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Methoxy Poly Ethylene Glycol-*b*-poly (D, L-lactide-*co*-glycolide) Films as Drug Delivery Systems for Ibuprofen

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Abstract: Methoxy poly (ethylene glycol)-*b*-poly (D,L-lactide-*co*-glycolide) diblock copolymers (MPEG-*b*-PDLLG) films containing a poorly water-soluble drug were prepared by evaporation method of MPEG-*b*-PDLLG and drug solution in dichloromethane. Ibuprofen was used as a poorly water-insoluble model drug. Influences of MPEG block length and DLL/G ratio on drug-loaded film character and drug release behavior were investigated. Inhibition of entrapped ibuprofen crystallization in the MPEG-*b*-PDLLG films was observed from thermal analysis. The drug release rates increased as the MPEG block length increased. Incorporation of G units in the PDLL block also induced the faster drug release rate. The drug had released from the films through diffusion mechanism.

Key words: Biodegradable polymers, diblock copolymers, mechanical properties, drug controlled-release

INTRODUCTION

In the recent years, interest in poly (DL-lactide) (PDLL) and polyglycolide (PG) for use as controlled-release drug carriers has increased because of their biodegradability and biocompatibility (Edlund and Albertsson, 2002). They can be degraded via a simple, non-enzymatic hydrolysis mechanism and gave non-toxic products (Yuehuei, 2000). Copolymers of DLL and G have all been reported either as random or block copolymers with partially matched with the requirements of the application such as mechanical properties and hydrolytic biodegradation (Kister *et al*., 1998; Jacobs *et al*., 1991). Use of these polyester films in biomedical, pharmaceutical and food packaging have already received wide attention (Wang *et al*., 2004; Plackett *et al*., 2006; Martino *et al*., 2006; Houchin *et al*., 2007).

The PDLL film is the most widely studied. However, the PDLL film is rigid and brittle below their glass transition temperature (T_g, 50-60°C) with low plastic deformation. Flexible PDLL films can be achieved by blending PDLL with plasticizers. The plasticizers such as poly ethylene glycol, Methoxy Poly Ethylene Glycol (MPEG), partial fatty acid esters, tributyl citrate, adipates and branched polylactides have been used for this purpose (Martin and Averous, 2001; Ljungberg and Wesslen, 2003; Martino *et al*., 2006; Ouchi *et al*., 2006). Moreover, partial migration of the plasticizers has been found (Martino *et al*., 2006). The MPEG plasticizer molecules which are chemically bonded to PDLLG chains with different MPEG block lengths and DLL/G ratios were successfully prepared and their film properties have been reported as previously described (Baimark *et al*., 2007; Morakot *et al*., 2008). The MPEG block attachment has affected to their mechanical and hydrolytic degradation properties. Although, the diblock copolymers of MPEG-*b*-PDLL, MPEG-*b*-PG, MPEG-*b*-PCL, MPEG-*b*-PDLLG and MPEG-*b*-PDLLCL have been widely investigated (Kim *et al*., 1998;

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1999, 2005; Ren *et al*., 2005; Beletsi *et al*., 1999). However, the controlled-release drug delivery application of MPEG-*b*-PDLLG films has been scarcely published. Therefore, this application of the MPEG-*b*-PDLLG films prepared from solution casting method is the focus of attention in the present work. It was hypothesized that drug release rates could be adjusted by varying the MPEG block length and DLL/G ratio of PDLLG block.

Ibuprofen was used as a poorly-water soluble model drug, in this study. This drug has been loaded into biodegradable matrices such as monofilaments (Zurita *et al*., 2006) and microspheres (Thompson *et al*., 2007). In this research, the ibuprofen-loaded MPEG-*b*-PDLLG films were prepared by film casting of MPEG-*b*-PDLLG and ibuprofen homogeneous blended solution. Influences of MPEG block length and DLL/G ratio on film characteristics and drug release behaviors were investigated and discussed.

MATERIALS AND METHODS

This research was conducted on June 2008-March 2009 at Mahasarakham University, Mahasarakham, Thailand.

MPEG-*b*-PDLLGs with different MPEG block lengths and DLL/G ratios were synthesized by ring-opening polymerization of DLL and G monomers in bulk under nitrogen atmosphere at 130°C for 24 h (Baimark *et al*., 2007). They were designed as MPEG2,000-PDLL, MPEG5,000-PDLL and MPEG5,000-PDLLG. The 2,000 and 5,000 were molecular weights of MPEG blocks, whereas the PDLL and the PDLLG contained DLL/G ratios of 100/0 and 85/15 mol%, respectively.

The MPEG (Fluka) was used after dried under reduced pressure at 120 °C for 4 h. The DLL and G monomers were prepared from D,L-lactic acid (85%, Acros Organics) and glycolic acid (99%, Acros Organics). The MPEG and stannous octoate (95%, Sigma) was used as the initiating system. The obtained MPEG-*b*-PDLLGs were characterized by various methods as previously described (Baimark *et al*., 2007) and summarized in Table 1. Ibuprofen (99.95%) was supplied by the Government Pharmaceutical Organization, Thailand. Dichloromethane (AR, CALRO ERBA) was used as without further purification.

Preparation of Ibuprofen-Loaded Films

MPEG-*b*-PDLLG films containing ibuprofen were prepared by solution casting as following method. Five hundred miligrams of MPEG-*b*-PDLLG and 5 mg of ibuprofen were completely dissolved in 15 mL of dichloromethane. The solution was poured on glass Petri dish (5 cm in diameter) and dried at room temperature for 24 h. Film was lifted off the glass Petri dish and dried in vacuum oven at room temperature for another week. The MPEG-*b*-PDLLG films without ibuprofen loading were also prepared by the same method as control. Table 2 shows each film formulation.

Characterization of Ibuprofen-Loaded Films

Thermal properties of the films were characterized by Differential Scanning Calorimetry (DSC) using a Perkin-Elmer DSC Pyris Diamond. For DSC analysis, film samples (5-10 mg) were heated at rate of 10°C min^{-1} under a helium atmosphere over a temperature range of 20-100°C.

Table 1: Characteristics of MPEG-b-PDLLG

MPEG-*b*-PDLLG	EO/DLL/G[c] (mol %)	DLL/G[c](mol%)	$\bar{M}_n^d$ (g mol^{-1})	MWD[d]
MPEG2,000-PDLL[a]	10:90:0:0	100:00	58,200	1.9
MPEG5,000-PDLL[b]	22:78:0:0	100:00	73,600	1.9
MPEG5,000-PDLLG[b]	21:63:16:0	85:15	68,800	1.8

[a]MPEG block length was 2,000 g mol^{-1}, [b]MPEG block length was 5,000 g mol^{-1}, Calculated from 1H-NMR spectra (EO: Ethylene oxide (repeating units of MPEG), DLL: D,L-lactide and G: Glycolide), [d]Number-average molecular weight and $(\bar{M}_n^d)$ Molecular Weight Distribution (MWD) obtained from gel permeation chromatography curves

Mechanical properties including tensile strength and percent of elongation at break of the films were measured by tensile tester using a Lloyds LRX+ Universal Mechanical Testing Machine. The films with 10×40 mm in size were performed at 25°C and 65% relative humidity with the speed of 20 mm min^{-1} and 1 kN load cell. The experimental values for mechanical properties represent averages of measurements from the five replicate films.

Mophological characteristics of film surface and cross section were determined by Scanning Electron Microscopy (SEM) using a JEOL JSM-6460LV SEM. The film samples were cut by paper scissors and coated with gold for enhancing conductivity before scan.

In vitro Drug Release Test

For *In vitro* drug release test, the film with 10×10 mm in size was incubated in 20 mL of Phosphate Buffer Saline (PBS) with pH 7.4 at 37°C in a Heto SBD50 shaking water bath at 150 rpm rotation speed. At appropriate times, the all PBS medium was removed to a separate tube and replaced with 20 mL of fresh PBS. The amount of released ibuprofen was assayed by UV-Vis spectrophotometry using a Lambda 25 UV-Vis spectrophotometer at 220 nm (Borovac *et al*., 2006). All the measurements were carried out in triplicate. The films after drug release test were dried in vacuum oven at room temperature for 2 weeks before morphology observation by using SEM.

Statistical Analysis

The data were expressed as Mean±SD. Statistical analysis was performed using a one-way Analysis of Variance (one-way ANOVA).

RESULTS AND DISCUSSION

The all MPEG-*b*-PDLLG films with and without ibuprofen entrapment appear as clear transparent and flexible films. The drug-loaded films were thicker than the drug-free films as presented in Table 2.

Thermal Properties

The MPEG5,000-PDLL, MPEG2,000-PDLL and MPEG5,000-PDLLG were completely amorphous state. The melting temperature did not observe from their DSC thermograms (Baimark *et al*., 2007). Figure 1 shows the DSC thermograms of ibuprofen and drug-loaded MPEG-*b*-PDLLG film. The DSC curve of ibuprofen presents a single melting temperature at 80°C with heat of melting of 58.5 J g^{-1}, while this melting temperature of ibuprofen disappeared in the DSC curve of drug-loaded MPEG5,000-PDLL film, as shown in Fig. 1 (b). The ibuprofen crystallites were also disappeared when the MPEG2,000-PDLL and MPEG5,000-PDLLG were used as the film matrices instead of the MPEG5,000-PDLL (Fig. 1c, d).

Mechanical Properties

The mechanical properties of films were determined from their tensile strength and elongation at break. These mechanical properties of the both drug-free and drug-loaded films are shown in

Table 2: Film formulations and thicknesses of drug-free and drug-loaded MPEG-b-PDLLG films

Film No.	Ibuprofen (mg)	Average film thickness (μm)[d]
1[a]	-	144±8
2[a]	5	188±6
3[b]	-	160±7
4[b]	5	200±8
5[c]	-	148±5
6[c]	5	159±6

[a]Prepared from MPEG5,000-PDLL. [b]Prepared from MPEG2,000-PDLL. [c]Prepared from MPEG5.000-PDLLG, [d]Measured from SEM micrographs

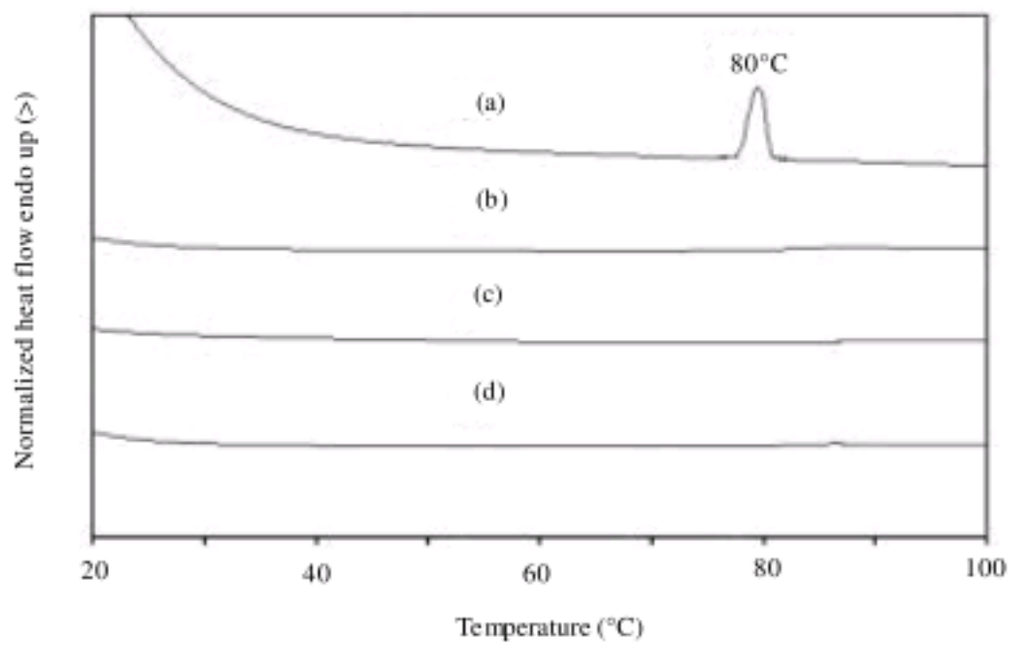

Fig. 1: DSC thermograms of (a) ibuprofen and Film No. (b) 2, (c) 4 and (d) 6

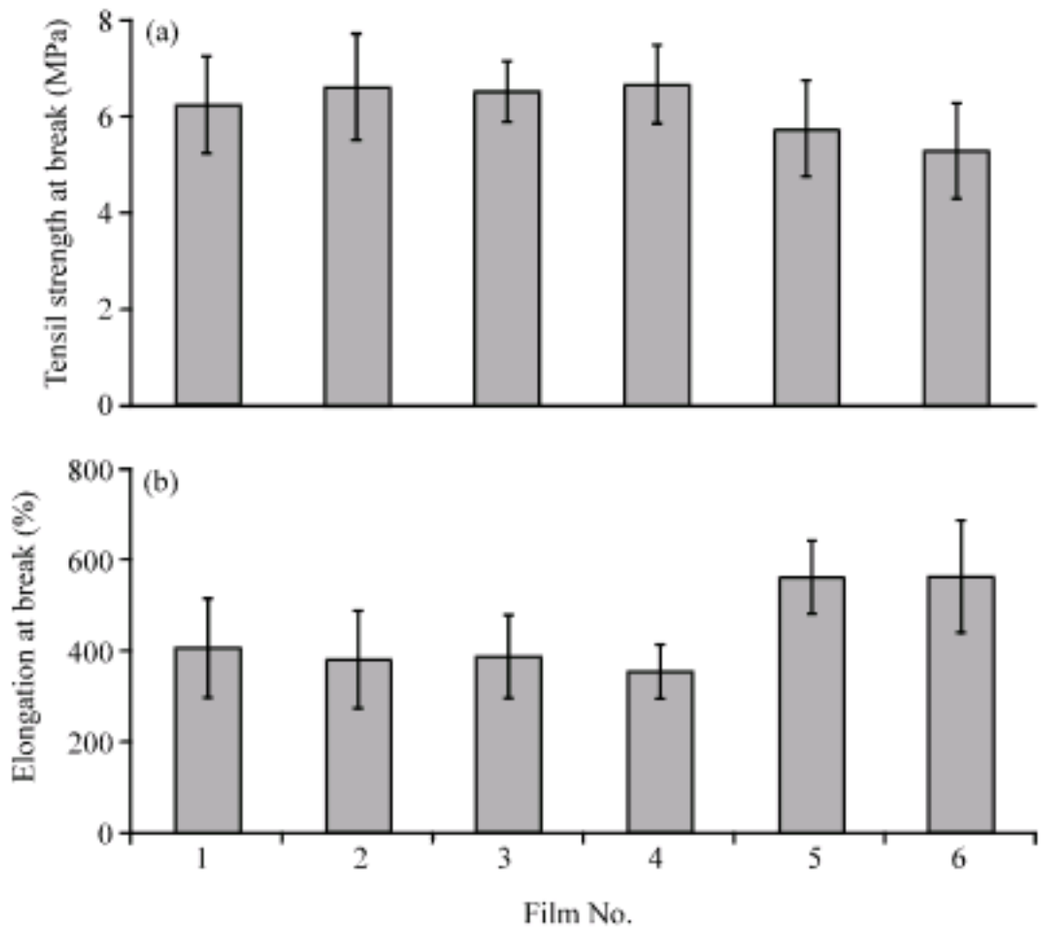

Fig. 2: (a) Tensile strengths and (b) Elongations at break of various film No.

Fig. 2a and b. For drug-free films (Film No. 1, 3 and 5), the results of mechanical properties accorded to the literature that the tensile strength at break of the diblock copolymer films decreased whereas the elongation at break increased when the MPEG block length was increased and the G units were copolymerized (Morakot *et al*., 2008). However, the mechanical properties of the films did not significantly change after drug entrapment for all MPEG-*b*-PDLLG films (Film No. 2, 4 and 6).

Film Morphology

The morphology of the films with and without drug entrapment was determined from SEM micrographs of their film cross sections and surfaces. Figure 3a and b show SEM micrographs of the drug-loaded films for Film No. 2, 4 and 6. They were smooth and uniform cross sections and surfaces without phase separation.

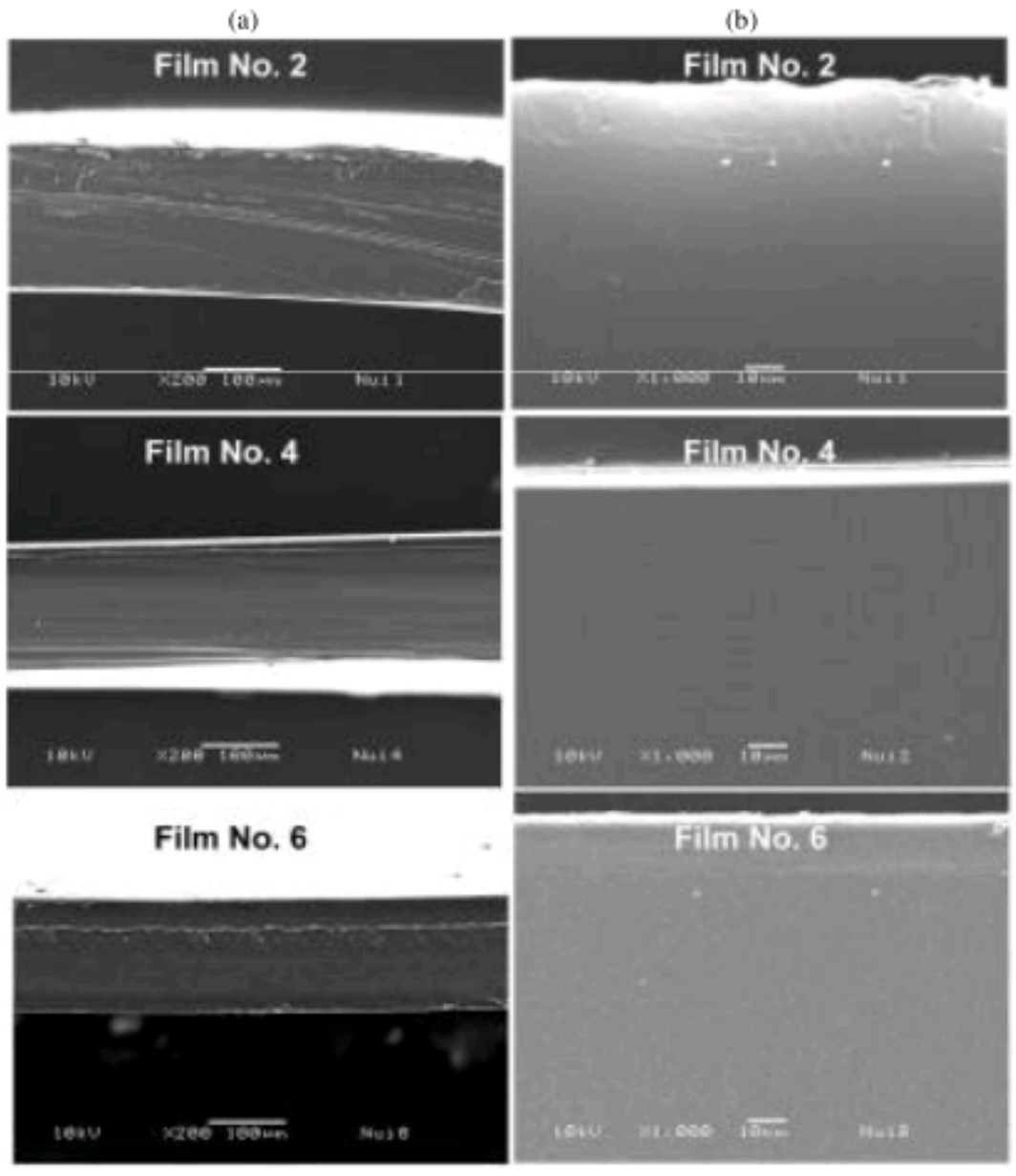

Fig. 3: SEM micrographs of (a) cross-sections and (b) surfaces of drug-loaded films before drug release test

Ibuprofen Release Studies

The influences of MPEG block length and incorporated glycolide on ibuprofen release behaviors were investigated as *in vitro*. Figure 4 shows ibuprofen release profiles from the drug-loaded films. The amount of drug released out from the films increased with the time. The effect of rapid initial burst release did not occur. The drug release rates were in sequence order of MPEG5,000-PDLLG>MPEG5,000-PDLL>MPEG2,000-PDLL films.

Thermal Properties

The melting transition of ibuprofen in DSC curve (Fig. 1a) indicated its crystalline state. However, the crystallizability of the ibuprofen was suppressed when it was entrapped in the MPEG-*b*-PDLLG films suggested the molecules of MPEG-*b*-PDLLG film matrix and loaded drug are well mixed together. Then the MPEG-*b*-PDLLG molecules can inhibit ibuprofen crystallization. The results suggest that the ibuprofen molecules are well distributed throughout the MPEG-*b*-PDLLG film matrices. This due to the dichloromethane is a good solvent for dissolving the both MPEG-*b*-PDLLG and ibuprofen to prepare well homogeneous solution before film casting.

Mechanical Properties

The mechanical properties of the drug-free MPEG-*b*-PDLLG films (Film No. 1, 3 and 5) depended upon the MPEG block length and copolymerized G units. It can be expected that the tensile

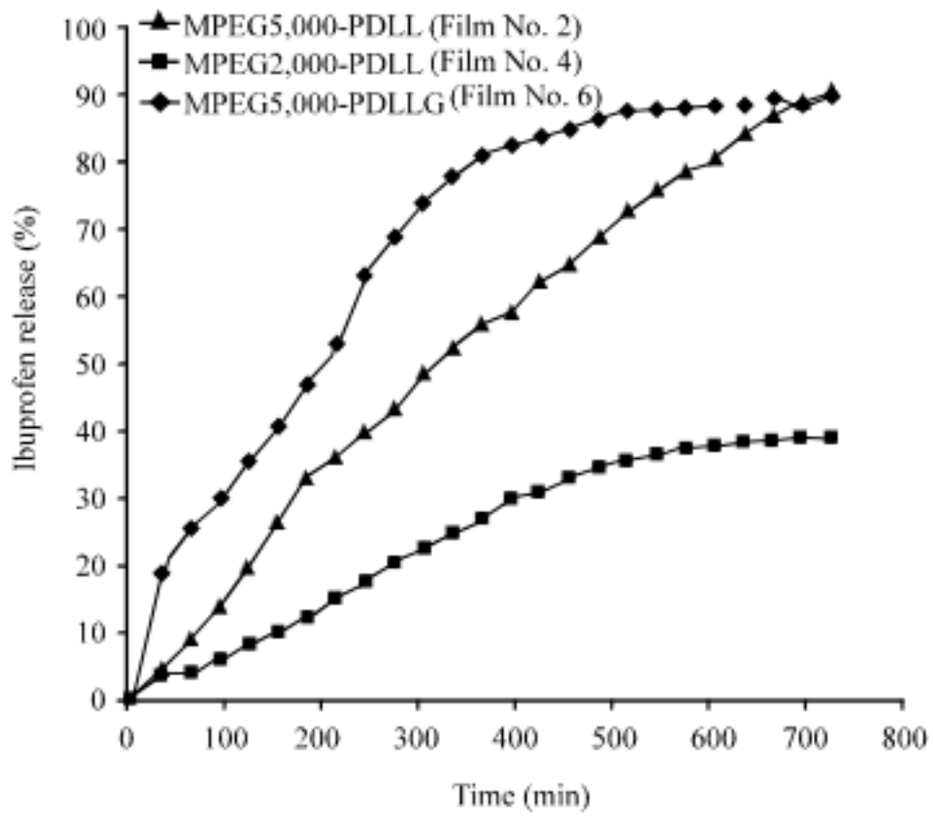

Fig. 4: Ibuprofen release from drug-loaded films

strength at break of films decreased, while the percentage elongation at break increased as the decreasing glass transition temperature (T_g) of the MPEG-*b*-PDLLG. The T_gs of MPEG2,000-PDLL, MPEG5,000-PDLL and MPEG5,000-PDLLG were 48, 37 and 28°C, respectively (Baimark *et al*., 2007).

The film mechanical properties were not affected from the drug loading suggested that the dispersed drug and MPEG-*b*-PDLLG film matrices with MPEG-*b*-PDLLG/ibuprofen ratio of 100/1 (w/w) were homogeneous blends for the all MPEG-*b*-PDLLG films (Film No. 2, 4 and 6). Thus, the mechanical properties of MPEG-*b*-PDLL/drug blended films did not differ from the pure MPEG-*b*-PDLLG films.

Film Morphology

The homogeneous cross sections and surfaces of drug-loaded films were clearly observed from their SEM micrographs (Fig. 3). This can be explained that the blended films were prepared from the MPEG-*b*-PDLLG/ibuprofen miscible blended solution in dichloromethane. The results of morphological characteristics supported that the ibuprofen was uniformly dispersed and distributed throughout the film matrices on the molecular level as previously described in DSC results.

Ibuprofen Release Studies

The ibuprofen release profiles in Fig. 4 show as sustained-release patterns suggested that the film matrices can control the drug releasing. The drug release rates decreased as the MPEG block length decreased from 5,000 to 2,000 g mol^{-1}. This may be explained that the drug release rate from the film was directly related to film swelling. The swelling of MPEG-*b*-PDLL film decreased with the hydrophilic MPEG block length (or MPEG molecular weight) (Morakot *et al*., 2008). Then drug release from the MPEG2,000-PDLL film showed slower than from the MPEG5,000-PDLL film. Moreover, the drug release rate also increased when the G units were incorporated into the PDLL block. Because of the G units had higher hydrophilic than the DLL units.

It is important to note that the ibuprofen-loaded films prepared in this work showed more nearly zero-order sustained-release of ibuprofen in comparison with the both ibuprofen-loaded monofilaments and microspheres as previously reported (Zurita *et al*., 2006; Thompson *et al*., 2007).

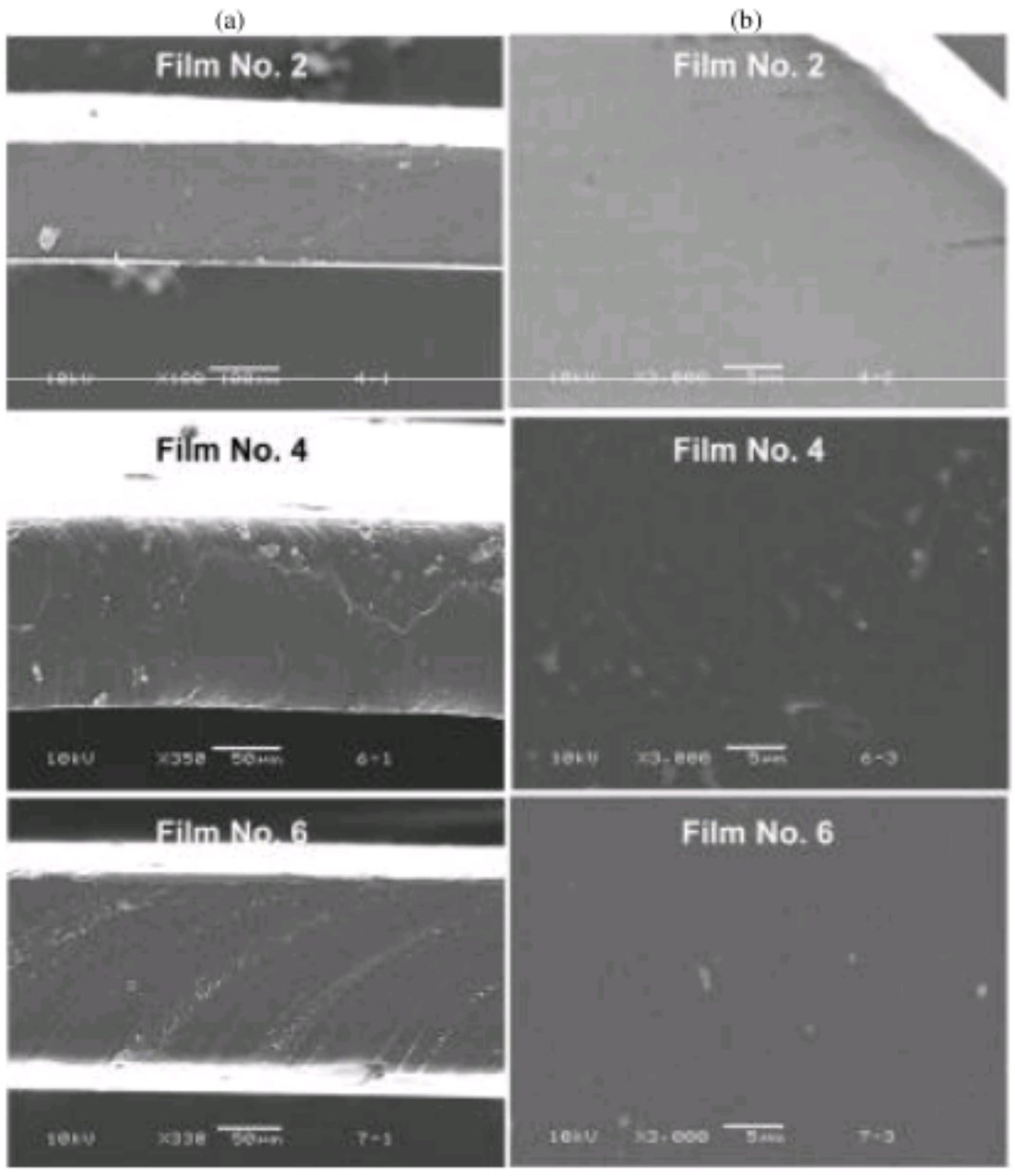

Fig. 5: SEM micrographs of cross-sections (left column) and surfaces (right column) of drug-loaded films after drug release test

In addition, the film opaque had appeared since the first 3 h of released time due to the water molecules diffused in the film matrices. However, the film transparency was recovered when they were dried to remove imbibed water molecules. This may be suggested that the ibuprofen molecules may release out through the intermolecular spaces that the water molecules had diffused to the film matrices. Then it can be proposed that releasing of ibuprofen from the film matrices occurred by diffusion process but did not induce surface erosion of film matrix. This is clearly confirmed by film morphological study after drug release test from the SEM micrographs as shown in Fig. 5a and b. The film cross sections and surfaces were still smooth and uniform after drug release test.

CONCLUSION

The ibuprofen-loaded MPEG-*b*-PDLLG films with uniform and transparent morphology were successfully prepared by film casting of MPEG-*b*-PDLLG and ibuprofen solution in dichloromethane. The ibuprofen crystallites had disappeared when it was entrapped in the films. The amount of drug released from the films was increased when the MPEG-*b*-PDLLG with longer MPEG block length and G copolymerization was used as the film matrix.

These biodegradable MPEG-*b*-PDLLG films are very interesting for use as controlled-release drug delivery systems, especially poorly water-insoluble drugs because the drug release rate can be adjusted by varying the MPEG block length and the DLL/G ratio.

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