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Controlled delivery of aspirin: Effect of aspirin on polymer degradation and *in vitro* release from PLGA based phase sensitive systems

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Abstract

The objective of this study was to develop poly (D,L-lactide-co-glycolide) (PLGA) based injectable phase sensitive *in situ* gel forming delivery system for controlled delivery of aspirin, and to characterize the effect of drug/polymer interaction on the *in vitro* release of aspirin and polymer degradation. Aspirin was dissolved into PLGA solution in 1-methyl-2-pyrrolidone. Poly(ethylene glycol)400 was used as plasticizer to reduce initial burst release. The solution formulation was injected into aqueous release medium to form a gel depot. Released samples were withdrawn periodically and assayed for aspirin content by high performance liquid chromatography. The effect of aspirin on the degradation of PLGA matrix was evaluated using Proton Nuclear Magnetic Resonance and Gel Permeation Chromatography. PLGA based *in situ* gel forming formulations controlled the *in vitro* release of aspirin for 7 days only. Analysis of PLGA matrix residuals revealed that PLGA in aspirin loaded formulations exhibited a significantly ($p < 0.05$) faster degradation compared to blank formulations. These findings suggest that aspirin causes an unusually faster degradation of PLGA. Such faster degradation of PLGA has not been noticed for any other drugs reported in the literature.

Keywords: PLGA; Aspirin; Controlled delivery; Phase sensitive *in situ* gel forming drug delivery system; Polymer degradation

1. Introduction

Aspirin is an important anti-platelet drug for preventing cardiovascular events, such as myocardial infarction and vascular occlusion in the cerebral and peripheral circulation. The administration of aspirin mainly relies on oral dosage form and usually requires daily use for long period. Unfortunately, aspirin has a poor oral bioavailability (∼40%). Furthermore, long-term oral administration could induce gastrointestinal (GI) mucosa ulcer and massive GI hemorrhage (Guslandi, 1997; Sztriha et al., 2005). Thus, parenteral administration method of aspirin is needed to avoid GI side effects. Clinical trials have demonstrated that the continuous administration of a very low dose of aspirin (3–30 mg/day) through intravenous infusion enhanced the selective inhibition of platelet function and minimized the GI side effects (Pedersen and FitzGeral, 1984; Lee et al., 1994). These clinical trials suggest that a controlled release of aspirin would favor the therapeutic efficacy of the drug.

In order to achieve parenteral controlled delivery of aspirin, efforts have been made for the development of new dosage forms, such as aspirin loaded vascular grafts, poly (β-propiolactone) and poly (*N*-isopropylacrylamide) films, and chitosan/polyethylene vinyl acetate beads (Hall et al., 1994; Vasudev et al., 1997; Cortizo et al., 2001; Tsukagoshi et al., 2007). However, administration of these dosage forms requires invasive surgical procedures. The surgical procedures not only increase difficulties in the drug administration, but also increase the risk of infection, hematoma formation, inflammation, and fibrosis at the site of application.

PLGA based phase sensitive *in situ* gel forming drug delivery system has recently attracted great attention, because of the advantages it possesses, which include ease of formulation manufacturing, less invasive administration by a single bolus injection, promised controlled release of incorporated drugs, biodegradability and excellent biocompatibility. PLGA polymer was first introduced in an injectable *in situ* gel forming implant system by Dunn et al. (1990). Briefly, the water insoluble PLGA is dissolved in a water miscible and biocompatible organic solvent to form an injectable polymer solution. Drug can be either dissolved or suspended in the polymer solution.

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Upon injection into aqueous environment, the solvent diffuses into aqueous surrounding and water penetrates into the polymer matrix. The exchange of organic solvent and water leads to the decrease in PLGA solubility and finally results in the gel formation. The *in situ* formed gel serves as a depot for controlled release of incorporated drug over a long period (1–6 months) (Lambert and Peck, 1995; Leton and Tipton, 1998; Ikada and Tsuji, 2000; Wang et al., 2004).

The purpose of this study was to investigate the feasibility of using PLGA based *in situ* gel forming drug delivery system for parenteral administration and controlled delivery of aspirin. The present study characterized the *in vitro* release of aspirin from the delivery system and the effects of aspirin on PLGA degradation.

2. Materials and methods

2.1. Materials

Aspirin (acetyl salicylic acid, ≥99.0%, crystalline), salicylic acid (≥99.0%) and polyethylene glycol 400 (PEG400, av. mol. wt. 400) were purchased from Sigma–Aldrich. (St. Louis, MO, USA). PLGA50:50 (Intrinsic Viscosity 1.05 dl/g) was obtained from DURECT Corporation (Pelham, AL, USA). 1-Methyl-2-pyrrolidinone (NMP, anhydrous, ≥95.0%) was purchased from Alfa-Aesar (Ward Hill, MA, USA). All other chemicals used were of analytical-grade.

2.2. Preparation of delivery system

The formulation compositions used in this study are showed in Table 1. Briefly, PLGA50:50 was dissolved in NMP to form a solution. The dissolution process was facilitated by incubating the polymer/organic solvent mixture at 37 °C for 24 h. Aspirin (200 mg/ml) was added into the polymer solution and then homogenized using Silverson homogenizer (East Long-Meadow, MA, USA) at 8000 rpm for 20 s.

2.3. In vitro release of aspirin

One milliliter of aspirin loaded polymer solution was injected through 21-gauge needle into a vial containing 90 ml phosphate buffer saline (PBS) pH 7.4 release medium. The polymer solution turned into a semi-solid gel quickly upon injection. The vial was kept in a reciprocal shaking water bath at 37 °C and 35 rpm during the entire release study. Aliquots of released sample were withdrawn at predetermined time points and replaced with the same amount of fresh PBS.

Table 1
Phase sensitive *in situ* gel forming formulations of aspirin

Formulation	Aspirin (w/v)	PLGA50:50 (w/v)	NMP (v/v)	PEG400 (v/v)
A	20%	30%	100	0
A-blank	0	30%	100	0
B	20%	30%	80	20
B-blank	0	30%	80	20

2.4. Analysis of aspirin samples

Aspirin can be hydrolyzed into salicylic acid and acetic acid in PBS (Bakar and Niazi, 1983). Therefore, both aspirin and salicylic acid in the released samples were measured. The measurement was performed on Hewlett Packard HPLC-1050 system equipped with reverse phase C_{18} column (300 mm × 3.9 mm, particle size 10 μm, Phenomenex, USA). The mobile phase used was methanol and water in the volume ratio of 35:65 containing 0.5% (v/v) of acetic acid at a flow rate of 1 ml/min. Ten microliters of properly diluted released sample was injected into HPLC-UV system and detected at 240 nm. The hydrolyzed aspirin was calculated by the following formula:

$$\begin{aligned}&\text{Hydrolyzed aspirin (mg)}\\&\quad = [\text{salicylic acid (mg)/molecular weight of}\\&\qquad \text{salicylic acid (138.123 g/mol)}]\\&\qquad \times \text{molecular weight of aspirin (180.160 g/mol)}\end{aligned}$$

Chemical stability of released aspirin was evaluated by comparing the percentages of chemically stable aspirin in released samples and those in "aspirin control samples" (200 mg aspirin dissolved in 90 ml PBS, kept in a reciprocal shaking water bath at 37 °C and 35 rpm for the same period of time as released samples).

2.5. Analysis of polymer degradation

At the end of release study, the polymer residuals were collected and lyophilized. The degradation of polymers was examined using ^{1}H-NMR and Gel Permeation Chromatography (GPC). The effect of aspirin on the degradation of PLGA polymer was evaluated by comparing the degradation status of PLGA with aspirin loaded formulations and in blank formulation (without aspirin).

2.5.1. ^{1}H-NMR analysis

Deuterated chloroform ($CDCl_3$) was used to dissolve the polymer residuals. Spectra were recorded at 300 MHz on a Varian Spectrometer at 25 °C. A tetramethylsilane (TMS) signal was taken as the zero chemical shift. The ratio of lactic acid (LA) to glycolic acid (GA) moieties of polymer residuals was determined by comparing the integration of the signals pertaining to each monomer, such as the peaks from CH_3 of LA and CH_2 of GA.

2.5.2. Gel Permeation Chromatography (GPC) analysis

Number average molecular weight (Mn), weight average molecular weight (Mw) and polydispersity index (PDI = Mw/Mn) were measured using Waters 515 system, equipped with a refractive index detector and two styragel® HR4E and HR5E columns. Tetrahydrofuran (THF) was used as mobile phase (flow rate 1.0 ml/min, column temperature 30 °C).

Polystyrenes (molecular weights range 162–6,035,000 Da) were used as standards for molecular weight calculation.

2.6. Data analysis and statistics

In vitro release of each formulation was studied in quadruplicates. Analysis of variance (ANOVA) and student *t*-test were used for statistical comparison. A probability value less than 0.05 was considered significant.

3. Results

3.1. In vitro drug release studies

Fig. 1 shows that the PLGA based *in situ* gel forming drug delivery system controlled the release of aspirin at a constant rate for 7 days. Addition of PEG400 significantly ($p < 0.05$) decreased the initial burst release of aspirin from $36.9 \pm 1.9\%$ to $30.9 \pm 1.2\%$. The release kinetics of aspirin showed the best fit for Higuchi model ($R^2 = 0.99$) followed by zero-order release kinetics ($R^2 = 0.91$).

Since aspirin loses its anti-platelet activity after hydrolysis, it is important for the controlled delivery system to release aspirin in its active form. Therefore, the percentage of chemically stable aspirin was measured for the released samples and for aspirin control samples (aspirin solution in PBS). Fig. 2 shows that the released samples had a significantly ($p < 0.05$) higher percentage of chemically stable aspirin than the aspirin control sample. These results confirmed that the delivery systems constantly released chemically stable aspirin into release medium.

3.2. Polymer degradation

After release study, polymer matrix residuals were collected for examining the polymer degradation. Residual of blank polymeric gel showed a solid structure. However, the residual of polymeric gel loaded with aspirin exhibited a hollow core–solid shell structure (Fig. 3). GPC measurements revealed that the polymer residuals from both blank and aspirin loaded formulations exhibited a noticeable degradation during the 7-day

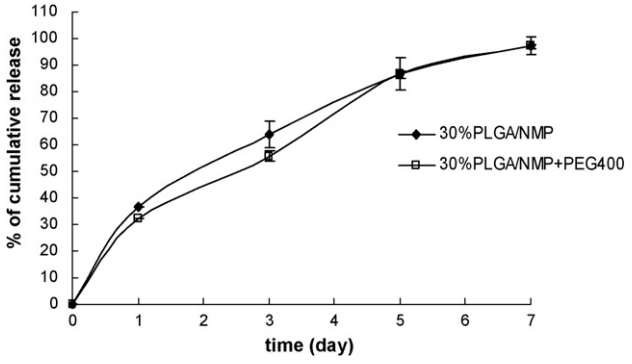

Fig. 1. *In vitro* release of aspirin from PLGA50:50 based phase sensitive *in situ* gel forming formulations. *Keys*: (♦) Formulation containing PLGA50:50 (30%, w/v)/NMP; (□) formulation containing PLGA50:50 (30%, w/v)/NMP (80%, v/v)/PEG400 (20%, v/v).

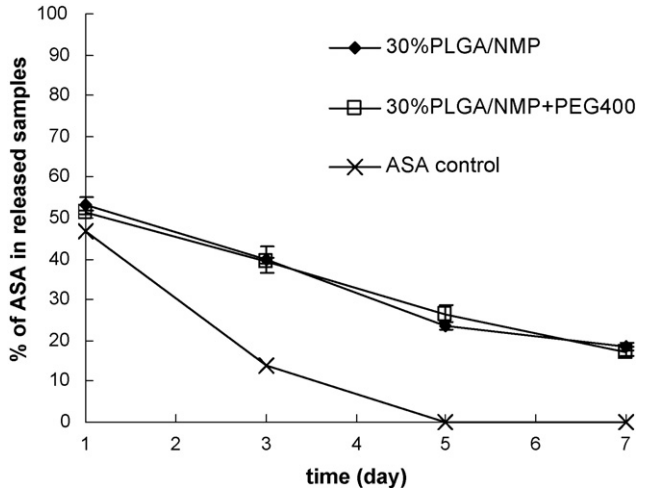

Fig. 2. Effects of formulations on the level of aspirin in released samples. *Keys*: (♦) Aspirin level in the released samples from formulation containing PLGA50:50 (30%, w/v)/NMP; (□) aspirin level in the released samples from formulation containing PLGA50:50 (30%, w/v)/NMP (80%, v/v)/PEG400 (20%, v/v); (×) aspirin level in the aspirin control sample (aspirin solution in PBS and incubated in the same conditions as released samples).

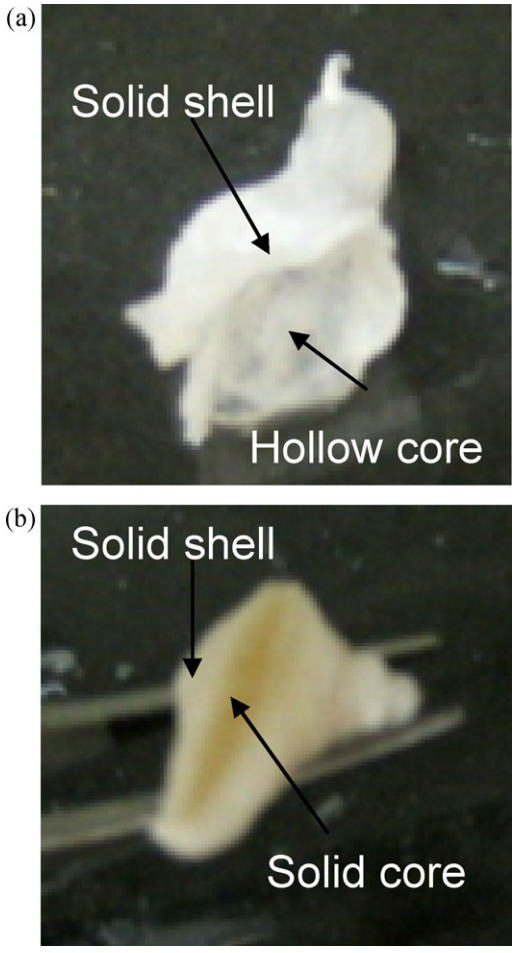

Fig. 3. The structure comparison between aspirin loaded gel and blank gel after release study. (a) Gel residual from aspirin loaded gel. (b) Gel residual from blank gel.

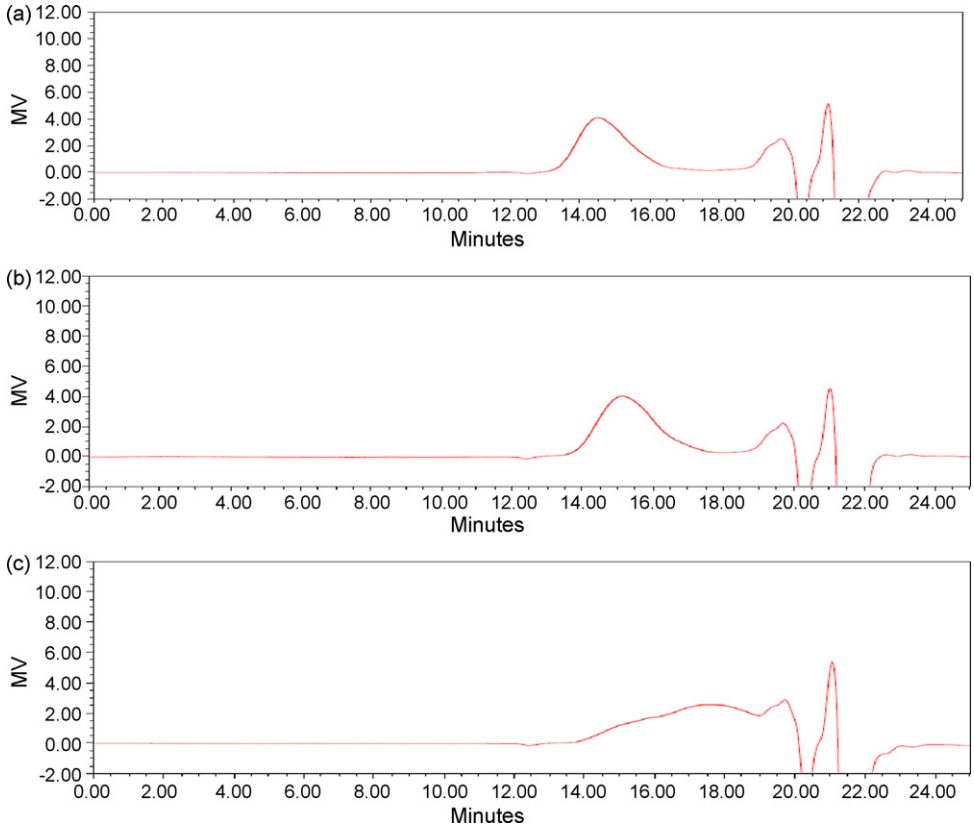

Fig. 4. The GPC graphs of PLGA polymer degradation. (a) Original PLGA50:50 (IV = 1.05 dl/g); (b) PLGA in blank PLGA/NMP formulation without aspirin after 7 days release study; (c) PLGA in aspirin loaded PLGA/NMP formulation after 7 days release study.

release study. Fig. 4 shows the GPC chromatograms of original PLGA polymer and PLGA polymer residuals from blank and aspirin loaded formulations after 7-day release study. The original PLGA polymer showed a unimodal bell shaped peak at 14.4 min (Fig. 4a). After 7-day release study, PLGA polymer residuals from blank formulation also showed a similar peak in the GPC chromatogram with a slightly extended retention time of 15.0 min (Fig. 4b). However, PLGA polymer residuals from aspirin loaded formulations displayed a bimodal (two peaks) GPC chromatogram with extended retention time ($t_{R1} = 15.3$ and $t_{R2} = 17.6$). Fig. 5 shows that the molecular weight of PLGA in aspirin loaded formulation and in blank formulation decreased to $12.5 \pm 1.6\%$ and $43.2 \pm 6.2\%$ of the original molecular weight, respectively. Moreover, the molecular weight of PLGA polymer residuals from aspirin loaded formulations was significantly ($p < 0.05$) lower than the polymer residuals from blank formulation. No significant difference was found between the formulations with and without PEG400. In this study, polydispersity index (PDI) was also used for evaluating polymer degradation (Fig. 6). The original PLGA polymer exhibited a PDI of 1.5 ± 0.1. PLGA residuals from blank formulation did not show appreciable change in polydispersity index (PDI = 1.6 ± 0.3). However, a significantly ($p < 0.05$) increased PDI was observed for PLGA residuals from aspirin loaded formulations (PDI = 2.7 ± 0.2) compared to the original PLGA polymer. Addition of PEG400 in the formulation did not affect the changes in polydispersity index of PLGA polymer.

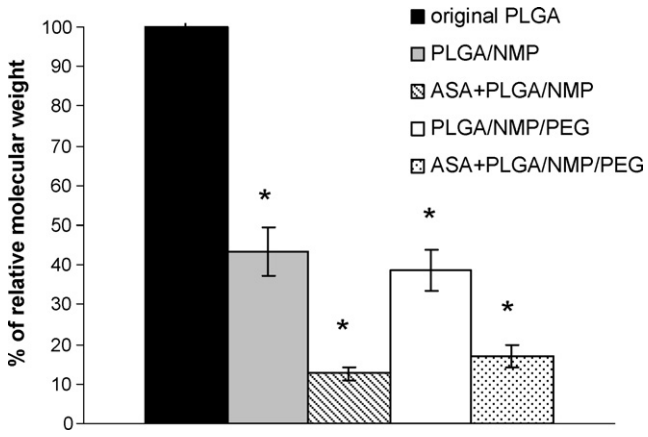

Fig. 5. The changes in relative molecular weight of PLGA polymer in formulations after 7 days release period. *Keys*: (■) The relative molecular weight of original PLGA50:50 (IV = 1.05 dl/g); (▨) The relative molecular weight of PLGA residuals from blank formulation of PLGA50:50 (30%, w/v)/NMP; (▧) The relative molecular weight of PLGA residuals from aspirin loaded formulation of PLGA50:50 (30%, w/v)/NMP; (□) The relative molecular weight of PLGA residuals from blank formulation of PLGA50:50 (30%, w/v)/NMP (80%, v/v)/PEG400 (20%, v/v); (⊡) The relative molecular weight of PLGA residuals from aspirin loaded formulation of PLGA50:50 (30%, w/v)/NMP (80%, v/v)/PEG400 (20%, v/v). *$p < 0.05$, $n = 4$, compared with original PLGA50:50 polymer. The original PLGA was considered to have a 100% of relative molecular weight.

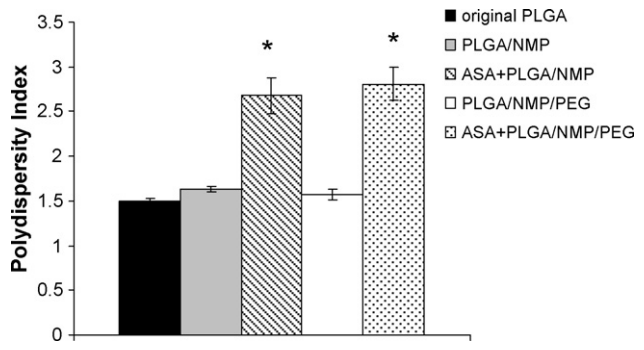

Fig. 6. The changes in the polydispersity index (PDI) of PLGA polymers in formulations after 7 days release period. *Keys*: (■) The PDI of original PLGA50:50 (IV = 1.05 dl/g); (▩) the PDI of PLGA residuals from blank formulation of PLGA50:50 (30%, w/v)/NMP; (▨) the PDI of PLGA residuals from aspirin loaded formulation of PLGA50:50 (30%, w/v)/NMP; (□) the PDI of PLGA residuals from blank formulation of PLGA50:50 (30%, w/v)/NMP (80%, v/v)/PEG400 (20%, v/v); (⊡) The PDI of PLGA residuals from aspirin loaded formulation of PLGA50:50 (30%, w/v)/NMP (80%, v/v)/PEG400 (20%, v/v). $*p < 0.05$, $n = 4$, compared with original PLGA50:50 polymer.

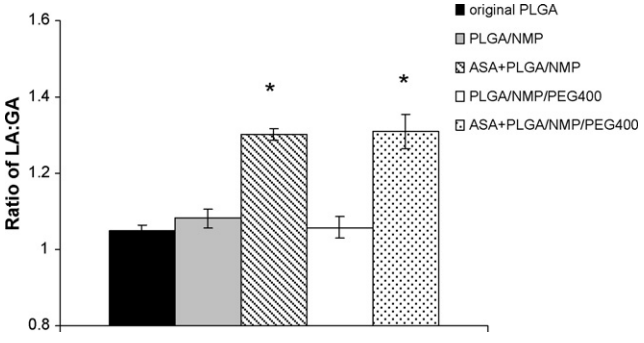

Fig. 7. The changes in LA/GA ratio of PLGA polymers in formulations after 7 days release period. *Keys*: (■) The LA/GA ratio of original PLGA50:50 (IV = 1.05 dl/g); (▩) the LA/GA ratio of PLGA residuals from blank formulation of PLGA50:50 (30%, w/v)/NMP; (▨) the LA/GA ratio of PLGA residuals from aspirin loaded formulation of PLGA50:50 (30%, w/v)/NMP; (□) the LA/GA ratio of PLGA residuals from blank formulation of PLGA50:50 (30%, w/v)/NMP (80%, v/v)/PEG400 (20%, v/v); (⊡) the LA/GA ratio of PLGA residuals from aspirin loaded formulation of PLGA50:50 (30%, w/v)/NMP (80%, v/v)/PEG400 (20%, v/v). $*p < 0.05$, $n = 4$, compared with original PLGA50:50 polymer.

Fig. 7 summarizes changes in the structural components (LA/GA ratio) of PLGA polymer which was characterized by ^{1}H-NMR. PLGA residuals from blank formulation showed a similar LA/GA ratio (LA/GA = 1.08 ± 0.02) as original PLGA polymer (LA/GA = 1.05 ± 0.02), but the PLGA residuals from aspirin loaded formulations displayed a significantly ($p < 0.05$) increased LA/GA ratio (LA/GA = 1.30 ± 0.03). PEG400 did not affect the changes in LA/GA ratio of PLGA polymers.

4. Discussion

The present study explored the feasibility of using PLGA/NMP based phase sensitive polymer *in situ* gel forming system for controlled release of aspirin. Due to high solubility of aspirin in NMP, the aspirin loaded polymeric formulations were clear solutions that can be easily injected through 21 G needle. This good injectability makes it suitable for the parenteral administration of aspirin thereby avoiding surgical implantation.

Upon injection into aqueous environment, aspirin loaded PLGA/NMP solution showed a fast sol–gel transition and formed a soft gel depot. This gel depot constantly released incorporated aspirin at a steady release rate for 7 days with an initial burst release (1st day release) of ∼36% (Fig. 1). The relatively high initial burst release of aspirin from the gel depot is considered to be directly related with the fast sol–gel transition of the formulation. The quick gel formation process was driven by the rapid dissipation of the water miscible organic solvent NMP from the solution formulation into aqueous environment with a concurrent fast phase separation of water insoluble hydrophobic PLGA polymer. Due to the fast phase separation, large pores and water accessible channels were created on the gel surface and inner core (Graham et al., 1999). Therefore, aspirin present on the surface and in the water accessible channels quickly diffused out from the gels. Triacetin, a sparingly water miscible organic solvent, was reported to decrease the initial burst release due to its ability to slow down the rate of phase separation resulting in a less porous gel structure (Graham et al., 1999). However, in the case of aspirin, addition of triacetin increased the initial burst release (∼65%, release profile is not shown), compared to the formulation without triacetin (initial burst release = ∼36.9%). Due to the poor solubility of aspirin in triacetin, aspirin could only be suspended in the PLGA/NMP/triacetin solution system. Upon injecting the suspension into PBS, aspirin was quickly released from the polymer system before the gel formed. Thus, the polymeric gel failed to entrap aspirin. Consequently, a high initial burst was observed for aspirin. Based on these observations, triacetin was not used for the phase sensitive polymer system.

PEG400 was reported to decrease the initial burst release of a drug from polymer matrix through its plasticizing effect (Tan et al., 2004). In the present study, addition of PEG400 into the PLGA/NMP based formulation suppressed the initial burst release of aspirin to ∼30%. However, the total release period was not prolonged by PEG400.

Aspirin can be hydrolyzed into salicylic acid and acetic acid in aqueous environment. Salicylic acid, the hydrolysis product, does not have the anti-platelet activity (Roberts et al., 1984). Thus, it is important for the drug delivery system to constantly release aspirin in its chemically stable form. Various polymer based aspirin implants, which controlled the release of aspirin for 5–10 days, have been reported (Hall et al., 1994; Vasudev et al., 1997; Cortizo et al., 2001). However, these studies did not confirm chemical stability of aspirin upon release. In the present study, the level of chemically stable aspirin was measured in the released samples and in the aspirin control samples (aspirin solution in PBS) during the release period. A significantly ($p < 0.05$) higher level of chemically stable aspirin was observed in released samples than the control samples. This result confirmed that the PLGA based phase sensitive *in situ* gel forming delivery system continuously released chemically stable aspirin into release medium (Fig. 2).

The PLGA 50:50 polymers usually control the release of incorporated drug over 1–6 months (Lambert and Peck, 1995; Leton and Tipton, 1998; Ikada and Tsuji, 2000; Huh et al., 2003; Wang et al., 2004). In these studies, drug diffusion was considered as the predominant mechanism for drug release from the polymer matrix for the first 20 days, since no significant evidence was found for polymer degradation (Lambert and Peck, 1995; Wang et al., 2004). However, the PLGA formulations in our study showed a relatively short release period (~7 days) (Fig. 1). In order to investigate the reason for such a relatively faster release of aspirin, the polymer matrix residuals were collected after release study. Aspirin loaded polymer gels were found to form a hollow core–solid shell structure after release of aspirin, whereas morphology of the blank gel was unaffected. The hollow core in the polymer matrix residuals is considered to be a significant sign of polymer degradation (Li et al., 1990a, 1990b). Thus, the relatively short controlled release period of aspirin was due to faster degradation of PLGA matrix.

Generally, the degradation of PLGA follows a three-phase mechanism (Ramchandani et al., 1997; Jain, 2000; Hasirci et al., 2001; Dong et al., 2006): (a) random chain scission process (cleavage of an ester bond randomly along the chain); (b) chain unzipping process (cleavage of the last unit at the end of the chain); and (c) complete solubilization of degradation products. During the random chain scission process (phase 1 degradation), PLGA polymer is subjected to a rapid loss of molecular weight but its polydispersity and LA/GA ratio do not change appreciably. In the phase 2 degradation, the PLGA polymer chain unzipping process becomes predominant. This process is represented by an increase in the LA/GA ratio and a change in the polydispersity. Since the lactic acid moieties are more hydrophobic than glycolic acid, the PLGA polymer chain with end group rich in glycolic acid moieties is hydrolyzed faster. The unequal hydrolysis rate results in an increase in LA/GA ratio and a change in polydispersity.

Based on the above knowledge, GPC and ^{1}H-NMR were chosen for examining the degradation of PLGA. The hollow core–solid shell structure and bimodal GPC chromatogram of aspirin loaded gel (Figs. 3 and 4) after release of aspirin suggested that the inner core of the gel was degraded faster compared to the surface. The PLGA polymer in aspirin loaded gels also showed a significantly larger reduction in molecular weight than PLGA polymer in blank gel (Fig. 5). Additionally, an appreciably increased polydispersity index of PLGA in aspirin loaded gel indicated that these PLGA polymers were subjected to the second phase degradation in which the chain unzipping process became predominant (Fig. 6). The unchanged polydispersity index of PLGA in blank gel implied the first phase degradation of these polymers (random chain scission process). Hence, GPC characterization suggested that aspirin facilitated the degradation of PLGA polymer matrix.

According to ^{1}H-NMR analysis, PLGA in aspirin loaded gels had a significant increase ($p < 0.05$) in the LA/GA ratio, but PLGA in blank gels did not show noticeable increase of LA/GA ratio (Fig. 7). Increase of LA/GA ratio represents the degradation of GA moieties from the PLGA back bone during the chain unzipping process (second phase degradation). Thus, ^{1}H-NMR analysis of PLGA residuals indicated that PLGA in aspirin loaded gel depots had an earlier onset of second phase degradation compared to PLGA in blank gels, which confirmed that aspirin facilitated the degradation of PLGA polymers.

Aspirin is a hydrophilic (solubility in water = 3.3 g/l) and acidic drug ($pK_a = 3.5$). Hydrophilicity of aspirin enhanced the water absorption of PLGA polymer matrix thereby affecting the rate of aspirin release and polymer degradation (Kiortosis et al., 2005; Siegel et al., 2006). Besides its hydrophilicity, the acidity of aspirin was also responsible for the facilitated degradation of PLGA polymer matrix (Graham et al., 1999; Li et al., 1990a, 1990b). Due to the acidic property, aspirin located in the water accessible zones of the gel was ionized quickly and increased the acidity inside the gel, leading to faster bulk erosion in the core of PLGA matrix. The hollow core–solid shell structure of polymeric matrix residues left after aspirin release was an evidence for the facilitated bulk erosion inside the gel. In agreement with this observation, both NMR and GPC examinations showed significantly faster degradation of PLGA polymer loaded with aspirin compared to the blank PLGA polymer. Thus, aspirin entrapped in the gel facilitated the degradation of PLGA matrix and resulted into relatively faster release.

5. Conclusion

The severe gastrointestinal side effects of aspirin could be avoided by parenteral administration of controlled release system. The feasibility of using PLGA based phase sensitive *in situ* gel forming delivery system was investigated in order to achieve the goal of parenteral delivery and controlled release of aspirin. The release of aspirin was controlled by both drug diffusion and polymer degradation. The total release period lasted for 7 days. Such a relatively faster release of aspirin resulted from facilitated degradation of PLGA polymer, which was catalyzed by aspirin. Hence, the release of incorporated drug from PLGA based *in situ* gel forming formulation was not only affected by the polymer's self-catalyzed degradation but also by the drug specific polymer degradation. Therefore, drug specific polymer degradation is an important consideration in developing the long-acting controlled release systems.

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