Biodegradable Poly(sebacic acid-*co*-ricinoleic-ester anhydride) Tamoxifen Citrate Implants: Preparation and *In Vitro* Characterization

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ABSTRACT: The aim of this study was to prepare tamoxifen citrate loaded cylindrical polymeric implants for application at tumor sites. The implant was based on poly (sebacic acid-*co*-ricinoleic-ester anhydride) 70 : 30 w/w [poly(SA-RA) 70 : 30 w/w], a low-melting, biodegradable, and biocompatible polymer. Implants were prepared by a standardized melt manufacturing method. Differential scanning calorimetry and scanning electron microscopy were used for implant characterization. *In vitro* drug release studies were performed in phosphate-buffered saline (pH 7.4) at 37 ± 2°C. The drug content was estimated by high-performance liquid chromatography. The differential scanning calorimetry studies showed that the tamoxifen citrate in the implants was in the amorphous state. The cumulative percentage of drug release from 10 and 20 wt % drug-loaded poly(SA-RA) 70 : 30 w/w implants after 30 days was found to be 42.36 and 62.60%, respectively. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 107: 2745–2754, 2008

Key words: biodegradable; drug delivery systems; implant; injection molding

INTRODUCTION

Breast cancer is one of the leading causes of cancer deaths among women. Nearly 1 million new cases are diagnosed each year.[1] Tamoxifen citrate is widely used in the chemotherapy of breast cancer.[2] Chemotherapy is a complicated procedure, and many factors are involved in determining its success or failure. It carries a high risk because of drug toxicity, and the most effective drugs tend to be more toxic. One of the major problems facing cancer chemotherapy is the achievement of the required therapeutic concentration of the drug at the tumor site for a desired period of time without causing undesirable effects on the other organs while it circulates in the body.[3] The vasculature of tumors is highly disorganized and unpredictable both in its structure and function. This disorganization is a major barrier to drug delivery to solid tumors.[4]

Biodegradable polyanhydrides and polyesters are useful materials for controlled drug delivery.[5–7] They have hydrophobic backbones with hydrolytically labile anhydrides and/or esters that may hydrolyze to dicarboxylic acids and hydroxy acid monomers when placed in an aqueous medium. Fatty acids are suitable candidates for the preparation of biodegradable polymers because they are natural body components and are hydrophobic and thus may retain an encapsulated drug for longer periods when used as drug carriers.[8,9]

Poly(sebacic acid-*co*-ricinoleic-ester anhydride) 70 : 30 w/w [poly(SA-RA) 70 : 30 w/w] is a biodegradable polyanhydride polymer for controlled drug delivery. The toxicity, biodegradation, and elimination of polyanhydrides and aliphatic polyesters have been reviewed.[10,11] The hydrolytic degradation of aliphatic polyesters and polyanhydrides depend on various physical, chemical, and biological parameters, including the hydrophobicity of the monomers and polymer, the crystallinity of the polymer, the water permeability of the polymer matrix, and the degradation medium and conditions.[11] The fatty acid components of these polymers undergo extensive metabolism in the body and are mainly excreted in the form of carbon dioxide, whereas the aromatic components are eliminated from the body unmetabolized mainly through urine and feces.[10] The toxicity data point to the fact that poly(SA-RA) 70 : 30 w/w is well tolerated by the tissues and can be generally considered biocompatible.[10]

Oral administration of a nonsteroidal antiestrogen such as tamoxifen is the treatment of choice for

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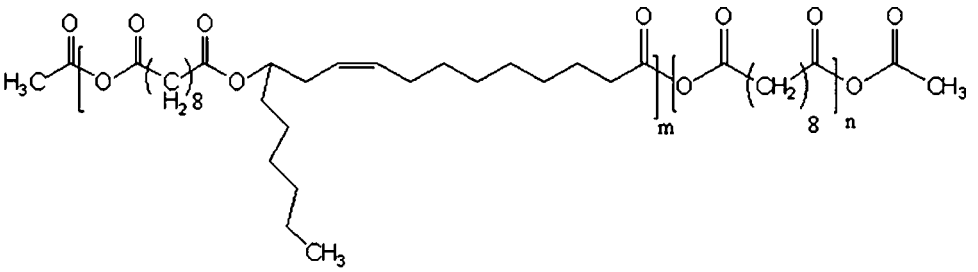

Figure 1 Structure of poly(sebacic acid-*co*-ricinoleic acid).

patients suffering from all stages of estrogen-receptor-positive breast cancer.[12]

Conventional therapy for breast cancer using tamoxifen citrate causes major side effects such as endometrial cancer and development of drug resistance, which may cause further progression of the tumor.[13–15] Another therapeutic approach to solid tumors is surgical removal followed by irradiation and/or systemic chemotherapy to kill malignant cells, but this causes possible recurrence and spread of surviving tumor cells, in addition to interfering drastically with the quality of the patient's life. The implantation of drug-loaded devices (including drug–polymer composites) into tumor or tumor resection sites has been investigated by several workers.[16–24] Hence, a possible approach to the administration of tamoxifen citrate for the treatment of localized tumors might be the use of controlled/sustained-release implants that could deliver pharmacologically effective doses of tamoxifen citrate to the tumor site.

Locally implanting a biodegradable device loaded with tamoxifen citrate provides a high local concentration of the drug at the tumor site. Thus, such a delivery method could improve the selectivity of treatment and improve patient compliance. In this study, we formulated tamoxifen citrate in biodegradable poly(SA-RA) 70 : 30 w/w implants, and this was followed by their physiochemical characterization, including an *in vitro* study.

EXPERIMENTAL

Materials

Poly(SA-RA) 70 : 30 w/w (weight-average molecular weight = 21,000; number-average molecular weight = 10,000) was synthesized as previously reported.[25] Tamoxifen citrate was obtained in the form of gift samples from Cipla, Ltd. (Mumbai Central, India). Sodium chloride, sodium dihydrogen orthophosphate, and potassium dihydrogen orthophosphate were purchased from SD Fine Chemicals (Mumbai, India). High-performance liquid chromatography (HPLC) grade chloroform (stabilized by ethanol), methanol, and triethyl amine (TEA) were purchased from Ranbaxy Chemicals (Bangalore, India).

Preparation of poly(SA-RA) 70 : 30 w/w implants by the melt manufacturing method

Poly(SA-RA) 70 : 30 w/w was synthesized as previously reported.[25] The polymer structure is shown in Figure 1. Implants were prepared by the melt manufacturing method with stainless steel molds specially designed for this study. All experiments with tamoxifen citrate were carried out under subdued light, as the drug is highly photosensitive. The drug was loaded in concentrations of 10 and 20 wt % into the polymer. Cylindrical implants were prepared by the incorporation of uniformly mixed tamoxifen citrate and poly(SA-RA) 70 : 30 w/w into a cylindrical mold 7.0 mm in diameter and 8.0 mm long, which was placed on and attached to a rod 6.9 mm in diameter (removable; Fig. 2). The entire unit was

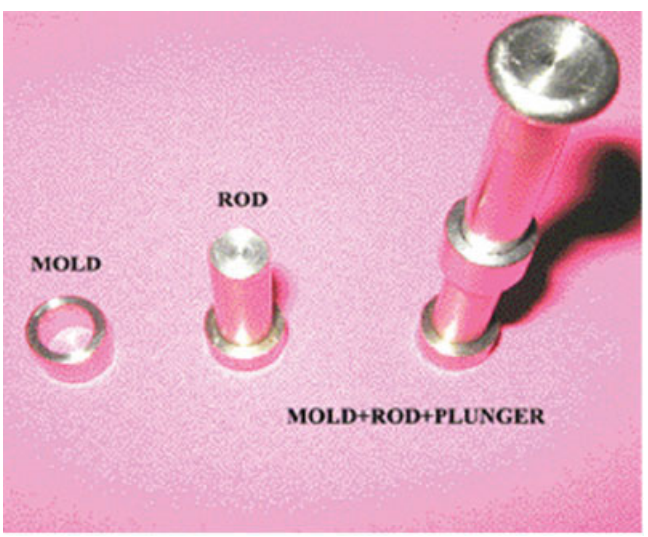

Figure 2 Designed and fabricated molds for the manufacture of tamoxifen citrate implants. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

heated up to 75–80°C. Once the polymer started plasticizing, it was mixed uniformly with a preheated stainless needle. After uniform mixing, the entire unit was removed from the heating mantel; when the mass started solidifying, another plunger with a diameter of 6.7 mm was introduced into the mold. The plunger was adjustable and could move a distance of 1.0–7.0 mm in the mold. The whole unit was cooled to room temperature; afterward, the plunger and rod were removed, and the solidified implant was extruded from the mold.

Physicochemical evaluation of the implants

The prepared implants were evaluated for physicochemical parameters, such as the color, weight, height (thickness), and area.

Instrument and chromatographic conditions

The HPLC system consisted of a Shimadzu SPD-10ATVP binary pump (Tokyo, Japan) equipped with a normal sample injector with a 50-μL loop, a Shimadzu SPD-10AVP variable-wavelength UV detector, and a Spincotech station (Bangalore, India) for data analysis.

Chromatographic separations were achieved with a Phenomenex C-8 column (4.6 × 250 mm, 5 μm) and a Phenomenex C-8 guard column cartridge (KJ0-4282; 4.0 × 3.0 mm, 5 μm) (USA). A mobile phase consisting of methanol, water, and TEA (90 : 10 : 0.1 % v/v) was passed through a 0.22-μm membrane filter and degassed by ultrasonication *in vacuo* before use. The analysis was performed at the flow rate of 1 mL/min with a UV detector at 265 nm, and the sensitivity was 1.0 absorbance unit force per second.

Drug content in the implants

A pure tamoxifen citrate sample and drug-loaded poly(SA-RA) 70 : 30 w/w implants were determined with the developed HPLC method. Pure tamoxifen citrate and 10 and 20 wt % tamoxifen citrate loaded implants were separately dissolved in 10 mL of chloroform and sonicated for 10 min; 10 mL of deionized HPLC water was added, and the mixture was vortexed vigorously and sonicated for 10 min. After precipitation of poly(SA-RA) 70 : 30 w/w centrifuged at 5000 rpm up to 10 min, the supernatant was discarded and filtered through a 0.22-μ nylon membrane (Millipore, Bangalore, India). The filtrate was evaporated under a stream of liquid nitrogen, and after the complete evaporation of chloroform, it was suitably diluted with the mobile phase and used for tamoxifen citrate analysis. The drug content of tamoxifen citrate was calculated as the ratio of the measured drug content in the implants to the loaded amount with the calibration curve.

Differential scanning calorimetry (DSC)

DSC was conducted with the Mettler–Toledo Star system (Metallurgy Department, Indian Institute of Science, Bangalore, India). Samples were weighed (5.00–8.00 ± 0.5 mg) and placed in sealed aluminum pans. The coolant was liquid nitrogen. The samples were scanned at 10°C/min from 20 to 160°C. DSC thermograms of pure tamoxifen citrate, pure poly (SA-RA) 70 : 30 w/w, physical mixtures of tamoxifen citrate and poly(SA-RA) 70 : 30 w/w, and tamoxifen-loaded poly(SA-RA) 70 : 30 w/w implants were obtained.

X-ray diffraction (XRD) studies

XRD patterns of the implants were determined with a diffractometer equipped with a rotating-target X-ray tube and a wide-angle goniometer (Department of Physics, Indian Institute of Science). The X-ray source was Kα radiation from a copper target with a graphite monochromator. The X-ray tube was operated at a potential of 50 kV and a current of 150 mA. The range (2θ) of scans was 0–70°, and the scan speed was 2°/min with increments of 0.02°. The XRD patterns of pure tamoxifen, pure poly(SA-RA) 70 : 30 w/w, physical mixtures of tamoxifen citrate and poly(SA-RA) 70 : 30 w/w, and tamoxifen-loaded poly(SA-RA) 70 : 30 w/w implants were obtained.

Fourier transform infrared (FTIR) measurements

Infrared spectroscopy (model A-1700 FTIR, Shimadzu Instruments) was performed for pure poly (SA-RA) 70 : 30 w/w, physical mixtures of tamoxifen citrate and poly(SA-RA) 70 : 30 w/w, blank implants, and tamoxifen-loaded poly(SA-RA) 70 : 30 w/w implants. Samples were cast onto NaCl plates from solutions in chloroform. Pure tamoxifen citrate was mixed with KBr and vacuum-packed to obtain pellets of the material, which were analyzed. All the spectra acquired scans between 500 and 4000 cm^{-1} at a resolution of 4 cm^{-1}.

Characterization of the implants by scanning electron microscopy (SEM)

The implants were subjected to surface morphology studies using SEM before and after *in vitro* release studies. The polymeric implants were first dried *in vacuo*. Samples were glued to aluminum sample holders (Materials Department, Indian Institute of Science) and gold-coated under an argon atmosphere. The coated samples were finally analyzed with a JSM 840 (USA). The surface morphology of the implants was observed at suitable 1000 and 4000 × magnifications.

In vitro hydrolytic degradation of the polymer

Cylindrical poly(SA-RA) 70 : 30 w/w based blank implants and drug-loaded implants, prepared by the melt manufacturing method, were placed in 50-mL, screw-capped bottles [phosphate-buffered saline (PBS), pH 7.4] at 37 ± 2°C for 30 days with a specially designed apparatus (Fig. 3). At specific intervals, the blank implants and drug-loaded implants were taken out of the buffer and weighed after lyophilization. The hydrolysis of the polymer was determined by the implant weight decrease and tamoxifen content in the remaining implants. At each time, the formulation was examined for the tamoxifen content in the degraded sample by HPLC.

In vitro drug release rate studies

The *in vitro* release studies of tamoxifen citrate implants were carried out at 37 ± 2°C in PBS (pH 7.4) for 30 days with a specially designed dissolution apparatus (Fig. 3). Tamoxifen citrate implants were placed in screw-capped bottles containing 50 mL of PBS (pH 7.4) as a release medium, which were fixed to stainless steel holders attached to a mechanical stirrer, and the entire platform was dipped in water maintained at 37 ± 2°C. The platform was rotated at an average speed of 100 ± 4 rpm to induce mixing in the release medium. At periodic intervals, initially at 12 h and then every 5 days, 5 mL of the release medium was sampled, and 5 mL of fresh release medium was added to provide the necessary sink condition. The samples were analyzed by HPLC for the tamoxifen citrate content by the solvent extraction method, as described previously. The amount of tamoxifen citrate released into the medium was calculated with the calibration curve. The cumulative drug release percentage was calculated to establish the drug release profile of the prepared implants.

RESULTS AND DISCUSSION

Macroscopic characterization of the implants

The implants were prepared by an indigenously developed melt manufacturing method with specially designed stainless molds. Macroscopically, all the implants were found to be cylindrical, smooth in surface, and similar in appearance (Fig. 4). The implants were yellow because of poly(SA-RA) 70 : 30 w/w, which is yellow. The 10 wt % drug-loaded implants had an area of 1.35 ± 0.29 cm^2, their height (thickness) was 1.13 ± 0.30 cm, and their total weight was 94.60 ± 1.60. The 20 wt % drug-loaded implants had an area of 0.31 ± 0.04 cm^2, their height (thickness) was 0.22 ± 0.01 cm, and their total weight was 46.12 ± 1.40 mg. The blank implant, with a weight of 87.2 ± 1.33 mg, had an area of 1.29 ± 0.44 cm^2, and its height (thickness) was 0.28 ± 0.02; the blank implant with a weight of 38.6 ± 1.20 mg had an area of 0.96 ± 0.28, and its height (thickness) was 0.19 ± 0.03. The implants' diameter and height (thickness) were measured with digital vernier calipers. The obtained data are shown in Table I.

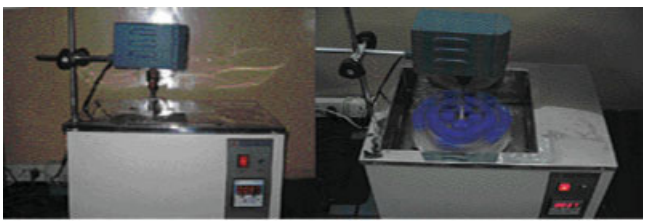

Figure 3 Standardized and developed dissolution apparatus. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

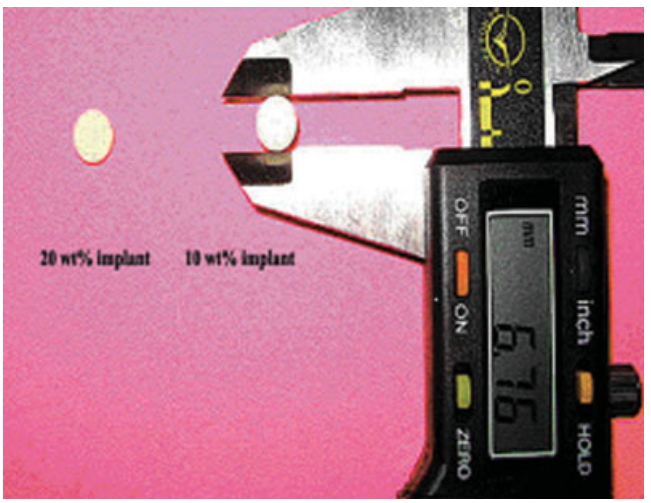

Figure 4 Photograph representing drug-loaded implants. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Qualification of the HPLC method

The HPLC method developed in this study for the estimation of tamoxifen citrate provided excellent sensitivity, accuracy, and precision. The retention time of tamoxifen citrate was 6.990 min. The detection limit was 20 ng/mL. There was good linearity over the concentration range of 20–5000 ng/mL. The typical equation describing the calibration curve is $y = 0.830x + 0.0513$, with a mean correlation coefficient of 0.9998. The recovery range of pure tamoxifen citrate by the chloroform extraction method was found to be 95–101%. The relative standard deviation (R.S.D) of interday and intraday (5 consecutive days) precision was 0.81–1.40 and 1.6–2.2%, respectively. The recovery range of 10 and 20 wt % drug-loaded implants was found to be between 93 and 96%, respectively (see data in Table I).

TABLE I
Physicochemical Properties and Drug Contents of Tamoxifen Citrate Poly(SA-RA) 70 : 30 w/w Implants

Sample	Drug loaded (mg)	Weight of implants (mg)[a]	Area of cylinder (cm^2)[a,b]	Height or thickness (cm)[a]	Amount of drug added (mg)	Recovery (%)
Implants	10	94.60 ± 1.65	1.35 ± 0.29	0.31 ± 0.04	10	93–95
	20	46.12 ± 1.46	1.10 ± 0.30	0.22 ± 0.01	10	93–96
Pure tamoxifen citrate	—	—	—	—	10	95–101

Tamoxifen citrate was determined by HPLC.
[a] Mean ± standard deviation (n = 6).
[b] Area = $2\pi r(h + r)$, where r is the radius and h is the height.

DSC studies of the poly(SA-RA) 70 : 30 w/w implants

The onset/peak/end-peak melting temperatures in the DSC thermograms of pure tamoxifen citrate, pure poly(SA-RA) 70 : 30 w/w, a physical mixture of the drug and poly(SA-RA) 70 : 30 w/w, and a drug-loaded implant are illustrated in Table II. Their respective generated scans are shown in Figure 5.

DSC experiments were carried out to evaluate the possibility of any interactions between the drug and the polymer within the matrix and crystallinity studies.[24,26] Pure tamoxifen citrate exhibited an onset/peak/end-set peak at 146.10/148.72/153.33°C [Fig. 5(A)]; pure poly(SA-RA) 70 : 30 w/w exhibited its first peak at 45.50/54.70/62.15°C and its second peak at 109.21/118.07/122.07°C [Fig. 5(B)]. The incorporation of tamoxifen citrate into the physical mixture resulted in an onset/peak/end-set peak at 45.93/53.31/61.91°C, another peak at 114.14/121.03/128.04°C, and finally a drug peak at 135.88/141.00/146.07°C [Fig. 5(C)]. These data indicate that in the physical mixture of poly(SA-RA) 70 : 30 w/w and tamoxifen citrate, the thermal properties of each component were not affected by the other, but the tamoxifen citrate melting point shifted to a lower temperature (7–9°C); the interaction may be attributed to poly(SA-RA) 70 : 30 w/w melting at a low temperature, and there is a possibility that tamoxifen citrate compounds may dissolve in the melt before reaching their melting point.[27] Because FTIR spectroscopy proved that no such interaction took place in the physical mixture of poly(SA-RA) 70 : 30 w/w and tamoxifen citrate, both the polymer and drug-functional groups were clear at all points.

The tamoxifen citrate peak in the physical mixture was small and not sharp as in the case of pure tamoxifen, and this can be explained by the dissolution of a part of the added tamoxifen citrate in the polymer during the heating. The drug-loaded implant showed an onset/peak/end-set peak at 40.47/51.62/59.47 and 117.13/120.63/125.00/°C [Fig. 5(D)], and this indicated that the drug and the method of preparation of the implant had no effect on the thermal properties of the polymer. However, a drug peak did not appear, and this probably was due to the conversion of tamoxifen citrate from a crystalline state to an amorphous state during the heating involved in the preparation of the implant.[28] Another explanation is that the low-molecular-weight drug incorporated into the poly(SA-RA) 70:30 w/w polymeric matrix during the melt manufacturing method interfered with the crystalline network and may have been dispersed in the amorphous phase of the polymer or at its surface.[27]

XRD studies of the poly(SA-RA) 70 : 30 w/w implants

Crystalline forms can be described as an arrangement of molecular chains that results in an ordered structure. Most polymers display crystallinity and are either amorphous or semicrystalline. Crystalline polymers such as poly(SA-RA) 70 : 30 w/w contain crystalline regions. Parameters that influence the crystallinity of a polymer are those that allow polymeric molecular chains to reorganize themselves into a more ordered and therefore lower energy state. An elevated temperature and a slow rate of cooling enable the chains to be mobile and to realign themselves into a more ordered solid structure.[27] Thus, the crystallinity of poly(SA-RA) 70 : 30 w/w can be altered as a result of the melt

TABLE II
Thermal Data for the Pure Drug, Pure Poly(SA-RA) 70 : 30 w/w, a Physical Mixture of the Drug and Poly(SA-RA) 70 : 30, and a Drug-Loaded Implant

Sample	Onset/peak/end-set melting points of the polymer (°C)
Pure tamoxifen citrate	146.10/148.72/153.33
Pure poly(SA-RA) 70 : 30 w/w[a]	45.50/54.70/62.15/109.21/118.07/122.77
Drug and poly(SA-RA) 70 : 30 w/w	45.39/53.31/61.91/114.14/121.03/123.34
Drug-loaded implant	40.47/51.62/59.47/117.13/120.63/125.00

[a] The two defined peaks of poly(SA-RA) 70:30 appeared at different melting points.

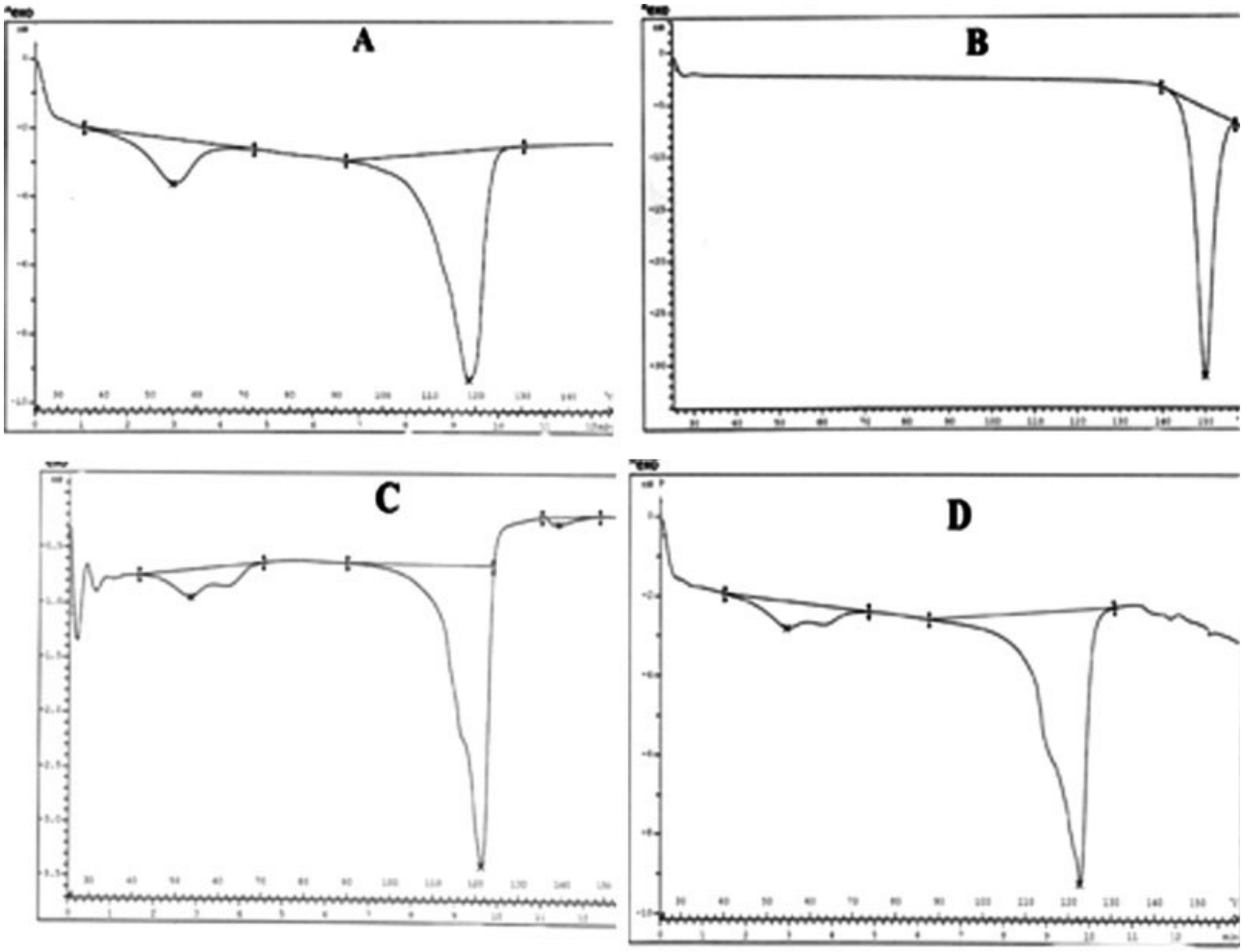

Figure 5 DSC thermograms of (A) pure tamoxifen citrate, (B) pure poly(SA-RA) 70 : 30 w/w, (C) a physical mixtures of the drug and poly(SA-RA) 70 : 30 w/w, and (D) a drug-loaded implant. The experiment was carried with crimped aluminum pans and a heating rate of 10°C/min; the samples were scanned at 10°C/min from 20 to 160°C. There are two defined peaks of poly(SA-RA) 70 : 30 w/w (weight-average molecular weight = 21,000; number-average molecular weight = 10,000), and the higher melting peak belongs to tamoxifen citrate.

manufacturing technique, in which heat is used, and the degree of crystallinity can depend on the rate of cooling during solidification from the melt. The aforementioned results show pure tamoxifen citrate, poly (SA-RA) 70 : 30 w/w, and a mixture of the drug in a crystalline state, and sharp peaks were obtained (Fig. 6). For the tamoxifen citrate loaded poly(SA-RA) 70:30 w/w implant, the drug peak disappeared in comparison with the mixture, and this study suggests that tamoxifen citrate may exist in a disordered, semicrystalline/dissolution amorphous state. In addition, it can be concluded that the developed melt manufacturing technique did not alter the crystalline network of the polymer.

FTIR spectroscopy studies

Figure 7 shows typical spectra of pure tamoxifen citrate, poly(SA-RA) 70 : 30 w/w, a physical mixture of tamoxifen citrate and poly(SA-RA) 70 : 30 w/w, a blank implant, and a drug-loaded implant. The spectrum of tamoxifen citrate shows characteristic absorption bands at 3027 (=C—H stretching), 1507 and 1477 (C=C ring stretching), and 3180 cm^{-1} ($—NH_2$). Poly(SA-RA) 70 : 30 w/w displays a characteristic absorption band at 1803 cm^{-1} (polyanhydride peak) and an ester peak at 1691 cm^{-1}. No changes in the spectrum of the physical mixture, blank implant, and drug-loaded implant were evident by FTIR spectroscopy. The polyanhydride peak and ester peak were clear at all points.

In vitro hydrolytic degradation of the polymer

The rate of weight loss of the polymer was determined as a function of time. The fastest rate of degradation was observed with the polymer without tamoxifen citrate. In the first week, the blank polymers

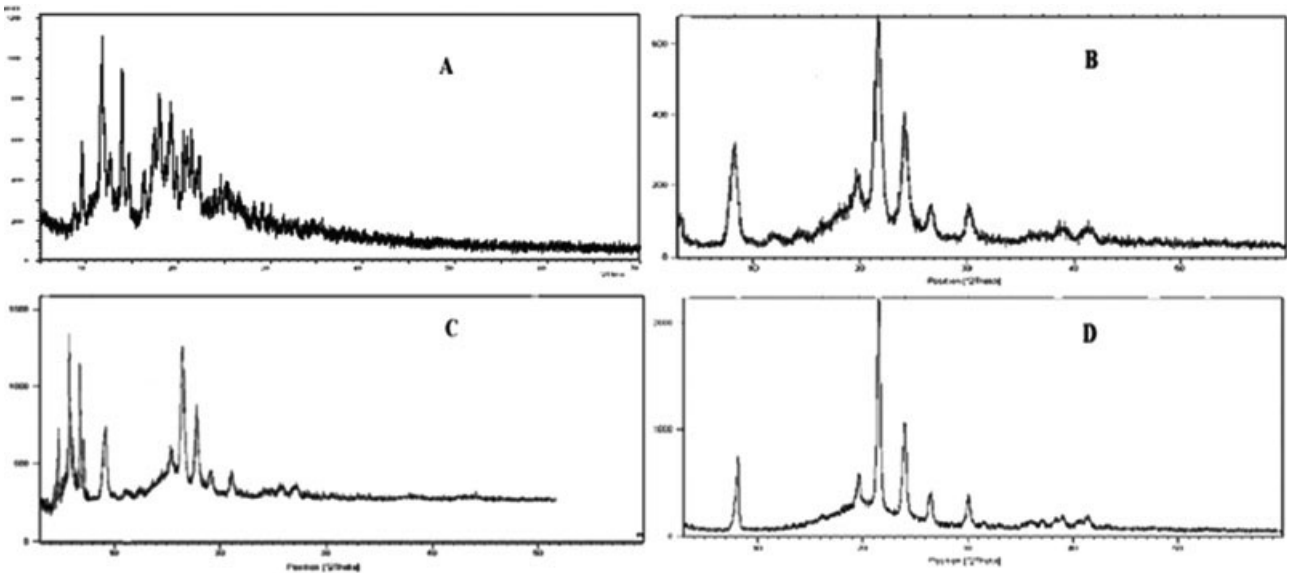

Figure 6 XRD graphs of (A) pure tamoxifen citrate, (B) pure poly(SA-RA) 70 : 30 w/w, (C) a mixture of poly(SA-RA) 70 : 30 w/w and tamoxifen citrate, and (D) a drug-loaded implant. The X-ray tube was operated at a potential of 50 kV and a current of 150 mA, the 2θ range of the scans was 0–70°, and the scan speed was 2°/min with increments of 0.02°.

(38.6 ± 1.20 and 89.2 ± 1.33 mg of implants without the drug) lost 14.55 ± 2.41 and 8.99 ± 1.17% of their initial weight and then gradually degraded; after 30 days, they lost 74.64 ± 2.53 and 55.85 ± 2.2% of their initial weight. The degradation rate of the 10 wt % drug-loaded poly(SA-RA) 70:30 w/w based implant was slower compared to that of the 20 wt % drug-loaded implant. The implant containing 10 wt % tamoxifen citrate during the first week lost 4.12 ± 1.2%, and after 30 days, it lost 35.60 ± 1.3%. The 20 wt % drug-loaded poly(SA-RA) 70:30 w/w implant during the first week lost 8.24 ± 1.0%, and after 30 days, it lost 64.28 ± 1.4%. The degradation of an implant depends on the polymer concentration, geometry of the implant, density of the matrix, and formation of microchannels and pores in the dissolution media, which cause hydrolysis of the polymer.

The tamoxifen citrate content in the degrading implants was determined. After 5 days in the degradation medium, the tamoxifen citrate content in the 10 wt % drug-loaded implant was 95.13 ± 1.3%, and after 30 days, it was 44.30 ± 2.0%. For the 20 wt % drug loading, the tamoxifen citrate content after 5 days was 83.33 ± 1.0%, and after 30 days, it was 24 ± 2.0%. As discussed previously, the release of a

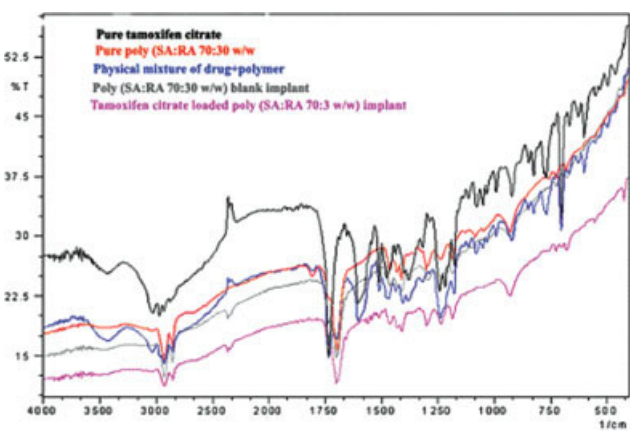

Figure 7 Transmission FTIR spectra of pure tamoxifen citrate, pure poly(SA-RA) 70:30, a physical mixture of poly (SA-RA) 70:30 w/w and tamoxifen citrate, a blank implant, and a drug-loaded implant. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

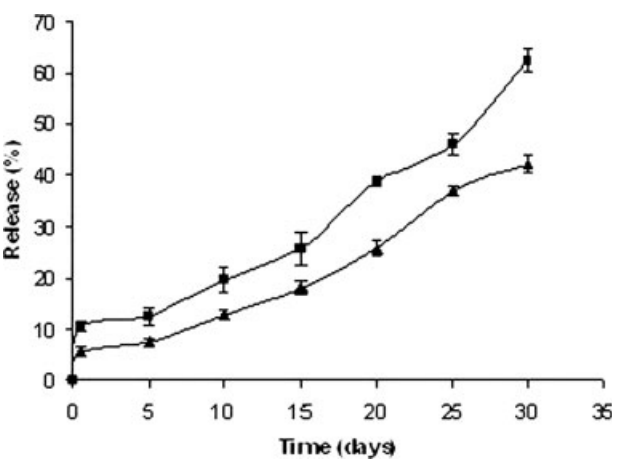

Figure 8 Release kinetics of tamoxifen citrate from poly (SA-RA) 70 : 30 w/w implants in PBS (pH 7.4): (▲) 10 wt % drug-loaded implant and (■) 20 wt % drug-loaded implant.

drug from an implant is based on the polymer and tamoxifen citrate concentration loaded.

In vitro drug release

Tamoxifen citrate is slightly soluble (0.5 mg/mL) in water at 37 ± 2°C (information available at Nolvadex, Rx List, and Internet Drug Index). Hence, PBS was used (pH 7.4) as a dissolution medium in the drug release studies. The tamoxifen citrate release kinetics in PBS (pH 7.4) from poly(SA-RA) 70 : 30 w/w based implants with 10 and 20 wt % drug loadings are shown in Figure 8. The cumulative percentage of drug release from the 10 wt % drug-loaded poly (SA-RA) 70 : 30 w/w implants after 30 days was found to be 42.36%. In the case of the 20 wt % drug

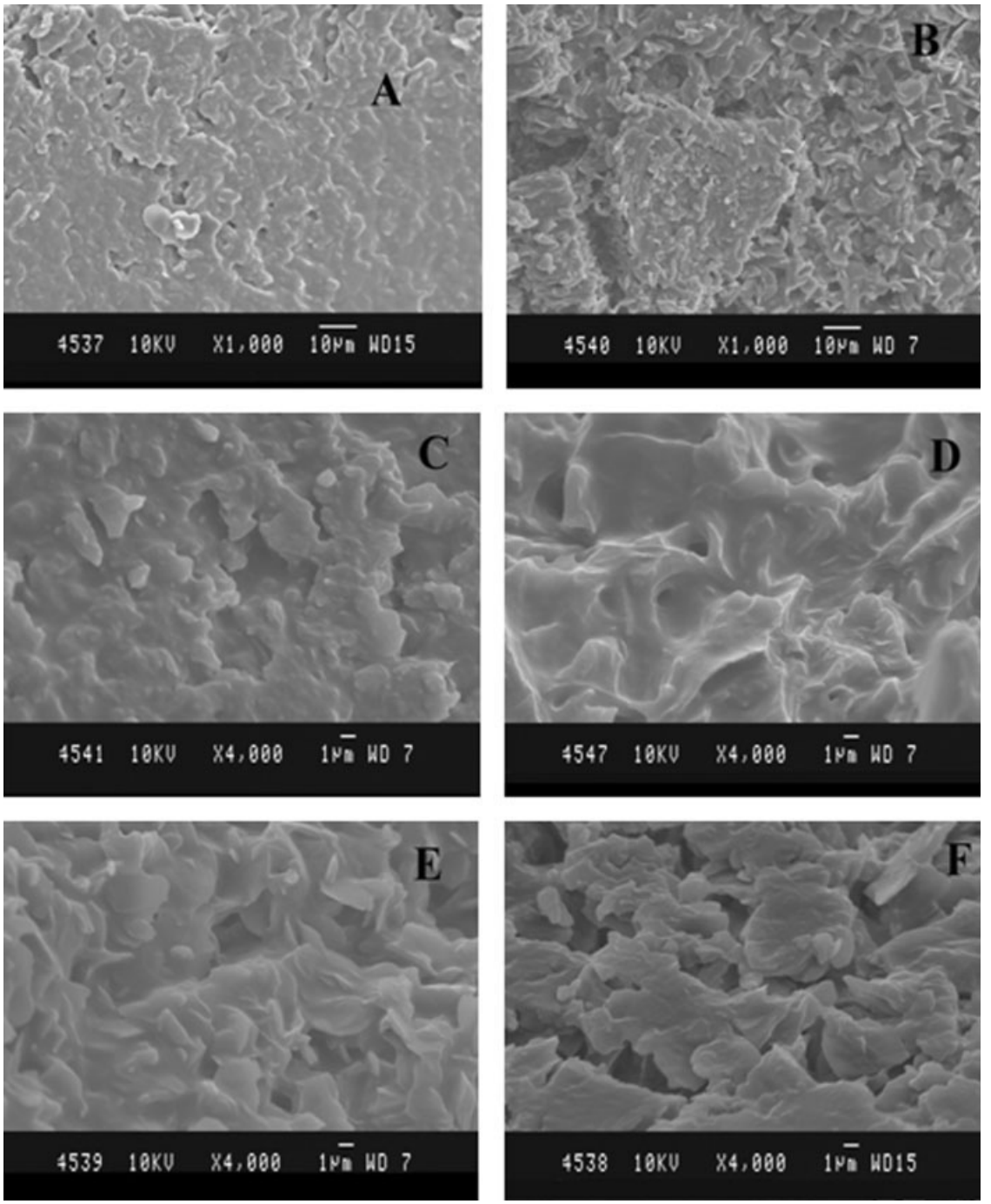

Figure 9 Scanning electron micrographs of drug-loaded poly(SA-RA) 70 : 30 w/w samples: (A,B) freshly prepared implants of poly(SA-RA) 70 : 30 w/w; (C,D) 10 wt % drug-loaded implants after 1 day of *in vitro* studies and after 30 days, respectively; and (E,F) 20 wt % drug-loaded implants after 1 day of *in vitro* studies and after 30 days, respectively.

loading, it was found to be 62.60%. Both the 10 and 20 wt % drug-loaded implants showed an initial burst release followed by a sustained-release effect. The initial burst effect may be due to the free drug, which might be present on the surface of the implants. Poly(SA-RA) 70 : 30 w/w in this study is a hydrophobic polymer built from natural fatty acids.[24] Hence, the lower drug release at the 10 wt % drug loading may have occurred because the incorporated polymer concentration was higher than the drug loading, fewer microchannels formed in the implant, and fatty degradation products[24] remained in the matrix and blocked further degradation. Another explanation could be the dependence of polymer hydrolysis on the geometry of the implant. The 20 wt % drug loading produced an implant that was thinner than the 10 wt % drug-loaded implant. Hence, the 20 wt % drug-loaded implants showed faster release because of the gradual higher penetration of water from the surface into the implant center, leading to an increased rate of hydrolysis of the polymer.[28]

On the basis of the *in vitro* studies conducted, it could be finally predicted that it would take 70 days for 100% drug release at a 10 wt % drug loading level (approximately). In the case of the 20 wt % drug-loaded poly(SA-RA) 70 : 30 w/w implants, it could be predicted that it would take 48 days for 100% drug release (approximately).

Characterization of implant degradation by SEM

Implants prepared by the melt manufacturing method were subjected to SEM for surface morphology studies. Both freshly prepared implants after *in vitro* release studies using PBS (pH 7.4) as the dissolution medium were analyzed. Recorded SEM images of the freshly prepared implants revealed a homogeneous surface [Fig. 9(A,B)]. In the case of the 10 wt % drug-loaded implants subjected to *in vitro* release degradation, SEM revealed a homogeneous surface at the end of 1 day in comparison with implants degraded at the end of 30 days. The implant after 30 days showed a porous surface and bulk erosion [Fig. 9(B,C)]. Importantly, the implant was intact even on the 30th day, and much less shrinkage in the implant dimensions was observed.

In the case of 20 wt % drug loading, implants after 1 day of the *in vitro* release study revealed a homogeneous surface in comparison with the sample at the end of 30 days, which showed a highly porous surface (the uptake of water was high) and random bulk erosion, with more loss of material from the outer surface, and samples also shrank more in their dimensions [Fig. 9(D,E)]. Thus, the difference in matrix degradation observed between different drug loadings could be attributed to the geometry of the implants, percentage of crystallinity, fatty degradation products,[24,28] amount of water penetration and dissolution of the drug, polymer concentration, or density of the matrix.

CONCLUSIONS

The indigenously developed melt manufacturing method for preparing cylindrical drug-loaded implants is a viable alternative method for thermostable drugs. We have successfully prepared implants with a uniform size, surface, and cylindrical shape. Poly(SA-RA) 70 : 30 w/w implants with different drug loadings, exhibiting sustained drug release for several weeks, have also been characterized *in vitro*. These implants can be directly placed on the tumor (intratumoral administration) to prevent systemic toxicity and endometrial cancer, which are associated with the conventional routes of administration of tamoxifen citrate for breast cancer. Hence, the developed sustained drug delivery system has potential to deliver the required pharmacologically effective concentration of the drug directly to tumors.

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