Iranian Polymer Journal **15** (1), 2006, 31-39

# Studying the Degradation of Poly(*L*-lactide) in Presence of Magnesium Hydroxide

Hamid Mobedi<sup>1\*</sup>, Mehdi Nekoomanesh<sup>2</sup>, Hossai Orafaei<sup>3</sup>, and Houri Mivehchi<sup>1</sup>

 Novel Drug Delivery Systems Department; (2) Petrochemical Department, Iran Polymer and Petrochemical Institute, Tehran, P.O. Box: 1497713115, I.R. Iran

(3) School of Pharmacy, Mashad University of Medical Sciences, Mashad, I.R. Iran

Received 5 April 2005; accepted 23 November 2005

# A B S T R A C T

ontrolling the rate and behaviour of the biodegradable polymer matrix is important in the development of drug delivery systems. In this project, we succeeded to control the speed of degradation and changing the degradation site from the bulk to the surface by addition of excipients. Antiacid excipients, such as Mg(OH)<sub>2</sub> have significant effects on rate and behaviour of biodegradation, by neutralization of the acidic microclimate pH in polymer. We synthesized high molecular weight poly(L-lactide) by using tin-2-ethyl hexanoate as catalyst. The polymer has been characterized by GPC, DSC and SEM. Mixtures of the polymer with Mg(OH)<sub>2</sub> at 1, 3 and 5% w/w were prepared and the degradation of the samples, kept at in vitro condition after 3 and 6 months, were studied. The results of average molecular weight changes, thermal characteristics and morphology of samples after 3 and 6 months revealed that it is possible to redirect the bulk degradation towards surface degradation. It is found that the ratio of bulk degradation to surface degradation and speed of degradation has reverse relationship with the additives concentration and when Mg(OH)<sub>2</sub> increases, the speed of degradation decreases as well. In samples with Mg(OH)2, the polymer degradation rates were reduced by 2-3 folds and the percentage of crystallinity increased by maximum 90% (3% Mg(OH)<sub>2</sub>) after 6 months.

# Key Words:

poly(*L*-lactide); magnesium hydroxide; surface erosion; bulk erosion; morphology.

(\*) To whom correspondence should be addressed. E-mail: H.mobedi@ippi.ac.ir

#### **INTRODUCTION**

Biodegradable polymers have become increasingly important in the development of drug delivery systems. These polymers can either function as a matrix to control diffusion of the drug, followed by polymer biodegradation and elimination of the degradation products from the body, or they can participate in and control the rate of drug release by polymer hydration and degradation [1-3]. A great number of biodegradable polymers have been developed and evaluated for drug delivery application, but the most widely investigated biodegradable polymers and systems achieving the most success in this decade are lactic/glycolic acid polymers. Lactic/glycolic acid polymers are biodegradable, biocompatible, and bioabsorbable. The major reasons are their reputation as safe suture materials and their degradation products that are friendly to normal body metabolites.

The behaviour of the biodegradable polymer matrix is very important in drug delivery systems. Biodegradable polymers can be categorized into two groups on the basis of the mechanism or process by which they degrade, bulk degradation and surface degradation. In the case of polymers that undergo bulk degradation, the rate of water penetration into the matrix is faster than the rate of polymer degradation. The process is homogeneous in which degradation occurs at a uniform rate throughout the polymer matrix. In contrast, for polymers that undergo surface degradation, the rate of water penetration into the matrix is slower than the rate of polymer degradation [4]. This process, therefore, is heterogeneous with degradation process confined to a thin surface layer of polymer. The degradation of lactic/glycolic acid polymers belongs to the category of polymers that undergo bulk degradation [5,6].

Many factors influence the degradation and drug release of PLA or PLGA polymers, including flow rate, sterilization, strain, presence of plasticizers, residual solvents, buffer concentration, porosity, temperature, size of the matrix, crystallinity, weight-average molecular weight ( $M_w$ ), composition and the enzymes. The degradation kinetic pattern is further altered by the presence of additives such as salts, basic and acidic compounds [7].

Many researchers have studied the possibility of reducing PLA bulk erosion and tried to push the mechanism toward surface erosion. One of the approaches in polymer degradation of PLA films can be modulated by incorporation of salts in polymer solutions prior to film casting.

Zhu et al. mentioned the mechanism by which  $Mg(OH)_2$  stabilizes encapsulated bovine serum albumin in poly(lactide-*co*-glycolide) implants relating to the neutralization of the acidic microclimate pH in polymer [8,9]. The microclimate pH inside PLGA implants can be controlled by selecting a particular type of basic salt, which would suggest a potential approach to optimize the stability of encapsulated phar-

maceuticals in PLGA including therapeutic proteins.

Zhang et al. reported that the degradation rates of film samples of poly(*DL*-lactide-*co*-glycolide) that contain sparingly soluble salts such as magnesium hydroxide, were reduced by 1.7-3.0 fold [10].

Kange et al. have studied to delineate the effects of microclimate pH and polymer water content on the stability of encapsulated bovine serum albumine(BSA) by comparing the effcts of  $Mg(OH)_2$  with those of another excipient, such as sucrose [11]. They reported that  $Mg(OH)_2$  has a greater stabilization effect on BSA encapsulated in PLGA implants than does sucrose. The base stabilizes BSA mainly by neutralizing the acidic microenvironment inside the PLGA device.

In spite of the investigations on the effects of  $Mg(OH)_2$  on the stability of proteins in polyesters, like PLA or PLGA implants, only little is known about the degradation of these polyesters in presence of  $Mg(OH)_2$ . In the current work, we examine the effects of  $Mg(OH)_2$  on the rate of polymer degradation, morphological changes and thermal analysis in PLA films. The results provide mechanistic information of PLA based devices for the controlled release of drugs or other medical applications.

#### EXPERIMENTAL

#### **Materials**

*L*-Lactide was prepared from a *L*-lactic acid solution (85%) (Merck, Darmstadt, Germany) and recrystallized three times from ethyl acetate (Merck, Darmstadt, Germany). Tin-2-ethyl hexanoate,  $Sn(Oct)_2$ , (Sigma, St. Louis, MO) was purified by vacuum distillation. Magnesium hydroxide (99%) was purchased from Merck.

#### **Polymerization**

*L*-Lactide was charged into a polymerization tube together with Sn  $(Oct)_2$  (0.03 wt %) as a polymerization catalyst. The tube was kept under a high vacuum at 70°C for 2 h, subsequently it was heat-sealed. After polymerization at 120°C for one week, the tube was broken and the crude polymer of each tube was dissolved in chloroform, filtered, and precipitated by hexane.

#### Film Preparation and Degradation

Films were prepared by solvent casting from a 25%

## A , Mobedi H∠et al.

solution of the polymer in chloroform and also by adding 1%, 3%, 5% magnesium hydroxide to the above solution and dried at room temperature for one day, then dried in vacuum for one week. Degradation studies were performed on square shaped samples (10 mm×30 mm×100  $\mu$ m), and placed in 10 mL distillated water at 37 ± 0.1°C in a sealed tube. At specific time intervals, one of the tubes was removed and the molecular weight, molecular weight distribution, glass transition temperature (T<sub>g</sub>), melting temperature (T<sub>m</sub>), enthalpy of crystallization ( $\Delta$ H<sub>c</sub>), enthalpy of fusion ( $\Delta$ H<sub>m</sub>), degree of crystallinity (X<sub>c</sub>) and scanning electron microscopy were monitored and examined.

#### **Instruments and Measurements**

The molecular weight and molecular weight distribution of the polymer samples were determined by sizeexclusion chromatography (SEC) (Waters-150C) on  $\mu$ styragel columns HT with 10 micron particle size, (refractive index detector), using dimethylformamide as solvent, with a flow rate of 1 mL/min at 50°C, and polystyrenes of low polydispersity as standards. Measurement of T<sub>g</sub>, T<sub>m</sub>,  $\Delta$ H<sub>c</sub> and  $\Delta$ H<sub>m</sub> were performed with a differential scanning calorimeter instrument (Prolab) in the temperature range from 20°C to 200°C at a scan speed of 20°C/min. The temperature scale was calibrated with an indium standard of high purity. The X<sub>c</sub> was calculated from the enthalpy change using the equation [12]:

 $X_{c}$  (%) = 100 × ( $\Delta H_{m} + \Delta H_{c}$ ) / $\Delta H$  100%

Where  $\Delta$ H 100% is the melting enthalpy of an infinitely large crystal and it is reported to be 93 Jg<sup>-1</sup>. The morphology of the films were studied with scanning electron microscopy (Cambridge.S.360) from the upper and lower surfaces and cross-section of the films. Also the percentage of Mg(OH)<sub>2</sub> at upper and lower surfaces were reported with scanning electron microscopy and EDAX. The EDAX qualitative and quantitative analysis for all elements were performed from carbon upwards (Cambridge.S.360).

#### **RESULTS AND DISCUSSION**

#### **Molecular Weight**

Degradation of a polymer is always accompanied by a

 Table 1. Effect of magnesium hydroxide on PLA molecular weight at 37°C in aqueous media.

 3 months
 6 months

Sample	3 months		6 months		
	M <sub>n</sub> ×10 <sup>-3</sup>	M <sub>n</sub> Reduced	M <sub>n</sub> × 10 <sup>-3</sup>	M <sub>n</sub> Reduced	
		(%)		(%)	
Original	356	-	356	-	
Control	126	65	47	87	
1 % Mg	217	39	59	83	
3 % Mg	242	32	84	76	
5 % Mg	284	20	200	44	

reduction of its molecular weight [13]. The synthesized PLA (original) has  $\overline{M}_n$  of 356000. Table 1 and Figure 1 both indicate that inclusion of Mg(OH)<sub>2</sub> into the control sample, largely reduces the rate of decline in  $\overline{M}_n$  both for 3 and 6 months period. It is also shown that with increasing the percent of Mg(OH)<sub>2</sub> from 1 to 5% the reduction of  $\overline{M}_n$  is quite, which is intended to improve the rate of degradation or reach a desirable course for polymer degradation. This clearly expresses the positive effect of the presence of Mg(OH)<sub>2</sub> for controlling the PLA degradation [14].

Figure 2 shows the SEC chromatograms of the samples after 3 months of the degradation. The chromatogram of the original sample shows a bimodal distribution consisting of a lower concentration of high  $\overline{M}_n$  and a normal distribution of lower  $\overline{M}_n$ . The chromatogram of the control shows that both high and low chains have shifted to lower  $\overline{M}_n$  chains which still



**Figure 1.** Time course of polymer degradation during degradation of PLA films containing various concentrations of Mg(OH)<sub>2</sub> at 37°C in aqueous media., control (x), added with 1% Mg(OH)<sub>2</sub> ( $\Delta$ ), 3% Mg(OH)<sub>2</sub> ( $\diamond$ ) and 5% Mg(OH)<sub>2</sub>( $\Box$ ).

ഷ്ഥ



**Figure 2.** Degradation profile of PLA films after 3 months of incubation at  $37^{\circ}$ C in aqueous media ., Original ( $\Box$ ), control (x), added with 1% Mg(OH)<sub>2</sub> (+), 3% Mg(OH)<sub>2</sub> ( $\circ$ ) and 5% Mg(OH)<sub>2</sub>(\*).

some high and low  $M_n$  chains remain. For the samples containing  $Mg(OH)_2$  apart from the percent of the base one can see that the lower  $\overline{M}_n$  sample almost has remained unchanged but the higher  $\overline{M}_n$  has degraded to various range of lower molecular weights (20-39%) so that the bimodality has been replaced by normal distribution (Table 1).

Figure 3 belongs to the samples after 6 months under degradation conditions and it is evident from this figure that all the chains of the control samples have degraded to very low  $\overline{M}_n$  chains (87%) and no sign of original chains exist (Table 1).

Figure 3 also shows that in all the sample containing  $Mg(OH)_2$  the SEC chromatograms indicate that the high  $\overline{M}_n$  portion of the original bimodality has van-



**Figure 3.** Degradation profile of PLA films after 3 months of incubation at 37°C in aqueous media, Original ( $\Box$ ), control (x), added with 1% Mg(OH)<sub>2</sub> (+), 3% Mg(OH)<sub>2</sub> ( $\circ$ ) and 5% Mg(OH)<sub>2</sub>(\*).

ished, but still some of the low  $M_n$  portion has remained unchanged and their concentrations are proportional to the Mg(OH)<sub>2</sub> concentration in the samples.

These results seem to provide enough evidence to conclude that  $Mg(OH)_2$  has an effect in controlling the degradation of polymer.

We can presume that  $Mg(OH)_2$  has serious effect on the manner of polylactide degradation at 37°C and this effect is more pronounced with increase of  $Mg(OH)_2$  concentration. It seems the presence of  $Mg(OH)_2$  plays a role of quasi cross-linking agent and has stronger effect on controlling the polymer degradation.

#### Morphology

The surfaces and cross-sections of the films under degradation analysis were monitored by SEM. Table 2 shows that distribution of  $Mg(OH)_2$  along the thickness of the films are not homogeneous and it is much higher for the lower surfaces probably due to precipitation of  $Mg(OH)_2$  in solvent (chloroform).

Figure 4 shows the upper and lower surfaces and the cross-section of the reference (original), control and samples containing  $Mg(OH)_2$  in PLA films after 3 and 6 months. These figures prove that the upper and lower surfaces of the original film are identical and the cross-section is a homogeneous bulky material.

After 3 months keeping the original sample under the degradation condition, some crystallites have grown identically over the upper and lower surfaces of the film. One can also see some empty spaces among the crystallites probably due to degradation and solubilization of the amorphous section of the film. The figure also shows that the empty spaces could be as big as the film thickness.

Degradation behaviour of the PLA samples containing  $Mg(OH)_2$  after 3 months indicates a different path in comparison with the original and the control samples. In each sample different crystalline pattern is

**Table 2.** Percentage of  $Mg(OH)_2$  in upper and lower surfaces of PLA films for the original sample.

PLA Site	1% Mg(OH) <sub>2</sub>	3% Mg(OH) <sub>2</sub>	5% Mg(OH) <sub>2</sub>
Upper surface	0.67 %	0.8 %	0.92 %
Lower surface	1.44 %	3.62 %	11.25 %



**Figure 4.** Lower and upper surfaces and the cross-section of the PLA films at  $37^{\circ}$ C in aqueous media, original(A), control after 3 months degradation (B), 1% - 3% - 5% Mg(OH)<sub>2</sub> after 3 months degradation(C,D,E) 1% - 3% - 5% Mg(OH)<sub>2</sub> after 6 months degradation(F,G,H), respectively.

Iranian Polymer Journal / Volume 15 Number 1 (2006)

ંગુ

observed for the upper and lower surfaces of the films due to different concentrations of  $Mg(OH)_2$ . Lower surfaces of the films which contain greater amount of  $Mg(OH)_2$  are relatively smooth and homogeneous while the upper surfaces with lower  $Mg(OH)_2$  represent specified crystalline structures.

In samples with 5%  $Mg(OH)_2$  opposite surfaces of the film are similar due to high level of  $Mg(OH)_2$  in the sample.

Studying the X-section of films containing  $Mg(OH)_2$  would reveal that the pore size inside the matrix of the films are smaller than those in the control sample. This could be related to the effect of  $Mg(OH)_2$  on controlling pH and degradation of PLA.

Scheme 1 shows the reaction between lactic acid and  $Mg(OH)_2$ .

Another significant conclusion from morphological studies shows that by addition of  $Mg(OH)_2$  the manner of polymer degradation was changed from bulk type to surface type. Its purpose is not only control of polymer degradation but also creation of physical connection between polylactide chains and Mg hydroxyl (because of hydrogen groups) and its result is fortification of polymer strings.

#### **Thermal Analysis**

Other important characteristics in detection of lactideglycolide polymers are the percentages of crystallinity and melting point ( $T_m$ ). X-Ray diffraction and DSC (differential scanning calorimetry) are common apparatus that are used for determination of the degree of lactide-glycolide crystallinity. Also glass transition ( $T_g$ ) and melting temperature ( $T_m$ ) are determined by DSC.

Synthesized PLA possesses high degree of crystallinity where for the original sample  $X_c$  is 42%. This result is confirmed by findings of other scientists [12].

Table 3 shows that crystallinity has been improved by about 30% for control samples which were kept 3 and 6 months under degradation conditions in respect to the original sample. This observation indicates that

**Table 3.** Effect of magnesium hydroxide on PLA crystallinity and melting point during 3 and 6 months of incubation at 37°C in aqueous media.

Sample	3 months		6 months	
	X <sub>c</sub>	T <sub>m</sub>	X <sub>c</sub>	Τ <sub>m</sub>
Original	42	179	42	179
Control	71	153	69	141
1 % Mg	70	167	70	163
3 % Mg	72	173	90	162
5 % Mg	80	170	89	160

the extent of crystallinity for pure PLA, which was kept under degradation conditions (37°C in aqueous media), is ultimately 70%. The effect of different percentages of Mg(OH)<sub>2</sub> on crystallinity of the samples is obvious from Figure 5. This figure shows that samples containing 1% Mg(OH)<sub>2</sub> almost is ineffective on the crystallinity of the sample for both samples kept 3 and 6 months under degradation conditions. Crystallinity for the sample having 3% Mg(OH)<sub>2</sub> after 3 months degradation has slightly changed while for the same sample after 6 months crystallinity shows a profound changes.

Samples with 5% Mg(OH)<sub>2</sub> have a considerable effect on the content of crystallinity of the mixtures for both 3 and 6 months degradation time. It also could result from Figure 5 that the ultimate extent of crystallinity of these samples is 90%, where the concentration of Mg(OH)<sub>2</sub> is higher than 3% it has no effect on  $X_c$  after 6 months.

The observation of increasing crystallinity with percent of  $Mg(OH)_2$  and time of degradation by considering  $T_m$  of the sample, leads one to conclude that presence of more than 1%  $Mg(OH)_2$  under degradation conditions probably acts as nucleating agent for oligomeric byproducts.

Figure 6 shows that  $T_m$  is reduced by increasing the degradation time for pure PLA samples, where samples having Mg(OH)<sub>2</sub> represent higher  $T_m$  after 3 and 6

$$2H-(-O-CHCH_3-CO-)-OH + Mg(OH)_2 \longrightarrow$$
$$H-(-O-CHCH_3-CO-)-O-Mg-O-(-O-CHCH_3-CO-)-H + 2H_2O$$

**Scheme I.** Shematic reaction between lactic acid and Mg(OH)<sub>2</sub>.



**Figure 5.** Effect of magnesium hydroxide on PLA crystallinity during the 3 and 6 months of incubation at  $37^{\circ}$ C in aqueous media., 3 month ( $\diamond$ ), 6 month ( $\Delta$ ).

months, respectively. This also indicates that  $T_m$  of samples containing more than 1% Mg(OH)<sub>2</sub> is independent from the percentage of Mg(OH)<sub>2</sub>.

The independency of  $T_m$  on Mg(OH)<sub>2</sub> percentage by considering gradual increase in crystallinity of the samples with increasing percentage of Mg(OH)<sub>2</sub> leads one to conclude that the extent of crystals inside the samples under degradation condition is related to Mg(OH)<sub>2</sub> but the size of crystals shown in Figure 5 has no relation to the percentage of Mg(OH)<sub>2</sub>.

Many investigations on the effects of  $Mg(OH)_2$  on the stability of proteins in polyesters, like PLA or PLGA implants have been performed.

Zhang et al. [10] investigated the effects of encap-



**Figure 6.** Effect of magnesium hydroxide percentage on PLA melting point during the 3 and 6 months of incubation at  $37^{\circ}$ C in aqueous media., original ( $\blacklozenge$ ), 3 month ( $\triangle$ ), 6 month( $\Box$ ).

sulated metal salts (10 wt%) on water absorption and degradation properties of PLGA 50/50. It was found that the degradation was strongly influenced by the presence and nature of salts. The control films without incorporated salts showed initial water absorption of about 2 % by wt during the first day. This was followed by a lag period during which there was negligible additional water uptake and a second phase of water uptake after 7 days. The effects of salts with low water solubility show an important initial increase of water absorption on the first day compared with the control film. Contrary to expectations, the increased water uptake by encapsulated salt-containing films did not bring about an increase in the rate of degradation. It was speculated that the reduced degradation rates were due to the alkaline properties of hydroxide and carbonates salts. This was also expected to disrupt the autocatalytic degradation brought about by carboxylic acids generated during polyester hydrolysis.

A number of forces and processes may contribute to the observed effects. These include: (1) porosity induced by the presence of salt particles, (2) osmotic forces due to the ionic nature of encapsulated salts, (3) neutralization by basic salts of protons evolved during hydrolysis of ester linkages, and (4) chemical interactions between ions and functional groups on the polymer [10].

In film samples that contain sparingly soluble salts such as magnesium hydroxide, magnesium carbonate, zinc carbonate, and calcium carbonate, polymer degradation rates were reduced 1.7-3.0 fold. The reduced degradation rates may be a consequence of the alkaline properties of hydroxide and carbonate salts, which would be expected to disrupt autocatalytic degradation brought by carboxylic acid groups generated during polyester hydrolysis. As a result, despite higher initial water uptake levels compared to control films, polymer degradation progressed more slowly.

Interactions of a similar nature have been observed between encapsulated anime salts. (e.g., gentamicin sulphate) and polylactic acid blends [10].

Some of the observed effects of salts on water up take, degradation and changes in morphology, and solubility upon hydration may also stem from chemical interactions between ions and polymer functionalities such as carboxylic acid or ester groups. Evidence supporting this possible mechanism includes the decrease in solubility after freeze-drying of hydrated films that contained magnesium hydroxide and magnesium car-

ഷ്പ

bonate [10].

The change in solubility could be reversed by incubation of the film sample in an aqueous EDTA solution, prior to lyophilization. This observation is consistent with the possible formation of inter-or intramolecular cross-links via coordination with  $Mg^{2+}$  ions [10].

The pH control of the inside polyesters polymer is very effective than the release medium. Wu and Wang [15] used PLGA having an equal molar ratio of lactic to glycolic acid (50/50) to conduct a series of experiments. The effect of the pH of the in vitro release medium on the rate of biodegradation/hydrolysis of the PLGA was not obvious within the first two weeks of immersion. It was observed that the rate of degradation increased in acidic medium (pH 5), but slowed down when the medium was alkaline (pH 9.24). While the degradation in pH 9.24 reached a plateau after a certain period of time, but in neutral (pH 7.4) and acidic media (pH 5.0) the polymer continued to degrade, with the fastest rate recorded at pH 5. The result suggests that the PLGA in a basic medium may degrade slower than in an acidic one. In the first few weeks, the integrity of the matrix is retained, although the polymer chains may have undergone hydrolytic scission, leading to a lowering of molecular weight. Presumably, the hydroxide ions from the medium outside and the hydronium (H<sub>3</sub>O<sup>+</sup>) ions generated by the initial matrix hydrolysis cannot diffuse in and out of the matrix freely, thus accounting for the non-significant difference in the rate of degradation during the initial stage.

In contrast, Makino et al. [16] reported that microcapsules of PLLA exhibited rapid weight loss in alkaline media (pH 8-9). Trends in the decrease of  $M_w$  indicated that such reductions occurred more readily in alkaline media of pH 8-9.

It can be reasonably concluded that both alkaline and strongly acidic media accelerate polymer degradation. The difference between slightly acidic and neutral media, however, is less pronounced due to autocatalysis by the carboxylic end groups.

The effect of  $Mg(OH)_2$  on the molecular weight, molecular weight distribution, morphology, crystallinity, termal behaviour and finally the PLA degradation behaviour has not been reported before. In this paper more detailed information on the role of  $Mg(OH)_2$  on PLA degradation is reported for first time.

#### CONCLUSION

Polylactide is a suitable biocompatible as well as the biodegradable polymer in implant systems by chemical control mechanism. In drug delivery system, the polymers main problem is the bulk degradation. In this project, we could control the speed of degradation and changing the site of degradation from the bulk to surface by addition of Mg(OH)<sub>2</sub>. The mechanism by which  $Mg(OH)_2$  stabilizes poly(L-lactide) implants relating to the neutralization of the acidic microclimate pH in polymer. It is observed that the ratio of bulk degradation to surface degradation and speed of degradation has reverse relationship with the Mg(OH)<sub>2</sub> concentration and when Mg(OH)<sub>2</sub> increases, the speed of degradation will decrease as well. Also the percentage of crystallinity has direct relationship with the Mg(OH)<sub>2</sub> concentration and during the degradation, for example in samples with Mg(OH)<sub>2</sub>, the percentage of crystallinity will increase 1.6-2.1 fold during 3 and 6 months of incubation at 37°C in aqueous media. In this procedure, crystallinity increases which is not due to the addition of Mg(OH)<sub>2</sub>, rather it is because of increasing the degradation time.

Addition of  $Mg(OH)_2$  also increases  $T_m$  indicating (in some samples) a serious effect on crystallinity. Its purpose is creation of physical connection between polylactide chains and Mg hydroxyl (because of hydrogen groups) and its result is fortification of polymer strings.

#### REFERENCES

- Cohn D., Younes H., Marom G., Amorphous and crystalline morphologies in glycolic acid lactic acid polymers, *Polymer*, 28, 2018-2022(1987).
- Miyajima M., Koshika A., Okada J., Ikeda M., Nishimura K., Factors influencing the diffusion-controlled release of papaverine from poly (*L*-lactic acid) matrix, *J. Cont. Rel.*, 56, 85-94(1998).
- Bernstein H., Zhang Y., Khan M.A., Tracy M.A., Uspto patent full text and image database, US Patent. 5,656,297 (1997).
- Izumikava S., Yoshioka S., Aso Y., Takeda Y., Preparation of poly (*L*-lactide) micro spheres of different crystalline morphology and effect of crystalline morphology on drug release rate, *J. Cont. Rel.*, **15**, 133-140 (1991).

## Mobedi Haet al.

- Mobedi H., Nekoomanesh M., Orafaei H., Role of magnesium hydroxide on poly (*L*-lactide) degradation (II) Microscopy study, *Proc. Br Pharm. Conf.* (2002).
- Vert M., Summing L., Garreav H., More about the degradation of La/Ga-derived matrices in aqueous media. *J. Cont. Rel.*, 16, 15-26 (1991).
- Alexis F., Factors affecting the degradation and drugrelease mechanism of poly(lactic acid) and poly[(lactic acid)-co-(glycolic acid)], *Polym. Int.*, 54, 36-46(2005)
- Zhu G., Mallery S.R., Schwendeman S.P., Stabilization of proteins encapsulated in injectable poly(lactide-*co*-glycolide). *Nat. Biotech.*, 18, 52-57 (2000).
- Zhu G., Schwendeman S.P., Stabilization of proteins encapsulated in cylindrical poly(lactide-*co*-glycolide) implants: mechanism of stabilization by basic additives, *Pharm. Res.*, **17**, 351-357 (2000).
- Zhang Y., Zale S., Sawyer L., Bernstein H., Effect of metal salts on poly(*DL*-lactide-*co*-glycolide) polymer hydrolysis, *J. Biomed. Mat. Res.*, 34, 531-538 (1997).
- Kange J., Schwendeman S.P., Comparison of the effects of Mg(OH)<sub>2</sub> and sucrose on the stability of bovine albumin encapsulated in injectable poly(*DL*-lactide-*co*-glycolide) implants, *Biomaterials*, 23, 239-245(2002)
- Tsuji H., Ikada Y., Properties and morphologies of *L*-lactide: Annealing condition effects on properties and morphologies of poly(*L*-lactide), *Polymer*, **36**, 2709-2716 (1995).
- Absano M., Fukusaki M., Yoshida M., Kumakura M., Application of poly(*DL*-lactic acid) of varying molecular weight in drug delivery systems, *Drug Des. Del.*, 5, 301-320 (1990),
- Mobedi H., Nekoomanesh M., Orafaei H., Role of magnesium hydroxide on poly(L-lactide) degradation (I) Effect of molecular weight, *Proc. Int. Symp. Cont. Rel. Bioact. Mater.*, p624 (2002).
- 15. Wu N.S., Wang N., Synthesis, characterisation, biodegradation, and drug delivery application of biodegradable lactic/glycolic acid polymers. Part I: Biodegradation, J. *Biomater. Sci. Polym. Edn.*, **12**, 21-34 (2001)
- Makino K., Oshima H., Kondo T.J., Mechanism of hydrolytic degradation of poly(*L*-lactide) microcapsules: effects of pH, ionic strength and buffer concentration. *Microencapsulation*, 3, 203-212 (1986).