentration, and molar ratio of L-lactide and glycolide were investigated. The polymerization product was dissolved in dichloromethane and precipitated with cold methanol. White solid was filtered out and dried under reduced pressure at room temperature for 24 hours. The identity and purity of the copolymers were investigated by ^{1}H and ^{13}C NMR spectroscopy.

From ^{1}H NMR spectrum in Figure A-3, and A-5 (Appendix A), chemical shift at 5.20 ppm was assigned for -C<u>H</u>CH_3 group, 4.77 ppm for -O-C<u>H_2</u>-COO- group, and 1.57 ppm for CHC<u>H_3</u> group. The spectrum of ^{13}C NMR in Figure A-4, and A-6 (Appendix A), was shown at 169 ppm for –COO group, 69 ppm for –COH group, 60 ppm for CH_2 and 17 ppm for CH_3 group.

Both L-lactide and glycolide were recrystallized in ethyl acetate before use. 1.70 g L-lactide (11.79 mmol) and 0.15 g glycolide (1.29 mmol) were mixed with a catalyst at 0.1-0.5 mol% (0.013 to 0.065 mmol) of monomers. The mixture was placed in 25 ml round bottom flask with continuous nitrogen flow (Figure 4.4). The round bottom flask was heated in silicone oil bath at 120°C for a certain time. After purified product, the white solid powder of PLLGA copolymer was obtained (Figure 4.5).

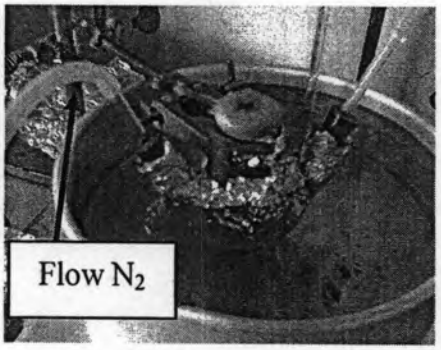

Figure 4.4 Experimental setup for PLLGA synthesis under nitrogen atmosphere.

Figure 4.5 PLLGA semicrystalline.

The effect of catalyst type and concentration, molar ratio of monomers, and reaction time on copolymer synthesis was studied. The copolymer yield and molecular weight obtained under difference synthetic condition were compared.

According to GPC chromatograms shown in Figure B-2 to B-11 (Appendix B), high molecular weight PLLGA cannot pass through the porous structure of gel in column, therefore it is eluted from column prior to low molecular weight PLLGA. For this reason, shorter retention time indicates higher molecular weight of PLLA as the highest peak in the chromatogram shifts to the left side of the X-axis.

4.2.1 Type of catalyst

Two commercial catalysts were used in this study. There two catalysts (Zn dust and $Sn(Oct)_2$) have been used for synthesis of polymer used for biomedical and pharmacological therapeutic applications. In general $Sn(Oct)_2$ provides efficient and rapid polymerization process compared with Zn dust.

Table 4.2 $\overline{M}_w$, $\overline{M}_n$, % yield, and physical appearance of PLLGA, when using different catalysts.

Sample ID	Catalyst	% yield ± S.D.	GPC			Physical Appearance
			$\overline{M}_w$	$\overline{M}_n$	PDI	
1	$Sn(Oct)_2$	75±3.88	4231	3579	1.18	White solid
2	Zn dust	54±3.21	3597	3177	1.20	White solid

$\overline{M}_w$ - Weight average molar mass, $\overline{M}_n$ - Number average molar mass, PDI- Polydispersity or heterogeneity index (PDI = $\overline{M}_w/\overline{M}_n$), and S.D. - Standard deviation.

The molecular weight, % yield and physical appearance of the crude products are shown in Table 4.2. Two PLLGA samples were prepared using $Sn(Oct)_2$ and zinc dust. Under the condition discussed above using $Sn(Oct)_2$ high yield and high molecular weight PLLGA were obtained. The result shows that different polymers were obtained when using different catalyst. This was because led to less transesterification, therefore provide rapid polymerimerization than zinc [Vert, *et al.*, 1998].

Transesterification reaction is the side reaction, that occurs both intramolecularly (backbiting leading to macrocyclic structures and shorter chains) and

intermolecularly (chain redistributions). It results in broader molecular weight distribution, sometimes making the molecular weight of the resulting polymers nonreproducible. The extent of these undesirable transesterification reactions was found to strong in polymerization using the metallic initiator.

From Table 4.2, it was found that copolymer yield and molecular weight were obtained when using $Sn(Oct)_2$ as the catalyst. Therefore, this catalyst was used for the further experiments in this research.

4.2.2 Concentration of catalyst

The effect of catalyst concentration on copolymer yield and molecular weight is shown in Table 4.3.

It was found that the highest copolymer yield of 75% was obtained at 0.3% mol $Sn(Oct)_2$. When increasing the molar ratio of catalyst, the molecular weight of copolymer was increased. The decrease in copolymer molecular weight was observed at the catalyst concentration higher than 0.3% due to copolymer decomposition from transesterification as previously discussed.

Table 4.3 $\overline{M}_w$, $\overline{M}_n$, % yield, and physical appearance of PLLGA, under different catalyst concentration.

Entry	catalyst concentration (% mol)	% yield ± S.D.	GPC			Physical Appearance
			$\overline{M}_w$	$\overline{M}_n$	PDI	
1	0.1	14±3.06	3497	3011	1.16	White solid
2	0.2	42±2.64	4261	3161	1.35	White solid
3	0.3	75±3.88	4231	3579	1.18	White solid
4	0.4	50±1.53	4382	3674	1.19	White solid
5	0.5	28±2.08	3914	3380	1.20	White solid

At low catalyst concentration, the reaction rate was slow leading to low molecular weight polymer and corresponding polymer yield. Increasing catalyst concentration led to the increase in molecular weight and polymer yield. However, too high catalyst concentration caused depolymerization resulting in low molecular weight and polymer yield.

4.2.3 Reaction time

The effect of reaction time was studied. 1.70 g L-lactide (11.79 mmol) was mixed with 0.15 g glycolide (1.29 mmol). 0.016 g $Sn(Oct)_2$ was added into the mixture with the molar ratio of catalyst to lactide/glycolide of 0.3%. The mixtures were heated in bulk at 120°C under N_2 atmosphere at different reaction times.

Table 4.4 $\overline{M}_w$, $\overline{M}_n$, % yield, and physical appearance of PLLGA, obtained from the polymerization at various reaction time.

Entry	Reaction time (hours)	% yield ± S.D.	GPC			Physical Appearance
			$\overline{M}_w$	$\overline{M}_n$	PDI	
1	4	10±2.00	3368	2941	1.14	White solid
2	12	37±1.53	3539	2988	1.18	White solid
3	24	75±3.88	4231	3579	1.18	White solid
4	48	47±3.60	4091	3388	1.21	White solid

When the reaction time increased, it resulted in the increase in copolymer yield (Table 4.4). However, excess reaction time led to the low copolymer yield due to polymer decomposition to monomers, L-lactic acid and glycolic acid, and oligomers. The higher molecular weight of copolymer was obtained at the longer reaction time as well. As previously discussed, excess reaction time caused copolymer decomposition, thus resulting in low molecular weight copolymer.

According to the results in Table 4.2-4.4, the optimal condition for PLLGA synthesis was at 120°C, 24 hours. The molar ratio of $Sn(Oct)_2$ to L-lactide/glycolide was 0.3 mol%.

4.2.4 Molar ratio of monomers

The effect of molar ratio of L-lactide and glycolide on % yield and the polymer molecular weight at 120°C under N_2 atmosphere, using 0.3 mol% $Sn(Oct)_2$ for 24 hours was studied. The molar ratio was varied as 50/50, 70/30, and 90/10 as shown in Table 4.5.

Table 4.5 $\overline{M}_w$, $\overline{M}_n$, % yield, and physical appearance of PLLGA, under different L-lactide and glycolide molar ratio.

Entry	PLLGA molar ratios	% yield ± S.D.	GPC			Physical Appearance
			$\overline{M}_w$	$\overline{M}_n$	PDI	
1	50/50	ND*	ND*	ND*	ND*	Viscous muddy white liquid
2	70/30	72±2.52	3915	3226	1.21	White solid
3	90/10	75±3.88	4231	3579	1.18	White solid

ND* = not determined because no copolymer was formed from highly viscous solution.

When more glycolide was used, it resulted in highly viscous solution during copolymer purification with dichloromethane and precipitation in methanol. This highly viscous copolymer could not be dried, causing difficulty in film preparation. L-lactide/glycolide apparent molar ratios were determined from ^{1}H NMR spectra, calculated from the peak intensities at 5.20 ppm and 4.77 ppm, where A is the amount of proton at chemical shift 5.14 ppm, T is the total area, and X is the mole fraction.

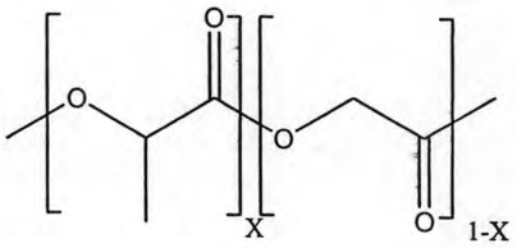

Figure 4.6 Structure of PLLGA.

The apparent molar ratio of PLLGA at the given molar ratio of 90/10.

$$A = 1X \quad (1)$$

$$T = 4X + 2(1-X) \quad (2)$$

$$A/T = X/(2X+2) \quad (3)$$

$$X = 2A/(T-2A) \quad (4)$$

$$X = \frac{21.02 \times 2}{(21.02 + 5.6 + 64.6) - (21.02 \times 2)}$$

$$X = 0.85$$

$$1-X = 0.15$$

Apparent copolymer composition in copolymers, was determined from ^{1}H NMR analysis (Table 4.6). For PLLGA 90/10, it was 85/15, and for PLLGA 70/30, 62/38.

Table 4.6 Composition of L-lactide/glycolide molar ratio on the basis of ^{1}H NMR and The glass transition temperature (T_g) of PLLGA.

Entry	Feed ratio of lactide:glycolide (mol:mol)	Composition on the basis of ^{1}H NMR (mol:mol)	T_g (°C)
1	90/10	85/15	35.8
2	70/30	62/38	32.0

Differential scanning calorimetry (DSC) showed no melting endotherms, suggesting the amorphous nature of the polymers (Table 4.6). T_g values were obtained from the thermograms, using the midpoint between the intersections of the two parallel baselines, before and after T_g. This was expected, since the glass transition is dependent on the free volume of polymer. It should be noted that T_g values decreased

due to the increasing ratio of glycolide monomer in the copolymer (Table 4.6). This was attributed to the relatively high hydrophilicity of glycolide monomer.

4.3 Preparation of controlled release PLLGA containing nicotine

The copolymer was prepared under the optimal polymerization condition obtained prior. Due to slightly low molecular weight of the copolymer, it could not be used alone to form film. Therefore, PVA was mixed with the PLLGA copolymer for film formation at different ratio for the preparation of nicotine transdermal patches.

The PVA has also gained wide pharmaceutical applications as drug delivery matrices. However, drug release rates from PVA tend to relatively rapid depending on the pore size, extent of cross-linking, and the nature of the incorporated drug. Theoretically, the release rates can be decreased through a composite drug release platform, which consists of particles containing drugs embedded within PVA [Soppimatha, *et al.*, 2001].

The preparation method was based on preparation of colloid, the emulsion solvent diffusion technique. The system consisted of a good solvent phase for the drug and polymer, and aqueous dispersion phase dissolved with dispersing agent. PVA was used in preparation of spontaneous emulsification solvent diffusion method with PLLGA. Drying of the aqueous colloidal polymer dispersions led to the formation of PLLGA film. The films were prepared in various formulations for study of the effects on the properties of colloidal polymer.

In the preliminary study it was found that, the component of the colloidal polymer played an important role in PLLGA film preparation process. Therefore, the film preparation using different ratios of PLLGA to PVA was observed.

4.3.1 Preparation of aqueous colloidal with various PLLGA content

Preparation of controlled release was studied the application of biodegradable polymers in the form of aqueous colloidal polymer dispersions for the preparation of latex films, as a new interesting approach for the development of pharmaceutical preparations. PLLGA/PVA ratio was varied between 0.5/2 and 2/2. Aqueous colloidal dispersion of the biodegradable PLLGA was prepared by a spontaneous emulsification solvent diffusion method. During evaporation of the organic solvents from the dispersed droplets of the organic PLLGA solution, the droplets were solidified in the aqueous solution. These solidified PLLGA droplets are designated nanospheres. The ^{1}H and ^{13}C NMR of the solidified PLLGA were shown in Figures A-7, and A-8 (Appendix A). Drying of the aqueous colloidal polymer dispersion led to the formation of PLLGA film.

The PLLGA in aqueous colloidal PLLGA dispersion was recovered by vacuum drying. The results are shown in Table 4.8. It was found that the lowest recovery was obtained at the ratio of PLLGA to PVA of 1.5 to 2. When the amount of PLLGA in PLLGA/PVA increased, the recovery percentage was decreased (Table 4.7).

Table 4.7 PLLGA recovery.

Ratio of the composition		Weight(g)		PLLGA recovery (%) ± S.D.	
PLLGA	PVA	PLLGA	PVA	70/30	90/10
0.5	2	0.1	0.4	40±2.12	42±2.19
1	2	0.2	0.4	36±1.73	41±1.53
1.5	2	0.3	0.4	28±1.53	30±1.53
2	2	0.4	0.4	50±1.53	53±2.52

Remark: calculated based on the weight ratio of the nanospheres and the starting PLLGA polymer, after vacuum drying.

The recovery of PLLGA decreased with increasing amount of PLLGA dissolved in solution of polymer. This was probably caused by the high viscosity of dispersed phase, resulting a poor dispersability of the PLLGA solution into the aqueous phase [Mainardes, *et al.*, 2005]. The maximum of PLLGA recovery was 2PLLGA/2PVA condition because of the high amount PLLGA and PLLGA complication structure; therefore, causing difficulty in blending PLLGA with PVA.

4.3.2 Preparation of PLLGA latex film

The drug-dispersed polymer solution and glutaraldehyde were poured carefully onto the Petri dish. Glutaraldehyde was used as a covalent cross-linking agent for enhancing the dissolution property of PLLGA films. The solvent was evaporated slowly in air at room temperature for 5 days and then cut into 1 cm^2. The film thickness, measured by Vernier caliper was controlled at 0.5 mm.

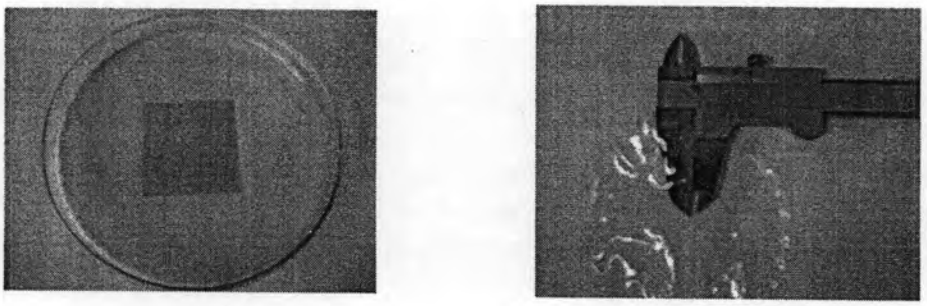

Figure 4.7 PLLGA latex film containing nicotine.

4.4 Film characterization (morphology of the film)

The surface topography of the PLLGA film containing nicotine was observed using the scanning electron microscopy (SEM). The effect of various ratios of PLLGA/PVA (colloidal polymer) was investigated. The microscopic images were taken in two magnifications for each formulation as illustrated in Figures 4.8- 4.9.

The film surface structure was one of key parameters used for the selection of the optimal copolymer film composition for nicotine release.

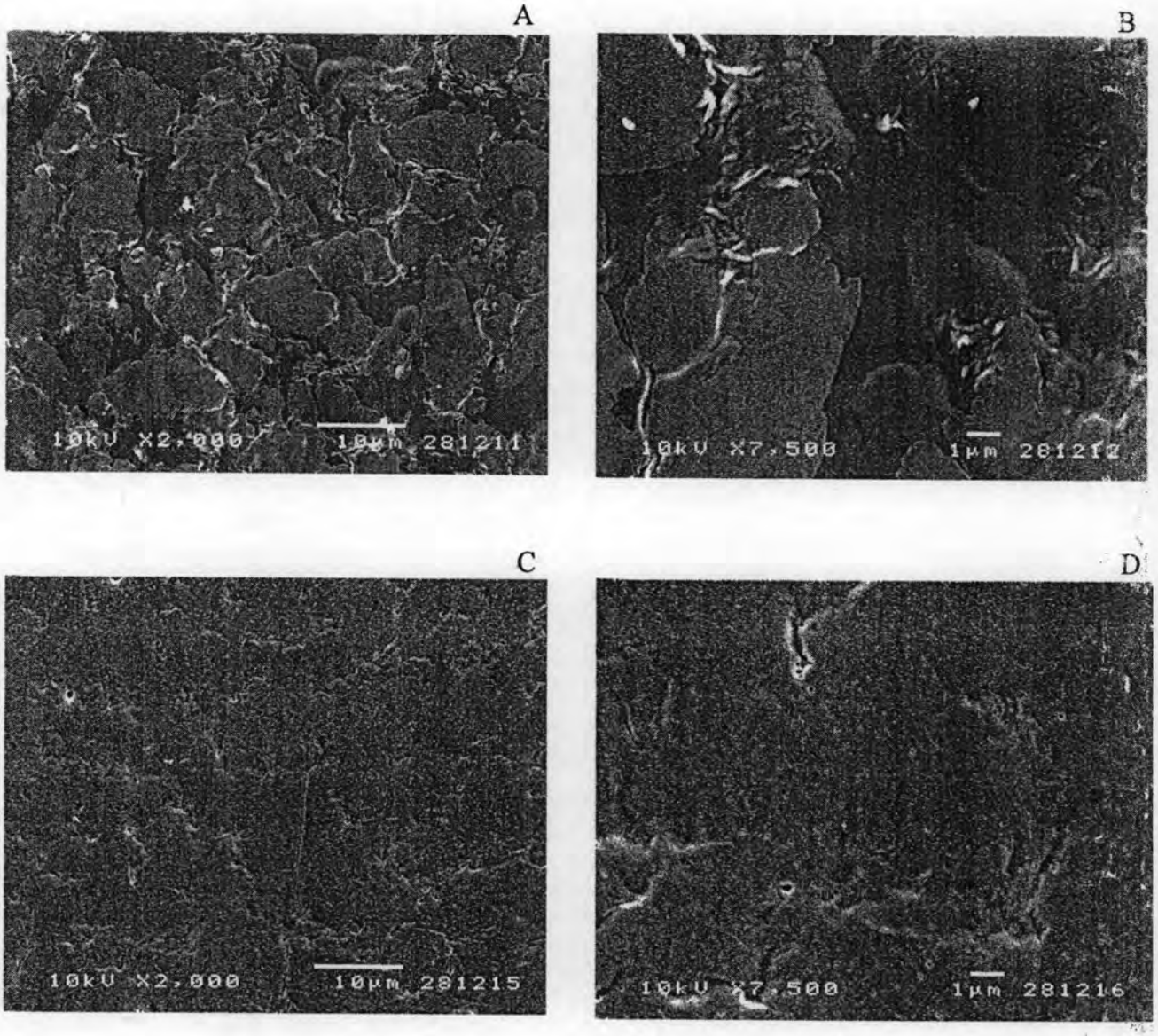

Figure 4.8 Scanning electron photomicrographs of the PLLGA (70/30)-blended PVA at PLLGA to PVA ratio of A. 0.5/2 at low magnification; B. 0.5/2 at high magnification; C. 1/2 at low magnification; and D. 1/2 at high magnification.

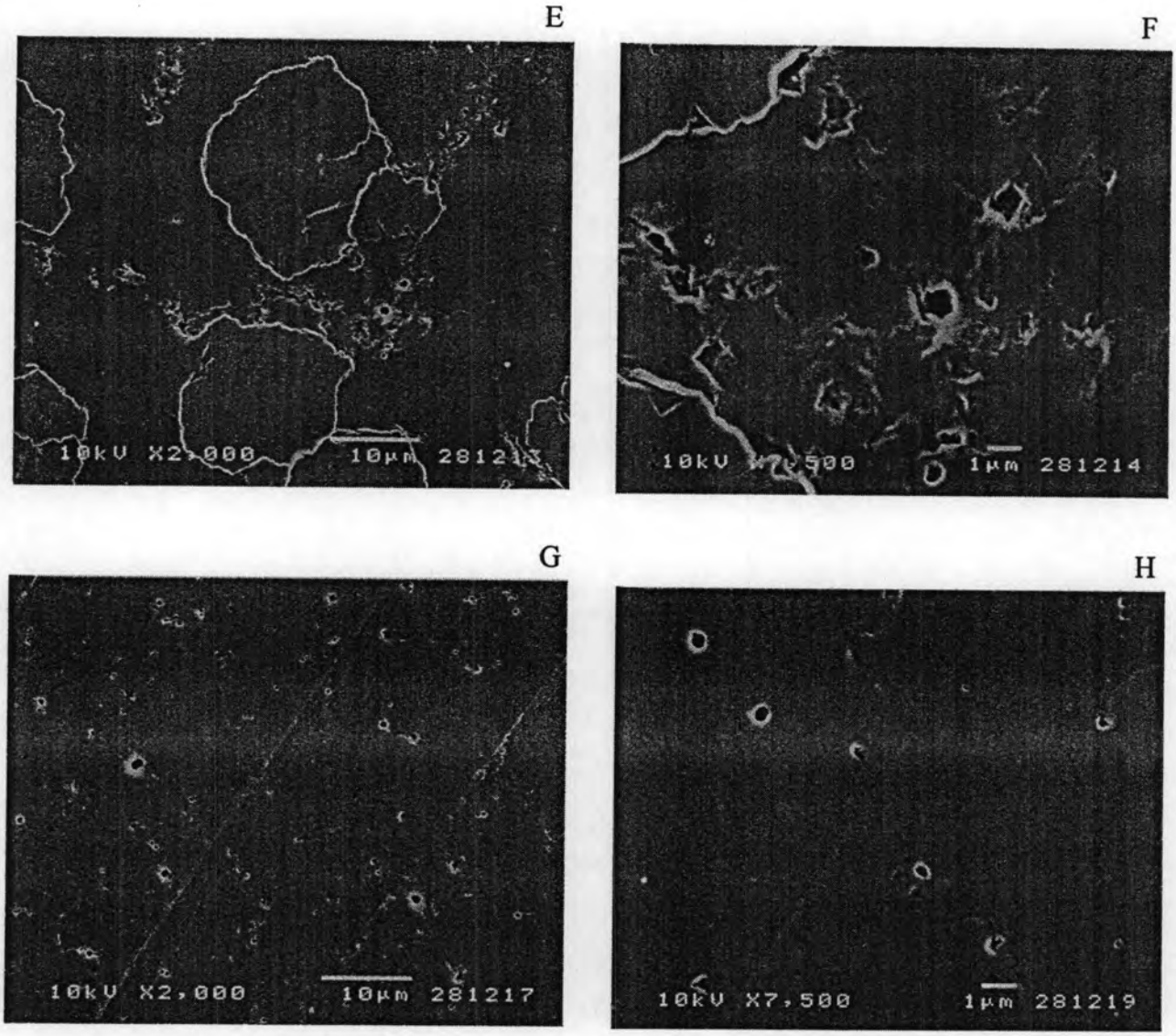

Figure 4.8 (continue) Scanning electron photomicrographs of the PLLGA (70/30)-blended PVA at PLLGA to PVA ratio of E. 1.5/2 at low magnification; F. 1.5/2 at high magnification; G. 2/2 at low magnification; and H. 2/2 at high magnification.

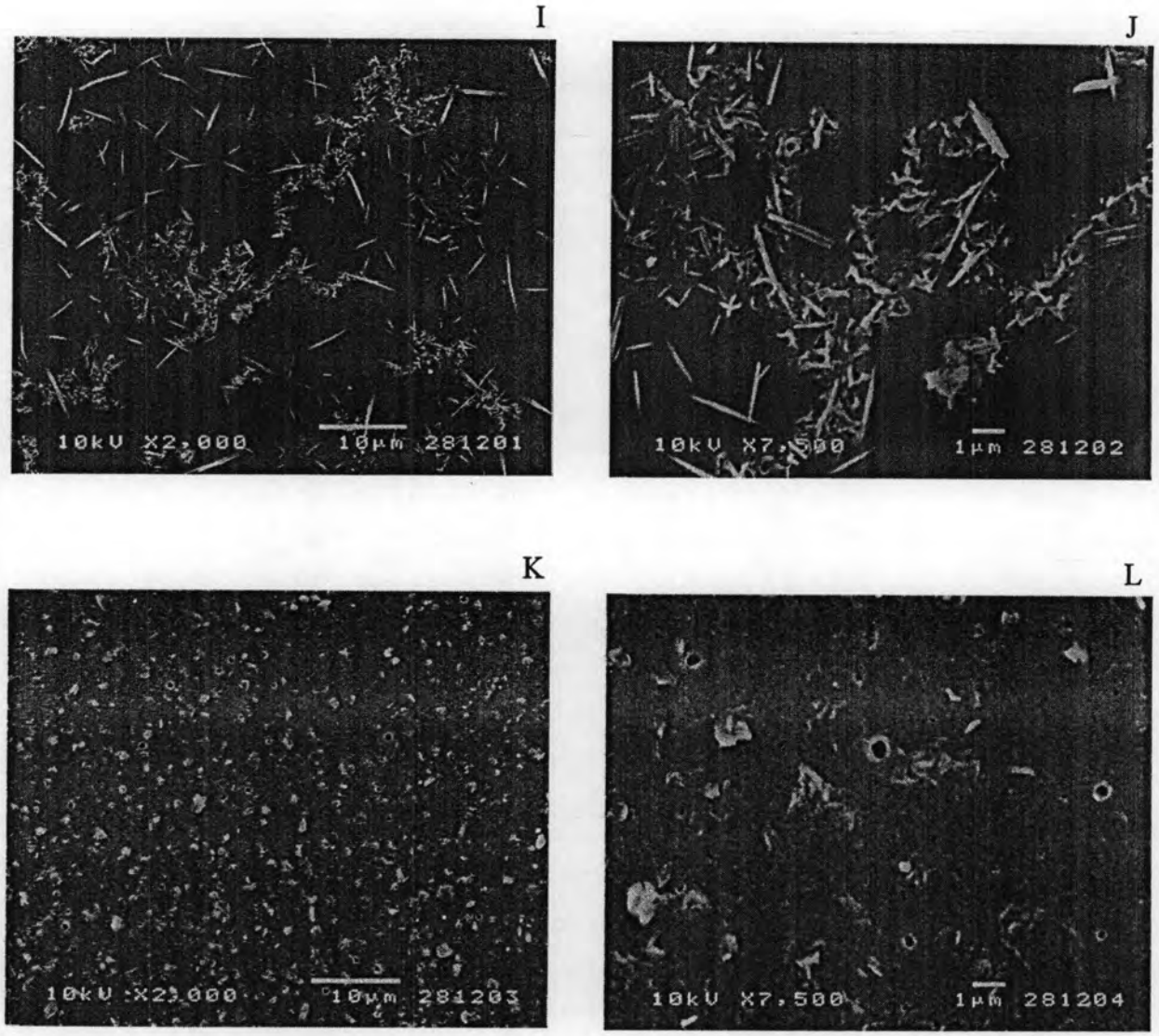

Figure 4.9 Scanning electron photomicrographs of the PLLGA (90/10)-blended PVA at PLLGA to PVA ratio of I. 0.5/2 at low magnification; J. 0.5/2 at high magnification; K. 1/2 at low magnification; and L. 1/2 at high magnification.

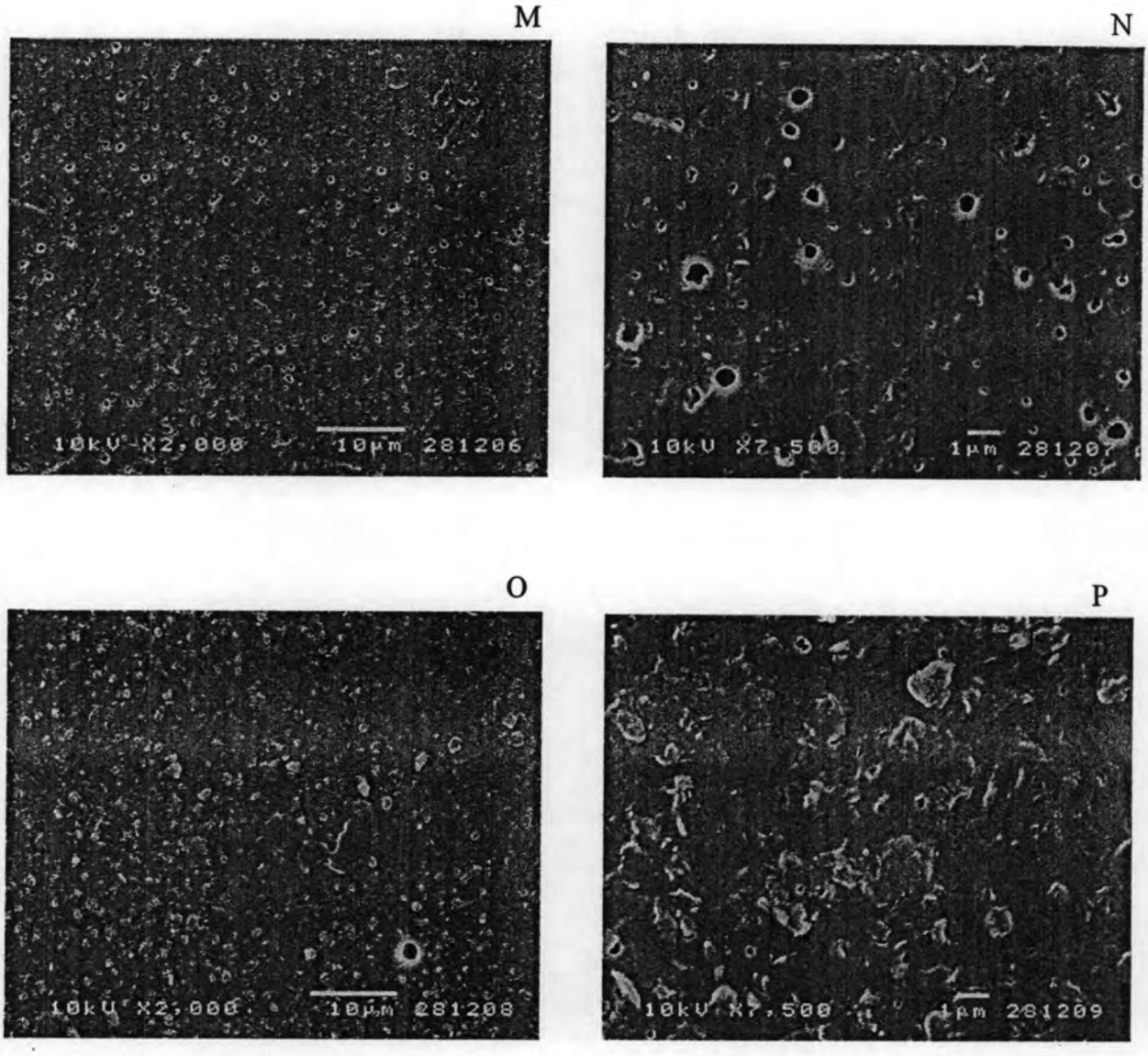

Figure 4.9 (continue) Scanning electron photomicrographs of the PLLGA (90/10)-blended PVA at PLLGA to PVA ratio of M. 1.5/2 at low magnification; N. 1.5/2 at high magnification; O. 2/2 at low magnification; and P. 2/2 at high magnification.

From the micrograph of the copolymer film prepared using 70/30 and 90/10 L-lactide/glycolide ratio, it is obvious that the nanoparticles were dispersed homogeneously in PVA, since the microspheres were randomly packed together resulting in a porous structure. But when using the copolymer at 90/10 L-lactide/glycolide ratio, the film surface was rougher. The pore size of the films under eight ratio of PLLGA/PVA is shown in Table 4.8.

The SEM micrographs of the film of the copolymer containing 70/30 L-lactide-co-glycolide showed the difference in pore size when using different ratio of PLLGA to PVA (Figure 4.8). When the amount of PLLGA was increased, the pore size increased, the increase the pore size with an increasing PLLGA concentration was observed.

When preparing the film from the copolymer containing 90/10 L-lactide-co-glycolide, the smaller pore size on the film surface was found compared with that containing 70/30 L-lactide-co-glycolide (Figure 4.9). The increase on the pore size with an increasing PLLGA level was observed.

Table 4.8 Pore size of the PLLGA-blended PVA copolymer film.

PLLGA/PVA ratio	Mean of pore size (μm) ± S.D.	
	70/30 L-lactide/glycolide	90/10 L-lactide/glycolide
0.5/2	Not found	0.257±0.04
1/2	0.190±0.07	0.417±0.01
1.5/2	0.828±0.17	0.457±0.09
2/2	0.351±0.03	0.187±0.01

When acetone was formulated into organic phase with dichloromethane, the mean diameter of pore sizes decreased dramatically to the order of submicron. It was found that the largest of pore size as 1.5PLLGA/2PVA ratio using the copolymer at 90/10 L-lactide/glycolide ratio because the interfacial tension between the organic and aqueous phase decreased with increasing amount of PLLGA copolymer in the PLLGA blended PVA solution [Niwa, *et al.*, 1993].

4.5 Swelling study

The PLLGA films with the same size and thickness were individually incubated in 20 ml of PBS solution at room temperature and pH 7.4. The degradation of aliphatic polyesters proceeded through hydrolysis of the ester bonds. Thus, the water content of the specimen was first measured. Figures 4.10- 4.11 and Tables D1-D2 (Appendix D) showed the swelling rate as the function of time of 70/30 and 90/10 PLLGA respectively. Swelling behaviour was mainly dependent on film composition and the pores, most likely caused by water diffusion from the formed films.

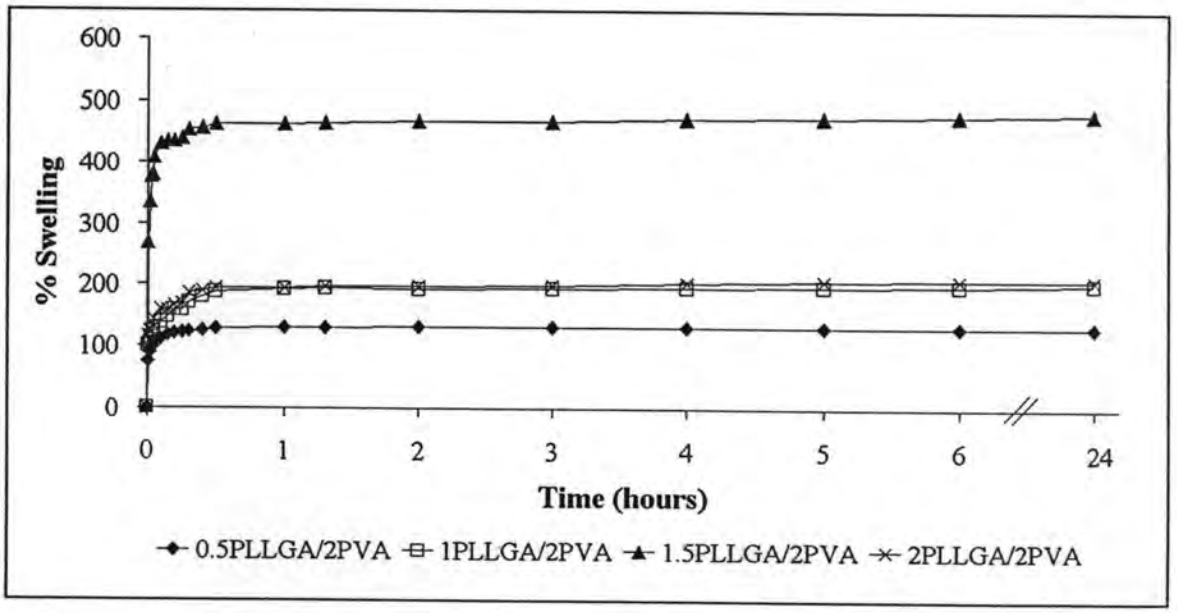

Figure 4.10 Swelling of 70/30 L-lactide/glycolide ratio behavior of various ratios of PLLGA and PVA (formulation A: 0.5PLLGA/2PVA, B: 1PLLGA/2PVA, C: 1.5PLLGA/2PVA, and D: 2PLLGA/2PVA).

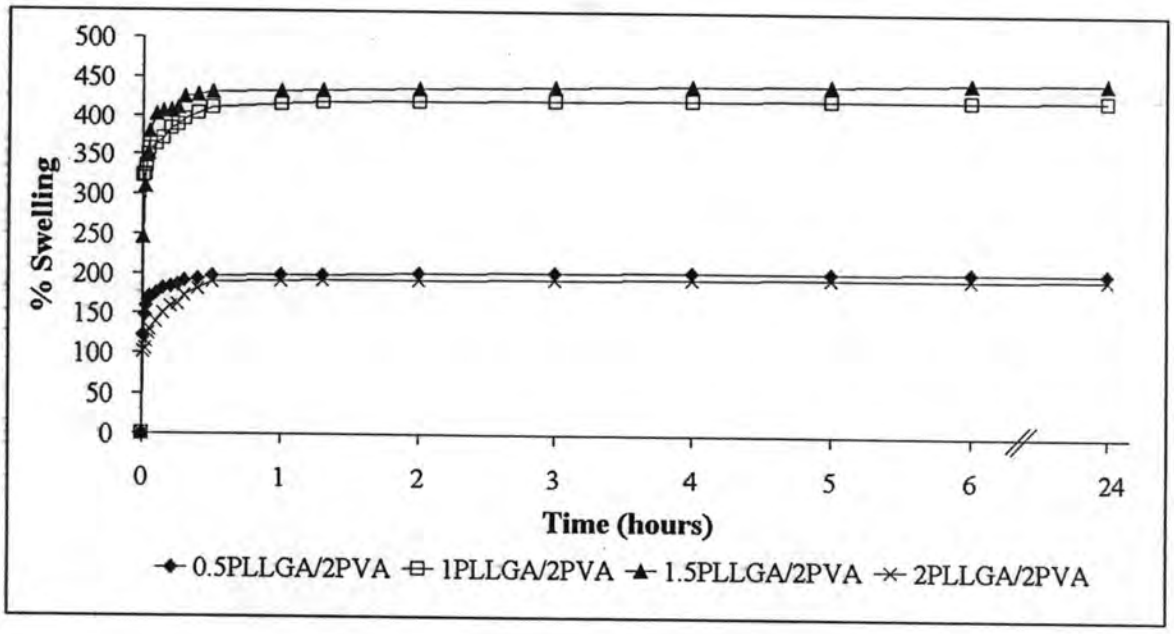

Figure 4.11 Swelling of 90/10 L-lactide/glycolide ratio behavior of various ratios of PLLGA and PVA (formulation E: 0.5PLLGA/2PVA, F: 1PLLGA/2PVA, G: 1.5PLLGA/2PVA, and H: 2PLLGA/2PVA).

The water content of the PLLGA/PVA films before 30 minutes was low. The water contents of PLLGA film increased significantly from the 30 minutes to 1 hour. The swelling rate reached the maximum values of approximately higher than 400% after 1 hour. The swelling was slight increased until 24 hours maximum about 460% for formulation C and 430 % for formulation G at about 1 hour and then slightly increased until 24 hours, this indicated that the water contents in the sample may reach saturation. This was caused by the water uptake of the polymer as a result of swelling. As the polymer chains were degraded during this period, more formed hydrophilic oligomers, the large pore sizes, and the pore size distribution enhanced the water uptake.

4.6 In Vitro Release Study

Study on nicotine release rate provides significant consequence in nicotine therapy. So a quantitative representation of the controlled release is necessary in order to accurately determine the nicotine release of the film. The quantitative nicotine release from various PLLGA/PVA films was determined.

The amount of nicotine loaded on the PLLGA/PVA films depended on the film porosity and the film swelling property at equilibrium. A predetermined equilibration release of the films provided a certain amount of nicotine loading onto the films. The nicotine releases from PLLGA/PVA films were shown in Figure 4.11-4.12. To determine the nicotine content, the patch was placed PBS solution (pH 7.4). The absorbancy at 260 nm was measured.

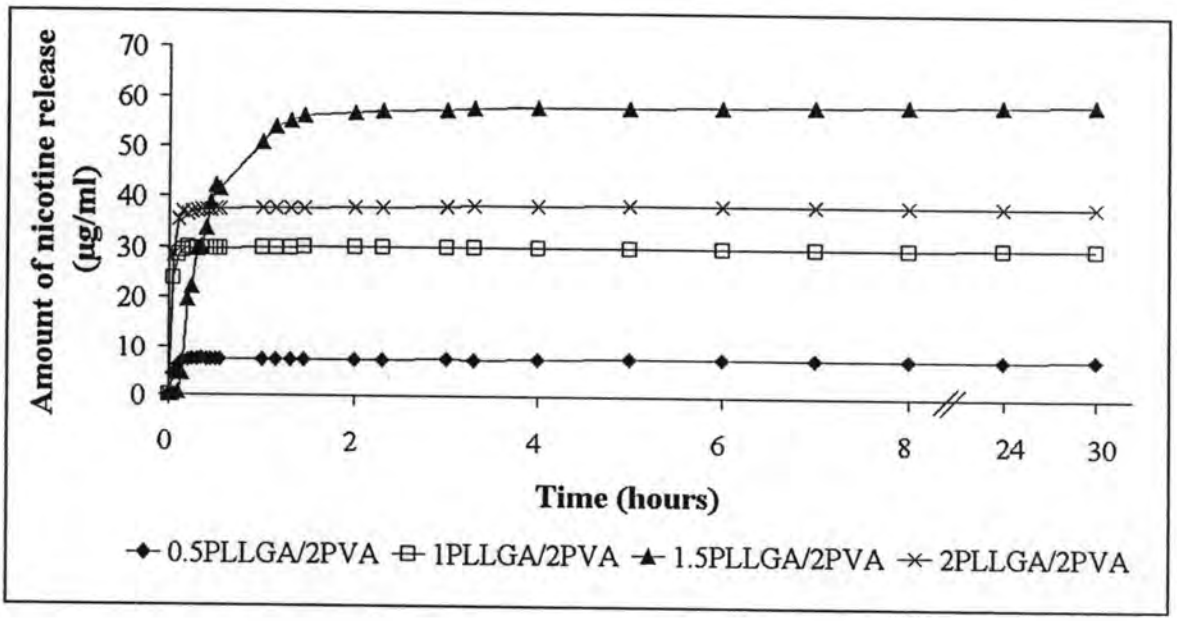

Figure 4.12 The release profiles of nicotine from the films of 70/30 PLLGA with various PLLGA/PVA in the PBS solution (formulation A, B, C, and D).

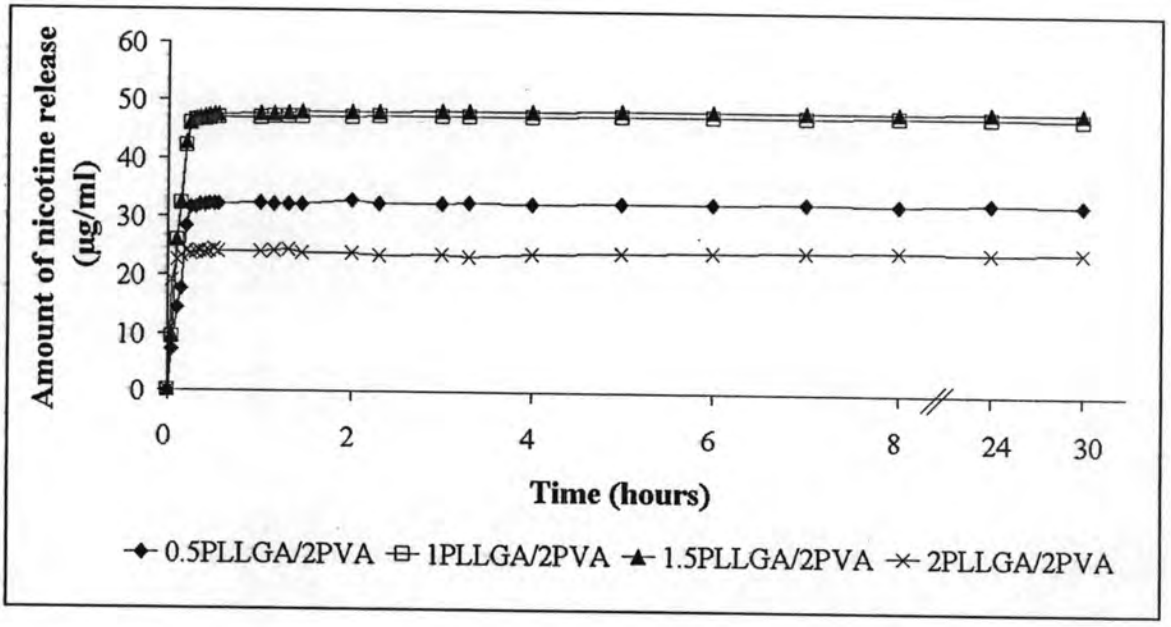

Figure 4.13 The release profiles of nicotine from the films of 90/10 PLLGA with various PLLGA/PVA in the PBS solution (formulation E, F, G, and H).

The release profiles of nicotine are given in Tables F1-F2 (Appendix F). A comparision of nicotine release profile from the eight conditions of PLLGA-blended PVA revealed that increased the pore size increased swelling and nicotine release.

The nicotine releases were calculated by dividing the difference of nicotine release at various time intervals with the time utilized to release that certain amount of nicotine. These results indicated that the pore size of polymer obviously affected the amount of nicotine release, increasing the size of the film pore significantly increasing the amount of nicotine release.

The nicotine release constant from the PLLGA-blended were achieved after 1 hour. It appears that formulation A and C provided the minimum and maximum nicotine release of 738 $\mu g\ cm^{-2}\ h^{-1}$ and 5,072 $\mu g\ cm^{-2}\ h^{-1}$, respectively. The release average of nicotine from the other PLLGA/PVA films was shown to follow Table 4.9.

Table 4.9 The release average of nicotine from the different PLLGA/PVA ratio in 70/30 and 90/10 L-lactide/glycolide with various PLLGA/PVA (formulation A to H).

Formulation	Ratio of PLLGA	Ratio of PLLGA/PVA	The release average of nicotine ($\mu g\ cm^{-2}h^{-1}$)
A	70/30	0.5/2	738
B	70/30	1/2	2985
C	70/30	1.5/2	5072
D	70/30	2/2	3765
E	90/10	0.5/2	3231
F	90/10	1/2	4702
G	90/10	1.5/2	4773
H	90/10	2/2	2405

Table 4.10 Nicotine patch specifications [Olivier *et al.*, 2003].

Patch	Nicotine content (mg)	Surface area (cm^2)	Application duration (hours)	Nicotine release $\mu g\ cm^{-2}h^{-1} \pm$ S.D.
Nicopatch	17.5	10	24	709 ± 56
Nicorette	8.3	10	16	501 ± 39

Table 4.10 shows two commertial transdermal patches, Nicopatch and Nicorette, containing different nicotine contents at different treatment period. It is well known nicotine release followed the polymer matrix diffusion-controlled process. Therefore, *in vitro* release of the films with different PLLGA/PVA ratio in 70/30 and 90/10 L-lactide/glycolide was compared with these of two commertial transdermal patches. The results in Table 4.9 and 4.10 indicate that the release of the nicotine in formulation A was similar to that in Nicopatch.

On the other hand, nicotine release rates from the films make from other formulations (D-H) were too high. Therefore they are not suitable to be used in people who would like to stop smoking due to lethal dosage. These were probably due to the crosslink density that not enough, so the releases were too rapid and high. Therefore increasing amount of GD may help control nicotine release rate in PLLGA film (Table 4.11).

Table 4.11 The release average of nicotine from the different PLLGA/PVA ratio in 70/30 and 90/10 L-lactide/glycolide with various GD crosslinking (formulation A to H).

Formulation	Ratio of PLLGA	Ratio of PLLGA/PVA	The release average of nicotine ($\mu g\ cm^{-2}h^{-1}$)		
			3% GD	5% GD	7% GD
A	70/30	0.5/2	738	639	585
B	70/30	1/2	2,985	1,882	1,803
C	70/30	1.5/2	5,072	2,718	2,603
D	70/30	2/2	3,765	2,530	2,464
E	90/10	0.5/2	3,231	1,924	1,852
F	90/10	1/2	4,702	2,609	2,482
G	90/10	1.5/2	4,773	2,645	2,609
H	90/10	2/2	2,405	1,833	1,730

Table 4.11, shows the release average of nicotine from the other PLLGA/PVA films with various GD crosslinking. All formulations (A to H) indicated the controlled release of nicotine decreased, when increased the percentage of GD crosslinking, but the release of nicotine (formulation B to H) was still high and danger to use in people. In addition the viscosity of the polymer solution increased, when increased crosslinking, so this was problem to cause difficulty in film preparation.