Trends in Applied Sciences Research

ISSN 1819-3579

Academic
Journals Inc.

www.academicjournals.com

Trends in Applied Sciences Research, 4 (2): 107-115, 2009
ISSN 1819-3579

Methoxy Poly (Ethylene Glycol)-*b*-Poly (D, L-lactide) Films for Controlled Release of Ibuprofen

T. Phromsopha and Y. Baimark
Center of Excellence for Innovation in Chemistry, Department of Chemistry,
Faculty of Science, Mahasarakham University, Mahasarakham 44150, Thailand

Abstract: Biodegradable films of methoxy poly (ethylene glycol)-*b*-poly (D, L-lactide) diblock copolymers (MPEG-*b*-PDLL) containing drug were prepared by solution casting of MPEG-*b*-PDLL and drug in dichloromethane. Ibuprofen was used as a poorly-water soluble model drug. Influences of MPEG-*b*-PDLL/drug ratio and film thickness on ibuprofen-loaded film characteristics and drug release behaviors were investigated. The hydrogen bonding between MPEG-*b*-PDLL and drug were detected from FTIR analysis. From FTIR and differential scanning calorimetric results indicated that the ibuprofen was well distributed throughout the MPEG-*b*-PDLL film matrices. The drug release rates increased as the drug ratio increased and the film thickness decreased. The drug release from the films occurred by drug diffusion mechanism.

Key words: Biodegradable polymer, diblock copolymer, drug delivery, intermolecular bonding, thermal properties

INTRODUCTION

In the recent years, interest in poly (DL-lactide) (PDLL) for 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). The use of polyester films in biomedical, pharmaceutical and food packaging have already received wide attention, especially the PDLL films (Wang *et al*., 2004; Plackett *et al*., 2006).

PDLL films were rigid and brittle below their glass transition temperatures (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 (Martino *et al*., 2006; Martin and Averous, 2001; Ljungberg and Wesslen, 2003). Moreover, partial migration of the plasticizers has been found by Martino *et al*. (2006). Localized drug delivery to the vessel wall is believed to be the optimal approach for preventing restenosis and three general strategies have been described: endoluminal, intraluminal and perivascular drug delivery (Jackson *et al*., 2004). Endoluminal delivery includes the use of drug coated stents. Intraluminal delivery involves the deposition of drug solution or drug loaded nanoparticles into the vessel wall via penetration of the endothelium using, for example, microporous angioplasty balloons. In perivascular drug delivery, polymer-based carriers loaded with drug are applied to the outer adventitial surface of the blood vessel. Drug uptake into the vessel wall occurs by passive diffusion and is facilitated by the extensive adventitial vasa vasorum that supplies the vessel wall. Although, the MPEG-*b*-PDLL has widely investigated as controlled release drug delivery systems (Kim *et al*., 2005; Ren *et al*., 2005). However,

Corresponding Author: Yodthong Baimark, Center of Excellence for Innovation in Chemistry, Department of Chemistry, Faculty of Science, Mahasarakham University, Mahasarakham 44150, Thailand Tel/Fax: +66-43-754246

the controlled release drug delivery application of MPEG-*b*-PDLL films has been scarcely published. Therefore, this application of the MPEG-*b*-PDLL films is the focus of attention in this present study. It was hypothesized that drug release rates could be adjusted by varying the drug content and film thickness.

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*-PDLL films were prepared by film casting of MPEG-*b*-PDLL and ibuprofen homogeneous blended solution. Influences of MPEG-*b*-PDLL/drug ratio and film thickness on film characteristics and drug release behaviours from the films were investigated.

MATERIALS AND METHODS

Materials

Methoxy poly (ethylene glycol) (MPEG) with molecular weight of 5,000 g mol^{-1} (Fluka, Germany) was used after dried in vacuum oven at 120°C for 4 h. D, L-lactide (DLL) was synthesized by well established procedures from D, L-lactic acid solution (90%, Fluka, Switzerland). It was purified by repeated re-crystallization from ethyl acetate and dried in vacuo at 50°C for 48 h before used. Stannous octoate ($Sn(Oct)_2$, 95%, Sigma, USA) was used as without further purification. Ibuprofen (99.95%) was supplied by the Government Pharmaceutical Organization, Thailand. All solvents in analytical grade were used.

Methods

Synthesis and Characterization of MPEG-*b*-PDLL

The MPEG-*b*-PDLL was synthesized by ring-opening polymerization of D,L-lactide monomer at 130°C for 24 h under nitrogen atmosphere as earlier described by Baimark *et al*. (2007). The MPEG and $Sn(Oct)_2$ were chosen as the initiating system with the $Sn(Oct)_2$ concentration kept constant at 0.02 mol%. The MPEG/DLL feed ratio of 1/416 by mole was used. The as-polymerized MPEG-*b*-PDLL was purified by dissolving it in chloroform before precipitating in cool n-hexane and then dried to constant weight in vacuum oven at room temperature. According to this procedure, the purified MPEG-*b*-PDLL was obtained with more than 95% yield.

Molecular weight characteristics of MPEG-*b*-PDLL were determined by Gel Permeation Chromatography (GPC) using a Waters 717 plus Autosampler GPC equipped with Ultrastyragel® column operating at 30°C and employing a refractive index detector. Tetrahydrofuran was used as the solvent at a flow rate of 1 mL min^{-1}. Functional groups of MPEG-*b*-PDLL were studied by Fourier Transform Infrared (FTIR) spectroscopy using a Perkin-Elmer Spectrum GX FTIR spectrometer with air as the reference. The FTIR spectrum was obtained from film with the resolution of 4 cm^{-1} and 32 scans. Thermal properties were characterized by Differential Scanning Calorimetry (DSC). For DSC analysis, sample (~10 mg) was heated at the rate of 10°C min^{-1} under a helium atmosphere.

Preparation of Ibuprofen-Loaded Films

The MPEG-*b*-PDLL films with and without drug loading were prepared by solution casting as following method. Appropriate amount of MPEG-*b*-PDLL and ibuprofen were dissolved in dichloromethane (15 mL). 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 a week. The MPEG-*b*-PDLL film without ibuprofen loading was prepared as the same method.

Characterization of Ibuprofen-Loaded Films

Functional groups and thermal properties of the films were determined by FTIR spectroscopy and DSC, respectively as described above. Morphological characteristics of film surface and cross section were observed by Scanning Electron Microscopy (SEM) using a JEOL JSM-6460LV SEM. The films were cut by paper scissors and coated with gold for enhancing conductivity before scan.

Ibuprofen Release Studies

For *in vitro* drug release study, the film with 10×10 mm in size was incubated in 20 mL of phosphate buffer solution pH 7.4 at 37°C in a Heto SBD50 shaking water bath at 150 rpm rotation speed. At appropriate times, all the 20 mL of buffer was removed to a separate tube and replaced with fresh buffer. The amounts of released ibuprofen were assayed by UV-V is spectrophotometry 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 as described earlier.

RESULTS

The number-average molecular weight and molecular weight distribution of MPEG-*b*-PDLL obtained from GPC curve were 73,600 g mol^{-1} and 1.88, respectively. The DSC curve of MPEG-*b*-PDLL revealed an amorphous morphology with a single-glass transition temperature at 36°C.

The all MPEG-*b*-PDLL films with and without ibuprofen loading appear as clear transparent and flexible films. The ibuprofen-loaded films with different MPEG-*b*-PDLL/drug ratios and film thicknesses were prepared as shown in Table 1. The film thickness was directly related to amounts of MPEG-*b*-PDLL and drug used.

FTIR Spectra

FTIR spectra of the films and ibuprofen are shown in Fig. 1a-e. The FTIR spectra of the MPEG-*b*-PDLL film (Fig. 1a) and the ibuprofen (Fig. 1e) shows carbonyl absorption bands at 1760 and 1721 cm^{-1}, respectively. It should be noted that the absorption band at 1560 cm^{-1} was also assigned to ibuprofen characteristic. The broader carbonyl absorption bands in the region of 1780-1730 cm^{-1} were observed for the FTIR spectra of drug-loaded films due to overlapping of the carbonyl bands of MPEG-*b*-PDLL and ibuprofen. The FTIR spectra of drug-loaded MPEG-*b*-PDLL films with different film thicknesses showed similar evidence.

Thermal Properties

Figure 2 shows the DSC thermograms of MPEG-*b*-PDLL film, drug-loaded MPEG-*b*-PDLL films and ibuprofen. The DSC curve of ibuprofen presents a single melting temperature at 80°C with heat of melting of 58.5 J g^{-1} (Fig. 2a), while the melting temperature did not be detected from the DSC curve

Table 1: Formulations of ibuprofen-loaded MPEG-*b*-PDLL films

Film No.	MPEG-*b*-PDLL/drug ratio (w/w)	MPEG-*b*-PDLL (mg)	Ibuprofen (mg)	Average film thickness (μm)[a]
1	500/0	500	-	144
2	400/1	500	1.25	145
3	200/1	500	2.50	154
4	100/1	500	5.00	188
5	100/1	250	2.50	64
6	100/1	125	1.25	30

[a]Measured from SEM micrographs (all SD were less than 3 μm)

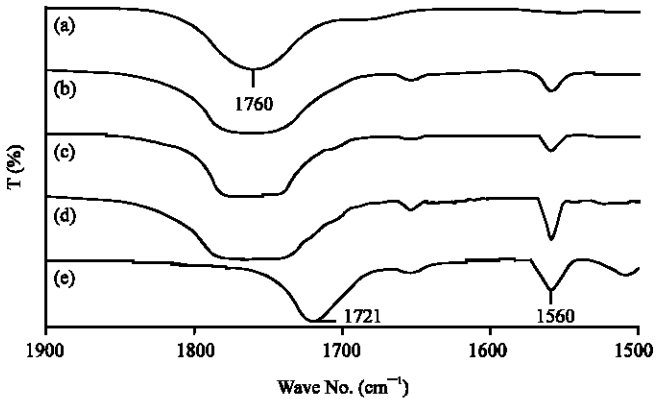

Fig. 1: FTIR spectra of films No. (a) 1, (b) 2, (c) 3, (d) 4 and (e) ibuprofen

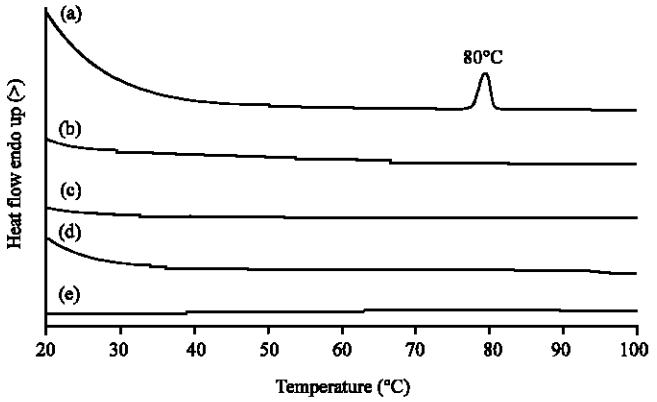

Fig. 2: DSC thermograms of (a) ibuprofen and the film Nos (b) 1, (c) 2, (d) 3 and (e) 4

of MPEG-*b*-PDLL film (Fig. 2e). The crystallinity of ibuprofen in drug-loaded films for all drug ratios did not be found (Fig. 2b-d). The disappearance of ibuprofen crystallites was also found for the drug-loaded MPEG-*b*-PDLL films with different film thicknesses.

Film Morphology

The morphology of the films with and without drug loading was determined from SEM micrographs. It was found that the morphology of all films shows smooth and uniformly surfaces and cross sections without phase separation as example of which is shown in Fig. 3a for the film No. 5.

Ibuprofen Release Studies

The influences of MPEG-*b*-PDLL/drug ratio and film thickness on ibuprofen release behaviors were investigated as *in vitro*. Figure 4 shows ibuprofen release profiles from the drug-loaded films with different drug contents. The ibuprofen release rates increased with the drug ratio. The ibuprofen release behaviors from the drug-loaded films with different film thicknesses are shown in Fig. 5. It can be observed that the faster ibuprofen release rates occurred when the film thickness was decreased.

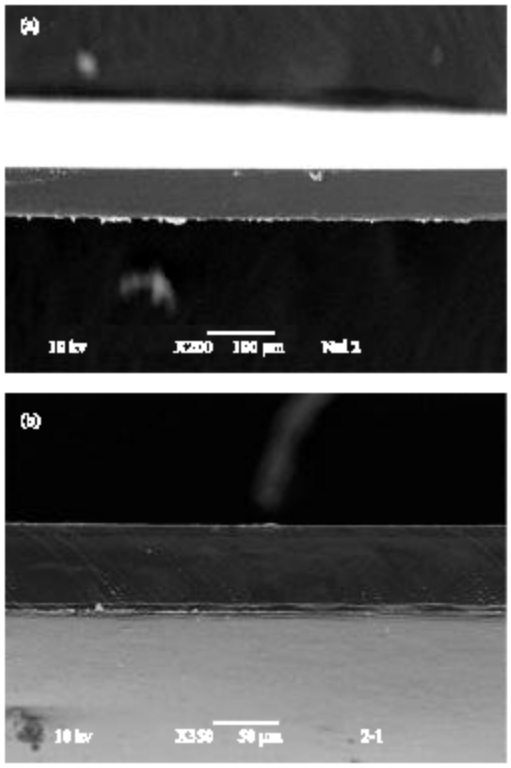

Fig. 3: SEM micrographs of film No. 5 (a) before and (b) after ibuprofen release test (bars = 100 and 50 µm for (a) and (b), respectively)

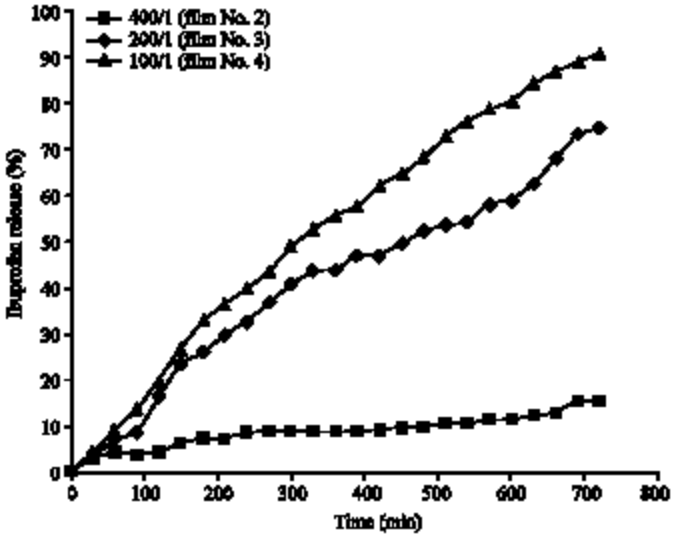

Fig. 4: Ibuprofen releases from MPEG-*b*-PDLL films with MPEG-*b*-PDLL/ibuprofen weight ratios

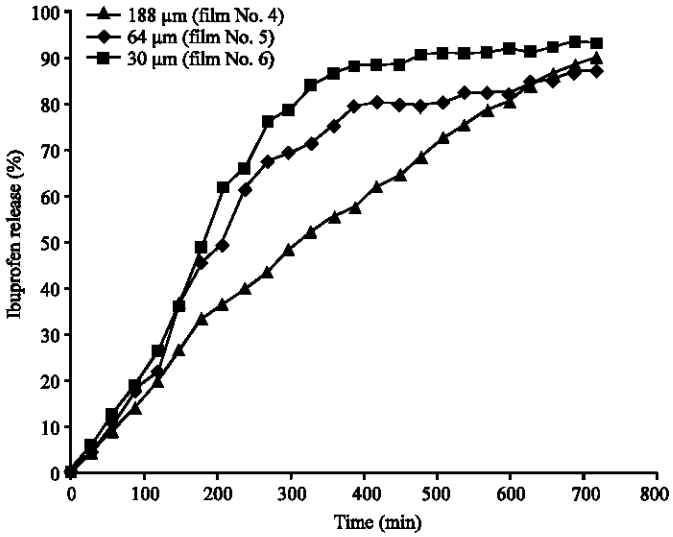

Fig. 5: Ibuprofen releases from MPEG-*b*-PDLL films with thicknesses

DISCUSSION

FTIR Spectra

Functional groups and interactions of the MPEG-*b*-PDLL and the ibuprofen were determined from FTIR spectra. The carbonyl absorption band at 1721 cm^{-1} indicated the crystalline form of ibuprofen (Kazarian and Martirosyan, 2002). This characteristic band of ibuprofen was shifted to higher wave number when the ibuprofen was loaded into the MPEG-*b*-PDLL films. Then, the broader carbonyl bands in the region of 1780-1730 cm^{-1} were observed, as shown in Fig. 1b-d. The results supported that the interactions between the MPEG-*b*-PDLL film matrices and the dispersed ibuprofen were existed. Ibuprofen-ibuprofen interactions in crystalline fraction may be destroyed indicated that the ibuprofen molecules are well dispersed in the film matrices. As would be expected, the intensities of absorption band at 1560 cm^{-1} assigned to ibuprofen characteristics increased as the ibuprofen ratio increased.

The intermolecular interactions were expected as hydrogen bonding between carbonyl groups of the MEPG-*b*-PDLL and hydroxyl groups of the ibuprofen as shown in Fig. 6. The existence of hydrogen bonding between poly (vinylpyrrolidone) matrix and ibuprofen has been reported by Kazarian and Martirosyan (2002).

Thermal Properties

The DSC results indicated that the ibuprofen and the MPEG-*b*-PDLL film were crystalline and amorphous states, respectively. It is significant to note that the crystallizability of the ibuprofen in all of the drug-loaded films was suppressed when loaded into the MPEG-*b*-PDLL films. This result indicated that the ibuprofen was well distributed into the MPEG-*b*-PDLL film matrices because of the MPEG-*b*-PDLL molecules can inhibited ibuprofen crystallization. The same phenomena had also occurred for the drug-loaded MPEG-*b*-PDLL films with different film thicknesses. This confirmed that the ibuprofen loaded in the films had a completely amorphous state according to the FTIR results.

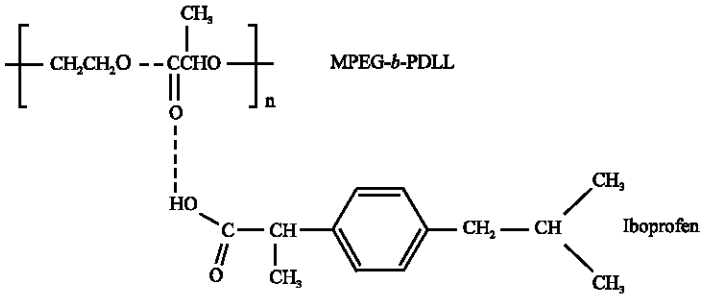

Fig. 6: Hydrogen bonding between carbonyl group of MPEG-*b*-PDLL and hydroxyl group of ibuprofen

Film Morphology

The homogeneous morphology of films was observed from the SEM micrographs. This can be explained that the dichloromethane is a good solvent for dissolving the both MPEG-*b*-PDLLG and ibuprofen. Then homogeneous blend solution was obtained before film casting. The results of morphological characteristics supported that the ibuprofen was uniformly dispersed and distributed throughout the film matrices on the molecular level.

Ibuprofen Release Studies

The ibuprofen release behaviors from the drug-loaded films with different drug ratios and film thicknesses are shown in Fig. 5 and 6, respectively. The rates of drug release increased as the drug ratio increased according to the literature (Thompson *et al*., 2007). The increase of ibuprofen will decrease the film matrices' tortuosity, which in turn increases the effect of accelerate of the drug release (Hsiue *et al*., 2001). It can be observed that the faster ibuprofen release rates occurred when the film thickness was decreased because the distance from film core to surface was short. Then the ibuprofen was faster diffused out from the film matrices for the thinner films. It is important to note that the ibuprofen-loaded films prepared in this study showed sustained-release of ibuprofen better than the both ibuprofen-loaded monofilaments and microspheres as previously reported by Zurita *et al*. (2006) and Thompson *et al*. (2007).

It can be proposed that ibuprofen released from the film matrices occurred by diffusion before film matrix erosion. This is confirmed by film morphological study after release testing as shown in Fig. 3b for the film No. 5. The percentage of ibuprofen release from the film No. 5 was approximately 75% after 12 h of release time. However, the film surface and cross section was still smooth without breakage.

In addition, the film opaque had appeared since the first 3 h of release time due to the water molecules diffused in the film matrices. However, the film transparency was recovered when they were dried for removing water molecules. This may be suggested that the ibuprofen molecules may be released out through the intermolecular spaces that the water molecules had diffused to the film matrices.

CONCLUSION

The amorphous MPEG-*b*-PDLL biodegradable films show very great potential for using as controlled release drug carriers, especially hydrophobic drugs. The homogeneous and transparent films containing ibuprofen, hydrophobic drug, were obtained. The interactions between carbonyl groups of MPEG-*b*-PDLL and hydroxyl groups of ibuprofen can interrupt the crystallization of dispersed

ibuprofen in the film matrices. The drug release rates from the film matrices were controlled by varying the drug content and film thickness. These biodegradable diblock copolymer films are very interesting for drug carrier and controlled release applications. The other hydrophobic drugs can be applied for this purpose.

ACKNOWLEDGMENTS

The authors would like to acknowledge the Research Development and Support Unit, Mahasarakham University, fiscal year 2008 and the Center of Excellence for Innovation in Chemistry (PERCH-CIC), Commission on Higher Education, Ministry of Education, Thailand for financial supports.

REFERENCES

Baimark, Y., M. Srisa-ard, J. Threeprom, R. Molloy and W. Punyodom, 2007. Synthesis and characterization of methoxy poly (ethylene glycol)-b-poly (D, L-lactide-co-glycolide-co-e-caprolactone) diblock copolymers: Effects of block lengths and compositions. e-Polymers, 138: 1-9.

Borovac, T., J.P. Pelage, A. Kasselouri, P. Prognon, G. Guiffant and A. Laurent, 2006. Release of ibuprofen from beads for embolization: *In vitro* and *in vivo* studies. J. Controlled Release, 115: 266-274.

Edlund, U. and A.C. Albertsson, 2002. Degradable microspheres for controlled drug delivery. Adv. Polym. Sci., 157: 67-112.

Hsiue, G.H., J.A. Guu and C.C. Cheng, 2001. Poly (2-hydroxyethyl methacrylate) film as a drug delivery system for pilocarpine. Biomaterials, 22: 1763-1769.

Jackson, J.K., J. Smith, K. Letchford, K.A. Babiuk, L. Machan, P. Signore, W.L. Hunter, K. Wang and H.M. Burt, 2004. Characterization of perivascular poly (lactic-co-glycolic acid) films containing paclitaxel. Int. J. Pharm., 283: 97-109.

Kazarian, S.G. and G.G. Martirosyan, 2002. Spectroscopy of polymer/drug formulations processed with supercritical fluids: *In situ* ATR-IR and raman study of impregnation of ibuprofen into PVP. Int. J. Pharm., 232: 81-90.

Kim, S.Y., Y.M. Lee and J.S. Kang, 2005. Indomethacin-loaded methoxy poly (ethylene glycol)/poly (D, L-lactide) amphiphilic diblock copolymeric nanospheres: Pharmacokinetic and toxicity studies in rodents. J. Biomed. Mater. Res., 74A: 581-590.

Ljungberg, N. and B. Wesslen, 2003. Tributyl citrate oligomers as plasticizers for poly (lactic acid): Thermo-mechanical film properties and aging. Polymer, 44: 7679-7688.

Martin, O. and L. Averous, 2001. Poly (lactic acid): Plasticization and properties of biodegradable multiphase systems. Polymer, 42: 6209-6219.

Martino, V.P., R.A. Ruseckaite and A. Jimenez, 2006. Thermal and mechanical characterization of plasticized poly (L-lactide-co-D, L-lactide) films for food packaging. J. Therm. Anal. Cal., 86: 707-712.

Plackett, D.V., V.K. Holm, P. Johansen, S. Ndoni, P.V. Nielsen, T. Sipilanien-Malm, A. Sodergard and S. Verstichel, 2006. Characterization of L-polylactide and L-polylactide-polycaprolactone co-polymer films for use in cheese-packaging applications. Packag. Technol. Sci., 19: 1-24.

Ren, J., H. Hong, J. Song and T. Ren, 2005. Particle size and distribution of biodegradable poly-D, L-lactide-co-poly (ethylene glycol) block polymer nanoparticles prepared by nanoprecipitation. J. Applied Polym. Sci., 98: 1884-1890.

Thompson, C.J., D. Hansford, S. Higgins, C. Rostron, G.A. Hutcheon and D.L. Munday, 2007. Evaluation of ibuprofen-loaded microspheres prepared from novel copolyesters. Int. J. Pharm., 329: 53-61.

Wang, Y., P. Challa, D.L. Epstein and F. Yuan, 2004. Controlled release of ethacrynic acid from poly (lactide-co-glycolide) films for glaucoma treatment. Biomaterials, 25: 4279-4285.

Yuehuei, H.A., 2000. Pre-clinic *in vivo* evaluation of orthopaedic bioabsorbable devices. Biomaterials, 21: 2635-2652.

Zurita, R., J. Puiggali and A. Rodriguez-Galan, 2006. Loading and release of ibuprofen in multi- and monofilament surgical sutures. Macromol. Biosci., 6: 767-775.