ORIGINAL ARTICLE

Paclitaxel loaded biodegradable poly (sebacic acid-co-ricinoleic acid) cylindrical implants for local delivery-*in vitro* characterization

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The aim of the present research work was to develop the biodegradable polymeric implant for the delivery of antineoplastic drug, paclitaxel (PTX) using poly (sebacic-co-recinoleic acid) 70:30 w/w. PTX loaded implants were prepared by indigenously developed melt molding technique. Implants were characterized in terms of physico-chemical evaluations, drug content, drug stability and intactness, thermal analysis, drug physical state and crystallinity, surface morphology, hydrolytic degradation, drug release and its kinetics. Prepared implants were yellow and cylindrical in shape with smooth surfaces. Drug in the implants was found to be stable, intact and uniformly dispersed as amorphous state within the polymer matrix. *In vitro* release, kinetic studies showed zero order and Korsmeyer-Peppas model release being exhibited. Drug release from the polymeric implants was occurred could be as results of diffusion.

Key words: *Biodegradable, implants, paclitaxel, poly (sebacic acid-co-ricinoleic acid) 70:30 w/w*

INTRODUCTION

Drug delivery is directly to the brain interstitium using polymeric devices release unpredictable levels of drug directly to an intracranial target in a sustained fashion for extended periods of time. The fate of a drug delivered to the brain interstitium from the biodegradable polymer is based on rates of drug transport through diffusion and fluid convection, rates of elimination from the brain via degradation, metabolism and permeation through capillary networks, rates of local binding and internalization.[1] The feasibility of polymer-mediated local drug delivery by using the standard chemotherapeutic agent 1,3 bis (2-chloroethyl)-1-nitrosourea and their obtained results showed that local treatment of gliomas by their method was effective in animal models of intracranial tumors. This led to clinical trials for glioma patients and subsequent approval of (Gliadel™) by the Food and Drug Administration.[2] Paclitaxel (PTX) is a naturally occurring microtubule-binding agent, which has been shown to have tumoricidal activity against several human neoplasms, including non-small lung cancer, breast cancer, ovarian cancer and brain cancer.[3] PTX is a hydrophobic molecule that is poorly soluble in water. Currently, cremophor EL a non-ionic (polyethoxylated castor oil) solubilizer is used to enable its clinical administration. Cremophor EL causes clinical acute hypersensitivity reaction, characterized by dyspnea, flushing, rash, chest pain, tachycardia, hypotension, angioedema and generalized urticaria.[4-6] Poly (sebacic acid [SA]-co-ricinoliec acid [RA]) (Poly [SA: RA] 70:30 w/w) is a polyanhydride biodegradable polymer for controlled drug delivery. Polyanhydrides have been considered to be useful biomaterials as carriers of drugs to various organs of the human body such as brain, bone, blood vessels and eyes. They can be prepared easily from available low cost resources and can be manipulated to meet desirable characteristics. Polyanhydrides undergo surface and bulk erosion, which is also termed heterogeneous erosion, by cleavage of hydrolytically sensitive bonds in the polymer that finally leads to polymer erosion type degradation.[7,8]

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Access this article online

Quick Response Code:

Website: www.asiapharmaceutics.info

DOI: 10.4103/0973-8398.120087

Biodegradable intratumoral cylindrical implants from different polymers can be prepared by either methods, such as direct compression, granulation compression, injection molding and melt extrusion methods. The injection molding and melt extrusion techniques are mostly used for preparation of biodegradable implants for intratumoral chemotherapy.[9] However, the availability of the originally designed machines cost is also very prohibitive. In this study, polyanhydride, based polymer (poly [SA-co-RA] 70:30 w/w) of biodegradable polymeric implants were prepared by developed simple melt technology and their *in vitro* characterizations were carried out.

MATERIALS AND METHODS

PTX was obtained as a gift sample from Naprod Life Sciences. Pvt. Ltd. (Mumbai, India), Poly (SA-RA) 70:30 w/w (weight-average molecular weight = 21,000; number-average molecular weight = 10,000) was synthesized as previously reported.[10] Briefly, poly (SA-RA) was prepared in a one-pot reaction in which poly (sebacic anhydride) was reacted with RA (70:30 w/w ratio) at 120°C for 2 h followed by anhydride polycondensiation at 130°C under vacuum (0.1 mmHg) using acetic anhydride for an activation of the carboxylic acid end groups. The formed polymers were used without further purification. Sodium chloride, sodium dihydrogen orthophosphate and potassium dihydrogen orthophosphate were purchased from SD Fine Chemicals, Bangalore, India. All high-performance liquid chromatography (HPLC) and analytical grade solvents were purchased from Ranbaxy Chemicals, Bangalore, India.

Methods

Instrumentation and chromatographic conditions

The HPLC system consists of a Shimadzu SPD-10ATVP, binary pump equipped with a normal sample injector with a 50 μL loop, SPD-10AVP variable wavelength Ultraviolet detector and Spincotech station for data analysis. Chromatographic separations were achieved using a Phenomenex C-18 column, (4.6 mm × 250 mm, 5 μm) and Phenomenex C-18 guard column cartridge (KJ0-4282, 4.0 mm × 3.0 mm, 5 μm). Mobile phase consisting for the estimation of PTX in bulk and formulation was acetonitrile: Water (60:40% v/v) was passed through a 0.22 μm Nylon membrane filter and degassed by ultrasonication under vacuum before use. The analysis was performed at the flow rate of 1.3 ml/min with Ultraviolet detector at 227 nm and the sensitivity was 0.02, absorbance unit force per second.

Preparation of biodegradable polymeric implants

PTX loaded implants were prepared by melt molding technique (very small scale preparation), Figure 1a. Drug was uniformly mixed in a concentration of 10 and 20% w/w in polymer, by using high speed homogenizer (Remi Instruments Pvt. Ltd., Bangalore, India). The mixture was stirred at 5000 ± 10 rpm (Teflon propeller) for 20 min. The mixed mass was transferred to cylindrical mold having a 7.0 mm diameter and 8.0 mm length, which was placed on and attached to a rod having a diameter of 6.9 mm (removable). The entire unit was heated up to 70 ± 5°C by using the digital temperature control heating mantle (Remi Instruments Pvt. Ltd., Bangalore, India) mixed, homogeneously. The molten mass was solidified slowly with gradually reducing temperature up to 30 ± 5°C. A plunger having a diameter of 6.7 mm was introduced into the mold, which was rotated clockwise and anti-clockwise direction. Immediately, the complete unit was kept at de freezer (−10 ± 5°C), (Remi Instruments Pvt. Ltd., Bangalore, India) for 30 min, after which the plunger and rod were removed and the solidified hard implant was taken out from the mold (The plunger is adjustable and can move through a distance of 1.0-7.0 mm in the mold). Blank formulations were prepared similarly without drug. The coded formulations are shown in Table 1 and Figure 1b.

Physical evaluations

The prepared implants were evaluated for their physical parameters such as weight, color, height and area. The implant diameter (d) and height (thickness) (h) were measured by using digital vernier callipers and area calculated using the formula. Results are shown in Table 1 and Figure 1b.

Estimation of drug content

The drug content in polymeric implants was determined by solvent extraction method. The extraction procedure was carried out according to a reported method[11] followed by a

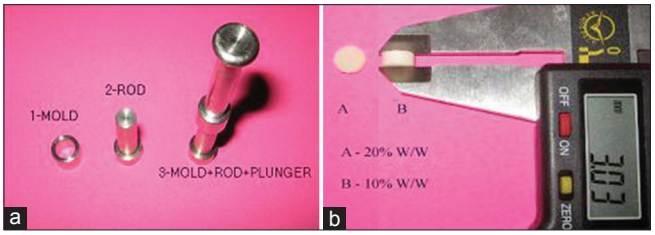

Figure 1: Designed and fabricated molds for preparation of implants (a) and formulation (b)

Table 1: Physicochemical evaluation and percentage recovery of implants

Polymers	B1 (Blank)	B2 (Blank)	F1	F2
Formulations	90	40	10% w/w	20%w/w
Weight of blank implants (mg)	84.55±2.400	34.94±1.100	93.69±1.400	44.88±1.200
Color	Yellow	Yellow	Yellow	Yellow
Shape	Cylindrical	Cylindrical	Cylindrical	Cylindrical
Area (cm^2)	1.291±0.044	0.964±0.028	1.360±0.014	1.184±0.058
Thickness (h) (cm)	0.282±0.022	0.196±0.003	0.309±0.025	0.228±0.002
% recovery			89.55-90.60	90.99-92.44

slight modification. The 10 and 20% w/w PTX loaded implants were dissolved in 10 ml of chloroform (CHL) to which 10 ml of acetonitrile: Water (60:40 v/v) was added and the mixture was vortexed vigorously. After complete evaporation of CHL, the solution was centrifuged for 5 min at 5000 rpm. Clear solution was filtered through 0.22 μm Nylon membranes (Millipore, India). The filtrate was further suitably diluted with the solvent mixture of Acetonitrile: Water (60:40 v/v) and used for PTX analysis by HPLC technique. The drug content of PTX was calculated as the percentage of the ratio of actually measured drug content in the implants to the loaded amount. Results are shown in Table 1. In order to take into account the amount of PTX lost throughout the above procedure the recovery efficiency was determined and used as the correction factor. To do so, a known amount of PTX and mixture of drug and polymer were dissolved separately in CHL and subjected to the same extraction procedure.

Fourier transform infrared analysis

Infrared spectroscopy (Thermo Nicolet Avtar 370, Japan) was performed for pure PTX, Pure poly (SA-RA), physical mixtures of PTX and poly (SA-RA) (1:1 ratio) and implant. Implant was cast onto Sodium chloride, plates from solutions in CHL. Other samples were mixed with potassium bromide and vacuum-packed to obtain pellets of the material, which were analyzed. All the spectra acquired scans between 400 cm^{-1} and 4000 cm^{-1} at a resolution of 4 cm^{-1}.

Differential scanning calorimetry studies

DSC was conducted using Mettler Toledo Star System. Samples were weighed (2.00-4.00 mg) and placed in sealed aluminum pans. The coolant was liquid nitrogen. The samples were scanned at 10°C/min from 10°C to 225°C. DSC of PTX pure, poly (SA-RA) pure mixture of drug and polymer (1:1 ratio) and implant

X-ray diffraction studies

X-ray diffraction patterns of the DSC of PTX pure, poly (SA-RA) pure mixture of drug and polymer (1:1 ratio) and implant were determined using a diffractometer equipped with a rotating target X-ray tube and a wide-angle goniometer. The X-ray source was Kα radiation from a copper target with graphite monochromater. The X-ray tube was operated at potential of 50 kV and a current of 150 mA. The range (2θ) of scans was from 0 to 70° and the scan speed was 2°/min at increments of 0.02°.

Surface morphology

Blank and drug loaded implants, immediately after manufacturing and after *in vitro* drug release were subjected to surface morphological characterization using scanning electron microscopy SEM. The polymeric implants were first dried under vacuum. Samples were glued to aluminum sample holders and gold coated under argon atmosphere. The coated samples were finally analyzed using scanning electron microscope (JSM 848, Joel, Japan) under suitable magnifications.

In vitro hydrolytic degradation of polymers and PTX implants

Cylindrical, blank and drug loaded implants prepared by melt molding method, were placed in 25 ml screw capped bottles containing phosphate buffer saline (PBS) pH 7.4 at 37 ± 2°C for a period of 30 days using horizontal water bath shaker (Remi Instruments Pvt. Ltd., Bangalore, India) to conduct *in vitro* hydrolytic degradation of polymer and drug accumulated in the implants. The platform was rotated at an average speed of 50 rpm to induce mixing in the release medium. At specific predetermined time intervals, the blank and drug loaded implants were taken out of the release medium, dried under vacuum and weighed. The hydrolysis of the polymer was determined by a decrease in weight of the drug loaded implant and PTX content in the remaining implants. At each time point, the formulations were examined for PTX content in the degraded sample by developed HPLC method.

In vitro drug release and kinetics

The *in vitro* release studies of PTX implants were carried out at 37 ± 2°C in PBS pH 7.4 for a period of 30 days using horizontal water bath shaker (Remi Instruments Pvt. Ltd., Bangalore, India). The platform was rotated at an average speed of 50 rpm to induce mixing in the release medium. At periodic intervals, initially at 24 h and then followed by every 5 days, 10 ml of the release medium was sampled and 10 ml of fresh release

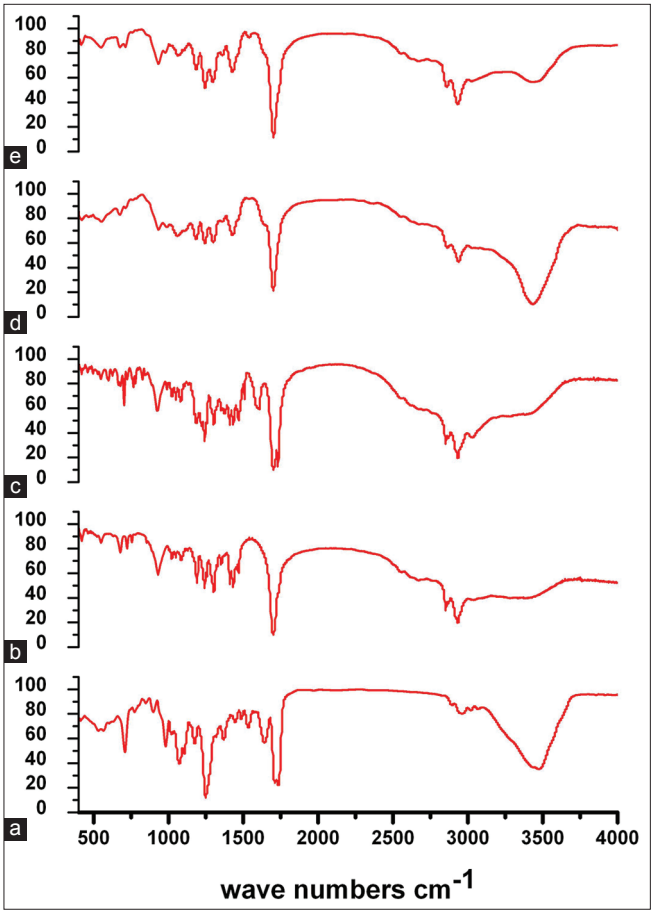

Figure 2: Transmission FT-IR spectra of pure PTX (a), poly(SA-RA) (b), physical mixture of PTX and poly(SA-RA) (c), F1 (d) and F2 (e)

medium was replaced to provide the necessary sink condition. The samples were analyzed for PTX content by using HPLC as described in the section 4.2. The cumulative percentage drug release was calculated to establish the drug release profile of the implants prepared by melt molding method. In order to determine the order of drug release, drug release profile of all the formulations evaluated were fitted into zero order, first order, Higuchi and Korsmeyer-Peppas models.

RESULTS AND DISCUSSION

Qualification of HPLC method

The standard curve was constructed for PTX by plotting the peak area as a function of PTX concentration. There is an excellent linearity over the concentration range of 25-5000 ng/ml. The typical equation describing the calibration curve is $y = 0.922 \times -0.058$, whereas y is the peak area of PTX and x is the concentration of PTX and c is the intercept, with a mean correlation coefficient (R^2) of 0.9993. PTX was eluted at retention time of 5.99 ± 0.2 min. With respect to intra-day and inter-day precision and accuracy, at the lowest drug concentration the percentage coefficient of variation is 2.5 and 2.6% when compared with the highest drug concentration 0.25 and 0.21%. However the percentage accuracy at lowest and highest drug concentrations was found to be more than 95%. The limit of detection (LOD) and the limit of quantification (LOQ) were determined. The LOD and the LOQ of PTX were found to be 5.57 and 16.12 ng/ml.

Physiochemical properties of PTX loaded implants

Macroscopically all the implants were found to be cylindrical in shape, smooth in surface, yellow color due to poly (SA-RA). Weight of the blank implants was 84.55 ± 2.4, 34.94 ± 1.10 mg and drug loaded implants were 93.69 ± 1.4 and 44.88 ± 1.2 mg, respectively. The percentage drug content in the implants was found to be 89-92%. The obtained

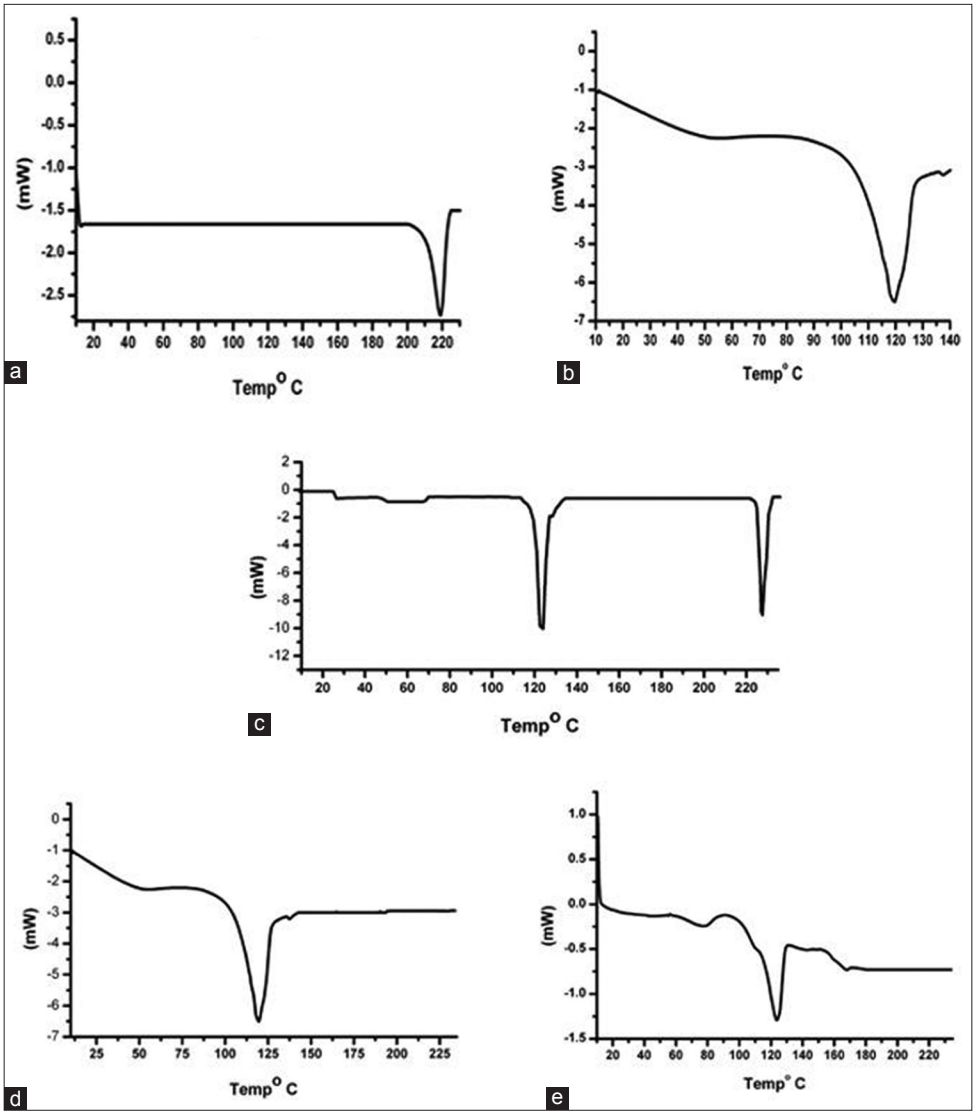

Figure 3: DSC thermograms of pure PTX (a), poly(SA-RA) (b), physical mixture of drug and polymer (c), F1 (d) and F2 (e). The experiment was carried with crimped aluminum pans and a heating rate of 10°C/min; the samples were scanned at 10°C/min from 10-225°C

results are tabulated in Table 1. Implants were prepared by indigenously developed mold technique using specially designed stainless steel molds. The implant's diameter and weight showed a very little difference (even though the mold of the unit had the same diameter). The slight difference is attributed to solidification from the melt and contraction properties of polymer. Area, weight and thickness of the implants depend on the different concentration of polymer loading. All average weights of the implants reflected the amount of polymer actually loaded. Macroscopically, all the formulations were found to be stable. There was no significant change in drug content in all the formulations.

FTIR

FTIR spectra of pure PTX, poly (SA-RA), physical mixture of PTX and poly (SA-RA) and drug loaded implants F1 and F2 are shown in [Figure 2]. The spectrum of PTX shows characteristics absorption bands at 3066.4 cm^{-1} (–CH sp^3 stretching), 1733.8 cm^{-1} (C = O stretching) of the amide group, 1640.8 cm^{-1} (N-H bending), 1444.6 cm^{-1} (C = C ring stretching). Poly (SA-RA) absorption bands were obtained at 2933.7 cm^{-1} (C-H stretching) and 1698.1 cm^{-1} (C = O stretching) and 1248.6 cm^{-1} (C-O bending) of anhydride group.[12] In case of formulations F1 and F2 only the characteristics bands of polymer was obtained at 2934.2, 1699.7, 1299.4 cm^{-1}, respectively. FTIR studies revealed that, physical mixture shows absorption bands for both drug and polymer, indicated that there was no chemical or physical interaction between drug and polymer during preparation of implants. While in case of formulations F1 and F2 an overlay FTIR spectra was observed these studies revealed that drug remain intact, stable and effectively dispersed within the polymer matrix in implant.

DSC

DSC thermograms of pure PTX, poly (SA-RA), physical mixture and PTX loaded F1 and F2 are shown in Figure 3. The melting endothermic peak of pure PTX appeared at 220.0°C. Sharp and broadened endothermic peaks of poly (SA-RA)[12] and physical mixture were observed at 119.41 and 120.27/226.42°C, respectively. In case of formulations F1 and F2, broadened endothermic peaks were generated at 121.52 and 122.74°C. DSC thermograms showed the presence of PTX in polymeric implants is in the form amorphous nature, which probably may be due to conversion of PTX from crystalline state to amorphous/dissolution during the heating involved in the preparation of implant. Also, might be due to the low molecular weight drug incorporated in the polymeric matrix during a melt manufacturing method, does interfere with the crystalline network and may be dispersed in the solid solution.[13]

X-ray diffraction

The diffraction peaks of PTX were observed at 10.82, 12.90, 14.96, 17.97, 25.08, 43.744° (2θ) [Figure 4a]. In case of pure polymer, diffraction peaks were observed at 5.27, 20.22, 21.73, 25.3° (2θ)[12] [Figure 4b]. Physical mixture of drug and polymer when subjected for XRD, same prominent diffraction peaks of drug and polymer were observed in the mixture at 7.61, 17.76, 19.58, 21.91° (2θ) [Figure 4c]. Formulation F1 and F2 characteristic peaks were appeared at 5.12, 21.80, 23.63, 25.86° (2θ) [Figure 4d] and 5.83, 20.43, 21.64, 23.82, 25.86° (2θ) [Figure 4e], respectively. XRD studies revealed that the drug peak did not appear in all the formulations indicating that elevated temperature and a slow rate of cooling enable the chains to be mobile and to realign themselves in a more ordered either semi-crystalline or solid solution.[9]

In vitro hydrolytic degradation aspects

The degradation rate of 10% drug loaded poly (SA-RA) 70:30 based implant was slower when compared to 20% drug loaded poly (SA-RA) 70:30 implants. The percentage weight loss in blank loaded implant B1 after 5 and 30 days was found to be 9.029 ± 1.3% and 44.747 ± 2.6%. The percentage weight loss in implant B2 after 5 and 30 days was found to be 14.565 ± 1.08% and 59.274 ± 0.99%. Similarly in case of formulations, F1 was 5.713 ± 1.2% and 31.960 ± 3.9%, in F2 implants 10.553 ± 2.5% and 43.722 ± 1.8% [Figure 5a]. The percentage of drug accumulation in F1 implant after 5 and 30 days was found to be, 92.752 ± 1.8% and 64.956 ± 1.3% while in case of F2, 90.429 ± 1.4% and 50.434 ± 1.55% [Figure 5b]. Average of three determinations was reported. *In vitro* hydrolytic degradation of blank

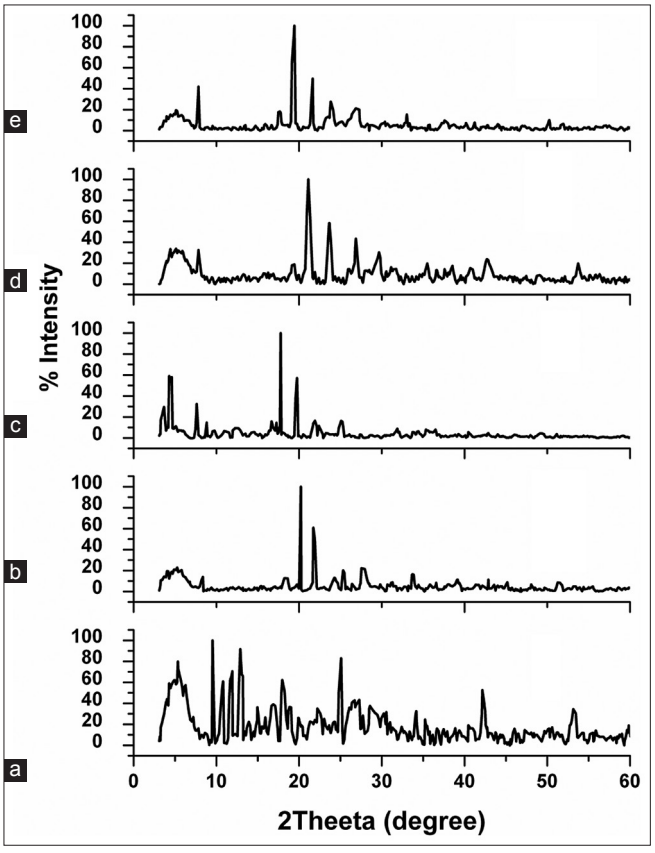

Figure 4: XRD patterns of pure TC (a), poly(SA-RA) 70:30 w/w (b), physical mixture (c), F1 (d) and F2 (e)

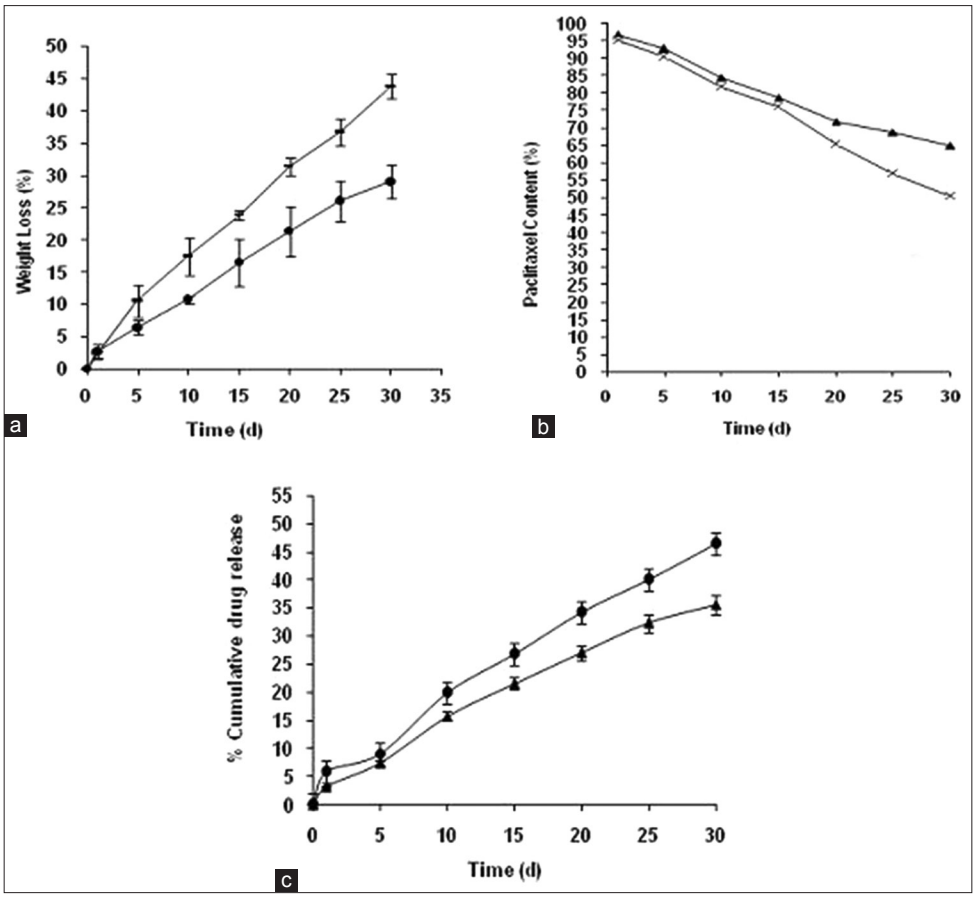

Figure 5: (a) *In vitro* hydrolytic degradation of percentage weight loss of drug loaded implants F1 (●) and F2 (■), (b) Paclitaxel content (accumulated) during hydrolytic degradation F1 (▲) and F2 (x), (c) Percentage cumulative drug release F1 (●) and F2 (▲), respectively

and PTX implants results showed that the highest rate of degradation (weight loss) was observed in blank implants when compared to PTX loaded implants. The degradation of implants depends upon the polymer concentration, fatty degradation product[9,14,15] geometry,[14-16] density of the matrix,[13,14,16,17] formation of microchannel/pores in the implant and the dissolution media, which causes hydrolysis of polymer. The PTX accumulation in 10% w/w drug loaded F1 was more when compared with 20% w/w drug loaded F2 implants.

In vitro PTX release studies

Figure 5 demonstrated the release pattern of PTX from formulation implants. The percentage cumulative drug release from F1 and F2 after 30 days was found to be 35.612 ± 3.5 and 46.308 ± 2.5%, respectively. Average of triplicate was reported. Figure 5 shows the *in vitro* drug release profile of implant formulations. Release profile demonstrated the initial small burst effect phase followed by slow and constant drug release. Initial small burst effect phase was considered as a result of rapid diffusion/dissolution of drug particles at the solid liquid interface. The magnitude of burst effect was dependent on the proportion of PTX on the outer surface of the implant. As described above, release of drug from the implants depends on various factors. In Implants, drug release occurred by surface and bulk diffusion/erosion actually visualized by SEM [Figure 6]. The initial rate of release from 20% w/w PTX loaded implant samples was very high compared to 10% w/w PTX loaded implant samples, may be due to high wetting system's surface with media (dissolution media), formation of continuous polymeric network, creation of more media filled pores, creation of more cracks and within the release rate limiting membranes[16] (thickness and permeability of drug) and also geometry and density of the devices. Zero order and Korsmeyer Peppas model gave a good fit for all the drug release profiles of implants with greater regression coefficients in comparison to other models. The fitting of these data to the Korsmeyer-Peppas model demonstrated [Table 2] that drug release occurs mainly through diffusion, surface and bulk erosion process.[18]

SEM

The SEM of blank [Figure 6], A (B1) and (B2) and drug loaded implants [Figure 6], E (F1) and F (F2) prepared by melt mold technique using poly (SA-RA), when subjected for SEM were found to be uniform, homogenous and nearly smooth in surface. At the end of 30 days of release studies, SEM analysis of both blank [Figure 6], C (B1) and D (B2) and drug

Table 2: *In vitro* drug release kinetic profile of PTX implants

Formulations	Zero order $Q_t=Q_o+K_ot$ R^2	First order ln $Q_t=lnQ_o+K_ot$ R^2	Higuchi $Q_t=K_H$ sq.t R^2	Korsmeyer-Peppas $Q_t/Q_{inf}=K_k t^n$ R^2	*P* (value)
F1	0.9629	0.8525	0.8781	0.9544 (*n*=0.73)	<0.001
F2	0.9736	0.8180	0.8734	0.8864 (*n*=0.64)	<0.002

PTX: Paclitaxel

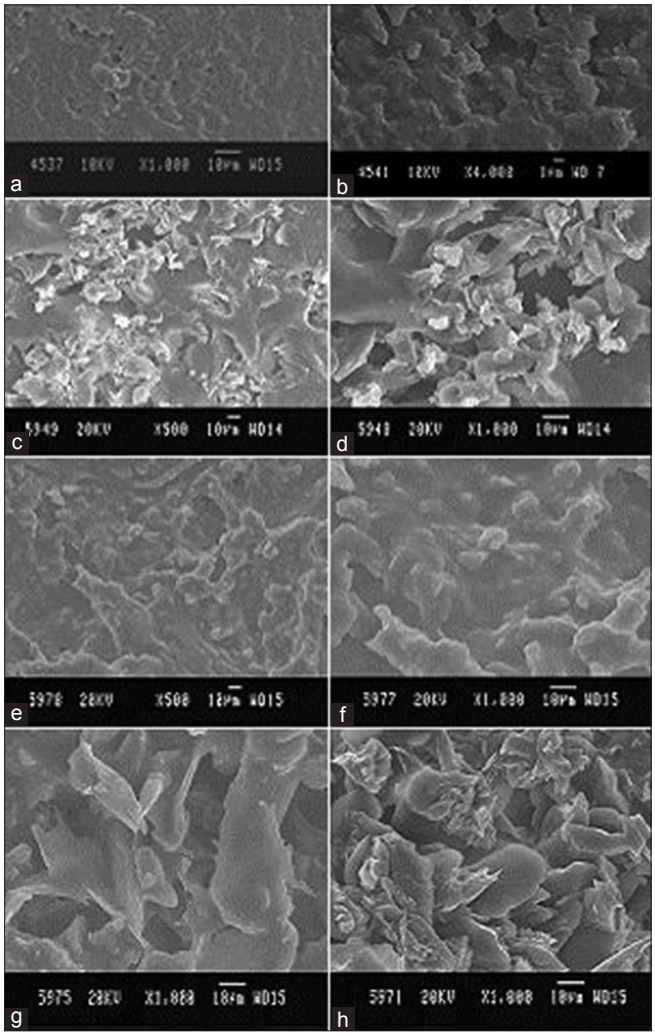

Figure 6: Scanning electron micrographs: Blank implants immediately after manufacturing [a(B1) and b(B2)], Blank implants after 30 days release [c(B1) and d(B2)], PTX loaded implants immediately after manufacturing [e(F1) and f(F2)] and PTX loaded implants after 30 days release [g(F1) and h(F2)]

loaded implants [Figure 6], G (F1) and H (F2) showed highly porous surface, water filled pores formation and formation of micro-channels were observed. The examination of surface of polymeric drug delivery systems can provide important information about the porosity, crystallinity and microstructure of the system.[16] the SEM micrographs demonstrated the appearance of pores, micro-channels, cracks in the formulations after release for a period of 30 days revealed that the drug release from the implants could be occurred by diffusion process

CONCLUSION

PTX loaded poly (SA-RA) implants have been successfully prepared by melt molding technique. The polyanhydride implants showed sustained prolong release of drug. Thus, poly (SA-RA) could be used as a potential vehicle in delivery of antineoplastic agents. This method is a basic technique for the preparation of biodegradable implants. From this technique could help to check the sensitivity of drugs and polymers in respect to their thermal properties and also biocompatibility for the preparation of biodegradable implants. This method is the most effective in academic research in developing preformuation aspects. The studies proved that the method developed have potential in terms of industrial feasibility. Further, we should essentially to adopt melt extrusion, injection molding or suitable technique for the production of pilot or large scale preparation of biodegradable implants

ACKNOWLEDGMENT

The authors are grateful to Abraham J. Domb, Institute for Drug Research, Medicinal Chemistry, School of Pharmacy, Faculty of Medicine Hebrew University of Jerusalem 91120, Israel, for the synthesis of the polymer. The authors thank to Indian Institute of Sciences, Bangalore, India and Indena SPA, Milano Italy, for providing DSC, XRD facility and gift sample of PTX.

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How to cite this article: Hiremath JG, Devi VK. Paclitaxel loaded biodegradable poly (sebacic acid-co-ricinoleic acid) cylindrical implants for local delivery-*in vitro* characterization. Asian J Pharm 2013;7:125-32.

Source of Support: Nil. **Conflict of Interest:** None declared.