Original Article

Development of implants for sustained release of 5-fluorouracil using low molecular weight biodegradable polymers

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ABSTRACT: Anticancer drugs have poor efficacy especially against solid tumors that hinder drug penetration into the tumor. Thus, the dose has to be increased, but toxicity is a limiting factor. Local administration of a polymeric biodegradable poly-L-lactic acid (PLA) and poly(L-lactic acid-co-glycolic acid) copolymer (PLGA) implant containing an anticancer drug may be an acceptable method of concentrating the drug near the tumor site. This work sought to synthesize low molecular weight PLA and PLGA by polycondensation to yield polymers with good physical properties to make them suitable for use in implantable therapy. The synthesized polymers were characterized by determining their molecular weight, melting point, and percentage crystallinity using DSC. Fourier transformation-infra red spectrum (FT-IR), nuclear magnetic resonance (NMR) and specific optical rotation measurement were also used to characterize the synthesized polymers. Morphological characteristics were assessed using scanning electron microscopy (SEM). Implants were manufactured using compression (C) and injection molding (IM) and were loaded with 12 mg 5-fluorouracil (5-FU) per 120 mg implant. *In vitro* release patterns of all implants were assessed in phosphate buffered saline pH 7.4 (PBS 7.4) at 37°C. Factors affecting the release of 5-FU from implants were the polymer species, manufacturing technique, drug particle size, drug concentration, implant dimensions, and coating of the implant. Implants prepared with PLGA had significantly faster release of 5-FU than those prepared with PLA. Those manufactured using compression had significantly faster drug release than those prepared by injection molding. A PLA implant that contained 12 mg 5-FU/120 mg with a diameter of 0.3 cm and that was loaded with a drug particle size smaller than 150 µm and prepared by injection molding and then subsequently coated with PLA had the longest release period of 45 days.

Keywords: Poly-L-lactic acid (PLA), poly(L-lactic acid-co-glycolic acid) copolymer (PLGA), 5-fluorouracil (5-FU), implants, injection molding, compression, dissolution

1. Introduction

In the past decade, research has shown that the lack of sensitivity of most tumors to treatment lies in the inability of drugs to penetrate to the tumor interstitium. The poor efficacy of conventional anticancer drugs can be explained by solid tumors' special structure that includes stromal components that can represent up to 90% of tumor mass, the heterogeneous vasculature within the tumor that isolates tumor cells from the blood supply, and the absence of a well-differentiated lymphatic network. Therefore, a dosage form needed to be able to concentrate the drug close to the tumor site and avoid too wide a distribution (*1*). Local delivery of chemotherapeutic drugs is recognized as a potential method of delivering a drug to the target site with minimal systemic exposure. Because systemic administration of chemotherapeutic drugs can result in severe toxicity, the local delivery of these drugs to pathological tissues may provide an important means of improving both the safety and efficacy of cancer chemotherapy (*2*).

Biodegradable and non-biodegradable polymers are often utilized as implant base materials. Biodegradable polymers, and particularly poly-L-lactic acid (PLA) and poly(L-lactic acid-co-glycolic acid) copolymer (PLGA), disappear from the body during or after drug release and thus are superior in reducing the burden on patients (*3*). To a great extent, polymer synthesis determines the molecular weight, purity, polymeric chain orientation, and the microporous structure and crystallinity of the polymer. The release pattern from biodegradable implants can be controlled by composition, molecular weight of the polymer, morphology, manufacturing

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technique, and structure of the implant (*4*).

This work sought to synthesize low molecular weight PLA and PLGA by polycondensation to yield polymers with good crystallinity and strength to make them suitable for implantation. Low molecular weight PLA and PLGA polymers were also synthesized in this study to prepare implants with a shorter degradation time in comparison to implants prepared from longer chain analogues as would be better suited to implantation in cancer tissue (*5*). Moreover, the synthesis process is much simpler and less costly, thus allowing preparation of implants on industrial large scale at an acceptable price. The synthesized polymers were used to manufacture implants loaded with a chemotherapeutic agent, 5-fluorouracil (5-FU), to achieve prolonged release *in vitro*. Different variables affecting drug release from implants were also studied to identify the factors that would prolong the drug release over a long period to decrease the frequency of implantation and thus increase patient compliance.

2. Materials and Methods

2.1. *Materials*

L-Lactic acid and glycolic acid were purchased from Merck. 5-FU was purchased from Beckmann Chemikalien KG. Sodium chloride, potassium dihydrogen phosphate, disodium hydrogen phosphate, potassium chloride, and zinc chloride were of analytical reagent grade.

2.2. *PLA and PLGA 50:50 polymer synthesis*

2.2.1. *Synthesis*

Low molecular weight PLA and PLGA 50:50 polymers were synthesized by a modified method of polycondensation (*6,7*) using L-lactic acid and glycolic acid as starting materials. Synthesis involves dehydration of the starting materials L-lactic acid and/or glycolic acid into oligo(L-lactic acid) or oligomer of L-lactic and glycolic acid at 125°C for 2 h and then boosting the polymerization process by adding a catalyst (0.4 wt% zinc chloride relative to the oligomer); the temperature is gradually increased to 180°C and then maintained for 22 h. This is followed by cooling to an intermediate temperature of 130°C and then maintaining this temperature for 2 h; afterwards, the polymer is molded into the required form for easy storage and later use.

2.2.2. *Characterization of synthesized biodegradable polymers*

Synthesized PLA and PLGA 50:50 polymers were characterized first by determining differential scanning calorimetry (DSC) (DSC PerkinElmer Thermal Analysis, USA) thermograms using a heating rate of 10°C/min, and the % crystallinity was calculated from the DSC thermograms. The viscosimetric molecular weights (Mv) for specimens of both PLA and PLGA synthesized polymers were determined from two samples with a Ubbelohde 0 viscosimeter (Ubbelohde viscometer, DC Scientific, USA). Chloroform was used as a solvent and eluent. Mark-Houwink constants k = 5.45×10^{-4} dL/g and a = 0.73 were used in molecular weight calculation (*8*). Fourier transformation infra red (FTIR-8400, Shimadzu, Japan) spectra were also measured. ^{13}C NMR and ^{1}H spectra of the synthesized polymers were recorded by a nuclear magnetic resonance (NMR) spectrometer (Joel NMR, 500 MHz, Japan) using chloroform as a solvent (*7*). Moreover, specific optical rotation, [α], was measured at 20°C for PLA and PLGA 50:50 synthesized polymers in a chloroform solution at a concentration of 0.5 g/dL with a spectropolarimeter (ADP 220, Bellingham + Stanly, Ltd., England) at a wavelength of 589 nm (*9*).

2.3. *Manufacture of implants*

Implants of both PLA and PLGA were prepared by two methods according to formulations in Table 1. Only one lot of PLA and PLGA was used to prepare all of the implants to prevent any possible variability due to polymer synthesis. Injection molding used a specially adapted injection molding instrument

Table 1. Composition of different 5-FU loaded implant formulations

Component (%, w/w)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
PLA	90	90	95	80	90		90	89.75	90	90
PLGA 50:50						90				
5-FU (particle size smaller than150 µm)	10		5	20	10	10	10	10	10	10
5-FU (particle size 500-150 µm)		10								
Magnesium stearate								0.25		
Coating with PLA (mg/implant)									100	200
Heating time (min)	10	10	10	10	10	10	180			10
Diameter (cm)	0.3	0.3	0.3	0.3	0.6	0.3		0.6		0.3
Total surface area (cm^2)	1.27	1.27	1.27	1.27	1.7	1.27	1.27	1.32	1.27#	1.27#
Preparation technique	IM	IM	IM	IM	IM	IM	IM	C	IM	IM

IM, injection molding; C, compression, implant weight = 120 mg; #, total surface area for uncoated implant.

capable of producing implants with different diameters (0.3 and 0.6 cm).

The implants were prepared by melting synthesized polymers at 150°C and then adding of 5-FU to the melted polymer in different concentrations (5%, 10%, and 20%) with continuous stirring until complete homogeneity. The melted mixture was poured into the molding instrument and allowed to cool to room temperature; implants were then cut to the required length, corresponding to a weight of 120 mg.

Implants were prepared by compression using an Erweka single punch compression machine fitted with a 6 mm flat punch. The method involved sieving the polymer from a 500 µm sieve and dry mixing the polymer with the specified weight of 5-fluorouracil for 10 min and then blending this mixture with 0.25% magnesium stearate for 5 min. The final mixture was then compressed into disks weighing 120 mg with a hardness of approximately 6 KP.

Implants were coated by dipping them into melted PLA polymer and allowing solidification several times to reach the required coated weight. Solidification of the coat was assisted by a weak stream of nitrogen.

2.4. *In vitro characterization of the prepared implants*

2.4.1. *Drug content*

Three randomly selected implants of each formulation loaded with 5-FU were weighed and their average weight was calculated. The three implants were ground up and the weight equivalent to one implant (120 mg) was collected and sonicated in PBS, pH 7.4, for 15 min; then, its 5-FU content was measured using UV-VIS spectrophotometer (Cary 100 BIO spectrophotometer, Varian, Australia) at 265 nm.

Drug loading content (DLC%) was calculated as follows:

$$\text{DLC (\%)} = \frac{\text{measured amount of 5-Fu}}{\text{implant sample weight}} \times 100$$

2.4.2. *Water absorption and polymer erosion*

After the release test, water absorption and polymer erosion were determined as follows (*3,10*): the implant was taken out of the dissolution media, the excess medium on the surface was removed by brief absorption with filter paper, and the weight of the wet implant (WW) was measured. Then, the wet implant was dried to a constant weight using a vacuum pump, and the weight of the dried implant (WD) was measured. The amount of drug released (WPR-R) was calculated from the results of the *in vitro* release. The weight (WS) of the salts contained in PBS absorbed by the implant was calculated from the salt concentration (1.13%, w/w) and amount of PBS by assuming the density of PBS to be 1. The water absorbed by the implant was determined using the following equation (*3,10*):

$$\text{Water absorbed (\%, w/w)} = 100 \times (WW - WD) / (WD - WS)$$

When the initial polymer amount before the release test was WP0, the polymer erosion from the implant was calculated as follows (*3,10*):

$$\text{Polymer erosion (\%, w/w)} = 100 \times ((120 - WPR\text{-}R) - (WD - WS))/WP0$$

Furthermore, the change in weight of the implants was examined during the incubation of F1, F6, F8, and F10 under the same conditions as for *in vitro* release. At appropriate time intervals, the implants were collected and weighed, and the increase in weight was used as the apparent amount of medium absorption.

2.4.3. *Mechanical properties of 5-FU loaded implants*

The average hardness of implants of different formulations was determined by measuring the hardness of 3 implants for each formulation using a Dr. Schleuniger Pharmatron Tablet Hardness Tester (8 M, Switzerland).

2.4.4. *Scanning electron microscopy (SEM) and porosity measurement*

Changes in the surface morphology of implants before and during *in vitro* release were evaluated by scanning electron microscopy (SEM, Jeol Scanning Electron Microscope, Japan).

The implants were sputter-coated with gold under a vacuum using an electron beam (10 kV). The implant surface was viewed under low (×10.6) and high (×342) magnifications and representative photomicrographs obtained. The pore morphology and pore size distribution of the samples were investigated by SEM at ×1,000 magnification.

2.4.5. *Differential scanning calorimetry and thermal analysis of implants*

To follow implant degradation, implants were analyzed by DSC before release in PBS pH 7.4 and after 1 month of dissolution by observing changes in thermograms. The heating rate was 10°C/min.

2.4.6. *In vitro release of 5-FU from loaded implants*

A release study was performed using a shaking water bath kept at 37°C. The release medium was 20 mL of

phosphate buffer saline (PBS), pH 7.4, contained in a stoppered glass bottle shaken at 30 strokes per min (*10*). Aliquots (10 mL) were taken at predetermined time intervals and were immediately replaced with fresh PBS, pH 7.4. The 5-FU sample content was measured spectrophotometrically at 265 nm.

2.5. *Statistical analysis*

Results of 3 samples for the various tests are presented as mean ± standard deviation (S.D.). One-way analysis of variance (ANOVA) was used to determine significant differences between the formulations with respect to *in vitro* release of 5-FU from F1 implants.

3. Results and Discussion

3.1. *Characterization of synthesized PLA and PLGA 50:50 polymers*

The thermal properties of both synthesized polymers were assessed using differential scanning calorimetry. DSC showed that the synthesized PLA polymer had a glass transition temperature (T_g) of 45°C, a crystallization exotherm at T = 85.5°C, and melting endotherm at T = 133°C. Crystallinity for the polymer was calculated from the following equation (*8*):

$$\text{Crystallinity (\%)} = \frac{\Delta Hm - \Delta Hc}{93.1} \times 100$$

where ΔHm is heat of fusion, ΔHc is heat of crystallization, and the constant 93.1 J/g is the ΔHm for 100% crystalline PLLA or PDLA homopolymers. The % crystallinity for the PLA polymer was 25.1%. According to DSC, PLGA 50:50 had a T_g = 37°C and had no melting or crystallization endotherms, suggesting the amorphous nature of the PLGA copolymer (*10*).

The calculated viscosimetric molecular weight (Mv) was 2,511 g/mol for PLA and 2,455 g/mol for PLGA 50:50.

Figure 1a shows FTIR spectra of the PLA homopolymer with the following absorbance peaks: OH- stretch at approximately 3,500 cm^{-1}, C=O ester at 1,750 cm^{-1}, CH bend at 1,450 and 1,360 cm^{-1}, C-O stretch at 1,130 and 1,090 cm^{-1}, and CH bend at 750 cm^{-1}. These absorbance peaks almost matched those reported (*6*). The FTIR spectra of copolymer PLGA 50:50 were found to be similar to the FTIR spectra of the homopolymer PLA, as shown in Figure 1b (*7*).

The structure of the synthesized PLA polymer was elucidated using ^{13}C NMR spectra. Figures 2a and 2b show the ^{13}C NMR spectra for PLA and PLGA (50:50), respectively. The ^{13}C NMR signals were at 169.8 ppm (C=O), 69 ppm (C-H), and 16.6 (CH_3) for PLA and at 168-170 ppm (C=O), 69 ppm (C-H), 66.6 ppm (CH_2, weak signal), and 16.6 ppm (CH_3) for PLGA (*7*). ^1H NMR spectra for PLA exhibited signals at 1.46 ppm (CH_3) and 5 ppm (C-H). ^1H NMR spectra for PLGA exhibited similar signals at 1.5 ppm (CH_3) and 5.2 ppm with an extra signal at 5 ppm (*7*). The specific optical rotation, [α], for PLA and PLGA 50:50 synthesized polymers was -130 and -94, respectively.

3.2. *In vitro characterization of the prepared implants*

3.2.1. *Drug content*

The different implant formulas listed in Table 1 were analyzed and the drug content results were ± 5% of the labeled amount of 5-FU.

3.2.2. *Water absorption and polymer erosion of 5-FU loaded implants*

The extent of medium absorption and polymer erosion following *in vitro* drug release were compared at different time intervals among several selected formulas. Water absorption, polymer erosion, and the drug release profile were determined to help study the factors that would affect polymer degradation and thus help to formulate implants with prolonged drug release. Such implants would decrease the frequency of implantation and thus increase patient compliance. The results for water absorption and polymer erosion for the selected formulas after 1 month of *in vitro* release in PBS, pH 7.4, are presented in Table 2. Comparison of results for F1 and F6 implants indicated greater water absorption for PLGA implants than PLA implants; such absorption would cause greater polymer degradation and erosion, and substantial physical changes were visually apparent. Results for F8 indicated water absorption slightly less than for F1, revealing that F8 had greater polymer erosion than F1. These results show that compression (F8) can cause faster polymer erosion in comparison to injection molding. Comparing implant results (F1 and F10) indicated that coating an injection-molded PLA implant with PLA substantially reduced water absorption and polymer erosion. This great reduction in water absorption can have a positive effect on prolonging drug release and retarding polymer degradation (*3,10*).

3.2.3. *Mechanical properties of 5-FU loaded implants*

Hardness results for selected implant formulas are presented in Table 3. The PLA (F1) and PLGA (F6) implants have nearly the same hardness. Increasing implant diameter to 0.6 cm (F5) instead of 0.3 cm for the PLA implant (F1) caused a slight increase in hardness to 2.9 KP. Implants manufactured using compression (F8) were much harder than those manufactured using injection molding (F1). Coating

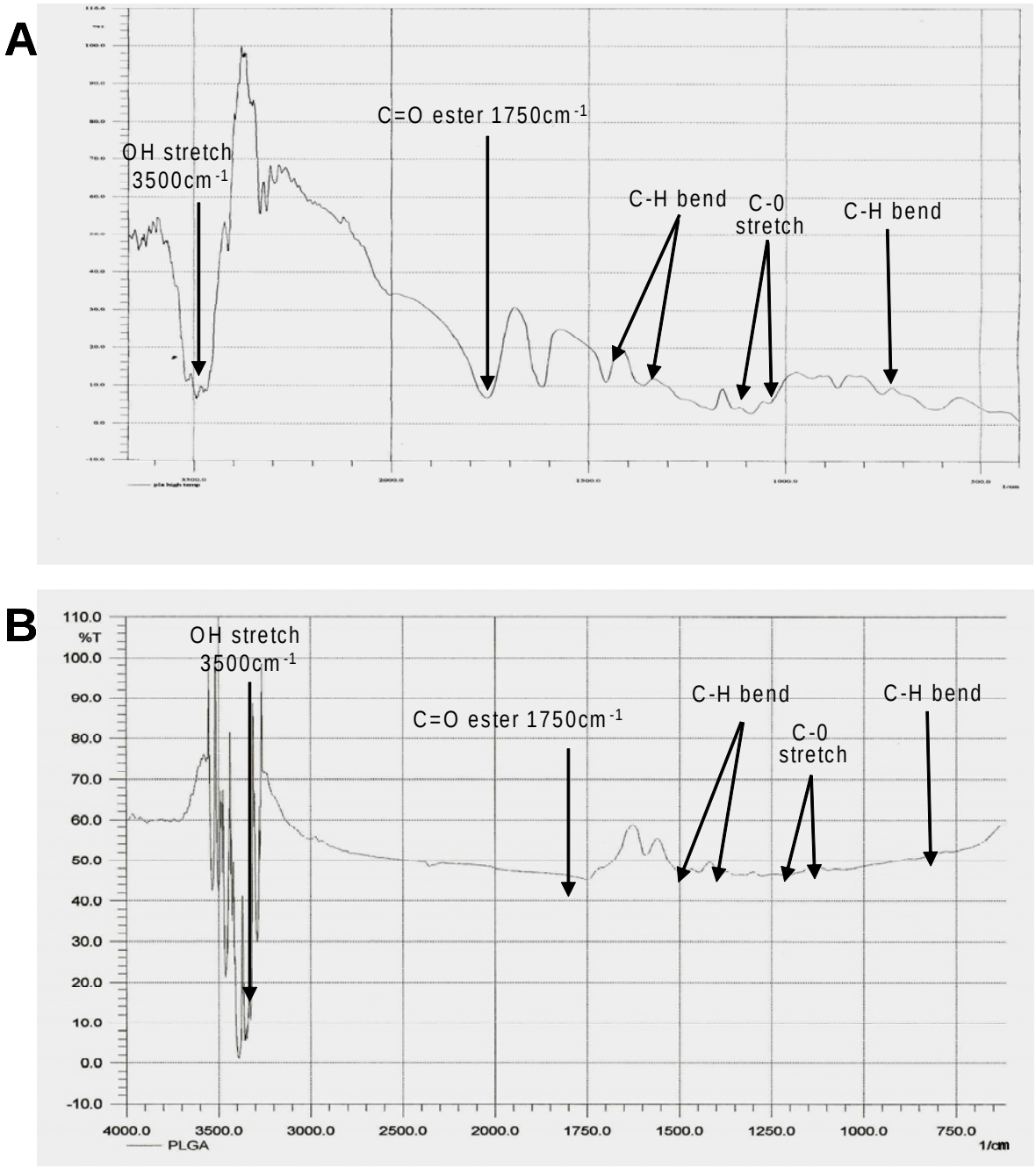

Figure 1. FTIR spectra for synthesized PLA (A) and PLGA 50:50 (B).

the implant (F10) also caused implant hardness to increase to 4 KP. Harder implants are better suited to the handling and insertion process.

3.2.4. *Scanning electron microscopy (SEM) and porosity measurement*

Porosity measurement using SEM was done one month after placing implants in PBS, pH 7.4 (*12*). Figure 3 shows that the manufacturing technique and particle size of loaded 5-FU had a substantial effect on implant pore size. Implants manufactured using compression (F8) and loaded with 5-FU with a smaller particle size had greater porosity (10-50 μm), while injection-molded (IM) implants loaded with 5-FU with the same particle size (F1) had less porosity (5 μm). Increasing the particle size of loaded 5-FU for IM implants (F2) resulted in increased porosity (10-30 μm). The IM technique produced implants with a condensed structure and lower porosity. Increasing the particle size of the loaded drug increased the porosity of implants due to pores left by the dissolved drug particles.

3.2.5. *Differential scanning calorimetry (DSC) and thermal analysis of implants*

DSC thermal analysis of implants was performed to follow polymer degradation during the release period.

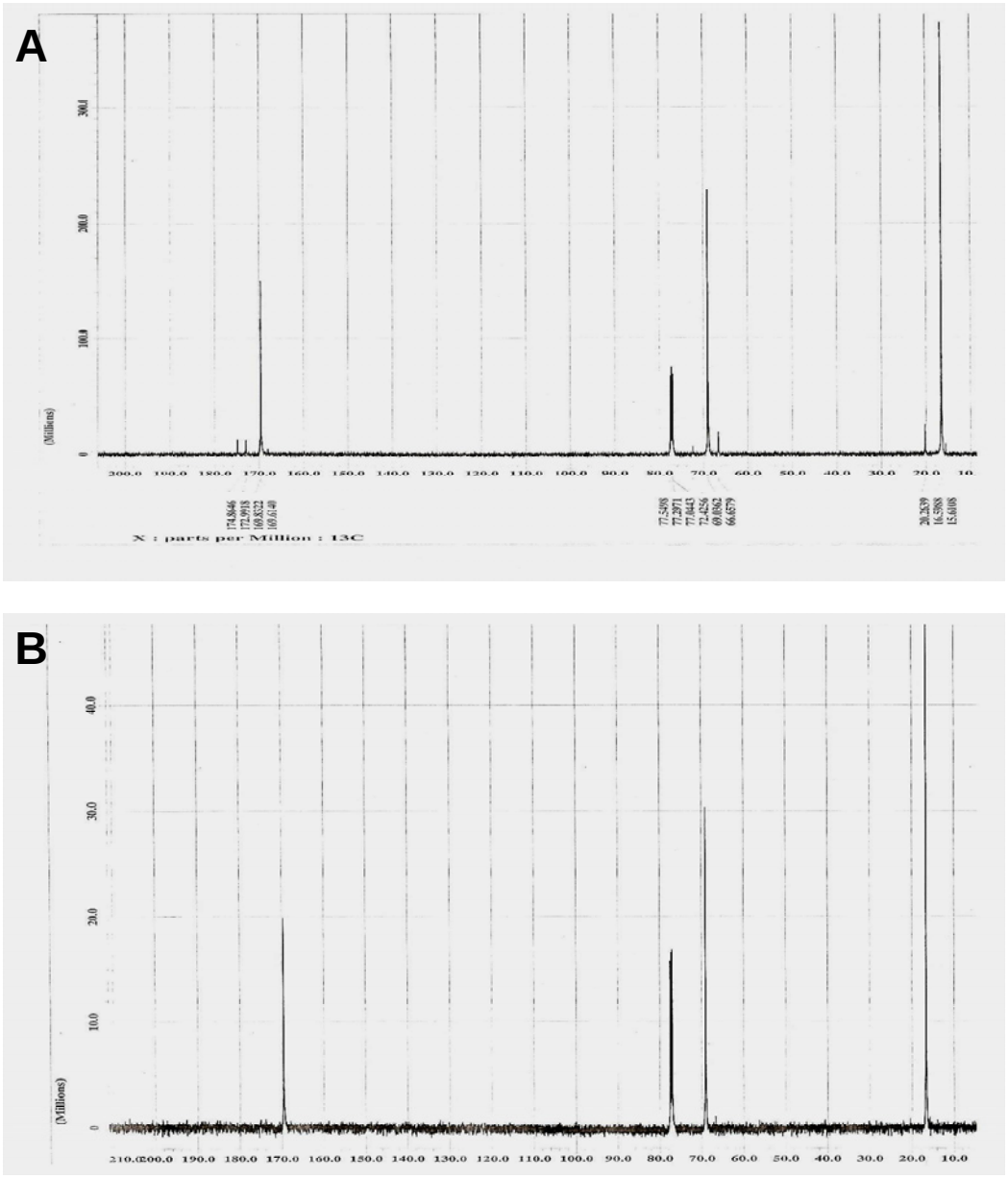

Figure 2. ^{13}C NMR for synthesized PLA (A) and PLGA 50:50 (B).

Table 2. Effect of polymer type and manufacturing technique on water absorption and polymer erosion

Implant formula (PT/MT)	*Water absorption (%, W/W)	*Polymer erosion (%, W/W)
F1 (PLA/IM)	81.9	14.7
F6 (PLGA/IM)	125.5	15.6
F8 (PLA/C)	78.2	19.8
F10 (PLA/IM+CT)	42	1

*: Water absorption and polymer erosion results 1 month after placement of implants in PBS, pH 7.4; PT: polymer type, MT: manufacturing technique; C: compression; CT: coating.

Table 3. Effect of polymer type and manufacturing technique on implant hardness

Implant formula (PT/MT)	Hardness (KP)
F1 (PLA/IM)	2.4
F5 (PLA/IM+ID)	2.9
F6 (PLGA/IM)	2.3
F8 (PLA/C)	6.1
F10 (PLA/IM+CT)	4

PT: polymer type; MT: manufacturing technique; C: compression; CT: coating; ID: increasing diameter.

PLA implants F1, F8, and F10 had a T_g of 40-45°C, recrystallization temperature (T_c) of 80-86°C, and melting temperature (T_m) of 120-133°C before placement in PBS, pH 7.4. After placement in PBS for one month, F1 and F8 had undetectable T_g and T_c and T_m of 80-90°C while F10 had a T_m of 114°C, which may indicate that implant coating decreased degradation of the implant as gauged by the shift in T_m of the PLA polymer (*2*,*8*). In DSC thermograms for PLGA implants (F6), no peaks were detected as a result of the amorphous nature of PLGA

(*11*). Thus, changes before and after implants were placed in PBS, pH 7.4, could not be studied.

3.2.6. *In vitro release of 5-FU by loaded implants*

Different implant formulas were assessed for drug release in PBS, pH 7.4, at 37°C. The release period of 5-FU was prolonged to approximately 45 days for some formulas. Drug particle size, implant surface area, and increasing heating time of drug-polymer dispersion did not produce significant changes in the *in vitro* release of 5-FU from implants. In contrast, polymer type, manufacturing technique, and implant coating had a marked effect on drug release. Figure 4 shows significantly faster release of 5-FU from PLGA implants (F6) than PLA implants (F1) ($p < 0.05$). This can be attributed to the amorphous nature of PLGA, as confirmed by DSC, that causes its faster degradation (*9*). Figure 5 illustrates the effect of the manufacturing technique on drug release of PLA implants prepared by injection molding and compression. A significantly faster release ($p < 0.05$) was noted from implants prepared by compression (F8) in comparison to those prepared by injection molding (F1) with almost the same surface area, although the latter (F8) had greater hardness than the former (F1) (Table 3). Increasing the 5-FU concentration per implant from 5% to 10% to 20% caused a significantly faster release ($p < 0.05$) due to the increase in matrix perforations by drug dissolution (*2*). Figure 6 shows that the release rate 5-FU was significantly reduced ($p < 0.05$) by coating the implants with PLA, and as the coat weight per implant increased, the retardation of the release rate increased.

These results can be explained using SEM pictures of different implants before and after they were placed in PBS pH 7.4 for one month. Figures 7 and 8 are SEM

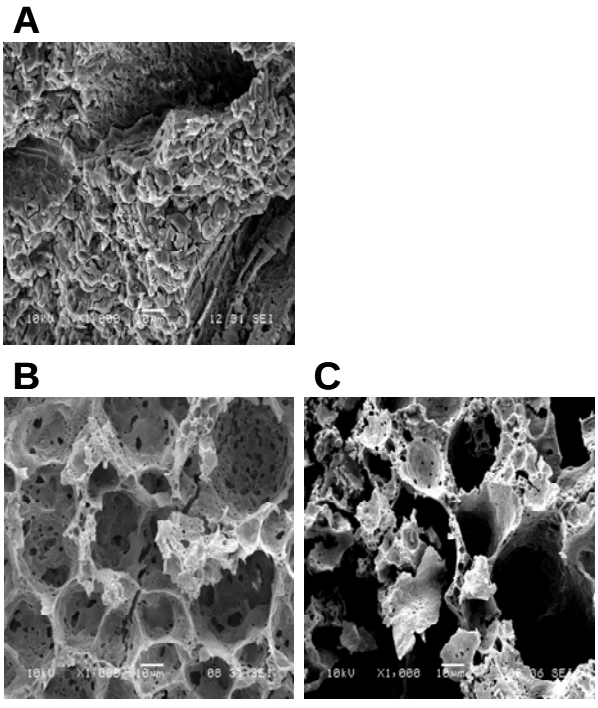

Figure 3. Effect of manufacturing technique on surface porosity of 5-FU loaded implants. (**A**) SEM picture of a PLA implant prepared by injection molding (F1). (**B**) SEM picture of a PLA implant prepared by injection molding (F2). (**C**) SEM picture of a PLA implant prepared by compression (F8).

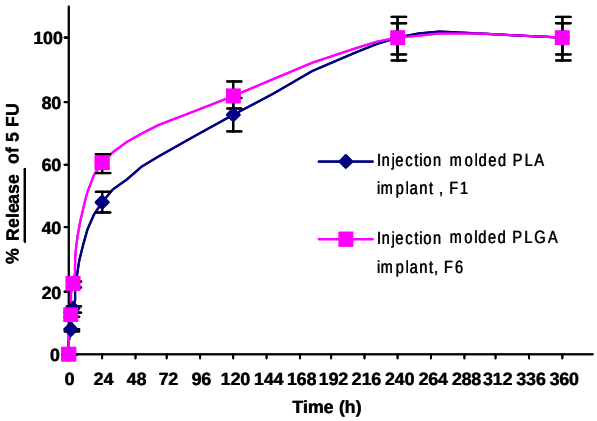

Figure 4. Effects of polymer type on 5-FU release from implants in PBS pH 7.4.

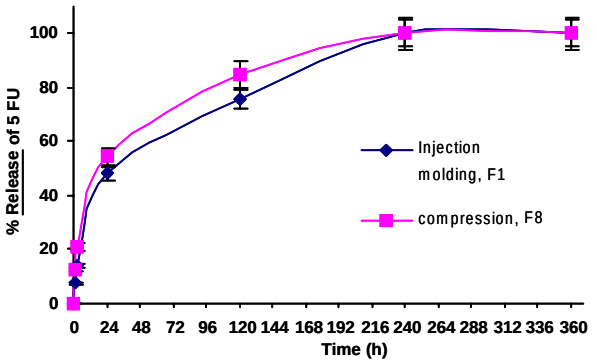

Figure 5. Effects of manufacturing technique on 5-FU release from PLA mplants in PBS pH 7.4.

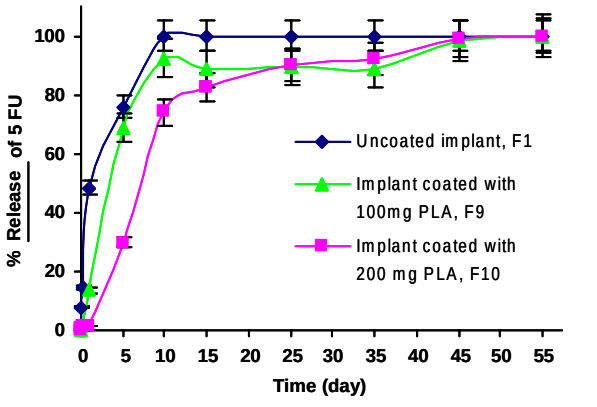

Figure 6. Effects of coating weight per implant on 5-FU release from coated PLA injection-molded implants in PBS pH 7.4.

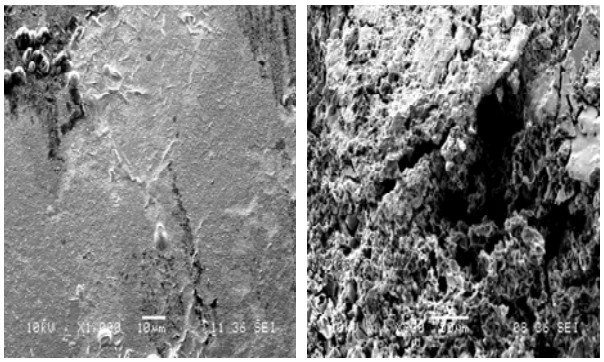

Figure 7. SEM picture of a PLA compressed implant loaded with 5-FU (F8) before and after placement in PBS, pH 7.4.

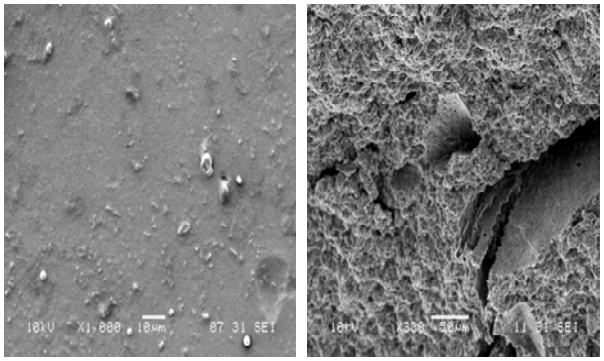

Figure 8. SEM picture of a PLA injection-molded implant loaded with 5-FU (F1) before and after placement in PBS, pH 7.4.

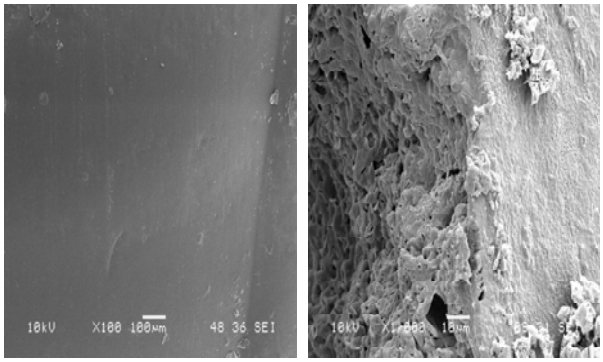

Figure 9. SEM picture of a PLA injection-molded implant loaded with 5-FU coated with 200 mg of PLA before and after placement in PBS, pH 7.4.

pictures of PLA implants prepared by compression and injection molding, respectively. While the surface of implants was smooth and non-porous at the beginning, SEM pictures of compressed implants revealed numerous microscopic perforations in comparison to injection molded implants one month after implants were placed in PBS, pH 7.4. This resulted in a spongy structure that caused an increase in polymer erosion and degradation (Table 2) and led to faster drug release from compressed implants than injection molded implants (*4*).

Coating implants with PLA caused a reduction in surface perforations (Figure 9), which helped to suppress the early release of hydrophilic drugs (*13*) like 5-FU, and reduced diffusion of water into the implant (Table 2). Implants coated with 100 mg per implant of PLA showed 90% of drug release after 10 days. When the coat weight was increased to 200 mg per implant, in contrast, the release of 90% of the drug took about 25 days. This coating process also caused the release period of 5-FU to be prolonged from 10 days to 45 days. The burst release (release after 1 day) of 5-FU was significantly reduced, causing a decrease in 5-FU release from 50% to only 2% ($p < 0.05$). The drug release mechanism of implants F9 and F10 is more complicated than that of others like F1 (*13*). This could be attributed to the change in the polymeric delivery system from a matrix type in uncoated tablets to a combination of a matrix and reservoir type in coated implants.

4. Conclusion

Synthesized polymers PLA and PLGA 50:50 prepared by polycondensation can be used successfully to prepare implants for use as a drug delivery system *via* injection molding and compression. Implants prepared from PLGA 50:50 had significantly faster release ($p < 0.05$) of 5-FU than those prepared with PLA. Implants manufactured using compression had significantly faster drug release ($p < 0.05$) than those prepared by injection molding. Coating an implant with PLA by dipping caused a significant reduction in burst release and a prolonged release period. An injected molded implant with PLA containing 12 mg of 5-FU with a particle size of less than 150 μm in 120 mg of implant that was then coated with 200 mg PLA had prolonged release for 45 days. The *in vitro* study will be expanded with an *in vivo* study on rats with induced liver cancer to further study *in vivo* release and the correlation with release *in vivo* and *in vitro*.

Acknowledgments

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