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DEGRADATION AND DRUG RELEASE STUDIES OF COPOLYMER OF (1,3-BIS(P-CARBOXYPHENOXY)PROPANE (CPP) AND SEBACIC ACID (SA) LOADED WITH CIS PLATIN

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ABSTRACT

The degradation and drug release studies of poly((1,3-bis(p-carboxyphenoxy))propane-co-sebasic acid) loaded with cis platin are studied through various means. The drug loaded samples were first prepared from compression molding technique and degraded in 0.01M phosphate buffer saline at 37°C with pH of 7.4 at predetermined time. Interaction of drug and the polymer was monitored through FTIR and DSC. The influence of the drug to the degradation behaviour of the copolymer was detected through mass loss and water uptake and also pH changes. Variable Pressure Scanning Electron (VPSEM) was used in studying of the effect of degradation to the surface topography of the samples. The drug release profile is monitored through the U.V. spectroscopy work.

Keywords: drug release; biodegradable polymer;

INTRODUCTION

Biodegradable polymers have open many opportunities and breakthrough in the biomedical applications. Biodegradability is the main key existed for many reasons particularly in the field of tissue engineering and controlled drug delivery. The development of implantable drug delivery systems is perhaps the most widely investigated application of biodegradable polymers. Due to their transient nature, biodegradable polymers do not require surgical removal after their intended application and thus can circumvent some of the problems related to the long-term safety of non-degradable implanted devices [1].

After implanted into the body, it is highly desirable that the materials ‘disappear’ to obviate the need for any post-application removal [2]. At present juncture, significant attractions have been widely focused on the synthesis and degradation of the biodegradable polymers. The chemistry of some polymers including copolymer composition, properties and monomer selection has been designated to control the degradation rate of these polymers. Surface erosion was entirely due to the matrix that erodes heterogeneously from the outermost part of the material that would lead to zero order drug release profile. In this release profile, the overall shape of the device is

maintained in which relatively constant surface area provides constant release of drug [3].

Polyanhydrides are a particularly promising class of bioerodible polymers that degrades by surface erosion [4]. This suited the best application of drug delivery systems. Polyanhydride contains water labile linkages which promote surface erosion and once drug is incorporated into the polymer, the drug is delivered mainly through polymer surface erosion and maybe very insignificant diffusion of drug traveling through the polymer matrix. [1]. For clarity, it is important to distinguish between the terms "degradation" and "erosion". The term "degradation" refers to the chain scission process by which polymer chains are cleaved into oligomer or monomer units. The term "erosion" refers to mass loss from the bulk polymer. In other words, erosion could be considered as the sum of several elementary processes, one of which is degradation [6]. There are several factors which influence the degradation and erosion behavior. These include chemical structure of the polymer, the type of monomers and their composition [7], size of the samples and also the morphology of the polymer where partially crystalline polymer degrades at much slower rate rather than amorphous structure. The purpose of this work is to elucidate the characteristics of poly((1,3-bis(p-carboxyphenoxy))propane-co-sebasic acid) synthesized in our laboratory (Figure 2) loaded with cis-platin (Figure 1).

This paper discusses the profiles of pH changes, monomer release, mass loss and water uptake of the degraded polymer. Interaction of the drug and the polymer was investigated through the chemical changes of the polymer during degradation. It is interesting to know how the drug can influence the degradation behavior of the polymer and this is revealed via the FTIR and DSC profiles of the degrading drug contained polymer. Using cis platin as the model drug, the drug release profile was investigated.

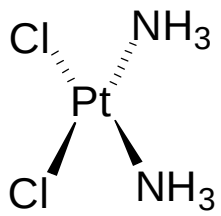

Figure 1: The chemical structure of drug cis platin loaded into the polymer

MATERIALS AND METHOD

Preparation of samples
To prepare the samples in disc form, having a mass of 0.25 g, diameter of 20 mm and thickness of 1 mm compression molding technique (Gabbrielli Crometro CR 415-E2 hydraulic press) was used. The pressure used is about 500 psi for 10 seconds. Samples containing 5 wt. % of the drug (cis platin) were prepared using similar technique.

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Degradation and drug release studies were performed in 0.01 M, pH 7.4 phosphate saline buffer at 37 ^{o}C with slow agitation at 20 rpm. The medium for the drug release studies was replaced with fresh buffer at predetermined time to maintain the sink condition. Cis platin release was detected using UV spectrophotometer at 701 nm by first reacting it with orthophenylene diammine (o-OPDA).

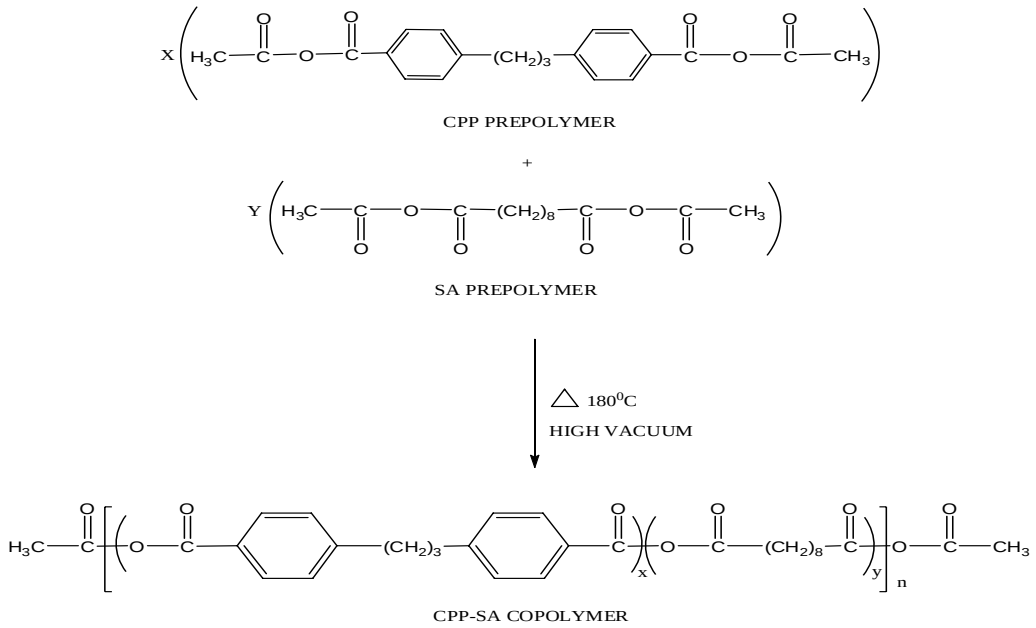

Figure 2: Schematic diagram of the synthesis of poly(CPP-co-SA) (20:80) [8]

Characterization

The degraded samples were characterized through various means in which the changes in the polymer morphology are monitored and used in interpreting the release profile of the drug. The stability of the polymer was monitored by measuring the changes of the polymer mass in the buffer solution. The samples were removed from the buffer solution, dabbed dry, and weighed for its wet weight and dried in a vacuum oven at 40 ^{o}C for three days for its dry weight. Water uptake and mass loss were measured using gravimetric method following the equations below:

$$M_{gain} = \left((M_w - M_d)/M_o\right) \times 100 \quad (1)$$

$$M_{loss} = \left((M_d - M_o)/M_o\right) \times 100 \quad (2)$$

where, M_{gain} is water uptake, M_w is wet weight, M_d is dry weight, M_o is initial weight and M_{loss} is mass loss of the sample taken at predetermined time points.

The chemical changes were demonstrated by the use of Fourier Transform Infrared (FTIR, Nicolet Magna IR 560 Spectrometer). Samples were pressed with KBr powder forming a pellet and analysed with the OMNIC software. The thermal behaviour of the

samples was recorded using Differential Scanning Calorimetry (DSC) (Mettler Toledo DSC 821e equipped with STARe software) with heating rate of 10 ^{o}C/min over a single heating cycle from 25 – 150 ^{o}C. X-Ray Diffraction (XRD) profiles of the samples were taken on a Bruker D8 Advance to determine the changes in the crystallinity percentage of the samples. The degree of crystallinity of the samples were calculated by taking the area under the crystalline peak and divided by the total area under the diffraction pattern, following the cutting and weighing technique. Variable pressure scanning electron microscopy (VPSEM)(Carl Zeiss, EVO LS 10), equipped with energy dispersive analyzer X-Ray (EDX) with pressure of 180 Pa was used to observe the changes in physical appearance of the degraded samples in semi dry condition. Drug release profile was recorded using the UV spectrophotometer (Perkin Elmer UV-visible) equipped with Lambda 25 software.

RESULTS AND DISCUSSION

The erosion and degradation processes that took place for the CPP-SA copolymer were monitored through various means, both physically and chemically. Variable pressure scanning electron microscope (VPSEM) was used in detecting the changes of the physical appearance of the degrading blank copolymer and comparison was made with the drug loaded copolymer. It is apparent from the micrographs (Figure 3) that blank samples exhibit some blobby feature with no slightest sign of cracks. An even smooth surface appearance was also observed for the drug loaded samples, in which white spots referring to the scattered cis platin was featured throughout the surface. The existence of cis platin on the surface of the samples was confirmed by the energy dispersive X-ray (EDX) spectra (Figure 4) which depicts the peaks related to platinum.

As degradation proceeds, as early as day 2, cracks were observed on the surface of both blank and drug loaded samples. Visual comparison depicts that smaller size of cracks appear on the surface of the drug loaded samples compared with those formed on the blank ones. The cis platin slowly disappears from the surface whilst, the buffer salts appear to be depositing on the sample surface. The cracks propagate on longer degradation period (day 4 and day 6) for both blank and drug loaded samples. Pores created by the loss of the polymer were seen on the surface of drug loaded samples and the pores appear to be larger on longer degradation period. Starting from day 8 and above, cracks were not as visible as before. A rough surface area was demonstrated for all samples. It is thought that the crack layers have been washed off, exposing the layer underneath. The formation of cracks and pores followed by peeling of the surface layer will be repeated continuously until the samples disappear from the sampling bottle. Surface cis platin on longer degradation period could no longer be observed as it could have been washed off once in contact with the degradation medium.

The loss of polymer from both blank and drug loaded samples were further verified via mass loss and water uptake profile (Figure 5). Initially, both water uptake and mass loss increased steadily for drug loaded samples for the first 6 days before being quite

constant on longer degradation period (day 8 to day 12). The blank samples however did not show a clear pattern in which we could consider a constant water uptake and mass loss occurred throughout the degradation period. Even though the influence of drug is quite insignificant in both water uptake and mass loss of the CPP-SA copolymer, it is quite apparent that cis platin slightly reduce the water uptake on the earlier state of the degradation period.

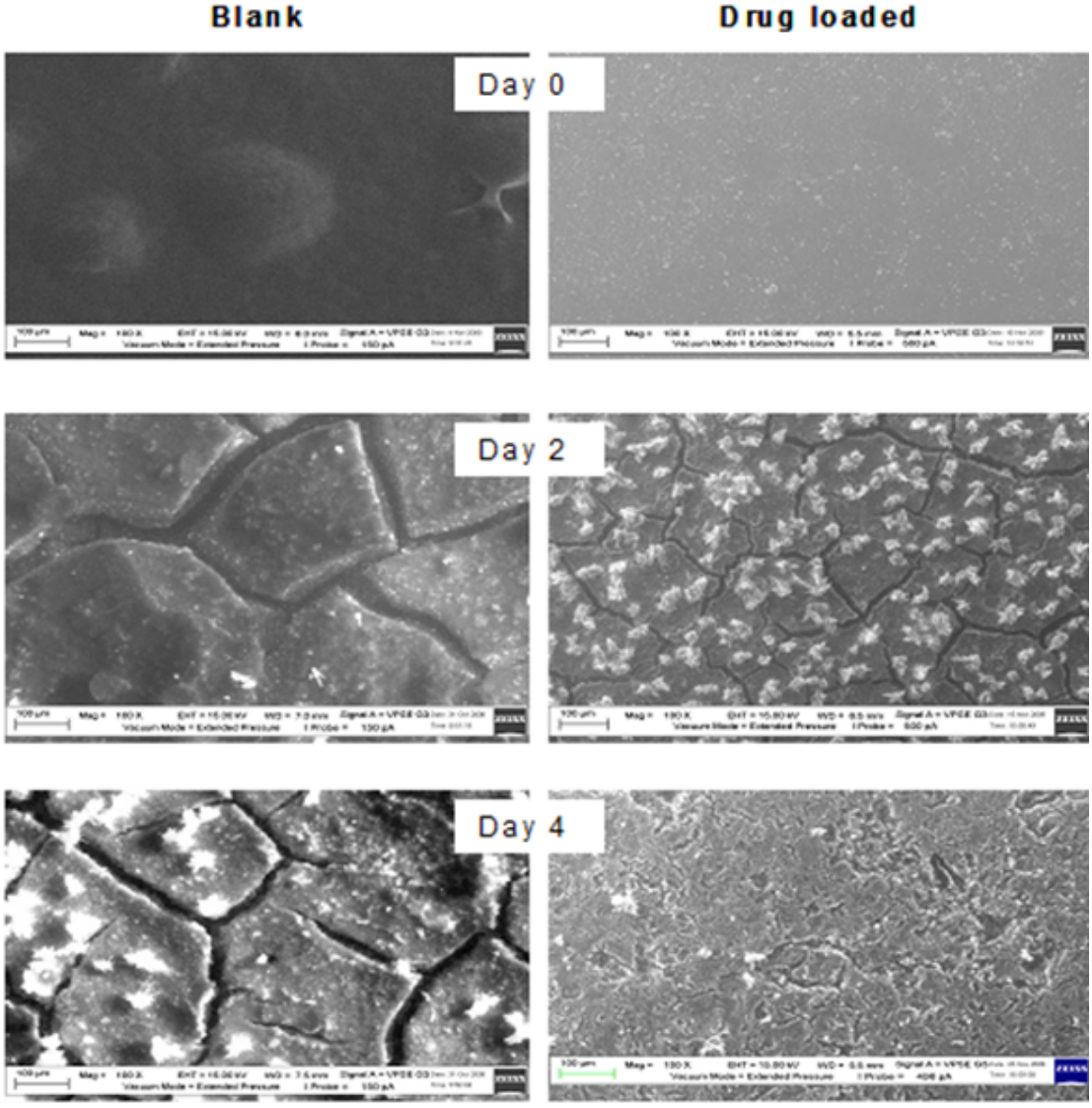

Figure 3: Scanning Electron Micrographs of degraded poly (CPP-co-SA)(20:80) blank and drug loaded

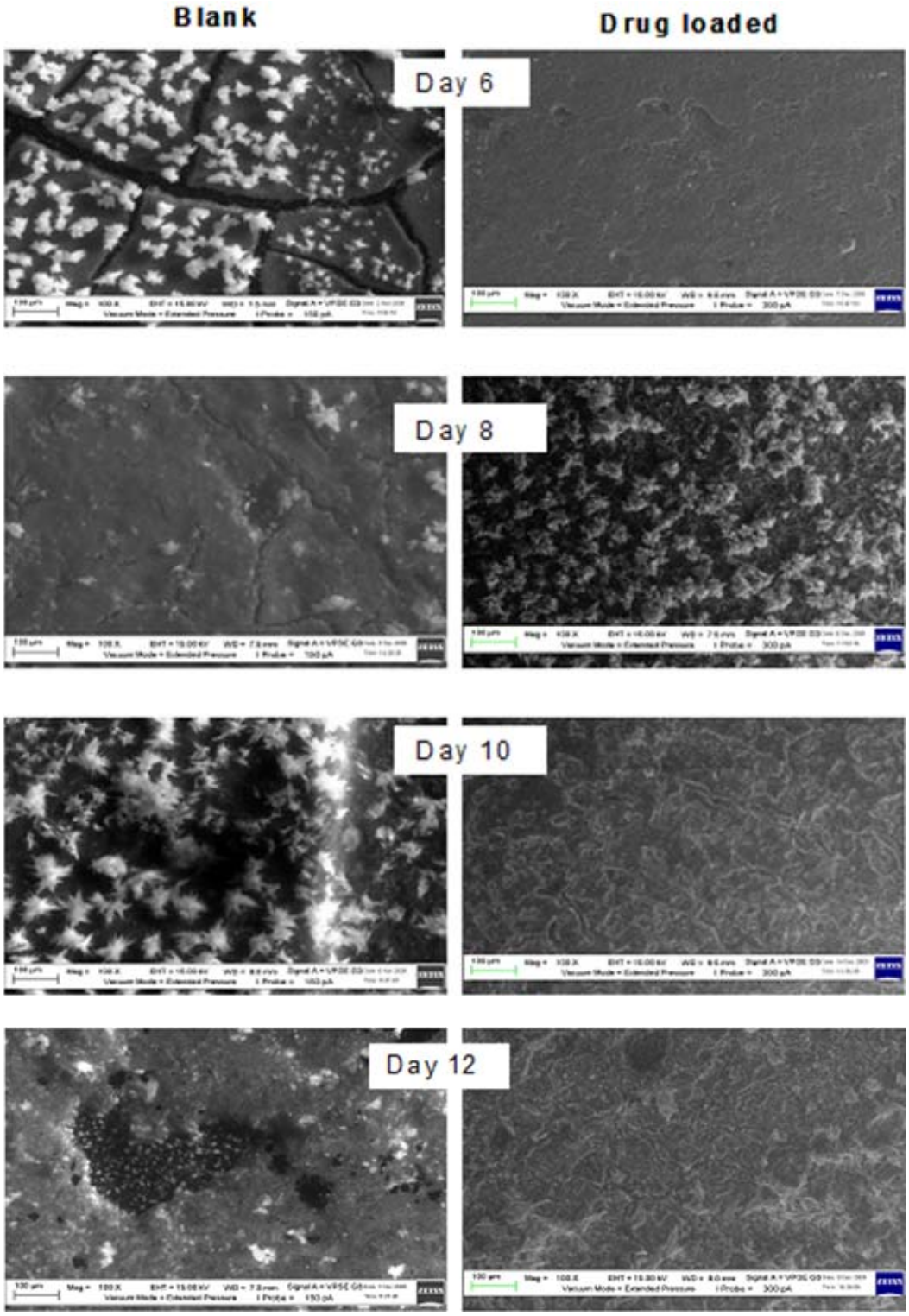

*Figure 3 continue

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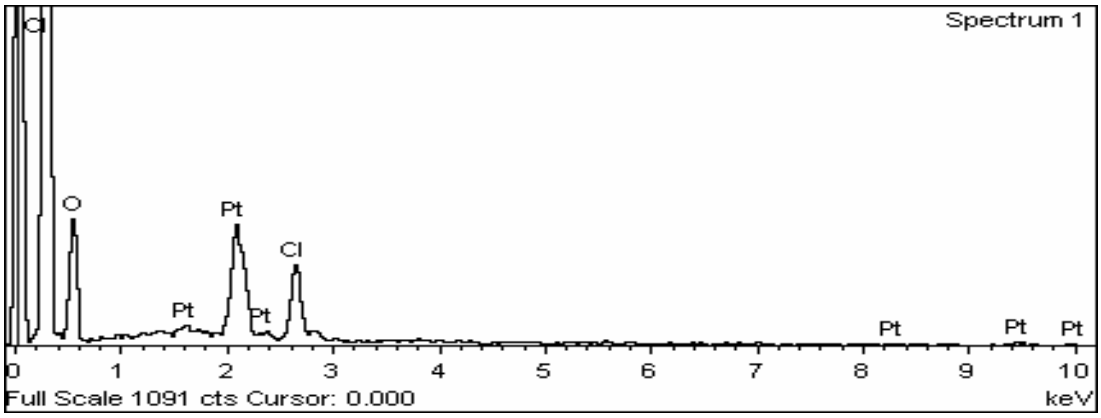

Figure 4: EDX-VPSEM spectrum of drug loaded polymer

It is important to note that erosion of the polymer depicts the mass of polymer that is loss from the polymer bulk. Once water cleaves the polymer backbone, the shorter chain monomer will at one time reaches its critical molecular weight before it can diffuse out of the polymer bulk. Theoretically, the CPP-SA copolymer degrades into their CPP and SA acidic monomers, this contributes to the mass loss seen in the results and also as the reduction in pH of the degradation medium (Figure 6). The initial pH of 7.4 drops to about 4.6 after two days and was quite constant throughout the degradation period. The drug loaded samples though showed a similar pattern to that of the blank ones, the slight difference could not be neglected. The pH reduction in drug loaded samples appear to be slightly slower than that of the blank ones which suggest the possibility of the cis platin's influence to the degradation behaviour of the copolymer. Cis platin could have possibly slower the diffusion of water into the copolymer as observed in the water uptake profile, hence, the slow degradation of the polymer which contributes to the slow diffusion of the acidic monomers into the degradation medium.
These phenomena are further supported by the monomer release experiment (Figure 7). As CPP-SA copolymer degrades into CPP and SA acidic monomers, the monomer diffusion into the degradation medium can be monitored through UV-vis spectra. With the aromatic benzene group located in the CPP monomers, this can be easily detected at λ_{max} 271 nm and the release of CPP monomers as a function of time is plotted. Figure 5 exhibits the faster release of CPP monomers from blank copolymer samples. Samples incorporated with cis platin appear to lower the release of CPP monomers into the degradation medium. This observation agrees with the water uptake and pH reduction profiles which demonstrate the influence of cis platin in a slightly slower degradation rate of the copolymer.

It is however worth noting that both CPP and SA monomers diffuse into the degradation medium. In general, the SA component degrades faster than that of the CPP, SA monomers will first be formed and will first diffuse out of the polymer bulk. This could create a competing diffusion process between the two acidic monomers. It is

safe to say that the SA monomers could possibly be the ones that diffused out earlier than its counterpart. As UV vis detects only CPP based on its aromatic groups, only CPP diffusion is being monitored.

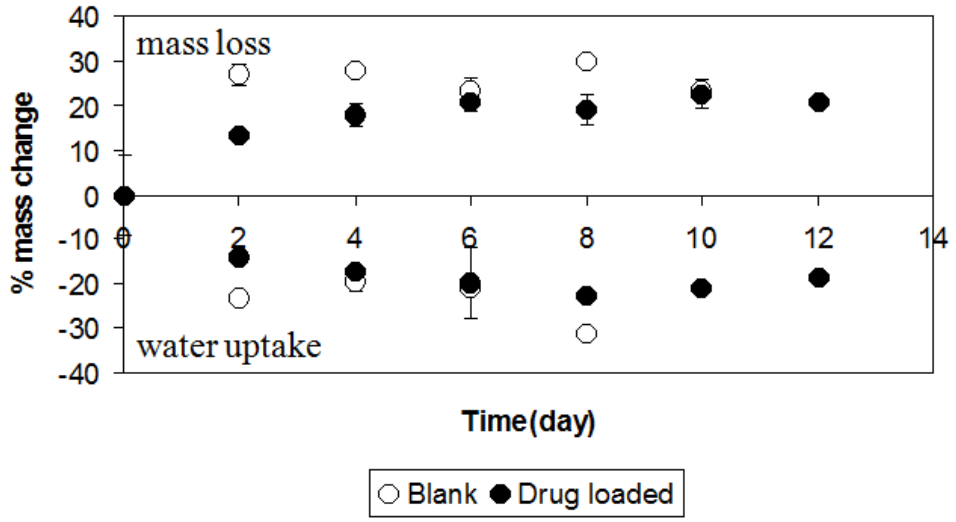

Figure 5: Water uptake and mass loss profile of poly(CPP-co-SA) blank and drug loaded as a function of degradation time

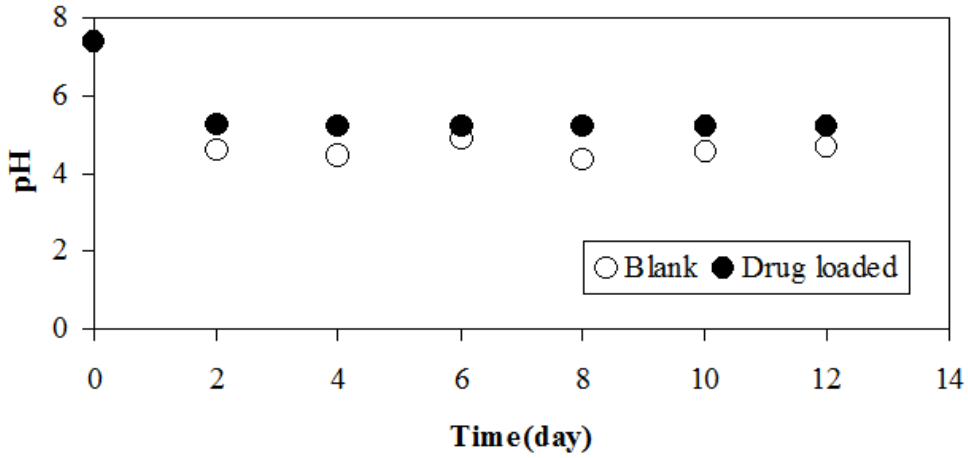

Figure 6: Change of pH of degradation medium of blank and drug loaded poly (CPP-co-SA) (20:80) with time

FTIR analysis shows a significant contribution in studying the degradation process where analysis of the infrared spectra enabled the identification of chemical bonds changes between the blank and drug loaded sample under the hydrolytic degradation. A typical IR spectrum of undegraded polyanhydride may present a peak of anyhydride bonds (COOCO) which appears at 1810-1700 cm^{-1}. The anhydride bonds that link the two prepolymers of CPP and SA will decrease as the polymer undergoes degradation

process which correlates to the chemical chain scission. In addition, the degradation also results in the formation of the acidic monomers and these peaks of (COO^-) can be observed at 1695 cm^{-1} which increases with degradation time.

Figures 8 and 9 depict the changes in the chemical structure of the copolymer with increasing degradation time. As expected, the blank samples (Figure 8) showed the existence of the anhydride group which decreases with time and the appearance of the COO^- group from the acidic monomers as early as day 2, increases with the degradation time. Similar observation was demonstrated for drug loaded samples, however, it is worth noting that the COO- group appears on the FTIR spectrum even on day 0 in which no contact with the degradation medium has been made. This shows the sign of early degradation of the copolymer on day 0 which could be due to the sample handling problem. Another difference is noted at the disappearance of the anhydride (COOCO) peak on day 6 onwards for blank samples which is not visible for drug loaded samples. The anhydride peak (COOCO) still exists even on day 12 for drug loaded samples which could possibly be due to the existence of the traces of the copolymer that could undergo slower degradation rate. The effect of incorporating the drug is again supported by these FTIR results.

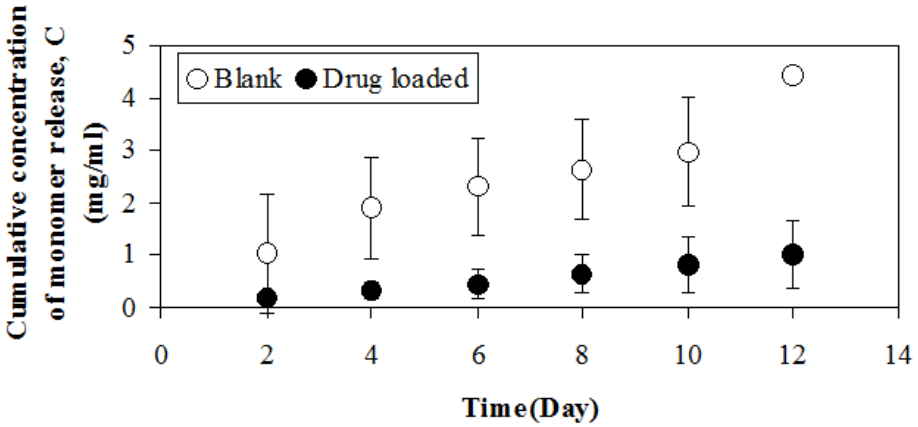

Figure 7: Change of monomer release due to degradation process of blank and drug loaded poly (CPP-co-SA) (20:80) with time

The thermal behaviour of the degrading CPP-SA copolymer was monitored by Differential Scanning Calorimetry (DSC). It is important to note the melting peaks for all components involved such that the melting peaks for poly (CPP-co-SA), SA monomer, CPP monomer and cis platin are 63 ^oC, 137 ^oC, 322 ^oC and 398 ^oC respectively (Figure 10, Tables 1 & 2). The appearance and disappearance of these peaks indicates the degradation behaviour of the copolymer indirectly. As the poly (CPP-co-SA) degrades into its acidic monomers of CPP and SA, the CPP-SA copolymer in general should be decreasing, whilst the acidic monomers increased with degradation time. These changes are observed in the DSC thermograms which depict the changes quite clearly.

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The DSC profile for the blank samples (Figure 10a, Table 1) showed only the melting peak referring to the copolymer initially (Day 0). Once in contact with the degradation medium, water cleaves the anhydride bonds of the copolymer into its acidic monomers. The melting peak of SA appears as early as day 2 which coexists with the copolymer in the polymer bulk. On longer degradation period starting from day 4, the melting peak of CPP appears in the thermogram and leaving the polymer bulk with three components comprising of the copolymer and its monomers.

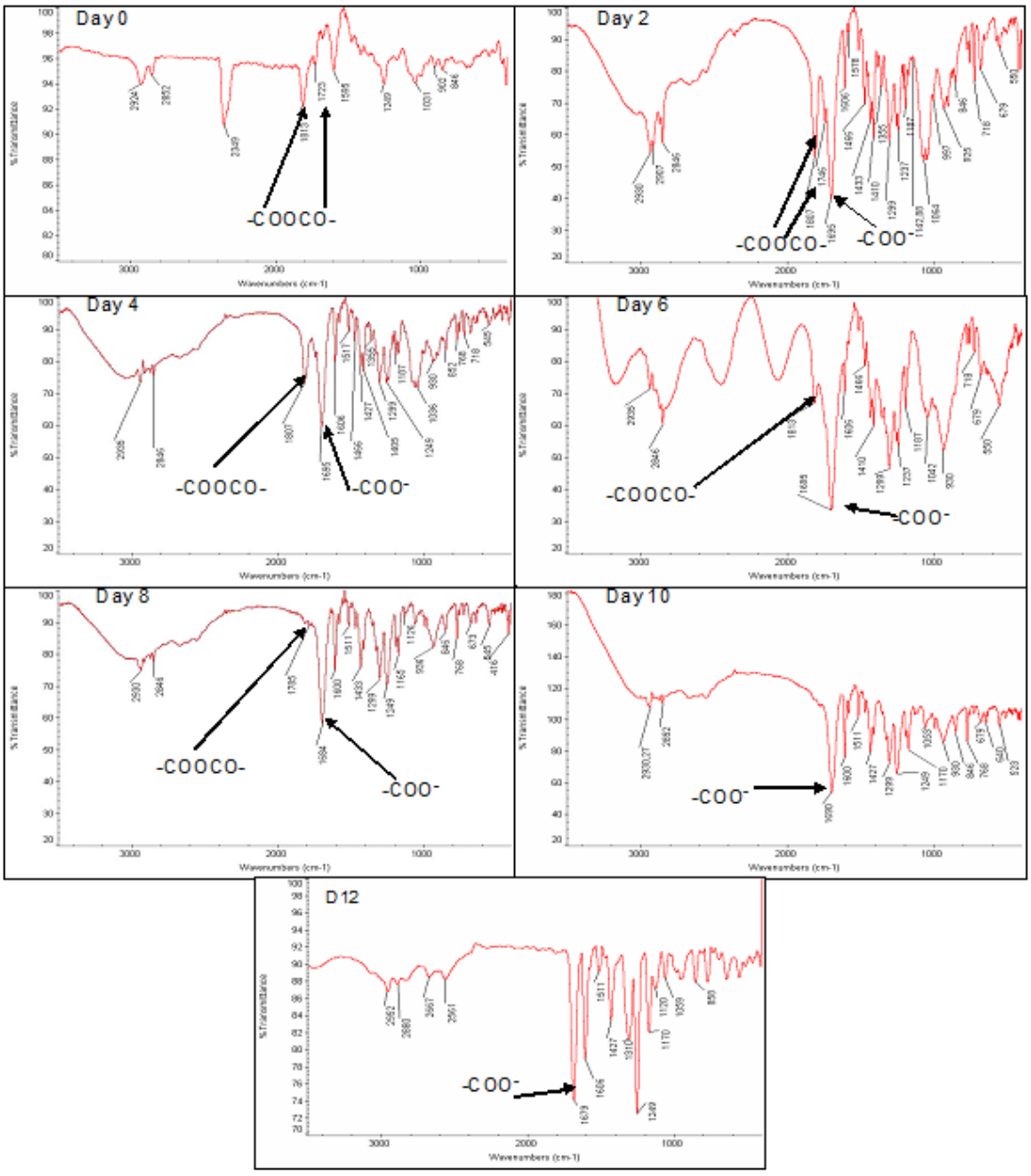

Figure 8: FTIR spectra of degraded blank poly(CPP-co-SA) (20:80)

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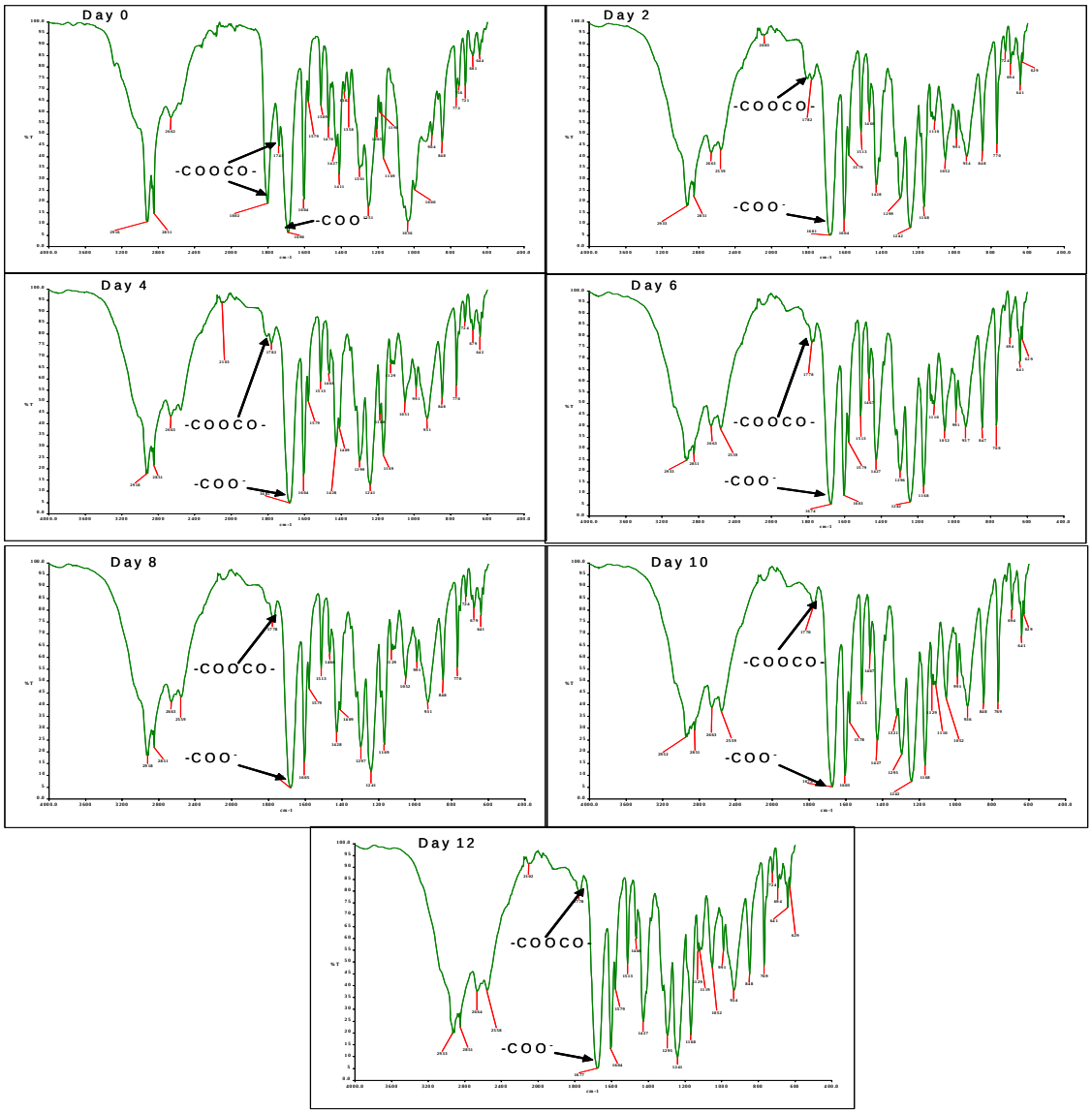


Figure 9: FTIR spectra of degraded drug loaded poly (CPP-co-SA) (20:80)

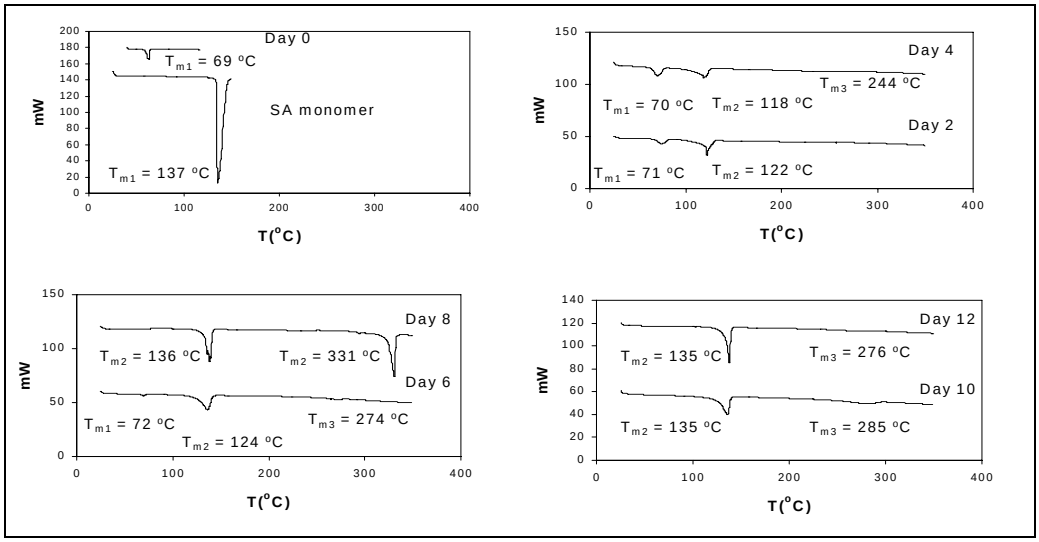
After 8 days, the melting peak of the copolymer disappears from the thermogram and both acidic monomers coexist in the polymer bulk until the end of the degradation period on study.

Similar thermal behaviour was demonstrated for the drug loaded samples (Figure 10b, Table 2) with a slight deviation resulted from the incorporation of cis platin. The melting peak of cis platin was not observed for undegraded samples (day 0) but on longer degradation period of day 6 and above, these peaks can be detected at around 350 ^{o}C. The melting of the copolymer was observed at 63 ^{o}C which prolongs to day 4

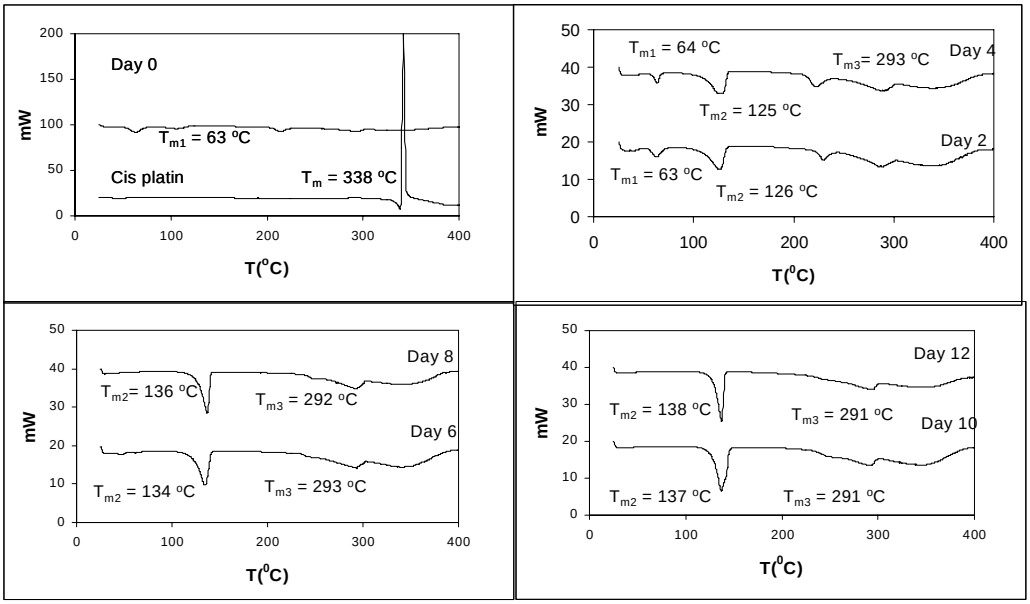
and from day 6 onwards the peak disappears from the thermogram. The appearance of SA monomers at 126 ^{o}C was detected as early as day 2, whilst CPP monomers appear on day 4 onwards. It is interesting to see that the copolymer disappear quite early (day 6) which differs from that of the blank samples (day 8). The DSC results suggest a faster degradation rate of the CPP-SA copolymer into its monomer which contradicts the FTIR results that suggest the existence of the anhydride bonds even on day 12. This is quite unexpected as one would have thought that the incorporation of cis platin could have slower down the degradation behaviour of CPP-SA copolymer judging from the mass loss, water uptake, pH, monomer release and FTIR data.

The XRD profiles which was translated into the percentage of crystallinity as a function of degradation time was shown in Figure 11. The crystallinity increases initially and remains constant throughout the degradation time. This supported the fact that degradation produces short chain oligomers and monomers that tend to realign themselves into an ordered structure which contributes to the increase in crystallinity. This agrees well with the DSC profiles that demonstrated the coexistence of the acidic monomers at longer degradation period.

Using all results obtained, the explanation of the zero order release profile (Figure 12) in which consistent amount of drug was released as a function of time is attempted. The VPSEM micrographs showed a possible surface erosion phenomenon in which the copolymer is degraded through its outermost surface area moving into the sample bulk. As the erosion phase moves from the surface into the interior part of the sample, drug which was located at the surface would first be released followed by the ones located inside the polymer bulk. This creates a consistent amount of drug being released over the surface area, provided the surface area decrease linearly with degradation time.



(a)



(b)

Figure 10: DSC thermograms of degraded poly (CPP-SA)(20:80) (a) blank and (b) drug loaded.

Table 1: Shifting of melting temperature (T_m) and the heat of fusion (ΔH_m) values for degraded blank poly (CPP-co-SA) as a function of degradation time.

Degraded blank poly(CPP-co-SA) (20:80)	$(T_{m1})_a$ (°C)	$(\Delta H_{m1})_a$ (Jg^{-1})	$(T_{m2})_a$ (°C)	$(\Delta H_{m2})_a$ (Jg^{-1})	$(T_{m3})_a$ (°C)	$(\Delta H_{m3})_a$ (Jg^{-1})
1. Day 0	69	76	-	-	-	-
2. Day 2	71	32	122	71	-	-
3. Day 4	70	46	118	74	244	13
4. Day 6	72	27	124	92	274	11
5. Day 8	-	-	136	122	331	0.34
6. Day 10	-	-	135	98	285	22
7. Day 12	-	-	135	137	276	6
8. SA monomer	-	-	137	199	-	-
9. CPP monomer	-	-	-	-	322	176

Other evidence obtained from the mass loss, water uptake, pH reduction and monomer release supports the fact that erosion occurs throughout the polymer with proofs from the FTIR, DSC and XRD profiles which gave a clear picture of the changes occurring to the polymer's morphology and chemical structure. However, they could not provide the exact surface erosion mechanism. The only evidence could come from the VPSEM images and of course the drug release profile which gives a fit of a straight line that is very typical of a surface erosion phenomenon.

As the erosion proceeds from the surface into the centre of the sample, drug will be released accordingly and release will be completed once the erosion reaches the centre of the sample and the sample is totally degraded. Polymer erosion clearly controls the release kinetic of cis platin from poly(CPP-co-SA).

Table 2: Shifting of melting temperature (T_m) and the heat of fusion (ΔH_m) values for degraded drug loaded poly (CPP-co-SA) as a function of degradation time

Degraded drug loaded poly(CPP-co-SA) (20:80)	$(T_{m1})_b$ (^oC)	$(\Delta H_{m1})_b$ (Jg^{-1})	$(T_{m2})_b$ (^oC)	$(\Delta H_{m2})_b$ (Jg^{-1})	$(T_{m3})_b$ (^oC)	$(\Delta H_{m3})_b$ (Jg^{-1})
1. Day 0	63	52	-	-	-	-
2. Day 2	63	15	126	71	-	-
3. Day 4	64	11	125	77	293	41
4. Day 6	-	-	134	98	293	37
5. Day 8	-	-	136	102	292	42
6. Day 10	-	-	137	118	291	30
7. Day 12	-	-	138	104	291	46
8. Cis platin	-	-	-	-	338	373

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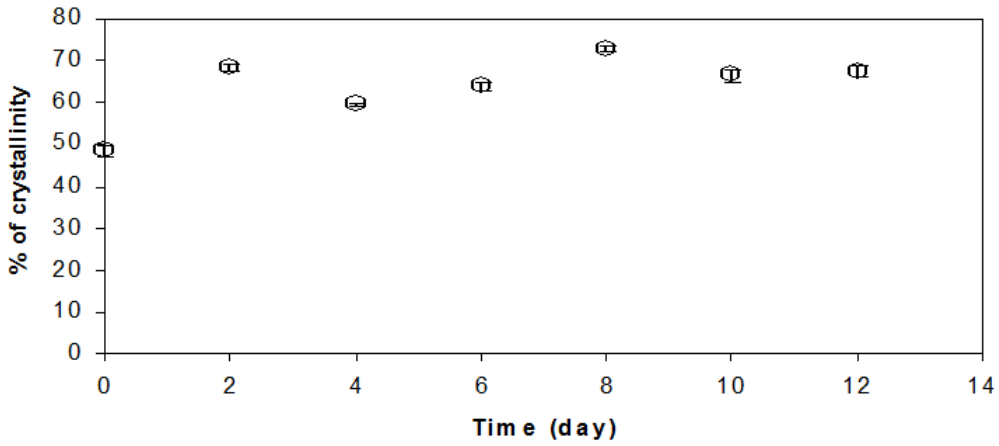

Figure 11: Percentage crystallinity plotted against time for degraded poly (CPP-co-SA) (20:80)

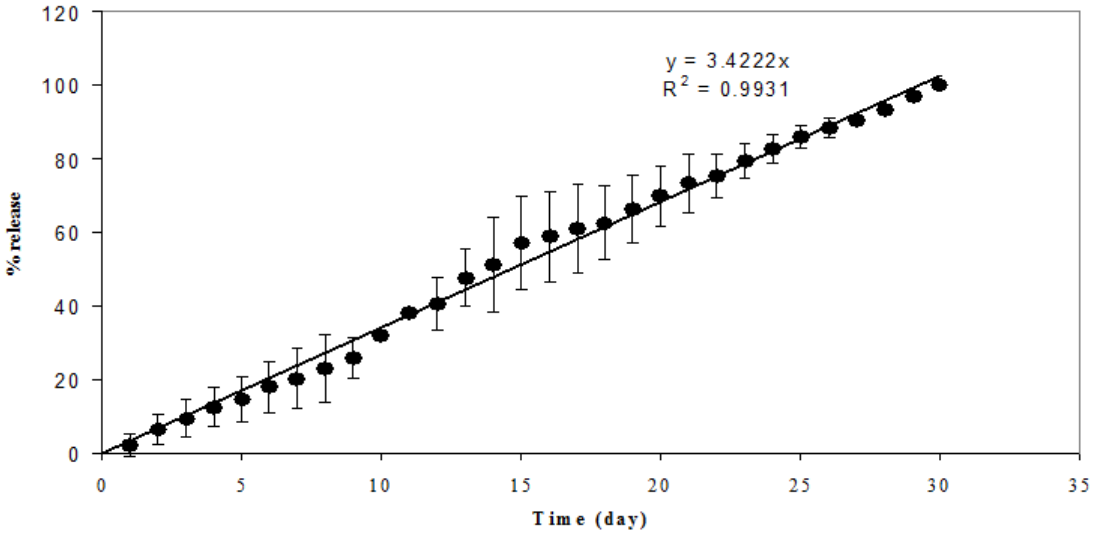

Figure 12: Drug release profile of poly (CPP-co-SA) following a zero order kinetic release

CONCLUSION

Poly(CPP-co-SA) (20:80) degrades into its acidic monomers of sebacic acid and CPP which is being supported by the mass loss, pH reduction, monomer release, FTIR, XRD and DSC profiles. Incorporation of cis platin was thought to slower down the degradation rate of the copolymer though the DSC data did not show a well correlated data. Drug is released mainly by surface erosion mechanism following zero order kinetic release.

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